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The Journal of COMMUNITY and Supportive ONCOLOGY®

— RESEARCH AND REVIEWS FOR THE PRACTICE-BASED ONCOLOGY CARE TEAM —

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The JCSO Editors and editorial staff thank all those who generously contributed to the peer-review process this past year. We are mindful of the many demands on you and value the time and expertise you put in to reviewing submissions.

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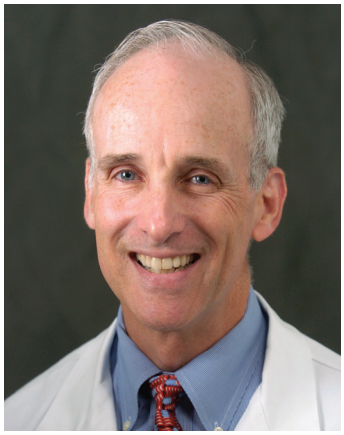
With this year's close, the end of an era

David H Henry, MD, FACP

This is the final issue of The Journal of Community and Supportive Oncology. Since our launch – separately as the Journal of Supportive Oncology in 2003 and Community Oncology in 2004 – and through the 2014 merger to form JCSO, our purpose has always been to connect with practice-based caregivers and to provide them with carefully selected, peer-reviewed information that could easily be incorporated into daily practice. Our overarching goal was to help ensure the delivery of the best-possible care and outcomes for our patients. We hope we achieved that, and the results of a 2016 readership survey seemed to confirm as much. But from a business perspective, and especially with the transition to online publishing and intensely competitive advertising landscape, economic survival became increasingly elusive, and management decided to close the journal.



JCSO was one of the few publications to span clinical and supportive care and to reach out to the entire oncology care team – oncologists, supportive care specialists, advanced practice providers, and pharmacists. Patients – their needs, concerns, and well-being – were always at the forefront of our thinking when we planned our issues. In the 2016 survey, our readers told us that they read the journal mainly to learn about clinical and supportive developments (72% and 57% of respondents, respectively), and almost 60% indicated that they routinely used information presented in our articles in their practice. To achieve those goals, we drew on the expertise and steady guidance of many over the course of our lifetime and we owe a deep gratitude to our editors emeriti, Lee Schwartzberg, MD, (Community Oncology) and Michael Fisch, MD, and Jamie von Roenn, MD (JSO), as well as the associate editors, members of the editorial advisory board, reviewers, authors, and of course, you, the reader.

I'd like specifically to thank the incumbent editors, Jame Abraham, MD; Howard Burris, MD; David Cella, PhD; Kevin Knopf, MD; and Thomas Strouse, MD for their support and invaluable contributions in recent years. Thank you too, to past associate editors Linda Bosserman, MD, (Community Oncology, JCSO; 2004-2018); Debra Patt, MD (Community Oncology, JCSO; 2012-2016); and Debra Barton, PhD (JSO, 2003-2013). And a special word of thanks to Jane de Lartigue, PhD, whose in-depth New Therapies articles and Community Translations reports helped describe and explain the science behind the therapies we use daily.

Looking ahead

From January 2019, JCSO's sister publications, Hematology News and Oncology Practice, will reside on a shared digital platform, MDedge Oncology, that will focus on news and conference coverage. Archives for JCSO, JSO, and Community Oncology will be available on this new platform at www.mdedge.com/oncology after the launch. In addition, I will host a weekly podcast focusing on current trends and advances in clinical and supportive care. It will include a long-form interview with an expert in oncology, along the lines of the former JCSO Interview, and with short end-segments on patient care, translating new research to daily practice, and a monthly journal round-up. You'll be able to subscribe to and download it at Apple podcasts, using the search terms *HemOnc* and *MDedge*.

In this issue

We end with a bumper crop of articles, beginning with a report by Hedden and colleagues on page e234 describing how they developed, implemented, and evaluated a supportive care program for patients with prostate cancer. That is followed by a literature-based review article by Ibrahim colleagues detailing the effectiveness of duloxetine in the treatment of painful chemotherapy-induced peripheral neuropathy (p. e243). In the original research section, on page e250, Palmisiano and colleagues report on mortality outcomes in hospitalized patients with cancer after rapid response team activation; Jeurkar and colleagues compare risk models guiding growth factor use in chemotherapy (p. e256); and Chao and colleagues describe the symptom burdens associated with chemotherapy-induced anemia in patients with late-stage cancer (e260).

Challenging and elusive are the key words in this issue's Case Reports in which Pollock and colleagues describe the difficulties in managing a cetuximab rash (p. e272), Roberts and colleagues write about elevated liver function tests in a patient on palbociclib and fulvestrant (p. e277), and

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Mukherjee and colleagues describe a patient with intravascular large B-cell lymphoma, who presented both a diagnostic and management challenge for the care team (p. e280). Turn to page e283, where our regular contributor, Jane de Lartigue, has written an in-depth review on everything you need to know about biosimilars. Susan London follows up on page e290 with an article on findings from studies on biosimilars for 3 oncology drugs that were reported at this year's annual meeting of the American Society of Clinical Oncology. Dr de Lartigue also reports on the approval of dabrafenib and trametinib for BRAF-mutant melanoma (e228) and osimertinib for advanced non–small-cell lung cancer (p. e231).

And finally...

I wish you and your colleagues and families all good things for the coming year. Thank you and goodbye – and stay in touch by downloading my podcast!

BRAF-MEK inhibitor combo approved for adjuvant melanoma therapy

On April 30, 2018, the US Food and Drug Administration expanded the indication for the combined use of dabrafenib and trametinib to include adjuvant treatment of *BRAF*-mutant melanoma following complete surgical resection. Dabrafenib is an inhibitor of the BRAF kinase, and trametinib is an inhibitor of the MEK kinase, both of which are components of the mitogen-activated protein kinase (MAPK) signaling pathway. The 2 drugs are already approved as both single agents and in combination for the treatment of *BRAF*-mutated metastatic melanoma.

The current approval was based on data from a phase 3, international, multicenter, randomized, double-blind, placebo-controlled trial. The COMBI-AD trial was carried out from January 2013 through December 2014 at 169 sites in 26 countries. A total of 870 patients with stage III melanoma and *BRAF V600E/K* mutations and pathologic involvement of regional lymph nodes following complete resection were randomly assigned to receive dabrafenib 150 mg twice daily in combination with trametinib 2 mg once daily, or 2 matched placebos for up to 1 year. Randomization was stratified according to *BRAF* mutation status (V600E or V600K) and disease stage (IIIA, IIIB or IIIC).

Eligible patients were aged 18 years or older and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (on a scale of 1-5, with higher scores indicating greater disability). Patients who had undergone previous systemic anticancer therapy or radiotherapy were excluded from the study.

The primary endpoint was relapse-free survival (RFS), defined as the time from randomization to disease recurrence or death from any cause. Secondary endpoints included overall survival (OS), distant metastasis-free survival (DMFS), freedom from relapse (FFR), and safety. Clinical examination and imaging by computed tomography, magnetic resonance imaging, or both was performed every 3 months for the first 2 years and then every 6 months until disease recurrence or trial completion.

As of the data cut-off, the combination of dabrafenib and trametinib reduced the risk of disease recurrence or death by 53% compared with placebo (hazard ratio [HR], 0.47; $P < .001$). Median RFS was not yet reached in the combination arm, compared with 16.6 months in the placebo arm. The RFS benefit was observed across all prespecified subgroups, and the combination was also found to improve OS, DMFS, and FFR.

The most common adverse events (AEs) included pyrexia, fatigue, nausea, rash, vomiting, diarrhea, chills, and myalgia. Overall, 97% of patients experienced an AE, 41% experienced a grade 3/4 AE, and 26% had an AE that led to treatment discontinuation. In patients treated with placebo, those numbers were 88%, 14%, and 3%, respectively.

The separate prescribing information for dabrafenib and trametinib detail warnings and precautions relating to their combined use, including the need to confirm BRAF status before starting therapy (because use in *BRAF* wildtype tumors can promote tumor cell proliferation), new primary malignancies, hemorrhage, cardiomyopathy, uveitis, serious

What's new, what's important

The expanded approval of the dabrafenib-trametinib combination for *BRAF*-mutant melanoma after complete resection is a welcome option for these patients who often face recurrence. The approval was based on data from the COMBI-AD trial in which 870 patients with stage III melanoma and *BRAF* V600E/K mutations and lymph-node involvement were randomised either to dabrafenib 150 mg twice daily in combination with trametinib 2 mg once daily, or to 2 matched placebos. Randomization was stratified according to *BRAF* mutation status and disease stage.

The primary endpoint was RFS, and secondary endpoints included OS, DMFS, FFR, and safety. As of the data cut-off, the dabrafenib–trametinib combination reduced the risk of disease recurrence or death by 53% compared with placebo (HR, 0.47; $P < .001$). Median RFS was not yet reached in the combination arm (placebo: 16.6 months). The RFS benefit was observed across all prespecified subgroups, and the combination was also found to improve OS, DMFS, and FFR. The most common AEs included pyrexia, fatigue, nausea, and rash, among others.

The prescribing information for the 2 drugs has warnings about their combined use, including the need to confirm *BRAF* status before starting therapy, new primary malignancies, hemorrhage, cardiomyopathy, uveitis, febrile reactions, skin toxicity, VTE, ocular toxicities, and embryofetal toxicity, some of which can lead to treatment discontinuation. Both drugs can cause fetal harm and patients should be warned of this risk.

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Mechanism of action: dabrafenib and trametinib

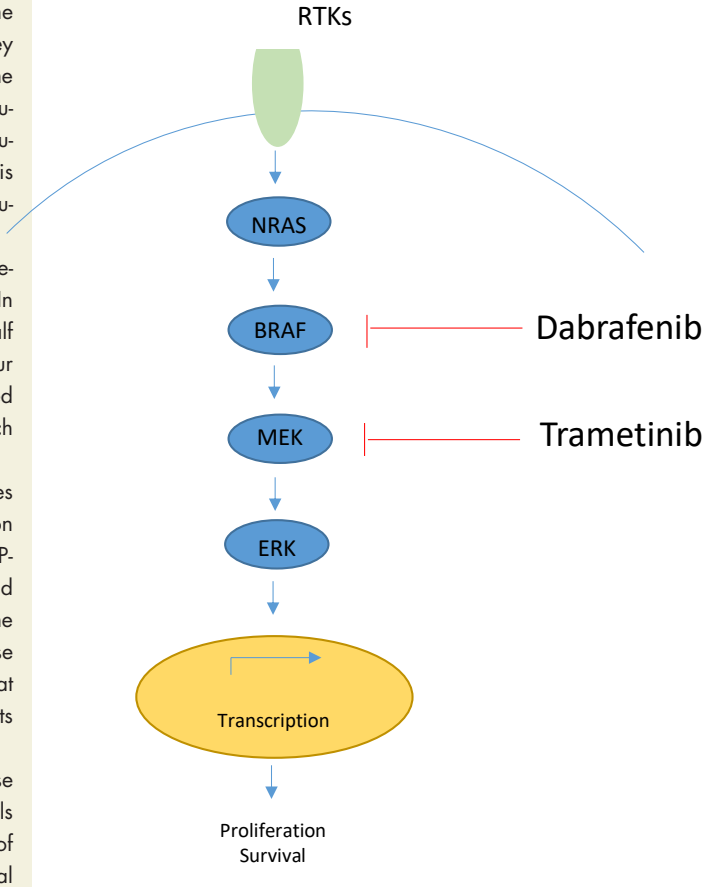
Double hit to a key cancer signaling pathway. The mitogen-activated protein kinase (MAPK) pathway is a key signaling cascade that transmits cell surface stimuli into the nucleus to regulate gene transcription and generate a cellular response. Given its central role in a number of vital cellular processes such as proliferation, growth, and survival, it is not surprising to find that this pathway is frequently dysregulated across tumor types.

This is exemplified by melanoma, in which the most frequently observed recurrent mutations occur in this pathway. In particular, one of the central kinases, BRAF, is mutated in half of all cases, and mutations in a second kinase, MEK, occur in just under 10% of cases. The most commonly observed BRAF mutations are the V600E and V600K mutations, which occur in 70%-95% and 5%-30% of cases, respectively.

Understandably, the development of targeted therapies for the treatment of metastatic melanoma have focused on the BRAF and MEK proteins. Dabrafenib is a selective, ATP-competitive inhibitor of the BRAF V600E mutant protein and trametinib is a selective ATP noncompetitive inhibitor of the MEK1/2 proteins. Both have shown considerable promise for the treatment of patients with metastatic melanoma that displays *BRAF* mutations and are approved as single agents for this indication.

However, only a proportion of patients respond to these drugs and, among those who do, resistance typically fuels treatment failure in less than a year. Because activation of other proteins within the MAPK cascade can offer a potential escape route for cancer cells treated with 1 targeted drug, double blockade of the pathway at 2 different points can prove more effective by blocking this route.

The combination of dabrafenib and trametinib has already borne out this hypothesis and is approved for the treatment of metastatic disease. The latest approval demonstrates that the combination is also effective earlier on in the course of the disease, in the adjuvant treatment of patients with melanoma after surgical resection.



BRAF and MEK, the targets of dabrafenib and trametinib, respectively, are 2 components of the mitogen-activated protein kinase (MAPK) pathway, which is activated by upstream receptor tyrosine kinases (RTKs). Combination therapy with dabrafenib and trametinib serves a double hit to the MAPK pathway, which is frequently upregulated in cancers, including melanoma, and helps to prevent the development of resistance that can arise after monotherapy. Figure generated by Jane de Lartigue.

febrile reactions, serious skin toxicity, hyperglycemia, glucose-6-phosphate dehydrogenase (G6PD) deficiency, colitis and gastrointestinal perforation, venous thromboembolism, ocular toxicities, interstitial lung disease, and embryofetal toxicity.

Dermatologic evaluations should be completed before starting therapy, every 2 months during and for up to 6 months after completion of therapy, and patients should be monitored closely for the signs and symptoms of noncutaneous primary malignancies. Treatment should be discontinued for all grade 4 hemorrhagic events and for any grade 3 events that do not improve, and withheld for grade 3 events until they resolve, at which point treatment can be resumed at the next lowest dose as described in the prescribing information.

Left ventricular ejection fraction (LVEF) values should be assessed before initiating therapy, after 1 month, and then at intervals of 2-3 months. Treatment should be withheld for up to 4 weeks if absolute LVEF values decrease by 10% and are less than the lower limit of normal (LLN) and it should be permanently discontinued for symptomatic cardiomyopathy or persistent, asymptomatic left ventricular dysfunction of >20% from baseline that is below LLN and does not resolve within 4 weeks.

Treatment should be withheld for fevers higher than

104°F or for serious febrile reactions or fever accompanied by hypotension, rigors or chills, dehydration, or renal failure. Serum creatinine levels should be monitored, along with other evidence of renal function, during, and after severe pyrexia. Antipyretics should be administered as secondary prophylaxis when treatment is resumed if the patient had previous episodes of severe febrile reaction or if fever was associated with complications. Corticosteroids should be administered for at least 5 days for second or subsequent pyrexia if the body temperature dose not return to baseline within 3 days of fever onset or for pyrexia associated with complications and no evidence of active infection.

Treatment should also be withheld for intolerable or severe skin toxicity and resumed at a lower dose as per guidelines in patients who improve or recover within 3 weeks. Serum glucose levels should be monitored at the start of treatment and as clinically appropriate in patients with pre-existing diabetes or hyperglycemia. Patients with G6PD deficiency should be monitored closely for signs of hemolytic anemia.

Patients should be monitored closely for signs and symptoms of colitis and gastrointestinal perforation and should be advised to immediately seek medical care if they develop symptoms of deep vein thrombosis (DVT) or pulmonary embolism (PE). Treatment should be permanently discontinued for life-threatening PE, or withheld for uncomplicated DVT and PE for up to 3 weeks and then resumed at a lower dose if the patient improves.

Ophthalmological evaluations should be performed periodically and within 24 hours of patient-reported loss of vision or other visual disturbances. Treatment should be permanently discontinued in patients with documented retinal vein occlusion and withheld for retinal pigment epithelial detachment. Treatment should also be withheld in patients presenting with new or progressive pulmonary symptoms and findings and permanently discontinued for treatment-related interstitial lung disease or pneumonitis.

Both dabrafenib and trametinib can cause fetal harm and patients should be warned of this risk and the need for adequate contraceptive measures. Dabrafenib and trametinib are marketed as Tafinlar and Mekinist by Novartis.

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Paradigm-changing osimertinib approval in front-line for advanced NSCLC

The US Food and Drug Administration awarded regulatory approval this spring to the third-generation epidermal growth factor receptor (EGFR) inhibitor osimertinib for the treatment of patients with exon 19 deletion- or exon21 L858R mutation-positive advanced non–small-cell lung cancer (NSCLC) not previously treated for advanced disease.

Osimertinib is designed to target both sensitizing and resistant mutant forms of EGFR, but not the wildtype protein, in an effort to improve safety and efficacy compared with other standard of care (SoC) EGFR inhibitors. It was previously approved in the second-line setting in NSCLC following failure of prior EGFR inhibitor therapy in 2015. The current approval represents a paradigm shift in the front-line treatment of advanced NSCLC, reinforcing the role of osimertinib, which has been recommended in this setting by the National Comprehensive Cancer Network Guidelines in Oncology for more than a year.

Approval was based on the phase 3, multicenter, international, randomized, double-blind, active-controlled FLAURA trial. A total of 556 patients were randomized 1:1 to receive an oral daily dose of 80 mg osimertinib or gefitinib 250 mg or erlotinib 150 mg. The trial was conducted during December 2014 through March 2016 at 132 sites in 29 countries.

Eligible patients were aged 18 or over and had locally advanced or metastatic NSCLC, had not previously received treatment for advanced disease, were eligible for first-line treatment with erlotinib or gefitinib, had locally or centrally confirmed *EGFR* exon 19 deletion or L858R mutations alone or concurrently with other *EGFR* mutations, and a World Health Organization Performance Status of 0 (fully active, able to carry on all predisease performance without restriction) or 1 (restricted in strenuous activity but ambulatory and able to carry out light work), and a minimum life expectancy of 12 weeks.

Patients with central nervous system metastases were eligible if their condition was neurologically stable. Patients who had previous definitive treatment or glucocorticoid therapy had to have completed it at least 2 weeks before the start of the trial. Patients were excluded from the trial if they had any previous treatment with any systemic anticancer therapy for advanced NSCLC, had major surgery within 4 weeks of the first dose of the study drug, had radiation therapy to more than 30% of the bone marrow or a wide field of radiation within 4 weeks of the first dose of the study drug, or were currently receiving potent inhibitors or inducers of cytochrome P450 3A4.

Osimertinib cut the risk of disease progression or death by more than 50% compared with standard TKI therapy. The estimated median progression-free survival (PFS) was 18.9 months with osimertinib, compared with 10.2 months for erlotinib or gefitinib (hazard ratio [HR]: 0.46; $P < .0001$). PFS benefit extended across all prespecified subgroups, including patients with CNS metastases (median PFS: 15.2 months vs 9.6 months; HR: 0.47; $P = .0009$). Confirmed overall response rate was 77% and 69% in the study and SoC groups, respectively, and estimated duration

What's new, what's important

Safety and encouraging improvement in PFS are the hallmarks of the approval of the EGFR inhibitor osimertinib for previously untreated advanced NSCLC. The approval was based on the FLAURA trial in which 556 patients were randomized to receive 80 mg osimertinib PO or gefitinib 250 mg or erlotinib 150 mg.

Osimertinib cut the risk of progression or death by more than 50% compared with standard TKI therapy. The estimated median PFS was 18.9 months with osimertinib (10.2 months for erlotinib/gefitinib). There was a PFS benefit across all prespecified subgroups, including patients with CNS metastases (15.2 months vs 9.6 months). Confirmed ORR was 77% and 69%, and estimated DoR was 17.6 months and 9.6 months. At the time of analysis, there were too few deaths to compare OS. The most common AEs were diarrhea, rash, dry skin, nail toxicity, stomatitis, and reduced appetite.

Prescribing information warns about ILD and pneumonitis, QTc interval prolongation, cardiomyopathy, keratitis, and embryofetal toxicity. Treatment should be withheld if patients present with respiratory symptoms indicative of ILD and discontinued on confirmation of ILD. Treatment should be permanently discontinued with QTc interval prolongation with signs and symptoms of life-threatening arrhythmia. Cardiac monitoring, including assessment of LVEF, should be done at baseline and during treatment in patients with cardiac risk factors. Patients with signs and symptoms of keratitis should see an ophthalmologist.

— Jame Abraham, MD, FACP (abrahaj5@ccf.org)

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Mechanism of action: EGFR inhibitors

The next generation. The epidermal growth factor receptor (*EGFR*) gene encodes a tyrosine kinase receptor protein that activates key intracellular signaling pathways involved in cell survival, proliferation, and other vital cellular processes. These pathways are often corrupted in cancer cells – commonly through activating mutations in the *EGFR* gene – to facilitate the transformation of a normal cell into a malignant one.

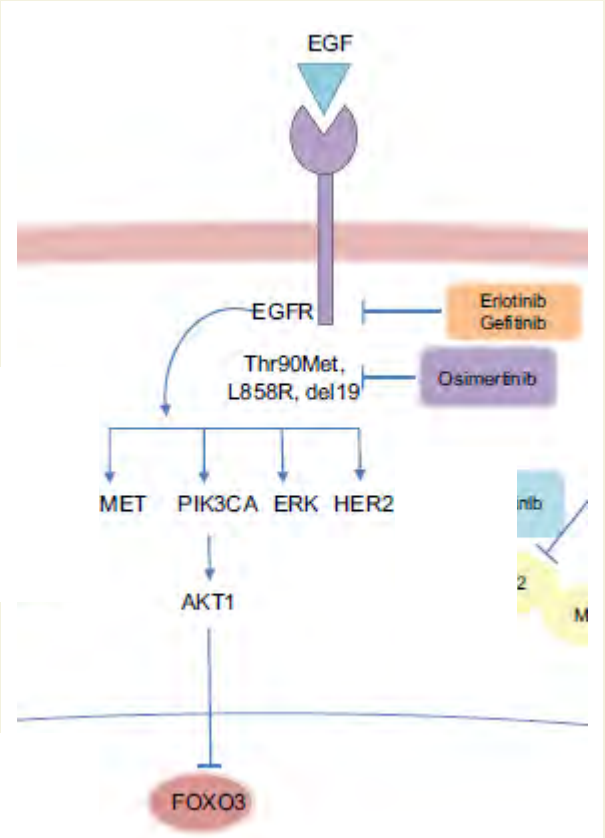
EGFR mutations are particularly common in non–small-cell lung cancers (NSCLCs) and represent one of the major drivers of this cancer type. This has served as the impetus for the development of small molecule inhibitors of the EGFR designed to block the activity of the most common mutant forms of the protein – those encoded by an *EGFR* gene with exon 19 deletions and exon 21 L858R point mutations (known as "sensitizing" mutations).

The first generation of EGFR inhibitors, which included erlotinib and gefitinib, revolutionized the treatment of patients with *EGFR*-mutant NSCLC. However, within a year, most patients who initially respond to these drugs typically develop acquired resistance that drives treatment failure.

Investigators have identified the most common mechanisms of resistance, which include the T790M mutation in more than half of cases. Known as a "gatekeeper mutation," it affects an amino acid residue that controls access to a hydrophobic pocket within the active site of the kinase, blocking the ability of the inhibitors to bind to their target, as well as altering the affinity of the mutant EGFR for adenosine triphosphate (ATP) and thus reducing the potency of ATP-competitive inhibitors.

A second generation of EGFR inhibitors was developed and designed to have activity against the T790M mutant form of the EGFR. These inhibitors also showed promise, but have been limited by the toxicity that results from their inhibition of the wildtype form of the EGFR.

Osimertinib represents one of the third generation of drugs that is designed not only to target both sensitizing and mutant forms of the EGFR, but to have limited efficacy against the wild-type form of the protein, in the hopes of improving efficacy and tolerability. Osimertinib has a distinct structure and pharmacology that render it 200-fold more selective for mutant forms over wild-type EGFR.



Mutations in the *EGFR* gene are central drivers of non-small cell lung cancer (NSCLC), which has served as the rationale for the development of EGFR-targeted tyrosine kinase inhibitors, such as erlotinib and gefitinib. Unfortunately, most patients rapidly develop resistance, most commonly due to additional *EGFR* mutations. Next-generation TKIs like osimertinib are able to target both sensitizing and resistant *EGFR* mutations. Recreated under a Creative Commons Attribution 4.0 International License. Denisenko TV et al. Cell death-based treatment of lung adenocarcinoma. Cell Death Dis. 2018;9:117.

of response (DoR) was 17.6 months and 9.6 months. At the time of analysis, there were too few deaths to compare overall survival.

The most common adverse events (AEs) experienced by patients treated with osimertinib were diarrhea, rash, dry skin, nail toxicity, stomatitis, and reduced appetite. Serious AEs occurred in 4% of patients treated with osimertinib, most commonly involving pneumonia, interstitial lung disease/pneumonitis, and pulmonary embolism (PE). The rate of grade 3/4 AEs was 33.7% in the osimertinib group and 44.8% in the SoC group. Patients treated with osimertinib were less likely to discontinue treatment due to AEs (13.3% vs 18.1% of those receiving SoC).

Osimertinib is marketed as Tagrisso by AstraZeneca and the recommended dose is 80 mg orally once daily, with or without food. The prescribing information details warnings and precautions relating to interstitial lung disease and pneumonitis, QTc interval prolongation, cardiomyopathy, keratitis, and embryofetal toxicity.

Treatment with osimertinib should be withheld in patients presenting with worsening of respiratory symptoms indicative of ILD and permanently discontinued if

ILD is confirmed. Electrocardiograms and electrolytes should be monitored periodically in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities or in patients taking medications known to prolong QTc interval. Treatment should be permanently discontinued in those who develop QTc interval prolongation with signs and symptoms of life-threatening arrhythmia.

Cardiac monitoring, including assessment of left ventricular ejection fraction should be performed at baseline and throughout treatment in patients with cardiac risk factors and treatment should be permanently discontinued in patients who develop symptomatic congestive heart failure. Patients with signs and symptoms of keratitis should be referred to an ophthalmologist. Osimertinib can cause fetal harm and patients should be advised of the potential risk and the need for effective contraception use during treatment and for 6 weeks after the final dose is administered.

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Development, implementation, and evaluation of a prostate cancer supportive care program

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Many men who are diagnosed with prostate cancer face long-term treatment-related health effects that will affect their quality of life and have cost implications for the health system. In this article, we describe and assess the use of and satisfaction with the Prostate Cancer Supportive Care (PCSC) Program, which is a comprehensive, evidence-based, modular program that aims to address these concerns. We include data from patient medical records, PCSC Program registration forms and attendance records, and anonymized participant feedback forms. We examine the clinical and sociodemographic characteristics of program participants, program participation rates, and satisfaction with individual program modules. Among the 1,269 registrants, 1,206 (84%) participated in the program. Modules that provided information on prostate cancer and treatment options and offered sexual health support had the most participants (29% and 55% of total program participants, respectively). Satisfaction with all program components was high among both survivors and their partners (average score, 3.6 out of 4). Robust evaluations of the program's effects on quality of life and health system costs are ongoing. There is a growing need to provide consistent and comprehensive support to prostate cancer survivors and their partners and families. As such, we recommend that alongside direct oncologic care, clinicians assess their patients' needs for supportive care services and refer them to programs that will provide comprehensive support throughout the disease and treatment journey. **Funding** The Michael Smith Foundation for Health Research (grant number 16605) and Prostate Cancer Canada (grant number PDF2016-1270)

Prostate cancer is the most common malignancy diagnosed in Canadian men. An estimated 21,300 Canadian men were diagnosed with the disease in 2017, representing 21% of all new cancer cases.[1] There are about 176,000 men living with prostate cancer in Canada.[1] In the United States, there were 2,778,630 survivors of prostate cancer as of 2012 and that population is expected to increase by more than 1 million (40%) to 3,922,600 by 2022.[2]

Although 96% of men diagnosed with prostate cancer now survive longer than 5 years[3], many will suffer from treatment-related sequelae that can have a profound effect on quality of life for themselves and their partners.[4,5] Impacts include sexual, urinary, and bowel dysfunctions[6] owing to treatment of the primary tumor as well as reduced muscle and bone mass, osteoporosis, fatigue, obesity, and glucose intolerance or diabetes[7] owing to androgen-deprivation therapy (ADT). Many men also suffer from psychological issues such as depression, anxiety, anger and irritability, sense of isolation, grief, and loss of masculinity.[8,9] The psychological impacts also continue well beyond the completion of treatment and can be significant for both patients and their partners.[5,8]

With posttreatment longevity and the associated complex sequelae, prostate cancer is being viewed increasingly as a chronic disease whose effects must be managed for many years after the completion of primary treatment. Supportive care that "[manages] symptoms and side effects, enables adaptation and coping, optimizes understanding and informed decision-making, and minimizes decrements in func-

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Disclosures: Dr Elliot served on the board for Aceras, and has given a lecture for Pentopharm. Dr Higano has received research grants from Aptero, Aragon, Astellas, Astra-Zenica, Bayer, Dentreon, Hoffman-Laroche, Medivation, and Pfizer. Dr Higano also served on the advisory board or in a consultancy role for Astellas, Bayer, Blue Earth, Cloris, Orion, and Tolmar.
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tioning"[10] is becoming recognized as a critical component of direct oncologic care before, during, and after treatment. Health care professionals, scientists, governments, and patient advocates are increasingly calling for the development of comprehensive supportive care programs improve the quality of life for people diagnosed with cancer. A common model for survivorship care is a general program for all cancer survivors that provides disease- and patient-specific care plans. These care plans outline patients' prior therapies, potential side effects, recommendations for monitoring (for side effects or relapse of cancer), and advice on how patients can maintain a healthy lifestyle.[11] However, there are few survivorship programs for men with prostate cancer and their partners, and the evidence base around best practices for these programs is scant.[12] Furthermore, up to 87% of men with a prostate cancer diagnosis report specific and significant unmet supportive care needs,[10,13] with sexuality-related and psychological issues[10,14] being the areas of greatest concern.

To address the complex supportive care needs of men with prostate cancer in British Columbia, Canada, the Vancouver Prostate Centre (VPC) and Department of Urologic Sciences at the University of British Columbia developed the multidisciplinary Prostate Cancer Supportive Care (PCSC) Program. The program aims to address the challenges of decision-making and coping faced by men with prostate cancer and their partners and family members along the entire disease trajectory. Services are provided at no cost to participants. Here, we outline the guiding principles for the PCSC program and its scope, delivery, and evaluation. We provide information on the more than 1,200 patients who have participated in the program since its inception in January of 2013, the rates of participation across the different program modules, and a selection of patient satisfaction measures. We also discuss successes and limitations and ongoing research and evaluation efforts, providing lessons learned to support the development of other supportive care programs in Canada and internationally.

