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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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FRONTLINE MEDICAL COMMUNICATIONS

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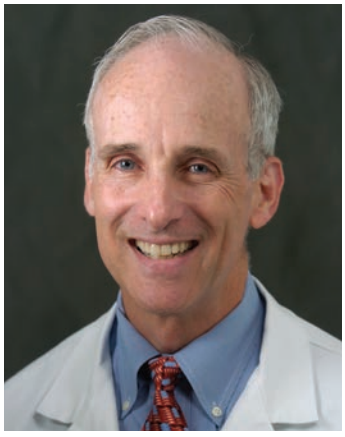
Biosimilars: same ol' – but with a suffix, and cheaper

David Henry, MD, FACP

Biosimilars have arrived, and chances are that you're already prescribing them. Last September, the US Food and Drug Administration (FDA) approved the first cancer-specific biosimilar, bevacizumab-awwb, for multiple cancer types (p. e60);[1] and in November, it approved trastuzumab-dkst for HER2-positive breast and gastrointestinal cancers (p. e63).[1] Briefly, biosimilars are biologic products that show comparable quality, efficacy, and safety to an existing, approved biologic known as the reference product.



Small-molecule drugs such as aspirin are easy to replicate identically, whereas biosimilars are large, complex proteins that are manufactured in nature's factory, a microorganism or biologic cell.[2] The manufacturing process must be nearly identical to that for the reference product, so that only insignificant/nonclinically significant impurities occur in the final product. The protein-amino acid sequence is key and must therefore be identical. The 2010 Biologics Price Competition and Innovation Act established an abbreviated pathway for the FDA to consider and approve biosimilars, and 5 years later, the bone marrow stimulant filgrastim-sndz became the first biosimilar approved for use in the United States.[3]

The development of biosimilars is not inexpensive. The law and the FDA approval system require preclinical and phase 1 testing, and a robust phase 3 trial against the reference product to demonstrate that safety and efficacy are statistically not different and that any chemical differences between the biosimilar and reference product are clinically and safety or immunogenically insignificant. When those criteria have been met, and the biosimilar approved, the clinical and cost benefits to patients could be significant. In general, the cost of a biosimilar is about 20% to 30% lower than that of the reference product.

Biosimilarity does not yet allow interchangeability. Small-molecule generics under FDA regulations are interchangeable in the drug store and the hospital without the prescriber or patient being aware. That is not yet the case with biosimilars, but their lower prices could have a notable impact on overall cost of care. In 2013, 7 of the top 8 best-selling drugs in the global market were biologics.[4] Three of the top 8 – rituximab, trastuzumab, and bevacizumab – were used to treat cancer, and 1 (pegfilgrastim) was for therapy-related neutropenia. Their total cost was US$27 billion. Biosimilars of those therapies could significantly lower that amount.

Nabhan and colleagues interviewed 510 US-based community oncologists about their understanding of biosimilars. They found that only 29% of respondents said they prescribed filgrastim-sndz for supportive care by personal choice, but upward of 73% said they would prescribe biosimilars for the active anticancer therapies, trastuzumab and bevacizumab. There's no question that biosimilars are here to stay. The requirements to make them have been well worked out. Their safety and efficacy therefore can be assured, and their lower prices promise cost savings for patients and society as a whole.

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Correspondence: David Henry, MD; David.Henry@uphs.upenn.edu. Disclosures: Dr Henry reports no disclosures or conflicts of interest.
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Bevacizumab-awwb becomes first biosimilar approved for cancer treatment

Targeted therapies have revolutionized the treatment of numerous different cancer types and ushered in an era of personalized medicine, yet they can be prohibitively costly. As patent protection expires on many of the first FDA-approved monoclonal antibodies developed for oncologic indications, the doors are opened for other companies to develop their own version of these drugs, known as biosimilars. The price of biosimilars is expected to be considerably lower than the original drugs upon which they are based.

Bevacizumab-awwb, marketed as Mvasi by Amgen and Allergen, became the first such drug to receive approval by the US Food and Drug Administration for the treatment of cancer in fall last year.[1] It is a biosimilar of Genentech's anti-angiogenesis drug, bevacizumab (Avastin), a monoclonal antibody that targets vascular endothelial growth factor-A (VEGF-A).

The approval of biosimilars is based on rigorous demonstration of a high level of similarity between the biosimilar and the already-approved reference drug, in terms of structure, function, pharmacokinetics, pharmacodynamics, and clinical efficacy and safety.

Bevacizumab-awwb was approved for the first- or second-line treatment of metastatic colorectal cancer (mCRC) in combination with 5-fluorouracil-based chemotherapy; the second-line treatment of mCRC in combination with fluoropyrimidine-oxaliplatin chemotherapy in patients who progressed on first-line bevacizumab; the first-line treatment of unresectable, locally advanced, recurrent or metastatic nonsquamous non-small cell lung cancer (NSCLC) in combination with carboplatin and paclitaxel; the second-line treatment of glioblastoma (GBM) as monotherapy; and in patients with persistent, recurrent, or metastatic cervical cancer in combination with paclitaxel and cisplatin or paclitaxel and topotecan. It was not approved for the treatment of ovarian cancer, for which bevacizumab is indicated.

The majority of the data used to support approval came from 2 studies – a 3-arm, single-dose pharmacokinetics study, and a comparative clinical study in patients with advanced/metastatic NSCLC. In the pharmacokinetics study, 202 healthy men received an infusion of 3 mg/kg of bevacizumab-awwb, US-approved bevacizumab, or EU-approved bevacizumab. Bevacizumab-awwb was shown to have pharmacokinetic similarity to both approved forms of bevacizumab, and safety and tolerability were comparable, with none of the participants developing binding or neutralizing antidrug antibodies.[2]

In the clinical study, 648 patients received an infusion of bevacizumab-awwb or EU-approved bevacizumab at a dose of 15 mg/kg every 3 weeks in combination with 6 AUC carboplatin and 200 mg/m^2 paclitaxel for 6 cycles. The overall response rate was 39% for bevacizumab-awwb, compared with 41.7% for EU-bevacizumab, and there were 2 complete responses in each group. The median duration of response for bevacizumab-awwb compared with EU-bevacizumab was 5.8 months versus 5.6 months,

What's new, what's important

Bevacizumab-awwb, marketed as Mvasi, became the first biosimlar approved for the treatment of cancer. It is a biosimilar of the anti-angiogenesis drug, bevacizumab (Avastin), a monoclonal antibody that targets vascular endothelial growth factor-A and was approved for numerous cancer types. In terms of safety, the rates of grade 3/4 adverse events were 42.9% in the biosimilar arm, compared with 44.3% for the reference drug. Overall, there were no clinically meaningful differences in AEs, serious AEs, deaths, or treatment discontinuations.

The recommended dose for bevacizumab-awwb in patients with mCRC is a 5 mg/kg intravenous dose administered every 2 weeks with bolus-IFL, a 10 mg/kg IV dose administered every 2 weeks with FOLFOX4, or a 5 mg/kg IV dose administered every 2 weeks or 7.5 mg/kg IV dose administered every 3 weeks with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin-based chemotherapy.

The prescribing information includes warnings and precautions of the risks of GI perforations, surgery and wound healing complications, and severe and potentially fatal pulmonary, GI, central nervous system, and vaginal bleeding. In addition, blood pressure should be monitored every 2-3 weeks during treatment and hypertension treated with antihypertensive therapy. Proteinuria should be monitored by dipstick urine analysis during treatment, and patients with a 2+ or greater reading (concentration, 100 mg/dL) should undergo further assessment with 24-hour urine collection.

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

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Mechanism of action: bevacizumab-awwb

An effective biosimilar of Avastin. Bevacizumab-awwb is a biosimilar of bevacizumab (Avastin), an FDA-approved inhibitor of angiogenesis. This means that the drug was developed to be the same as an already-approved drug that is a biological product, such as a monoclonal antibody. Because it is not possible for biological products to be identical to one another owing to their complexity and variations in the manufacturing process, "copies" of biological drugs are referred to as *biosimilars*.

These drugs have been thoroughly tested to ensure that they don't differ from the original drug in any clinically meaningful way, in terms of their structure, function, drug characteristics, and clinical efficacy and safety. Studies of bevacizumab-awwb included an evaluation of its mechanism of action and demonstrated that it works via the same mechanism as bevacizumab.

Beyond embryonic development when the vascular network is developed through a process called vasculogenesis, new blood vessels are usually formed from pre-existing vessels through angiogenesis. Angiogenesis is a tightly regulated process, kept in check by a delicate balance between pro-and anti-angiogenic signals.

Cancer cells co-opt these signals, pushing the balance in favor of pro-angiogenic signals to create a tangled network of blood vessels around the tumor to help provide it with the oxygen and nutrients required to grow beyond a certain size.

One of the signaling molecules that plays a key role in angiogenesis is vascular endothelial growth factor (VEGF), which binds to the VEGF receptors (VEGFRs) on the surface of endothelial cells, the major cell type involved in the formation of blood vessels. There are several different isoforms of VEGF, but VEGF-A is the best studied, and its binding to VEGFR-2 triggers activation and phosphorylation of the receptor and recruitment of a number of signaling proteins inside the cell and ultimately promotes a variety of endothelial cell functions, including angiogenesis.

As a key regulator of angiogenesis, it was hypothesized that blocking the activity of VEGF-A could provide a means of treating cancer by reducing angiogenesis and effectively starving the cancer cell of oxygen and nutrients. Bevacizumab is a monoclonal antibody designed to bind to VEGF-A and has been approved for the treatment of a range of different cancer types. Bevacizumab-awwb is now also approved for all but one of the same indications.

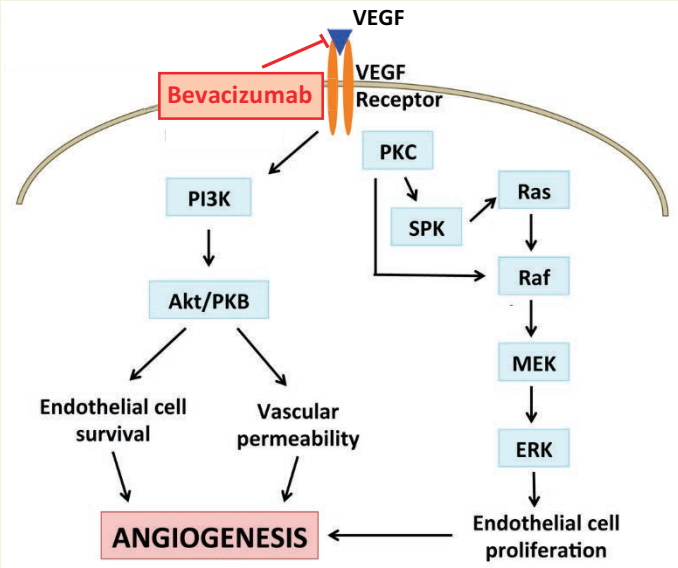

FIGURE Bevacizumab-awwb is a biosimilar of bevacizumab and works via the same mechanism; it binds to the VEGF-A ligand, preventing it from binding to the VEGFRs and therefore blocking their cellular effects on survival, proliferation and angiogenesis. Reproduced under a Creative Commons Attribution-ShareAlike License. Source: Wikipedia.com. Angiogenesis Inhibitor. https://en.wikipedia.org/wiki/Angiogenesis_inhibitor. Last updated December 18, 2017. Accessed online February 5, 2018.

respectively, and median progression-free survival was 6.6 months versus 7.9 months.[3]

In terms of safety, the rates of grade 3/4 adverse events (AEs) were 42.9% in the biosimilar arm, compared with 44.3% for the reference drug. Overall, there were no clinically meaningful differences in AEs, serious AEs, deaths, or treatment discontinuations.

The recommended dose for bevacizumab-awwb in patients with mCRC is a 5 mg/kg intravenous dose administered every 2 weeks with bolus-IFL, a 10 mg/kg IV dose administered every 2 weeks with FOLFOX4, or a 5 mg/kg IV dose administered every 2 weeks or 7.5 mg/kg IV dose administered every 3 weeks with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin-based chemotherapy.

For patients with NSCLC, bevacizumab-awwb should be administered at a 15 mg/kg IV dose every 3 weeks with the carboplatin–paclitaxel combination; for GBM patients, a 10 mg/kg IV dose should be administered every 3 weeks; and for patients with cervical cancer, an IV dose of 15 mg/kg every 3 weeks in combination with paclitaxel–cisplatin or paclitaxel–topotecan is recommended.

The prescribing information outlines warnings and precautions to advise clinicians administering the new biosimilar of the risks of gastrointestinal (GI) perforations, surgery and wound healing complications, and severe and potentially fatal pulmonary, GI, central nervous system, and vaginal bleeding.[4]

Treatment should be discontinued if GI perforation occurs. Patients should not take bevacizumab-awwb in the 28 days before elective surgery and after surgery until the wound is healed, and treatment should be discontinued if the surgical wound breaks open. Bevacizumab-awwb

should not be administered to patients with severe hemorrhage or those with hemoptysis.

Blood pressure should be monitored every 2-3 weeks during treatment and hypertension treated with antihypertensive therapy. Treatment should be temporarily suspended in patients with severe hypertension that is not controlled with antihypertensive therapy and discontinued in patients who experience hypertensive crisis or hypertensive encephalopathy.

Proteinuria should be monitored by dipstick urine analysis during treatment, and patients with a 2+ or greater reading (concentration, 100 mg/dL) should undergo further assessment with 24-hour urine collection. Treatment should be suspended if proteinuria levels are ≥2 g/24h and can be resumed when they fall below that level, but should be discontinued in patients with nephrotic syndrome. Treatment should also be discontinued in patients who develop posterior reversible encephalopathy syndrome, and patients should be advised of the potential for fetal harm

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Trastuzumab-dkst approval adds to the biosimilar cancer drug market

The human epidermal growth factor receptor-2 (HER2)-targeting monoclonal antibody trastuzumab-dkst, was approved by the US Food and Drug Administration in 2017 for the treatment of patients with HER2-positive breast or metastatic gastric or gastroesophageal junction adenocarcinoma.[1]

Trastuzumab-dkst, marketed as Ogviri by Mylan NV and Biocon Ltd, is a copy, known as a biosimilar, of Genentech's trastuzumab (Herceptin), which has been approved in the US since 1998. Genentech's patent on trastuzumab expires in 2018, paving the way for other companies to produce their own versions of this targeted therapy. It becomes the second biosimilar approved for a cancer indication, following approval of a bevacizumab biosimilar earlier last year.

Approval was based on a comparison of the 2 drugs, which demonstrated that there were no clinically meaningful differences between the biosimilar and the reference product (trastuzumab) in terms of structure and function, pharmacokinetics (PKs), pharmacodynamics, and clinical efficacy and safety.

In structural and functional studies, trastuzumab-dkst was shown to have an identical amino acid sequence and a highly similar 3-dimensional structure, as well as equivalency in an inhibition of proliferation assay, a HER2-binding assay, and an antibody-dependent cellular cytotoxicity assay, compared with trastuzumab.

Two nonclinical animal studies were performed in cynomolgus monkeys; a single-dose comparative PK study and a 4-week, repeat-dose toxicity study. That was further supported by data from a single-dose, randomized, double-blind, comparative 3-way PK study (MYL-HER-1002) in which 120 healthy men were given an 8 mg/kg infusion of trastuzumab-dkst, US-approved trastuzumab, or European Union (EU)-approved trastuzumab.

The key clinical study was the phase 3 HERiTAge trial, a 2-part, multicenter, double-blind, randomized, parallel group trial that was performed in patients with HER2-positive metastatic breast cancer who had not been previously treated with either chemotherapy or trastuzumab in the metastatic setting.[2]

Eligible patients included males or females with measurably HER2-positive disease (as defined by HER2 overexpression determined by immunohistochemistry performed by a central laboratory), no exposure to chemotherapy or trastuzumab in the metastatic setting, an Eastern Cooperative Oncology Group Performance Status of 0 or 2, left ventricular ejection fraction (LVEF) within institutional range of normal, and who had completed adjuvant trastuzumab therapy at least 1 year before.

Patients with central nervous system metastases had to have stable disease after treatment, and hormonal agents were required to be discontinued before the start of the study. Patients with a history of unstable angina, heart failure, myocardial infarction less than 1 year from randomization, other clinically significant cardiac disease, grade 2 or higher peripheral neuropathy, a history of any other cancer within 4 years before screening, or any significant medical

What's new, what's important

The human epidermal growth factor receptor-2-targeting monoclonal antibody trastuzumab- dkst, was approved for the treatment of patients with HER2-positive breast or metastatic gastric or gastroesophageal junction adenocarcinoma. It is marketed as Ogviri as a biosimilar trastuzumab (Herceptin).

The safety of the biosimilar and reference product were highly similar. Serious adverse events occurred in 39.3%, compared with 37% of patients, respectively, with neutropenia the most frequently reported in both arms. Overall, treatment-emergent AEs occurred in 96.8%, compared with 94.7% of patients, respectively, with the majority of events mild or moderate in severity in both groups.

The prescribing information details the recommended doses of trastuzumab-dkst for each approved indication and warnings and precautions for cardiomyopathy, infusion reactions, pulmonary toxicity, exacerbation of chemotherapy-induced neutropenia and embryofetal toxicity. Patients should undergo thorough cardiac assessments, including baseline LVEF measurement immediately before starting therapy, every 3 months during therapy, and upon completion of therapy. Patients who complete adjuvant therapy should have cardiac assessments every 6 months for at least 2 years. Treatment should be withheld for ≥16% absolute decrease in LVEF from pre-treatment values or an LVEF value below institutional limits of normal and ≥10% absolute decrease in LVEF from pre-treatment values.

— Jame Abraham, MD, FACP (abrahaj5

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Mechanism of action: trastuzumab-dkst

Same MoA as Herceptin. Structural and functional studies determined that the biosimilar trastuzumab-dkst works by the exact same mechanism of action as trastuzumab across all indications. These drugs are monoclonal antibodies that target HER2.

HER2 is a tyrosine kinase receptor that resides in the plasma membrane of numerous cell types. To date, no activating ligand for HER2 has been identified and it is generally thought that it is switched on instead by forming pairs with other members of the EGFR family of receptors, when they are activated by ligands.

This dimerization leads to phosphorylation of the parts of the HER2 protein that protrude into the cell, which then serves as a binding platform for a number of downstream proteins and triggers a variety of signaling pathways, such as the phosphatidylinositol-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway and the mitogen-activated protein kinase (MAPK; Ras-Raf-MEK-ERK) pathway. This culminates in the transcription of genes in the nucleus that are involved in a variety of key cellular processes, such as survival and proliferation.

The *HER2* gene is amplified or its protein product overexpressed in a number of different types of cancer; most notably 18-20% of breast cancers and a similar percentage of gastric cancers are "HER2-positive." Trastuzumab serves as a prime example of the power of personalized medicine in targeting a specific oncogenic adaptation of cancer cells.

In patients with breast cancer, evidence suggests that the use of trastuzumab has altered the natural history of HER2-positive disease, which historically correlated with a highly aggressive and metastatic form of breast cancer, but trastuzumab-treated HER2-positive patients now have a better prognosis than their HER2-negative counterparts.

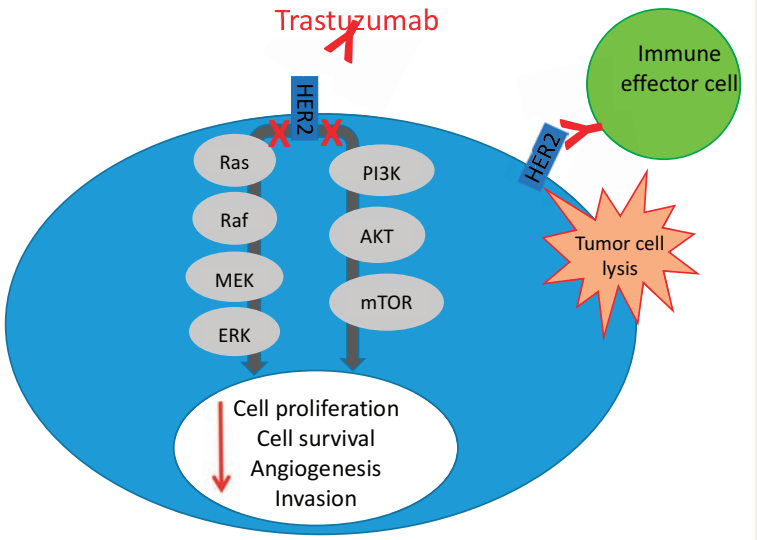

FIGURE Trastuzumab-dkst is a biosimilar of trastuzumab and works by the same mechanism; it binds to HER2 expressed on the surface of cancer cells and blocks the downstream signaling networks initiated by this receptor, which in turn dampens its cellular effects. Trastuzumab can also mediate tumor-cell killing through its immune effector functions, including antibody-dependent cellular cytotoxicity. Produced by Jane de Lartigue.

Genentech's patent on trastuzumab is due to expire in 2018, which has opened the door for other companies to produce biosimilar drugs, which are copies of trastuzumab that must be demonstrated to have no clinically meaningful differences to the original in terms of their structure, function, drug properties and clinical efficacy and safety.

Mylan and Biocon have negotiated a deal with Genentech to allow them to begin marketing their biosimilar prior to the patent expiration, the details of which have not been made public. Biosimilars have the potential to increase competition and help to reduce healthcare costs for patients. Trastuzumab-dkst is only the second biosimilar to be approved for the treatment of cancer.

illness that increased treatment risk or impeded evaluation, were excluded from the study.

Patients were randomly assigned 1:1 to receive trastuzumab-dkst or trastuzumab, both in combination with paclitaxel or docetaxel, at a loading dose of 8 mg/kg, followed by a maintenance dose of 6 mg/kg, every 3 weeks for a minimum of 7 cycles in part 1 of the study. Patients who had stable disease or better were enrolled in part 2 and continued treatment until disease progression or unacceptable toxicity.

The primary endpoint was overall response rate (ORR) and, after 24 weeks, the ORR was 69.6% in the trastuzumab-dkst arm, compared with 64% in the trastuzumab arm, with a ratio of ORR of 1.09. Progression-free survival was also nearly identical in the 2 groups and median overall survival had not been reached in either arm.

The safety of the biosimilar and reference product were also highly similar. Serious adverse events occurred in 39.3%, compared with 37% of patients, respectively, with neutropenia the most frequently reported in both arms. Overall, treatment-emergent AEs occurred in 96.8%, compared with 94.7% of patients, respectively, with the majority of events mild or moderate in severity in both groups. This study also confirmed the low immunogenicity of the 2 drug products.

The prescribing information details the recommended doses of trastuzumab-dkst for each approved indication and warnings and precautions for cardiomyopathy, infusion

reactions, pulmonary toxicity, exacerbation of chemotherapy-induced neutropenia and embryofetal toxicity.[3]

Patients should undergo thorough cardiac assessments, including baseline LVEF measurement immediately before starting therapy, every 3 months during therapy, and upon completion of therapy. Patients who complete adjuvant therapy should have cardiac assessments every 6 months for at least 2 years. Treatment should be withheld for ≥16% absolute decrease in LVEF from pre-treatment values or an LVEF value below institutional limits of normal and ≥10% absolute decrease in LVEF from pre-treatment values. When treatment is withheld for significant LVEF cardiac dysfunction, patients should undergo cardiac assessment at 4-week intervals.

To combat infusion reactions, infusion should be interrupted in all patients experiencing dyspnea or clinically significant hypotension and medical therapy administered. Patients should be evaluated and monitored carefully until signs and symptoms resolve and permanent discontinuation considered in patients with severe reactions. Patients should be warned of the potential for fetal harm with trastuzumab-dkst and of the need for effective contraceptive use during and for 6 months after treatment

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Integrating survivorship care planning in radiation oncology workflow

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Various groups, including the American College of Surgeons' Commission on Cancer and the National Accreditation Program for Breast Centers, are mandating the provision of a survivorship care plan (SCP) to cancer survivors who have completed curative-intent treatment as a requirement for oncology practice accreditation. This article reviews the development of survivorship care, including survivorship care in radiation oncology. Challenges of developing treatment summaries and SCPs and implementing their delivery are explored. Details of the article include how the University of Wisconsin Health radiation oncology department integrated a survivorship visit into the existing radiation oncology workflow. Oncology practices may benefit from the model described here to meet accreditation requirements for SCP delivery to cancer survivors.

In January 2016 there were an estimated 15.5 million people in the United States who were living with a cancer diagnosis, representing 4.8% of the population. That number is expected to increase to 20.3 million by 2026.[1] The 5-year relative survival rate for all cancers diagnosed during 2005 to 2011 was 69%.[2] As more individuals with a cancer diagnosis now live longer, cancer survivorship is receiving increased attention. A report from the Institute of Medicine[3] identified the essential components of survivorship care, including the provision of a survivorship care plan (SCP) containing specific diagnosis, treatment, and follow-up information (Table 1). To maintain accreditation in their respective organizations, the American College of Surgeons' Commission on Cancer and the National Accreditation Program for Breast Centers (NAPBC) have included standards on providing treatment summaries and SCPs in person to those patients who have completed cancer treatments given with curative intent.[4,5]

SCPs are personalized documents presented to cancer patients at the end of treatment that summarize key aspects of cancer treatment and recommend appropriate ongoing medical care and self-management. The purpose of the SCP is both to educate cancer survivors and to create a portable document that can be shared with primary care providers to facilitate coordinated care.[6] There are multiple barriers to SCP implementation, which may include the time required to create an SCP, inadequate reimbursement for the time spent creating and delivering the plan, a lack of risk-stratified guidelines for coordinated care, and the incomplete automation of diagnosis and treatment summarization by the electronic health record (EHR).[7]

Survivorship care in radiation oncology

The American College of Radiology includes the recommendation for regular, ongoing follow-up in the standards for accreditation for radiation oncology practice.[8] Radiation oncology practices often provide the initial follow-up appointment about a month after the prescribed radiation treatment has been completed. The twofold purpose of this appointment is to assess the response to treatment and to evaluate acute treatment-related effects.[9] The appointment may include a skin evaluation, assessment for any acute treatment effects, informal counseling on maintaining a healthy lifestyle, and rec-

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TABLE 1 Elements of the treatment summary and survivorship care plan[a]

Treatment summary
Survivor general information
Clinical care team/supportive/survivor care team and contact information
Diagnostic tests performed & results (including genetic testing)
Cancer stage
Treatment details (surgery, chemotherapy, radiation, endocrine therapy)
Survivorship care plan
Follow-up plan/schedule
Late/long-term effects of treatment
Psychosocial effects of cancer & treatment
Possible signs of recurrence & second cancers
Ongoing health maintenance
Recommended cancer screening
Referrals
Cancer-related resources

[a]Based on recommendations from the American Society of Clinical Oncology[12] and the National Comprehensive Cancer Network.[13]

ommendations for posttreatment care and follow-up. The appointment may also be an opportune time for delivering the SCP because radiation therapy is often the final treatment modality in active therapy for breast cancer patients.

