Volume 16 • Number 5 • September-October 2018

The Journal of COMMUNITY and Supportive ONCOLOGY®

RESEARCH AND REVIEWS FOR THE PRACTICE-BASED ONCOLOGY CARE TEAM

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Aims and Scope

The Journal of Community and Supportive Oncology (e-ISSN 2330-7757) is published six times a year (January-February, March-April, May-June, September-October, September-October, and November-December) by Frontline Medical Communications Inc, 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609.

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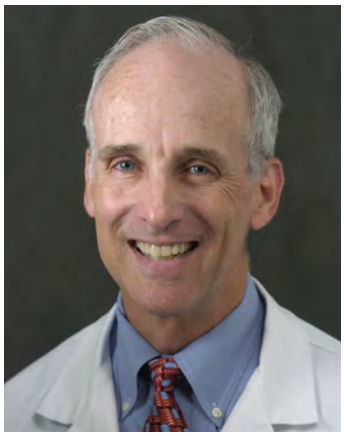
Finding that sweet spot where science, practice, and best-possible outcomes come together

David H Henry, MD, FACP

The practice of oncology and the science driving it have undergone substantial change in recent years, so it was particularly exciting when this year's Nobel Prize for Physiology or Medicine was awarded to James Allison and Tasuko Honjo for their discovery that the body's immune system can be harnessed to fight cancer. The advent of immunotherapy has expanded our therapeutic options, especially for patients whose previous treatments have failed, and in some patients, improvement in overall survival and safety profiles have been encouraging. But we still have a way to go: not all patients respond to immunotherapies, and they are costly. In addition, while chemotherapy supresses the immune system, immune-checkpoint inhibitors can hyperactivate it, and patients can experience serious immune-related adverse events that can result in life-threatening toxicities. Among the many things we grapple with in our daily practice is pairing these new and thrilling findings with our patients on a case-by-case basis to ensure the best-possible outcomes at every level – clinical, psychosocial, financial.



In recent years, we have seen an uptick in the number of FDA approvals, and as our therapeutic options have expanded, we have been able to refine and microtarget our treatment approaches, with encouraging clinical and quality-of-life outcomes. Our approach to practice has changed as well – our care is more patient focused, and we work more as part of a team, rather than individually, to ensure that our patients' clinical and supportive needs are met. We hope our content reflects these shifts. For example, on page e188, Ibrahimi and colleagues looked at the time from admission to treatment initiation (TAT) in patients who were newly diagnosed with acute myeloid leukemia to see if it had an impact on overall survival (OS) and event-free survival. They obtained retrospective data over 5 years, focusing on patients with a TAT of 0-4 days and those with a TAT of >4 days, and found that the median OS in the 0-4 days group was almost double that of the <4 days group (1.3 years and 0.57 years, respectively). Median event-free survival for the groups was 1.21 years and 0.57 years, respectively. Moreover, that association remained significant in a multivariate analysis adjusting for age, white blood cell count, molecular risk group, and undergoing allogeneic stem cell transplant.

Marriage and survival

Does marital status have a prognostic bearing on outcomes in patients with cancer? Vyfhuis and colleagues addressed that question in their study of patients with stage III non–small-cell lung cancer (NSCLC) who had been treated uniformly with curative intent (p. e194). Specifically, they looked at OS and freedom from recurrence and they adjusted for patient-, disease-, and treatment-specific factors, as well as the interaction with racial, nutritional, and immunologic status.

In all, 52% of patients in the study were married, and were more likely to self-identify as white; live in areas with a higher household median income; undergo surgery; and have insurance, an ECOG of 0, and higher pretreatment albumin. The authors report that on multivariate analysis, marital status remained an independent predictor of survival and was associated with a 40% decreased risk of death, further stratifying outcomes beyond gender and stage grouping. Freedom from recurrence was comparable between the married and not-married patients. These findings suggest that in a cancer such as NSCLC, for which survival is modest despite therapeutic advances and which is associated with considerable treatment-related toxicities, marital status might be an independent predictor for survival. The authors suggest that marriage is likely a surrogate for better psychosocial support, and that the survival improvements might justify investment in supportive care interventional strategies to help advance overall outcomes.