Program description

Guiding principles

The PCSC Program is a clinical, educational, and research-based program, with 4 guiding principles: it is comprehensive, patient- and partner-centered, evidence-based, and supports new research. The program serves patients, partners, and families along the entire disease trajectory, recognizing that cancer is a family disease, affecting both the individual and social network, and that the psychological stress associated with a diagnosis of prostate cancer is borne heavily by partners. It has been designed, implemented, and refined with the best available evidence and with the intention to undergo consistent and repeated evaluation. Finally, it was designed to provide opportunities for targeted research efforts, supporting the growth of the evidence base in this area.

Patient entry and module descriptions

Patients can be referred to the program by a physician or other allied health professional. They may also self-refer, having been made aware of the program through our website, a variety of print materials, or by word of mouth. On referral, the program coordinator collects patients' basic clinical and demographic data, assesses health literacy and lifestyle factors, and provides them with information on the program modules. As of December 2015, the program consisted of 6 distinct modules, each focusing on different elements of the disease trajectory or on addressing specific physical or mental health concerns. Modules are led by licensed health professionals with experience in oncology. No elements of the program are mandatory, and participants are free to pick and choose the components that are most relevant to them and their partners.

Introduction to prostate cancer and primary treatment options. This is a group-based module that focuses on educating newly diagnosed patients (and those going on or off active surveillance) on the basic biology of prostate cancer, the primary treatment options for localized disease, and the main side effects associated with the treatments. It also includes information about the other services offered by the program and any ongoing research studies. The session is held twice a month in the early evening and is run collectively by a urologist, radiation oncologist, patient representative, and program coordinator. It includes a brief one-on-one discussion between each patient and their partner or family member and the urologist and radiation oncologist to address any remaining questions. A copy of the patient's biopsy report is on hand for the physician(s). Attendance of this session has been shown to significantly reduce pretreatment distress in both patients and their partners.[15]

Managing sexual function and intimacy. Sexual intimacy is tied to overall health outcomes, relationship satisfaction, and quality of life.[16] Primary therapy for prostate cancer can be associated with substantial side-effects (eg, erectile dysfunction, incontinence, altered libido, penile shortening) that negatively affect sexual intimacy and have an impact on the patient individually as well as the sexual relationship he has with his partner.[17]

The program's Sexual Health Service (SHS) provides patients and partners with information on the impact of treatment on sexual health.[18] The SHS offers educational sessions led by a sexual rehabilitation nurse and clinical psychologist with a specialization in sexual health. Sessions focus on the impact of prostate cancer treatments on sexual function and therapeutic modalities, promote an understanding of the barriers to sexual adaptation posttreatment,

and present options for sexual activity that are not solely dependent on the ability to achieve an erection. Once participants have attended an educational session, they are offered individual consultations with the sexual health nurse every 3 to 6 months for 2 years or longer, depending on the patient's or couple's needs. They are referred to the SHS's sexual medicine physician if further medical intervention is warranted. The sexual health nurse works with the patient and partner to develop an individualized Sexual Health Rehabilitation Action Plan (SHRAP), which assists the couple in sexual adaptation going forward. The SHRAP is a tool devised by the sexual health nurse based on her clinical experience with couples affected by prostate cancer.

Couples who have been evaluated within the SHS are also invited to attend a second workshop on intimacy that is offered quarterly. Workshop participants discuss the impact of sexual changes on relationships, and strategies on how to enhance intimacy and sexual communication are presented. A resource package is provided to each couple to help re-establish and/or strengthen their various dimensions of intimacy.

Lifestyle management. The lifestyle management modules include separate nutrition and physical activity or exercise components. Referral to the smoking cessation program in the Vancouver Coastal Health Authority is made at program registration, if appropriate. The nutrition group-based education session is delivered by a registered dietitian from the British Columbia Cancer Agency who specializes in prostate cancer. The session focuses on evidence-based recommendations on diet after a diagnosis of prostate cancer, the use of dietary supplements, body weight and health, and practical nutrition tips. The exercise session is delivered by an exercise physiologist who specializes in working with cancer patients. It covers the value of exercise in terms of safety, prevention and reduction of treatment side effects (including from ADT), treatment prehabilitation and recovery, advanced cancer management, and long-term survival. A one-on-one exercise counseling clinic is also offered and aims to increase exercise adoption and long-term adherence in line with Canadian Physical Activity guidelines and exercise oncology guidelines,[19,20] with follow-up appointments at 3, 6, and 12 months to help patients stay motivated and ensure they are exercising correctly. The individual consultations with the exercise physiologist include physical measures, exercise volume, treatment side effects, and coconstructed goal setting with an individualized formal exercise regimen (exercise prescription).

Adapting to ADT. This is an educational module offered to patients with metastatic prostate cancer who are starting hormone therapy treatments that lower serum testosterone into the castrate range. This program was one of several available through TrueNTH, a portfolio of projects funded by the Movember Foundation, through Prostate Cancer Canada. The session is delivered by a patient facilitator and focuses on strategies to recognize and adapt to the side effects of ADT[21] while maintaining a good quality of life and strong intimate relationships with partners.[22,23]

Pelvic-floor physical therapy for urinary incontinence. This module includes a group-based and individualized education session for patients (either pre- or posttreatment) focused on reducing the effects of surgery and/or radiation therapy on urinary and sexual continence as well as on how to cope with these symptoms and minimize the effect they have on quality of life.[24] The session is conducted by a physical therapist who is certified as a pelvic-floor specialist. Supervised pelvic-floor re-education and/or exercise has been shown to successfully reduce the degree of incontinence in this population.[25] The module therefore also includes 3 one-on-one clinical appointments for patients who are still experiencing bother from incontinence 12 weeks after a radical prostatectomy or postradiation treatment.

Psycho-oncology. In recognition of the emotional and psychological burden associated with prostate cancer and the important role partners play in facilitating treatment of these psychological and/or psychosocial issues, the program offers appointments with a registered clinical counselor to address acute emotional distress. These are usually 1-hour appointments offered to both patients and partners, either separately or together. Appointments can be attended in person or conducted by telephone. When appropriate, patients are referred for further long-term individual support or couple support with their partners. A group therapy workshop was also initiated in 2016. In this program, men participate in a guided autobiographical life review through a process that focuses on developing a cohesive working group, learning strategic communication skills, and understanding and learning how to manage difficult emotions and transitional life stressors associated with prostate cancer. It also focuses on processing and integrating critical events that contribute to the men's identity and psychological function and involves the consolidation of the personal learning that occurs. Postgroup referral plans are developed on an individual basis as needed.

Methods

Data

We obtained sociodemographic, diagnostic, and treatment information as well as clinic visit records for all PCSC Program registrants from the electronic medical record held at the VPC. Clinical variables included age at diagnosis, Gleason score, and primary treatment modality (including active surveillance and ADT use). The Gleason score

determines the aggressiveness of a patient's prostate cancer based on biopsy results. A score of 6 or less indicates that the disease is likely to grow slowly. A grade of 7 is considered intermediate risk (with primary score of 3 and secondary 4 being lower risk than those with a primary score of 4 and secondary of 3). A Gleason score of 8 or higher indicates aggressive disease that is poorly differentiated or high grade. Sociodemographic characteristics included age, travel distance to the clinic, and income quintile. We obtained attendance records for the modular education sessions from the program's database. Patients who did not have any medical visits at the VPC (referred to henceforth as non-VPC patients) did not have a clinic record, so we excluded them from the subset of the analyses that depended on specific clinical variables.

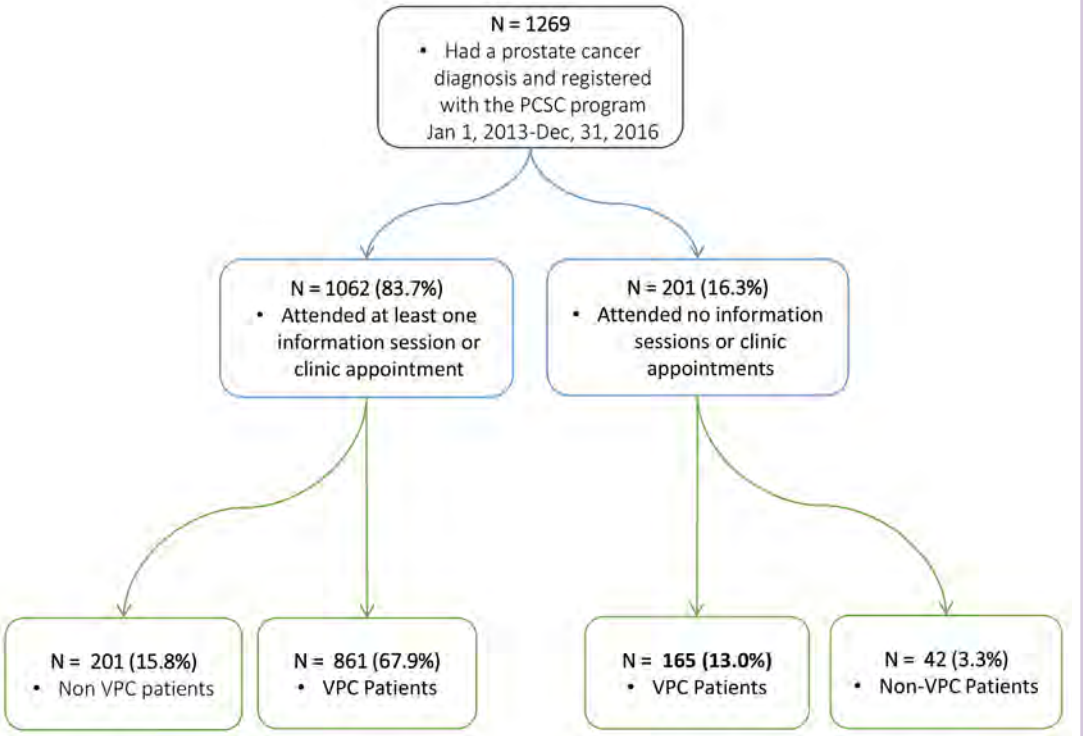

FIGURE Registrants, participants, and nonparticipants in the Prostate Cancer Supportive Care Program

VPC, Vancouver Prostate Centre; PCSC, Prostate Cancer Supportive Care

All patients and partners who participate in any PCSC Program education sessions (introduction to prostate cancer, sexual health, nutrition, exercise, ADT, and pelvic-floor physical therapy) are asked to complete voluntary, anonymous feedback forms. These forms assess participant satisfaction using a series of Likert-based and Boolean response items as well as qualitative commentary. They include questions that assess the timing, structure, and content of each session.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Statistical approach

Descriptive statistics were used to analyze participant characteristics, program participation rates, and participant satisfaction. For each module's education session, we compared the overall satisfaction between patients and partners using *t* tests. We also compared the level of satisfaction across the different modules using a 1-way analysis of variance. For the sexual health and pelvic-floor physical therapy sessions, we compared satisfaction between participants who attended the education sessions before to those who attended following their primary treatment using *t* tests. We provide the eta squared (for analyses of variance) and Cohen d (for *t* tests) to provide an effect size estimate of any significant differences observed.

Results

Participants

From the program's founding in January of 2013 to December 31, 2016, a total of 1,269 patients registered (an average of 317 patients a year). Of those, 1,026 (80.9%) had at least 1 prostate cancer–related visit at the VPC. The remaining 243 (19.1%) were non-VPC patients (Figure). Overall, 1,062 men (83.4%) who registered with the program went on to attend at least 1 education session or clinic appointment.

Average age among male program participants was 67.7 years, and age at diagnosis was 62.5 years (Table 1). In all, 273 men (31.7%) had Gleason 3+4, and 117 (13.7%) had Gleason 4+3. Most of the participants (76.9%) elected to undergo radical prostatectomy for primary treatment. Ninety-five men (8.9%) received at least some ADT treatment as an adjunct to radiation or to treat recurrent dis-

TABLE 1 Demographic and treatment characteristics of participants in the Prostate Cancer Supportive Care Program (N = 1,062)

Characteristic	Value
Mean age on Dec 31, 2016, y (SD)[a]	67.7 (7.6)
Mean age at diagnosis, y (SD)[bc]	62.5 (11.9)
Gleason score, n (%) [bd]	
<7	264 (30.7)
3+4	273 (31.7)
4+3	117 (13.6)
8	99 (11.5)
9-10	108 (12.5)
Primary treatment, n (%)[bc]	
Prostatectomy	616 (71.5)
Prostatectomy with EBRT	19 (1.5)
EBRT	26 (2.3)
Brachytherapy	38 (4.4)
EBRT and brachytherapy	7 (0.8)
Untreated[e]	97 (11.3)
Androgen deprivation therapy, n (%)[b]	
Continuous blockade	16 (1.9)
Intermittent suppression	72 (8.4)
Mean distance to clinic, km/mi (median)[f]	83.1 km (16.9) 51.6 mi (10.5)
Socioeconomic quintile, n (%)[f]	
1	104 (10.9)
2	129 (13.5)
3	178 (18.6)
4	231 (24.1)
5	301 (31.5)

Characteristic	Value
Time (y) from diagnosis to first participation, n (%)[g]	
Prior to diagnosis	1 (0.1)
<1 y	431 (50.1)
1 – <2 y	130 (5.1)
2 – <3 y	63 (7.3)
3 – <4 y	53 (6.2)
4 – <5 y	33 (3.8)
5+	150 (17.4)
No. of education sessions attended, n (%)	
0	363 (34.2)
1-2	544 (51.2)
3-4	130 (12.2)
5+	25 (2.4)
No. of clinic visits attended, n (%)	
0	335 (31.5)
1-2	305 (28.7)
3-4	215 (20.3)
5+	207 (19.5)
Partner/family member attended at least 1 session, n (%)	497 (46.8)

EBRT, external beam radiotherapy

[a]Missing data for 23 participants. [b]Excludes 201 non–Vancouver Prostate Centre participants. [c]Missing data for 7 participants. [d]Gleason scores lower than 7 have a more favorable prognosis. A grade of 7 is considered intermediate risk (with primary score of 3 and secondary 4 being lower risk than those with a primary score of 4 and secondary of 3). Scores of 8 or more are poorly differentiated and more likely to spread. [e]Active surveillance, no treatment recorded, or treatment scheduled in future. [f]Missing data for 105 participants. [g]Missing data for 119 participants.

ease. Participants traveled an average of 83.1 km (51.6 miles; median, 6.9 km and 10.5 miles, respectively) to attend the program; 10% of participants traveled further than 112 km (70 mi) to the clinic. One hundred and four (10.9%) and 301 (31.5%) of registrants were in the lowest and highest income quintiles respectively. Four hundred and ninety-seven (46.8%) attended at lesson 1 session or clinic appointment with a partner or family member.

Program participation

Of the 1,062 men who participated in the program, 867 (80.1%) were patients of the VPC, and 205 (19.1%) were non-VPC patients. The education sessions for the introduction to prostate cancer and sexual health modules had the largest numbers of participants (309 and 265, respectively; Table 2); however, pelvic-floor physical therapy had the highest participation rate per quarter (25 patients). The clinical services offered within the sexual health module had the larger number of participants and highest participation rate per quarter (590 total patients, 42/quarter). Timing of program participation was highly variable, ranging from 6 days to 18.5 years after diagnosis (SD, 1,301 days). More than half of participants attended a session or clinic visit within the first year of their diagnosis. A total of 17% of patients who registered did not attend any part of the program.

TABLE 2 Number and percentage of Prostate Cancer Supportive Care Program participants who attended each module (N = 1,062)

	Education session		Clinical services		
Modules	**n (%)**	**Participants/ quarter**	**n (%)**	**Participants/ quarter**	**Total n (%)[a]**
Introduction	309 (29.1)	19	NA	NA	309 (29.1)
Sexual health	265 (25.0)	19	590 (55.6)	42	686 (54.6)
Lifestyle management					
Nutrition	165 (15.5)	13	NA	NA	165 (15.5)
Exercise	89 (8.4)	9	84 (6.5)	14	152 (14.3)
Adapting to ADT	159 (12.5)	11	NA	NA	159 (150)
Pelvic-floor physical therapy	303 (28.5)	25	269 (25.3)	21	418 (39.4)
Psycho-oncology	NA	NA	97 (7.9)	16	109 (10.3)

ADT, androgen-deprivation therapy

[a]Reflects the total number of program participants who attended any part of the module (education session, clinical appointment, or both)

TABLE 3 Patient and partner feedback on the education sessions by program module

		No. of affirmative responses (%)		
Module	**No. of feedback forms submitted**	**Q: Was the information clear & easy to understand?**	**Q: Was any information missed?**	**Q: Was the session an appropriate length?**
Introduction and treatment options	249	242 (97.1)	21 (8.4)	229 (92.0)
Sexual health	259	258 (99.6)	12 (4.5)	251 (96.9)
Lifestyle management	317	317 (100)	25 (7.9)	240 (92.7)
Adapting to ADT	229	Not asked	Not asked	Not asked
Pelvic-floor physical therapy	310	306 (98.7)	26 (8.4)	294 (94.8)

ADT, androgen-deprivation therapy

Satisfaction

Most patients and partners said that they found the information presented at the modular education sessions comprehensive, clear, and easy to understand (Table 3). Although the overall average satisfaction score varied significantly across sessions, ranging from 3.5 (out of a possible 4) for pelvic-floor physical therapy to 3.8 for introduction to prostate cancer ($F = 3.8$, $P < .001$), the effect size of this difference was small ($\eta 2 = .039$; Table 4A). We found no difference in the level of satisfaction between patients and partners, with the exception of the sexual health module, which was rated better by partners than by patients (patients: 3.6, partners: 3.8; $t = 2.0$; $P = .03$); however, the effect size of this difference was again small (Cohen $d = .29$). A total of 86% of patients found the inclusion of their partners at the sessions useful. For both pelvic-floor physical therapy and sexual health, attendees were more satisfied if they attended before treatment initiation rather than after completion (Table 4B).

Discussion

The purpose of this descriptive analysis was to outline a comprehensive, multidisciplinary supportive care program for men with prostate cancer and to present initial data on the population that has used the program and their satisfaction with the services provided. Within the first 5 years of the PCSC Program, 1,269 patients registered to participate. However, nearly 1 in 6 men who registered for the program did not subsequently attend any education sessions or use any clinical services offered, despite the fact that all services were free of charge. It is possible that nonparticipation may be related to men on active surveillance choosing not to engage with the program until they are faced with making a treatment decision, which may not happen until several years after an initial positive biopsy.[26] This and other factors that affect a patient's decision not to participate will be investigated in a future study. There is existing evidence documenting high levels of distress and anxiety for patients and their partners resulting from decision-making

TABLE 4 Mean (SD) patient and partner satisfaction scores for education sessions by Prostate Cancer Supportive Care Program module

A						
		Score (out of possible 4)				
Module	No. of feedback forms submitted	Total*	Patients	Partners	*t* value (*P* value)	Cohen d
Introduction and treatment options	249	3.8 (0.4)	3.7 (0.5)	3.8 (0.4)[a]	2.0 (.06)	0.24
Sexual health	259	3.7 (0.5)	3.6 (0.5)	3.8 (0.4)	2.0 (.03)*	0.29
Lifestyle management	317					
Nutrition	207	3.5 (0.7)	3.6 (0.5)	3.7 (0.9)	0.9 (.4)	0.18
Exercise	110	3.6 (0.5)	3.6 (0.5)	3.7 (0.5)	1.3 (.2)	0.53
Adapting to ADT	229	3.7 (0.5)	3.7 (0.5)	3.7 (0.5)[4]	2.0 (.9)	0.084
Pelvic-floor physical therapy	310	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)[5]	2.0 (.9)	0.023
B						
		Score (out of possible 4)				
Module	No. of feedback forms submitted	Total*	Pretreatment	Posttreatment	*t* value (*P* value)	Cohen d
Sexual health	259	3.7 (0.5)	3.8 (0.4)	3.6 (0.6)	2.0 (.002)*	0.40
Pelvic-floor physical therapy	310	3.5 (0.5)	3.6 (0.6)	3.4 (0.6)	2.0 (.03)	0.25

ADT, androgen-deprivation therapy

[a]Analysis of variance comparing satisfaction across modular education sessions (excludes psycho-oncology); $F = 11.04$; $P < .0001$; $\eta^2 = 0.039$

*$P < .05$

around prostate cancer treatment,[27,28] and many face both decisional conflict and subsequent regret.[15,29] Further work to help patients access the program could include defining a prehabilitation program for which patients can sign up that automatically selects the education sessions and clinical services most relevant to them.

The number of attendees varied across the 6 education sessions, with introduction to prostate cancer and sexual health being the best attended. This is consistent with the literature concerning the specific unmet supportive care and information needs in this population[10,13] and with the value that men have placed on taking an active role in the decisions around their prostate cancer treatment.[30] It is also possible that attendance varied because modules were introduced in a stepwise fashion and were offered on different schedules. Patients and partners both reported a high degree of satisfaction with all of the modules' education sessions, reporting that the length, content, and delivery were appropriate.

Since 2013, a wide research portfolio has grown alongside the program. It has acted as a recruitment site for multicenter national studies and has attracted funding for several in-house research projects and evaluations. In addition, the VPC has implemented clinic-wide electronic collection of several patient-reported outcome measures using iPads. Patients have the option of contributing their data to Canadian (PC360°) and Global (TrueNTH Global Registry – Prostate Cancer Outcomes) registries for prostate cancer. The program has also created educational opportunities by supporting postdoctoral fellows. It has also provided a rich environment for urology and radiation oncology residents and fellows to participate in a multidisciplinary supportive care team, ensuring that the next generation of surgeons and oncologists recognize the importance of this approach to care.

Limitations

This is a brief descriptive study that relies on a mixture of anonymized survey and clinical chart data. Because the program's patient feedback forms are anonymous, we are not able to link satisfaction scores to differences in sociodemographic, clinical, or prognostic factors. We also have not directly measured clinical, psychological, or quality of life outcomes; however, all 3 will be included in future studies of the program. An additional limitation is that not all program modules were offered for the entirety of the study duration and are offered at different frequencies. Thus, some modules have disproportionally higher participation rates than others. Lastly, we are missing clinical information for 16% of our participants who are not patients at the VPC.

The program is offered within an academic and teach-

ing hospital in a major metropolitan center and depends on the work of a large interdisciplinary team. Cancer programs that are not embedded within a similar environment, such as those located in smaller rural communities, may not have access to the specialized clinical professionals who run our program, affecting its direct generalizability to these locations. Other specialists, such as palliative care teams, could be well positioned to provide support in locations that do not have a similar level of resource available. Furthermore, some program elements will be adapted to be delivered using telemedicine technology, which is an additional approach to improving access for patients who are beyond the reach of a tertiary care facility.

Conclusions

There is a growing need to provide consistent and comprehensive supportive care to patients with prostate cancer and their partners and families throughout the disease and treatment journey. The PCSC Program uses a multidisciplinary, evidenced-based, disease-focused approach to support informed treatment decision-making and address the physical, psychological, and psychosocial effects of prostate cancer diagnosis and treatment. We proactively collect data on disease, personal demographic details, and symptoms or quality of life, supporting opportunities to partner with researchers with the goal of further improving quality of life based on evidenced-based practices. Going forward, we will conduct detailed examinations of the costs and benefits (in terms of symptom management and quality of life) of the PCSC Program, further contributing to the development of evidence-based best practices for supportive care for men with prostate cancer and their families.

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Effectiveness of duloxetine in treatment of painful chemotherapy-induced peripheral neuropathy: a systematic review

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Chemotherapy-induced peripheral neuropathy (CIPN) is a serious side effect that can be dose limiting and affect patient quality of life. To date, the therapeutic options for CIPN are limited. We performed a systematic literature search of the PubMed and Scopus databases to assess the effectiveness of duloxetine in the treatment of pain in patients with CIPN. The search included randomized controlled trials, nonrandomized controlled trials, retrospective studies, and single-arm studies of duloxetine in treatment of CIPN. A descriptive analysis of the studies was performed. The PubMed database online search identified 41 publications, and a second database search through Scopus identified 29 publications. A total of 10 full-text articles were assessed for eligibility, with 5 articles excluded. Altogether, the included studies reported 431 patients with painful CIPN. An improvement in pain scores was the primary and/or secondary endpoint in the included studies. Pain was assessed by 6 different scores. Comparator drugs were used in 4 studies in our review. The comparator drug was placebo in 1 study only, and the remaining 3 studies used other antineurotoxicity therapy. The chemotherapeutic agents used in the studies were the following: paclitaxel (52.9%), oxaliplatin (39.7%), R-CHOP (rituximab, doxorubicin, vincristine, and cyclophosphamide; 3.30%), combined bortezomib–dexamethasone (1.89%), FOLFOX (folinic acid, fluorouracil, and oxaliplatin; 1.18%), and other taxanes (0.94%). From the descriptive analyses, and from the available data of relatively small sample sized studies, it can be concluded that despite the above limitations, duloxetine remains a useful therapeutic option for pain in CIPN patients, regardless of the type of chemotherapeutic agent used.

Chemotherapy-induced peripheral neuropathy (CIPN) is a serious side effect that can be dose limiting and affect patient quality of life for prolonged time,[1] with an overall incidence of about 38% in patients who are treated with multiple chemotherapeutic agents.[2] CIPN has various clinical presentations – affecting the motor, sensory, and autonomic nerves – but the most common manifestations are numbness, tingling, and burning pain affecting the upper and lower extremities (the stocking-and-glove distribution).[3-5] It can also lead to numerous negative effects on activities of daily living, functioning,[6] leisure activities, dressing, household and work activities, going barefoot or wearing shoes, and driving. The incidence of CIPN is variable, depending on many factors such as type of chemotherapy, total dose, dose per cycle, infusion duration, and comorbidities as diabetes mellitus.[5-7]

The most common antineoplastic agents causing peripheral neuropathy are oxaliplatin, cisplatin, taxanes, Vinca alkaloids, bortezomib, and thalidomide.[3,8,9]

Different components of the nervous system are targets of various chemotherapeutic agents, from dorsal root ganglion (DRG) cells to the distal axon. The DRG is the most vulnerable to neurotoxicity because it is less protected by the nervous system blood barrier, hence the predominance of sensory symptoms in CIPN.[10] The pathogenesis of CIPN is not fully understood, and it is most probably multifaceted and not always related to the antineoplastic mechanism. Findings from experimental studies have shown an accumulation of chemotherapeutic compounds in the cell bodies of the DRG, resulting in decreased cellular metabolism and axoplasmic transport. Another proposed mechanism is the induction of apoptosis in sensory neuron of the posterior spinal ganglion after binding to DNA strands.[7,11]

Opioids had been used for managing pain in patients with cancer, but their addictive side effects limit use in the treatment of chronic pain,[12] so several drugs called coanalgesics have been introduced as a treatment for CIPN, including antidepressants (tricyclic antidepressants, serotonin [5HT], and norepinephrine [NE] reuptake inhibitors), anticonvulsants (carbamazepine, and gabapentin), topical lidocaine patch, and topical gel.[13] Duloxetine has been shown to be effective as a treatment option for

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painful diabetic neuropathy,[14-16] but there is a lack of data on its effectiveness in patients with CIPN.[17,18] To date, the therapeutic options for CIPN remain limited.[12,13,19]

The imbalance of 5HT and NE in the pain inhibitory pathways may contribute to the peripheral neuropathic pain.[20] Duloxetine hydrochloride is a 5HT–NE reuptake inhibitor used to treat depression and generalized anxiety disorder.[21] Duloxetine effect in decreasing pain transmission through increasing synaptic concentrations of NE and 5HT, which results in blocking input signals to the dorsal horn neurons in the spinal cord.[12]

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA statement) guidelines during the preparation of this systematic review.[22]

Inclusion criteria

Trial or study type. Articles publishing findings from randomized controlled trials, nonrandomized controlled trials, retrospective studies, and single-arm studies of duloxetine in the treatment of CIPN were included in our review.

Intervention. The intervention was duloxetine with all doses, either administered alone or with other antineuropathic drugs.

Comparator. The comparator was placebo (control group) or other antineuropathic drugs or no control group.

Population. The population included cancer patients with painful CIPN.

Outcome. At least one of the following outcomes was used for pain assessment: visual analog scale (VAS) score; Brief Pain Inventory-Short Form (BPI-SF), neuropathic pain score using National Cancer Institute's Common Toxicity Criteria for Adverse Events, version 3 or version 4 (NCI-CTCAE v3.0, v4.0), or Functional Assessment of Cancer Therapy-Taxane (FACT-Tax) Scales.

Exclusion criteria

Studies in a non-English language, animal studies, studies whose full-text article was not available, and thesis and conference papers were not included.

Objective and study design

The objective of this systematic review was to systematically assess the effectiveness of duloxetine in the treatment of pain in patients with CIPN.

Information sources and search

Medical electronic databases. PubMed and Scopus, from inception to January 2018, were searched using the following search queries: *(((duloxetine) AND chemotherapy induced peripheral neuropathy)) OR ((((chemotherapy) AND (neuropathic pain OR peripheral neuropathy))) AND duloxetine)*.

Selection of studies. The authors selected eligible studies. The screening of search results was performed in the following 2 steps:

- Screen title and abstracts against the selection criteria. Articles that were unclear from their title or abstract were reviewed against the selection criteria through the full text.
- Retrieve and screen full-text articles of eligible abstracts for eligibility to systematic review.

Data extraction

Two authors extracted the following data independently: sample size, mean age, chemotherapeutic drug, duloxetine dosage, and outcomes for pain assessment using at least one score from VAS, BPI-SF, neuropathic pain score using the NCI-CTCAE v3.0 and v4.0, or FACT-Tax, and other secondary outcomes. The data was exported from the online forms as a Microsoft Excel sheet.

Statistical analysis

We calculated the mean age and associated standard deviations (SDs) for all patients by using the pooled mean and pooled SD equation, according to Cochrane handbook of systematic reviews of interventions 5.1.0 (updated March 2011).[23] When data are expressed as median and interquartile range, we used Hozo and colleagues' BMC Research Methodology equation to calculate or estimate the mean and SD.[24]

Data are expressed as means with SD (unless stated otherwise); statistical results were considered significant when the *P*-value was less than .05. Data analysis was performed using the SPSS Statistical Package, version 23 (IBM Corp., Armonk, NY).

Synthesis of data and analysis

Because of heterogeneity and low sample size of studies, no statistically justified analyses could be performed on the provided data. Instead, a descriptive analysis of published studies was performed.

Summary measures

The search strings, the list of relevant reviews, the data coding, and the quality criteria that were used can be requested from the corresponding author.

Results

Selection of articles

The systematic literature search and subsequent selection are summarized in a flow diagram (Figure). The PubMed database online search identified 41 publications, and a

second database search through Scopus identified 29 publications. After 27 duplicate publications were removed, a total of 43 publications were screened for title and abstract. All articles with animal instead of human patients, review articles as well as articles not written in the English language were excluded (n = 33 articles). A total of 10 full-text articles were assessed for eligibility, with 5 being excluded for the following reasons: full text not available (n = 1), review article (n = 2), secondary analysis (n = 1), and primary outcome not met (n = 1).