A review of the literature yields scant data on the incorporation of SCPs into a radiation oncology practice. A 2014 survey of members of the American Society of Radiation Oncology[10]for a response percentage of 14.7%. Almost all providers follow their patients after treatment (97% (n = 574 respondents/3987 total membership, 14.4% response rate) showed that although most radiation oncologists provide long-term follow-up care to their patients after treatment completion (97%), fewer than half of those surveyed indicated that they delivered SCPs for curative-intent patients (40%), and even fewer delivered for palliative-intent patients (19%). Standards for the American Society for Radiation Oncology's Accreditation Program for Excellence[11] outline content for end-of-treatment documentation. Typically, the documentation includes a detailed treatment summary prepared by the treating radiation oncologist. This treatment summary includes the patient's diagnosis, the area treated, radiation doses received, number of fractions delivered, therapy start date, therapy completion date, and overall tolerance of treatment in a clinical summary. The treatment summary is communicated to other providers involved in the patient's care to promote care coordination, but it is not typically provided to patients.

Development of University of Wisconsin survivorship care planning

As an important component of maintaining NAPBC accreditation, the University of Wisconsin (UW) Health Breast Center began the process of formalizing and optimizing SCPs for breast cancer survivors who are followed at the center. Multidisciplinary input from surgical, medical, and radiation oncology was obtained. Representatives from those disciplines met regularly to reach consensus on the treatment summary and SCP content. The following 3 documents were created for use during a transition visit at the end of treatment: the written individualized SCP to be provided to the survivor and his/her primary care providers, a general survivorship patient education booklet, and a patient questionnaire to identify survivors' concerns and additional resources that may be beneficial.

Treatment summary

Working in collaboration with IT specialists, we enabled out-of-the-box functionality within our EHR. This cancer-specific functionality provides a central and standard location within each survivor's problem list to systematically document information regarding cancer diagnosis, stage, and treatment associated with a specific cancer diagnosis. Each treating provider (surgeon, medical oncologist, radiation oncologist, genetic counselor, etc) is responsible for entering and updating the relevant components within the treatment summary (ie, the surgeon enters and maintains the surgical details, the medical oncologist does likewise for chemotherapy and other medical therapies, etc). Information is updated and current, creating a dynamic documentation of diagnosis and treatment that can be used in clinic notes, patient after-visit summaries, and SCPs.

Survivorship care plan

This same EHR functionality is leveraged to generate, populate, and maintain the individualized SCP for each breast cancer survivor. The Treatment Summary section of the SCP can be quickly prepared within the EHR by autopopulating data previously entered by treating providers. Content and language for SCP templates in breast, colorectal, prostate, and gynecologic cancers are in use at the time of publication. The templates are developed as a collaborative effort between oncology subspecialists, with input from the UW Health survivor and family advocacy councils.

Each template contains a Treatment Summary section and an SCP section. The Treatment Summary section includes survivor general information, diagnosis and treatment information, and the clinical and supportive/survivor care team names and contact information. The SCP section includes follow-up recommendations, signs of recurrence and/or symptoms to report, healthy lifestyle and maintenance, chronic or late effects of specific treatment if appli-

cable (eg, surgery, chemotherapy by drug, radiation therapy, and endocrine therapy), and general resources for common psychosocial concerns (Table 1).[12,13]

Each SCP is visible to the entire health care team, including other specialists and primary care, as long as they have access to UW Health's EHR.[14] The result is a readily accessible, comprehensive document that is individualized for each survivor, residing in a standard location with standardized format and content to facilitate review and use.[15]

General survivorship patient education booklet

Many cancer survivors request additional information about their posttreatment concerns. The "UW Health Facts for You: Cancer Survivorship, Carbone Cancer Center" booklet was developed by a multidisciplinary team including oncologists, advanced practice providers (APPs), navigators, social workers, program leadership, cancer survivors, and caregivers. The guide includes detailed information for the cancer survivor on topics including nutrition, exercise, sleep, tobacco cessation, sexual health, and spirituality. Common concerns and symptom management are addressed as well as a comprehensive list of community resources. The booklet can be found at http://www.uwhealth.org/healthfacts/cancer/7834.

Survivorship questionnaire

Breast cancer survivors often have multiple concerns as they transition from active treatment to the survivorship phase of their cancer journey. Specific concerns may vary slightly form one survivor to another. Guided by recommendations for the American Society of Clinical Oncology and the National Comprehensive Cancer Network, we developed a 10-question, 2-page questionnaire to identify those concerns with input from members of the Breast Cancer Steering Committee. Members of the committee include surgical, medical, and radiation oncologists, AAPs, radiologists, pathologists, program leadership, and nurses, along with breast cancer survivors. Elements in the questionnaire include nutrition, activity, mood, sleep, sexual health, employment/insurance, pain/swelling, desires regarding pregnancy or prevention, memory/concentration, smoking, alcohol, genetic testing/counseling, and assistance with establishing care with a primary care provider. By completing the questionnaire, breast cancer survivors identify specific concerns within each category and are able to request additional information about those concerns and/or a referral to appropriate resources. They may also select the *I need nothing further* option if the concern is present but already being addressed.

SCP delivery and the transition visit

The next task in implementation of the care process for survivors encompassed the development of clinical workflows and processes to provide the document to the breast cancer survivor at the completion of treatment. In a study of breast cancer survivors, it was found that the preferred format for survivorship care planning is generally an in-person consultation at completion of treatment with an oncology professional.[16] The best time for distribution of the written SCP is, however, unclear. Intuitively, it seems optimal to distribute SCPs around the time of completion of active treatment. However, for SCP delivery to be feasible and sustainable, delivery must be integrated into existing clinical care-delivery processes, and content must be streamlined and focused to meet the needs of their intended recipients without becoming overly burdensome to prepare and deliver.[17]

Ultimately, and after significant multidisciplinary discussion, it was determined that Stage 0-III breast cancer patients would have a visit focusing on symptoms and transitioning to surveillance follow-up (Transition Visit) as they completed active curative-intent cancer treatment. During this Transition Visit, the SCP document would be provided and reviewed with survivors. The Transition Visit for breast cancer survivors would be conducted by an APP following the completion of their final stage of active, primary treatment (surgery, chemotherapy, and/or radiation therapy). Additional long-term adjuvant therapy for breast cancer survivors (ie, trastuzumab, endocrine therapy) would continue as indicated during and after delivery of the SCP.

The radiation oncology clinic was chosen as a venue for these Transition Visits for breast cancer survivors whose treatment included radiotherapy. Despite little historical experience with delivery of SCPs in radiation oncology clinics, this was a logical choice given that radiotherapy is usually the final phase of active treatment for these breast cancer survivors, and a follow-up visit about a month after completing radiotherapy is already part of standard practice. Collaborating with the multidisciplinary UW Health Breast Center, we therefore integrated the formal breast survivorship care planning process and provision of the SCP into the current radiation oncology workflow. About 40% of the roughly 600 breast cancer patients treated by surgical and/or medical oncology at our institution annually also receive radiation therapy at our site. For the remaining 60% of breast cancer survivors who do not receive radiation therapy or who completed radiotherapy at an outside facility, the SCP is provided by an APP within the UW Health Breast Center.

UW radiation oncology survivorship transition visit

The overall workflow of our Transition Visit is depicted in the Figure. Toward the end of the breast cancer survivor's radiation treatments, the radiation oncologist instructs the schedulers to arrange the 1-month, post-radiation Transition Visit with the APP and informs the

survivor about the nature of the appointment. The Transition Visit is scheduled as a 60-minute appointment. Before the survivor's arrival, an APP generates the written SCP. The activity includes completing the Treatment Summary, or verifying the accuracy of a prepopulated Treatment Summary, and individualizing the SCP section for the patient based on treatment received and follow-up recommendations using drop-down functionality. As the SCP is printed for review with the survivor, it is simultaneously sent to the survivor's primary care provider. This is accomplished by using EHR functionality to route the document internally to UW primary care providers or automatically faxing the document to external primary care providers. Each SCP is also marked as complete within the EHR for the purposes of documenting compliance with this activity for later data analysis.

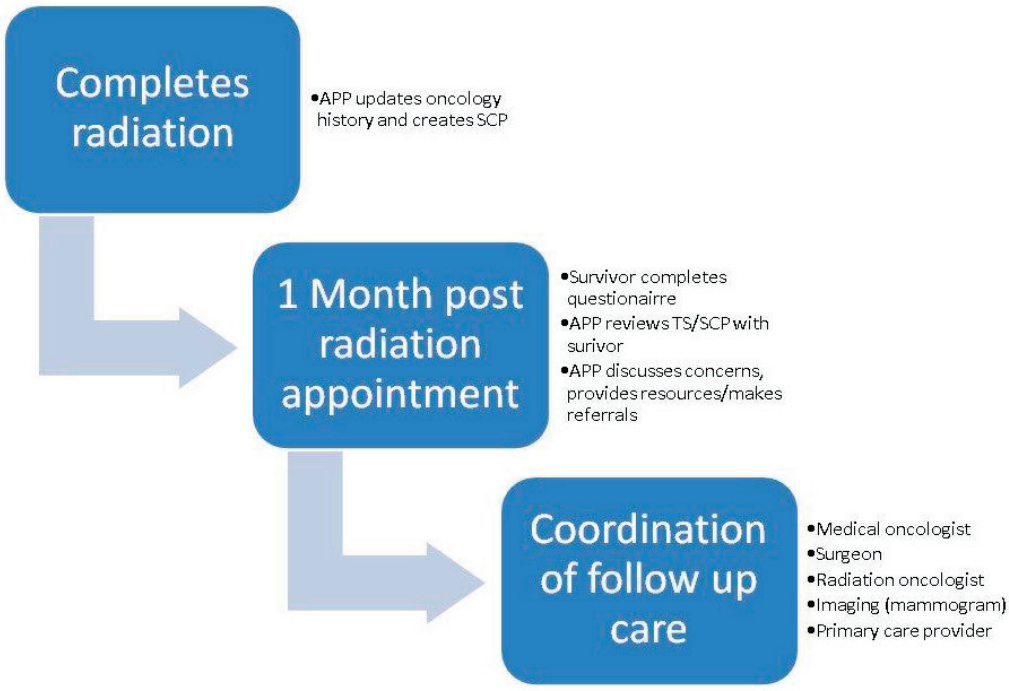

FIGURE Transition visit workflow.

APP, advanced practice provider; SCP, survivorship care plan; TS, treatment summary

On arrival for the appointment, each breast cancer survivor completes the survivorship questionnaire. During the Transition Visit, the questionnaire is reviewed with the survivor and additional information is provided. Referral options are discussed if indicated with desired referrals made by the APP. The survivor is interviewed and examined for any persistent side effects of treatment. Next, the Treatment Summary and SCP are reviewed with the survivor, emphasizing the follow-up plan, signs or symptoms of breast cancer recurrence, and chronic or late treatment-related toxicities. Ample opportunity is provided for the survivor to ask questions and voice concerns.

Follow-up appointments with members of the patient's care team (ie, medical, surgical, or radiation oncology) as well as necessary breast imaging (ie, mammogram, MRI) are coordinated and scheduled before the survivor leaves the department. A survey of oncologists (medical, surgical, radiation) identified specific cancer-related components of survivorship care that oncologists felt most responsible for as well as opportunities to improve the quality and efficiency of care provided by oncologists.[18] At our institution, the breast surgical, medical, and radiation oncologists all generally participate in follow-up care through at least 1 year following completion of active, primary treatment.

Outcomes, quality improvement opportunities, and continued challenges with the process

There is presently a lack of long-term outcome data about the impact of SCPs. As mandates for the provision of SCPs are made, research focusing on whether SCPs result in improved health behaviors and outcomes, reduced burden in care transitions from the oncology setting, and increased cost-effectiveness will be needed.[19] The long-term effects of SCPs on psychological, oncologic, and resource outcomes should be evaluated,[20] as well as the impact on health behaviors, such as smoking cessation or participation in rehabilitation programs.[21]

Following the implementation of our Transition Visits in 2015, we conducted a quality improvement review. This review included summation of 69 recent breast cancer questionnaires from Transition Visits with our APPs (Table 2 and Table 3). The most common concerns raised by our breast cancer survivors include desire for weight loss, improving diet, and increasing physical activity. Of note, concerns did not often translate into a desire for more information or referrals.[22] Survivors were generally satisfied with the timing of the Transition Visits and generally indicated that the visits were helpful, with self-reported improvements in their understanding of planned follow-up. A Canadian group evaluating breast and head and neck cancer survivors has suggested that SCPs could produce long-term improve-

TABLE 2 Findings from questionnaires completed on arrival for Transition Visits (N = 69)

Symptom	At least 1 concern selected by a survivor, n (%)[a]	Information requested	Referral requested
Nutrition	51 (74)	8[b]	11[b]
Activity	41 (59)	3	3
Sleep or fatigue	37 (54)	4	0
Sexuality	36 (52)	7	1
Pain	23 (33)	1	0
Mood	17 (25)	2	1

[a]Survey questions allowed patients to select more than 1 concern (eg, for nutrition, could select *I want to lose weight* and *I want to improve my diet*). These numbers were calculated based on the number of patients who selected the *No concerns* option or left all options blank. [b]Some patients requested both information and referral, others may have selected only 1 option.

TABLE 3 Survivor satisfaction with utility and timing of Transition Visit (N = 69)

Question topic	No. of patients responding, n (%)
Understanding of diagnosis/ treatment after TV[a]	
Changed a lot	20 (29)
Changed a little	20 (29)
No change	3 (1.4)
Understanding of follow-up after TV[b]	
Changed a lot	35 (51)
Changed a little	20 (29)
No change	3 (1.4)
Timing of TV[c]	
Keep as is (4-6 wk after end of active treatment)	51 (73)
Earlier	5 (7)
Later	2 (3)
Reporting TV as helpful[d]	56 (81)

[a]26, [b]11, and [c]11 missing responses. [d]Three response options: Helpful, Unsure if helpful, Unaddressed concerns (13 missing responses).

ments in healthy lifestyle behaviors; however, further research is needed to determine the extent to which SCPs might improve follow-up care over the long term.[23]

Finally, although efforts to date have been focused on the breast cancer survivor at the completion of treatment, long-term survivors may also benefit from receiving the SCP. A study by the American Cancer Society found that long-term cancer survivors had unmet informational needs, particularly with regard to screening, long-term cancer and treatment effects, and healthy lifestyle behaviors.[24] Identifying and subsequently delivering an SCP to eligible long-term survivors is a challenging prospect, which depends on further refinement of EHR-based tracking of the date of diagnosis, cancer stage, and end-of-treatment date.

Summary and recommendations

Survivorship care has been efficiently integrated into our 1-month post-radiation follow-up appointment for breast cancer survivors. By using current resources in the radiation oncology department, the process has provided an effective way to deliver the SCP to breast cancer survivors. Future plans include implementing the process for all patients receiving curative-intent radiation for additional solid tumor survivors. Quality improvement projects will be developed to assess survivor satisfaction and the impact on health behaviors.

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Enhancing communication between oncology care providers and patient caregivers during hospice

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Background When patients enroll in hospice, they and their close family and friends (ie, caregivers) often report feeling a sense of abandonment because of the break in routine communication with their oncology clinicians (physicians, nurse practitioners [NP], registered nurses [RN], and/or physician assistants [PA]).
Objective To assess the feasibility of an intervention to facilitate communication between oncology clinicians and caregivers of patients in hospice care.
Methods Caregivers of patients with cancer who enrolled in home hospice were eligible to participate. The intervention consisted of supportive phone calls from their oncology clinicians, an optional clinic visit, and a bereavement call. The primary outcome was feasibility, defined as >70% of caregivers receiving >50% of phone calls and >70% of caregivers completing >50% of questionnaires. We also assessed caregiver satisfaction with the supportive intervention, stress, decision regret, and perceptions of end-of-life care.
Results Of 38 eligible caregivers, 6 declined participation, 7 could not be reached, and 25 (81%) enrolled in the study. Of those, 22 caregivers were evaluable after 2 patients died before the intervention began and 1 caregiver withdrew. Oncology clinicians completed 164 of the expected 180 calls (91%) to caregivers. The majority of the calls were made by the RN or NP. Caregivers completed 78 of the expected 99 (79%) questionnaires. All of the caregivers received >50% of scheduled phone calls, and 73% completed >50% of the questionnaires. During exit interviews, caregivers reported satisfaction with the intervention.
Limitations Single-institution, small sample size
Conclusions This intervention proved feasible because caregivers received the majority of planned phone calls from oncology clinicians, completed the majority of study assessments, and reported satisfaction with the intervention. A randomized trial to evaluate the impact on caregiver outcomes is warranted.
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Improving the delivery of end-of-life care for patients with advanced cancer has become a priority in the United States.[1,2] Quality metrics identifying the components of high-quality end-of-life care have focused on improved symptom management, decreased use of chemotherapy at the end of life, fewer hospitalizations, and increased use of hospice care. Patients and caregivers also consider good communication with the medical team to be a critical component of end-of-life care.[3-5] Interventions to improve the quality of end-of-life care are needed.

Caregivers of patients with advanced cancer who receive hospice services report better quality of care and death than those receiving end-of-life care in other settings.[6-9] However, the transition for patients from active cancer therapy delivered by their oncologists to end-of-life care delivered by a hospice care team can be abrupt. Patients and their caregivers often feel abandoned by oncology clinicians because of the lack of continuity of care and poor communication.[10-13] Caregivers who note continued involvement and communication with their oncology clinicians experience a lower caregiving burden, report higher satisfaction with care, and recount a higher quality of death for their loved one.[14-16] Therefore, interventions that prevent abrupt transitions in care from oncology to hospice by ensuring continued communication with oncology clinicians are needed to improve the quality of end-of-life care.[17] Recent

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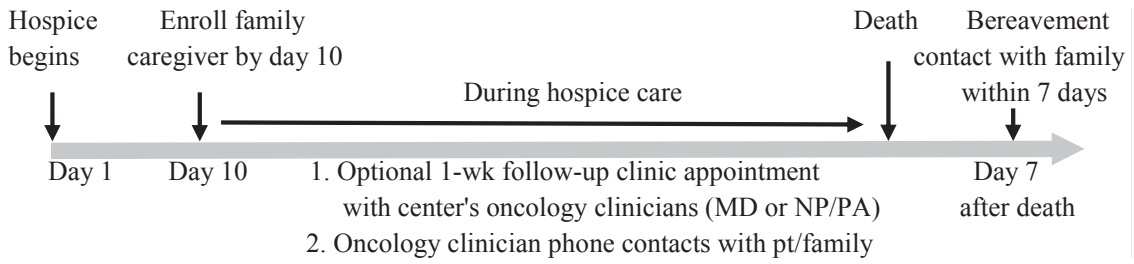

FIGURE 1 The ECHO intervention assists in fostering to communication between oncology clinicians and caregivers of patients who enroll in hospice.

ECHO, Ensuring Communication in Hospice by Oncology

findings have shown that providing concurrent oncology and palliative care is not only feasible but beneficial for patients with advanced cancer and their caregivers.[18-24] However, there is no standard of care for the involvement of oncology clinicians in the care of patients receiving hospice services and their families.

Although interventions may be needed, it could be challenging to deliver them given the multiple demands of caregiving during hospice and the lack of regular contact in clinic. We sought to assess the feasibility of an intervention, Ensuring Communication in Hospice by Oncology (ECHO), to facilitate communication between oncology clinicians and caregivers of patients who enroll in hospice. We also explored caregiver-reported outcomes during hospice care, including satisfaction with care, attitudes toward caregiving, stress, decision regret, and perception of the quality of patients' end-of-life care.

Methods

Study design

During March 2014-June 2015, caregivers of patients with advanced cancer who enrolled in home hospice services were eligible to participate in the study at Massachusetts General Hospital (MGH) in Boston. The Dana Farber/Harvard Cancer Center Institutional Review Board approved all methods and materials. The study opened with an enrollment goal of 30 participating caregivers. However, due to staff transitions, we closed the study early in June 2015 after 25 caregivers enrolled.

Participants

Caregivers of patients receiving care at the cancer center's thoracic, head and neck, sarcoma, melanoma, and gynecological disease centers were eligible within 10 days after a patient's enrollment in hospice. Five disease sites were selected to participate in the intervention. We defined caregivers as relatives or friends serving as the primary caregiver of the patient at home during hospice care. Other caregiver eligibility criteria included the ability to read and respond to questions in English or with a translator, access to a telephone and/or computer to communicate with oncology clinicians, and willingness to complete questionnaires. Caregivers were ineligible if the patient was participating in an ongoing palliative care trial.

To identify eligible caregivers, case managers from both the inpatient and outpatient settings, as well as the nurses based in participating disease centers, notified the research team of all patients referred to hospice. If the patient had received oncology care in one of our participating disease centers, the research team contacted their oncology clinician/s (physicians, nurse practitioners [NP], registered nurses [RN], and/or physician assistants [PA]) to inquire if the patient had an involved caregiver and to obtain permission to offer study participation. If the oncology clinician/s did not grant permission, we documented the reason. Otherwise, with permission, research staff contacted the caregiver by telephone to offer study participation and obtain verbal consent. We then sent participating caregivers a copy of the informed consent by mail or e-mail.

Intervention

The ECHO intervention consisted of: supportive phone calls from an oncology clinician to the caregiver; an optional clinic visit with the oncology clinician for the patient to address clinical questions or concerns that was offered during the initial telephone consent; a bereavement call to the participating caregiver (Figure 1). Initially, we designed the intervention to have phone calls occurring twice weekly until the patient died. However, 3 months after starting the study, we received feedback from oncology clinicians and caregivers that calls were too frequent, so we amended the protocol to include phone calls twice weekly for the first 2 weeks of the study and then weekly thereafter. Seven months into the study, we again decreased the number of phone calls to weekly for the first 4 weeks, every other week for 4 weeks, and then monthly until patient death. We informed caregivers of changes by e-mail.

Before we started the study, we conducted training sessions with oncology clinicians from the participating disease centers to review study procedures and expectations

of the phone calls. Supportive phone calls during hospice were not a part of standard practice prior to the study. The RN, NP or PA, and/or physician who had an established relationship with the patient and caregiver completed the phone calls. They decided based on their respective relationships with the patients and their workloads who would call each week, though the majority of calls were conducted by the RN or NP. All the clinicians had experience comanaging patients with hospice agencies, and our general practice is for the oncology physician to serve as the hospice attending of record. The calls were intended to offer support and reassurance to caregivers. We did not script the calls so that clinicians could tailor their content to the individual needs of the caregiver, as informed by their established relationship. The calls could include the patient if he/she was able to and interested in speaking to the clinician. There was no standardized communication with hospice as part of the intervention. If a caregiver raised concerns about symptom management during a call, the clinician would advise the caregiver to contact the hospice team directly or the clinician would call the hospice to discuss, depending on the clinical scenario and the clinician's judgment. Research staff reminded oncology clinicians to call caregivers on the scheduled date and to document the discussion in the electronic medical record. The hospice phone number was included in the e-mail. If the call was not documented, research staff sent a reminder e-mail to the oncology clinicians 24 hours after the call was due.

Caregiver-reported measures

Caregivers completed a demographic questionnaire at baseline in which they reported their age, gender, race, ethnicity, religion, employment status, and relationship to the patient. We collected information about patient characteristics from the electronic medical record, including age, gender, and cancer type. In addition, we administered validated, self-report measures (see below). We limited the number of measures to decrease caregiver burden:

- The **Family Appraisal of Caregiving Questionnaire-Palliative Care** (FACQ-PC) measures positive and negative aspects of providing care for patients receiving palliative services at home.[25] The 25-item measure consists of 4 subscales measuring caregiver strain, positive caregiving appraisals, caregiver distress, and family well-being with good construct validity. Items are scored on a 5-point Likert scale (1, Strongly Disagree, to 5, Strongly Agree), with higher scores indicating more positive ratings.
- We used 6 items from the **FAMCARE-20 Scale**, which measures family satisfaction with advanced cancer care.[26] Items are scored on a 5-point Likert scale (0, Very Dissatisfied, to 4, Very Satisfied), with higher scores indicating greater satisfaction.
- The **Perceived Stress Scale** (PSS) measures caregiver stress.[27] This 10-item scale assesses perceptions of stress using a 5-point Likert scale (0, Never, to 4, Very Often). The scale is scored from 0-40, with higher scores indicating greater stress, and with mean threshold scores for stress in the general population of 12.1 for men and 13.7 for women.[28]
- The **Decision Regret Scale** measures regret about the decision to enroll the patient in hospice.[29] The 5 items are scored on a 5-point Likert scale (1, Strongly Disagree, to 5 Strongly Agree), with a higher summated score indicating greater decision regret.
- We used 6 questions from the **Toolkit After-Death Bereaved Family Member Interview** and a single question from the **Quality of End-of-Life Care** scale to measure quality of hospice care at the end-of-life and the quality of the patient's death.[30,31] The toolkit interview is scored on a scale from 0-10, with higher scores indicating higher quality of care. The question, *In your opinion, how would you rate the overall quality of the patient's death?*, was also scored on a scale of 0-10 Likert (0, Worst Possible, to 10, Best Possible), with higher scores indicating better perceived quality of death.

The baseline questionnaire included the FACQ-PC, the FAMCARE scale, the PSS, and the Decision Regret Scale. Initially, the study involved weekly questionnaires after baseline that included the FACQ-PC, the FAMCARE scale, and the PSS. However, after 3 months of study enrollment, we received feedback that the questionnaires were too frequent, so we amended the protocol and changed the frequency to weekly for 2 weeks, then monthly thereafter until the patient died.