JCSO 2018;16(5):e180-e181. ©2018 Frontline Medical Communications. doi: https://doi.org/10.12788/jcso.0431

Cancer in children and AYAs

Two articles in this issue examine cancers in pediatric patients and in adolescents and young adults (AYAs), and by doing so, demonstrate the importance of having evidence-based research findings to help us refine and deliver better-quality, patient-focused care. On page e217, Sharon Worcester documents the growing efforts by researchers and clinicians to understand and address the disparities in survival outcomes between AYAs with cancer and their pediatric and adult counterparts.

It has been known for a while that some cancers are more common among AYAs compared with the other 2 populations, and others are less common. More recent findings suggest that the biology and molecular make-up of AYA cancers might also be different and therefore necessitate different therapeutic protocols, and that the social and psychological needs unique to this population also require specifically tailored supportive care. What about treatment setting for AYAs with cancer – would outcomes be better in a pediatric or adult care center? There is evidence that the pediatric setting might have some advantage, but a recent study from Canada suggests that the cost of care in that setting might be higher. Despite these encouraging findings, there are very few trials designed specifically for the AYA cancer population, and the "pediatric-versus-adult" question also applies to AYA participation in trials. Worcester's comprehensive article weaves together these issues and offers insights and useful explanations from a number of experts who study or care for AYAs with cancers.

Pediatric cancers are rare, representing just 1% of all new cancers diagnosed annually in the United States, but they are the second leading cause of death in children aged 1 to 14 years and therefore warrant attention, writes Jane de Lartigue in an article on page e210. She echoes Worcester's point that better understanding of cancers in this younger population has brought to light their unique molecular drivers and challenged the assumption that drugs developed for adults can be used in children and young adults. Dr de Lartigue drills down into the science behind the unique biology and molecular aberrations in pediatric cancers and provides a useful list of ongoing clinical trials of targeted therapies in this population. She notes that because of their rarity, pediatric cancers are difficult to study and adequate enrollment in trials is challenging, although that is changing with researchers' greater awareness of the uniqueness of these cancers and need for age-specific trials.

Also included in this issue are Community Translation articles on the approval of an immunotherapy combination – nivolumab plus ipilimumab – for the treatment of advanced RCC (p. e182), and for venetoclax as a therapy for patients with chronic lymphocytic leukemia, regardless of genotype (p. e185); and 2 Case Reports, one describing a diagnostic dilemma relating to a patient eventually diagnosed with primary renal synovial sarcoma (p. e202), and another detailing prolonged survival in a patient with adenocarcinoma of unknown primary who was treated with chemoradiotherapy (p. e206).

Nivolumab and ipilimumab combination promises new standard of care for advanced RCC

In April 2018, the US Food and Drug Administration expanded the approval of the combination of nivolumab and ipilimumab into a new indication, following a previous approval in patients with metastatic melanoma. The double immune checkpoint inhibitor combination was approved on the basis of the phase 3 CheckMate-214 study for the treatment of patients with intermediate- or poor-risk, previously untreated advanced renal cell carcinoma (RCC).[1]

Nivolumab monotherapy is already approved in the second-line setting for the treatment of advanced RCC, and the demonstration of significantly improved overall survival (OS) in this study suggests that the combination should supplant sunitinib in the front-line setting in the treatment of this type of cancer.

A total of 1,096 patients at 175 sites in 28 countries were randomized 1:1 to receive nivolumab (3 mg/kg) and ipilimumab (1 mg/kg) intravenously every 3 weeks for 4 doses in an induction phase, followed by nivolumab monotherapy (3 mg/kg) every 2 weeks in a maintenance phase or sunitinib (50 mg) orally daily for 4 weeks of each 6-week cycle.

Eligible patients were 18 years or older, had previously untreated advanced RCC with a clear-cell component, had measurable disease according to Response Evaluation Criteria in Solid Tumors (version 1.1), and had a Karnofsky performance status of at least 70 (on a scale from 0 to 100, with lower scores indicating greater disability). Patients with central nervous system metastases or autoimmune disease who were being treated with glucocorticoids and immunosuppressants were excluded from the study.