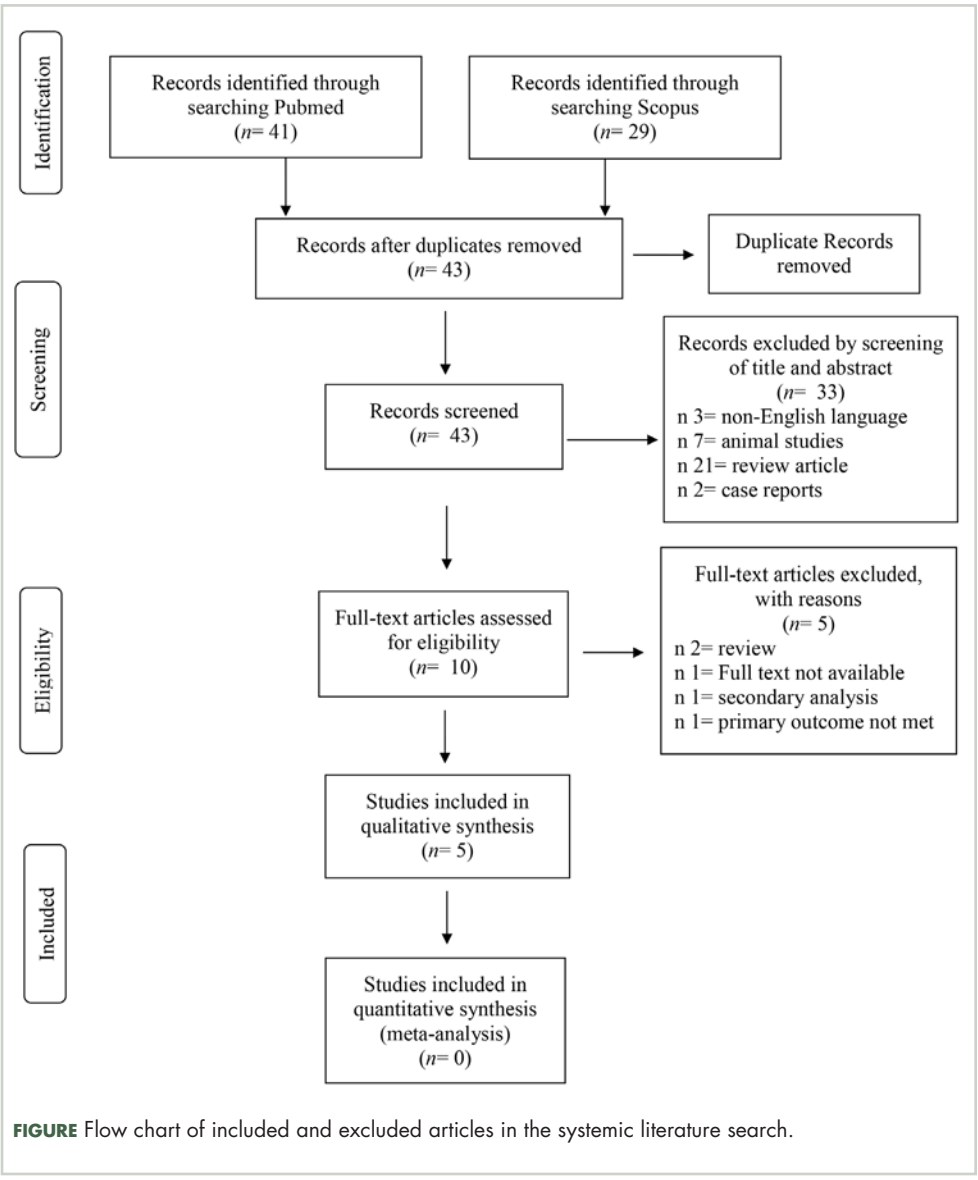

FIGURE Flow chart of included and excluded articles in the systemic literature search.

Study characteristics

Characteristics of the included studies and patient outcome are summarized in Table 1 and Table 2. A total of 5 studies from 2012 through 2017 were included in the descriptive analysis and systematic review. In all, 4 trials were prospective studies, and 1 trial was retrospective; among all trials, 2 studies were single arm and 3 were placebo-controlled and/or crossover.

Baseline characteristics of included studies

There were 431 participants in the total 5 studies included in this systematic review. The number of patients per study ranged from 25 to 231. Patients were mostly older, with mean sample ages ranging from 47.9 to 63 years, and the pooled mean age for all participants in the total 5 studies was 57.7 years.

In all included studies, duloxetine was given in varying doses of 20 mg, 30 mg, 40 mg, or 60 mg. Also, different therapeutic regimens of duloxetine were used, including placebo control or crossover with vitamin B12; 80% of the studies used escalation of doses over time (only 1 trial used fixed doses for each group of patients in the study). Escalation of duloxetine by doubling the dose was done in all 4 studies, with duloxetine doses of 30 mg and 60 mg used in 75% of those studies (3 out of 4 studies).

Comparator drug was used in 4 studies (1 was single arm) in our review analysis. The comparator drug was placebo in 1 study only, and the remaining 3 studies used other antineurotoxicity or antineuropathic pain therapy, mainly vitamin B12 (as only comparator in 1 study), fish oil, pregabalin, selective 5HT reuptake inhibitors, and nonsteroidal anti-inflammatory agents.

Regarding CIPN, the chemotherapeutic agents used in the studies were as follows (after exclusion of 11 patients who never received treatment in 1 study): 224 patients (52.9%) were on paclitaxel, 168 (39.7%) on oxaliplatin, 14 (3.30%) on R-CHOP, 8 (1.89%) on combined bortezomib–dexamethasone, 5 (1.18%) on FOLFOX, and 4 (0.94%) on other taxanes.

Improvement in pain scores was the primary and/or secondary endpoint in the included studies (Table 2). Pain was assessed by 6 different scores, including the VAS, BPI-SF, neuropathic pain score using NCI-CTCAE v3.0 and v4.0, and FACT-Tax, with all reported once except the VAS score, which was reported in 2 studies. Only 1 study, by Yang and colleagues,[25] measured pain by 2 scores (the VAS and NCI-

TABLE 1 Baseline characteristics of included studies

Study	Study, *cancer type*	Group/arm, A or B (n)	Duloxetine dose	Mean age, y (SD)	Type of chemotherapy (n)	Pain score	Pretreatment pain score (SD)	Pretreatment pain grade, n
Smith, 2013	Randomized phase 3 *Different cancer types, mainly breast and gastrointestinal tract*	**A** Duloxetine, followed by crossover to placebo (115) **B** Placebo, followed by crossover to duloxetine (116)	30 mg for first wk, followed by 60 mg for 4 wk	**A** 59 (10.4) **B** 60 (10.6)	**A** Paclitaxel (44) Oxaliplatin (63) Other taxanes (2) **B** Paclitaxel (43) Oxaliplatin (66) Other taxanes (2) *P* not reported	Average pain, using BPI-SF	**A** Mean, 6.1 (1.7) **B** Mean, 5.6 (1.6) *P* = .02	**A** NCIC. CTCAE v3.0 Gr 1, 1 Gr 2, 77 Gr 3, 31 **B** NCIC. CTCAE v3.0 Gr 1, 2 Gr 2, 84 Gr 3, 24
Wang, 2017	Cohort prospective *Breast cancer*	**A** Duloxetine (53) **B** Other anti neurotoxicity therapy, eg, fish oil, vitamin B12, NSAIDs (49)	30 mg for the first 4 wk, then 60 mg for additional 8 wk	**A** 47.9 (7.8) **B** 49.6 (9.7)	Paclitaxel	FACT-Tax	**A** Median, 12(10-16) Est mean, 12.5 (1.73) **B** Median, 11(8–14) Est mean, 11(1.74)	NA
Yang, 2012	Single arm *Stage III/IV colorectal cancer with chronic oxaliplatin-induced CIPN*	39 patients	30-mg capsules. 30 mg/day, escalated to 60 mg/day in 1 week (if no intolerance)	64.8 (range, 34-83)	Oxaliplatin	VAS NCI. CTCAE v3.0	NA	NCIC.CTCAE v3.0 Gr 3, 1 Gr 2, 21 Gr 1, 17
Otake, 2015	Retrospective single arm *Gynecologic tumors: ovarian, endometrium, cervical*	Duloxetine, first line (10) and second line (15)	Maintenance dosage 20 mg/day for 18 pts; 40 mg/day for 7 pts	Median, 62(40-77) Est mean, 60.3(9.3)	Paclitaxel	NCI. CTCAE v4.0	NA	NA
Hirayama, 2015	Open-label, randomized, phase 2 *Different cancer types: lymphoma, colon, breast, gastric, multiple myeloma*	**A** Duloxetine, followed by crossover to vitamin B12 (17) **B** Vitamin B12, followed by crossover to duloxetine (17)	20 mg/day orally for the first wk, and 40 mg/day for the next 3 wk	**A** Median, 61(48-75) Est mean, 61.25 (6.75) **B** Median, 64(49-75) Est mean, 63 (6.5)	**A** R-CHOP (7) FOLFOX (3) Paclitaxel (4) bort+dex (4) **B** R-CHOP (7) FOLFOX (2) Paclitaxel (6) bort+dex (4)	VAS score	NA	NA

bort+dex, bortezomib plus dexamethasone; BPI-SF, Brief Pain Inventory-Short Form; CIPN, chemotherapy-induced peripheral neuropathy; Est, estimated; FACT-Tax, Functional Assessment of Cancer Therapy-Taxane; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; Gr, grade; NA, not applicable; NCI.CTCAE v3.0, National Cancer Institute's Common Toxicity Criteria for Adverse Events, version 3 or 4; NSAIDs, nonsteroidal anti-inflammatory drugs; pts, patients; R-CHOP, rituximab, doxorubicin, vincristine, and cyclophosphamide; VAS, visual analog scale

CTCAE v3.0), with the rest of the studies assessing pain by just 1 of the aforementioned scores. The pretreatment pain score was reported in only 2 studies, by Smith and colleagues and Wang and colleagues, using BPI-SF and FACT-Tax scores, respectively, with total respective mean scores of 5.8 (SD, 1.7) and 11.77 (SD, 1.73).[17,26]

Secondary endpoints were related mainly to pain score, drug adverse effect, and assessment of quality of

TABLE 2 Outcome summary of included studies

Study	Primary endpoint	Secondary endpoint
Smith, 2013	Mean difference in the average pain score was 0.73 (95% CI, 0.26-1.20) from start to end of the initial treatment period (wk 1 to wk 5). Mean change score in Arm A, 1.06 (95% CI, 0.72-1.40) Mean change score in Arm B, 0.34 (95% CI, 0.01-0.66) (P = .003)	Mean difference in the FACT/GOG-Ntx was 1.58 (95% CI, 0.15-3.00; P = .03). Mean difference of BPI-SF interference score was 4.40 (95% CI, 0.93-7.88; P = .01).
Wang, 2017	Decrease in the severity of paclitaxel-induced CIPN (OR, 5.426; 95% CI, 1.898–15.514; P = .002). The median (25th-75th percentiles) decrease of FACT-Tax pain score in the duloxetine and control groups was 4 (2-6) and 1 (0-4), respectively (P = .005).	Nonneuropathic adverse events that are attributed to chemotherapy were mild and similar in both groups. No significant differences were observed in the incidence of paclitaxel-induced CIPN.
Yang, 2012	Subjective response based on VAS scores was seen in 19 pts (63.3%). 9 pts (47.4%) showed a simultaneous objective grade improvement (Gr 3 to 2, n = 1; Gr 2 to 1, n = 8), and 10 pts (52.6%) maintained a stable grade (Gr 2, n = 4; Gr 1, n = 6), according to NCI.CTCAE v3.0.	9 pts (28.1%) discontinued duloxetine because of intolerable adverse events, including dizziness/giddiness/nausea (n = 4), restlessness/insomnia (n = 2), somnolence (n = 2), and urinary hesitancy (n = 1).
Otake, 2015	Response (improvement) seen in 14/25 pts (56%). 20 mg/day, OR = 1 40 mg/day, OR = 0.64 (95% CI, 0.078-5.2)	Adverse events were very mild and usually well tolerated, including somnolence (n = 3, 12%), giddiness (n = 3, 12%), nausea (n = 1, 4%), constipation (n = 1, 4%), dysgeusia/distortion of taste (n = 1, 4%).
Hirayama, 2015	Hazard ratio for ≥30% and ≥50% reduction in numbness for duloxetine vs vitamin B12 were 0.25 and 0.40, respectively. Hazard ratio for ≥30% and ≥50% reduction in pain for duloxetine vs vitamin B12 were 0.28 and 0.25, respectively.	All adverse events were Gr 1, including fatigue (n = 6, 17.6 %), nausea (n = 3, 8.8 %), somnolence (n = 2, 5.9%), and insomnia (n = 2, 5.9 %).

BPI-SF, Brief Pain Inventory-Short Form; CI, confidence interval; CIPN, chemotherapy-induced peripheral neuropathy; FACT-Tax, Functional Assessment of Cancer Therapy-Taxane; GOG-Ntx, Gynecologic Oncology Group-Neurotoxicity; Gr, grade; NCI.CTCAE v3.0, National Cancer Institute's Common Toxicity Criteria for Adverse Events, version 3 or 4; OR, odds ratio; pts, patients; VAS, visual analog scale

life (Table 2). In the study by Yang and colleagues,[25] 9 patients (28.1%) discontinued duloxetine because of intolerable adverse events, with dizziness or giddiness as the most common cause (44.4% of patients who discontinued treatment). Studies by Otake and colleagues[12] and Hirayama and colleagues[2] reported duloxetine adverse events that were very mild and usually well tolerated in collectively 22 patients, with fatigue (n = 6) and somnolence (n = 5) as the most reported adverse effects. Wang and colleagues[17] reported nonneuropathic adverse events that were attributed to chemotherapy and were mild and similar in both study groups.

Discussion

To our knowledge, this is the first systematic review to discuss the effectiveness of duloxetine specifically in treatment of pain in CIPN. The administration of chemotherapeutic agents such as paclitaxel, cisplatin, oxaliplatin, and vincristine was accompanied by CIPN. The currently available treatment options for CIPN are limited. To date, no drug has been approved specifically for treatment of pain in CIPN.[12]

In our review, we included cancer patients with CIPN and associated pain. Several previous studies[8,27,28] discussed tingling and numbness as a common adverse effect in CIPN, and usually about 20% to 42% of patients develop chronic pain.

Six different pain assessment scores were reported in the total 5 studies in our review, with VAS and NCI-CTCAE scores reported in more than 1 study. This reflects the major challenges facing the assessment of CIPN, as various scales and tools are available for pain assessment but without a standardized approach for CIPN that can be precisely implemented.[8] Several other challenges regarding pain scores were observed, with Smith and colleagues as the only authors to report both pretreatment pain score and grade, while the rest of the studies failed to report either pain score or grade, or even both.

Another difficulty observed in our review was the variability in study participants in both population size and

type of cancer treated. The population size in largest study included in our review was 231 patients and the smallest was 25 patients; collectively, there were only 431 patients in the included studies. Although the type of primary cancer varied in between studies, gynecologic malignancies comprised most cases (215 patients), followed by gastrointestinal tumors, and few cases of hematologic and genitourinary malignancies were reported. Similar results were observed by Geber and colleagues in their large study screening pain in cancer patients, in which gynecologic malignancies were diagnosed in 28 patients out of 61 with CIPN, representing the highest percentage (45.9%) of malignancy type in that study.[26]

In the study by Otake and colleagues[12] examining duloxetine for CIPN in patients with gynecologic cancer, the authors concluded that duloxetine dosage either 20 mg/day or 40 mg/day was not associated with the effectiveness of duloxetine treatment by either univariate or multivariate analysis. Previous authors have provided an explanation for the difference in duloxetine response among CIPN patients and attributed those differences to the underlying pain mechanisms.[14,29] In other words, pain in those patients is both peripheral nociceptive and central neuropathic, and it is likely to be caused by mixed mechanisms.

Another variation observed among CIPN patients in our review was the chemotherapeutic agents used. That was noted by Smith and colleagues,[26] who reported that patients with cancer who received platinum therapies (oxaliplatin) experienced more benefit from duloxetine in terms of pain improvement than those who received taxanes ($P = .13$). We found no other published studies on the response to duloxetine among different chemotherapeutic agents used. However, 2 studies of duloxetine response in patients with other pain-related disorders (painful diabetic peripheral neuropathy and fibromyalgia) showed significant improvement in pain symptoms compared with placebo. In a study of pain in chemotherapy-induced neuropathy (CIN) by Geber and colleagues,[29] the preexisting pain medication was not reported, but the authors concluded that treatment for CIN-related neuropathic pain differs from that for nonneuropathic (ie, musculoskeletal) pain, with the former being treated mainly with pharmacotherapy and the latter with physiotherapy and behavioral exercises. They asserted that different pain patterns could help flag neuropathic or musculoskeletal pain so that the selected treatments would be more specific. Differences in pain improvement related to duloxetine may be attributed to the underlying pain mechanism, and whether it is mixed or centrally or peripherally related was also discussed by Geber and colleagues.[29]

In the study by Geber and colleagues, the chemotherapeutic protocols comprised a combination of chemotherapeutic agents so that the symptoms and signs of CIPN could not be attributed to a single agent.[29] By contrast, all the studies included in our review used a chemotherapeutic protocol with single agent so that specific symptoms and signs of CIPN could be attributed to an individual chemotherapeutic agent.

Findings from studies on the effect of duloxetine in treatment of pain in diabetic peripheral neuropathy have shown that duloxetine at a dose of 60 mg/day effectively improves pain in 43% to 68% of patients.[15,16,30] Similarly, in our review, the study by Yang and colleagues[25] showed a 63% subjective reduction in pain severity by VAS score in CIPN patients but lower improvement of 47.4% by NCI-CTCAE v3.0; this can be attributed to the simplistic 4-grade rating scale of the latter.

During our analysis of studies, we noticed that no diagnostic criteria were implemented for diagnosis or inclusion of CIPN patients in any of the included studies, and this represents a major challenge in any analysis of studies with neuropathic pain patients. In 2016, Finnerup and colleagues updated the previous 2008 grading system for diagnosis of neuropathic pain, which is intended to determine the level of certainty with which the pain in question is neuropathic.[31] The system defines the diagnostic certainty into 3 levels: Possible, Probable, and Definite. Although the number of studies used the grading system during the inclusion of neuropathic pain patients increased from 5% in 2009 to 30% in 2014, still more than two-thirds of studies do not use a standardized system for diagnosis and/or inclusion of neuropathic pain in patients.

Strength and limitations

The first strength of this review is that it identifies gaps in our current knowledge about duloxetine in the treatment of pain in cancer patients with CIPN. Second, we collected all available articles from inception until January 2018. Third, this review can serve as a model for future studies investigating the effectiveness of duloxetine in treatment of CIPN.

There are also limitations to this review that should be discussed. First, the studies vary greatly in samples, methodologies, and outcomes measured. Second, the diagnostic criteria for CIPN and the pain assessment tools vary among the studies. Third, there is also variability in the duloxetine doses and administration regimens among the studies, and some articles did not report the precise outcome in pain scores. Furthermore, the articles reviewed included retrospective, single-arm, or nonrandomized controlled studies with relatively small numbers of participants.

To improve the results, more placebo-controlled or head-to-head trials (with other agents used in treatment of CIPN) with large sample sizes would be needed.

Conclusions

Our purpose was to describe the effectiveness of duloxetine in improving pain scores among CIPN patients, but because

of heterogeneity, the low sample size of available studies, and lack of high-quality evidence, we were only able to perform a descriptive analysis of published studies. From the descriptive analyses and from the available data of relatively small sample sized studies, it can be concluded that despite the aforementioned limitations, duloxetine remains a useful therapeutic option for pain in CIPN patients, regardless of the type of chemotherapeutic agent used.

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Mortality outcomes in hospitalized oncology patients after rapid response team activation

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Background The prognosis of hospitalized oncology patients varies widely, and physicians are poor at predicting outcomes in cancer patients. Discrete signifiers of prognosis in hospitalized oncology patients are widely sought.
Objective To test the hypothesis that oncology patients who have had rapid response team (RRT) activations would have high rates of in-hospital and 100-day mortality, and that these might differ based on malignancy type and other clinical factors.
Methods A retrospective study was performed at a single, 900+ bed academic center in the northeastern United States during a 2-year study period using an RRT-specific database. We included patients 18 years or older with a cancer diagnosis, including solid tumor and hematologic malignancy, as well as those who were status post–bone marrow transplantation, who required RRT activation. Surgical and intensive care unit patients were excluded. Primary outcome variables of interest were inpatient and 100-day mortality post-RRT activation as well as the clinical variables leading up to RRT activation.
Results RRT activation was associated with a high inpatient mortality in patients with solid tumor and hematologic malignancies (43% and 35%, respectively) and a 100-day mortality (solid tumors, 78%; hematologic malignancies, 55%). In multivariate analysis, female sex was associated with significantly higher inpatient and 100-day mortality.
Limitations This retrospective review of a single center's data on oncology patients may not apply to all hospitals.
Conclusions These findings demonstrate high inpatient and 100-day mortality in a selected population of oncology patients. The event of an RRT activation may be a useful predictor of prognosis in oncology patients and can be used to help patients and families improve advance care and end-of-life planning.
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Cancer is the second leading cause of death in the United States, exceeded only by heart disease.[1] Despite the overall decline in cancer death rates from 2000 through 2014, physicians struggle to accurately predict disease progression and mortality in patients with cancer who are within 6 months of death.[2-8] This prognostic uncertainty makes clinical decision making difficult for patients, families, and health care providers. On a health care system level, an insight into end-of-life prognostication could also have substantial financial implications. In 2013, $74 billion was spent on cancer-related health care in the United States.[9] Studies have shown that from 5% to 6% of Medicare beneficiaries with cancer consumed up to 30% of the annual Medicare payments, with a staggering 78% of costs being from acute care in the final 30 days of life.[10]

Rapid response teams (RRTs) were first introduced in 1995 and are now widely used at many hospitals to identify and provide critical care at the bedside of deteriorating patients outside of the intensive care unit (ICU) to prevent morbidity and mortality.[11-15] Although not the original aim, RRTs are commonly activated on patients at the end of life and have therefore come to play an important role in end-of-life care.[11,16] RRT activation in the oncology population is of special interest because the activation may predict higher inpatient mortality.[17] In addition, RRT activation can serve as a sentinel event that fosters discussion on goals of care, change in code status, and initiation of palliative care or hospice use, particularly when also accompanied by an upgrade in level of care.[11,18] As such, the ability to predict mortality after an RRT event, both inpatient and at 100 days after the event, could be of great help in deciding whether to pursue further treatments or, alternatively, palliative or hospice care.

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To that end, the purpose of this study was to identify baseline patient characteristics, causes of deterioration leading to the RRT event, and vital signs and laboratory abnormalities in the peri-RRT period – the 24-hour periods preceding and following the time of the RRT event – that are associated with increased mortality, both inpatient and at 100 days after RRT activation. By choosing this acutely decompensated population, the knowledge gained may be able to guide improved advance care and end-of-life planning for terminally ill cancer patients.

Methods and materials

A retrospective study was performed at a single, 900+ bed academic center in the northeastern United States during a 2-year study period from October 2014 through November 2016. The Institutional Review Board at Thomas Jefferson University Hospital in Philadelphia, Pennsylvania, reviewed and approved the study.

Through our institution's RRT database, all consecutive RRT activations during the study period involving hospitalized oncology patients were reviewed. We included patients 18 years or older with a cancer diagnosis, including solid tumor and hematologic malignancy, as well as those who were status post–bone marrow transplantation (BMT), who required rapid response activation while hospitalized at our institution. We excluded patients who activated rapid response while they were in the ICU, including the BMT unit, those on the surgical floors, and those with RRT activation at other hospitals before transfer to our institution. Data for both in-hospital mortality as well as 100-day mortality for all admitted oncology patients was obtained from a separate electronic health record database at our institution from a similar time period.

Our goal was to identify patient characteristics, reasons for the RRT activation, and vital sign and laboratory abnormalities in the peri-RRT period that were associated with increased mortality, both inpatient and at 100 days after RRT activation. Our institution's RRT database and electronic health records were accessed for data collection. Primary outcome variables for this study were inpatient and 100-day mortality post-RRT activation. We investigated the following predictor variables: age, sex, cancer diagnosis, code status at the time of RRT activation, duration from hospital admission to RRT event, length of hospital stay, time of the day the RRT event occurred (daytime vs nighttime), change in level of care (telemetry upgrade and ICU transfer), previous ICU treatment during the same hospital stay, hospice discharge, reasons cited for the RRT event (increased work of breathing, hypotension, tachyarrhythmia, change in mental status, stroke, gastrointestinal bleed, and seizure), peri-RRT lactate level, international normalized ratio (INR), hemoglobin, positive blood cultures, peri-RRT blood product administration, and scores for systemic inflammatory response syndrome (SIRS) and quick sequential organ failure assessment (qSOFA) in the 24 hours preceding the RRT activation. The SIRS includes abnormal temperature (>38°C or <36°C), heart rate of >90 bpm, increased respiratory rate of >20 times/min, and abnormal white blood cell count (>12,000 cells/mm^3, <4,000/mm^3, or >10% bands). Its score ranges from 0 to 4, based on the number of SIRS criteria documented. The qSOFA includes hypotension (systolic blood pressure of ≤100 mmHg), increased respiratory rate of ≥22 times/min, and altered mentation and ranges from 0 to 3 based on the number of qSOFA score documented.

Descriptive statistics were generated, and we then conducted bivariate analysis using chi-square tests or Fisher exact tests for categorical variables and simple logistic regression for continuous variables. Multivariable logistic regression models were performed to identify predictors of inpatient and 100-day mortality. Regression models were fit separately for subsets defined by the type of cancer diagnosis. Variables with $P < .2$ were included in the models, and backward selection method was performed, keeping variables with $P < .2$. The results are presented as odds ratios (OR) and 95% confidence intervals (CI). C-statistics were used to measure goodness of fit for the models. A c-statistic value of 0.5 indicates the model is not better than random chance; a value higher than 0.7 indicates moderate accuracy, whereas a value higher than 0.8 indicates strong accuracy. $P < .05$ was considered significant. All analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, NC).

Results

A total of 179 hospitalized oncology patients had an RRT activation during the 2-year study period during October 2014 through November 2016. During that time, 4,654 medical oncology patients were admitted to the hospital, resulting in a rate of RRT activation of 38.4 events per 1,000 admissions. In all, 179 patients were included in the analyses for inpatient mortality, and 175 patients were included for 100-day mortality post-RRT. Patients with unknown mortality status (n = 4) at 100 days after RRT were excluded from the analyses.

The average age of the study patients was 62.3 years (standard deviation [SD], 13.3; Table 1). They comprised equal proportions of men (52%) and women (48%). Just more than half (52%) of the patients carried a diagnosis of solid malignancy, 39% of hematologic malignancy, and 9% status post-BMT. Most of the patients were full code (80%) at the time of RRT activation. The average number of days from admission to RRT event was 9.5 days (SD, 12.1). Equal proportions of RRT events took place during the daytime (52%) and nighttime (48%), and more than half of the study patients (56%) were transferred to the ICU within 24 hours of the RRT activation. Of all the study patients, 11.7% were discharged to hospice

TABLE 1 Demographic and clinical characteristics of hospitalized oncology patients requiring a rapid response team activation (N = 179)

Characteristic	Value
Mean age, y (SD)	62.3 (13.3)
Sex, n (%)	
Male	93 (52)
Female	86 (48)
Cancer category, n (%)	
Solid	93 (52)
Hematologic	70 (39)
Status post-BMT	16 (9)
Inpatient mortality, n (%)	
No	110 (61)
Yes	69 (39)
100-day mortality after RRT, n (%)	
No	58 (33)
Yes	117 (65)
Unknown	4 (2)
Code status before RRT, n (%)	
Full code	143 (80)
DNR/DNI	36 (20)
Mean no. days, admission-RRT (SD)	9.5 (12.1)
Mean length of stay, d (SD)	19.8 (17.0)
RRT time, n (%)	
Night	86 (48)
Day	93 (52)
Telemetry upgrade within 24 h of RRT, n (%)	
No	151 (84)
Yes	28 (16)
ICU transfer within 24 h of RRT, n (%)	
No	78 (44)
Yes	101 (56)
Prior ICU stay within same admission, n (%)	
No	149 (83)
Yes	30 (167)
Hospice discharge, n (%)	
No	158 (88)
Yes	21 (12)
Reasons for the RRT activation	
Increased work of breathing, n (%)	
No	83 (46)
Yes	96 (54)
Hypotension, n (%)	
No	142 (79)
Yes	37 (21)
Tachyarrhythmia, n (%)	
No	128 (72)
Yes	51 (28)
Altered mental status, n (%)	
No	133 (74)
Yes	46 (26)
Mean no. of SIRS criteria within 24 h preceding RRT (SD)	2.8 (1.1)
Mean qSOFA score within 24 h preceding RRT (SD)	1.4 (0.8)
Lactate level peri-RRT[a] (mmol/L), n (%)	
<2	45 (25)
≥2	88 (49)
Missing/not ordered	46 (26)
INR peri-RRT	
<1.2	47 (26)
≥1.2	104 (58)
Missing/not ordered	28 (16)
Mean HB peri-RRT, g/dL (SD)	8.5 ± 1.9
Positive blood culture peri-RRT (n, %)	
No	153 (85)
Yes	26 (15)
No. of units of blood products given peri-RRT (SD)	1.2 (2.1)

BMT, bone marrow transplantation; DNR/DNI, do not resuscitate/do not intubate; HB, hemoglobin; ICU, intensive care unit; INR, international normalized ratio; RRT, rapid response team; SIRS, systemic inflammatory response syndrome; qSOFA, quick sequential organ failure assessment

[a]Peri-RRT, the 24-hour periods preceding and following the time of the RRT event.

after the RRT event, and 53% required RRT evaluation for increased work of breathing. Forty-nine percent of the total study patients had peri-RRT lactate levels ≥2 mmol/L (reference range, 0.5-2.0 mmol/L), and 58% had peri-RRT INR levels ≥1.2 (reference range, 0.85-1.15). The average SIRS score was 2.8 (SD, 1.1), and the qSOFA score was 1.4 (SD, 0.8) in the 24 hours preceding the RRT activation.

Over the 2-year study period, the inpatient mortality rate for all admitted oncology patients was 2.3% (108 deaths in 4,654 oncology inpatients), according to claims

data. By comparison, of the 179 patients who required an RRT activation, 39% did not survive to discharge. When those patients were categorized based on their cancer type, 43% of the solid malignancy patients died within the same hospital stay after an RRT event, 35% of the hematologic malignancy patients died, and 25% of the status post-BMT patients died. Of the 175 patients with known mortality status at 100 days after RRT, 65% of total patients had died within that time compared with only 15.7% (347 deaths in 2,217 patients) of all admitted patients with cancer who did not experience an RRT event. When categorized based on their cancer type, significantly more patients (78%) with solid tumors had died within 100 days after RRT activation, whereas only 55% of those with a hematologic malignancy and 50% of those who were post-BMT died within the same time period.