Caregiver exit interview

Exit interviews included the toolkit interview, the Quality of End-of-Life Care scale, and the Decision Regret Scale. Caregivers also reported patients' place and date of death. After the first 6 caregivers enrolled, we amended the exit interview to include open-ended feedback from caregivers. Specifically, we evaluated caregivers' perceptions of the ECHO intervention by asking them about their perception of and satisfaction with the content and frequency of the oncology clinicians' phone calls, whether they had an in-person visit with their oncology clinicians after the start of hospice care, whether the clinician/s contacted them after the patient died, and whether there were ways in which the clinician/s could help in the future.

Data collection and storage

Caregivers were given the option of completing study measures by telephone or e-mail so that they could complete them on a computer when it was convenient for them. Caregivers received a link to Research Electronic Data Capture (REDCap), a web-based, HIPAA-compliant application that allows participants to answer questionnaires online. The exit interviews were completed by phone, and research staff entered the data into the REDCap data-

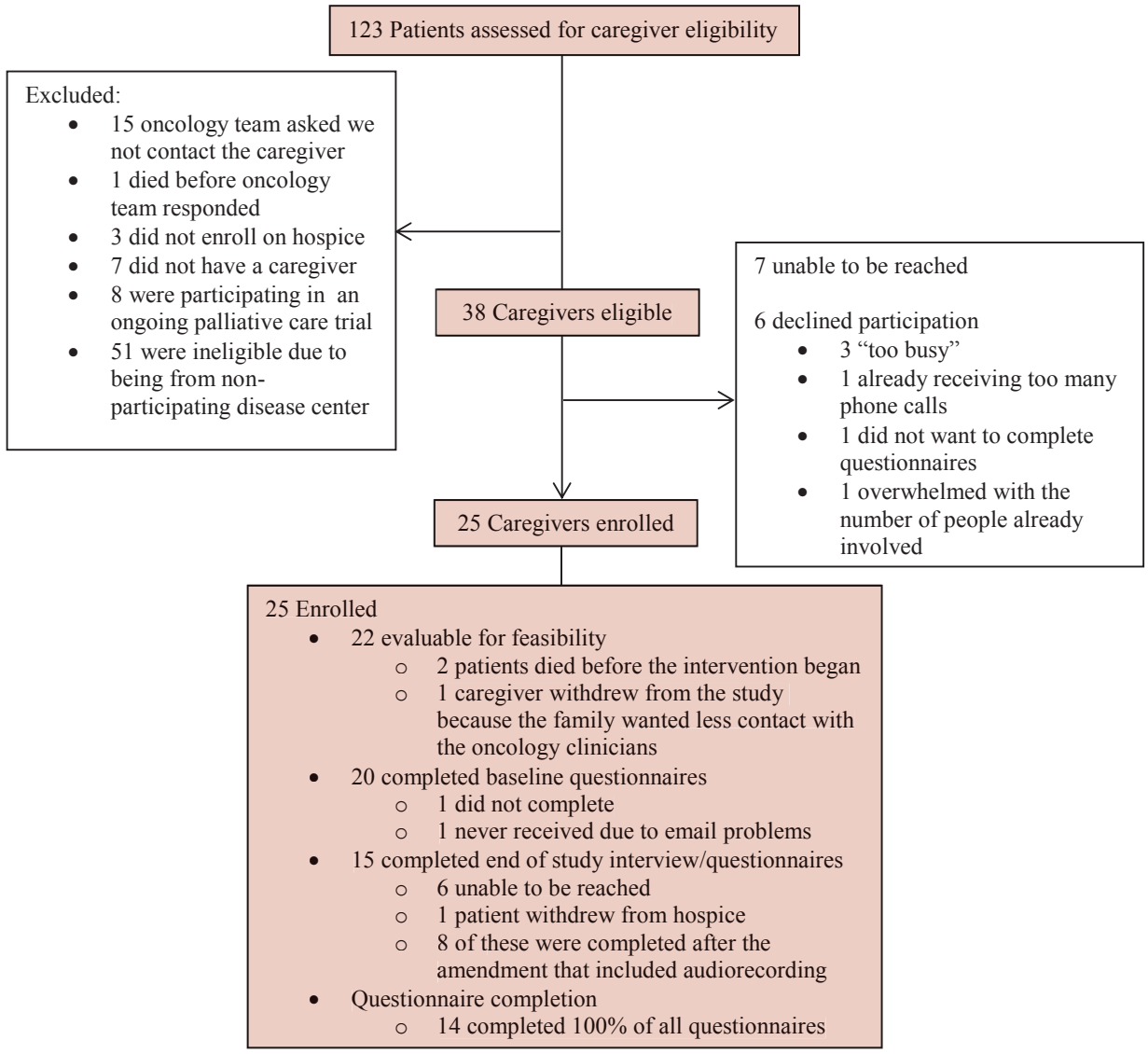

FIGURE 2 The consort diagram of the ECHO study.

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base. In addition, with we obtained caregiver permission to audiorecord the exit interviews, which were then transcribed and de-identified.

Statistical analysis

The primary outcome for the study was feasibility, which we defined as >70% of the caregivers receiving >50% of the phone calls from an oncology clinician, and >70% of the caregivers completing >50% of the questionnaires. All time points for the questionnaires and the exit interview counted toward feasibility. Exploratory endpoints included caregiver-reported satisfaction, stress, quality of end-of-life care, and decision-making regret.

Using STATA (v9.3; StataCorp, College Station, Texas) for all statistical analyses, we summarized participants' characteristics and outcomes as frequencies and percentages for categorical variables and mean standard deviation for continuous variables. We used the repeated-measures *t* test to assess changes in caregiver outcomes over time. We used the Fisher exact test to compare clinically meaningful threshold scores of perceived stress between men and women.

We examined caregivers' open-ended feedback using descriptive analyses to summarize comments about the intervention and to inform possible refinements for a future study.

TABLE 1 Patient and caregiver characteristics (N = 22)

Characteristic	n (%) or [range]
Patients (n = 22)	
Age, y	71 [45-83]
Gender, women	14 (64)
Tumor type	
Head and neck	3 (14)
Lung	9 (41)
Melanoma	4 (18)
Gynecologic	5 (23)
Sarcoma	1 (5)
Stage IV disease	22 (100)
Caregivers (n = 22)	
Age, y	59 (19-84)
Gender, women	12/22 (55)
Education	
Part college or greater	19/20[a] (95)
High school graduate	1/20 (5)
Race	
African-American	1/20 (5)
Asian	1/20 (5)
White	18/20 (90)
Religion	
Catholic	5/20 (25)
Protestant	5/20 (25)
Jewish	1/20 (5)
Other	9/20 (45)
Employment	
Full-time	6/20 (30)
Part-time	4/20 (20)
Retired	7/20 (35)
Other	3/20 (15)
Relationship to patient	
Spouse or partner	12/20 (60)
Son or daughter	6/20 (30)
Other	2/20 (10)
Length of relationship, y	46 (16-59)
Lives with patient, Yes	16/20 (80)
Cares for others	
Children <18 y	4/20 (20)
Parents	6/20 (30)
Other	2/20 (9)

[a] n = 20 here and subsequently because only 20 of the 22 caregivers filled out baseline surveys, which is where the remainder of the data is from.

Results

Baseline characteristics

During March 2014-June 2015, we enrolled caregivers of patients with advanced cancer from 5 participating disease centers: thoracic, head and neck, sarcoma, melanoma, and gynecological malignancy. We screened 123 patients to determine the eligibility of their caregivers (Figure 2). Of 38 eligible caregivers, 7 could not be reached, 6 declined participation, and 25 enrolled in the study (81% enrollment rate). Of the 25 caregivers who enrolled, 3 withdrew – 2 because the patients they were caring for died before the intervention began, and 1 who withdrew from the study because the family wanted less contact with the oncology clinician/s. Thus, we had data for 22 caregivers for our feasibility evaluation. One caregiver stopped study assessments after 3 months because the patient dis-enrolled from hospice. Median time from the patients' hospice enrollment to caregiver study enrollment was 3 days (range, 1-9). Median time from study enrollment to patient death was 36 days (range, 2-135). Patients were receiving care from 10 different hospice agencies.

All of the patients had metastatic cancer, and 64% were women (Table 1). Most of the caregivers were white (n = 18, 90%) and women (n = 12, 55%). The majority were the patient's spouse (n = 12, 60%) or child (n = 6, 30%), and they lived with the patient (n = 16, 80%). Many of the caregivers had other responsibilities in addition to caring for the patients, including part- or full-time work (n = 10, 50%) or caring for others in addition to the patient (n = 10, 50%).

Feasibility

Over the study period, oncology clinicians completed 164 of 180 possible phone calls (91%). All 22 caregivers received >50% of the phone calls. Caregivers completed 78 of 99 possible questionnaires (79%), and 16 of 22 completed >50% of the questionnaires (73%). None of the caregivers/patients wanted to schedule the optional visit with an oncology clinician that was offered as part of the intervention; however, 5 patients had a clinic visit after hospice enrollment. In addition, 2 oncologists visited a patient and caregiver at home. All caregivers received bereavement contact from the oncology team.

Caregiver-reported outcomes

In all, 20 of the 22 enrolled caregivers completed baseline measures (Table 2), and they all chose to complete questionnaires by e-mail. Caregivers' attitudes toward caregiving and satisfaction with hospice services were overall positive. They reported high mean scores on the 2 domains on the FACQ-PC of positive caregiver appraisal (mean, 4.25; SD, 0.52) and family well-being (mean, 4.09; SD, 0.45). The majority of caregivers (75%-95%) reported they were satisfied or very satisfied with vari-

TABLE 2 Caregiver-reported outcomes and baseline (n = 20) and end-of-study (n = 15)

	Measure	Mean score (SD)
	Characteristic	**OR *n (%)***
Baseline	**FACQ-PC**[a]	
	Caregiver strain	2.54 (0.59)
	Positive caregiving appraisals	4.25 (0.52)
	Caregiver distress	3.33 (0.52)
	Family well-being	4.09 (0.45)
	FAMCARE[a]	'Very satisfied or satisfied'
	Control of my loved one's discomfort	*15/20 (75)*
	Answers hospice team gives to my questions	*18/19 (95)*
	How much the hospice team cares about my loved ones	*16/19 (84)*
	How much attention hospice pays to my loved one's symptoms	*17/19 (89)*
	How well is coordinated among different providers	*16/19 (84)*
	The availability of the hospice team to my loved one	*18/19 (95)*
	Perceived Stress Scale[b]	13.55 (6.08)
	Above threshold for stress	*8/20 (40) total*
	Decision Regret scale[b]	10.25 (14.37*)*
End of study	**Decision Regret scale**[b]	6.67 (13.37)
	Quality of End-of-Life Care[a]	8.46 (1.13)
	Toolkit After-Death Bereaved Family Member Interview [a]	
	How well did hospice communicate about illness and likely outcomes of care?	8.53 (1.60)
	How would you rate hospice in providing care that respected the patient's wishes?	8.93 (1.53)
	How well did hospice control symptoms?	7.83 (2.12)
	How well did hospice make sure patient died with dignity?	9.00 (2.66)
	How well did hospice provide emotional support?	8.54 (1.56)
	How would you rate overall hospice care?	8.17 (1.83)

FACQ-PC, Family Appraisal of Caregiving Questionnaire-Palliative Care; FAMCARE, Family Satisfaction With Advanced Cancer Care
[a]Higher scores signify more positive ratings or better care. [b]Higher scores signify greater stress or regret.

ous dimensions of hospice care based on the FAMCARE questionnaire.

Overall, caregivers reported moderate levels of stress (mean, 13.55; SD, 6.08) based on the PSS scores. Of the 20 caregivers who completed the baseline measures, 8 had clinically meaningful stress, and stress was numerically higher in female caregivers than in their male counterparts, but it did not reach statistical significance (55% vs 22%, P = .197). Finally, at baseline, caregivers indicated relatively low levels of decisional regret about enrolling in hospice, although there was considerable variation (mean, 10.25; SD, 14.37).

We conducted exit interviews with 15 caregivers because we were not able to reach 6 of the original 21 (Table 2). Caregivers rated hospice services highly for communication, symptom control, emotional support, and overall care. They also rated quality of death highly (mean, 8.46; SD 1.13). Regret was lower at the end of the study, but this did not reach statistical significance (baseline mean 9.29; end of study mean 3.57; P = .161).

In the recorded exit interviews, all of the caregivers responded they were satisfied with the phone calls. Two caregivers commented that they would have preferred the calls were more scheduled or at more suitable times. Overall, they described the phone calls as *excellent*, *supportive*, *responsive*, *comfortable*, and *appreciated*. All caregivers reported contact with the oncology team after the patient died, but one caregiver was disappointed she was only contacted by the nurse practitioner and not the oncologist. Participants did not feel as if there were other ways that the oncology team could have been helpful for them while their loved one was in hospice. Table 3 highlights other representative comments from the exit interviews.

TABLE 3 Caregiver themes and comments about ECHO study from exit interviews

Theme	Comment
Maintaining relationship with oncology clinician	I appreciated them. I did. It was a connection back to the hospital. And there wasn't a need to engage any more than that at that point.
Emotional support	The [oncology] nurse practitioner called me. We had a pretty close relationship [before hospice] so it was nice to be able to touch base once a week whether it was pertaining to my mom or my own emotional needs.
Continuity of care	Anytime we needed anything or needed clarification on anything, [the oncology team] was always there for us. In fact, some of the things that [the hospice team] usually explains, it was actually the oncology team that explained and guided us.
Closure	I think [there was] an unstated acknowledgment that everything that could have been done was done.

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Discussion

As far as we know, this is the first study to assess the feasibility of an intervention to facilitate communication between oncology clinicians and caregivers of patients with advanced cancer who are receiving hospice care. Despite the challenges of oncology clinicians delivering an intervention to caregivers during hospice, we found this intervention was feasible and acceptable. Although the transition to hospice can be stressful, caregivers reported high satisfaction with hospice care and the quality of the patient's death. In exit interviews, they also reported high satisfaction with the intervention and appreciation for maintaining their relationship with the oncology team. It is worth noting that no caregiver requested the optional clinic visit after hospice enrollment, and most caregivers were not seen again in clinic after hospice enrollment.

These results suggest that a simple, telephone-based intervention of scheduled calls from the oncology team at prompted intervals is not only feasible, but may also help foster continuity between the patient and caregiver and the oncology team. We received feedback from both oncology clinicians and caregivers that the initial call frequency was too often, suggesting that communication may not need to be very frequent to maintain continuity and provide support. This also suggests that if the calls are too frequent, they may be more intrusive than helpful for both oncologists and caregivers. Alternatively, caregiver suggestion for fewer phone calls may indicate that concerns about abandonment are less prevalent than existing literature has suggested.

Limitations

Our study has several important limitations. The sample size was small as this was a feasibility study conducted at a single tertiary care hospital, and the population was 90% white and 95% college educated, which may limit the generalizability of our results. In addition, the median length of stay in hospice for patients on this study was 36 days, which is long compared with national averages,[32,33] and thus the outcomes may not represent the experience of a more heterogeneous population. The longer length of stay in hospice may have contributed to caregivers' high satisfaction with the quality of end-of-life care.

Oncologists did not grant permission for the study team to approach all eligible caregivers, which may have introduced selection bias. We were also not able to reach 6 participants for exit interviews. People less satisfied with the intervention or with hospice may be more likely to have

missing data, which could introduce bias into the satisfaction ratings. Furthermore, we did not explore the oncology clinicians' perspective of the intervention or assess the time commitment of the calls. Oncology clinicians have many competing responsibilities and have variable experience and comfort with hospice care. Therefore, future studies should explore the perspective of oncology clinicians in regard to the intervention.

Finally, we did not require communication with the hospice agency as part of the intervention as there were ten different hospices involved. Thus, we do not know how the intervention impacted the hospice team's care of the patient. However, based upon the success of this pilot study, future larger studies should explore the impact of the intervention from the perspective of the hospice care team and include oncology clinician communication with the hospice agency.

Conclusion

These findings demonstrate the feasibility and acceptability of an intervention to enhance communication between oncology clinicians and caregivers of patients with advanced cancer receiving hospice care. Importantly, the high caregiver satisfaction with the intervention in this study suggests that maintaining communication with the primary oncology team during hospice care may be an important component of high quality end-of-life care, though the desire for decreased calls suggests that this communication need not be frequent to maintain the continuity. A randomized study with a larger and more diverse patient/caregiver sample would allow us to explore the impact of the intervention on caregiver feelings of abandonment by the oncology team and short- and long-term caregiver outcomes, as well as to understand the perspective of the oncology and hospice clinicians involved.

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The impact of patient education on consideration of enrollment in clinical trials

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Background Advances in clinical care depend on well-designed clinical trials, yet the number of adults who enroll is suboptimal.
Objective To evaluate whether providing brief educational material about clinical trials would increase willingness to participate.
Methods From October 23, 2015, through November 12, 2015, 1511 adults in the United States completed an anonymized electronic survey in a single-group, cross-sectional-design study to measure the impression of and willingness to enroll in a hypothetical cancer clinical trial before and after reading brief educational material on the topic.
Results Participants had a worse impression of and were less likely to enroll in a clinical trial before reading the material. Most participants (86.2%) noted that the educational material was believable, easy to understand (84.8%), and included information that was new (81.5%). After reading the material, the overall impression of clinical trials improved (mean standard deviation [SD], 0.42; 95% confidence interval [CI], 0.35-0.50). This improved outlook was greater among participants with a lower level of completed education ($P_{interaction}$ < .001). Education level effect was no longer significant after reading the document. Similar results were observed for likeliness of enrolling.
Limitations The study was not randomized, so it is uncertain if the increase in interest and likelihood of enrolling in a clinical trial was solely a result of the intervention; the findings may not be generalizable to a cancer-only cohort, and only English-speaking participants were included.
Conclusion Participants were receptive of educational material and expressed greater interest and likelihood of enrolling in a clinical trial after reading the material. The information had a greater effect on those with less education, but it increased the willingness of all participants to enroll.
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The low rate of participation in clinical trials is partly owing to the lack of awareness of these trials not only among potential participants but the US population as a whole.[1] This lack of awareness, however, can be reversed. For example, findings from a single-institution observational study showed that systematically sending letters about clinical trial participation to all new lung cancer patients was associated with increased trial participation.[2] More recently, a large, multicenter, randomized experiment showed that attitudes toward clinical trials were improved through preparatory education about clinical trials before a patient's first oncologic visit.[3]

Such clinical trial education can be used before any medical diagnosis to increase clinical trial awareness in the general population. It may be advantageous to do so because people tend to process information more effectively during less stressful times.[4] Clinical trial awareness in the US population has increased

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slightly over time, but in 2012, one study reported that 26% of its participants lacked general awareness about clinical trials.[5]

Comprehensive educational material, such as a multimedia psychoeducational intervention,[6] a 28-video library,[3] or a 160-page book,[7] which have been proposed for oncology patients, may be too intensive for someone who is not immediately deciding whether to participate in a clinical trial. However, a simple, concise form of education might be preferable and appropriate to increase basic knowledge and awareness among the general population, especially among those who are less educated.[8]

Our aim in the present study was to evaluate whether providing brief educational material about clinical trials would increase patient willingness to participate in these trials.

Methods

This is a single-group, cross-sectional design study in which all participants were administered the questions and the 240-word educational statement in the same order.

Sample

An electronic survey was conducted by Marketing and Planning Systems (the analytics practice of Kantar Millwardbrown) on behalf of the Memorial Sloan Kettering Cancer Center (MSK). The survey included a national sample of 1011 participants and a local sample of 500 participants from the MSK catchment area (22 counties across the 5 boroughs of New York City, Long Island, southern New York State, northern New Jersey, and southwestern Connecticut).

Survey participants were aged 18 to 69 years in the national sample and 25 to 69 years in the local sample, representing 87% and 75% of the adult populations of those areas, respectively. Respondents who were or who had a family member currently working in the fields of news, advertising/marketing, or medical care were not surveyed. Participants were sourced from an online incentivized panel with millions of potential respondents representative of the US adult population.

Questionnaire

The questionnaire collected data on participant demographics and main medical history (including previous participation in a clinical trial), and asked questions about clinical trials, focusing on:

- **Awareness** about clinical trials, assessed using a 5-point scale, with response options ranging from *Never heard of clinical trials before today* to *Extremely familiar with what clinical trials are*.
- **Perceptions** toward clinical trials – accurate perceptions (eg, *Clinical trials play a very important role in the development of new medicine and treatments*) and inaccurate perceptions (eg, *Clinical trials are only appropriate for people in life or death situations*) were measured using 8 items with 10-point response scales (1, *Strongly disagree* to 10, *Strongly agree*). After reverse coding negatively worded items, an average score was calculated (possible range, 1-10).
- **Impression of and willingness to enroll in clinical trials,** measured using two 10-point response scales asking about overall impression of clinical trials (1, *Very negative impression* to 10, *Very positive impression*) and likeliness to enroll in a future hypothetical clinical trial (1, *Very unlikely* to 10, *Very likely*). The same questions were asked twice, before and after reading the brief educational material about a cancer clinical trial.
- **Information about clinical trials,** provided through the brief educational statement (Table 1) explaining the goals and procedures of cancer clinical trials. The statement was presented to the participants after collecting data on their awareness and perception of clinical trials as well as their baseline impression of and willingness to enroll in a clinical trial. Participants were asked to provide feedback on whether the information was new to them (1, *None was new* to 4, *Almost all was new*), easy to understand (1, *Very difficult* to 5, *Very easy*), and believable (1, *Very hard to believe* to 5, *Very believable*).

TABLE 1 Information about cancer clinical trials provided to survey participants

Clinical trials are research studies in which patients volunteer to help test new ways to treat, diagnose, or prevent diseases. They are used to determine if a new test or treatment works and is safe. These trials are used for thousands of medical conditions, including many types of cancer.

By participating in clinical trials for cancer, you have the opportunity to:

- Receive drugs or therapies years before they are available elsewhere.
- Receive the newest treatment being studied (in the majority of cases) in addition to the standard current treatment available.
- Better manage symptoms or side effects from the treatment of cancer or improve your overall well-being.
- Receive a higher level of oversight and care.

Treatments studied can include new drugs, new surgical procedures, or devices or new ways to use existing treatments or improve them.

Typically, one group of the study receives the new treatment in addition to the standard treatment, while a comparison group receives the current standard treatment. Note that regardless of the treatment group you are in, you are free to leave a trial at any time. The costs of the new treatment are typically covered by the clinical trial, while the standard treatment is covered by the patient or his/her insurance.

Clinical trials are key in helping physicians develop medical breakthroughs. Nearly all cancer drugs in use today were first tested and made available to patients through clinical trials.

TABLE 2 Participant characteristics and awareness and knowledge of clinical trials (overall and by education level; N = 1,507)

		Level of education		
	Overall, %	**High school or less, %**	**At least some college, %**	***P* value**
Participant characteristic				
Age ≥65 years	9.7	7.6	10.2	.213
Female	50.4	56.3	49.1	.027
White (non-Hispanic)	63.2	68.3	62.0	.048
Residency in an urban area	77.6	72.5	78.8	.018
Household income <US$25,000	23.0	42.2	18.6	<.001
Does not have health insurance	10.6	21.3	8.2	<.001
Cancer diagnosis (current or past)	9.0	5.6	9.8	.027
Current medical condition	57.8	57.0	58.0	.775
Previous "contact" with CT				<.001
No	81.8	89.9	79.9	
Never participated, but know someone who participated	8.6	5.3	9.4	
CT awareness and perceptions				
Never heard of CTs before today	6.1	15.6	3.9	<.001
Accurate perceptions, mean (SD) [range, 1-10]	6.8 (1.5)	6.5 (1.4)	6.9 (1.5)	<.001
Brief information about CTs				
How much of this information was new to you?				<.001
None of it was new to me	18.5	10.2	20.4	
Some of it was new to me	43.1	35.7	44.9	
Most of it was new to me	25.2	35.6	22.8	
Almost all of it was new to me	13.2	18.6	11.9	
How easy or difficult was this information to understand?				<.001
Somewhat/very difficult to understand	2.9	4.6	2.5	
Neither easy nor difficult to understand	12.3	20.0	10.5	
Somewhat easy to understand	27.4	29.2	27.0	
Very easy to understand	57.3	46.2	59.9	
How believable was this information?				<.001
Somewhat/very hard to believe	1.5	1.8	1.4	
Neither believable nor hard to believe	12.4	17.1	11.3	
Somewhat believable	35.1	37.4	34.6	
Very believable	51.1	43.8	52.7	

CT, clinical trial; SD, standard deviation

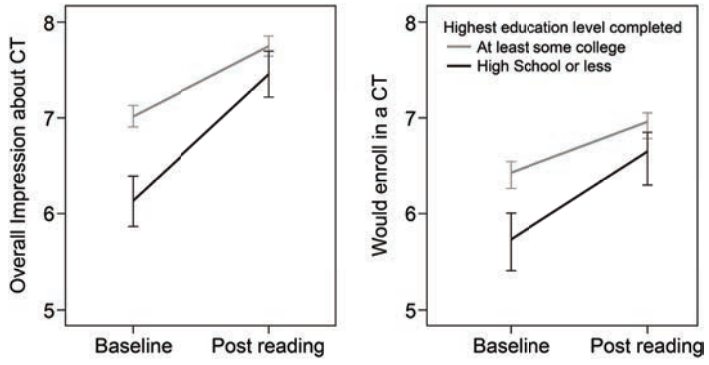

FIGURE 1 Changes in impression about clinical trials and willingness to enroll after reading educational material stratified by education level. Mean level (range 1-10; 1 = very negative impression, very unlikely; 10 = very positive impression, very likely). Error bars represent 95% CIs. CT, clinical trial.

- **Concerns about participation in a hypothetical cancer clinical trial,** measured using 10-point response scales (1, *Not a critical concern at all* to 10, *Critical concern*). Eleven potential barriers and drivers of cancer clinical trial participation were presented to participants.[9]

Analyses

Descriptive and bivariate statistical analyses of participants' characteristics were weighted to ensure national representativeness for gender, age, ethnicity, and income. Mean standard deviation (SD) was computed for every quantitative variable. Categorical variables were expressed as proportions.