Around three-quarters of patients with advanced RCC have intermediate- or poor-risk disease and experience worse outcomes than patients with favorable-risk disease. Patients in CheckMate-214 were stratified according to International Metastatic Renal Cell Carcinoma Database Consortium risk score as favorable (score of 0), intermediate (score of 1 or 2) or poor risk (score of 3-6), according to the number of risk factors present.

Risk factors included a Karnofsky performance score of 70, time from initial diagnosis to randomization of <1 year, a hemoglobin level below the lower limit of normal, a corrected serum calcium concentration of >10 mg/dL, or an absolute neutrophil count or platelet count above the upper limit of normal. Patients were also stratified according to geographic region (United States versus Canada and Europe versus the rest of the world).

The coprimary endpoints were objective response rate (ORR), progression-free survival (PFS), and OS in a subset

What's new, what's important

This approval of the nivolumab–ipilimumab combination for patients with advanced RCC heralds a new standard of care RCC that will likely sideline sunitinib as a first-line therapy given the significant improvements in OS with the double-immunotherapy combination.

The approval was informed by findings from the phase 3 CheckMate-214 study in which patients received either the nivolumab–ipilimumab combination or sunitinib alone. Patients were stratified by risk score (favorable, intermediate, poor risk) and by geographic region. The endpoints were ORR, PFS, and OS in intermediate- and poor-risk patients. Over a median follow-up of 25.2 months, there was a significant improvement in OS and ORR in the study group patients (mPFS not reached; ORR, 41.6%), compared with the controls (OS, 25.9 months; ORR, 26.5%), with P <.001 for both. The combination was favored across subgroups.

The most common AEs with the immunotherapy combination included fatigue, rash, diarrhea, musculoskeletal pain, pruritus, nausea, and others. The combination was associated with fewer grade 3/4 AEs (63% vs 46% for sunitinib), but a higher rate of AE-related treatment discontinuations (31% vs 21%). The study group had 8 treatment-related deaths; the control group, 4.

Warnings include mostly immune-mediated AEs, and risk of infusion reactions and for embryofetal toxicity. Patients should be monitored for hyperglycemia and for changes in liver, thyroid, renal, and neurologic function. New-onset moderate to severe neurologic signs or symptoms warrant treatment being withheld, and immune-mediated encephalitis should lead to treatment discontinuation. Patients should be advised of the potential for fetal harm and the need for effective contraception during and after treatment.

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

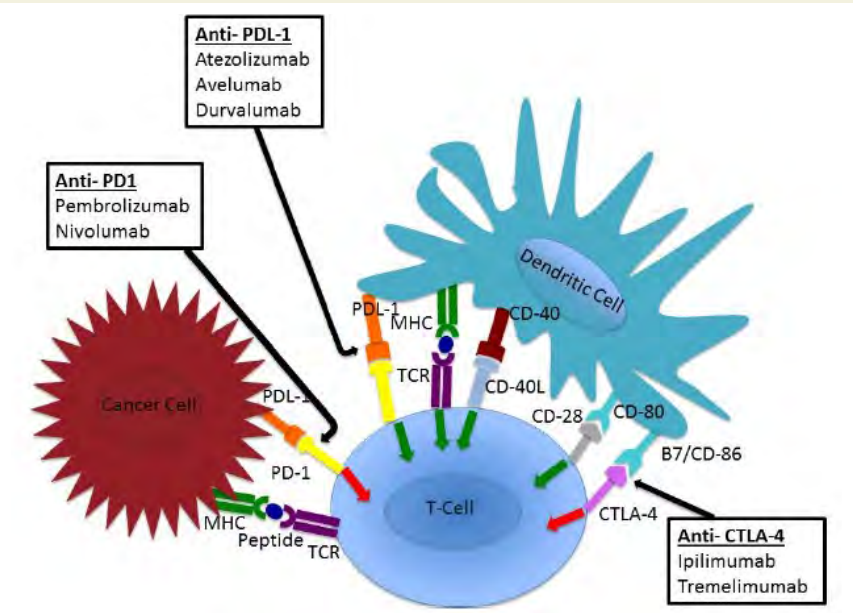
Report prepared by Jane de Lartigue, PhD. JCSO 2018;16(5):e182-e184. ©2018 Frontline Medical Communications. doi: https://doi.org/10.12788/jcso.0421

Mechanism of action: immune checkpoint inhibitors

Dual blockade of immune checkpoints. T cells are central effectors of the adaptive immune response and have also been shown to be activated in response to tumor-cell antigens as part of the anti-tumor immune response, with many tumor types demonstrating high levels of infiltrating T cells in the tumor microenvironment.