Tables 2 and 3 present major findings from regression models with a moderate to strong level of prediction. The characteristics associated with increased odds of inpatient mortality among solid tumor patients after an RRT event were female sex (OR, 4.91; 95% CI, 1.45-16.6), increased work of breathing as the reason for the RRT activation (OR, 5.53; 95% CI, 1.69-18.1), having no lactate level ordered (OR, 5.12; 95% CI, 1.05-25.1), each unit increase in SIRS score (OR, 1.92; 95% CI, 1.01-3.66), each unit increase in qSOFA score (OR, 3.32; 95% CI, 1.45-7.56), and each unit increase in peri-RRT blood products being given (OR, 1.74; 95% CI, 1.03-2.94). Among hematologic malignancy patients, ICU transfer within 24 hours of the RRT (OR, 3.85; 95% CI, 1.14-13.0) was associated with increased inpatient mortality, whereas having no lactate level ordered (OR, 0.09; 95% CI, 0.01-0.96) was associated with lower odds of inpatient mortality.

The characteristics associated with increased odds of 100-day mortality in patients with solid tumors were female sex (OR, 4.99; 95% CI, 1.22-20.3), increase in each day from admission to RRT event (OR, 1.14; 95% CI, 1.01-1.18), and each

TABLE 2 Odds ratios and 95% confidence intervals for in-hospital mortality by cancer type

Variable	OR (95% CI)	*P*-value
Solid tumors (n = 93)		
Sex (female vs male)	4.91 (1.45-16.6)	.010*
Work of breathing (Yes vs No)	5.53 (1.69-18.1)	.005*
Peri-RRT[a] lactate level (≥2 vs <2)	3.61 (0.76-17.1)	.10
Peri-RRT lactate level (missing/not ordered vs <2)	5.12 (1.05-25.1)	.044*
SIRS within 24 h preceding RRT	1.92 (1.01-3.66)	.048*
qSOFA within 24 h preceding RRT	3.32 (1.45-7.56)	.004*
Blood products received 48 h peri-RRT	1.74 (1.03-2.94)	.038*
C-statistic	*0.86 (0.78-0.93)*	
Hematologic malignancies (n = 70)		
Tachyarrhythmia (Yes vs No)	0.36 (0.10-1.26)	.11
ICU transfer within 24 h of RRT (Yes vs No)	3.85 (1.14-13.0)	.030*
Peri-RRT lactate level (≥2 vs <2)	0.64 (0.18-2.33)	.50
Peri-RRT lactate level (missing/not ordered vs <2)	0.09 (0.01-0.96)	.046*
C-statistic	*0.78 (0.67-0.86)*	

ICU, intensive care unit; RRT, rapid response team event; SIRS, systemic inflammatory response syndrome; qSOFA, quick sequential organ failure assessment

[a]Peri-RRT, the 24-hour periods preceding and following the time of the RRT event.

*Significance at $P < .05$.

TABLE 3 Odds ratios and 95% confidence intervals for 100-day mortality by cancer type

Variable	OR (95% CI)	*P*-value
Solid tumors (n = 92)		
Sex (female vs male)	4.99 (1.22-20.3)	.025*
Days from admission-RRT	1.14 (1.01-1.28)	.033*
Tachyarrhythmia (Yes vs No)	3.91 (0.69-22.1)	.12
Telemetry upgrade within 24 h of RRT (Yes vs No)	0.21 (0.04-1.16)	.07
Hospice discharge (Yes vs No)	6.67 (0.64-68.9)	.11
SIRS within 24 h preceding RRT	2.04 (1.02-4.07)	.044*
C-statistic	*0.82 (0.72-0.92)*	
Hematologic malignancies (n = 67)		
Code status (DNR/DNI vs full code)	7.65 (1.21-48.2)	.030*
Peri-RRT[a] lactate level (≥2 vs <2)	3.22 (0.88-11.7)	.08
Peri-RRT lactate level (missing/not ordered vs <2)	0.42 (0.08-2.25)	.31
qSOFA	2.03 (0.95-4.34)	.07
C-statistic	*0.78 (0.67-0.89)*	

DNR/DNI, do not resuscitate/do not intubate; RRT, rapid response team; SIRS, systemic inflammatory response syndrome; qSOFA, quick sequential organ failure assessment

[a]Peri-RRT, the 24-hour periods preceding and following the time of the RRT event.

*Significance at $P < .05$

unit increase in SIRS score (OR, 2.04; 95% CI, 1.02-4.07). For hematologic malignancy patients, being do not resuscitate (DNR) or do not intubate (DNI) (OR, 7.65; 95% CI, 1.21-48.2) was associated with increased odds of 100-day mortality.

Discussion

The results of the study highlight the very high mortality rates associated with oncology patients requiring RRT activations, with 39% of patients dying within the same hospital stay and 65% dying within 100 days of the RRT event. These results are particularly notable when contrasted with the 2.3% inpatient and 15.7% 100-day postdischarge mortality rates in the total oncology patient population over a similar time period. The inpatient mortality rate after an RRT activation in our study closely resembled the rate reported by Austin and colleagues, which was 33% (hospital mortality in oncology patients cited during the time was 48.2 deaths per 1,000 patient admissions).[17] Of note in our study is that solid tumor patients had higher mortality than the hematologic malignancy patients; 43% died within the same hospital stay and 78% died within 100 days, compared with 35% and 55%, respectively, in patients with hematologic malignancies. The poor prognosis of oncology patients requiring an RRT evaluation must be conveyed to the patients and families and taken into consideration by health care team to determine the most appropriate course of care subsequent to RRT activation.

Our finding that female sex is significantly and strongly associated with increased inpatient and 100-day mortality in patients with solid tumors was unexpected. The cause for this disparity remains elusive. We noted that, in our study, the following types of malignancies were more common in women than men (comparison of women vs men shown in parentheses): lung (53% vs 47%), colon (60% vs 40%), acute lymphoblastic leukemia (83% vs 17%), diffuse large B-cell lymphoma (64% vs 36%), and multiple myeloma (58% vs 42%). Whether these types of cancers are more clinically aggressive and associated with earlier mortality post-RRT could not be ascertained from our data. Gender bias in clinicians' bedside determination of severity of illness may also play some role in this substantial mortality gap.

Among all the causes for RRT activation, increased work of breathing was the only variable associated with increased inpatient mortality in solid tumor patients. In a study by Austin and colleagues, decreased oxygen saturation was the most common reason for the RRT evaluation, though it did not reach statistical significance as a predictor of inpatient mortality.[17] SIRS and qSOFA scores in the 24 hours preceding the RRT event along with peri-RRT blood product administration were all significant predictors of inpatient mortality among patients with solid tumors but were not so for those with hematologic malignancies. It is interesting to note that low hemoglobin was found to be associated with inpatient mortality in a study on 456 hospitalized patients with solid tumors (there was no data on RRT evaluation in their dataset).[13] The fact that these well-validated measurements of illness severity correlate positively with RRT activation and increased mortality is intuitive and lends external credibility to other findings in this study.

In patients with hematologic malignancies, ICU transfers within 24 hours of the RRT activation were associated with 4-fold increased odds of inpatient death. This was not shown to be the case in patients with solid tumors. This should be explored in future studies because it could be crucial in conducting goals-of-care discussions in terminally ill cancer patients. The study also showed that patients with hematologic malignancies who were DNR or DNI were associated with almost 8-fold increased odds of 100-day mortality. This argues for a fair predictive ability of the care teams in this particular subgroup. Conversely, hospice referral is underused; of the patients that died at 100 days after the RRT event, only 16.2% were referred to hospice at the time of discharge.

Limitations

Limitations of the study include its retrospective nature at a single medical center on a small group of study participants. Variables such as lactate dehydrogenase level and Eastern Conference Oncology Group Performance Status, which have been found to be predictive of increased mortality in hospitalized oncology patients,[19] were not consistently available for analysis in the data set. We had 4 patients whose mortality status was not known at 100 days and were excluded from the study. Because of a lack of documentation, we were also not able to reliably collect the data on patients with multiple RRT events. This presumably would be associated with increased mortality on its own. We only included the data associated with the earliest RRT activation in our electronic health records.

In addition, it is important to note that 26% and 16% of the study patients had missing lactate and INR values, respectively. Given the small size of the study and the unclear significance of the missing lactate and INR, we opted to include the patients with the missing data for final analyses of the regression models. The significance of a care team not ordering a lactate level is perhaps associated with the reason for RRT activation (ie, the patient seemed to be less ill) and perhaps could be associated with non–sepsis-related RRT events.

Conclusions

This study reports on the outcomes of oncology patients admitted to the hospital whose clinical deterioration required activation of a rapid response team. Female sex, increased qSOFA and SIRS scores in the 24 hours preceding the RRT event, and the need for blood product administrations around the time of the RRT event correlated

with increased inpatient mortality. Hospitalized oncology patients' d undestood and response evaluation if perPatientoutcomes, both regarding inpatient and 100-day mortality, demonstrated surprisingly poor survival, with solid malignancy patients bearing significantly higher burden of both inpatient mortality and mortality at 100 days after the RRT event. The findings from the study could help patients, families, and providers make informed decisions regarding advance care and end-of-life planning for terminally ill cancer patients.

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Comparing risk models guiding growth factor use in chemotherapy

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Background The National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) have guidelines for using colony-stimulating factors (CSF) for chemotherapy-induced neutropenia (CIN). Both groups recommend CSF if the chemotherapy has a risk for febrile neutropenia of more than 20%. The guidelines are less definitive if the risk is intermediate (10%-20%). Two risk models developed by Hosmer and Bozcuk and their respective colleagues may provide guidance regarding CSF decision making in this intermediate risk population.
Objective To examine whether risk models developed by Hosmer and Bozcuk had adjunct value to the NCCN and ASCO guidelines when applied to patients with lung cancer who were receiving intermediate-risk chemotherapy.
Methods Male and female patients aged 18-75 years with a diagnosis of any stage lung cancer, small or non–small cell, who required and received their initial chemotherapy at Drexel University in Philadelphia were included in this study. Patients who received growth factor before their chemotherapy were excluded. The Hosmer and Bozcuk calculators for febrile neutropenia risk and the NCCN and ASCO guidelines for using CSF for CIN were applied to this group of patients.
Results 43 patients were included in the study. The Hosmer and Bozcuk calculators and NCCN and ASCO guidelines recommended giving CSF to 26, 22, 25, and 38 patients, respectively. The sensitivities for detecting severe CIN were 89%, 78%, 67%, and 97%, and the specificities were 44%, 56%, 45%, and 14%, respectively.
Limitations Small cohort size; data were limited in scope.
Conclusions In lung cancer patients receiving intermediate-risk chemotherapy, the Hosmer calculator had the best combination of sensitivity, specificity, and ease of use. The NCCN guidelines were less sensitive, whereas the ASCO guidelines were the least specific. Based on these findings, we recommend using the Hosmer calculator because it lends to accurate but judicious use of CSF.

Chemotherapy-induced neutropenia (CIN) and its corollary febrile neutropenia (FN) are well recognized, and they are serious consequences of many agents used in the treatment of malignancy. FN in particular has been associated with a considerable risk of morbidity and mortality, namely sepsis with multiorgan failure and eventual death.[1] The mainstay of prophylaxis for patients who are deemed to be at high risk for CIN and FN is colony-stimulating factors (CSF). These agents have been shown to significantly decrease FN-related mortality, and therefore their use is potentially lifesaving.[2] However, CSF are not cheap, with the cost of peg-filgrastim as much as US $6195.99 per cycle of chemotherapy.[3] Therefore, not only do FN and CIN pose significant risk to patients, they also carry a high burden of cost to the patient and health care system both in treatment and prophylaxis.[4] As such, it is prudent for oncologists to accurately identify high-risk patients and judiciously use CSF in an evidence-based manner.

However, this has proven to be difficult because of the extent of variability between patients and the heterogeneity of the various risk models in the literature. Currently, there are 2 widely used guidelines, 1 developed by the National Comprehensive Cancer Network (NCCN) and another by the American Society of Clinical Oncology (ASCO). Both guidelines suggest the use of prophylactic CSF if the chemotherapy regimen has an FN risk of more than 20% (high risk). If the chemotherapy is deemed to be of intermediate risk (10%-20% FN risk), then patient-specific factors need to be considered.[5,6]

In lung cancer, the NCCN lists only topotecan for small cell carcinomas as being high risk for FN, and therefore it is the only regimen that would warrant definitive use of prophylactic CSF.[5] The most recent ASCO guidelines do not list chemotherapy regimens that are high risk for FN.[6] For intermediate-risk regimens, the NCCN states that CSF prophylaxis should be considered if the patient has had previous chemotherapy or radiation therapy, persistent neutropenia, bone marrow involvement by

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tumor, recent surgery or open wounds, liver dysfunction (total bilirubin, >2.0 mg/dL), or renal dysfunction (creatinine clearance, <50 mL/min), or is older than 65 years.[5]

ASCO guidelines state that in intermediate-risk chemotherapy regimens, the following factors are to be considered: age >65 years, advanced disease, previous chemotherapy or radiation therapy, pre-existing neutropenia or marrow involvement by tumor, infection, open wounds or recent surgery, poor performance status or nutritional status, poor renal function, liver dysfunction (most notably bilirubin elevation), cardiovascular disease, multiple comorbid conditions, and HIV infection. However, in the ASCO guidelines, there is no suggestion as to whether CSF should be administered if patients have one of these risk factors, only to "consider these factors when estimating patients' overall risk of febrile neutropenia."[6]

There is some uncertainty with the NCCN and ASCO guidelines as to whether prophylactic CSF should be given to these intermediate-risk patients. There are suggestions but no definitive guidelines. In our study, we looked at lung cancer patients treated with intermediate-risk chemotherapy regimens and applied 2 different risk models created by Hosmer[7] and Bozcuk[8] and their respective colleagues (Hosmer and Bozcuk hereinafter). Our goal was to assess the efficacy differences between the 2 risk models and to compare their outcomes and recommendations with the NCCN and ASCO guidelines. This was done to showcase the tools available to a clinical oncologist who must decide whether to prescribe prophylactic CSF in these more challenging clinical situations.

Methods

Study population

This was a cross-sectional, retrospective study looking at male and female patients aged 18 to 75 years who were treated in the hematology–oncology offices of Drexel University in Philadelphia, Pennsylvania, from 2005 through 2016, who had a diagnosis of lung cancer and were, at some point during their disease, treated with chemotherapy. By using ICD-10 codes for any type of lung cancer, we identified 242 patients. Of those, 106 patients were excluded because they had never received chemotherapy, 16 were excluded either because of miscoding of the type of cancer or because they never actually had cancer, and 61 were excluded either because chemotherapy had not been delivered at our institution or because there were insufficient data to apply the 2 risk models. Of the remaining 59 patients, 16 were excluded because they had received prophylactic CSF with their first cycle of chemotherapy, leaving a total of 43 patients to whom the various risk models and guidelines could be applied (Table 1). If any of the 43 patients were found to be neutropenic, they were given growth factor shortly thereafter.

TABLE 1 Patient characteristics per specific demographic information (N = 43)

Characteristic	n (%)
Age >60 y	27 (62.7)
Male	16 (37.2)
Lung cancer type	
Adenocarinoma	26 (60.4)
Squamous cell	12 (27.9)
Small cell	3 (6.9)
Undifferentiated	2 (4.6)
Stage at time of chemotherapy	
I	5 (11.6)
II	5 (11.7)
III	19 (44.1)
IV	14 (32.5)
Chemotherapy regimen	
Platinum doublet	32 (74.4)
Monotherapy	11 (25.6)

Chemotherapy for these 43 patients consisted of either a platinum doublet (cisplatin or carboplatin with either etoposide, pemetrexed, gemcitabine, or paclitaxel) or monotherapy with either paclitaxel, abraxane, navelbine, or pemetrexed. Of the 43 patients, 32 had platinum-based doublets, and 11 had monotherapy with one of the listed agents (Table 1).

Formal patient consent was not required because this was a retrospective study.

Defining CIN and FN

Neutropenia was defined as an absolute neutrophil count (ANC) of less than 1500 neutrophils per microliter. The levels of neutropenia were defined as mild (ANC, 1000-1500 neutrophils/μL), moderate (ANC, 500-1000 neutrophils/μL), and severe (ANC, <500 neutrophils/μL). The NCCN guidelines define FN as a single temperature of >38.3°C orally or >38.0°C over 1 hour, with an associated ANC of <500 or <1000 with a predicted decline to <500 over the next 48 hours.[5]

Risk models

It should be noted that the Hosmer and Bozcuk calculators were powered to detect occurrence of FN.[7,8] However, we also applied them for the risk of any CIN. In scoring for the Hosmer calculator, points are given to each risk factor and are added together to give a final risk score. This risk score correlates to a percentage of predicted FN. The score for the Hosmer calculator is from minus 18 to plus 19, in

TABLE 2 Sensitivity and specificity values for the Hosmer and Bozcuk risk models and the NCCN and ASCO guidelines for FN risk

Risk model/ guideline	Severe CIN sensitivity	Severe CIN patients not recommended CSF	FN sensitivity	CIN and FN specificity
Hosmer	89	1	100	44
Bozcuk	78	2	75	56
NCCN	67	3	50	45
ASCO	97	1	100	14

ASCO, American Society of Clinical Oncology; CIN, chemotherapy-induced neutropenia; CSF, colony-stimulating factors; FN, febrile neutropenia; NCCN, National Comprehensive Cancer Network

which a score of 13 or higher correlates to a 15% predicted risk of FN, and a score of 0 or less correlates to a 1.6% risk of FN.[7] For the Bozcuk calculator, a nomogram is used to calculate risk. Individual points are given to each risk factor and are then summed to give a total that correlates to a risk of FN. The score range for the Bozcuk calculator is 0 to 300, with a score of greater than 190 correlating to a greater than 90% risk of FN, and a score of 0 correlating to a 0% predicted risk of FN.[8]

For sensitivity and specificity threshold values, Hosmer reported using a risk score of 10 or above as being a reasonable value for the use of prophylactic CSF. They reported this score would predict an FN risk of about 10%, sensitivity of 24%, and specificity of 93% in detecting FN.[7] Bozcuk reported that using 110 as a cutoff value would correlate to about a 50% FN risk, sensitivity of 100%, and specificity of 49%. However, they did not suggest that value be applied as a threshold for the use of prophylactic CSF as Hosmer did.[8] Despite that, we used the thresholds of 10 and 110 for sensitivity and specificity analyses.

Regarding the current cycle of chemotherapy, the Hosmer calculator looked only at the first cycle, whereas the Bozcuk calculator looked at any cycle of chemotherapy.[7,8] In our study, we used the cycle correlating to the lowest ANC nadir the patient achieved. For example, if a patient achieved a nadir of 1,000 in cycle 1 but 200 in cycle 2, then we used the cycle 2 data to complete the calculators.

With respect to the NCCN and ASCO guidelines, we evaluated our cohort of 43 patients for the risk factors listed in the respective guidelines. If a patient had 1 or more of the risk factors, they were deemed to be high risk and therefore were recommended to receive CSF.

Results

General data

Of the 43 patients studied, 21 developed some level of CIN. Nine patients developed severe CIN, 4 developed moderate CIN, and 8 developed mild CIN. Of the severely neutropenic patients, 4 developed FN. None of the 16 patients who received prophylactic CSF developed FN, although 2 developed severe neutropenia despite CSF administration. Nadirs of ANC were seen on average during cycle 3 of chemotherapy. In all, 15 of the 43 patients achieved lowest ANC nadir during cycle 1.

Risk models

The Bozcuk calculator. A total of 22 patients had risk scores above the calculator's threshold value of 110. Of those 22 patients, 7 developed severe CIN, 5 developed either mild or moderate CIN, and 3 developed FN. Of the remaining 21 patients who had risk scores of below 110, 2 developed severe CIN, 7 developed mild or moderate CIN, and 1 developed FN. Sensitivity and specificity values are shown in Table 2.

The Hosmer calculator. A total of 26 patients had risk scores above the calculator's threshold value of 10. Of those 26 patients, 8 developed severe CIN, 4 developed either mild or moderate CIN, and 4 developed FN. Of the remaining 17 patients who had risk scores of less than 10, 1 developed severe CIN, 8 developed mild or moderate CIN, and none developed FN. Sensitivity and specificity values are listed in Table 2.

Current guidelines

NCCN guidelines. If one were to use the NCCN guidelines on our cohort of 43 patients, 25 would have been recommended to receive prophylactic CSF. Of those 25, 6 developed severe CIN (2 with FN), 2 moderate CIN, and 5 mild CIN. Of the 18 patients who would not have been recommended to receive CSF, 3 developed severe CIN (with 2 FN), 2 moderate CIN, and 3 mild CIN. Sensitivity and specificity values are listed in Table 2.

ASCO guidelines. Using the ASCO guidelines on our cohort of 43 patients, 38 had 1 or more of the high-risk features, and, therefore, CSF would have been considered for them. Of those 38 patients, 8 developed severe CIN (4 with FN), 4 developed moderate CIN, and 7 developed mild CIN. Of the 5 patients who would not have received CSF, 1 developed severe CIN and 1 mild CIN. Sensitivity and specificity values are listed in Table 2.

Discussion

In our study, we looked at 2 CIN risk models and compared them with the current NCCN and ASCO guidelines. The models were created to predict risk of FN, but we also looked at their predictive value for any level of CIN. To this end, we found that the Hosmer and Bozcuk calculators both were acceptable for predicting risk of severe CIN and FN. Because of the small number of patients in this study, differences in sensitivities and specificities cannot be quantitatively compared. Nevertheless, qualitatively, it can be said that both calculators were accurate in assigning high-risk scores to patients who developed severe CIN or FN. However, both calculators had many patients with high-risk scores who never developed CIN.

When comparing the 2 risk models with the NCCN and ASCO guidelines, the ASCO guidelines tended to be more liberal in their consideration of CSF use, whereas the NCCN guidelines tended to be more conservative and more similar to the 2 risk models we tested. The NCCN guidelines suggested not giving prophylactic CSF to 2 of our patients who developed FN and to not give CSF to an additional patient who developed severe CIN. The ASCO guidelines suggested considering using CSF for most of our patients, with only 5 patients not to be considered for CSF administration.

The differences in efficacy between the current guidelines and the 2 risk models may be indicative of the fact that the risk models are more accurate in assigning risk in older patients who are clinically more complicated. In our patients, the chemotherapies used were all considered to be intermediate risk, so patient-specific factors were used to guide the administration of CSF. However, because many our patients had at least 1 of the risk factors listed by the NCCN or ASCO, they were automatically deemed to be high risk and to receive prophylactic CSF.

Consequently, the Hosmer and Bozcuk calculators may be of greatest utility in more clinically complicated patients and those who have more comorbidities. The best approach may be a combination of either the NCCN or ASCO guidelines with 1 of the calculators, in our opinion the Hosmer system, for these complicated patients. Likely, the 2 risk models would not be as useful for chemotherapies deemed to have a high risk for FN because, in those situations, the efficacy and benefit of prophylactic CSF are clear.[9] Rather, their use could be beneficial in the grayer areas in which the risk is intermediate and decision-making is more difficult.

Limitations

There were several limitations in our study. First, the size of the cohort was small, and, therefore, the data that we gathered was limited in its scope. However, the goal of this study was to help provide guidance to oncologists in real-world settings about the validity and use of the available risk calculators. A further study should compare the calculators and guidelines in a much larger cohort to see if present results still hold true.

The second possible limitation of the study was our application of the Hosmer calculator because our patient population did not fit the criteria for inclusion in their original study. Hosmer had included only the first cycle of chemotherapy, whereas we included all cycles of chemotherapy. However, despite that, the calculator still performed well and could predict severe CIN and FN even with later cycles of chemotherapy. Therefore, we suggest using this calculator in any cycle of chemotherapy rather than just the first. This would expand its scope and utility in clinical practice.

Conclusions

This article provides oncologists with a comparison of 2 CIN risk models with the currently available NCCN and ASCO guidelines for use in patients with lung cancer. We prefer the Hosmer calculator over the Bozcuk calculator because of its simplicity of use and the accuracy of results. We anticipate that it may be useful and practical as an adjunct tool to the NCCN or ASCO guidelines in patients receiving intermediate-risk chemotherapy regimens. Larger studies combining the calculators and determining accuracy need to be completed to prove this hypothesis.

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Symptom burdens related to chemotherapy-induced anemia in stage IV cancer

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Background Chemotherapy-induced anemia (CIA) is associated with many symptoms that negatively impact quality of life. However, a systematic examination of symptoms in patients with CIA is lacking.
Objective To describe the occurrence of a comprehensive list of symptoms in patients with stage IV malignancies by CIA status.
Methods Patients diagnosed with stage IV non-Hodgkin lymphoma, breast, and lung cancer at Kaiser Permanente Southern California (2010-2012) were eligible. CIA was defined as hemoglobin <10 g/dL after the initiation of chemotherapy. Standardized record review evaluated the occurrence of symptoms for all patients who developed CIA (n = 402), and a random sample of patients who did not develop CIA (n = 98). The prevalence of each symptom and the distribution of number of symptoms per patient were described overall and by anemia grade.
Results Mean number of symptoms during chemotherapy for patients who did and did not develop CIA was 6.8 and 4.1, respectively ($P < .01$). Fatigue (90%), dyspnea or shortness of breath (58%), nausea or vomiting (56%), and loss of appetite (56%) were documented in >50% of patients who developed CIA, whereas only fatigue (77%) was noted in >50% patients without CIA. Several symptoms, including depression, diarrhea, dizziness or lightheadedness, and dyspnea, particularly demonstrated a clearly increasing prevalence with declining hemoglobin level. The mean number of symptoms per patient increased as CIA grade increased (3.6 symptoms for grade 2, and 5.4 symptoms for grades 3 and 4, respectively).
Limitations No causal relationship was examined due to descriptive design.
Conclusions High-grade CIA correlates with an increased symptom burden in patients with stage IV malignancies.
Funding Amgen Inc, maker of ESA used in the treatment of anemia

Anemia is a common complication of cancer treatment as well as of cancer itself. Most cancer patients undergoing chemotherapy experience anemia sometime during their treatment course.[1,2] Moderate to severe anemia is associated with an array of symptoms that are known to compromise the physical functioning and quality of life of cancer patients. Common anemia-related symptoms include fatigue, drowsiness, depression, dyspnea, tachycardia, and dizziness.[1,3-7]

Symptoms produced by cancer itself or the disease treatment (ie, side effects such as anemia) collectively compose a patient's symptom burden.[8] Although the occurrence of anemia-related fatigue has been described more systematically, other clinical presentations of chemotherapy-induced anemia (CIA) are not well characterized. Furthermore, the overall symptom burdens associated with different ranges of hemoglobin (Hb) concentrations have also not been well reported. Although various tools have been developed to facilitate the reporting of fatigue and other symptoms experienced by patients with CIA, such as the Functional Assessment of Cancer Therapy-Anemia (FACT-An) questionnaire and the MD Anderson Symptom Inventory (MDASI),[9-11] these questionnaires have not been extensively used outside of the research context. As such, knowledge on symptom burdens associated with CIA in real-world patient populations remains lacking.

Given the common occurrence of CIA, manage-

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ment of CIA and associated symptoms plays an important role to patients' quality of life during cancer treatment. Symptom control is often the main goal for patients with stage IV cancers, as treatment for disease is most likely palliative or noncurative. To facilitate supportive care planning, it is important to understand patient symptom burdens as chemotherapy progresses over cycles and Hb levels decline. We conducted a comprehensive medical record review study in patients diagnosed with stage IV non-Hodgkin lymphoma (NHL), breast cancer, and lung cancers at Kaiser Permanente Southern California (KPSC), a large community-based health care delivery system. The objective of this study was to report the occurrence of CIA-related symptoms throughout the course of chemotherapy and by Hb levels.

Methods

Study setting and population

KPSC is an integrated managed-care organization that provides comprehensive health services for 4 million racially, ethnically, and socioeconomically diverse members who broadly represent the population in Southern California.[12] The organization maintains electronic records of health care received by its members, including physician record notes and clinical databases such as laboratory test results, diagnosis codes, medical procedures, medication dispenses, and disease registries. KPSC's cancer registry is Surveillance, Epidemiology, and End Results, which is affiliated and routinely collects information on age, sex, race and/or ethnicity, cancer type, histology, and stage at diagnosis.

Patients who met the following inclusion criteria were included in this study: diagnosed with stage IV NHL, breast cancer, or lung cancer at age 18 years or older at KPSC between March 25, 2010 and December 31, 2012; initiated myelosuppressive chemotherapy at KPSC before June 30, 2013 (only the first chemotherapy course was included in this evaluation); and had at least 1 Hb measurement during the course of chemotherapy. Of those who met the inclusion criteria, patients who met the following criteria were excluded if they had less than 12 months KPSC membership before start of chemotherapy, missing information on cancer stage or chemotherapy regimen/agents, a diagnosis of myelodysplastic syndrome before chemotherapy initiation, a diagnosis of inherited anemia, an Hb concentration <10 g/L within 3 months before chemotherapy initiation, a transfusion within 2 weeks before chemotherapy initiation, radiation within 4 months before chemotherapy initiation, or bone marrow transplantation within 12 months before chemotherapy initiation or during the chemotherapy course. These exclusion criteria were applied to evaluate symptom burdens most likely related to CIA as opposed to other cancer treatment or pre-existing anemia.

CIA in this study was defined as moderate to severe anemia with Hb <10 g/dL after chemotherapy initiation. Based on this definition for CIA, all patients who developed CIA between the first chemotherapy administration to 60 days after the last dose of chemotherapy were included for the record review. In addition, a random sample of 100 patients who did not develop CIA (ie, did not reach an Hb <10 g/dL during chemotherapy) but otherwise met study eligibility criteria was also reviewed to serve as a comparison group. Of those, 2 patients were subsequently excluded after record review because of findings of ineligibility, so only 98 patients were presented. The large number of patients (ie, >4,000) who did not develop CIA made record review of all patients infeasible.

Data collection

Data on anemia-related symptoms or signs and anemia-related comorbidities (Table 1) were collected by standardized review of physician record notes in the electronic medical records. A set of 24 anemia-related symptoms were identified based on the literature and clinical expertise and included abdominal pain, blurred vision/double vision/loss of vision, cold intolerance/coldness in hands or feet, depression/anxiety, diarrhea, dizziness/lightheadedness, dyspnea/shortness of breath/tachypnea, edema, fatigue, headache, heart failure, heat intolerance, hypotension, insomnia, leg pain, loss of appetite, nausea/vomiting, pale skin, palpitations/tachycardia, paralysis/ataxia/numbness or tingling in extremities, pectoral angina/chest pain, sweating/diaphoresis, syncope, and vertigo. Record review period was defined as 1 month before chemotherapy to 60 days after the last dose of chemotherapy in the first course. To understand the development of new symptoms during chemotherapy treatment, pre-existing symptoms documented within 1 month before chemotherapy initiation were recorded. The entire record review process was standardized between 2 trained abstractors, including the training, instruction manual, ongoing feedback, abstraction form/database, and coding.