Student *t* tests and analyses of variance (ANOVAs) were used to compare continuous variables, while chi-square tests were used to compare categorical data. Repeated measures ANOVAs were then used to determine the sociodemographic and medical characteristics associated with the impression of and willingness to enroll in a clinical trial before and after reading the educational material. The interaction between education level and time (pre- or postreading assessment) was tested to determine if the changes after reading the brief statement were different depending on education level.

All statistical analyses were 2-tailed and considered statistically significant at $P < .05$. Analyses were performed using SPSS PAWS Statistics 24 (IBM Inc, Armonk, New York). Effect sizes (standardized mean differences) and their 95% confidence intervals (CIs) were computed using the compute.es package for R 3.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Participants

From October 23, 2015, through November 12, 2015, 1511 US participants responded to the survey request, including 1507 respondents (99.7%) who reported their education level and are included in the analyses of this report. The mean age of the respondents was 43.5 years (SD, 4.6). More than half of the respondents (57.8%) reported a current medical condition, mainly cardiovascular (20.0%), arthritis (20.0%), or other type or chronic pain (20.0%), and 9.0% reported a cancer diagnosis (current, 2.9%; previous, 6.1%).

Participants who at most had completed high school (18.9%, including 1.4% who had never even attended high school) were more often white women, lived outside urban areas, had lower household income, and were less likely to have health care insurance (Table 2). They also reported a current or previous cancer diagnosis less often than those of similar age who had attended college.

Previous participation in a clinical trial was reported by 9.6% of participants. Most of the clinical trials (75.0%) were testing a new drug. Previous trial participants were more likely to be older than those who had not participated in trials (46.1 years [SD, 14.8] vs 43.3 [SD, 4.6], repectively; $P = .033$), have a current health condition (86.2% vs 54.8%; $P < .001$), and know another trial participant (39.9% vs 9.5%; $P < .001$).

Education level and baseline impression of and willingness to enroll in a clinical trial

A lower level of education was associated with a decreased likelihood of previous trial participation or of knowing a trial participant, as well as with less awareness and inaccurate perceptions of clinical trials (Table 2).

Participants with a high school degree or less were more likely to have a worse impression of and were less likely to enroll in a future hypothetical clinical trial before reading the educational material (Figure 1). Multivariable analyses confirmed that lower education level was associated with lower baseline overall impression, regardless of other personal characteristics (Table 3). Lowest household income was also associated with a more negative impression of trials, whereas participants with a current medical condition and with previous contact with clinical trials had a more positive impression of them. The same effects were observed with likeliness to enroll in a future hypothetical clinical trial (correlated with the overall impression: r, 0.63; $P < .001$), except that the negative effect of female gender was statistically significant (Table 3).

Posteducation impression of and willingnes to enroll willingness to enroll in a clinical trial

The brief educational material was mostly considered believable (86.2%), easy to understand (84.8%), and included information that was new to participants (81.5%; Table 2). Participants with a high school diploma or less more often noted that the material provided them with new information, but they also reported more difficulties in

fully understanding and believing the information. Overall, however, few participants found the information difficult to understand (4.6%) or hard to believe (1.8%; Table 2).

Most participants had an improved overall impression of clinical trials (standardized mean difference, 0.42; 95% CI, 0.35-0.50; $P < .001$) after reading the educational material. This increase was higher among participants with a lower completed level of education (Figure 1; standardized mean difference, 0.62; 95% CI, 0.45-0.79; $P_{interaction} < .001$). The same effects were observed for likeliness to enroll in a future hypothetical clinical trial ($P < .001$; Figure 1).

After reading the informational statement, education level effect was no longer significantly associated with the overall impression of clinical trials ($P = .23$) and willingness to enroll in a clinical trial ($P = .34$), whereas the effects of income, current medical condition, and previous engangement with clinical trials remained statistically significant (Table 3).

Remaining challenges

Regarding hypothetical participation in a future clinical trial after a cancer diagnosis, the most critical concerns were related to side effects and the uncertainty of insurance coverage (Figure 2).[10] The lack of understanding of clinical trials was the least critical concern; however, it was significantly higher among participants with a lower completed level of education. These participants also expressed more critical concerns about feeling like a "guinea pig," inconvenient trial location, and the frequent visits needed.

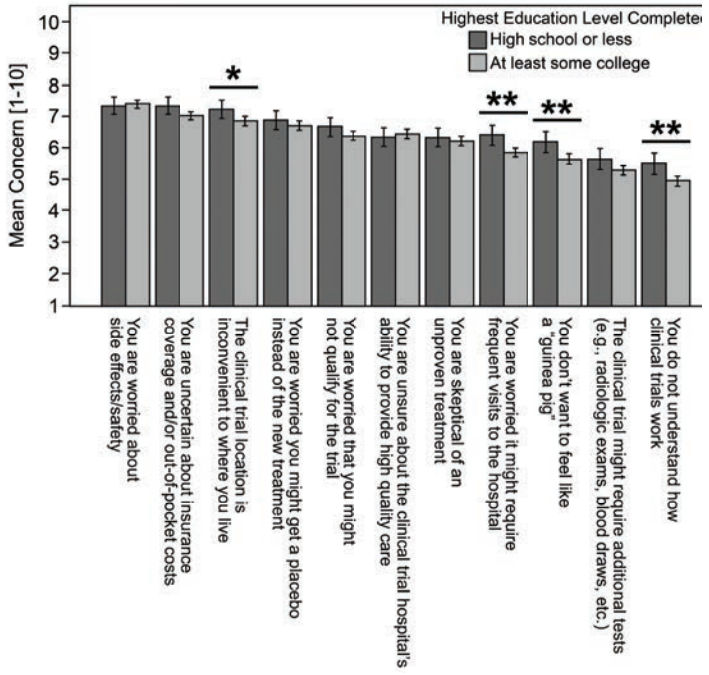

FIGURE 2 Concerns about hypothetical cancer clinical trial participation depending on education level. Mean level (range 1-10; 1 = not a critical concern at all, 10 = critical concern). Error bars represent 95% CIs. *$P < .05$. **$P < .01$. CI, confidence interval.

Discussion

Findings from this survey demonstrated that providing brief educational material about cancer clinical trials was associated with a more favorable impression of clinical trials and higher interest in trial participation. Furthermore, as far as we can ascertain, this is the first report showing how a simple intervention such as this may help close the knowledge gap on clinical trials among people of different educational backgrounds. Although most respondents in this interventional survey noted an increased willingness to consider participation in a clinical trial after reading the educational material, those with a lower level of education and knowledge about clinical trials received the most benefit. Previous participation in a clinical trial was also strongly associated with the impression of and willingness to enroll in a trial, both before and after reading the statement.[11]

Most of the interventions evaluated to date[12] have focused on patients who are faced with having to decide whether to participate in a clinical trial[2,3] or on very specific populations, such as select ethnic communities.[13,14] However, it may be beneficial to provide simple, concise educational information about clinical trials to the general population, especially to those with minimal education. Although level of education concerns the minority of our sample (19%) sourced from an online panel, in the 2015 Current Population Survey, 41% of US participants aged 25 and older had not reached college education.[15] Those with a lower level of education have reported a general lack of familiarity with clinical trials and were more likely to have inaccurate perceptions about trials. This is consistent with previous studies that have shown the lack of awareness and knowledge of clinical trials in this population.[5,16,17] Our findings suggest that this knowledge gap can be reversed through a simple educational intervention and result in an increased willingness to participate.

The provision of information on clinical trials was positively associated with the 2 outcomes analyzed – improved impression of clinical trials and increased likelihood to enroll in a hypothetical trial. Such improvement might not translate to improved accrual,[18] but it is a step toward closing the overall knowledge gap related to clinical trials and increasing the number of people who would consider trial participation. The lack of awareness of clinical trials has been reported as a legitimate explanation for why participation rates are lower in less-educated patient populations.[19,20] This brief educational intervention is a simple, technology-sparing way to increase clinical trial awareness in the general population. In a similar survey, most physicians who reviewed an educational statement noted they were likely to use it with patients.[21]

Less-educated patients, those who lived outside of

TABLE 3 Factors associated with overall impression of clinical trials and willingness to enroll before and after reading educational material (repeated measures ANOVAs)

Dependent variable	Explanatory variables	Before reading the brief statement		After reading the brief statement	
		Parameter estimate [95% CI]	*P* value	Parameter estimate [95% CI]	*P* value
Impression of CTs	Household income <US$25,000	−0.6 [−0.9 to −0.4]	<.001	−0.5 [−0.8 to −0.3]	<.001
	High school or less	−0.6 [−0.9 to −0.3]	<.001	−0.2 [−0.4 to 0.1]	.226
	Residency in an urban area[a]	0.0 [−0.2 to 0.3]	.811	−0.1 [−0.3 to 0.2]	.921
	Female	−0.2 [−0.4 to 0]	.054	0.2 [0 to 0.4]	.067
	No health insurance	−0.1 [−0.4 to 0.3]	.644	0 [−0.4 to 0.3]	.794
	White (non-Hispanic)	0 [−0.2 to 0.2]	.926	0 [−0.2 to 0.2]	.784
	Cancer diagnosis (current/past)	0.2 [−0.1 to 0.6]	.239	0.1 [−0.2 to 0.5]	.385
	Age ≥65 years	0.3 [−0.1 to 0.6]	.098	0.3 [0 to 0.6]	.091
	Current medical condition	0.3 [0.1 to 0.5]	.004	0.3 [0.2 to 0.6]	<.001
	Previous "contact" with CTs				
	No	0 [reference]		0 [reference]	
	Never participated but know someone who participated	0.6 [0.3 to 1]	0.001	0.4 [0.1 to 0.8]	.011
	Previous CT participation	1.5 [1.1 to 1.9]	<0.001	0.9 [0.5 to 1.2]	<.001
	Intercept	6.7 [6.4 to 7.1]	<0.001	7.4 [7.1 to 7.8]	<.001
Would enroll in a CT	Household income <US$25,000	−0.5 [−0.9 to −0.2]	.001	−0.6 [−0.9 to −0.4]	<.001
	High school or less	−0.6 [−0.9 to −0.3]	<.001	−0.1 [−0.5 to 0.2]	.338
	Residency in an urban area[a]	−0.3 [−0.6 to −0.1]	.008	0 [−0.2 to 0.2]	.953
	Female	0.3 [−0.1 to 0.7]	.161	0 [−0.4 to 0.4]	.902
	No health insurance	0 [−0.2 to 0.3]	.791	0 [−0.3 to 0.2]	.745
	White (non-Hispanic)	−0.1 [−0.4 to 0.3]	.736	−0.1 [−0.4 to 0.2]	.577
	Cancer diagnosis (current/past)	0.1 [−0.3 to 0.6]	.547	0.2 [−0.2 to 0.6]	.364
	Age ≥65 years	−0.2 [−0.6 to 0.2]	.353	−0.1 [−0.4 to 0.3]	.769
	Current medical condition	0.7 [0.4 to 0.9]	<.001	0.4 [0.2 to 0.6]	.001
	Previous "contact" with CTs				
	No	0 [reference]		0 [reference]	
	Never participated but know someone who participated	0.9 [0.4 to 1.3]	<.001	0.8 [0.4 to 1.2]	<.001
	Previous CT participation	2.2 [1.8 to 2.6]	<.001	1.5 [1 to 1.9]	<.001
	Intercept	5.9 [5.5 to 6.4]	<.001	6.7 [6.3 to 7.1]	<.001

ANOVA, analysis of variance; CI, confidence interval; CT, clinical trial
[a]Ten respondents who did not have a zip code match in the Rural-Urban Commuting Area codes file were excluded.

urban areas, and those with lower household incomes were most concerned about trial location and the frequent visits needed when participating in a trial (Figure 2). Living in a nonurban area was not associated with participant impression of clinical trials or willingness to enroll in a trial. However, rural residency may be a barrier to enrollment depending on distance to the hospital[22] and out-of-pocket expenses related to travel.[23] Some comprehensive cancer centers, such as MSK, have developed alliances with community centers[24] as a means of overcoming geographical barriers and increasing clinical trial participation rates.

Another concern shared by most respondents was the uncertainty in insurance coverage and potential out-of-pocket costs related to care. Lower household income, unlike location of residence and lack of insurance, was significantly associated with negative impressions of clinical trials and lower willingness to enroll in a trial, even after adjusting for education level. Cancer patients with higher financial burden have reported more attitudinal barriers, even after accounting for the negative effect of lower education level.[25] Recent studies have also discussed the negative impact of lower income on cancer clinical trial participation,[19,20,26,27] and new attention has been paid to the negative financial implications or "financial toxicity" of participating in a trial.[23,28]

White and older survey participants showed similar interest in clinical trial participation after accounting for other characteristics. There is growing evidence that outcome differences attributed to race may in fact be more dependent on socioeconomic status.[8] A recent study among breast cancer patients showed that low socioeconomic status, but not race, was associated with decreased participation in clinical trials.[29,30] Previous findings have also indicated that interest in clinical trials and barriers to enrollment among older, less-educated patients[31] are often related to ineligibility, comorbidity, or communication difficulties.

Among our participants, the fear of side effects also was a common attitudinal barrier to clinical trial participation, as has been reported in previous studies.[3,20] However, contrary to one previous study,[20] this fear was not significantly increased among our less-educated participants.

Less-educated participants also reported more difficulties in understanding the information they were provided with, and they remained more concerned about being treated like "guinea pigs." These concerns are consistent with other results showing that decisional conflict about clinical trial participation among patients with a high school diploma or less remained high even after they had received a National Cancer Institute text as pre-education material.[3]

Limitations

The lack of randomization makes it difficult to attribute with certainty that the change in acceptability of clinical trial participation is owing to the reading of the educational statement. The survey also sampled only English-speaking and well-educated participants from an online panel (81.1% had at least attended college) despite the use of a weighting procedure to ensure representativeness regarding gender, age, ethnicity, and income. Health literacy level or more specific trial literacy level was not evaluated; however, we were able to show less accurate perceptions of clinical trials among participants with a lower level of education by using agreement toward 8 statements about trials. The responses to hypothetical questions from these participants in the general population may also not be generalizable to a restricted population of patients with cancer. In addition, we measured impression of and willingness to enroll in a clinical trial immediately after providing participants with the educational material. We would have to confirm whether the positive effects of the education persist over time and translate to higher clinical trial participation rates.

Conclusions

Participants were receptive of educational material and expressed greater interest in and likelihood of enrolling in a clinical trial after reading it. The information had a greater effect on those with less education, but increased the willingness of all participants to enroll.

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Qualitative assessment of organizational barriers to optimal lung cancer care in a community hospital setting in the United States

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Background Lung cancer is a major public health challenge in the United States with a complicated process of care delivery. In addition, it is a challenge for many lung cancer patients and their caregivers to navigate health care systems while coping with the disease.

Objective To explore the organizational barriers to receiving quality health care from the perspective of lung cancer patients and their caregivers.

Methods In a qualitative study involving 10 focus groups of patients and their caregivers, we recorded and transcribed guided discussions for analysis by using Dedoose software to investigate recurrent themes.

Results Analysis of the transcriptions revealed 4 recurring themes related to organizational barriers to quality care: insurance, scheduling, communication, and knowledge. The participants perceived support with navigating the health care system, either through their own social network or from within the health care systems, as beneficial in coping with the lung cancer, seeking information, expediting appointments, connecting patients to physicians, and receiving timely care.

Limitations Institutional and geographic differences in the experience of lung cancer care may limit the generalizability of the results of this study.

Conclusions This study offers insights into the perspectives of lung cancer patients and caregivers on the organizational barriers to receiving quality care. Targeting barriers related to insurance coverage, appointment scheduling, provider-patient communication, and patient or family education about lung cancer and its treatment process will likely improve patient and caregiver experience of care.

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Lung cancer is a major public health challenge in the United States. It is the leading cause of cancer death in the United States, accounting for 27% of all cancer deaths, and it has an aggregate 5-year survival rate of 18%.[1] Advances in diagnostic and treatment options are rapidly increasing the complexity of lung cancer care delivery, which involves multiple specialty providers and often cuts across health care institutions.[2-4] Navigating the process of care while coping with the complexities of the illness can be overwhelming for both the patient and the caregiver.[5] With increasing regulations and cost-cutting measures, the health care system in the United States can pose many challenges, especially for those dealing with catastrophic and life-threatening illnesses. Any barrier to accessing care often increases anxiety in patients, who are already trying to cope with the management of their disease.[6-8]

The concept of barriers to quality care (such as the receipt of timely and appropriate diagnostic and staging work-up and treatment selection according to evidence-based guidelines) is generally used in the context of improving health care management or prevention programs.[9-13] Barriers might include high costs, transportation, distance, underinsurance, limited hours for access to care, patient sharing by physicians, and a lack of access to information about physicians' recommendations.[10,14-16] Such bar-

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riers have been categorized as organizational (leadership and workforce), structural (process of care), clinical (provider-patient encounter), and macro (policy and population).[17,18] Organizational barriers are defined as impediments encountered within the medical system and health care organizations when accessing, receiving, and delivering care.[12] Several organizational barriers have been identified in the literature based on characteristics of the targeted population (eg, race, ethnicity, type of illness), key stakeholder views, and aspects of care (eg, screening, preventive practice, care, and treatment).

In a systematic review, Betancourt and colleagues reported provider-patient interactions, processes of care, and language as some of the barriers to receiving quality care.[17] Although cancer screening has been shown to reduce mortality in the adult population for several types of cancer,[19-21] barriers that impede access to services have been identified as emanating not only from the macro level (eg, age of screening, reimbursement problems, screening guidelines) or inter- and intra-individual levels (eg, awareness of screening, various perspectives on life and cancer, comorbidities, social support), but also from the organization (organizational infrastructure that inhibits screening because of limited participation in research trials) and provider levels (impaired communication regarding screening between patient and physician, low commitment to shared decision-making, provider's awareness of screening and screening guidelines).[18] Other organizational barriers, such as difficulty navigating the health care system, poor interaction between patients and medical staff, and language barriers, have been identified in a systematic review of breast cancer screening in immigrant and minority women.[22]

Other barriers to quality cancer care reported by patients include knowledge about the disease and treatment, poor communication with providers, lack of coordination and timeliness of care, and lack of attention to care. Providers have identified other barriers to quality care, which include a lack of access to care, reimbursement problems, poor psychosocial support services, accountability of care, provider workload, and inadequate patient education.[23] Few qualitative studies have been conducted to understand the organizational barriers that lung cancer patients and their caregivers face within the health care system.

Through the use of focus groups, we sought the perspectives of lung cancer patients and their caregivers on the organizational barriers that they experience while navigating the health care system. Identifying and understanding these barriers can help health care professionals work with patients and their caregivers to alleviate these stressors in an already difficult time.[3,24] In addition, a more thorough understanding of patients' and caregivers' perspectives on organizational barriers may help improve health care delivery and, thus, patient satisfaction.

TABLE 1 Number of participants per focus group[a]

Group no.	No. of patients [no. of caregivers] (n = 22 [24])
1	6 [7][a]
2	5 [5]
3	2 [2]
4	5 [5]
5	4 [5][a]

[a]Some patients brought more than 1 caregiver.

Methods

With the approval of the Institutional Review Boards of the University of Memphis and the Baptist Memorial Health Care Corporation, we conducted focus groups with lung cancer patients and their informal caregivers to understand the challenges they encounter while navigating the health care system during their illness. The Baptist Memorial Health Care system is centered in the Mid-South region of the United States, which has some of the highest US lung cancer incidence rates.[25]

Research staff identified potential participants from a roster of patients provided by treatment clinics within the system. Patients eligible for this study had received care for suspected lung cancer within a community-based health care system within 6 months preceding the date of the focus group. Eligible patients were approached by the research staff by cold calling or in-person contact during clinic visits for their consent to participate in the study. From a compiled list of 219 patients, 89 received initial contact to gauge interest. Of those, 42 patients were formally approached and asked to participate; 22 agreed to participate, and 20 did not participate for reasons including illness, previous participation in other forms of patient feedback, lack of interest, failure to show up to focus group sessions, change of mind, lack of transportation, or other commitments. Patients identified their informal caregivers to form patient-caregiver dyads. All patients and caregivers provided written informed consent before participating in the focus groups.

We conducted 10 focus groups during March 2013 through January 2014 – 5 with 22 patients and 5 with 24 caregivers (Table 1). Eight of the focus groups were conducted in Memphis, Tennessee, and to obtain the perspectives of patients from a rural setting, we conducted 2 focus groups in Grenada, Mississippi. All of the focus groups were facilitated by a medical anthropologist (SK) and a clinical psychologist (KDW), neither of whom was affiliated with the health care system. Each facilitator was accompanied by a note-taker. Patient-caregiver dyads came to the designated location together. Two focus groups (one

for patients, the other for caregivers) were then conducted simultaneously in 2 separate rooms. The facilitators used a pilot-tested focus group interview guide during each session. The items in the focus group guide revolved around experience with the health care system in diagnosis and treatment; timeliness with appointments and procedures for diagnosis and subsequent care; physician communication in being informed about the disease, treatment, and getting questions answered; coordination of care; other challenges in receiving quality care; and suggestions for improving the patient and caregiver experience with the health care system.

The focus group sessions lasted 1 to 2 hours and were audio-recorded and transcribed verbatim. The data were analyzed by using Dedoose software version 5.0.11 (Sociocultural Research Consultants, Los Angeles, California). Data collection and analysis were conducted concurrently to achieve theoretical saturation. Creswell's 7-step analysis framework was used as a guide to code and interpret the data.[26] The process involved collecting raw data, preparing and organizing transcripts, reading the transcripts, coding the data with the help of qualitative software, analyzing the data for themes and subthemes, interpreting the themes, and devising the meaning of the themes.[26] Initial codes were categorized and compared to determine recurrent themes. Three members of the research team independently reviewed the transcripts, extensively discussed the content, and developed consensus around the identified themes. Critical and rigorous steps were taken throughout data collection and analysis to ensure the credibility, transferability, dependability, and confirmability of the qualitative data.[27-29] In addition, elements of the Consolidated Criteria for Reporting Qualitative Research checklist were used to strengthen the data collection, analysis, and reporting process.[30]

Results

The 10 focus groups included 46 participants: 22 patients and 24 caregivers (some patients brought multiple caregivers). Of the 22 patients, 12 were women and 7 were black. An equal proportion of patients had at least a high school education as had a college or postgraduate degree. Although all of the patients had had a lung lesion suspicious for lung cancer, 19 eventually had a histologic diagnosis of lung cancer. The remaining 3 patients were all evaluated in a thoracic oncology clinic but were eventually found to have metastatic breast cancer, lymphoma, and a granuloma. Nine patients were either currently in the treatment decision-making process or actively receiving treatment, 11 had completed treatment within the preceding 6 months, and 2 had completed treatment more than 6 months previously. Treatment covered the spectrum from curative intent to palliative care. Of the 24 caregivers, 18 were women and 7 were black; 12 caregivers had at least a college education, of whom 2 had postgraduate degrees (Table 2).

Based on participants' feedback, we identified 4 main levels within the system where barriers to optimal care occurred: policy, institutional, provider, and patient. From our qualitative analyses, we identified a central theme associated with each level, around which the barriers coalesced. The themes were insurance, scheduling, provider communication, and patient knowledge. At the *policy level*, medical insurance was perceived to affect the timeliness of care and to be a deterrent to timely diagnosis and quality treatment. Lack of insurance was a daunting obstacle for indigent patients. However, even those who were insured felt that dealing with insurance companies was a significant barrier to care. At the *institutional level*, appointment scheduling caused problems for both patients and their caregivers. At the health care *provider level*, communication was perceived as a major problem. And finally, at the *patient level*, both patient and caregiver lack of knowledge of lung cancer and the processes inher-

TABLE 2 Patient and caregiver characteristics

Characteristic	Patients (n = 22)	Caregivers (n = 24)
Sex		
Female	12	18
Male	10	6
Race		
Black	7	7
White	15	17
Education		
High school (any)	11	7
College	9	12
Postgraduate	2	5
Histology		
Confirmed lung cancer	19	NA
Suspected lung cancer[a]	3	NA
Stage of lung cancer		
IA-IB	7	NA
IIA-IIB	2	NA
IIIA-IIIB	3	NA
IV	7	NA
Treatment phase		
Treatment planning or treatment ongoing	9	NA
Treatment completed ≤6 mo.	11	NA
Treatment completed >6 mo.	2	NA

[a]Three patients were seen in a lung-cancer-specific clinic for nodules suspected to be lung cancer, which, on histologic diagnosis, were determined to be metastatic breast cancer, lymphoma, and a granuloma.

TABLE 3 Themes common to patient and caregiver perceptions of organizational barriers

Theme (level)	Examples
Insurance (policy)	Lack of insurance and lag time in insurance processing caused delays in treatment and/or diagnosis Insurance caps on tests and office visits presented difficulties in getting second opinions
Scheduling (institutional)	Long wait times before seeing provider during appointment Rescheduling and/or cancellation of appointments Difficulty obtaining appointments with providers
Communication (provider)	Insensitive disclosure of condition to patient Provider not properly preparing patient for procedure and/or outcomes Patient not formerly informed of condition
Knowledge (patient)	Patients/caregivers not knowledgeable about lung cancer, treatment options, or duration of treatment

ent in lung cancer treatment were barriers for optimal diagnosis and treatment (Table 3).

Insurance barriers

At the policy level, health insurance was reported as a significant barrier to accessing health care. Patients and caregivers reported delays in diagnosis and/or treatment because of either lack of insurance or lag time in insurance processing of clinician requests. Insurance restrictions on tests, procedures, and office visits presented difficulties in getting additional opinions from providers regarding diagnosis, prognosis, or treatment plans. Some patients were no longer able to see providers after they had met the test or office visit limit allotted by insurance providers. One patient shared the following experience with office visits leading up to their lung cancer diagnosis:

> **Patient** *… with my insurance I just had only 12 office visits … and I had already maxed those out.*

In other instances, insurers would not cover hospital or clinic visits if certain logistic protocols were not met. This would sometimes leave patients stranded for a period of time without receiving any care.

> **Caretaker** *… went home and went to one of those minor emergency clinics and they sent her to [xx hospital in another city]. There they did nothing. That was then over the weekend, and my son wanted to get her out of there to get her into practice because they weren't doing anything. They said, 'No. Your insurance won't pay for it unless you stay here till we sign the papers to be transferred.' … It was a bandage. Period.*

Some insurers would not cover certain health services outside of routine testing protocols for the patients' conditions. This lack of coverage caused patients to pay out of pocket for needed care.