The data elements extracted included the date the symptom was documented, date the symptom started, symptom duration (when available), and any relevant comments regarding the symptom (ie, if dyspnea was at rest or on exertion, whether the symptom was a side effect caused by chemotherapy, or change in symptom severity). Ten percent of the records were reviewed independently by 2 abstractors to ensure quality control. Additional quality control measures included SAS algorithms (SAS Institute, Inc., Cary, North Carolina) to check reasonability and logical consistency in the abstracted data.

Patient demographic characteristics, cancer stage, additional selected comorbidities (Table 1), chemotherapy information, Hb test results, and anemia treatment, including erythrocyte stimulating agent (ESA) use and red blood cell transfusion, were collected using KPSC's cancer regis-

TABLE 1 Distribution of patient demographic and clinical characteristics

Characteristic	Patients who developed CIA, n (%)				Patients who did not develop CIA, n (%)				*P*-value[a]
	NHL 112 (28%)	**Breast 43 (11%)**	**Lung 247 (61%)**	**Overall 402 (100%)**	**NHL 30 (31%)**	**Breast 11 (11%)**	**Lung 57 (58%)**	**Overall 98 (100%)**	
Mean age at diagnosis, y (SD)	67.7 (13.5)	55.8 (15.2)	67.4 (9.5)	66.3 (12.0)	59.8 (11.8)	52.5 (13.5)	65.0 (11.9)	62.0 (12.6)	**<.01**
Race/ethnicity, n (%)									
White	61 (54.5)	15 (34.9)	151 (61.1)	227 (56.5)	12 (40.0)	5 (45.5)	35 (61.4)	52 (53.1)	.18
Black	8 (7.1)	8 (18.6)	45 (18.2)	61 (15.2)	3 (10.0)	1 (9.1)	4 (7.0)	8 (8.2)	
Asian	11 (9.8)	5 (11.6)	22 (8.9)	38 (9.5)	3 (10.0)	1 (9.1)	10 (17.5)	14 (14.3)	
Hispanic	32 (28.6)	15 (34.9)	25 (10.1)	72 (17.9)	10 (33.3)	4 (36.4)	8 (14.0)	22 (22.4)	
Other	0 (0)	0 (0)	4 (1.6)	4 (1.0)	2 (6.7)	0 (0)	0 (0)	2 (2.0)	
Female sex, n (%)	49 (43.8)	43 (100)	116 (47.0)	208 (51.7)	13 (43.3)	11 (100)	26 (45.6)	50 (51.0)	0.90
Comorbidities, n (%)									
Autoimmune disorder (RA, SLE, MS, IBD)[b]	7 (6.3)	1 (2.3)	8 (3.2)	16 (4.0)	1 (3.3)	0 (0.0)	1 (1.8)	2 (2.0)	0.55
Cerebrovascular disease[b]	7 (6.3)	3 (7.0)	23 (9.3)	33 (8.2)	0 (0.0)	0 (0.0)	1 (1.75)	1 (1.0)	0.01
Congestive heart failure[b]	12 (10.7)	3 (7.0)	19 (7.7)	34 (8.5)	0 (0.0)	0 (0.0)	1 (1.75)	1 (1.0)	0.01
Cirrhosis[b]	6 (2.4)	3 (7.0)	6 (2.4)	15 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.05
COPD/emphysema[b]	20 (17.9)	4 (9.3)	91 (36.8)	115 (28.6)	4 (13.3)	0 (0.0)	14 (24.6)	18 (18.4)	0.04
Gastritis[c]	9 (8.0)	2 (4.7)	8 (3.2)	19 (4.7)	1 (3.3)	0 (0.0)	1 (1.75)	2 (2.0)	0.40
Gastroesophageal reflux disease[c]	38 (33.9)	11 (25.6)	49 (19.8)	98 (24.4)	5 (16.7)	2 (18.2)	12 (21.1)	19 (19.4)	0.30
Hemorrhoids[c]	14 (12.5)	3 (7.0)	21 (8.5)	38 (9.5)	2 (6.7)	2 (18.2)	4 (7.02)	8 (8.2)	0.69
Hepatitis[b]	3 (2.7)	1 (2.3)	11 (4.5)	15 (3.7)	3 (10.0)	0 (0.0)	0 (0.0)	3 (3.1)	1.00
History of angina[c]	6 (5.4)	0 (0.0)	12 (4.9)	18 (4.5)	0 (0.0)	0 (0.0)	1 (1.75)	1 (1.0)	0.14
Ischemic heart disease[b]	19 (17.0)	0 (0.0)	37 (15.0)	56 (13.9)	2 (6.7)	0 (0.0)	5 (8.8)	7 (7.1)	0.07
Malnutrition[c]	44 (39.3)	12 (27.9)	71 (28.7)	127 (31.6)	2 (6.7)	1 (9.1)	5 (8.8)	8 (8.2)	<0.01
Liver disease[b]	4 (3.6)	1 (0.4)	0 (0.0)	5 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.59
Renal failure[b]	25 (22.3)	2 (4.7)	45 (18.2)	72 (17.9)	1 (3.3)	1 (9.1)	5 (8.8)	7 (7.1)	0.01
Peptic ulcer disease[c]	4 (3.6)	0 (0.0)	7 (2.8)	11 (2.7)	0 (0.0)	0 (0.0)	1 (1.75)	1 (1.0)	0.48
Peripheral vascular disease[b]	8 (7.1)	2 (4.7)	24 (9.7)	34 (8.5)	0 (0.0)	1 (9.1)	0 (0.0)	1 (1.0)	0.01
Splenomegaly/ splenic enlargement[c]	19 (17.0)	1 (2.3)	2 (0.8)	22 (5.5)	5 (16.7)	0 (0.0)	0 (0.0)	5 (5.1)	0.88
Thromboembolic events[b]	13 (11.6)	3 (7.0)	22 (8.9)	38 (9.5)	0 (0.0)	0 (0.0)	2 (3.5)	2 (2.0)	0.02
Thyroid disorder[b]	17 (15.2)	7 (16.3)	23 (9.3)	47 (11.7)	6 (20.0)	1 (9.1)	3 (5.3)	10 (10.2)	0.68
Underweight[b]	6 (5.4)	2 (4.7)	31 (12.6)	39 (9.7)	0 (0.0)	1 (9.1)	4 (7.02)	5 (5.1)	0.15

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Characteristic	Patients who developed CIA, n (%) NHL 112 (28%)	Breast 43 (11%)	Lung 247 (61%)	Overall 402 (100%)	Patients who did not develop CIA, n (%) NHL 30 (31%)	Breast 11 (11%)	Lung 57 (58%)	Overall 98 (100%)	*P*-value[a]
Mean no. of chemotherapy cycles per patient (SD)	4.7 (2.3)	6.4 (4.3)	4.7 (3.3)	4.9 (3.2)	5.8 (1.3)	5.2 (4.1)	5.5 (4.0)	5.5 (3.4)	0.03
HB measurements									
Mean baseline HB level, g/dL (SD)	12.1 (1.7)	12.2 (1.4)	12.4 (1.4)	12.3 (1.5)	13.1 (1.3)	13.7 (1.0)	13.7 (1.5)	13.5 (1.4)	<0.01
Worst mean HB level during chemotherapy, g/dL (SD)	8.4 (1.0)	8.7 (0.9)	8.5 (0.9)	8.5 (1.0)	11.5 (0.9)	11.4 (0.6)	11.4 (1.1)	11.4 (1.0)	<0.01
Mean no. of Hb measurements throughout chemotherapy course per patient (SD)	22.5 (20.2)	15.7 (8.1)	12.9 (8.4)	15.9 (13.4)	8.7 (4.4)	7.9 (4.1)	8.2 (6.1)	8.3 (5.4)	<0.01
Mean no. of Hb measurements in a chemotherapy cycle/ person									
Cycle 1	8.3	4.3	3.5	4.9	1.9	2.2	1.9	1.9	—
Cycle 2	5.0	3.0	2.7	3.4	1.4	1.9	1.4	1.5	—
Cycle 3	3.3	2.6	2.4	2.7	1.6	1.6	1.5	1.5	—
Cycle 4	3.4	1.8	2.9	2.9	1.3	1.5	1.4	1.4	—
Cycle 5	3.8	3.4	2.2	2.7	1.4	1.0	1.2	1.3	—
Cycle 6	2.8	1.9	2.7	2.6	1.5	0.8	1.5	1.4	—
Anemia treatment									
Any ESA use during chemotherapy, n (%)	5 (4.5)	0 (0)	7 (2.8)	12 (0.3)	—	—	—	—	—
Red blood cell transfusion, n (%)	52 (46.4)	10 (23.3)	92 (37.2)	154 (38.3)	—	—	—	—	—
Cycle 1	19 (17.0)	4 (9.3)	20 (8.1)	43 (10.7)	—	—	—	—	—
Cycle 2	12 (12.4)	2 (5.0)	17 (8.1)	31 (8.9)	—	—	—	—	—
Cycle 3	7 (8.0)	1 (2.7)	17 (9.0)	25 (8.0)	—	—	—	—	—
Cycle 4	12 (15.2)	0 (0)	23 (14.2)	35 (12.9)	—	—	—	—	—
Cycle 5	10 (14.0)	1 (2.7)	18 (15.8)	29 (13.9)	—	—	—	—	—
Cycle 6	9 (15.8)	0 (0)	12 (12.8)	21 (11.9)	—	—	—	—	—

CIA, chemotherapy-induced anemia; COPD, chronic obstructive pulmonary disease; ESA, erythropoiesis-stimulating agents; HB, hemoglobin; IBD, inflammatory bowel disease; MS, multiple sclerosis; NHL, non-Hodgkin lymphoma; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus

[a]*P*-value comparing overall between patients with and without CIA. [b]Captured using electronic medical records with diagnosis codes or laboratory test results (for renal failure). [c]Captured using chart review.

try and clinical databases. Anemia was defined by severity as grade 1 (10 g/dL to lower limit of normal, ie, 14 g/dL for men and 12 g/dL for women), grade 2 (8.0-9.9 g/dL), grade 3 (6.5-7.9 g/dL), and grade 4 (<6.5 g/dL) following the National Cancer Institute's Common Terminology Criteria for Adverse Events.[13]

Statistical analysis

Distributions of demographic, cancer, and treatment characteristics were calculated by CIA status, overall and by cancer type. Differences between patients who did and did not develop CIA were assessed using chi-square test and Kruskal-Wallis test. For those who developed CIA, the dis-

TABLE 2 Number of anemia episodes by anemia grade in each chemotherapy cycle for patients who developed chemotherapy-induced anemia

Grade	Patients with anemia episode, n (%)[a]					
	Cycle 1 (n = 402)	Cycle 2 (n = 347)	Cycle 3 (n = 314)	Cycle 4 (n = 271)	Cycle 5 (n = 209)	Cycle 6 (n = 176)
1[b]	197 (56.6)	172 (54.8)	142 (49.3)	96 (38.4)	81 (40.9)	70 (48.6)
2[b]	119 (34.2)	121 (38.5)	124 (43.1)	129 (51.6)	94 (47.5)	60 (41.7)
3[b]	29 (8.3)	19 (6.1)	22 (7.6)	22 (8.8)	22 (11.1)	12 (8.3)
4[b]	3 (0.9)	2 (0.6)	0 (0)	3 (1.2)	1 (0.5)	2 (1.4)

[a]Percentage does not add up to 100% because some patients did not have an anemia episode in some chemotherapy cycles. [b]Worse anemia grade in a cycle for each person.

tribution of the worst anemia grade was also calculated for each cycle of chemotherapy.

Next, the distributions for the following symptom categories were calculated in the 2 study samples defined by CIA status: pre-existing symptoms that occurred before chemotherapy, any symptoms during chemotherapy (ie, whether they started before chemotherapy), and incident symptoms during chemotherapy (ie, new symptoms that only started after chemotherapy). Specifically, the proportion of patients with each individual symptom and the distribution of the number of symptoms per patient were calculated. Differences in symptom distribution by CIA status were assessed using chi-square test.

The distribution of symptoms in each chemotherapy cycle was calculated up to 6 chemotherapy cycles (as >80% of the patients only had treatment up to 6 cycles) in the 2 study samples defined by CIA status. For this analysis, a symptom was "mapped" to a cycle if the date (or date range) of the symptom fell within the date range of that chemotherapy cycle. In patients who developed CIA, the distribution of symptoms was also calculated by anemia grade. This was again done on the chemotherapy cycle level. For each chemotherapy cycle, an anemia grade was assigned (no anemia or anemia grade 1, 2, 3, and 4) using the lowest Hb measurement in that cycle. Symptoms that occurred in a chemotherapy cycle were then "mapped" to the anemia grade of that cycle. Some patients had more than 1 anemia event of the same grade (eg, if a patient's grade 2 anemia persist across cycles). For these patients, we randomly selected only 1 anemia event of the same grade from each patient to be included in this analysis. Patients could still contribute multiple events of different grades to this analysis. We calculated the mean number of symptoms per patient for each anemia grade (ie, 1-4) separately. Because of the small number of patients who developed grade 4 anemia (n = 11), they were combined with the grade 3 patients when the distributions of individual symptoms were evaluated.

All analyses were repeated stratified by gender. *P* values for differences between men and women were calculated using chi-square test or *t* test. All analyses were conducted using SAS version 9.3.

Results

A total of 402 stage IV NHL, breast, and lung cancer patients who developed CIA and 98 patients who did not develop CIA during the first course of chemotherapy were included (Figure 1). The distribution of cancer types in the study sample were similar across CIA status (Table 1). The mean age at diagnosis was 66 years in patients who developed CIA and 62 years in patients who did not develop CIA. Women accounted for half of the patients in both study samples (52% and 51%, respectively). Most of the study patients were of non-Hispanic white race/ethnicity. Chronic obstructive pulmonary disease/emphysema and gastroesophageal reflux disease were among the most common comorbidities examined in both study samples, while malnutrition and moderate to severe renal disease were also common in patients who developed CIA (Table 1).

The mean Hb level before chemotherapy was lower for patients who developed CIA compared with patients who did not develop CIA (12.3 g/dL and 13.5 g/dL, respectively; Table 1). The mean lowest Hb level during chemotherapy was 8.5 g/dL for patients who developed CIA and 11.4 g/dL for patients without CIA (Table 1). The number of anemia events by grade in each chemotherapy cycle in patients who developed CIA is shown in Table 2. Use of ESA was extremely rare in the study population. About 23% to 46% of patients who developed anemia received red blood cell transfusion throughout the chemotherapy cycles. There was no clear trend of use of red blood transfusion over cycles (Table 1).

Table 3 shows the number and proportion of study patients with each of the symptoms documented before and after chemotherapy initiation for the 2 study samples. Patients who developed CIA had statistically significantly more pre-existing symptoms, incident symptoms, or any symptoms that occurred during chemotherapy compared with patients who did not develop CIA. The mean number of pre-existing symptoms was 1.7 (standard deviation

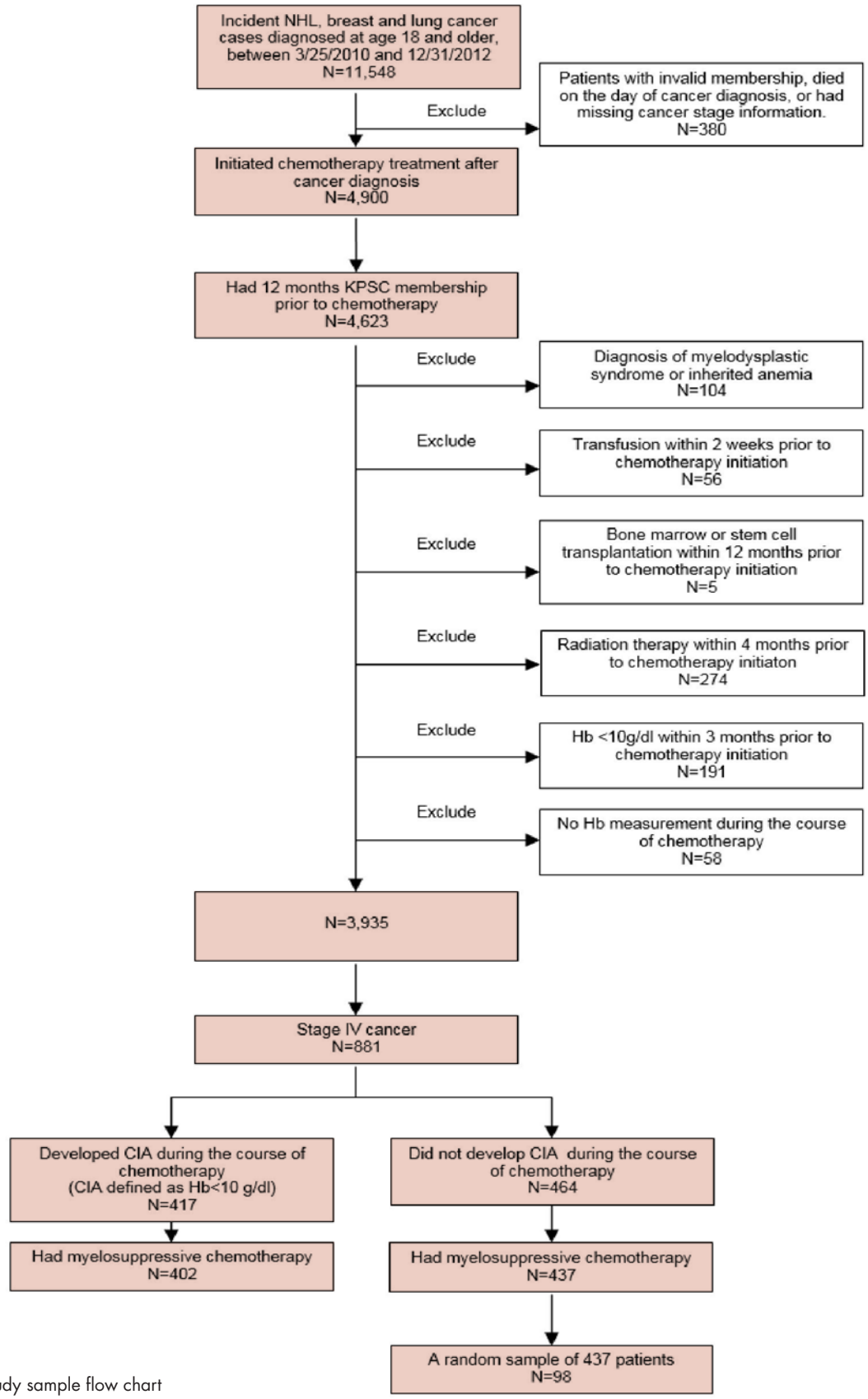

FIGURE Study sample flow chart

TABLE 3 Distribution of symptoms in patients who developed CIA and those who did not (n = 98)

Symptoms	Symptoms before start of chemotherapy (pre-existing)		Symptoms occurring during chemotherapy		Symptoms occurring during but not before chemotherapy (incident)	
	Developed CIA	Did not develop CIA	Developed CIA	Did not develop CIA	Developed CIA	Did not develop CIA
Mean no. per patient (SD)	1.7 (2.0)*	1.2 (1.5)*	6.8 (3.4)**	4.1 (2.7)**	5.5 (3.1)**	3.3 (2.4)**
Individual symptom, no. of patients (%)						
Abdominal pain	31 (7.7)	7 (7.1)	139 (34.6)	22 (22.4)	118(29.4)	17(17.5)
Blurred vision/double vision/loss of vision	5 (1.2)	1 (1.0)	48 (11.9)	7 (7.1)	45 (11.2)	6 (6.1)
Cold intolerance/coldness in hands or feet	2 (0.5)	0 (0)	16 (4.0)	1 (1.0)	14 (3.5)	1 (1.0)
Depression/anxiety	38 (9.5)	9 (9.2)	173 (43.0)	24 (24.5)	144 (35.8)	19 (19.4)
Diarrhea	13 (3.2)	1 (1.0)	118 (29.4)	10 (10.2)	111(27.6)	9 (9.2)
Dizziness/lightheadedness	14 (3.5)	2 (2.0)	119 (29.6)	15 (15.3)	110 (27.4)	14 (14.3)
Dyspnea/shortness of breath/tachypnea	115 (28.6)	22 (22.4)	231 (57.5)	40 (40.8)	131 (32.6)	21 (21.4)
Edema	35 (8.7)	6 (6.1)	157 (39.1)	18 (18.4)	125 (31.1)	14 (14.3)
Fatigue	132 (32.8)	20 (20.4)	362 (90.1)	75 (76.5)	237 (59.0)	57 (58.2)
Headache	19 (4.7)	7 (7.1)	96 (23.9)	17 (17.3)	84 (20.9)	14 (14.3)
Heart failure	0 (0)	0 (0)	16 (4.0)	1 (1.0)	16 (4.0)	1 (1.0)
Heat intolerance	1 (0.3)	0 (0)	4 (1.0)	0 (0)	4 (1.0)	0 (0)
Hypotension	7 (1.7)	0 (0)	72 (17.9)	1 (1.0)	69 (17.2)	1 (1.0)
Insomnia	27 (6.7)	3 (3.1)	114 (28.4)	19 (19.4)	98 (24.4)	17 (17.3)
Leg pain	22 (5.5)	2 (2.0)	92 (22.9)	9 (9.2)	81 (20.1)	8 (8.2)
Loss of appetite	60 (14.9)	6 (6.1)	225 (56.0)	18 (18.4)	180 (44.8)	15 (15.3)
Nausea/vomiting	33 (8.2)	4 (4.1)	223 (55.5)	42 (42.9)	199 (49.5)	41 (41.8)
Pale skin	1 (0.2)	3 (3.1)	32 (8.0)	1 (1.0)	31 (7.7)	0(0)
Palpitations/tachycardia	19 (4.7)	3 (3.1)	138 (34.3)	14 (14.3)	127 (31.6)	12 (12.2)
Paralysis/ataxia/numbness/tingling in extremities	13 (3.2)	3 (3.1)	109 (27.1)	32 (32.7)	103 (25.6)	30 (30.6)
Pectoral angina/chest pain	56 (13.9)	9 (9.2)	138 (34.3)	24 (24.5)	100 (24.9)	20 (20.4)
Sweating (perspiration, diaphoresis)	18 (4.5)	6 (6.1)	53 (13.2)	7 (7.1)	43 (10.7)	4 (4.1)
Syncope	8 (2.0)	0 (0)	36 (9.0)	3 (3.1)	34 (8.5)	3 (3.1)
Vertigo	0 (0)	0 (0)	9 (2.2)	0 (0)	9 (2.2)	0 (0)

CIA, chemotherapy-induced anemia

*P = .04. **P < .01.

[SD], 2.0) for those with CIA and 1.2 (SD, 1.5) for those without CIA (P = .04). The mean number of symptoms that occurred during chemotherapy was 6.8 (SD, 3.4) and 4.1 (SD, 2.7), respectively (P < .01). Of individual symptoms, fatigue was the most commonly documented symptom during chemotherapy in patients who developed CIA, noted in 90% of the study sample (Table 3). Dyspnea/shortness of breath (58%), nausea/vomiting (56%), and

TABLE 4 Distribution of symptoms by chemotherapy cycle

Symptoms	Patients who developed CIA					
	Cycle 1 (n = 402)	Cycle 2 (n = 347)	Cycle 3 (n = 314)	Cycle 4 (n = 271)	Cycle 5 (n = 209)	Cycle 6 (n = 176)
Mean no. per patient (SD)	2.6 (2.6)	1.9 (2.1)	1.8 (1.9)	1.7 (2)	1.6 (2)	2.2 (2)
Individual symptom, no. of patients (%)						
Abdominal pain	71 (17.7)	35 (10.1)	26 (8.3)	25 (9.2)	20 (9.6)	27 (15.3)
Blurred vision/double vision/ loss of vision	17(4.2)	9(2.6)	12(3.8)	8(3.0)	2(1.0)	9(5.1)
Cold intolerance/coldness in hands or feet	7(1.7)	5(1.4)	4(1.3)	2(0.7)	0 (0)	1(0.6)
Depression/anxiety	79 (19.7)	43 (12.4)	42 (13.4)	30 (11.1)	25 (12.0)	38(21.6)
Diarrhea	51 (12.7)	26 (7.5)	25 (8.0)	21 (7.7)	14 (6.7)	17 (9.7)
Dizziness/lightheadedness	41 (10.2)	35 (10.1)	22 (7.0)	26 (9.6)	21 (10.1)	16 (9.1)
Dyspnea/shortness of breath/ tachypnea	120(29.9)	84(24.2)	82(26.1)	68(25.1)	43(20.6)	43(24.4)
Edema	76 (18.9)	46 (13.3)	46 (14.6)	30 (11.1)	22 (10.5)	29 (16.5)
Fatigue	205 (51.0)	159 (45.8)	149(47.5)	128(47.2)	88 (42.1)	97 (55.1)
Headache	54 (13.4)	27 (7.8)	16 (5.1)	16 (5.9)	12 (5.7)	15 (8.5)
Heart failure	13 (3.2)	1 (0.3)	0 (0)	1 (0.4)	1 (0.5)	0 (0)
Heat intolerance	3 (0.7)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)
Hypotension	36 (9.0)	11 (3.2)	10 (3.2)	8 (3.0)	7 (3.3)	6 (3.4)
Insomnia	50 (12.4)	37 (10.7)	31 (9.9)	15 (5.5)	12 (5.7)	17 (9.7)
Leg pain	30 (7.5)	30 (8.6)	18 (5.7)	17 (6.3)	16 (7.7)	13 (7.4)
Loss of appetite	124 (30.8)	62 (17.9)	51 (16.2)	44 (16.2)	27 (12.9)	38 (21.6)
Nausea/vomiting	123(30.6)	74(21.3)	59(18.8)	41(15.1)	33(15.8)	41(23.3)
Pale skin	15 (3.7)	6 (1.7)	3 (1.0)	5 (1.9)	4 (1.9)	2 (1.1)
Palpitations/tachycardia	58(14.4)	37(10.7)	20(6.4)	25(9.2)	12(5.7)	15(8.5)
Paralysis/ataxia/numbness/ tingling in extremities	33 (8.2)	38 (11.0)	31 (9.9)	34 (12.6)	23 (11.0)	29 (16.5)
Pectoral angina/chest pain	63 (15.7)	43 (12.4)	35 (11.1)	29 (10.7)	24 (11.5)	17 (9.7)
Sweating (perspiration, diaphoresis)	29 (7.2)	9 (2.6)	12 (3.8)	8 (3.0)	7 (3.3)	8 (4.5)
Syncope	8 (2.0)	8 (2.3)	6 (1.9)	9 (3.3)	4 (1.9)	2 (1.1)
Vertigo	4 (1.0)	0 (0)	2 (0.6)	1 (0.4)	1 (0.5)	1 (0.6)

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loss of appetite (56%) were documented in 50% or more of these patients. Abdominal pain (35%), depression/anxiety (43%), dizziness/lightheadedness (30%), edema (39%), palpitations/tachycardia (34%), and pectoral angina/chest pain (34%) were documented in 30% or more of these patients. In patients who did not develop CIA, fatigue remained the most prevalent symptom (77% of the patients). Other than fatigue, only dyspnea/shortness of breath (41%), nausea/vomiting (43%) and paralysis/ataxia/tingling in extremities (33%) were noted in 30% or more of this study sample.

Table 4 shows the number and proportion of study patients with symptoms that occurred during each chemotherapy cycle. Again, fatigue is the predominant symptom documented throughout cycles for all patients. In patients who developed CIA, the proportion of patients experiencing the following symptoms was relatively stable across chemotherapy cycles: depression/anxiety, dizziness/lightheadedness, fatigue, pale skin, and sweating. The proportion of patients experiencing paralysis/ataxia/numbness/tingling in extremities increased over cycles. For headache, loss of appetite, hypotension, and nausea/vomiting, the proportion of patients with symptom documentation was

Continued from previous page

Symptoms	Patients who did not develop CIA					
	Cycle 1 (n = 98)	Cycle 2 (n = 91)	Cycle 3 (n = 80)	Cycle 4 (n = 74)	Cycle 5 (n = 59)	Cycle 6 (n = 57)
Mean no. per patient (SD)	1.4 (1.6)	1.2 (1.2)	1.3 (1.2)	1.5 (1.5)	1.0 (1.0)	1.5 (1.5)
Individual symptom, no. of patients (%)						
Abdominal pain	11 (11.2)	5 (5.5)	3 (3.8)	4 (5.4)	3 (5.1)	4 (7.0)
Blurred vision/double vision/ loss of vision	1(1.0)	3(3.3)	3(3.8)	0 (0)	1(1.7)	1(1.8)
Cold intolerance/coldness in hands or feet	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1(1.8)
Depression/anxiety	7 (7.1)	6 (6.6)	5 (6.3)	9 (12.2)	2 (3.4)	7 (12.3)
Diarrhea	2 (2.0)	5 (5.5)	1 (1.3)	2 (2.7)	2 (3.4)	3 (5.3)
Dizziness/lightheadedness	7 (7.1)	1 (1.1)	4 (5.0)	2 (2.7)	0 (0)	2 (3.5)
Dyspnea/shortness of breath/ tachypnea	23(23.5)	15(16.5)	19(23.8)	11(14.9)	9(15.3)	11(19.3)
Edema	7 (7.1)	4 (4.4)	7 (8.8)	8 (10.8)	4 (6.8)	5 (8.8)
Fatigue	40 (40.8)	36 (39.6)	31 (38.8)	34 (46.0)	22 (37.3)	31 (54.4)
Headache	8 (8.2)	6 (6.6)	4 (5.0)	5 (6.8)	0 (0)	2 (3.5)
Heart failure	1 (1.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Heat intolerance	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hypotension	0 (0)	0 (0)	1 (1.3)	0 (0)	0 (0)	0 (0)
Insomnia	12 (12.2)	9 (9.9)	8 (10.0)	10 (13.5)	3 (5.1)	3 (5.3)
Leg pain	3 (3.1)	5 (5.5)	4 (5.0)	2 (2.7)	2 (3.4)	2 (3.5)
Loss of appetite	12 (12.2)	7 (7.7)	6 (7.5)	7 (9.5)	2 (3.4)	4 (7.0)
Nausea/vomiting	23(23.5)	21(23.1)	11(13.8)	12(17.6)	10(16.9)	6(10.5)
Pale skin	1 (1.0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.8)
Palpitations/tachycardia	5(5.1)	1(1.1)	2(2.5)	3(4.1)	3(5.1)	3(5.3)
Paralysis/ataxia/numbness/ tingling in extremities	5 (5.1)	6 (6.6)	16 (20.0)	13 (17.6)	12 (20.3)	14 (24.6)
Pectoral angina/chest pain	9 (9.2)	7 (7.7)	6 (7.5)	8 (10.8)	3 (5.1)	6 (10.5)
Sweating (perspiration, diaphoresis)	3 (3.1)	3 (3.3)	3 (3.8)	3 (4.1)	3 (5.1)	1 (1.8)
Syncope	1 (1.0)	1 (1.1)	1 (1.3)	0 (0)	0 (0)	0 (0)
Vertigo	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

CIA, chemotherapy-induced anemia

highest in cycle 1, stabilizing in subsequent cycles (Table 4). In patients without CIA, the cycle-level prevalence of most of the symptoms did not increase over cycles, except for paralysis/ataxia/numbness or tingling in extremities. For insomnia, loss of appetite, and nausea/vomiting, the cycle-level prevalence dropped after the first cycle. There was no clear increasing trend of the mean number of symptoms per patient across chemotherapy cycles in both study samples (Table 4).

Table 5 shows the distribution of symptoms by anemia grade in patients who developed CIA. In general, the prevalence of symptoms increased with higher grades of anemia. The following symptoms especially have a clear increase in prevalence as the severity of anemia progressed: abdominal pain, depression, diarrhea, dizziness/lightheadedness, dyspnea, edema, fatigue, heart failure, headache, hypotension, insomnia, leg pain, loss of appetite, pale skin, palpitations, pectoral angina, and sweating. The mean number of symptoms per patient increased as CIA grade increased, from 3.6 (SD, 2.9) for grade 2 CIA to 5.4 (SD, 3.5) for grades

3 and 4 CIA (specifically, 5.3 [SD, 3.4] for grade 3 CIA and 6.4 [SD, 4.1] for grade 4 CIA; data not shown) (Table 5).

When stratified by gender, there are no material differences between men and women in most analyses. In men, the mean number of pre-existing symptoms was 1.7 (SD, 1.8) and 1.0 (SD, 1.2) for those with and without CIA, respectively ($P = .02$). The mean number of symptoms that occurred during chemotherapy was 7.0 (SD, 3.4) and 4.2 (SD, 2.4), respectively ($P < .01$). In women, the mean number of pre-existing symptoms was not statistically different in those with and without CIA (1.6 [SD, 2.2] and 1.3 [SD, 1.8], respectively; $P = .46$). However, like in men, the mean number of symptoms that occurred during chemotherapy was significantly more in those with CIA (6.5 [SD, 3.3] and 4.0 [SD, 2.9], respectively; $P < .01$). As in the overall analysis, there was no clear increasing trend of the number of symptoms per patients across chemotherapy cycles in both men and women, but the average number of symptoms increased as the CIA grade increased. For men, the mean number of symptoms per patient increased from 3.7 (SD, 3.0) for grade 2 CIA to 6.0 (SD, 3.5) for grades 3 and 4 CIA (data not shown). For women, the mean number of symptoms per patient increased from 3.6 (SD, 2.9) for grade 2 CIA to 4.7 (SD, 3.3) for grades 3 and 4 CIA (data not shown).

TABLE 5 Distribution of symptom by grade of anemia episodes for patients who developed chemotherapy-induced anemia

Symptoms	Grade 1[a] (n = 297)	Grade 2 (n = 355)	Grade 3+4 (n = 119)
Mean no. of symptoms per patient (SD)	1.8 (1.9)	3.6 (2.9)	5.4 (3.5)
By individual symptom, no. of events with symptom (%)			
Abdominal pain	23 (7.7)	51 (14.4)	34 (28.6)
Blurred vision/double vision/loss of vision	10 (3.4)	13 (3.7)	7 (5.9)
Cold intolerance/coldness in hands or feet	3 (1)	5 (1.4)	5 (4.2)
Depression/anxiety	20 (6.7)	80 (22.5)	40 (33.6)
Diarrhea	14 (4.7)	54 (15.2)	30 (25.2)
Dizziness/lightheadedness	23 (7.7)	47 (13.2)	23 (19.3)
Dyspnea/ shortness of breath/tachypnea	48 (16.2)	121 (34.1)	60 (50.4)
Edema	25 (8.4)	72 (20.3)	46 (38.7)
Fatigue	106 (35.7)	234 (65.9)	94 (79)
Headache	20 (6.7)	33 (9.3)	19 (16)
Heart failure	0 (0)	10 (2.8)	4 (3.4)
Heat intolerance	1 (0.3)	3 (0.8)	0 (0)
Hypotension	4 (1.3)	30 (8.5)	22 (18.5)
Insomnia	21 (7.1)	47 (13.2)	23 (19.3)
Leg pain	21 (7.1)	34 (9.6)	12 (10.1)
Loss of appetite	50 (16.8)	115 (32.4)	51 (42.9)
Nausea/vomiting	55 (18.5)	115 (32.4)	39 (32.8)
Pale skin	0 (0)	13 (3.7)	9 (7.6)
Palpitations/tachycardia	16 (5.4)	63 (17.7)	41 (34.5)
Paralysis/ataxia/numbness, tingling in extremities	30 (10.1)	40 (11.3)	15 (12.6)
Pectoral angina/chest pain	27 (9.1)	57 (16.1)	42 (35.3)
Sweating (perspiration, diaphoresis)	11 (3.7)	23 (6.5)	13 (10.9)
Syncope	3 (1)	17 (4.8)	7 (5.9)
Vertigo	0 (0)	6 (1.7)	3 (2.5)

[a]Although grade 1 anemia was not considered chemotherapy-induced anemia in this study, here, we presented symptoms documented for grade 1 anemia in patients who developed chemotherapy-induced anemia (ie, grade 2 and higher) during chemotherapy.

Discussion

In this study, we described the number and type of symptoms documented in the medical record notes among stage IV NHL, breast cancer, and lung cancer patients who did or did not develop CIA during chemotherapy. Patients who developed CIA had significantly greater numbers of different symptoms documented during chemotherapy than those who did not develop CIA (6.8 vs 4.1). This difference is clinically significant because most symptoms described in this study can be expected to have a negative impact on a patient's quality of life. In patients who developed CIA, fatigue was the most commonly documented symptom, noted for 90% of the study population. In addition to fatigue, many other symptoms were noted in a large proportion of patients. In contrast, in patients who did not develop CIA, only a few symptoms (including fatigue) were more commonly noted in this sample. We observed more symptoms in chemotherapy cycles with higher grades of anemia. Of the symptoms examined, abdominal pain, depression, diarrhea, dizziness/lightheadedness, dys-

pnea, edema, fatigue, heart failure, headache, hypotension, insomnia, leg pain, loss of appetite, nausea/vomiting, pale skin, pectoral angina, sweating, and syncope particularly demonstrated a clearly increasing prevalence with declining Hb level. We also reported that patients who developed severe anemia (grades 3 and 4) experienced an average of 5 to 6 different symptoms at the time of the anemia episode. These data demonstrated a significant symptom burden in cancer patients with CIA seen in community-based oncology practices. Findings on the types of symptoms most commonly noted in various grades of CIA episodes provided some guidance for supportive care planning. As previous studies have shown a reduction in symptom burden after anemia treatment in patients with CIA,[14-16] our results support the idea of early lab draws and active management of CIA in maintaining quality of life in cancer patients undergoing chemotherapy.

Our findings on the prevalence of fatigue are in line with other studies in the literature. Maxwell reported that the prevalence of fatigue was 80% to 96% in cancer patients.[17] Cella and colleagues found that using FACT-General questionnaire, 75% of cancer patients reported fatigue.[11] The comparability of our estimate and those found in studies based on patient self-report offered some assurance of the validity of assessing symptom prevalence through physician record notes. In addition to fatigue, we described prevalence of 23 additional symptoms, most of which have not been extensively studied in the literature. Gabrilove and colleagues found that a substantial proportion of patients with CIA had moderate to severe score for lack of appetite (36%) and disturbed sleep (41%) using the MDASI.[10] The prevalence of loss of appetite and insomnia was around 50% and 25%, respectively, in our study samples. A 2013 systematic review of 21 multinational studies reported the pooled prevalence of several nonfatigue symptoms in cancer patients including headache (23%), sleep disturbance/insomnia (49%), appetite changes (45%), nausea/vomiting (26%), diarrhea (15%), depression (34%), dyspnea (44%), dizziness (26%), numbness/tingling (42%), edema (14%), and sweating (28%).[18] Our prevalence estimates in patients with CIA for most of these symptoms were higher, likely because Reilly and colleagues used source studies that included any cancer patients undergoing treatment and not just those with CIA. Our findings on the increased symptom burden in patients who experienced episodes of advanced anemia compared with patients with mild anemia were also consistent with the literature. To this end, several studies using MDASI or the FACT-An reported differential symptom burdens by Hb level based on patient self-report,[10,11,19] including data on improvement in symptom burden and quality of life after anemia was amended with the use of ESA.[20,21]

We found that the number of pre-existing symptoms was significantly higher in patients who went on to develop CIA than in patients who did not develop CIA. Specifically, fatigue, loss of appetite, and pale skin before chemotherapy seemed to be significantly more common in patients who went on to develop CIA. This finding suggested that presentation of these symptoms before chemotherapy initiation may be a predictor for developing moderate or severe anemia during treatment. This is a novel hypothesis, as no studies have evaluated the relationship between pretreatment symptom and risk of CIA. However, our study was not designed to address this specific question. Additional investigation is needed to further shed light on whether the occurrence of anemia-related symptoms in nonanemic patients can be used to effectively risk-stratify patients for subsequent CIA.

Contrary to our expectation, the prevalence of most symptoms did not clearly increase as chemotherapy progressed. There are several possible explanations to this phenomenon, with the most likely being related to reporting of anemia-related symptoms. For example, patients might stop reporting the same symptom repeatedly or become adjusted to the new Hb levels, leading to less symptom manifestation. Clinicians may also be less likely to ask about symptoms in later treatment cycles and/or to document chronic symptoms. Several symptoms were rarely documented altogether, such as cold intolerance, heat intolerance, heart failure, and vertigo. Symptoms reported in earlier cycles could also be managed successfully. Another possible explanation is differential loss of follow-up. Patients who experienced severe adverse events or symptoms may terminate treatment prematurely. Thus, symptom burden found toward later cycles may not represent the true symptom burden should everyone who initiated the chemotherapy treatment complete all planned cycles.

Limitations

In addition to the limitations already discussed, there are several others that should be considered when interpreting our results. We did not have a consistent measure of symptom severity in the medical records. Duration of symptoms was also often poorly documented by physicians. Therefore, our results are not directly comparable with studies such as the MDASI that incorporate severity or duration in their prevalence measure. There may also be "reporting bias" by the clinicians owing to different perceived levels of severity or clinical relevance of the different symptoms. As a result, some symptoms may be underdocumented, leading to undercounting.

We also did not distinguish the exact cause of the symptoms (ie, owing to anemia, cancer, chemotherapy itself, or other chemotherapy-induced complications), as it was not possible to reliably ascertain the cause from record review. Furthermore, symptom assessment was not separately performed for grade 4 anemia because of the small number of events in the study population. We also did not plan to

evaluate the impact of anemia treatment on symptom burden, as our goal was to comprehensively describe a wide spectrum of symptoms experienced by patients with different Hb levels. However, previous studies have shown the benefit of treatments that correct CIA in symptom management.[14-16] Finally, this study does not inform about the relative importance of these symptoms to patients' quality of life. To this end, a qualitative study found fatigue, shortness of breath, and lightheadedness/dizziness to be the most important symptoms ranked by patients with CIA.[22]

Despite the potential limitations, our study has several important strengths. In addition to fatigue, patients with CIA suffer from a wide range of other anemia-related symptoms, but data on the prevalence of these symptoms have been lacking. To our knowledge, this is among the first studies that collected data on a comprehensive list of symptoms and provided detailed analysis by chemotherapy cycle and anemia grade. The combined use of KPSC's clinical databases and medical record review allowed us to provide detailed characterization of the study population in terms of their treatment history, history of comorbidities, and laboratory data.

Conclusions

Our data provide physicians a comprehensive picture of prevalence of various types of symptoms and how symptom burden evolves as chemotherapy cycle and anemia severity progress. High-grade CIA correlates with an increased symptom burden. Such an understanding can be crucial in facilitating supportive care planning by helping physicians anticipate the timing and proactively determine the management approach of chemotherapy-related anemia and its symptoms.

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The challenge of managing a cetuximab rash

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Epidermal growth factor receptor antibodies (EGFR) such as cetuximab have been approved for use as first-line management as well as salvage therapy for head and neck and colorectal cancers. Among the most common expected toxicity is a cutaneous eruption described as acneiform. The presence of a rash has been postulated to predict a more favorable treatment outcome for cancers of the head and neck[1] but not for colorectum.[2] With more severe drug reactions, patients may require a treatment break, which has been shown to reduce locoregional control and survival, particularly in patients with head and neck cancer.[3] This has prompted clinicians to affect rapid therapy to reverse the drug eruption. Given the controversy around rapid and effective reversal of this drug reaction, this report aims to address the current status of clinical management using an actual patient vignette.

Case presentation and summary

The patient was a 57-year-old white man who had been diagnosed with stage 4 T4N0M1 grade 3 cutaneous squamous cell carcinoma (SCC) of the right postauricular soft tissues, with erosion into the right mastoid and biopsy-proven metastatic disease involving the contralateral left supraclavicular fossa and bilateral lungs. His disease became chemotherapy-refractory, and he was referred for palliative local therapy to the base of skull. Because of the size of the tumor (4 cm × 5 cm), he was considered for sensitizing chemotherapy, but cisplatin was not appropriate because of chronic hearing loss.[4] The patient was recommended sensitizing doses of cetuximab. This EGFR antibody has been shown to offer similar benefits to those seen with cisplatin in the definitive management of head and neck SCC.[5]

The standard loading dose of cetuximab was given at 400 mg/m^2 intravenously (IV). The following week, the sensitizing dose of 250 mg/m^2 IV was given along with daily radiotherapy to the target volumes. The weekly dose of cetuximab continued at 250 mg/m^2. The radiotherapy prescription was for 6,000 cGy in 200 cGy daily fractions, encompassing the gross tumor volume as identified on a computed-tomographic scan with 3-mm cuts. We used a noncoplanar arc radiotherapy beam arrangement because it inherently spreads the dose over a larger volume of normal tissue while conformally delivering its largest dose to the gross tumor volume. As such, a volume of the patient's oropharynx and oral cavity was included within the radiotherapy dose penumbra. After receiving 3 weekly doses of cetuximab (1 loading dose and 2 weekly sensitizing doses) and 2,000 cGy of radiotherapy, the patient developed a robust grade 2 cutaneous eruption delimited to the face, with few scattered lesions on the upper anterior chest. He was seen in the medical oncology department and was prescribed doxycycline 100 mg orally twice daily and topical clindamycin 2% ointment twice daily.

In the radiation oncology clinic, his drug therapy was manipulated. His cetuximab cutaneous reaction was a grade 2, manifested by moderate erythema with nonconfluent moist desquamation. Because of concern that the patient would develop oral candida, which would further delay his therapy, the oral and topical antibiotics were discontinued, as was the oral prednisone. He was prescribed triamcinolone cream 0.1% to be applied to the facial and few chest wall areas twice daily and an oncology mouth rinse to address early nonconfluent mucositis. The accompanying images show the extent of the patient's cetuximab cutaneous reaction at baseline before

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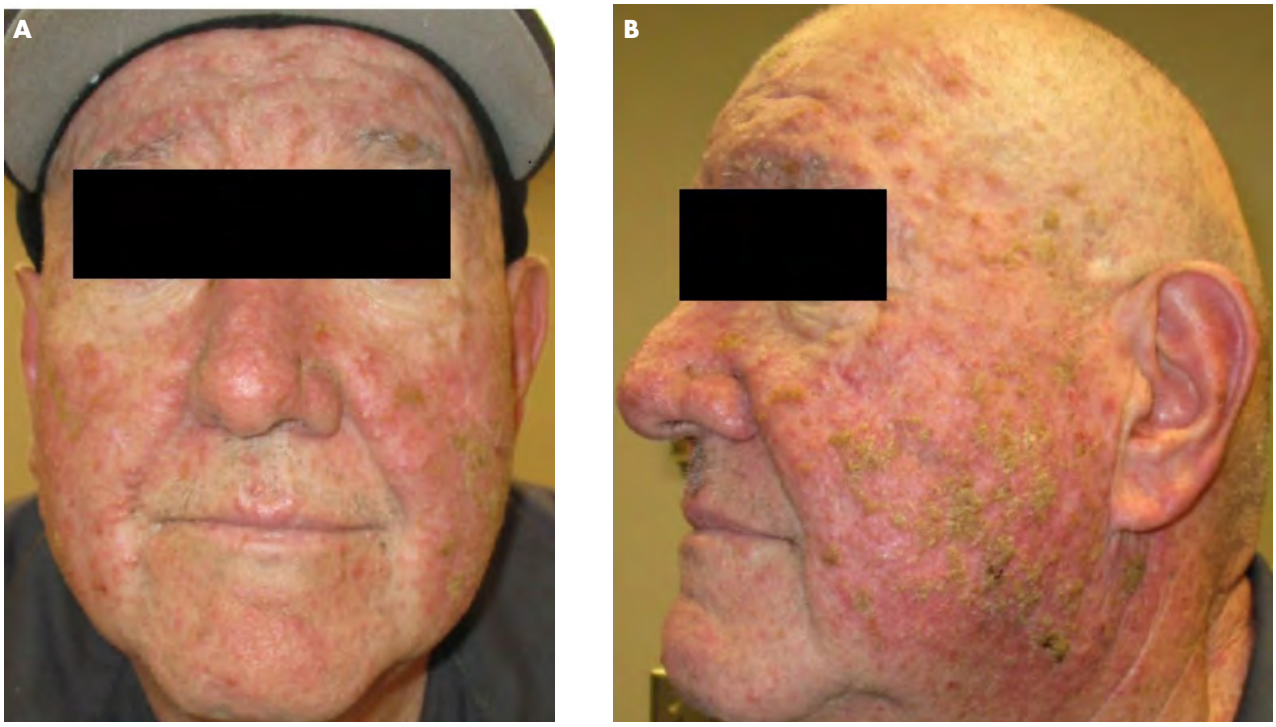

FIGURE 1 The patient at baseline, before treatment initiation for a robust grade 2 cetuximab cutaneous reaction manifested by moderate erythema with nonconfluent moist desquamation. **A**, front view, and **B**, side view.

treatment initiation (Figure 1), at 4 days after the intervention (Figure 2), and again at 6 days after the intervention (Figure 3). The patient consented to having his photographs taken and understood that they would be used for educational and research publication purposes.

As can be seen from the photographs, the patient's rash began to dry and peel by day 4 after the intervention, and there were no new eruptions. The pruritus that accompanied the rash had entirely resolved. By day 6, the rash had completely subsided. Because of the response to the topical steroid, the patient continued cetuximab without a dose modification. He was recommended to continue with the triamcinolone cream until the chemoradiotherapy course concluded.

Discussion

A cetuximab-induced rash is common. In a 2011 meta-analysis quantifying grades 1 to 4 in severity, about 75% of patients treated with an EGFR inhibitor experienced a rash. Most of the rashes were lower than grade 3, and the drug was either dose-reduced or temporarily held, but it was not generally discontinued.[6] Of note is that in a nonselected survey of medical oncologists who were prescribing cetuximab, 76% reported holding the drug owing to rash severity, 60% reported dose reductions for a drug rash, and 32% reported changing the drug because of rash severity.[7]

In the initial pharmaceutical registration trial, 76% to

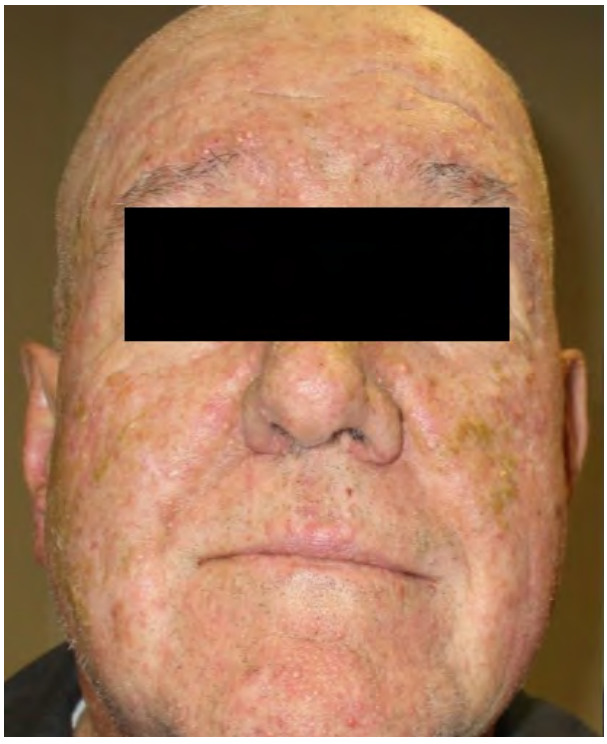

FIGURE 2 The patient 4 days after intervention with doxycycline 100 mg orally twice daily and topical clindamycin 2% ointment twice daily for a grade 2 cetuximab cutaneous reaction.

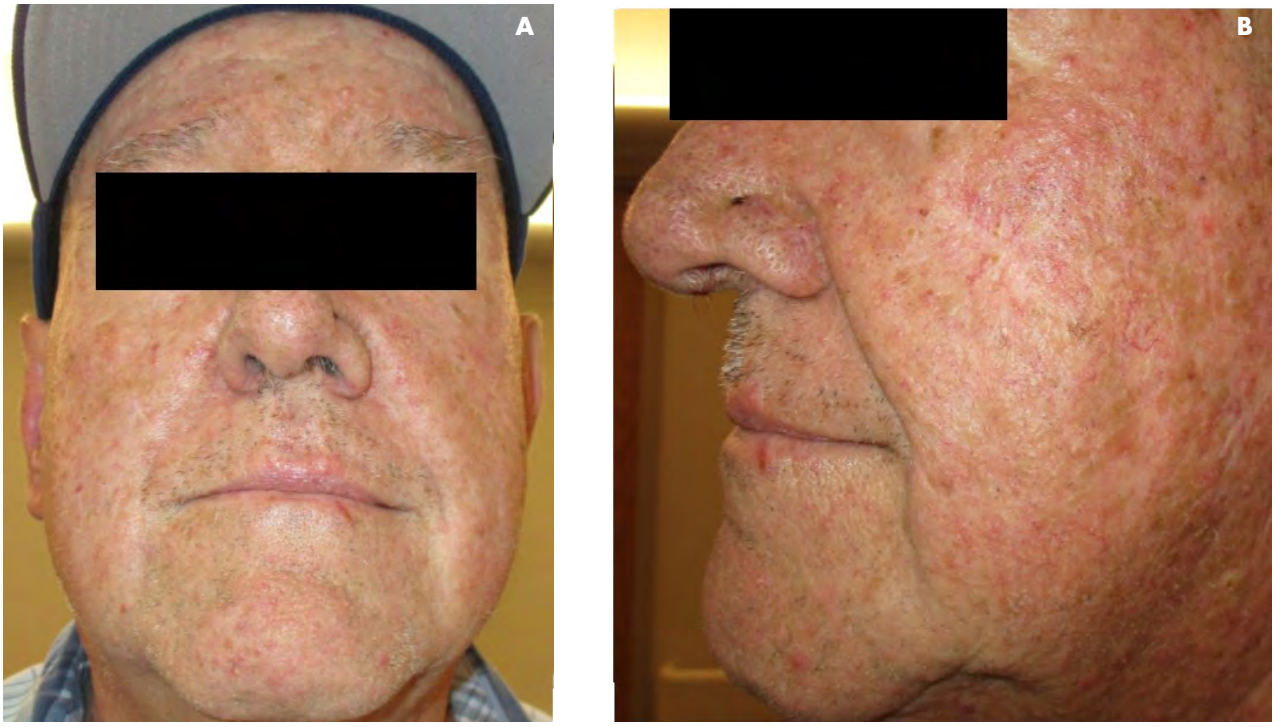

FIGURE 3 The patient 6 days after intervention with doxycycline 100 mg orally twice daily and topical clindamycin 2% ointment twice daily for a grade 2 cetuximab cutaneous reaction. **A**, front view, and **B**, side view.

88% of patients who received cetuximab developed a rash, 17% of which were at least grade 3. The pharma recommendations for managing the drug rash include a drug delay for up to 2 weeks for a rash of grade 3 or less and to terminate use of the drug if there is no clinical improvement after 2 weeks.[8] Biopsies of the rash confirm a suppurative inflammatory reaction separate from an infectious acne reaction,[9] resulting in a recommendation to treat with topical steroid therapy. In some circumstances, the drug reaction can become infected or involve the paronychia, often related to *Staphylococcus aureus*.[10] Despite what would otherwise be a problem addressed by anti-inflammatory medical therapy, the clinical appearance of the rash marked by pustules, coupled with the relative immunosuppressed state of a cancer patient, has prompted medical oncologists to prescribe antibiotic therapy.

To address the many single-institutional reports on management of the EGFR rash, several guidelines have been published. The earliest guideline – after a report that concurrent cetuximab and radiotherapy was superior to radiotherapy alone in locally advanced head and neck cancer, which documented a 23% incidence of at least grade 3 cutaneous toxicity in the cetuximab arm[1] – attempted to score the severity of the rash according to the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE). Under those criteria, the authors defined grade 2 toxicity as moderate to brisk erythema with patchy moist desquamation, mostly confined to skin folds and creases. Grade 3 toxicity was described as moist desquamation other than skin folds and creases with bleeding induced by minor trauma, and grade 4 skin toxicity was defined as skin necrosis or ulceration of full thickness dermis with spontaneous bleeding from the involved site. The authors went on to describe a grade-related treatment algorithm that included gently washing the skin, keeping it dry, and using topical anti-inflammatory agents, including steroids. Antibiotics should be used in the presence of a suspected infection after culturing the area, and grade 4 toxicity should be referred to a wound care center.[11]

In a consensus statement from the National Comprehensive Cancer Network, the authors noted that most management recommendations were anecdotal. They recommended against the use of astringents and other drying agents because they exacerbate pain. The ultimate choice of topical steroids or antibiotics was based entirely on subjective judgement given the absence of prospective data.[12]

A Spanish consensus conference report argued against any prophylaxis against a skin reaction, other than keeping the skin clean and dry.[13] The authors of the report recommended against washing the affected skin more than twice a day to avoid excess drying, and they advocated for moisturizers and debridement of skin crusting with hydrogels to reduce superinfection and bleeding.[13] The authors also noted that some guidelines have suggested that topi-

cal steroids might exacerbate a skin rash,[14] but they concluded that topical steroids are beneficial as long as they are used for less than 2 weeks. Any use of antibiotics should be based on clear evidence of an infection.[13]

In the first modification of the NCI's CTCAE rash grading scale, an international panel addressed the increasing number of reports in the literature suggesting that the previous toxicity scale was possibly inadequate in its recommendations for appropriate treatment. The initial scale had defined only the skin reaction and not what therapy should be administered; therefore, in the update, the descriptions for grades 1 and 2 toxicity remained unchanged, but oral antibiotics were recommended for grade 3 lesion, and parenteral antibiotics with skin grafting were required with grade 4 toxicity.[15]

An Asian expert panel suggested modifying the bioradiation dermatitis scale, defining a grade 3 dermatitis as >50% moist desquamation of the involved field with formation of confluent lesions because of treatment. They recommended both topical and oral therapy, wound care, and possible hospitalization in severe cases. The panel suggested topical and systemic steroids and antibiotics.[16]

Finally, in an Italian consensus report, the members again modified the skin toxicity grading and were notably more aggressive in terms of their management recommendations. They defined grade 2 toxicity as pustules or papules covering 10% to 30% of the body surface area, with potential pruritus or tenderness. They also noted the psychosocial impact of skin toxicities on patients and the limits to their activities of daily living. They recommended vitamin K1 (menadione) cream, topical antibiotics, topical intermediate potency steroids, and oral antibiotic therapy for up to 4 weeks for grade 2 toxicity. Despite this aggressive treatment course, the authors admitted that the utility of topical steroids and antibiotics was unknown. They defined grade 3 toxicity as pustules or papules covering more than 30% of the body surface area, with signs of possible pruritus and tenderness. Activities of daily living and self-care were affected, and there was evidence of a superinfection. The panel suggested use of antibiotics pending culture results, oral prednisone, antihistamines, and oral analgesics. Topical therapy was not included.[17] It is noteworthy that only the Italian panel recommended the use of vitamin K1 cream. In a prospective randomized, double-blinded, placebo-controlled phase 2 trial of 30 patients, menadione exhibited no clinical benefit in terms of reducing the severity of cetuximab skin lesions.[18]

Figure 4 illustrates our institutional approach to treating cetuximab rash based on a combination of the Spanish and NCI approaches.

The ultimate choice of therapy to manage a cetuximab rash must be patient and treatment specific. Our institutional approach, like that of the Spanish series,[13] is to avoid chemoprophylaxis against a rash; rather, we recommend daily washing of the skin with a gentle soap followed by thorough rinsing and adequate, nonaggressive drying. Moisturizing the intact skin has been shown to reduce exfoliation, and we have incorporated that approach into our regimen.[19]

In our patient, whose head and neck radiotherapy tumor volume included a portion of the oral cavity and oropharynx, systemic antibiotic and steroid therapy would likely lead to further complications with the development of oral candidiasis. Therefore, while the severity of the reaction remained a grade 2, it seemed appropriate to treat with topical intermediate potency steroids and skin cleansing only. If the reaction had become more severe, then cultures would have been obtained to guide our decision on antibiotic therapy. Our patient's response to topical steroids was predictable and effective, and he was able to proceed with his course of cancer therapy.

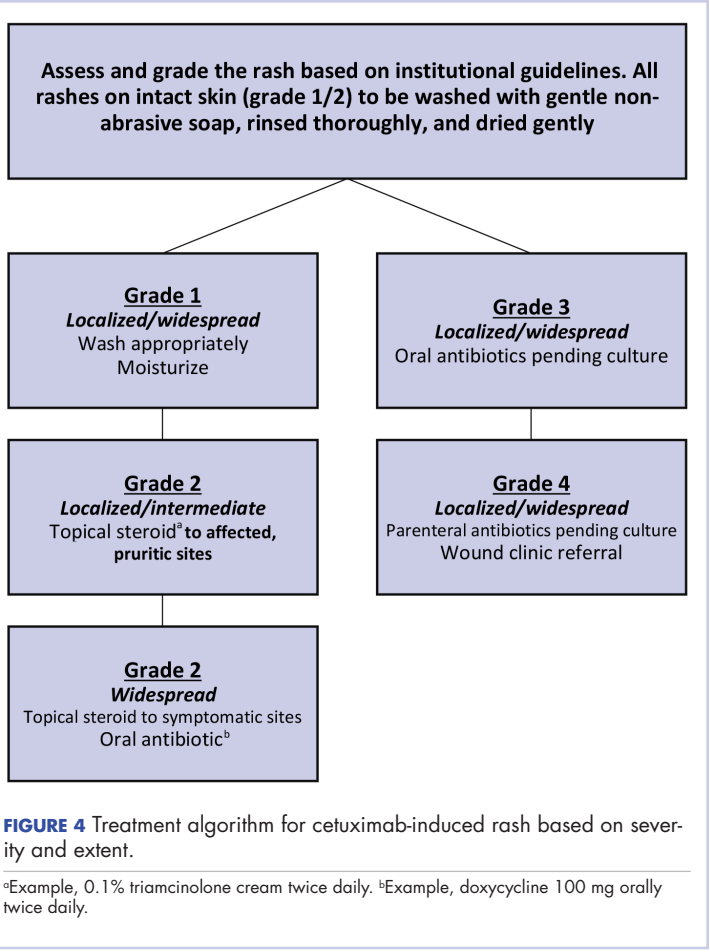

FIGURE 4 Treatment algorithm for cetuximab-induced rash based on severity and extent.