> **Patient** *Nothing in the lymph nodes, but if it hadn't been for me going ahead with this [coronary] calcium score, the insurance wasn't gonna pay anything. If it wouldn't been for the 79 bucks or the family situation, I wouldn't be sitting [here] today.*

Individuals who had not yet met the age requirement for Medicare reported being without insurance for a period of time, which contributed to delays in accessing care.

> **Caregiver** *[xx patient] probably … could've been diagnosed maybe even months ago, but she is in that in-between where she gets Social Security but she's not 65 until November, so she has no insurance.*

Scheduling barriers

At the institutional level, patients and caregivers reported problems with appointment scheduling. Logistic problems with adjusting work schedules and arranging for transportation as well as long wait times before evaluation by a provider were recurrent themes expressed by both patients and caregivers. Many had become resigned to the expectation of long wait times during appointments.

> **Patient** *I have to call the month before to make the appointment because they don't take appointments so far—'Oh, we're not working on that yet.' I find that very annoying ….*

> **Caregiver** *The last time I was there I waited four hours.*

> **Caregiver** *… your appointment at 9:00 and you get called back at 9:30 or 10:00 and you get to see the doctor by 11:00, but that's not any different than anywhere, unfortunately ….*

Rescheduled appointments also posed a problem for participants. Constant rescheduling was an inconvenience

for both patients and caregivers. Many were unhappy with rescheduling because both patients and caregivers had prepared mentally and physically for an appointment, only to be told that they would have to reschedule, which caused delays in the care process.

> **Patient** *I think every single visit I had with him gets rescheduled at least twice ….*

> **Caregiver** *Three times this week we've been geared up, ready to have chemo and they keep changing it.*

> **Patient** *Everything was fine with me, but they keep cancelling my appointments ….*

Some participants perceived that the popularity of physicians might explain the difficulty with scheduling. Patients suggested that it is challenging to get appointments with better-known physicians, so they are more accepting of appointments at any time, even if the time is inconvenient for them.

> **Caregiver** *Of course, … if you have a popular doctor, sometimes you don't always get the appointment you want …*

Participants also expressed frustration with the way appointments were rescheduled. They felt as though the physicians were not concerned about their lives outside of office visits.

> **Patient** *… patients actually have lives. Many of them have jobs or families or responsibilities.*

Communication barriers

At the provider level, poor communication between health care providers and patients was perceived as a major impediment to the quality of care patients received. Both patients and caregivers emphasized the importance of open patient-provider interactions and that there was a lack of such open communications in many instances. There was concern regarding the way diagnoses or prognoses were relayed to patients. Many times, physicians were insensitive and disregarded the sentiments of the patients and caregivers when delivering news about the patients' condition, as one caregiver shared,

> **Caregiver** *… the pulmonary man came … in the room and said, 'Oh, don't worry about your lungs. Something else will get you first,' which was a very, very bad thing to say.*

Participants also expressed concerns that they were not properly prepared for treatments by their physicians because vital information was not discussed. They felt as if physicians were not realistic about potential outcomes. This resulted in patients and caregivers being too optimistic and later disappointed when the outcome was not what they had originally expected.

> **Patient** *Until I got to this office, I was totally oversold on everything. I was told surgery … robotic, not invasive. Day one, surgery. Day two, tubes out. Day three, go home. I expected to be home on Sunday night, stir-frying vegetables, and making dinner, feeding my cat. I was in ICU four days … I went home with oxygen. I mean I thought I was just gonna walk outta there…. You take a little thing out and you put a Band-Aid on, and you go home.*

Data also revealed that patients were unsure of their condition, even following treatment. Information was not communicated to patients about the specifics of their disease, either because of miscommunication or minimal patient-provider time spent during office visits. This lack of communication between patients and providers often left patients and caregivers uncertain about exactly what condition they had or what they were being treated for.

> **Patient** *I just can't have the time with Dr. xx, cuz he's so busy…*

> **Patient** *… I didn't understand. Which exactly what type of cancer did I have, cuz I'm—really to tell you the truth—I'm still wondering.*

Knowledge barriers

Patients and caregivers also identified a lack of education and knowledge about lung cancer diagnosis and treatment as a barrier to their care. Patients and caregivers were not always fully knowledgeable about lung cancer, treatment options, or the duration of treatments. They relied on the provider to disclose such information or direct them to credible sources. In many instances, patients were misinformed about the causes of lung cancer. There were misconceptions that lung cancer was only caused by a history of smoking or genetic predisposition. Patients who did not smoke or did not have a family history of lung cancer were often confused and dismayed by the diagnosis.

> **Patient** *I was trying to figure out, why do I have lung cancer. Never smoked a day in my life.*

Patients were often unaware of treatment options or side effects of various treatments. They relied on physicians to relay information and make decisions for them about treatment plans.

Patient *I was told chemo would probably be the best thing for me, and I just had faith that Dr. xx knows more about it than me.*

Patient *I'm doing chemo but it's — what I'm doing is different. Of course, I don't know anything about it actually either. It's what I hear from other people.*

Other patients relied on their own sources for information about their condition, either through the Internet, from family members and/or friends, or from preconceived notions.

Patient *Well — of course in the meantime, I read — because they said it was a small cell, very aggressive, so I felt like everything I read — that's the deal. I think we've become where we can get on the internet and look up so much, that to me, I was gonna be gone.*

Patient *When he said, 'Cancer,' I said, 'Well, I thought cancer was a heredity thing? That you have to have somebody in your family that has it…'*

Discussion

Organizational barriers are an important consideration in the delivery and receipt of high-quality, patient-centered lung cancer care. This qualitative study of patients being treated for lung cancer and their informal caregivers revealed several common perceived organizational barriers to receiving care, including health insurance coverage restrictions, appointment scheduling difficulties, quality of communication with physicians, and failure to properly educate the patient and family about the disease and what to expect of the treatment process.

The provider communication and patient knowledge barriers seem to reinforce each other and could be improved through focused efforts on the quality of communication between patients and their caregivers and clinical care providers. Patients expect, but are often deprived of, open and active dialogue with their providers. Improved communication can be helpful in educating patients and their caregivers about their disease, prognosis, and treatment goals. Although communication ranks highly as a patient and caregiver priority, there is often a disconnect between patients and caregivers and their physicians.[31] Patients and caregivers often want to be more involved in the decision-making process, and effective communication between physicians and patients has been linked to the patient's ability to understand, and also receive high-quality care.[32,33] Failure to communicate effectively and educate patients on key aspects of their condition strips them of their autonomy in decision-making.

The involvement of a navigator for patients being treated for lung cancer could be pivotal in relieving the communication and scheduling barriers. The nurse navigator assists with coordinating effective communication and providing needed information between providers and patients and their caregivers. A navigator also serves as a single point of contact for patients and caregivers to communicate questions outside of physician visits or concerns that may not be urgent enough to warrant immediate physician response.[34] The navigator coordinates patients' appointment schedules and physician referrals and communicates the details of the next steps in the care-delivery process. This helps remove the barriers to care and improve patient outcomes and the quality of health care delivery, especially for patients and caregivers dealing with a life-threatening illness within a complex referral process.[35]

Multidisciplinary care, a much-recommended alternative care-delivery model, should, in theory, promote connectivity of providers and collaboration between providers, patients, and family members. This model could help reduce barriers for patients and caregivers.[3,24,36] A network of connected providers can better coordinate treatment plans, easily share test results, and provide built-in second opinions. Given the increasingly multimodal approach to the diagnosis, staging, and treatment of lung cancer, the multidisciplinary model could allow physicians to consider multiple perspectives and care-delivery options and, ideally, develop consensus around the optimal approach for each individual patient in one setting. This can shorten the length of time before treatment and establish a plan that is tailored to the patient's needs.[24]

The National Academy of Medicine (formerly, Institute of Medicine) proposes that modern health care systems have 6 aims for quality improvement: safety, effectiveness, patient-centeredness, timeliness, efficiency, and equity.[37] It would take changes in the design and implementation of organizational support systems at the policy, institutional, and provider level for those aims to be achieved. Further investigation of the problems identified by patients and caregivers could lead to innovative solutions to improve lung cancer care. Future work should evaluate the most effective communication styles in patient-provider interactions, particularly in regard to to lung cancer diagnosis and treatment, and investigate how multidisciplinary models influence patient-provider communication and patient care.

Limitations

This study has several limitations. Less than half of those approached for the study participated in the study for various reasons, which may have introduced selection bias in terms of not having the perspectives of patients not willing or able to participate in the study. Though focus groups are known to generate rich in-depth views of certain issues, they have been criticized as potentially lacking rigor and generalizability. To address this concern, we used a standardized script for each focus group and involved multiple

members of the research team in data analysis and interpretation. Also, this study enrolled participants from a single health care institution and did not use a comparison group. There might be institutional and geographic differences in the experience of lung cancer care, which might further limit the generalizability of the results of this study.

Conclusions

Despite those limitations, this study offers valuable insight into the barriers that lung cancer patients and caregivers encounter while navigating a community-level health care system. Eliminating or minimizing these barriers will require strategic plans that help mitigate insurance-related, scheduling, provider-patient communication, and patient/caregiver knowledge acquisition problems and translate them into tactical actions for quality improvement. This is one of the first qualitative studies conducted to understand the organizational barriers that lung cancer patients and their caregivers face within a health care system. Additional research is needed to explore these barriers and develop viable solutions.

Disclaimer

All statements in this report, including its findings and conclusions, are solely those of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute or its Board of Governors or Methodology Committee.

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Rare paraneoplastic dermatomyositis secondary to high-grade bladder cancer

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The clinical presentation of bladder cancer typically presents with hematuria; changes in voiding habits such as urgency, frequency, and pain; or less commonly, obstructive symptoms. Rarely does bladder cancer first present as part of a paraneoplastic syndrome with an inflammatory myopathy. Inflammatory myopathies such as dermatomyositis have been known to be associated with malignancy, however, in a meta-analysis by Yang and colleagues of 449 patients with dermatomyositis and malignancy there were only 8 cases reported of bladder cancer.[1] Herein, we report a paraneoplastic dermatomyositis in the setting of a bladder cancer.

Case presentation and summary

A 65-year-old man with a medical history of hypertension and alcohol use presented to the emergency department with worsening pain, stiffness in the neck, shoulders, and inability to lift his arms above his shoulders. During the physical exam, an erythematous purple rash was noted over his chest, neck, and arms. Upon further evaluation, his creatine phosphokinase was 3,500 U/L (reference range 52-336 U/L) suggesting muscle breakdown and possible inflammatory myopathy. A biopsy of the left deltoid and quadriceps muscles was performed and yielded a diagnosis of dermatomyositis. He was treated with prednisone 60 mg daily for his inflammatory myopathy. The patient also reported an unintentional weight loss of 20 lbs. and increasing weakness and inability to swallow, which caused aspiration events without developing pneumonia.

The patient's symptoms worsened while he was on steroids, and we became concerned about the possibility of a primary malignancy, which led to further work-up. The results of a computed-tomography (CT) scan of the abdomen and pelvis showed right-sided hydronephrosis and hydrourteter with an irregular, soft-tissue density mass of 4.7 x 3.2 x 4.2 cm along the posterior wall of the bladder (Figure 1). A cystoscopy was performed with transurethral resection of a bladder tumor that was more than 8 cm in diameter. Because the mass was not fully resectable, only 25% of the tumor burden was removed. The pathology report revealed an invasive, high-grade urothelial cell carcinoma (Figure 2). Further imaging ruled out metastatic spread.

The patient was continued on steroids. He was not a candidate for neoadjuvant chemotherapy because of his comorbidities and cisplatin ineligibility owing to his significant bilateral hearing deficiencies. Members of a multidisciplinary tumor board decided to move forward with definitive surgery. The patient underwent a robotic-assisted laparoscoptic cystoprostatectomy with bilateral pelvic lymph node dissection and open ileal conduit urinary diversion. Staging of tumor was determined as pT3b N1 (1/30) M0, LVI+. After the surgery, the patient had resolution of his rash and significant improvement in his muscle weakness with the ability to raise his arms over his head and climb stairs. Adjuvant chemotherapy was not given since he was cisplatin ineligible as a result of his hearing loss. Active surveillance was preferred.

Four months after his cystoprostatectomy, he experienced new-onset hip pain and further imaging, including a bone scan, was performed. It showed metastatic disease in the ischium and iliac crest (Figure 3). The patient decided to forgo any palliative chemotherapy and to have palliative radiation for pain and enroll in hospice. He died nine months after the initial diagnosis of urothelial cell carcinoma.

Discussion

Dermatomyositis is one of the inflammatory myopa-

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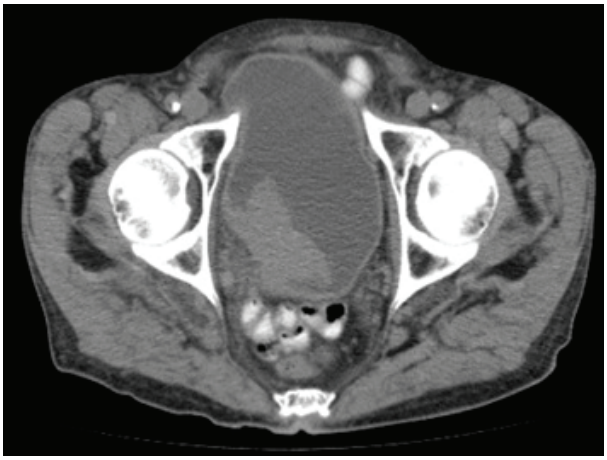

FIGURE 1 Computed-tomography scan of the abdomen and pelvis, revealing a right-sided hydronephrosis and hydrourteter with an irregular, soft-tissue density mass of 4.7 x 3.2 x 4.2 cm along the posterior wall of the bladder.

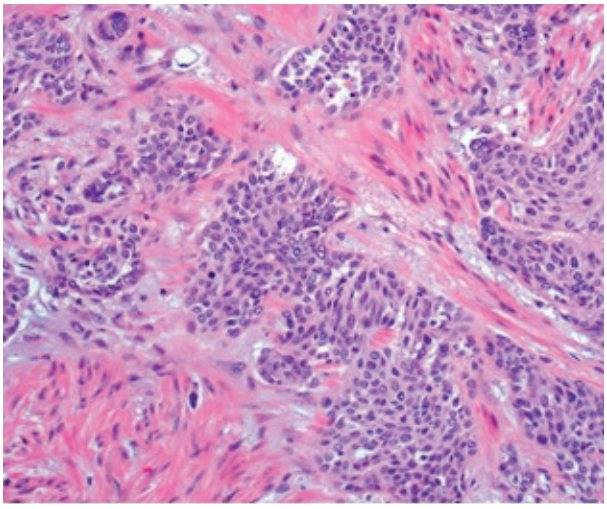

FIGURE 2 Invasive, high-grade urothelial cell carcinoma infiltrating the muscularis propria muscle bundles of the bladder.

thies with a clinical presentation of proximal muscle weakness and characteristic skin findings of Gottron papules and heliotrope eruption. The most common subgroups of inflammatory myopathies are dermatomyositis, polymyositis, necrotizing autoimmune myopathy, and inclusion body myopathy. The pathogenesis of inflammatory myopathies is not well understood; however, some theories have been described, including: type 1 interferon signaling causing myofiber injury and antibody-complement mediated processes causing ischemia resulting in myofiber injury.[2,3] The diagnoses of inflammatory myopathies may be suggested based on history, physical examination findings, laboratory values showing muscle injury (creatine kinase, aldolase, ALT, AST, LDH), myositis-specific antibodies (antisynthetase autoantibodies), electromyogram, and magnetic-resonance imaging. However, muscle biopsy remains the gold standard.[4]

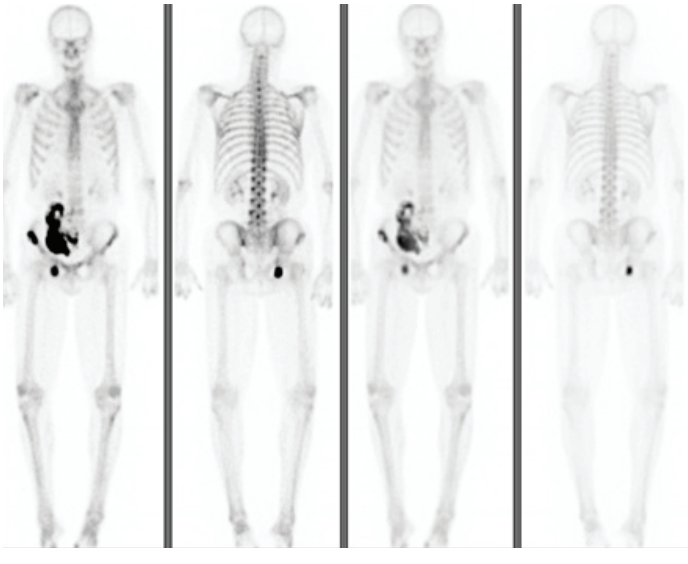

FIGURE 3 Skeletal scintigraphy (bone scan) showing diffuse metastatic lesions in the right acetabulum and ischium, right iliac crest, and left iliac bone.

The initial treatment of inflammatory myopathies begins with glucocorticoid therapy at 0.5-1.0 mg/kg. This regimen may be titrated down over 6 weeks to a level adequate to control symptoms. Even while on glucocorticoid therapy, this patient's symptoms continued, along with the development of dysphagia. Dysphagia is another notable symptom of dermatomyositis that may result in aspiration pneumonia with fatal outcomes.[5,6,7] Not only did this patient initially respond poorly to corticosteroids, but the unintentional weight loss was another alarming feature prompting further evaluation. That led to the diagnosis of urothelial cell carcinoma, which was causing the paraneoplastic syndrome.

A paraneoplastic syndrome is a collection of symptoms that are observed in organ systems separate from the primary disease. This process is mostly caused by an autoimmune response to the tumor and nervous system.[8] Inflammatory myopathies, such as dermatomyositis, have been shown to be associated with a variety of malignancies as part of a paraneoplastic syndrome. The most common cancers associated with dermatomyositis are ovarian, lung, pancreatic, stomach, colorectal, and non-Hodgkin lymphoma.[9] Although an association between dermatomyositis and bladder cancer has been established, very few cases have been reported in the literature. In the Yang meta-analysis, the relative risk of malignancy for patients with dermatomyositis was 5.5%, and of the 449 patients with dermatomyositis who had malignancy, only 8 cases of bladder cancer were reported.[1]

After a patient has been diagnosed with an inflammatory myopathy, there should be further evaluation for an underling malignancy causing a paraneoplastic process. The risk of these patients having a malignancy overall is 4.5 times higher than patients without dermatomyositis.[1] Definite screening recommendations have not been established, but screening should be based on patient's age, gender, and clinical scenario. The European Federation of Neurological Societies formed a task force to focus on malignancy screening of paraneoplastic neurological syndromes and included dermatomyositis as one of the signs.[10] Patients should have a CT scan of the chest, abdomen, and pelvis. Women should have a mammogram and a pelvis ultrasound. Men younger than 50 years should consider testes ultrasound, and patients older than 50 years should undergo usual colonoscopy screening.

The risk of malignancy is highest in the first year after diagnosis, but may extend to 5 years after the diagnosis, so repeat screening should be performed 3-6 months after diagnosis, followed with biannual testing for 4 years. If a malignancy is present, then treatment should be tailored to the neoplasm to improve symptoms of myositis; however, response is generally worse than it would be with dermatomyositis in the absence of malignancy. In the present case with bladder cancer, therapies may include platinum-based-chemotherapy, resection, and radiation. Dermatomyositis as a result of a bladder cancer paraneoplastic syndrome is associated with a poor prognosis as demonstrated in the case of this patient and others reported in the literature.[11]

Even though dermatomyositis is usually a chronic disease process, 87% of patients respond initially to corticosteroid treatment.[12] Therefore, treatment should be escalated with an agent such as azathioprine or methotrexate, or, like in this case, an underlying malignancy should be suspected. This case emphasizes the importance of screening patients appropriately for malignancy in patients with an inflammatory myopathy and reveals the poor prognosis associated with this disease.

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Resolution of refractory pruritus with aprepitant in a patient with microcystic adnexal carcinoma

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Substance P is an important neurotransmitter implicated in itch pathways.[1] After binding to its receptor, neurokinin-1 (NK-1), substance P induces release of factors including histamine, which may cause pruritus.[2] Recent literature has reported successful use of aprepitant, an NK-1 antagonist that has been approved by the US Food and Drug Administration for the treatment of chemotherapy-induced nausea and vomiting, for treatment of pruritus. We report here the case of a patient with microcystic adnexal carcinoma (MAC) who presented with refractory pruritus and who had rapid and complete resolution of itch after administration of aprepitant.

Case presentation and summary

A 73-year-old man presented with a 12-year history of a small nodule on his philtrum, which had been increasing in size. He subsequently developed upper-lip numbness and nasal induration. He complained of 2.5 months of severe, debilitating, full-body pruritus. His symptoms were refractory to treatment with prednisone, gabapentin, doxycycline, doxepin, antihistamines, and topical steroids. At the time of consultation, he was being treated with hydroxyzine and topical pramocaine lotion with minimal relief.

At initial dermatologic evaluation, his tumor involved the lower two-thirds of the nose and entire upper cutaneous lip. There was a 4-mm rolled ulcer on the nasal tip and a 1-cm exophytic, smooth nodule on the left upper lip with palpable 4-cm submandibular adenopathy (Figure). Skin examination otherwise revealed linear excoriations on the upper back with no additional primary lesions. The nodule was biopsied, and the patient was diagnosed with MAC with gross nodal involvement. Laboratory findings including serum chemistries, blood urea nitrogen, complete blood cell count, thyroid, and liver function were normal. Positron emission tomography-computed tomography (PET-CT) imaging was negative for distant metastases.

Treatment was initiated with oral aprepitant – 125 mg on day 1, 80 mg on day 2, and 80 mg on day 3 –with concomitant weekly carboplatin (AUC 1.5) and paclitaxel (30 mg/m^2) as well as radiation. Within hours after the first dose of aprepitant, the patient reported a notable cessation in his pruritus. He reported that after 5 hours, his skin "finally turned off" and over the hour that followed, he had complete resolution of symptoms. He completed chemoradiation with a significant disease response. Despite persistent MAC confined to the philtrum, he has been followed for over 2 years without recurrence of itch.

Discussion

MAC is an uncommon cutaneous malignancy of sweat and eccrine gland differentiation. In all, 700 cases of MAC have been described in the literature; a 2008 review estimated the incidence of metastasis at around 2.1%.[3] Though metastasis is exceedingly rare, the tumor is locally aggressive and there are reports of invasion into the muscle, perichondrium, periosteum, bone marrow, as well as perineural spaces and vascular adventitia.[4]

The clinical presentation of MAC includes smooth, flesh-colored or yellow papules, nodules, or plaques.[3] Patients often present with numbness, par-

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esthesia, and burning in the area of involvement because of neural infiltration with tumor. Despite the rarity of MAC, pruritus has been reported as a presenting symptom in 1 other case in the literature.[4] Our case represents the first report of MAC presenting with a grossly enlarging centrofacial mass, lymph node involvement, and severe full-body pruritus. Our patient responded completely, and within hours, to treatment with aprepitant after experiencing months of failure with conventional antipruritus treatments and without recurrence in symptoms in more than 2 years of follow-up.

Aprepitant blocks the binding of substance P to its receptor NK-1 and has been approved as an anti-emetic for chemotherapy patients. Substance P has been shown to be important in both nausea and itch pathways. The largest prospective study to date on aprepitant for the indication of pruritus in 45 patients with metastatic solid tumors demonstrated a 91% response rate, defined by >50% reduction in pruritus intensity, and 13% recurrence rate that occurred at a median of 7 weeks after initial treatment.[5] Aprepitant treatment has been used with success for pruritus associated with both malignant and nonmalignant conditions in at least 74 patients,[6] among whom the malignant conditions included cutaneous T-cell lymphoma, Hodgkin lymphoma, and metastatic solid tumors.[5-7] Aprepitant has also been used for erlotinib- and nivolumab-induced pruritus in non–small cell lung cancer, which suggests a possible future role for aprepitant in the treatment of pruritus secondary to novel cancer therapies, perhaps including immune checkpoint inhibitors.[8-10]

However, despite those reports, and likely owing to the multifactorial nature of pruritus, aprepitant is not universally effective. Mechanisms of malignancy-associated itch are yet to be elucidated, and optimal patient selection for aprepitant use needs to be determined. However, our patient's notable response supports the increasing evidence that substance P is a key mediator of pruritus and that disruption of binding to its receptor may result in significant improvement in symptoms in certain patients. It remains to be seen whether the cell type or the tendency toward neural invasion plays a role. Large, randomized studies are needed to guide patient selection and confirm the findings reported here and in the literature, with careful documentation of and close attention paid to timing of pruritus relief and improvement in patient quality of life. Aprepitant might be an important therapeutic tool for refractory, malignancy-associated pruritus, in which patient quality of life is especially critical.

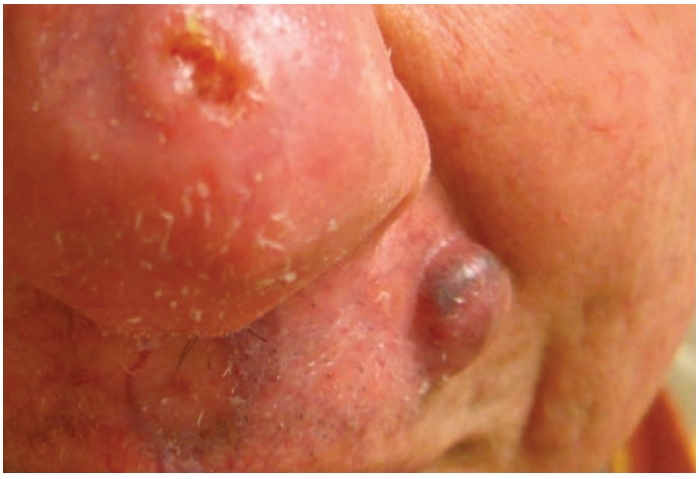

FIGURE Microcystic adnexal carcinoma: centrofacial mass infiltrating the lower two-thirds of the nose, philtrum and entire upper lip.