[a]Example, 0.1% triamcinolone cream twice daily. [b]Example, doxycycline 100 mg orally twice daily.

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Elevated liver function tests in a patient on palbociclib and fulvestrant

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About 12.4% of women in the United States will be diagnosed with breast cancer at some point in their lifetime.[1] A percentage of these women will develop metastatic disease and are estimated to have a 5-year survival rate of 22%.[2] There have been meaningful improvements in survival because of earlier detection and more effective systemic therapies. Patients with hormone-sensitive disease often respond to endocrine therapy, and this frequently represents front-line treatment for these patients, resulting in palliation of symptoms while maintaining quality of life.

However, endocrine resistance inevitably occurs, and a great deal of research has been focused on developing strategies to combat resistance. One mechanism of endocrine resistance is though the Cyclin-dependent kinases 4 and 6 (CDK4/6) complexes. Among the most promising of the strategies to prevent resistance are the CDK4/6 inhibitors. There are now 3 approved CDK4/6 inhibitor drugs that can be used in combination with endocrine therapy, 1 of which can also be used as a single agent. When used in combination with endocrine therapy, the use of CDK 4/6 inhibitors has significantly improved progression-free survival (PFS) in patients with hormone-sensitive *HER2*-negative metastatic breast cancer by inhibiting cellular division and growth.[3] In postmenopausal women, endocrine therapy plus CDK4/6 inhibitors are the preferred first-line regimen for metastatic disease.

Since the approval of palbociclib by the US Food and Drug Administration in 2015, the most common hematologic lab abnormalities are anemia, leukopenia, neutropenia, and thrombocytopenia. The most common nonhematologic adverse events (AEs) are fatigue, infection, nausea, and stomatitis. Hepatic toxicity has not been commonly observed. We report here the case of a 57-year-old woman on palbociclib and fulvestrant who developed significant elevation of liver function tests after starting palbociclib, suggesting a possible drug-induced liver injury from palbociclib.

Case presentation and summary

A 57-year-old woman with history of hypothyroidism and hypertension presented in May 2016 with a lump in her right breast and back pain. The lump was biopsied and revealed invasive ductal carcinoma, moderately differentiated, estrogen receptor (ER) positive 100%, progesterone receptor (PR) positive 95%, and *HER2* negative. A positron emission tomography (PET)–computed tomography (CT) scan and magnetic resonance imaging showed bone metastasis at several vertebral levels, and the results of a bone biopsy confirmed metastatic adenocarcinoma of breast origin, ER positive 60%, PR positive 40%, and *HER2* negative. No liver lesions were seen on imaging, but there was suggestion of fatty liver. She was started on letrozole 2.5 mg daily in July 2016 while undergoing kyphoplasty and subsequent radiation. A restaging PET scan revealed progression of disease on letrozole, with possible new rib lesion and progression in the breast. No liver disease was noted. Therapy was changed to fulvestrant and palbociclib. Fulvestrant was started in March 2017 with standard dosing of 500 mg intramuscular on days 1, 15, and 29, and then once a month thereafter. Her first cycle of palbociclib was started on April 5, dosed at 125 mg by mouth daily for 21 days, followed by 7 days off, repeated every 28 days (all dates hereinafter fell within 2017, unless otherwise stipulated).

Labs checked on April 28 and May 26 were unremarkable. A restaging CT scan of the chest, abdomen, and pelvis was done on June 21 after completion of 3 cycles of fulvestrant and palbociclib. There was no evidence of liver metastases, only the fatty infiltration of the liver that had been seen previously.

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On June 23, 2017, lab results showed a transaminitis with an alanine aminotransferase (ALT) level of 446 IU/L (reference range 10-33 IU/L) and aspartate aminotransferase (AST) level of 183 IU/L (reference range 0-32 IU/L).

The patient's liver enzyme levels continued to increase and peaked on July 3 at ALT >700 IU/L and AST at 421 IU/L. Her total bilirubin and alkaline phosphatase levels remained within normal limits. She had received her final dose of fulvestrant on May 31 and had taken her last dose of palbociclib on June 20, 2017. She had no history of elevated liver enzymes or liver disease, although the initial PET scan done at diagnosis had suggested hepatic steatosis. She said she had not recently used antibiotics, alcohol, or over-the-counter medications or supplements. There was no family history of liver problems, inflammatory bowel disease, or gastrointestinal malignancy. The only other medications she had taken recently were denosumab, levothyroxine for hypothyroidism, and amlodipine for hypertension. She was seen by hepatology for evaluation of acute hepatitis. Other etiologies for her elevated liver enzymes were ruled out, and she was diagnosed with a drug-induced liver injury from one of her anticancer medications. Her treatments with fulvestrant and palbociclib were held, and the results of her liver function tests normalized by September 2017.

Fulvestrant was restarted on August 24, and her lab results remained normal through November of that year, when restaging scans showed progression with new axillary adenopathy suspicious for metastasis. Imaging also showed a 1.6-cm hepatic lesion suggestive of a focal area of fat deposition or atypical hemangioma without definitive evidence of metastasis. Follow-up imaging was recommended. She was therefore rechallenged with palbociclib at a reduced dose of 100 mg by mouth daily and received the first dose on November 30. On December 8, repeat labs again showed elevated liver function tests (ALT, 285 IU/L; AST, 112 IU/L). Treatment with palbociclib was discontinued on December 10. Because the patient was not able to tolerate palbociclib, and fulvestrant alone was not controlling the disease, she was started on an alternate endocrine therapy with tamoxifen on December 26. The patient's liver function tests normalized again by January 2018.

Discussion

The use of targeted therapies has changed the landscape of oncologic treatments. Several studies have evaluated the safety and efficacy of palbociclib in combination with endocrine therapy. The Palbociclib Ongoing Trials in the Management of Breast Cancer (PALOMA)-1 study, an open-label, randomized, phase-2 trial involving patients with newly diagnosed metastatic hormone sensitive *HER2*-negative breast cancer, demonstrated that palbociclib in combination with letrozole was associated with significantly longer PFS than letrozole alone.[4] These results were later confirmed in the larger PALOMA-2 study, a randomized, double-blind, phase-3 trial that evaluated 666 postmenopausal patients with no prior systemic therapy. In that study, median PFS for the palbociclib–letrozole group was 24.8 months, compared with 14.5 months for the letrozole-alone group (hazard ratio [HR] for disease progression or death, 0.58 [0.46–0.72], $P < .001$).[5] The most recent PALOMA-3 study, a phase-3 trial involving 521 patients with advanced hormone receptor–positive, *HER2*-negative breast cancer that had progressed during initial endocrine therapy, evaluated the efficacy of combined palbociclib and fulvestrant in a randomized, double-blind, placebo-controlled, parallel-group trial. The result was that the palbociclib–fulvestrant combination resulted in longer median PFS of 9.2 months, compared with 3.8 months with fulvestrant alone ($P < .001$).[6]

These trials also monitored the number of AEs as secondary aims. The most commonly reported AEs in the PALOMA trials for those patients in the palbociclib group were hematologic, with neutropenia being the most common, followed by leukopenia, anemia, and thrombocytopenia. The most common nonhematologic AEs reported in the palbociclib-fulvestrant group were fatigue, nausea, and headache. Elevated liver function tests were a rare but reported AE in 7.2% of the palbociclib-treated patients in the PALOMA-1 study.[7] In the PALOMA-2 study, ALT and AST elevations were reported as AEs (all grades) in 9.9% and 9.7% of palbociclib-treated patients, respectively.[5] In the PALOMA-3 study, there was 1 fatal serious AE of hepatic failure with grade 5 disease progression in the palbociclib group; however, the patient's medical history included progressive liver metastasis and disease progression.[6] A pooled safety analysis conducted across all PALOMA studies demonstrated that grade 3/4 AST and ALT elevations occurred in 3.3% and 2.3% of palbociclib-treated patients, respectively, again highlighting a reported but rare occurrence.[8]

The patient described in the present case report started on combination fulvestrant and palbociclib after her disease showed progression on letrozole. She developed an increase in transaminases after completing 3 cycles of palbociclib. Liver function tests increased nearly 12 weeks after beginning her first cycle of the CDK 4/6 inhibitor. Staging scans of the patient demonstrated fatty liver. It is not known if her fatty liver contributed to her transminitis; however, her baseline labs showed normal liver function tests, and they did not increase until after therapy with fulvestrant–palbociclib was started. It might have been that her fatty liver caused her to be at higher risk of transaminitis with administration of palbociclib, although we cannot be certain. Her lab results remained normal while she was on fulvestrant alone, and the liver function test results increased only after palbociclib was started, making this drug the more likely culprit.

Both events of increased liver enzymes occurred within a week of the last palbociclib dose; however, we note that hepatotoxicity developed at a faster rate when the patient was rechallenged with palbociclib at a lower dose, with elevated liver function tests increasing 1 week after restarting treatment as opposed to the first episode that occurred after 3 cycles of the palbociclib. After discontinuation of the medication, liver function tests again normalized, suggesting that palbociclib was most likely the causative agent. In addition, the degree of elevated liver enzymes was less severe on re-exposure at the lower dose of 100 mg, which raises the possibility that there could be a dose-dependent association between palbociclib and hepatotoxicity. There have been few case reports of increased liver enzymes associated with palbociclib, and it is only recently that this association has been more recognized. A meta-analysis by Zaw and colleagues has demonstrated that CDK 4/6 inhibitor–based regimens are associated with a higher risk of elevated AST and ALT; however, their relation with dose dependence was not described. In particular, they found that CDK 4/6 inhibitors increased the risk of high-grade, elevated ALT with a relative risk of 4.33 (95% confidence interval, 2.15-8.71; $P < .0001$). The meta-analysis also included other CDK 4/6 inhibitors such as abemaciclib and ribociclib, which have been more commonly associated with liver toxicity than palbociclib has.[9] Our case report highlights the specific association between palbociclib and elevated liver enzymes.

In conclusion, this case report illustrates that our patient's elevated liver enzymes were likely related to palbociclib. This is further supported by the fact that this AE occurred twice, both times after palbociclib exposure. In each instance, liver enzymes normalized after discontinuation of palbociclib. One cannot entirely rule out that fulvestrant might have been the culprit medication, but the patient's normal hepatic panel for several months after starting fulvestrant suggests that is less likely. This case report is indicative of an uncommon complication in the treatment of metastatic breast cancer, one that is starting to gain more recognition, and we must think of palbociclib as a possible cause of drug-induced liver injury when targeted CDK 4/6–based regimens are used.

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Intravascular large B-cell lymphoma: an elusive diagnosis with challenging management

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Intravascular large B-cell lymphoma (IVBCL) is an aggressive and systemically disseminated disease that affects the elderly, with a median age of diagnosis around 70 years and no gender predilection. It is a rare subtype of extranodal diffuse large B-cell lymphoma (DLBCL) characterized by selective growth of neoplastic cells within blood vessel lumen without any obvious extravascular tumor mass. Hence, an absence of marked lymphadenopathy and heterogeneous clinical presentation make it difficult to diagnose accurately and timely, with roughly half of the cases found postmortem in previous case reports.[1,2] The exact incidence of this disease is not known, but more recently, the accuracy of diagnosis of this type of lymphoma has improved with random skin and bone marrow biopsy.[1,2] We present here a clinical case of this disease with an atypical presentation followed by a detailed review of its clinical aspects.

Case presentation and summary

A 43-year-old white woman with a history of hypothyroidism and recurrent ovarian cysts presented to clinic with 3 months of loss of appetite, abdominal distension, pelvic pain, and progressive lower-extremity swelling. A physical examination was notable for marked abdominal distension, diffuse lower abdominal tenderness, and pitting lower-extremity edema. No skin rash or any other cutaneous abnormality was noted on exam. Laboratory test results revealed a lactate dehydrogenase (LDH) level of 1652 U/L and a CA-125 level of 50 U/mL (reference range, 0-35 U/mL). No significant beta-human chorionic gonadotropin and alpha-fetoprotein levels were detected. Computed-tomographic (CT) imaging revealed small bilateral pleural effusions and gallbladder wall thickening with abdominal wall edema, but it was otherwise unrevealing. An echocardiogram showed normal cardiac structure and function, with a left ventricular ejection fraction of 60%. No protein was detected in the patient's urine, and thyroid function tests were unrevealing. Doppler ultrasound studies of her lower extremities and abdomen revealed no thrombosis. Given the patient's continued pelvic pain, history of ovarian cysts, and elevation in CA-125, she underwent a laparoscopic total abdominal hysterectomy and bilateral salpingoopherectomy.

Histologic examination revealed neoplastic cells involving only the vascular lumina of the cervix, endomyometrium, bilateral fallopian tubes, and bilateral ovaries (Figure 1). Immunohistochemistry stains were positive for CD5, CD20, PAX-5, CD45, BCL-2, and BCL-6 and focally positive for CD10. Peripheral smear showed pseudo-Pelger–Huet cells with 5% atypical lymphoma cells (Figure 2). Complete staging with positron-emission and CT (PET–CT) imaging revealed no metabolic activity, and a bone marrow biopsy showed trilineage hematopoiesis with adequate maturation and less than 5% of the marrow involved with large B-cell lymphoma cells. A diagnosis of IVBCL was made.

Further work-up to rule out involvement of the central nervous system (CNS) included magnetic-resonance imaging (MRI) of the brain and cerebrospinal fluid (CSF) cytology and flow cytometry, which were negative.

Our patient underwent treatment with 6 cycles of infusional, dose-adjusted R-EPOCH (rituximab, etoposide phosphate, prednisone, vincristine sulfate, cyclophosphamide, doxorubicin hydrochloride) and 6 doses of prophylactic intrathecal chemotherapy with alternating methotrexate and cytarabine (Ara-C),

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and initial and subsequent CSF sampling showed no disease involvement. Consolidation with high-dose chemotherapy with R-BEAM (rituximab, carmustine, etoposide, Ara-C [cytarabine], melphalan) followed by rescue autologous stem cell transplantation (ASCT) was performed, and the patient has remained in clinical and hematologic remission for the past 24 months.

Discussion

Clinical presentation

The clinical manifestation of this disease is highly variable, and virtually any organ can be involved. Besides causing constitutional symptoms, including fatigue, B symptoms, and decline in performance status, heterogeneity of the clinical presentation depends on the organ system involved. One of the exceptional features of this disease is the difference in clinical presentation based on the geographical origin of the patient.[2-4]

Western-variant IVBCL has a higher frequency of CNS and skin involvement, whereas Asian-variant IVBCL shows preferential involvement of bone marrow with hemophagocytosis, hepatosplenomegaly, and thrombocytopenia. However, these 2 clinical variants have no difference in clinical outcome, except with the cutaneous-variant kind.[2,4] A retrospective case series of 38 Western-variant IVBCL cases showed that 55% of patients had B symptoms with poor performance status.[3] Brain and skin were the organs that were most frequently involved, with 68% of patients having involvement of at least 1 of those organs. Ten patients in this case series had disease that was exclusively limited to the skin and described as a "cutaneous variant" of IVBCL.[3]

Similarly, a retrospective case series of 96 cases of Asian-variant IVBCL showed B symptoms in 76% of patients, with predominant bone marrow involvement in 75% of patients, accompanied by hemophagocytosis in 66% and hepatosplenomegaly and anemia/thrombocytopenia in 77% and 84% of the patients, respectively.[4] This difference in clinical presentation might have existed as a result of ethnic difference associated with production of inflammatory cytokines, including interferon gamma, tumor necrosis factor-alpha, interlukin-1 beta, and soluble interlukin-2 receptor, with levels of soluble interlukin-2 receptor found to be significantly higher in Asian patients than non-Asian patients.[2]

Diagnosis

Involved organ biopsy is mandatory for establishing the diagnosis of IVBCL. Laboratory findings are nonspecific, with the most common abnormality being increased serum LDH and beta-2 microglobulin levels observed in 80% to 90% or more of patients. Despite its intravascular growth pattern, IVBCL was associated with peripheral blood involvement in only 5% to 9% of patients.[1]

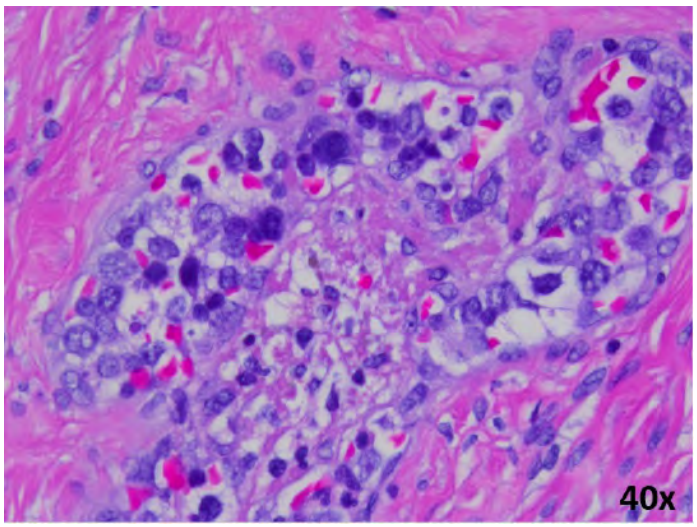

FIGURE 1 Large atypical lymphoma cells (some hyperchromatic/dark nuclei, many with vesicular/bubbly chromatin, can be seen with some red blood cells) within the vascular lumina (H&E stain, 40×)

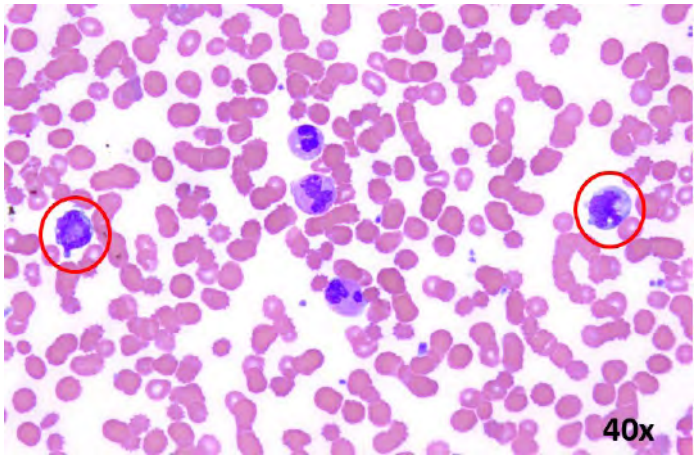

FIGURE 2 Peripheral blood smear showing large atypical lymphoid cells circled red (Wright-Giemsa Stain, 40×)

Staging

Clinical staging work-up suggested for IVBCL patients by International Extranodal lymphoma study group in 2005 included physical examination (with emphasis on nervous system and skin), routine blood studies, peripheral blood smear, total body CT scan with contrast or PET–CT scan, MRI brain with contrast, CSF cytology, and bone marrow or organ biopsy.[1] The role of fluorodeoxyglucose-PET scan is controversial but can be helpful to detect unexpected locations for biopsy and to assess treatment response.[5,6]

Morphology and immunophenotyping

In general, IVBCL histopathology shows large neoplastic lymphoid cells with large nuclei along with one or more

nucleoli and scant cytoplasm within blood vessel lumen. Immunophenotypically, IVBCL cells mostly express non-germinal B-cell–associated markers with CD79a (100%), CD20 (96%), MUM-IRF4 (95%), CD5 (38%), and CD10 (12%) expressions. IVBCL cells have been demonstrated to lack cell surface protein CD29 and CD54 critical to transvascular migration. Similarly, aberrant expression of proteins such as CD11a and CXCR3 allows lymphoma cells to be attracted to endothelial cells, which might explain their intravascular confinement.[7]

Genetics

No pathognomic cytogenetic abnormalities have been reported in IVBCL to date, and the genetic features of this disease are not yet completely understood.[2,7]

Management

IVBCL is considered a stage IV disseminated disease with an International Prognostic Index score of high-intermediate to high in most cases. Half of the patients with IVBCL who were treated with anthracycline-based chemotherapy relapsed and died within 18 months of diagnosis. One third of the relapses involved the CNS, thereby highlighting the importance of prophylactic CNS-directed Intrathecal therapy in an induction treatment regimen.[2-4] Ferreri and colleagues reported in their case series response rates of about 60%, with an overall survival (OS) of 3 years of 30% in patients who were treated with anthracycline-based chemotherapy. A multivariate analysis of the entire series showed cutaneous variant of the disease to be an independent favorable prognostic factor for OS.[3]

In the Murase and colleagues case series, the authors reported 67% response rates and a median OS of 13 months with CHOP (cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone) or CHOP-like regimens. Multivariate analysis showed older age, thrombocytopenia, and absence of anthracycline-based chemotherapy to be an independent negative prognostic factor for OS.[4] Another retrospective analysis by Shimada and colleagues of 106 patients with IVBCL showed improved outcome with the addition of rituximab to CHOP-based chemotherapy (R-CHOP). Complete response rate (CR), 2-year progression-free survival, and OS were significantly higher for patients in rituximab-chemotherapy group than for those in the chemotherapy-alone group (CR, 82% vs 51%, respectively, $P = .001$; PFS, 56% vs 27%; OS, 66% vs 46%, $P = .001$), thereby establishing rituximab with CHOP-based therapy as induction therapy for IVBCL patients.[8]

The role of high-dose chemotherapy followed by ASCT could also be used as consolidation therapy to improve clinical outcomes as reported in 7 patients, showing durable remission after transplant in these 2 case series.[3,4] Another retrospective analysis of 6 patients with IVBCL who were treated with 6 cycles of R-CHOP as induction therapy and consolidated with ASCT reported all patients to be alive and in complete remission after a median follow-up of 56 months.[9] Based on the retrospective case series data by Kato and colleagues and considering that more than 80% of the patients with IVBCL were in the high-risk International Prognostic Index group, ASCT in first remission might be a useful treatment option for durable remission; however, because the median age for the diagnosis of IVBCL is about 70 years, ASCT may not be a realistic option for all patients.

Conclusions

IVBCL is a rare, aggressive, and distinct type of DLBCL with complex constellations of symptoms requiring strong clinical suspicion to establish this challenging diagnosis. Rituximab with anthracycline-based therapy along with prophylactic CNS-directed therapy followed by consolidative ASCT may lead to long-term remission. More research is needed into the genetic features of this disease to better understand its pathogenesis and potential targets for treatment.

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Emerging biosimilars market presents opportunities and challenges

Jane de Lartigue, PhD

The development of biologic therapies has led to some of the most significant advances in the treatment of cancer, but these drugs are also very expensive. As patents for the biologics begin to expire, the development of biosimilars has the potential to dramatically cut therapy costs thereby making the therapies more readily accessible to patients. Here, we discuss biosimilar development and the challenges that need to be overcome to create a robust market.

Biosimilar, not generic

Biologic therapies are derived from living organisms and include the targeted monoclonal antibodies (mAbs) and cell-based therapies that have revolutionized the treatment of certain cancer types. Yet, their greater complexity makes them more difficult to manufacture, store, and administer, making them a costly therapeutic option that ultimately drives up health care costs. According to a 2011 drug expenditure analysis, biologic therapies accounted for more than half of the total expenditure on anticancer drugs in the US health care system.[1,2]

Generally, when drug patents expire, other companies can develop their own identical generic versions to increase competition in the marketplace and drive down costs. However, the paradigm for generic development cannot be applied to biologic therapies because the way in which they are manufactured makes it impossible to generate an identical copy.

Instead, the Biologics Price Competition and Innovation Act, a provision of the Patient Protection and Affordable Care Act, has allowed for submission of an application for "licensure of a biologic product based on its similarity to a licensed biologic product".[3]

These "biosimilars" have been positioned as game-changers in oncology, with the potential to reduce costs and improve access to biologic therapies. With the patents on several blockbuster cancer biologics already expired or due to expire by 2020, an increasing number of biosimilars are being developed.[4]

Totality of evidence

Biosimilars require more rigorous testing than generics, but they don't require the same type of scientific data that the original biologic products, termed "reference products," did. Therefore, they are governed by legislation unique to them and approved by different regulatory pathways. The US Food and Drug Administration (FDA) has established a unique shortened regulatory pathway for their approval, known as the 351(k) pathway. So whereas the pathway for reference products is geared toward demonstrating patient benefit, biosimilars are required instead to show equivalence to the reference product.[5]

Biosimilars are produced through reverse engineering the reference product. Then, through a stepwise process, to generate what the FDA calls a "totality of evidence," biosimilar manufacturers must demonstrate structural and functional similarities (through comparative quality studies) and comparable pharmacokinetics and pharmacodynamics (through comparative nonclinical and clinical studies) to the reference product. Final approval is based on 1 or more comparative clinical studies performed in the most sensitive patient population(s) (Figure 1).[6]

The primary endpoint of biosimilar clinical trials is chosen to detect clinically relevant differences and may not be the same as that used in pivotal trials of the reference product. Endpoints such as progression-free survival (PFS) and overall survival (OS) may not be feasible or sensitive enough to demonstrate biosimilarity.

Clinical trials of biosimilars should also be carried out in the most sensitive patient population, so that any potential differences can be attributed to the drug and not the patient population itself. If the reference product is approved across several different indications and there is sufficient scientific evidence to allow it, including the demonstration that the mechanism of action of the drug is the same across all indications, the FDA can extend the approval of the biosimilar to all of these indications without the need for individual clinical trials through a process known as extrapolation.

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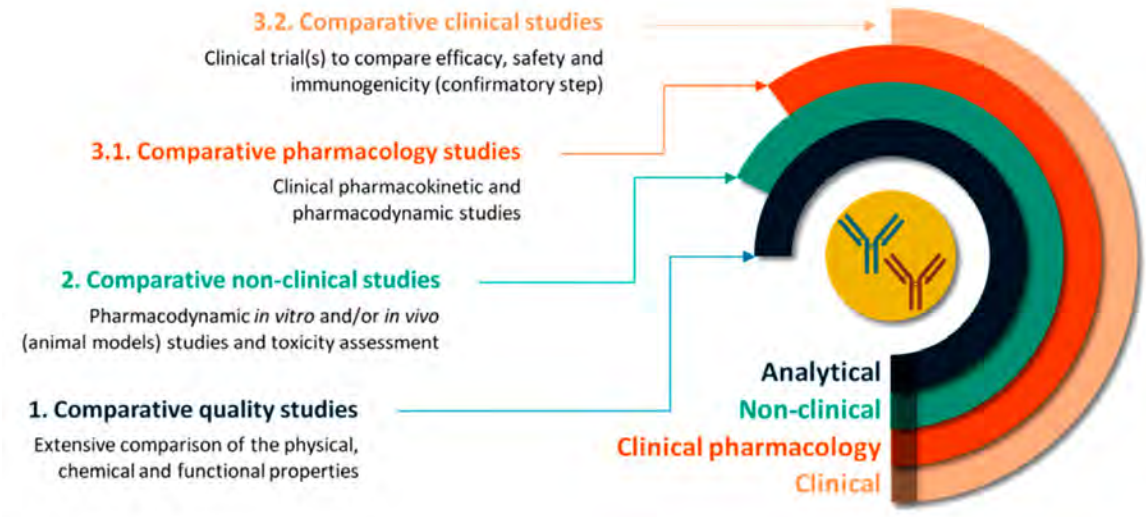

FIGURE 1 'Totality of evidence.' Development of biosimilars is a step-wise process that begins with analytical and nonclinical comparisons of the structural and functional characteristics of the proposed biosimilar to the already FDA-approved 'reference product'. Final approval is based on one or more comparative clinical studies performed in the most sensitive patient population(s). A decision by the FDA on whether or not to grant regulatory approval is based upon the 'totality of evidence' from this stepwise process, in addition to considerations relating to the manufacturing process.[6] Reproduced under a Creative Commons Attribution License.

Biosimilar manufacturers must also provide evidence of the composition of their formulation and of quality control in their manufacturing processes, to ensure that biosimilarity can be maintained from batch to batch. As with the reference product, even small changes in the manufacturing process can have serious ramifications for clinical efficacy and safety.[7,8]

A flurry of approvals

The first biosimilar approvals in oncology in the United States came in the supportive care niche (Table 1). Filgrastim-sndz (Zarxio), approved in March 2015, is a biosimilar of the granulocyte-macrophage colony stimulating factor (G-CSF) analog filgrastim (Neupogen). Owing to its mechanism of action in stimulating the production of neutrophils in the bone marrow, filgrastim is used to help reduce the risk or severity of neutropenia in patients undergoing myelosuppressive chemotherapy regimens.

Filgrastim-sndz was approved for use across all 5 indications for which the reference product is approved, based on the totality of evidence, which included results from the key phase 3 PIONEER study.[9] Market entry was initially delayed by lawsuits filed by Amgen, the maker of the reference product, but the biosimilar was subsequently cleared by the US Court of Appeals for the Federal Circuit. The wholesale acquisition cost (WAC) for a 300µg syringe is $324.30 for filgrastim and $275.66 figrastim-sndz, representing a 15% reduction on the reference product.[10]

In 2018, the FDA approved a second filgrastim biosimilar, filgrastim-aafi (Nivestym),[11] in addition to 2 biosimilars of the pegylated form of filgrastim, pegfilgrastim-jmdb (Fulphila)[12] and pegfilgrastim-cbqv (Udenyca)[13] – these forms of filgrastim have been modified by the addition of polyethylene glycol polymer chains that help to increase circulation time.

Approval for the 2 pegfilgrastm biosimilars was originally delayed by complete response letters (CRLs) from the FDA. For pegfilgrastim-jmdb, the CRL was reported to be related to a pending update of the Biologic's License Application (BLA) to include information regarding facility requalification activities that had been taken after the addition of plant modifications. The CRL for pegfilgrastim-cbqv requested that the company provide additional manufacturing information and reanalyze a subset of samples with a revised immunogenicity assay.