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Durable response to pralatrexate for aggressive PTCL subtypes

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Peripheral T-cell lymphoma (PTCL) is a heterogeneous group of mature T- and natural killer-cell neoplasms that comprise about 10%-15% of all non-Hodgkin lymphomas in the United States.[1,2] The development of effective therapies for PTCL has been challenging because of the rare nature and heterogeneity of these lymphomas. Most therapies are a derivative of aggressive B-cell lymphoma therapies, including CHOP (cyclophosphamide, hydroxydaunorubicin, vinicristine, prednisone) and CHOEP (cyclophosphamide, hydroxydaunorubicin, vinicristine, etoposide, prednisone).[1] Many centers use autologous or allogeneic stem cell transplant in this setting,[1] but outcomes remain poor and progress in developing effective treatments has been slow.

Pralatrexate is the first drug to have been approved by the US Food and Drug Administration specifically for treating patients with relapsed or refractory PTCL.[3] As a folate analog metabolic inhibitor, pralatrexate competitively inhibits dihydrofolate reductase and reduces cellular levels of thymidine monophosphate, which prevents the cell from synthesizing genetic material and triggers it to undergo apoptosis.[4] The agency's approval of pralatrexate was based on results from the PROPEL study, which is possibly the largest prospective study conducted in patients with relapsed or refractory PTCL (109 evaluable patients).[2] Findings from the study showed an overall response rate (ORR) of 29%, and a median duration of response (DoR) of 10 months.[2]

Pralatrexate is administered intravenously at 30 mg/m2 once weekly for 6 weeks of a 7-week treatment cycle. It is generally continued until disease progression or an unacceptable level of toxicity.[2] Alternative dosing schedules have been described, including 15 mg/m2 once weekly for 3 weeks of a 4-week treatment cycle for cutaneous T-cell lymphomas.[5]

In this case series, we examine the outcomes of 2 patients with particularly aggressive subtypes of PTCL who were treated with pralatrexate. The significance of this report is in describing the long duration of response and reporting on a PTCL subtype – subcutaneous panniculitis-like T-cell lymphoma, alpha/beta type – that was underrepresented in the PROPEL study and is underreported in the literature.

Case presentations and summaries

Case 1

A 23-year-old Asian American man with a medical history of osteogenesis imperfecta presented to Emergency Department at the Hospital of University of Pennsylvania with bilateral lower extremity edema, low-grade fevers, a weight loss of 25 lb, and flat hyperpigmented scaly skin patches across his torso. Symptoms had started manifesting around five months prior to the visit. A punch biopsy of a skin lesion revealed skin tissue with focal infiltrate of small- to medium-sized, atypical lymphocytes infiltrating subcutaneous adipose tissue (panniculitis-like) and adnexa. Immunohistochemical stains showed that the abnormal lymphocytes were positive for CD3, CD8, perforin, granzyme B, TIA-1 (minor subset), and TCR beta; and negative for CD4, CD56, and CD30. Proliferation index (Ki67) was 70%. The findings were consistent with primary subcutaneous panniculitis-like T-cell lymphoma, alpha/beta type (Figure 1). A staging positron-emission tomography–computed tomography (PET–CT) scan demonstrated stage IVB lymphoma with subcutaneous involvement without nodal disease.

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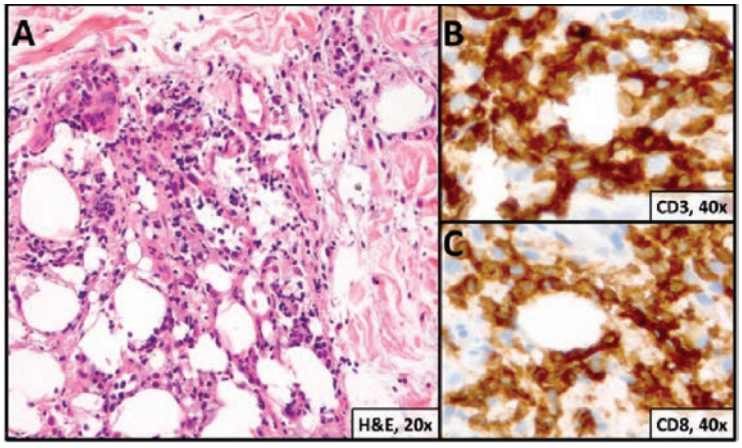

FIGURE 1 Case 1. A, Skin biopsy showing atypical lymphocytes infiltrating subcutaneous adipose tissue (hematoxylin-eosin, x20); **B**, CD3-positive cells (immunohistochemical stain, x40); and **C**, CD8-positive cells neoplastic T-cells, some rimming individual fat cells (magnification highlight, x40).

He was initially treated with aggressive combination regimens including EPOCH (etoposide, prednisolone, vincristine, cyclophosphamide, hydroxydaunorubicin) and ICE (ifosfamide, carboplatin, etoposide), but he had no response and his disease was primary refractory. Because of his osteogenesis imperfecta, he was not a candidate for allogenic stem cell transplant.

He responded to hyperCVAD B combination therapy (methotrexate and cytarabine), but the course was complicated by cytarabine-induced ataxia and dysarthia. He was then treated with 3 months of intravenous alemtuzumab without response. Intravenous methotrexate (2,000 mg/m^2) was then used for 3 cycles, but this exacerbated his previous cytarabine-induced neurological symptoms and resulted in only partial response with persistent fluorine-18-deoxyglucose (FDG) avid lesions on a subsequent PET–CT scan.

At that point, the patient was started on pralatrexate at 15 mg/m^2 weekly for 3 weeks on a 4-week cycle schedule. This was his fifth line of therapy and at 16 months from his initial diagnosis. This dosage was continued for 6 months, and he tolerated the therapy well. He reported no exacerbations of his dysarthia, and by the second month, he had achieved clinical and radiographic remission with complete resolution of B symptoms (fevers, night sweats, and weight loss). The dosing was modified to 15 mg/m^2 every 2 weeks for 3 months. A whole body PET–CT scan showed resolution of previously FDG avid lesions.

The patient was then continued on 15 mg/m^2 pralatrexate every 3 weeks for 1 year and he has been maintained on once-a-month dosing for a second and now third year of therapy. He continues to tolerate the therapy and remains disease free at nearly 2 years since starting pralatrexate.

Case 2

A 64-year-old white man with a medical history of myasthenia gravis (in remission) and invasive thymoma (after thymectomy) presented with diffuse bulky lymphadenopathy and lung lesions to outpatient clinic at the Abramson Cancer Center at the University of Pennsylvania. His LDH was elevated (278 U/L, reference range 98-192 U/L). Excisional biopsy of a left inguinal lymph node revealed sheets of mitotically active large cells with oval to irregular nuclei, clumped chromatin, conspicuous and sometimes multiple nucleoli, and ample eosinophilic cytoplasm. Immunohistochemical staining showed that the neoplastic cells were positive for CD3, CD4, CD30, BCL2 (variable), and MUM1; and negative for ALK 1, CD5, CD8, CD15, CD43, and CD56. Proliferation index (Ki67) was 90% (Figure 2). PET-CT scan showed widespread hypermetabolic lymphoma in the chest, neck, abdomen, and pelvis with pulmonary metastases. Imaging also demonstrated FDG-avid lesions in the gastric and sinus area. The findings were consistent with ALK-negative, anaplastic large cell lymphoma. He was stage IVA; had gastric, lung, and sinus involvement; and disease above and below the diaphragm.

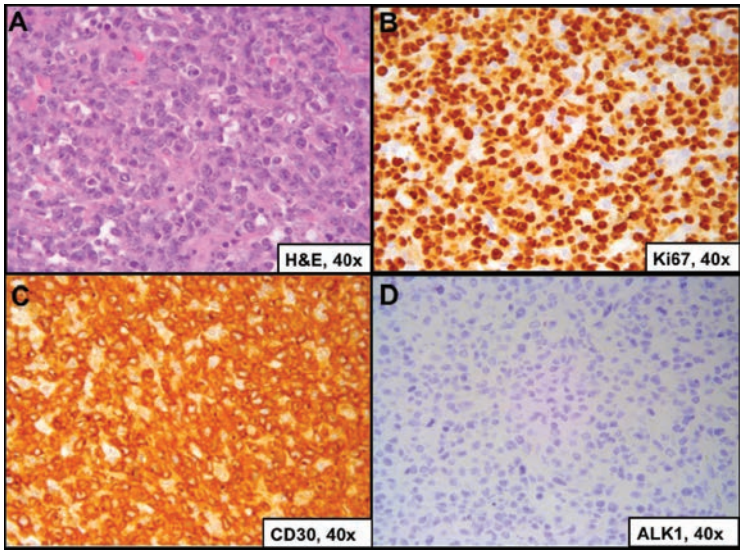

FIGURE 2 Case 2. A, Work-up of excisional biopsy for left inguinal lymph node (hematoxylin-eosin, x40); **B**, Ki67, x40; **C**, CD30-positive cells (immunohistochemical stain, x40); and **D**, cells positive for anaplastic lymphoma kinase-1 (immunohistochemical stain, x40).

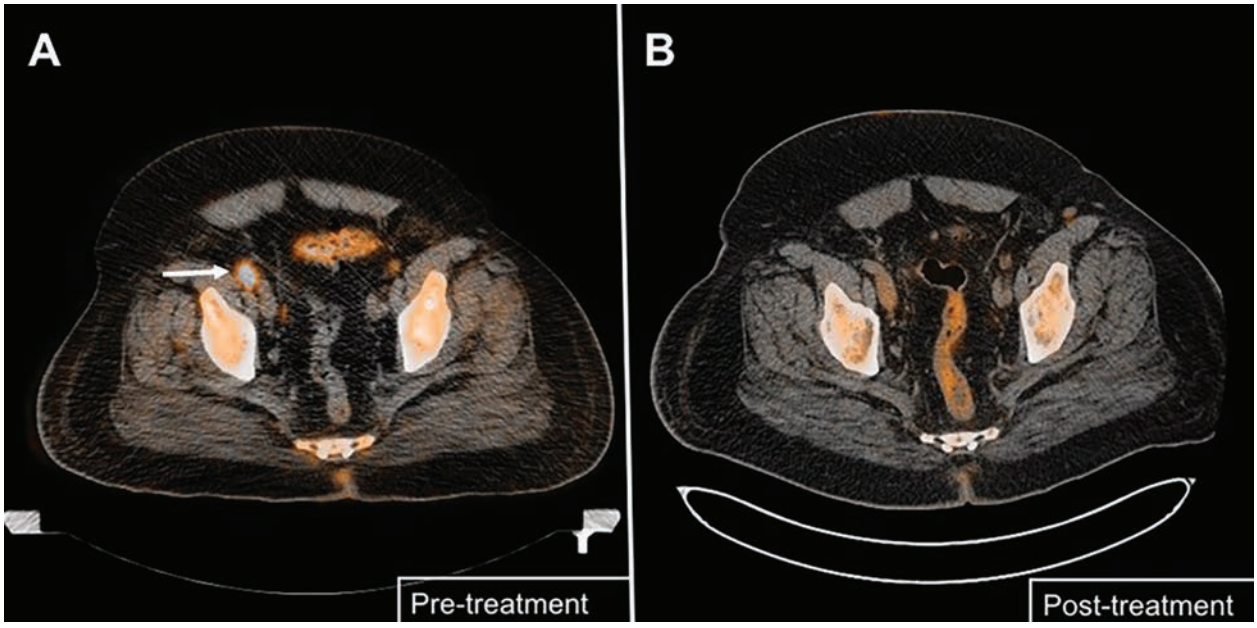

FIGURE 3 Case 2. PET-CT scans A, pretreatment, pelvic region, showing fluorine-18-deoxyglucose -activity in the right external iliac lymph nodes. **B**, post-treatment, pelvic region, showing interval resolution of FDG uptake in the right external iliac lymph nodes.

The patient was initially treated with 6 cycles of CHOP and intrathecal methotrexate injections. His post-treatment PET–CT scan showed persistent FDG-avid disease and his LDH level remained elevated. He underwent 1 cycle of ICE and then BCV (busulfan, cyclophosphamide, etoposide) autologous stem cell transplant. Post-transplant PET–CT scan showed improvement from previous 2 scans but still showed several hypermetabolic lymph nodes consistent with persistent disease.

The patient was started on a pralatrexate regimen of 30 mg/m^2 once weekly for 6 weeks of a 7-week treatment cycle. After 5 doses, he developed thrombocytopenia and mucositis, which were deemed pralatrexate related. The dosage was reduced to 20 mg/m^2 once weekly with variable frequency depending on tolerability. His response assessment with PET–CT scan demonstrated radiographic complete response with resolution of hypermetabolic lesions (Figure 3B). He then proceeded with pralatrexate for 4 more doses. PET-CT imaging 2 months after the last dose of pralatrexate was consistent with metabolic complete response, and he opted to hold further therapy. His last imaging at 4 years after completion of therapy showed continued remission. At press time, he had been clinically disease free for more than 6 years after his last dose of pralatrexate.

Discussion

PTCL is a rare and heterogeneous lymphoma with poor prognosis. Only 3 agents – pralatrexate, belinostat, and romidespin – have been approved specifically for the treatment of PTCL and all of them have an ORR of less than 30%, based on findings from phase 2 studies.[2,6,7] In the PROPEL study, pralatrexate showed an ORR of 29% and a median DoR of 10 months.[2] Those results could be considered discouraging, but some PTCL patients may have durable response to pralatrexate monotherapy.

In this case series, each of the patients presented with a particularly aggressive subtype of PTCL, and 1 suffered from a notably rare subtype for which there was scant clinical data to guide treatment. Both patients went through several lines of aggressive treatment that were ineffective and resulted in minimal response. However, both were able to achieve complete resolution of their disease and maintained remission for a significant duration of time after treatment with pralatrexate. In addition, each patient has maintained his remission – one for 6 years after the last dose. These are noteworthy results, and give both patients and clinicians hope that this therapy can be highly effective in some settings.

A better understanding at the molecular level of the oncogenic mechanisms in PTCL patients will be necessary to guide our therapy choices. In these 2 cases, it is likely that the tumor demonstrated superior sensitivity to dihydrofolate reductase inhibition by pralatrexate. In the future, we hope that analysis of the tumor tissue from PTCL patients will allow us to better categorize the tumor sensitivities to particular therapeutic agents. We believe that individualized treatment will lead to better overall outcomes in this challenging group of lymphomas.

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Isolated ocular metastases from lung cancer

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Non–small cell lung cancer constitutes 80%-85% of lung cancers, and 40% of NSCLC are adenocarcinoma. It is rare to find intra-ocular metastasis from lung cancer. In this article, we present the case of a patient who presented with complaints of diminished vision redness of the eye and was found to have intra-ocular metastases from lung cancer.

Case presentation and summary

A 60-year-old man with a 40-pack per year history of smoking presented to multiple ophthalmologists with complaints of decreased vision and redness of the left eye. He was eventually evaluated by an ophthalmologist who performed a biopsy of the anterior chamber of the eye. Histologic findings were consistent with adenocarcinoma of lung primary (Figures 1 and 2).

After the diagnosis, a chest X-ray showed that the patient had a left lower lung mass. The results of his physical exam were all within normal limits, with the exception of decreased visual acuity in the left eye. The results of his laboratory studies, including complete blood count and serum chemistries, were also within normal limits. Imaging studies – including a computed-tomography (CT) scan of the chest, abdomen, and pelvis and a full-body positron-emission tomography–CT scan – showed a hypermetabolic left lower lobe mass 4.5 cm and right lower paratracheal lymph node metastasis 2 cm with a small focus of increased uptake alone the medial aspect of the left globe (Figures 3 and 4).

An MRI orbit was performed in an attempt to better characterize the left eye mass, but no optic lesion was identified. A biopsy of the left lower lung mass was consistent with non–small-cell lung cancer (NSCLC). Aside from the isolated left eye metastases, the patient did not have evidence of other distant metastatic involvement.

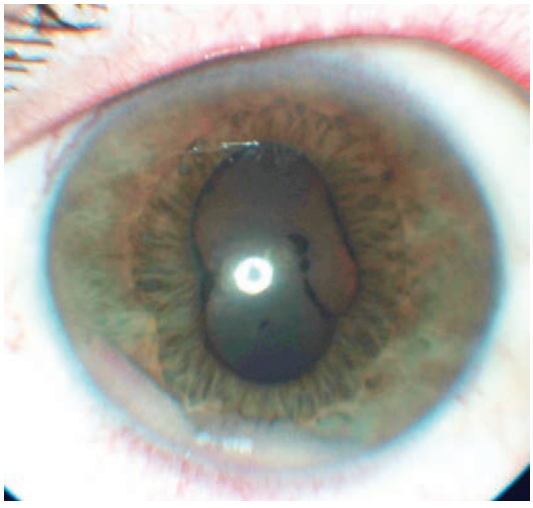

FIGURE 1 The anterior chamber of the eye, showing cellular keratin precipitates, 1+ cellular debris inferiorly, without any iris nodules or lesions.

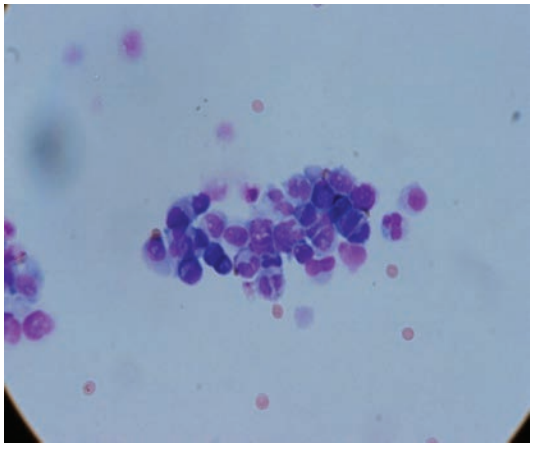

FIGURE 2 Histopathology of the anterior chamber fluid showing cellular debris and malignant cells consistent with adenocarcinoma of the lung. The stain was CK7 positive, CK20 negative, and TTF-1 positive.

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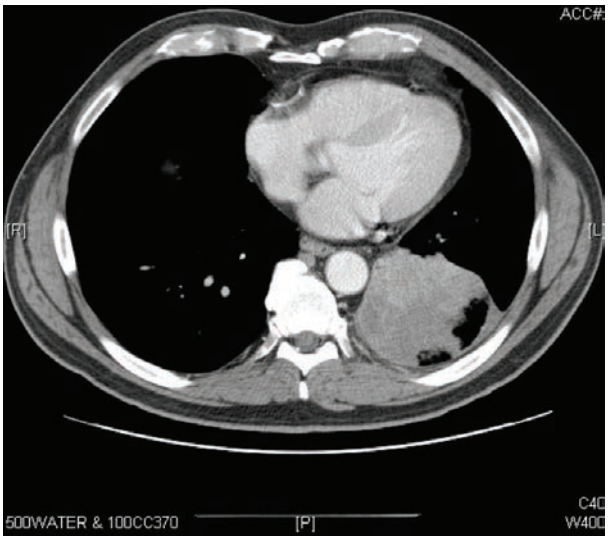

FIGURE 3 Computed-tomography chest scan with contrast demonstrating a left lower lung mass.

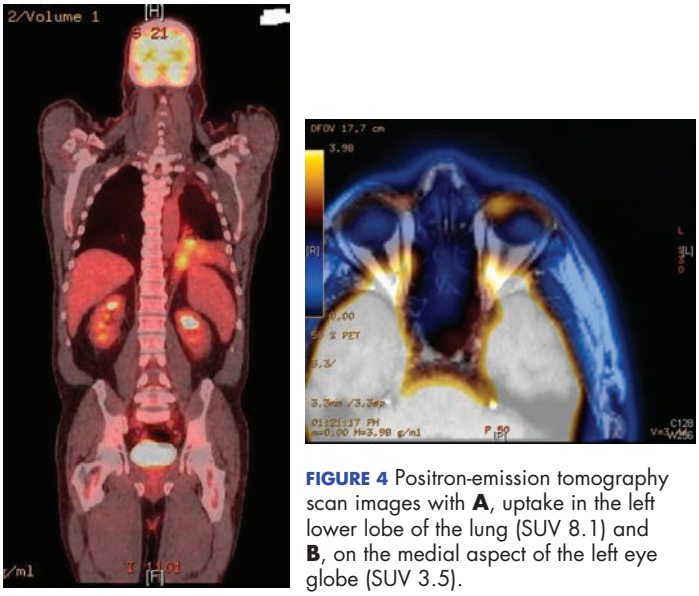

FIGURE 4 Positron-emission tomography scan images with **A**, uptake in the left lower lobe of the lung (SUV 8.1) and **B**, on the medial aspect of the left eye globe (SUV 3.5).

He was started on palliative chemotherapy on a clinical trial and received intravenous carboplatin AUC 6, pemetrexed 500 mg/m^2, and bevacizumab 15 mg/kg every 3 weeks. He received 1 dose intraocular bevacizumab injection before initiation of systemic chemotherapy as he was symptomatic from the intraocular metastases. Within 2 weeks after intravitreal bevacizumab was administered, the patient had subjective improvement in vision. Mutational analysis to identify if the patient would benefit from targeted therapy showed no presence of EGFR mutation and ALK gene rearrangement, and that the patient was K-RAS mutant.

After treatment initiation, interval imaging studies (a computed-tomography scan of the chest, abdomen, pelvis; and magnetic-resonance imaging of the brain) after 3 cycles showed no evidence of disease progression, and after 4 cycles of chemotherapy with these drugs, the patient was started on maintenance chemotherapy with bevacizumab 15 mg/kg and pemetrexed 500 mg/m^2.

Discussion

Choroidal metastasis is the most common site of intraocular tumor. In an autopsy study of 230 patients with carcinoma, 12% of cases demonstrated histologic evidence of ocular metastasis.[1] A retrospective series of patients with malignant involvement of the eye, 66% of patients had a known history of primary cancer and in 34% of patients the ocular tumor was the first sign of cancer.[2] The most common cancers that were found to have ocular metastasis were lung and breast cancer.[2] Adenocarcinoma was the most common histologic type of lung cancer to result in ocular metastases and was seen in 41% of patients.[3]

Decreased or blurred vision with redness as the primary complaint of NSCLC is rare. Only a few case reports are available. Abundo and colleagues reported that 0.7%-12% of patients with lung cancer develop ocular metastases.[4] Therefore, routine ophthalmologic screening for ocular metastases in patients with cancer has not been pursued in asymptomatic patients.[5] Ophthalmological evaluation is recommended in symptomatic patients.

Metastatic involvement of two or more other organs was found to be a risk factor for development of choroidal metastasis in patients with lung cancer though in our patient no evidence of other organ involvement was found.[5] The most common site of metastases in patients with NSCLC with ocular metastases was found to be the liver. Choroidal metastases was reported to be the sixth common site of metastases in patients with lung cancer.[5]

Treatment of ocular manifestations has been generally confined to surgical resection or radiation therapy, but advances in chemotherapy and development of novel targeted agents have shown promising results.[7] Median life expectancy after a diagnosis of uveal metastases was reported to be 12 months in a retrospective study, which is similar to the reported median survival in metastatic NSCLC.[8]

Our patient was enrolled in a clinical trial and was treated with a regimen of carboplatin, paclitaxel, and bevacizumab. On presentation, he had significant impairment of vision with pain. He was treated with intravitreal bevacizumab yielding improvement in his visual symptoms. Bevacizumab is a vascular endothelial growth factor receptor monoclonal antibody approved for use in patients with metastatic lung cancer. Other pathways that have been reported in development of lung cancer involve the ALK gene translocation, and EGFR and K-RAS mutations, and

TABLE NSCLC patients treated with targeted therapy

Case	Patient age, y (sex)	Mutations	Chemotherapy	Clinical outcomes
Kim[11]	57 (F)	No mention	Intravitreal bevacizumab and oral erlotinib	Improved vision, regression of metastases
George[12]	42 (F)	No mention	Systemic chemotherapy with carboplatin/paclitaxel/bevacizumab	Improved vision, regression of metastases
Inoue[13]	68 (F)	No mention	Oralgeftinib	Improved vision, regression of metastases
Singh[6]	42 (F)	No mention	Systemic chemotherapy with cisplatin, paclitaxel with intravitreal bevacizumab, followed by gefitinib for disease progression	Patient lost to follow-up, but eye symptoms improved after intravitreal bevacizumab
Singh[6]	53 (M)	No mention	Systemic chemotherapy with cisplatin, permetrexed and intravitreal bevacizumab, followed by systemic bevacizumab and oral erlotinib on disease prrogression	Vision did not improve due to retinal detachment. Patient died after 16 mo with disease progression
	52 (F)	EGFR+	Oral geftinib	Improved vision
Feng[15]	62 (F)	ALK+	Systemic chemotherapy with carboplatin and pemetrexed with radiation to the eyes with no response; crizotinib started when ALK results were positive.	Improvement in vision with complete resolution of ocular lesions on imaging
Current case	60 (M)	EGFR–, K-RAS+, ALK translocation negative	Systemic chemotherapy with carboplatin, paclitaxel and bevacizumab; intravitreal therapy with bevacizumab	Improvement in vision after first intravitreal bevacizumab injection and regression of systemic metastases

targeted therapy has shown good results in cancer patients with these molecular defects. Randomized clinical trials in patients with advanced NSCLC and an EGFR mutation have shown significant improvement in overall survival with the use of erlotinib, a tyrosine kinase inhibitor targeting the epidermal growth factor receptor.[9] Similarly, crizotinib has shown promising results in patients with metastatic NSCLC who have ELM-ALK rearrangement.[10] As our patient's tumor did not have either of these mutations, he was initiated on chemotherapy with bevacizumab. The presence of a K-RAS mutation in this patient further supported the use of front-line chemotherapy given that it may confer resistance against agents that target the EGFR pathway.

In our review of the literature, we found cases of patients with ocular metastases who responded well to therapy with targeted agents (Table). Singh and colleagues did a systematic review of 55 cases of patients with lung cancer and choroidal metastases and found that the type of therapy depended on when the diagnosis had been made in relation to the advent of targeted therapy: cases diagnosed before targeted therapy had received radiation therapy or enucleation.[6] As far as we could ascertain, there have been no randomized studies evaluating the impact of various targeted therapies or systemic chemotherapy on ocular metastases, although case reports have documented improvement in vision and regression of metastases with such therapy.