Once the CRL concerns were addressed, regulatory approval was awarded and Mylan recently confirmed that pegfilgrastim-jmdb has been launched in the US marketplace at a WAC that reflects a 33% discount over the reference product.[14]

Approval data for filgrastim-aafi and pegfilgrastim-cbqv have not yet been published, however the respective manufacturers reported that approval was based on totality of evidence demonstrating a high degree of similarity to the reference products. Filgrastim-aafi was approved for all of the indications of the reference product and launched in the US on October 1, 2018 at a 30% discounted WAC.[15]

Epoetin alfa-epbx (Retacrit), a biosimilar of epoetin alfa, was also approved in 2018. It is a recombinant analog of erythropoietin (EPO), which stimulates the production of

TABLE 1 Biosimilars approved by the US food and Drug Administration as of November 4, 2018

Drug	Manufacturer	Reference product/MOA	Approved indications
Filgrastim-sndz (Zarxio)	Sandoz	Filgrastim (Neupogen)/ GM-CSF	Supportive care to reduce the risk or severity of FN in patients with cancer receiving myelosuppressive chemotherapy
FIlgrastim-aafi (Nivestym)	Pfizer	Filgrastim (Neupogen)/ GM-CSF	Supportive care to reduce the risk or severity of FN in patients with cancer receiving myelosuppressive anticancer treatment or undergoing bone marrow transplantation and in patients with AML receiving induction or consolidation chemotherapy
Pegfilgrastim-jmdb (Fulphila)	Mylan	Pegfilgrastim (Neulasta)/ GM-CSF	Supportive care to reduce the risk or severity of FN in patients with cancer receiving myelosuppressive chemotherapy or undergoing bone marrow transplantation and in patients with AML receiving induction or consolidation chemotherapy
Pegfilgrastim-cbqv (Udenyca)	Coherus	Pegfilgrastim (Neulasta)/ GM-CSF	Supportive care to reduce the risk or severity of FN in patients with cancer receiving myelosuppressive chemotherapy
Epoetin alfa-epbx (Retacrit)	Pfizer	Epoetin alfa (Epogen, Procrit)/ESA	Supportive care to reduce the risk of anemia in patients with cancer receiving myelosuppressive chemotherapy, when there is a minimum of 2 additional months of chemotherapy planned
Trastuzumab-dkst (Ogivri)	Mylan/Biocon	Trastuzumab (Herceptin)/ HER2-targeting mAb	Treatment of patients with HER2-positive breast cancer and metastatic gastric or GEJ adenocarcinoma
Bevacizumab-awwb (Mvasi)	Amgen/Allergan	Bevacizumab (Avastin)/ VEGF-targeting mAb	Treatment of metastatic colorectal cancer in combination with 5-FU-based chemotherapy in first- or second-line settings or with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy in first-line setting; of unresectable, locally advanced, recurrent or metastatic nonsquamous NSCLC in combination with carboplatin and paclitaxel in first-line setting; of progressive GBM; of metastatic RCC in combination with IFN-alpha; of persistent, recurrent or metastatic cervical cancer in combination with paclitaxel and topotecan

5-FU, 5-fluorouracil; AML, acute myeloid leukemia; BMT, bone marrow transplant; ESA, erythropoiesis stimulating agent; FN, febrile neutropenia; GBM, glioblastoma; GEJ, gastroesophageal junction; GM-CSF, granulocyte-macrophage colony stimulating factor; HER2, human epidermal growth factor receptor 2; IFN-alpha, interferon alpha; NSCLC, non–small-cell lung cancer; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor

blood cells and has proved useful for the treatment of anemia, including in cancer patients receiving myelosuppressive chemotherapy. Approval of the biosimilar followed earlier receipt of a CRL from the FDA citing concerns relating to the manufacturing facility, which the company addressed. Pfizer has said that it expects to launch the biosimilar this year (2018), but a WAC has not been disclosed.[16]

The FDA also recently approved the first biosimilars for the treatment of cancer. Trastuzumab-dkst (Ogivri) and bevacizumab-awwb (Mvasi) were approved in the second half of 2017 for the same indications as their respective reference products, which are mAbs directed at the human epidermal growth factor receptor 2 (HER2) and vascular endothelial growth factor, respectively.[17,18]

Approval data for bevacizumab-awwb included a comparative clinical trial in patients with advanced/metastatic non–small-cell lung cancer (NSCLC), which was considered the most sensitive patient population. The BLA for trastuzumab-dkst included data from the phase 3 comparative HERiTAge clinical trial, in which the biosimilar was compared with the reference product, both in combination with docetaxel or paclitaxel, in patients with previously untreated HER2-positive metastatic breast cancer. Neither biosimilar has been launched on the US market yet because the patents for their reference products do not expire until 2019, so it is not clear what the price discount will be for these drugs (Table 2).[9,19-22]

Biosimilars in development

While numerous other biosimilars of filgrastim and pegfilgrastim are in development, the major focus has been on the development of more biosimilars to treat cancer (Table 3). BLAs have been submitted for 4 biosimilars of trastuzumab and 1 bevacizumab biosimilar. Approval for several of the trastuzumab biosimilars has been delayed by CRLs from the FDA, mostly regarding issues with the manufacturing process or facility. Several other trastuzumab and bevacizumab biosimilars are in late-stage clinical trials.

TABLE 2 Phase 3 comparative trial data for biosimilar therapies and their corresponding reference products

Drug	Trial design	Key data
Filgrastim-sndz (Zarxio)	vs US-approved Neupogen in 218 patients with breast cancer treated with myelosuppressive chemotherapy SC injection 5 µg/kg body weight a day from day 2 of each cycle until ANC recovered to 10 x 10^9 cells/L or for a max of 14 days	Mean DSN: 1.17 d (biosimilar) vs 1.20 d (reference product) AEs: 20.6% vs 19.6%[9]
Pegfilgrastim-jmdb (Fulphila)	vs EU-approved Neulasta in 194 chemotherapy and radiation-naïve patients with newly diagnosed breast cancer treated with myelosuppressive chemotherapy	Mean DSN: 1.2 d (biosimilar) vs 1.2 d (reference product) 95% CI of least squares means differences within -1 day, +1 day range[19]
Epoetin alfa-epbx (Retacrit)	Pooled analysis of 2 trials in patients with CKD	No clinically meaningful difference in efficacy Similar AE profile[20]
Trastuzumab-dkst (Ogivri)	vs EU-approved Herceptin in 458 patients with previously untreated HER2-positive MBC Loading dose of 8 mg/kg body weight and maintenance dose of 6 mg/kg every 3 weeks for a minimum of 8 cycles, continuing until progression Patients who had stable disease or better could continue treatment with trastuzumab (biosimilar or reference product) until disease progression	ORR: 70% (biosimilar) vs 67% (reference product) ; ratio, 1.09 Wk 48 PFS: 44.3% vs 44.7%. Wk 48 OS: 89.1% vs 85.1% Serious AEs: 39.3% vs 37% (most frequently neutropenia for both)[21]
Bevacizumab-awwb (Mvasi)	vs EU-approved Avastin in 642 patients with advanced/ metastatic NSCLC IV infusion 15 mg/kg every 3 weeks in combination with 6 AUC carboplatin and 200 mg/m^2 paclitaxel for 6 cycles	ORR: 39% (biosimilar) vs 41.7% (reference product); ratio, 0.93 mPFS: 6.6 months vs 7 months No meaningful differences in AEs or serious AEs Grade 3/4 AEs: 42% vs 44%[22]

DSN, duration of severe neutropenia; AE, adverse event; ANC, absolute neutrophil count; AUC, area under the curve; CI, confidence interval; CKD, chronic kidney disease; EU, European Union; HER2, human epidermal growth factor receptor 2; IV, intravenous; MBC, metastatic breast cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SC, subcutaneous

The results of several phase 3 comparative clinical trials were recently published or reported at annual conferences. Pfizer's PF-05280014 was compared with the European Union (EU)–approved trastuzumab, both in combination with paclitaxel, in patients with previously untreated HER2-positive metastatic breast cancer. Data reported at the European Society for Medical Oncology congress in 2017 demonstrated equivalence between the reference product and biosimilar in overall response rate (ORR).[23]

Another recently published trial compared this biosimilar to EU-trastuzumab, both in combination with carboplatin and docetaxel, as neoadjuvant treatment for patients with resectable HER2-positive breast cancer. Among 226 patients randomized to receive 8 mg/kg in cycle 1 and 6 mg/kg thereafter of the biosimilar or reference product, every 3 weeks for 6 cycles, the pathologic complete response (pCR) rates were 47% and 50%, respectively.[24]

The results of a phase 3 study comparing Samsung Bioepis/Merck's joint offering SB3 were recently published. A total of 875 patients were randomized 1:1 to receive SB3 or reference trastuzumab in combination with chemotherapy (4 cycles docetaxel followed by 4 cycles 5-fluorouracil/epirubicin/cyclophosphamide) prior to surgery, followed by 10 cycles of adjuvant SB3 or trastuzumab reference. Rates of event-free survival (EFS) were comparable between the 2 groups at 12 months (93.7% vs 96.1%, respectively).[25]

Amgen's ABP980 was evaluated in the phase 3 LILAC trial, which measured the effect of the biosimilar on pCR in women with HER2-positive early breast cancer compared with reference trastuzumab. After 4 cycles of run-in anthracycline-based chemotherapy, ABP980 or reference trastuzumab were administered in combination with paclitaxel. This was followed by surgery and then ABP980 or reference trastuzumab in the adjuvant setting for up to 1 year, with the option to continue on the same drug as the neoadjuvant setting or to switch to the other. Among 696 assessable patients, the pCR rates were 48% and 42%, respectively.[26]

Most advanced in clinical testing among the upcoming bevacizumab biosimilars is Pfizer's PF-06439535, for which the results of a phase 3 comparative trial were presented at the 2018 annual meeting of the American Society for Clinical Oncology. PF-06439535 was compared with the EU-approved bevacizumab, both in combination with paclitaxel and carboplatin, as first-line therapy for patients with advanced non-squamous NSCLC. Among 719 patients, the primary endpoint of ORR was 45.3% and 44.6%, respectively.[27]

Biosimilars of a third blockbuster cancer drug, the CD20-targeting mAb rituximab (Rituxan) are also in

TABLE 3 Biosimilars in development as of November 4, 2018

Drug (manufacturer)	Reference product	Stage of development
PF-05280014 (Pfizer)	Trastuzumab (Herceptin)	FDA approval pending; delayed by CRL (April 2018)
SB3 (Samsung Bioepis/Merck)	Trastuzumab (Herceptin)	FDA approval pending
ABP980 (Amgen)	Trastuzumab (Herceptin)	FDA approval pending; delayed by CRL (June 2018)
CT-P6/Herzumab (Celltrion)	Trastuzumab (Herceptin)	FDA approval pending; delayed by CRL (June 2018)
HLX-02 (Shanghai Henlius Biotech)	Trastuzumab (Herceptin)	Phase 3 comparative trial ongoing (NCT03084237)
AryoTrust (AryoGen)	Trastuzumab (Herceptin)	Phase 3 comparative trial ongoing (NCT03425656)
HD201 (Prestige Biopharma)	Trastuzumab (Herceptin)	Phase 3 comparative trial ongoing (TROIKE; NCT03013504)*
CT-P10/Truxima (Celltrion/Teva)	Rituximab (Rituxan)	FDA approval pending
PF-05280586 (Pfizer)	Rituximab (Rituxan)	FDA approval pending
ABP798 (Amgen/Allegan)	Rituximab (Rituxan)	Phase 3 comparative trial ongoing (NCT02747043)
SAIT0191 (Archigen Biotech)	Rituximab (Rituxan)	Phase 3 comparative trial ongoing (RAMO-2; NCT02809053)
PF-06439535 (Pfizer)	Bevacizumab (Avastin)	FDA approval pending
CT-P16 (Celltrion)	Bevacizumab (Avastin)	Phase 3 comparative trial ongoing (NCT03676192)
BEVZ92 (mAbxience)	Bevacizumab (Avastin)	Phase 1 trial completed, phase 3 comparative trial not yet launched
BI 695502 (Boehringer Ingelheim)	Bevacizumab (Avastin)	Phase 3 comparative trial ongoing (NCT02272413)*
SB8 (Samsung Bioepis)	Bevacizumab (Avastin)	Phase 3 comparative trial ongoing (NCT02754882)
Grastofil (Apotex)	Filgrastim (Neupogen)	FDA approval pending
Adello-filgrastim (Adello Biologics)	Filgrastim (Neupogen)	FDA approval pending
MYL-1401H	Pegfilgrastim (Neulasta)	FDA approval pending
Lapelga (Apotex)	Pegfilgrastim (Neulasta)	FDA approval pending
LA-EP2006 (Sandoz)	Pegfilgrastim (Neulasta)	FDA approval pending

FDA, United States Food and Drug Administration; CRL, complete response letter

development and FDA approval is pending for 2. The patent for Rituxan expired in 2016, so these drugs could hit the market as soon as they are approved.

In a race to the finish for the first US-approved rituximab biosimilar, Celltrion-Teva's CT-P10 (Truxima) seems most likely to come first; the Oncologic Drugs Advisory Committee voted unanimously in October 2018 to recommend its approval. Phase 3 comparative data were recently published; patients with newly diagnosed advanced-stage follicular lymphoma were randomized to receive intravenous infusions of 375 mg/m^2 CT-P10 or reference rituximab, both in combination with cyclophosphamide, vincristine, and prednisone, on day 1 of 8 21-day cycles. The ORRs were identical (92.6%) for both drugs, pharmacokinetics data also suggested bioequivalence, and the incidence of AEs was also comparable (83% vs 80%).[28]

Biosimilars of the epidermal growth factor receptor (EGFR)-targeting mAb cetuximab are also listed in the pipeline for several biosimilar developers, but there is no indication of their developmental status as yet and no clinical trials are ongoing in the US.

Sorrento is developing STI-001, a cetuximab biosimilar, and reported that a phase 3 trial had been completed. Instead of a comparison with the reference product, however, the trial compared STI-001 in combination with irinotecan with irinotecan alone. They reported significantly higher ORR, PFS, and OS with the biosimilar compared with irinotecan alone, and a significant increase over historical data with the reference product, as well as fewer side effects and immunogenicity, which they attribute to its manufacture in a different cell line. However, no data has been published and no trials are ongoing in the United States, so the status of its development remains unclear.[29]

Challenges to a robust market

It is an exciting time for biosimilars, with many approvals and drugs being brought to market in the US in the past several years and more poised to follow suit as patents expire. Yet many challenges remain around the growth of a robust biosimilars market.

Several surveys conducted in recent years have demonstrated suboptimal knowledge of all aspects of biosimi-

lars and highlighted the need for evidence-based education across specialties.[30,31] In response, the FDA recently announced that it was launching an educational campaign to further understanding of biosimilars, including naming conventions (Figure 2).[32,33] Numerous other medical professional societies have produced or are in the process of producing biosimilar guidelines.

Educational outreach by the FDA forms part of their 4-step plan to aid biosimilar development, which also aims to improve the efficiency of biosimilar development and approval, to provide regulatory clarity for manufacturers, to facilitate public understanding and acceptance, and to support a competitive marketplace.

Among the most critical educational gaps is confusion over the issue of interchangeability. Once approved by the FDA, generic drugs are considered interchangeable with the brand name drug and can be substituted at the pharmacy level without referring to the prescribing physician. This is not the case for biosimilars; owing to their more complex nature, biosimilars require a separate designation for interchangeability and none of those approved so far have been given this designation by the FDA.

There has been some confusion about what will be required to demonstrate interchangeability, and the FDA recently produced draft guidance, saying that essentially it should be proven that switching out the reference product for a biosimilar does not increase risk in terms of diminished efficacy or safety. Several companies are beginning to incorporate a switching component into their clinical trials of biosimilars.

Continued postmarketing and real-world studies will also be particularly important for biosimilars to increase confidence in prescribing them by demonstrating their continued efficacy and safety in the long-term. Several real-world studies are now ongoing, including the MONITOR-GCSF trial of filgrastim biosimilars.

Shared core name + distinct suffix

Filgrastim-	**sndz**
Filgrastim-	**aafi**
Pegfilgrastim-	**jmdb**
Pegfilgrastim-	**cbqv**

FIGURE 2 FDA nonproprietary naming conventions. An area of concern for pharmacists was the lack of clarity over naming conventions for biosimilars. In 2015, the FDA introduced guidance regarding this topic and they require that the nonproprietary names of biosimilars share a core that matches the reference product, each with a unique identifying suffix. Studies have shown that this naming convention engenders the greatest level of confidence in dispensing biosimilars.[32,33]

Another major barrier to the development of a thriving biosimilars market that achieves the goals of reduced costs and increased access is the financial burden of their development. They are vastly more costly to develop and produce than generics. Added to litigation costs, this can limit their ability to compete in terms of price, which has been reflected in the lower-than-anticipated cost savings with some approved biosimilars thus far.

Experts have suggested that there might be much to learn from the European market, where biosimilars have been available for more than a decade and over time have reached even higher-than-expected savings. With high financial stakes and an increasingly important role in the treatment of cancer, the need to iron out the kinks is more pressing than ever.[7,8,34,35]

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Trio of biosimilars have good showing

Susan London

Biosimilars for three widely used oncology drugs showed efficacy and safety in lung cancer and breast cancer similar to those of the reference products, according to findings reported at the 2018 annual meeting of the American Society of Clinical Oncology in Chicago.

Oncology biosimilars for bevacizumab (Avastin), trastuzumab (Herceptin), and filgrastim (Neupogen and others) have yielded positive results in various patient populations and clinical settings, investigators reported at the annual ASCO meeting. The findings advance the promise of new agents that have no clinically meaningful differences in efficacy and safety when compared with their reference drugs but have substantially lower cost.

"Biosimilars are here," said Michael A Thompson, MD, PhD, of Aurora Health Care in Milwaukee, Wisconsin, "[although] issues remain, including clinical decision support and pathway adoption, naming differences across the world, competition and lower prices versus the illusion of a free market, and adoption to decrease costs and increase value to our patients." Dr Thompson was commenting during an invited discussion at the meeting. He is the medical director of the Early Phase Cancer Research Program and the Oncology Precision Medicine Program at Aurora Health (also see Commentary, p. e292).

Bevacizumab biosimilar

The REFLECTIONS trial (NCT02364999) was a multinational, first-line, randomized, controlled trial among 719 patients with advanced nonsquamous non–small-cell lung cancer (NSCLC). Patients were randomized to paclitaxel and carboplatin chemotherapy plus either bevacizumab (sourced from the European Union) or the candidate bevacizumab biosimilar PF-06439535 on a double-blind basis, followed by monotherapy with the same assigned agent.

DR SOCINSKI

The overall response rate by week 19, confirmed by week 25 – the trial's primary endpoint – was 45.3% with the biosimilar and 44.6% with bevacizumab, reported lead author Mark A Socinski, MD, executive medical director of the Florida Hospital Cancer Institute in Orlando. The confidence interval (CI) for the risk difference fell within the equivalence margins set by European Union regulators (-13% and +13% for the 95% CI). And the confidence interval for the risk ratio fell within the equivalence margins set by the US Food and Drug Administration (0.73 and 1.37 for the 90% CI) and Japanese regulators (0.729 and 1.371 for the 95% CI).

Median progression-free survival (PFS) was 9.0 months with the biosimilar and 7.7 months with bevacizumab (hazard ratio [HR], 0.974; P = .814), and corresponding 1-year rates were 30.8% and

Study takeaways

Key clinical points Biosimilars for bevacizumab, trastuzumab, and filgrastim showed similar efficacy and safety compared with their reference drugs. **Major findings** *Bevacizumab* In patients with advanced nonsquamous NSCLC, the ORR was 45.3% with a candidate bevacizumab biosimilar and 44.6% with bevacizumab. *Trastuzumab* In patients with HER2+ advanced breast cancer, 48-week median PFS was 11.1 months for both trastuzumab-dkst and trastuzumab. *Filgrastim* The rate of chemotherapy-induced febrile neutropenia among breast cancer patients given a biosimilar for filgrastim was 5.1% in a trial population and 6.2% in a real-world population. **Study details** Randomized, controlled trials of first-line therapy among 719 patients with advanced nonsquamous NSCLC (REFLECTIONS trial with bevacizumab) and among 458 patients with HER2+ advanced breast cancer (HERITAGE trial with trastuzumab). Comparison of outcomes in a randomized, controlled trial among 217 patients with nonmetastatic breast cancer (PIONEER trial with filgrastim) and a real-world cohort study of 466 patients with any-stage breast cancer (MONITOR-GCSF with filgrastim). **Disclosures and sources** See pp. e291 and e293.

JCSO 2018;16(6):e290-e293.

29.3%, respectively, Dr Socinski reported. Median overall survival was 18.4 months and 17.8 months (HR, 1.001; *P* = .991), and corresponding 1-year rates were 66.4% and 68.8%.

Rates of grade 3 or higher hypertension, cardiac disorders, and bleeding did not differ significantly with the 2 agents. Patients also had similar rates of grade 3 or higher serious adverse events (AEs) and of fatal (grade 5) serious AEs with the biosimilar and bevacizumab (5.3% and 5.9%, respectively).

"Similarity between PF-06439535 and bevacizumab-EU was demonstrated for the primary efficacy endpoint of overall response rate. ... There were no clinically meaningful differences in safety profile shown in this trial, and similar pharmacokinetic and immunogenicity results were seen across treatment groups," Dr Socinski summarized. "These results confirm the similarity demonstrated in earlier analytical, nonclinical, and clinical studies of PF-06439535 with bevacizumab-EU."

Funding Pfizer sponsored the REFLECTIONS trial. **Disclosures** Dr Socinski disclosed that his institution receives research funding from Pfizer. **Source** Socinski MA et al. A comparative clinical study of PF-06439535, a candidate bevacizumab biosimilar, and reference bevacizumab, in patients with advanced non-squamous non-small cell lung cancer. ASCO 2018, Abstract 109. https://meetinglibrary.asco.org/record/161702/abstract. **Clinical trial registry number** NCT02364999 https://clinicaltrials.gov/ct2/show/NCT02364999

Trastuzumab biosimilar

The phase 3 HERITAGE trial was a first-line, randomized, controlled trial that compared biosimilar trastuzumab-dkst (Ogivri) with trastuzumab in combination with taxane chemotherapy and then as maintenance monotherapy in 458 patients with HER2+ advanced breast cancer. The 24-week results, previously reported (JAMA. 2017 Jan 3;317[1]:37-47), showed a similar overall response rate with each agent when combined with chemotherapy. Rates of various AEs were essentially the same.

The 48-week results showed a median PFS of 11.1 months with trastuzumab-dkst and 11.1 months with trastuzumab (HR, 0.95; *P* = .842), reported senior investigator Hope S Rugo, MD, a clinical professor of medicine and director of the Breast Oncology Clinical Trials Program at the University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center. "The overall survival is immature but is impressive at over 80% at 52 weeks," she noted.

Presence of overall response at 24 weeks correlated with duration of PFS at 48 weeks (biserial r = .752). "Additional patients achieved a response during the monotherapy portion of the treatment, which is intriguing and clearly emphasizes the importance of monotherapy, as well as the importance of having alternate agents at lower cost available," Dr Rugo commented.

Common AEs through week 48 were much the same as those seen at week 24, with few additional [events] occurring during monotherapy. "No new safety issues were observed, and in fact, toxicity during monotherapy was quite minor," she noted. "One thing that's interesting here is that there was more arthralgia during the first 24 weeks with trastuzumab-dkst than with trastuzumab, but in monotherapy, this fell to a very low number and was identical between the 2 arms. Paclitaxel, which people stayed on for longer [with the biosimilar], may have been the cause of this."


DR RUGO

The 48-week rates of AEs of special interest – respiratory events, cardiac disorders, and infusion-related AEs – and of serious AEs were similar for the 2 agents.

"We didn't see any additional serious cardiac events during monotherapy," Dr Rugo noted. Mean and median left ventricular ejection fraction over 48 weeks were similar, as was the rate of LVEF, which dropped below 50% (4.0% with trastuzumab-dkst and 3.3% with trastuzumab). The incidences of antidrug antibody and neutralizing antibody were also comparably low in both groups.

"HERITAGE data, now at week 48, supports trastuzumab-dkst as a biosimilar to trastuzumab in all approved indications," Dr Rugo said. "Final overall survival will be assessed after 36 months or after 240 deaths, whichever occurs first. Based on current data, this is predicted to conclude by the end of 2018, with final overall survival data available next year."

Dr Rugo emphasized that trastuzumab-dkst provides "an additional high-quality treatment option for patients with HER2+ breast cancers in any setting. This study shows that biosimilars offer the potential for worldwide cost savings and improved access to life-saving therapies. It's sobering to think that the patients enrolled in this study would not otherwise have had access to continued trastuzumab therapy, and so many of them are still alive with longer follow-up."

Funding Mylan sponsored the HERITAGE trial. **Disclosures** Dr Rugo disclosed that she receives travel, accommodations, and/or expenses from Mylan. **Source** Manikhas A et al. Biosimilar trastuzumab-dkst monotherapy versus trastuzumab monotherapy after combination therapy: Toxicity, efficacy, and immunogenicity from the phase 3 Heritage trial. ASCO 2018, Abstract 110. https://meetinglibrary.asco.org/record/161572/abstract. **Clinical trial registry number** NCT02472964 https://clinicaltrials.gov/ct2/show/NCT02472964

Incorporating biosimilars into cancer care

A variety of issues are influencing whether and how clinicians incorporate biosimilars into cancer care, according to Michael A Thompson, MD, PhD, of Aurora Health Care in Milwaukee, Wisconsin.

"Competition is highly relevant to biosimilars," Dr Thompson said at the ASCO annual meeting, with questions being raised about whether the oncology drug market is a free market, whether competition lowers drug prices, who owns the biosimilar companies, and whether, if biosimilars don't decrease drug cost, we should bother pursuing them. "We are seeing examples in which the biosimilars have been developed, they appear to work, they appear safe, and really the proof will be [to what extent that] is pushing the market to decrease cost," he noted.

Real-world data provide some insight into how biosimilars are being incorporated into oncology care. For example, in patients with non-Hodgkin lymphoma, hematologists tend to use rituximab (Rituxan) biosimilars in later lines of therapy, in patients with a better performance status and fewer comorbidities, and in cases of indolent or incurable disease (J Clin Oncol. 2018;36[suppl; abstr 112]). "So it appears that prescribers are acting tentatively to cautiously test the waters," Dr Thompson said.

Use will be influenced by clinical decision support and pathways, whether those are developed by institutions or insurers. These tools generally look at efficacy first, safety second, and cost third.

The relevance of patient choice (especially when physicians decreasingly have a choice) and perception of biosimilars may, or may not, be important, according to Dr Thompson. In some areas of medicine, there is evidence of a nocebo effect: Patients perceive worsening of symptoms when they believe they are getting a nonbranded medication, although that might not be valid in oncology, where many older chemotherapy drugs, the generics, are already being used, he said.

DR THOMPSON

ASCO recently published a statement on the use of biosimilars and related issues, such as safety and efficacy; naming and labeling; interchangeability, switching, and substitution; and the value proposition of those agents (J Clin Oncol. 2018 Apr 20;36[12]:1260-5).

One concern about the uptake of biosimilars is the possibility of an actual increase in patient cost related to single sources and potentially differing reimbursement rates, which could diminish the financial benefit of these drugs. Technically, if biosimilars have similar efficacy and safety, and lower cost, they provide greater value than the reference drugs.

But there may still be reasons for not using a higher-value drug, according to Dr Thompson. Clinicians may have lingering questions about efficacy and safety despite trial data, a situation that is being addressed in Europe by postmarketing pharmacovigilance. Other issues include delays in pathway implementation and pharmacies contracting with companies. "These are all minor but potential barriers to as fast an implementation as possible," he said.

— Dr Michael A Thompson is the medical director of the Early Phase Cancer Research Program and the Oncology Precision Medicine Program at Aurora Health Care in Milwaukee, Wisconsin.

Filgrastim biosimilar

Investigators led by Nadia Harbeck, MD, PhD, head of the Breast Center and chair for Conservative Oncology in the department of OB&GYN at the University of Munich (Germany), compared efficacy of filgrastim-sndz (Zarxio), a biosimilar of filgrastim (recombinant granulocyte colony-stimulating factor, or G-CSF), in a trial population with that of a real-world population of women receiving chemotherapy for breast cancer.

DR HARBECK

Data for the former came from PIONEER, a phase 3, randomized, controlled trial among patients with nonmetastatic breast cancer undergoing docetaxel, doxorubicin, and cyclophosphamide (TAC) chemotherapy in the neoadjuvant or adjuvant setting (Ann Oncol. 2015;26[9]:1948-53). Data for the latter came from MONITOR-GCSF, a postmarketing, open-label, observational cohort study among patients from 12 European countries receiving chemotherapy for various solid and hematologic malignancies (Support Care Cancer. 2016;24[2]:911-25).

Dr Harbeck and her colleagues compared 217 women who had nonmetastatic breast cancer from the trial with 466 women who had any-stage breast cancer (42% metastatic) from the real-world cohort.

Results showed that the 6.2% rate of chemotherapy-induced febrile neutropenia in any cycle seen in the real-world population was much the same as the 5.1% rate seen previously in the trial/biosimilar population. Findings were similar for temperature exceeding 38.5°C in any cycle: 3.4% and 5.6%, respectively. The real-world population had a lower rate of severe neutropenia than did the trial population (19.5% and 74.3%) and higher rates of infection (15.5% and 7.9%) and hospitalization caused by febrile neutropenia (3.9% and 1.8%). Findings were essentially the same in cycle-level analyses.

The real-world cohort had many fewer any-severity safety events of special interest than did the trial cohort, such as musculoskeletal/connective tissue disorders (20 and 261 events, respectively) and skin/subcutaneous tissue disorders (5 and 258 events). "Seeing these data, you have

to keep in mind that the patients received totally different chemotherapy. TAC chemotherapy has a lot of chemotherapy-associated side effects," Dr Harbeck noted. "The other thing is that MONITOR was a real-world database, and one could assume that there is some underreporting of events that are not directly correlated to the events that are of particular interest."

Additional results available only from the trial showed that no patients developed binding or neutralizing antibodies against G-CSF.

"From a clinician's point of view, it is very reassuring that we did not see any other safety signals in the real-world data than we saw in the randomized controlled trial and the efficacy was very, very similar," Dr Harbeck commented. "Having seen the discrepancies in the data, I think it's important to have randomized controlled trials to assess and monitor AEs for registration purposes and real-world evidence to reflect the daily clinical routine," she concluded.

Funding Sandoz sponsored the PIONEER and MONITOR-GCSF trials. **Disclosures** Dr Harbeck disclosed that she has a consulting or advisory role with Sandoz. **Source** Harbeck N et al. Comparison of efficacy and safety of biosimilar filgrastim in a RCT (PIONEER) and real-world practice (MONITOR-GCSF). ASCO 2018, Abstract 111. https://meetinglibrary.asco.org/record/161688/abstract. **Clinical trial registry number** NCT01519700 https://clinicaltrials.gov/ct2/show/NCT01519700

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