Conclusion

The goal of therapy in metastatic lung cancer is palliation of symptoms and improvement in patient quality of life with prolongation in overall survival. The newer targeted chemotherapeutic agents assist in achieving these goals and may decrease the morbidity associated from radiation or surgery with improvement in vision and regression of ocular metastatic lesions. Targeted therapies should be considered in the treatment of patients with ocular metastases from NSCLC.

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Immunotherapy may hold the key to defeating virally associated cancers

Jane de Lartigue, PhD

Infection with certain viruses has been causally linked to the development of cancer. In recent years, an improved understanding of the unique pathology and molecular underpinnings of these virally associated cancers has prompted the development of more personalized treatment strategies, with a particular focus on immunotherapy. Here, we describe some of the latest developments.

The link between viruses and cancer

Suspicions about a possible role of viral infections in the development of cancer were first aroused in the early 1900s. The seminal discovery is traced back to Peyton Rous, who showed that a malignant tumor growing in a chicken could be transferred to a healthy bird by injecting it with tumor extracts that contained no actual tumor cells.[1]

The infectious etiology of human cancer, however, remained controversial until many years later when the first cancer-causing virus, Epstein-Barr virus (EBV), was identified in cell cultures from patients with Burkitt lymphoma. Shortly afterward, the Rous sarcoma virus was unveiled as the oncogenic agent behind Rous' observations.[2]

Seven viruses have now been linked to the development of cancers and are thought to be responsible for around 12% of all cancer cases worldwide. The burden is likely to increase as technological advancements make it easier to establish a causal link between viruses and cancer development.[3]

In addition to making these links, researchers have also made significant headway in understanding how viruses cause cancer. Cancerous transformation of host cells occurs in only a minority of those who are infected with oncogenic viruses and often occurs in the setting of chronic infection.

Viruses can mediate carcinogenesis by direct and/or indirect mechanisms (Figure 1). Many of the

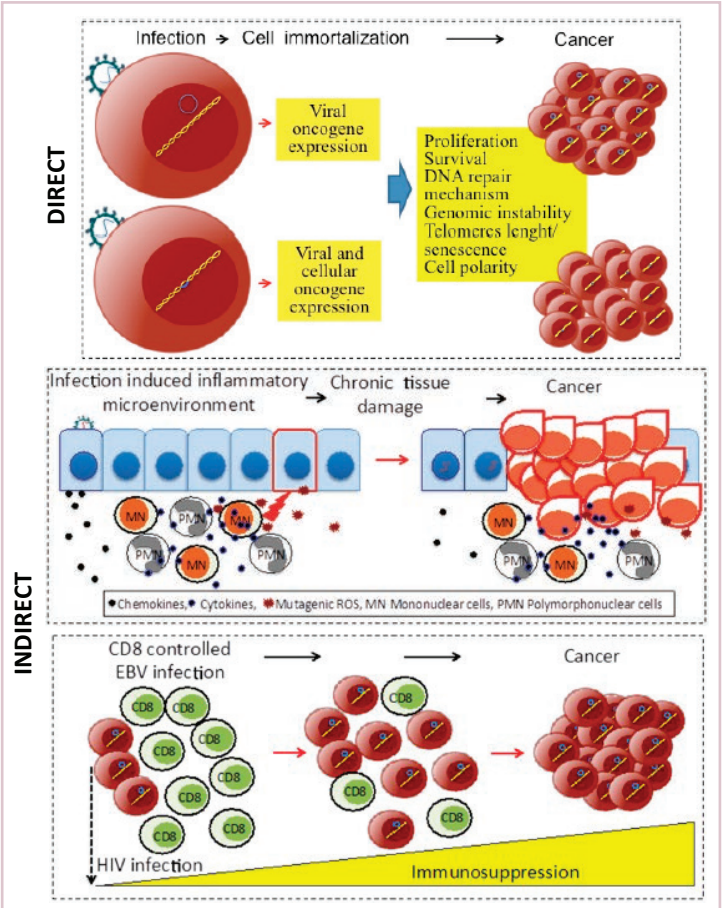

FIGURE Direct and Indirect Mechanisms of Viral Carcinogenesis. Viruses can directly mediate carcinogenesis by integration of viral oncogenic genes or by enhancement of already existing oncogenic genes into the host genome, thereby promoting many of the hallmarks of cancer (top panel). They can also indirectly promote cancer development by fostering a chronic inflammatory microenvironment and local tissue damage (middle panel) and via immunosuppression (bottom panel).

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TABLE 1 The burden of virally associated cancers

Virus type	Type of virus	Associated cancer(s)	Incidence	Percentage of global cancers
Hepatitis B (HBV)	DNA	Hepatocellular carcinoma	>50% cases	4.9
Hepatitis C (HCV)	RNA	Hepatocellular carcinoma	27% cases	4.9
Human papillomavirus (HPV)	DNA	Cervical cancer Anal cancer Vulvar cancer Vaginal cancer Head and neck squamous cell carcinoma Penile cancer	>99% cases Up to 93% cases 50% cases 65% cases 45-90% cases 35%	5.2
Human T-lymphotropic virus 1 (HTLV-1)	RNA	Adult T-cell leukemia/lymphoma	<10% cases	.03
Kaposi sarcoma-associated herpesvirus/human herpesvirus 8 (KSHV/HHV-8)	DNA	Kaposi sarcoma Multicentric Castleman disease Primary effusion lymphoma	All cases	0.9
Merkel cell polyomavirus (MCV)	DNA	Merkel cell carcinoma	80% cases	Unknown
Epstein-Barr virus (EBV)	DNA	Burkitt lymphoma Nasopharyngeal Classic Hodgkin lymphoma Posttransplantation lymphoproliferative disease Diffuse large B-cell lymphoma Gastric cancer	99% cases >99% cases 40% cases Most cases 20% cases 8.7% cases	1-1.5

hallmarks of cancer, the key attributes that drive the transformation from a normal cell to a malignant one, are compatible with the virus's needs, such as needing to avoid cell death, increasing cell proliferation, and avoiding detection by the immune system.

Viruses hijack the cellular machinery to meet those needs and they can do this either by producing viral proteins that have an oncogenic effect or by integrating their genetic material into the host cell genome. When the latter occurs, the process of integration can also cause damage to the DNA, which further increases the risk of cancer-promoting changes occurring in the host genome.

Viruses can indirectly contribute to carcinogenesis by fostering a microenvironment of chronic inflammation, causing oxidative stress and local tissue damage, and by suppressing the antitumor immune response.[4,5]

Screening and prevention efforts have helped to reduce the burden of several different virally associated cancers. However, for the substantial proportion of patients who are still affected by these cancers, there is a pressing need for new therapeutic options, particularly since genome sequencing studies have revealed that these cancers can often have distinct underlying molecular mechanisms.

Vaccines lead the charge in HPV-driven cancers

German virologist Harald zur Hausen received the Nobel Prize in 2008 for his discovery of the oncogenic role of human papillomaviruses (HPVs), a large family of more than 100 DNA viruses that infect the epithelial cells of the skin and mucous membranes. They are responsible for the largest number of virally associated cancer cases globally – around 5% (Table 1).

A number of different cancer types are linked to HPV infection, but it is best known as the cause of cervical cancer. The development of diagnostic blood tests and prophylactic vaccines for prevention and early intervention in HPV infection has helped to reduce the incidence of cervical cancer. Conversely, another type of HPV-associated cancer, head and neck squamous cell carcinoma (HNSCC), has seen increased incidence in recent years.

HPVs are categorized according to their oncogenic potential as high, intermediate, or low risk. The high-risk HPV16 and HPV18 strains are most commonly associated with cancer. They are thought to cause cancer predominantly through integration into the host genome. The HPV genome is composed of 8 genes encoding proteins that regulate viral replication and assembly. The E6 and E7 genes are the most highly oncogenic; as the HPV DNA is inserted into the host genome, the transcriptional regulator of E6/E7 is lost, leading to their increased expression. These genes have significant oncogenic potential because of their interaction with 2 tumor suppressor proteins, p53 and pRb.[6,7]

The largest investment in therapeutic development for HPV-positive cancers has been in the realm of immunotherapy in an effort to boost the anti-tumor immune response. In

TABLE 2 Ongoing clinical trials in HPV-associated tumors

Drug	Developer	Mechanism of action	Stage of development/indication
Axalimogene filolisbac (AXAL/ADXS11-001)	Advaxis	Therapeutic vaccine	Phase 3 cervical cancer (AIM2CERV; NCT02853604) Phase 2 NSCLC (NCT02531854) Phase 1/2 HNSCC (NCT02291055)
TG4001	Transgene	Therapeutic vaccine	Phase 1/2 HNSCC (NCT03260023)
GX-188E	Genexine	Therapeutic vaccine	Phase 1/2 cervical cancer (NCT03444376)
VGX-3100	Inovio	Therapeutic vaccine	Phase 3 cervical cancer (REVEAL; NCT03185013) Phase 2 vulvar cancer (NCT03180684)
MEDI-0457 (INO-3112)	Inovio	Therapeutic vaccine	Phase 2 HPV+ cancers (NCT03439085) Phase 1/2 HNSCC (NCT03162224)
INO-3106	Inovio	Therapeutic vaccine	Phase 1 HPV+ cancers (NCT02241369)
TA-CIN	Cancer Research Technology	Therapeutic vaccine	Phase 1 cervical cancer (NCT02405221)
TA-HPV	Cancer Research Technology	Therapeutic vaccine	Phase 1 cervical cancer (NCT00788164)
ISA-101	Isa	Therapeutic vaccine	Phase 2 HNSCC (NCT03258008)
PepCan	University of Arkansas	Therapeutic vaccine	Phase 2 cervical cancer (NCT02481414)
Nivolumab (Opdivo)	Bristol-Myers Squibb	Immune checkpoint inhibitor	Phase 2 HNSCC (NCT03342911)
AMG319	Amgen	PI3K inhibitor	Phase 2 HNSCC (NCT02540928)
BKM120	Novartis	PI3K inhibitor	Phase 1 HNSCC (NCT02113878)
HPV-specific T cells	Baylor College of Medicine, National Cancer Institute	Adoptive cell therapy	Phase 1 HPV+ tumors (NCT02379520) Phase 1 vulvar cancers (NCT03197025)

HPV, human papillomavirus; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; PI3K, phosphatidylinositol-3-kinase

particular, there has been a focus on the development of therapeutic vaccines, designed to prime the anti-tumor immune response to recognize viral antigens. A variety of different types of vaccines are being developed, including live, attenuated and inactivated vaccines that are protein, DNA, or peptide based. Most developed to date target the E6/E7 proteins from the HPV16/18 strains (Table 2).[8,9]

Leading the pack is axalimogene filolisbac (AXAL; ADXS11-001), a live, attenuated vaccine in which the *Listeria monocytogenes* bacterium is bioengineered to secrete the HPV16 E7 protein, fused to a fragment of listeriolysin O, the main virulence factor of this bacterium.[10,11]

The vaccine showed significant promise in early-stage clinical trials, with a good safety profile and evidence of antitumor activity. The results of a phase 2 study (GOG/NRG 0265) were presented at the 2017 Society of Gynecology Oncology annual meeting. A total of 50 patients with recurrent metastatic cervical cancer had been treated with AXAL, all of whom had received at least 1 prior line of systemic therapy for metastatic disease. Researchers reported a 1 year survival rate of 38%, unprecedented in this patient population.[12]

In a separate phase 2 trial AXAL was evaluated as monotherapy or in combination with cisplatin in patients with previously treated cervical cancer and demonstrated a 1 year survival rate of 32%.[13] The phase 3 AIM2CERV trial of AXAL as adjuvant monotherapy, to prevent recurrence in patients with high-risk cervical cancer treated with chemoradiation is currently ongoing, as are several trials in other types of HPV-positive cancer.

Other immunotherapies are also being evaluated, including immune checkpoint inhibitors, antibodies designed to target one of the principal mechanisms of immune evasion exploited by cancer cells. The combination of immune checkpoint inhibitors with vaccines is a particularly promising strategy in HPV-associated cancers. At the European Society for Medical Oncology Congress in 2017, the results of a phase 2 trial of nivolumab in combination with ISA-101 were presented.

Among 24 patients with HPV-positive tumors, the majority oropharyngeal cancers, the combination elicited an overall response rate (ORR) of 33%, including 2 complete responses (CRs). Most adverse events (AEs) were mild to moderate in severity and included fever, injection site reactions, fatigue and nausea.[14]

TABLE 3 Ongoing clinical trials in HBV/HCV-associated tumors

Drug	Developer	Mechanism of action	Approved indication/clinical testing
Regorafenib (Stivarga)	Bayer	Multitargeted TKI	FDA approved Phase 1 + pembrolizumab (NCT03347292)
Ramucirumab (Cyramza)	Eli Lilly	VEGFR2-targeted mAb	Phase 3 (REACH-2; NCT02435433)
Sorafenib (Nexavar)	Bayer	Multitargeted TKI	FDA approved Phase 3 (NCT01730937, NCT02774187)
Lenvatinib (Lenvima)	Eisai	Multitargeted TKI	Phase 3 (NCT01761266)
Cabozantinib (Cabometyx/ Cometriq)	Exelixis	Multitargeted TKI	Phase 3 (NCT01908426)
Apatinib	LSK	VEGFR2 inhibitor	Phase 3 (NCT02329860, NCT02702323)
Axitinib (Inlyta)	Pfizer	Multitargeted TKI	Phase 2 (NCT01334112)
Capmatinib (INC280)	Novartis	MET inhibitor	Phase 2 (NCT01737827, NCT02795429)
Galunisertib	Eli Lilly	TGF-betaR inhibitor	Phase 2 (NCT01246986, NCT02178358)
TRC105	Tracon	Endoglin-targeted mAb	Phase 2 (NCT02560779)
Tivozanib	Aveo Oncology	VEGFR inhibitor	Phase 2 (NCT01835223)
Vorinostat (Zolinza)	Merck	HDAC inhibitor	Phase 1 (NCT01075113)
Nivolumab (Opdivo)	Bristol-Myers Squibb	Immune checkpoint inhibitor	Phase 3 (NCT03383458, NCT02576509)
Pembrolizumab (Keytruda)	Merck	Immune checkpoint inhibitor	Phase 3 (NCT02702401, NCT03062358)
Durvalumab (Imfinzi)/ tremelimumab	AstraZeneca/ MedImmune	Immune checkpoint inhibitors	Phase 3 (NCT03298451)
Avelumab (Bavencio)	EMD Serono/Pfizer	Immune checkpoint inhibitor	Phase 2 (NCT03389126)

FDA, United States Food and Drug Administration; HBV, hepatitis B virus; HCV, hepatitis C virus; HDAC, histone deacetylase; mAb, monoclonal antibody; TGF-betaR, transforming growth factor beta receptor; TKI, tyrosine kinase inhibitor; VEGFR2, vascular endothelial growth factor receptor 2

Hepatocellular carcinoma: a tale of two viruses

The hepatitis viruses are a group of 5 unrelated viruses that causes inflammation of the liver. Hepatitis B (HBV), a DNA virus, and hepatitis C (HCV), an RNA virus, are also oncoviruses; HBV in particular is one of the main causes of hepatocellular carcinoma (HCC), the most common type of liver cancer.

The highly inflammatory environment fostered by HBV and HCV infection causes liver damage that often leads to cirrhosis. Continued infection can drive permanent damage to the hepatocytes, leading to genetic and epigenetic damage and driving oncogenesis. As an RNA virus, HCV doesn't integrate into the genome and no confirmed viral oncoproteins have been identified to date, therefore it mostly drives cancer through these indirect mechanisms, which is also reflected in the fact that HCV-associated HCC predominantly occurs against a backdrop of liver cirrhosis.

HBV does integrate into the host genome. Genome sequencing studies revealed hundreds of integration sites, but most commonly they disrupted host genes involved in telomere stability and cell cycle regulation, providing some insight into the mechanisms by which HBV-associated HCC develops. In addition, HBV produces several oncoproteins, including HBx, which disrupts gene transcription, cell signaling pathways, cell cycle progress, apoptosis and other cellular processes.[15,16]

Multitargeted tyrosine kinase inhibitors (TKIs) have been the focal point of therapeutic development in HCC. However, following the approval of sorafenib in 2008, there was a dearth of effective new treatment options despite substantial efforts and numerous phase 3 trials. More recently, immunotherapy has also come to the forefront, especially immune checkpoint inhibitors.

Last year marked the first new drug approvals in nearly a decade – the TKI regorafenib (Stivarga) and immune checkpoint inhibitor nivolumab (Opdivo), both in the second-line setting after failure of sorafenib. Treatment options in this setting may continue to expand, with the TKIs cabozantinib and lenvatinib and the immune checkpoint inhibitor pembrolizumab and the combination of durvalumab and tremelimumab hot on their heels.[17-20] Many of these drugs are also being evaluated in the front-line setting in comparison with sorafenib (Table 3).

At the current time, the treatment strategy for patients

TABLE 4 Ongoing clinical trials in other virally associated tumors

Drug	Developer	Mechanism of action	Approved indication/Clinical testing
ATA129 (Tabelecleucel)	Atara	Adoptive cell therapy	Phase 3 EBV+ lymphoproliferative disease (NCT03394365/ALLELE, NCT03392142/MATCH)
EBVST	Tessa	Adoptive cell therapy	Phase 3 EBV+ nasopharyngeal carcinoma (NCT02578641)
CMD-003 (Baltaleucel-T)	Cell Medica	Adoptive cell therapy	Phase 2 EBV+ lymphomas (NCT02763254, NCT01948180/CITADEL)
Avelumab (Bavencio)	EMD Serono/Pfizer	Immune checkpoint inhibitor	Phase 1/2 MCV+ MCC (NCT02584829)
Pembrolizumab (Keytruda)	Merck	Immune checkpoint inhibitor	Phase 2 EBV+ gastric cancer (NCT03257163) Phase 1 KSHV+ Kaposi sarcoma (NCT02595866)
Nivolumab (Opdivo)	Bristol-Myers Squibb	Immune checkpoint inhibitor	Phase 2 EBV+ lymphoproliferative disorders and NHL (NCT03258567) Phase 2 HTLV+ T-cell lymphomas (NCT03075553) Phase 2 MCC (NCT03071406, NCT02196961) Phase 1 KSHV+ Kaposi sarcoma (NCT03316274
Talimogene laherparepvec (Imlygic; T-VEC)	Amgen	Vaccine	Phase 2 MCV+ MCC (NCT02819843, NCT02978625)
Ruxolitinib (Jakafi)	Incyte	JAK inhibitor	Phase 2 HTLV-1+ tumors (NCT01712659)
HBI-8000	Huya	HDAC inhibitor	Phase 2 HTLV-1+ tumors (NCT02955589)
Belinostat (Beleodaq)	Spectrum	HDAC inhibitor	Phase 2 HTLV-1+ tumors (NCT02737046)
Tocilizumab	Hoffman La Roche	IL-6 receptor-targeting mAb	Phase 2 KSHV+ multicentric Castleman disease (NCT01441063)
Pomalidomide (Pomalyst)	Celgene	Immunomodulatory agent	Phase 1/2 KSHV+ Kaposi sarcoma (NCT01495598)
Lenalidomide (Revlimid)	Celgene	Immunomodulatory agent	Phase 1/2 KSHV+ large cell lymphoma (NCT02911142)
Sapanisertib (MLN0128)	Millennium	mTOR inhibitor	Phase 1/2 MCV+ MCC (NCT02514824)
Ibrutinib (Imbruvica)	Pharmacyclics	BTK inhibitor	Phase 2 EBV+ DLBCL (NCT02670616)

BTK, Bruton's tyrosine kinase; DLBCL, diffuse large B cell lymphoma; EBV, Epstein-Barr virus; HDAC, histone deacetylase; HTLV-1, human T lymphotropic virus 1; JAK, Janus kinase; KSHV, Kaposi sarcoma herpesvirus; mAb, monoclonal antibody; MCC, Merkel cell carcinoma; MCV, Merkel cell polyomavirus; mTOR, mammalian target of rapamycin; NHL, non-Hodgkin lymphoma

with HCC is independent of etiology, however, there are significant ongoing efforts to try to tease out the implications of infection for treatment efficacy. A recent meta-analysis of patients treated with sorafenib in 3 randomized phase 3 trials (n = 3,526) suggested that it improved overall survival (OS) among patients who were HCV-positive, but HBV-negative.[21]

Studies of the vascular endothelial growth factor receptor 2-targeting monoclonal antibody ramucirumab, on the other hand, suggested that it may have a greater OS benefit in patients with HBV, while regorafenib seemed to have a comparable OS benefit in both subgroups.[22-25] The immune checkpoint inhibitors studied thus far seem to elicit responses irrespective of infection status.

A phase 2 trial of the immune checkpoint inhibitor tremelimumab was conducted specifically in patients with advanced HCC and chronic HCV infection. The disease control rate (DCR) was 76.4%, with 17.6% partial response (PR) rate. There was also a significant drop in viral load, suggesting that tremelimumab may have antiviral effects.[26,27,28]

Adoptive cell therapy promising in EBV-positive cancers

More than 90% of the global population is infected with EBV, making it one of the most common human viruses. It is a member of the herpesvirus family that is probably best known as the cause of infectious mononucleosis. On rare occasions, however, EBV can cause tumor development, though our understanding of its exact pathogenic role in cancer is still incomplete.

EBV is a DNA virus that doesn't tend to integrate into the host genome, but instead remains in the nucleus in the form of episomes and produces several oncoproteins, including latent membrane protein-1. It is associated with a range

of different cancer types, including Burkitt lymphoma and other B-cell malignancies. It also infects epithelial cells and can cause nasopharyngeal carcinoma and gastric cancer, however, much less is known about the molecular underpinnings of these EBV-positive cancer types.[26,27]

Gastric cancers actually comprise the largest group of EBV-associated tumors because of the global incidence of this cancer type. The Cancer Genome Atlas Research Network recently characterized gastric cancer on a molecular level and identified an EBV-positive subgroup as a distinct clinical entity with unique molecular characteristics.[29]

The focus of therapeutic development has again been on immunotherapy, however in this case the idea of collecting the patients T cells, engineering them to recognize EBV, and then reinfusing them into the patient – adoptive cell therapy – has gained the most traction (Table 4).

Two presentations at the American Society of Hematology annual meeting in 2017 detailed ongoing clinical trials of Atara Biotherapeutics' ATA129 and Cell Medica's CMD-003. ATA129 was associated with a high response rate and a low rate of serious AEs in patients with posttransplant lymphoproliferative disorder; ORR was 80% in 6 patients treated after hematopoietic stem cell transplantation, and 83% in 6 patients after solid organ transplant.[30]

CMD-003, meanwhile, demonstrated preliminary signs of activity and safety in patients with relapsed extranodal NK/T-cell lymphoma, according to early results from the phase 2 CITADEL trial. Among 6 evaluable patients, the ORR was 50% and the DCR was 67%.[31]

Newest oncovirus on the block

The most recently discovered cancer-associated virus is Merkel cell polyomavirus (MCV), a DNA virus that was identified in 2008. Like EBV, virtually the whole global adult population is infected with MCV. It is linked to the development of a highly aggressive and lethal, though rare, form of skin cancer – Merkel cell carcinoma.

MCV is found in around 80% of MCC cases and in fewer than 10% of melanomas and other skin cancers. Thus far, several direct mechanisms of oncogenesis have been described, including integration of MCV into the host genome and the production of viral oncogenes, though their precise function is as yet unclear.[32-34]

The American Cancer Society estimates that only 1500 cases of MCC are diagnosed each year in the United States.[35] Its rarity makes it difficult to conduct clinical trials with sufficient power, yet some headway has still been made.

Around half of MCCs express the programmed cell death ligand 1 (PD-L1) on their surface, making them a logical candidate for immune checkpoint inhibition. In 2017, avelumab became the first FDA-approved drug for the treatment of MCC. Approval was based on the JAVELIN Merkel 200 study in which 88 patients received avelumab. After 1 year of follow-up the ORR was 31.8%, with a CR rate of 9%.[36]

Genome sequencing studies suggest that the mutational profile of MCV-positive tumors is quite different to those that are MCV-negative, which could have therapeutic implications. To date, these implications have not been delineated, given the challenge of small patient numbers, however an ongoing phase 1/2 trial is evaluating the combination of avelumab and radiation therapy or recombinant interferon beta, with or without MCV-specific cytotoxic T cells in patients with MCC and MCV infection.

The 2 other known cancer-causing viruses are human T-lymphotropic virus 1 (HTLV-1), a retrovirus associated with adult T-cell leukemia/lymphoma (ATL) and Kaposi sarcoma herpesvirus (KSHV). The latter is the causative agent of Kaposi sarcoma, often in combination with human immunodeficiency virus (HIV), a rare skin tumor that became renowned in the 1980s as an AIDS-defining illness.

The incidence of HTLV-1- and KSHV-positive tumors is substantially lower than the other virally associated cancers and, like MCC, this makes studying them and conducting clinical trials of novel therapeutic options a challenge. Nonetheless, several trials of targeted therapies and immunotherapies are underway.

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Gastrointestinal cancers: new standards of care from landmark trials

David H Henry, MD,[1] interviews Daniel G Haller, MD, FACP, FRCP[2]

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ASCO 2017 was very eventful with many groundbreaking studies reported across numerous tumor types and subspecialties. Gastrointestinal cancers were no exception. Dr Daniel Haller, former editor of the Journal of Clinical Oncology, discusses some of these breakthroughs in this interview. They include adjuvant therapy in colorectal cancer with the IDEA trial detailing 3 versus 6 months of adjuvant therapy and the subgroup in which 3 months of therapy might be adequate. The right and left colon primary location is becoming more important. Right colon cancers seem worse than left and there are mutations that might explain this. In gastroesophageal cancer, the FLOT trial looked quite promising for response and progression-free survival. Data that led to an FDA approval for checkpoint inhibitor therapy in MSI-high colon cancer was particularly interesting especially given that MSI-high tumors might enjoy a higher response rate. The BILCAP adjuvant trial for biliary cancer demonstrated surprisingly impressive results with capecitabine postoperatively in these difficult patients.

DR HENRY I am Dr David Henry, the Editor-in-Chief of The Journal of Community and Supportive Oncology (JCSO; JCSO-online.com). I'm with Dr Dan Haller, former Editor-in-Chief of the Journal of Clinical Oncology and currently the Editor-in-Chief of American Society of Clinical Oncology (ASCO) University. He is also my friend and former mentor at University of Pennsylvania Abramson Cancer Center, where he is Professor Emeritus. We're going to talk about colorectal cancer and a lot of things that came out of the ASCO meeting this year that were practice changing, or certainly interesting and worth further discussion. I thought we'd start talking about the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration, in which for patients with colorectal cancer who were considering adjuvant postoperative therapy, there was a discussion of 3 cycles versus 6 cycles of FOLFOX (fluorouracil [5-FU] plus oxaliplatin) or XELOX (capecitabine plus oxaliplatin, also CAPOX) (Figure 1).[1] Could you comment on what they did, and how that study turned out?

Dr Haller

DR HALLER The IDEA collaboration was the brainchild of the late Dan Sargent, a biostatistician who was at the Mayo Clinic. It was his idea, since 6 international groups were all testing the same question of 3 months for oxaliplatin to 6 months of oxaliplatin, to combine the data in an individual patient database – which is the best way to do it – so there were these six trials that were all completed.

Three of them were individually reported at ASCO this year, and then the totality was presented at the plenary session – the first time in 12 years that a gastrointestinal (GI) cancer trial made the plenary session. The whole point, obviously, is neuropathy. With 6 months of FOLFOX or XELOX, about 13% or more patients will develop grade 3 neuropathy, even if people stop short of the full-cycle length, and that is a big deal for the 50,000 patients or so who get adjuvant therapy. At the plenary session, the data were presented and the next day three individual trials were presented and discussed by Jeff Meyerhardt (of Dana-Farber Cancer Institute, Boston).

There were 6 different trials: a few included rectum, some included stage II, some used CAPOX and FOLFOX-4 or 6. The only trial that used only FOLFOX was the Cancer and Leukemia Group B (CALGB) trial in the United States (US). There was a lot of heterogeneity, but when Dan was around, I asked him whether that was a problem, and he said

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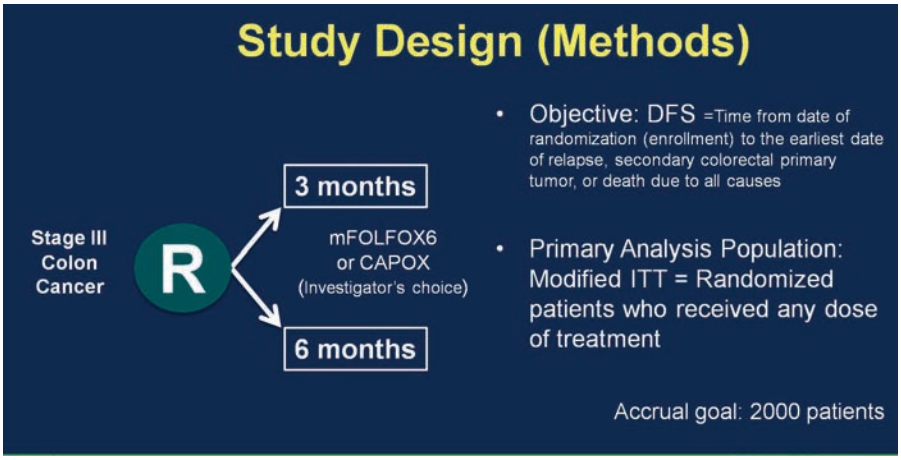

FIGURE 1 The study design of the IDEA [International Duration Evaluation of Adjuvant Chemotherapy] collaboration in which patients with colorectal cancer who were considering adjuvant postoperative therapy, received either 3 cycles or 6 cycles of FOLFOX (fluorouracil [5-FU] plus oxaliplatin) or XELOX (capecitabine plus oxaliplatin, also CAPOX). Reprinted with permission. ©2017 American Society of Clinical Oncology. All rights reserved. Andre T et al: J Clin Oncol 35(15_suppl),2017:3500-3500.

on the contrary, was a better thing because it allowed for real-life practice.

The primary endpoint of the study was to look for noninferiority of 3 months versus 6 months of treatment. The noninferiority margin was at a hazard ratio of 1.12, so they were willing to barter down a few percentage points from benefit. If you looked at the primary disease-free survival analysis, the hazard ratio was 1.07, which was an absolute difference of 0.9%, favoring 3 months of therapy. But because the hazard ratio crossed the 1.12 boundary, it was considered inconclusive and not proven.

If you looked at the regimens, CAPOX outperformed FOLFOX. That's a regimen we don't do much in the US. We tend to use more FOLFOX, but CAPOX looked better. What they then did was look at the different subsets of patients, and the subsets that it was obviously as good in was the group that had T1-3N1 disease, where 3 months of therapy was clearly just as good as 6 months of therapy, with only a 3% risk of grade 3 neuropathy.

DR HENRY That would be one to three nodes?

DR HALLER Exactly. That's about 50% of patients. In the T4N2 patients, neither regimen did very well and the 3-year disease-free survival was in the range of 50%, which is clearly unacceptable. Jeff discussed two things. Why could CAPOX be better? If you do the math, when you do CAPOX, you get more oxaliplatin during the first few months of therapy, because it's 130 mg every 3 weeks, rather than 85 mg every 2 weeks. His conclusion was, "for my next patient who has T4N2 disease, I'll offer 6 months of FOLFOX." The study that really needs to be done in these patients is FOLFOX versus FOLFIRINOX (folinic acid, 5-FU, irinotecan, oxaliplatin) or FOLFOXIRI (folinic acid, 5-FU, oxaliplatin, irinotecan), because we're clearly not doing well with this population of patients. But for the T1-3N1 disease, discuss the toxicities and logistics of CAPOX or FOLFOX with the patient. They'll probably offer 3 months of CAPOX.

He discussed the two new trials. One is a study called ARGO, which is being done by the National Surgical Adjuvant Breast and Bowel Project, where people get standard adjuvant chemotherapy, and they're then randomized to either 24 months of regorafenib 120 mg per day or a placebo. This is an attempt to recreate the transient benefit from bevacizumab in the NSABP C-08 trial. It's accruing slowly because regorafenib has some toxicity associated with it, but it probably will be completed. Will it continue the benefit as seen in the 12 months of bevacizumab and C-08? We'll see.

The other, more interesting study is being done in the cooperative groups looking at FOLFOX plus atezolizumab, one of the checkpoint inhibitors. The difficulty here is that only 15% of people with stage III disease have microsatellite instability (MSI)-high tumors, but it's certainly compelling. This is a straight up comparison. It's 6 months of FOLFOX in the control arm, or 6 months of FOLFOX plus atezolizumab concurrently for 6 months, and then an additional 6 months of atezolizumab. These are both very fascinating ideas.

DR HENRY To go back to one of your original points, this 3 versus 6 months: the neuropathy is significantly less in those getting the 3 months?

DR HALLER It went to 3%.

DR HENRY We all see that is very bothersome to patients. Before we leave colorectal, I must ask about the right-sided versus left-sided colorectal cancer that we hear a lot about now. Could you comment on how right-sided is worse than left-sided, and do we understand why?

DR HALLER There are two things to consider. If you look back even to simple trials of 5-FU or biochemical modulated 5-FU from 20 years ago, there were clear differences showing worse prognosis in patients with right-sided tumors, so that's one point to be made. It's been consistently seen but never acted upon. Then, the explanation for it, possibly, is that the right colon and left colon are two biologi-

cally different organs – and they are. Embryologically, the right colon comes from the midgut and the left colon comes from the hindgut, and there were several presentations at ASCO and at prior meetings showing that when you look at different mutations, they differ between the right and left colons. The right-sided tumors are more MSI-high and more *BRAF*-mutated, left-sided mutations less so.

Then, people started analyzing many of the very large colon cancer trials, including the US trial CALB/SWOG C80405 and the FIRE-3 trials in Europe, where backbone chemotherapy of FOLFIRI or FOLFOX was given with either cetuximab or bevacizumab in RAS wild-type patients. For one study, C80405, they saw that for cetuximab, on the right side, the median survival was 16.7 months and on the left side, it's 36 months – a 20-month difference. In fact, if you look at the totality of the data, 16.7 almost looks like cetuximab is harming them, as if you were giving it to a RAS-mutated patient, but they were not. They were all RAS wild-type.

For bevacizumab, the right side was 24 months; the left side was 31.4 months. If you look at the left, cetuximab was 36 months and bevacizumab was 31.4 months, so it appears left-sided tumors should get more cetuximab than they are now getting in the US with a 5-month difference, but that decrement is much different on the right, where there's an 8-month benefit for bevacizumab compared with cetuximab. There is a very good review by Dirk Arnold, who looked at a totality of 6 studies to really examine this more carefully.[2]

The National Comprehensive Cancer Network has chimed in on this, and is suggesting that for the 25% of people who have right-sided tumors, epidermal growth factor receptor (EGFR) agents not be considered in first-line therapy. NCCN did not go as far to say that EGFR agents should be given on the left side. As I said, the differences are much more impressive in the right, so this is a real sea change for people to consider which side of the tumor affects outcome.

Deb Schrag (Dana-Farber Cancer Institute) presented data at last year's ASCO not only for stage IV disease showing the same thing, but also stage III disease where there are also right-versus-left differences in terms of recurrence, with a hazard ratio on the right side of about 1.4 compared with the left-sided tumors. Maybe it should be true that 3 months is especially good if you're treating left-sided tumors, and maybe the right-sided tumor needs to be also calculated with the factors we just talked about. These are two big changes in an area in which we literally haven't made any change since FOLFOX was introduced a decade ago.

DR HENRY That's really fascinating, and if not practice changing, then practice challenging. Staying with the mutations idea, in my patients, I'm checking the RAS family and the BRAF mutation, where I've learned that's a particularly bad mutation. I wonder if you might comment on the Kopetz trial, which took a cohort of BRAF mutants and treated them (Figure 2).3 How did that turn out?

DR HALLER It turned out well. We're turning colon cancer into non–small cell lung cancer in that we're getting small groups of patients who now have very dedicated care. The backstory here is that there was some thought that you should be treating mutations, not tumor sites. Drugs such as vemurafenib, for example, which is a *BRAF* inhibitor, worked well in melanoma for the same mutation that's in colon cancer, *V600E*. But when vemurafenib was used in the *BRAF*-mutant patients – these are 10% of the population – median survivorship was one-third that of the rest of the patients, so roughly 12 months. People looked like they were doing worse when vemurafenib was used. They had no benefit.

Scott Kopetz at MD Anderson (Houston, Texas) is a very good bench-to-bed-and-back sort of doc. He looked at this in cell lines and found that when you give a BRAF inhibitor, you upregulate EGFR so you add an EGFR inhibitor. He did a phase 1 and 1B study, and then in the co-operative groups, a study was done – a randomized phase 2 trial for people who had the *BRAF-V600E* mutation failing first-line therapy, and then went on to receive either irinotecan single agent or irinotecan plus cetuximab or a triple arm of irinotecan, cetuximab, and vemurafenib. There was a crossover, and so the primary endpoint was progression-free survival. It accrued rapidly.

Again, small study, about 100 patients, but for the double-agent arm, or cetuximab–irinotecan, the median survivorship was 2 months. It was 4.4 months for the combina-

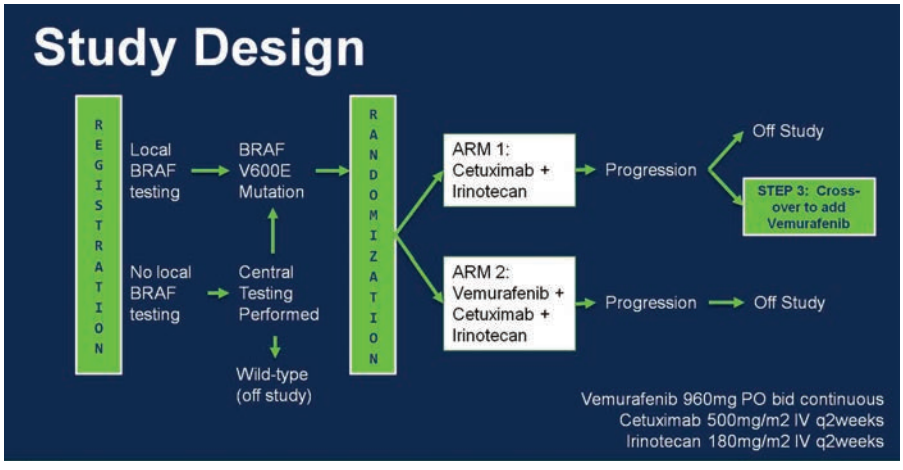

FIGURE 2 The design of the SWOG S1406 study in which patients with BRAF-mutant metastatic colorectal cancer were randomized to receive irinotecan and cetuximab with or without vemurafenib. Reprinted with permission. ©2017 American Society of clinical Oncology. All rights reserved. Kopetz S et al. J Clin Oncol 35(4_suppl),2017:520-520.

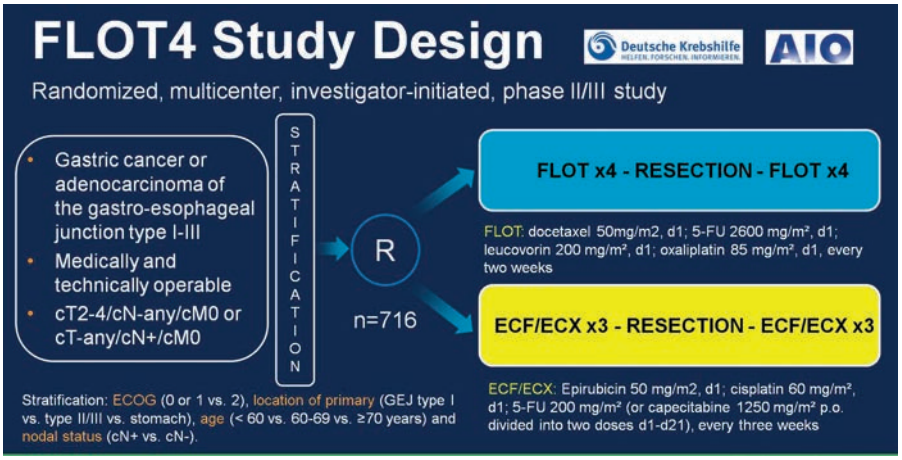

FIGURE 3 The design of the FLOT4 study, a randomized, multicenter phase II/III trial comparing FLOT [docetaxel, fluorouracil, leucovorcin, oxaliplatin) with epirubicin-cisplatin-capecitabine. Reprinted with permission. ©2017 American Society of clinical Oncology. All rights reserved. Al-Batran S-E et al. J Clin Oncol 35(15_suppl),2017:4004-4004.

tion, so more than double. The response rate quadrupled from 4% to 16%, and the people who had disease control tripled, from 22% to 67%. Many of these patients had bulky disease, *BRAF* mutations. They need response, so this is a very important endpoint.

Overall survival was not different, in part because it was a crossover, and the crossover patients did pretty well. This is going to move more toward first-line therapy, because we don't talk about fourth- and fifth-line therapies, TAS-102 or regorafenib. These patients don't make it to even third line. We're chipping away at what we think is a very homogenous group of peoples' metastatic disease. They're obviously not.

DR HENRY In the BRAF-mutant patient, the vemurafenib might drive them toward EGFR, and then the cetuximab could come in and handle that diversion of the pathway. Fascinating.

DR HALLER The preferred regimen in first-line therapy for a *BRAF* mutant might be FOLFIRI, cetuximab, and vemurafenib, especially on the left side.

DR HENRY Certainly makes sense. We'll continue the theme at ASCO of "new standard of care." Let's move to gastroesophageal junction. There was a so-called FLOT (5-FU, leucovorin, oxaliplatin, Taxotere) presentation in the neoadjuvant/adjuvant setting, 4 cycles preoperatively and 4 cycles postoperatively. Could you comment on that study?

DR HALLER Gastric cancer for metastatic disease has a very large buffet of treatment regimens, and some just become entrenched, like the ECF regimen with epirubicin (epirubicin, cisplatin, 5-FU), where most people don't exactly know what the contribution of that drug is, and so some people use EOX (epirubicin, oxaliplatin, capecitabine), some people use FOLFOX, some people use FOLFIRI. It gets a little bit confusing as to whether you use taxanes, platinums, or 5-FU or capecitabine.

The Germans came up with a regimen called FLOT – it's sort of like FOLFOX with Taxotere attached. They did a very large study comparing it with ECF or ECX (epirubicin, cisplatin, capecitabine; Figure 3).[4] The overall endpoint with over 700 patients was survival. This is an adjuvant regimen. Only 37% of people got ECF or ECX postoperatively, and 50% of the FLOT patients got the regimens postoperatively.

One of the reasons FLOT might be more beneficial is that more people were given postoperative treatment, and it's one reason why many adjuvant regimens are being moved completely preoperatively, because so few people get the planned treatment. The FLOT regimen improved overall survival with a *P* value of .0112 and a hazard ratio of 0.77. The difference was 35 months versus 50 months. With the uncertainty as to what epirubicin actually does and the fact that it's been around for a while and that fewer people receive postoperative treatment, with that 15-month benefit, if you're using chemotherapy alone, and there's no radiotherapy component for true gastric cancer, this is a new standard of care.

DR HENRY I struggle with this in my patients as well. This concept of getting more therapy preoperatively to those who can't get it postoperatively certainly resonates with most of us in practice.

DR HALLER If I were redesigning the trial, I would probably say just give 4-6 cycles of treatment, and give it all preoperatively. In rectal cancer, there's the total neoadjuvant approach, where it's being tested in people who get all their chemotherapy first, then chemoradiotherapy, then surgery, and you're done.

DR HENRY Yes, right. Thank you for mentioning that. Staying with the gastric GE junction, you couldn't get away from ASCO this year without hearing about the checkpoint inhibitor immunotherapies in this population. In the CHECKMATE-142 trial with nivolumab versus placebo, response rates were good, especially in the MSI-high (microsatellite instability). Could you comment on that study?

DR HALLER We already know that in May and July 2017,

pembrolizumab and nivolumab were both approved for any MSI-high solid tumor based on phase 2 data only, and based on response. That's the first time we've seen that happen. It's remarkable. For nivolumab, the approval was based on 53 patients with MSI-high metastatic colon cancer. So these were people who failed standard therapy and got nivolumab by standard infusion every 2 weeks. The overall response rate was almost 30% in this population, which is typically quite resistant to any treatment, so one expects much lower response rates with anything in that setting – chemotherapy, TAS-102, regorafenib, et cetera (Table).[5]

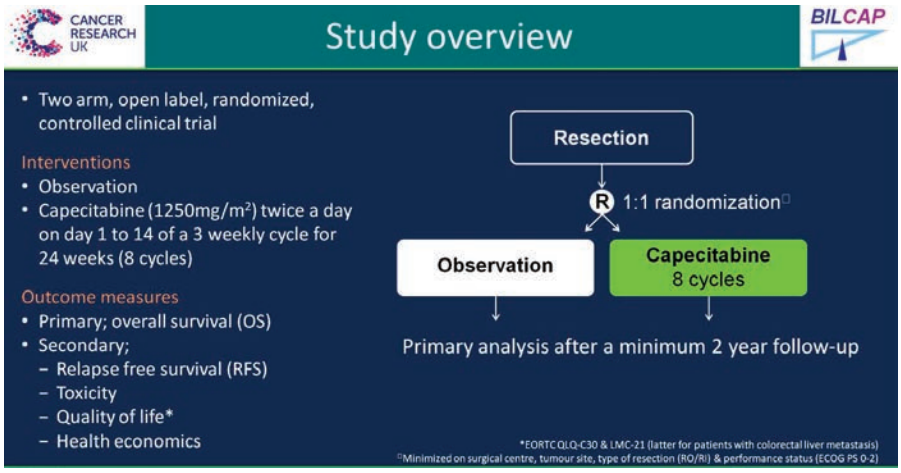

FIGURE 4 The design of the randomized, controlled BILCAP study in which patients received adjuvant capecitabine for biliary tract cancer and were compared with an observation group. Reprinted with permission. ©2017 American Society of clinical Oncology. All rights reserved. Primrose JN et al. J Clin Oncol 35(15_suppl),2017:4006-4006.

More importantly, as we're seeing with Jimmy Carter with checkpoint treatment (for melanoma that had metastasized to the brain), responses lasted for more than 6 months in about two-thirds of patients, even a complete response, so this is just off the wall. I mean, this is not what you would expect with almost any other treatment. The data are the same for atezolizumab and for pembrolizumab. What seems to be true is that in the GI tumors and colon cancer, MSI-high seems more important than expression of PD-1 or PD-L1 (programmed cell death protein-1 or programmed cell death protein-ligand 1).

In different tumor sites, PD-1 or PD-L1 measurement may be important, but in these tumors, and in colorectal cancer, it looks as if MSI-high is the preferred measurement. Recently ASCO, together with the American Society for Clinical Pathology, College of American Pathologists, and Association for Molecular Pathology, came out with guidelines on what you should measure in colorectal cancer specimens. Obviously, one is extended RAS. They say you should get *BRAF* for prognosis, but it may also be a prognostic factor that leads you to treat, which ultimately makes it a predictive factor, so the data from Kopetz might suggest that will move up to something you also must measure. If patients have the *BRAF* mutation, it's important they know that it's a poor prognostic sign. But if they come in with literature saying they might live 36 months when their actual outcome is about a third of that, you need to frame your discussion in that regard and make sure they understand it.

The guidelines also suggested getting MSI-high, and certainly prognostically in early-stage disease, but now it's going to be a predictive factor, so in the month in which these recommendations are made, two of them are already out of date. They also didn't include human epidermal growth factor receptor 2 (HER2), and what we've heard from the HERACLES (HER2 Amplification for Colorectal Cancer Enhanced Stratification) trial is that for those patients who got the trastuzumab and pertuzumab combination – and this is another 5% of patients – almost the same data was seen as in the MSI-high patients with checkpoint inhibitors. That is double-digit response rates and durable responses. As I said, we're very much nearing in colorectal cancer what's now being done in non-small cell lung cancer.

DR HENRY Indeed. Could you comment on the BILCAP study and adjuvant capecitabine for biliary tract cancer?

DR HALLER There are large meta-analyses looking at adjuvant therapy for biliary tract cancers typically from fairly small, fairly old studies that all suggest that in certain stages of resected biliary tumors, either bile duct or gall bladder, adjuvant treatment works, and typically either chemotherapy and radiotherapy, or chemotherapy alone, but not radiotherapy alone.

Capecitabine has been used for metastatic disease for years, mostly by default, and because most GI tumors have some response to fluoropyridines. But we're finally able now to do large trials in biliary tumors, so this trial was a very large study with almost 450 patients from the United Kingdom over an 8-year period. About 20% were gallbladder, so the R0 surgery was about 60%, R1 at about 40% (Figure 4).[6]

The endpoint of the study was survival advantage, and when they did the protocol analysis, the survival for the treated population was 53 months and for the observation arm, 36 months, so that was a hazard ratio of 0.75, which is acceptable in an adjuvant study. It's simple drug to give, and usually tolerable, so this will represent a new standard of care. Of course, in the advanced disease setting, the gemcitabine–cisplatin combination is the standard of care for

Pt	Local Testing		Central Testing	Clinical History of LS
	Method	Result		
1	IHC	dMMR	MSS	NA
2	IHC	dMMR	MSS	No
3	IHC	dMMR	MSS	Yes
4	IHC	dMMR	MSS	Yes
5	IHC/PCR	dMMR (IHC)/MSI-H (PCR)	MSS	NA
6	IHC	dMMR	MSS	Yes
7	IHC	dMMR	MSS	No
8	PCR	MSI-H	MSS	NA
9	IHC/PCR	dMMR (IHC)/MSI-H (PCR)	MSS	NA
10	IHC	dMMR	MSS	No
11	IHC	dMMR	MSS	NA
12	PCR	MSI-H	MSS	NA
13	IHC	dMMR	MSI-L	NA
14	IHC	dMMR	MSS	NA

TABLE In the CHECKMATE-142 trial with nivolumab versus placebo (n = 74), 14 patients had a central test that did not match local test results of whom 3 with a clinical history of LS were identified locally as dMMR but centrally as MSS. Reprinted with permission. ©2017 American Society of clinical Oncology. All rights reserved. Kopetz S et al. J Clin Oncol 35(15_ suppl),2017:3548-3548.

metastatic disease. It's a little more toxic combination, but we know that's standard. There's an ongoing study in Europe called the ACTICCA-1 trial, and this is gemcitabine–cisplatin for 6 months versus not capecitabine, but a control arm. My guess is if the capecitabine study was positive, that this also will be a positive trial, because gemcitabine–cisplatin is probably more active. Then, we'll have 2 standards, and I don't think anyone is going to compare capecitabine with gemcitabine–cisplatin.

What you'll have are two regimens for two different populations of patients. Perhaps for the elderly and people who have renal problems, capecitabine alone will give them benefit, and then you'll have gemcitabine–cisplatin, which may be just a more toxic regimen, but also more effective for the younger, healthier people with fewer comorbidities.

DR HENRY Great data and a small population, but a population in need. That moves us on to pancreatic cancer, and I don't know if this is happening nationwide, but in my practice, I'm seeing more. These patients tend to present beyond surgery, so they have metastatic or advanced pancreatic cancer. Any comment on where you think this field is going?

DR HALLER We were a bit bereft of new pancreatic cancer studies at ASCO this year. We're certainly looking more at neoadjuvant therapy for pancreatic cancer, primarily because of ease of administration and the increased ability to tolerate treatments in the preoperative setting. There aren't many people that get downstaged, but some are. Unfortunately, even in the MSI-high pancreas, which is a small subset, they don't seem to get as big a bang out of the checkpoint inhibitors as in other tumor sites, so I'm afraid I didn't come home with much new about this subset of patients.

DR HENRY We've covered a nice group of studies and practice-changing new standard-of-care comments from ASCO and other studies. Thank Dr Dan Haller for being with us and commenting. This podcast and discussion are brought to you from The Journal of Community and Supportive Oncology, the JCSO. I'm Dr David Henry, and you can listen to this and other archived articles or podcasts at JCSO-online.com. Thanks for listening.

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