To mount an effective immune response, T cells must receive 2 signals, 1 from the T-cell receptor, which is activated by antigen presented by specialized immune cells, and a secondary signal that essentially decides whether the T cell is turned on or off in response to the particular antigen.

The secondary signal is often referred to as an immune checkpoint, can be either stimulatory (the on switch) or inhibitory (the off switch), and helps to ensure that T-cell–mediated immunity is able to eliminate a threat without causing any collateral damage to healthy tissue. It can also be exploited by tumor cells to help them evade the anti-tumor immune response by switching off infiltrating T cells.



Nivolumab and ipilimumab are immune checkpoint inhibitors with complementary mechanisms of action that yield synergistic anti-tumor immune activity. Reproduced under a Creative Commons Attribution license. Good EF, Smyth EC. Immunotherapy for gastroesophageal cancer. J Clin Med. 2016;5:84-98.

Programmed cell death-1 receptor (PD-1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) are 2 of the main inhibitory signals and their ligands are often expressed by tumors. Immune checkpoint inhibitors (drugs targeting these receptors and their ligands) have been successfully used as anticancer therapeutics and are being approved in an expanding range of tumor types.

Nivolumab, which targets PD-1, in particular has proved highly effective as monotherapy. However, a significant number of patients don't respond to nivolumab or develop resistance. Ipilimumab targets CTLA-4 and has been approved for the treatment of metastatic melanoma. Due to their distinct mechanisms of action on different T-cell inhibitory pathways, a combination of nivolumab and ipilimumab has demonstrated synergistic anti-tumor activity in preclinical models and the combination has already been approved for the treatment of metastatic melanoma.

of 847 intermediate- and poor-risk patients. Over a median follow-up of 25.2 months, there was a statistically significant improvement in OS and ORR in patients treated with nivolumab and ipilimumab (mPFS not reached; ORR, 41.6%), compared with sunitinib (OS, 25.9 months; ORR, 26.5%), with $P < .001$ for both. The immunotherapy combination was favored across subgroups.

The most common adverse events (AEs) in patients treated with nivolumab and ipilimumab included fatigue, rash, diarrhea, musculoskeletal pain, pruritus, nausea, cough, pyrexia, arthralgia, and decreased appetite. The combination was associated with fewer grade 3/4 AEs (63% vs 46% for sunitinib), but a higher rate of treatment discontinuations because of AEs (31% vs 21%, respectively). There were 8 deaths in the combination arm, and 4 in the sunitinib arm that were reported to be treatment related.[2]

The warnings and precautions related to nivolumab–ipilimumab combination therapy outlined in the prescribing information include mostly immune-mediated AEs, such as immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin adverse reactions, and encephalitis. There are also warnings relating to the risk of infusion reactions and the potential for embryofetal toxicity.

Patients should be monitored for hyperglycemia and for changes in liver, thyroid, renal, and neurologic function. Treatment with nivolumab and ipilimumab should be withheld for moderate and permanently discontinued for severe or life-threatening immune-mediated pneumonitis, colitis, and hepatitis, as well as transaminase or total bilirubin elevation. It should also be withheld for moderate or severe hypophysitis and serum creatinine

elevation, moderate adrenal insufficiency and severe hyperglycemia, and permanently discontinued for life-threatening hypophysitis and serum creatinine elevation, severe or life-threatening adrenal insufficiency, and life-threatening hyperglycemia.

New-onset moderate to severe neurologic signs or symptoms warrant treatment being withheld, and immune-mediated encephalitis should lead to treatment discontinuation. For mild or moderate infusion reactions, the infusion rate can be slowed or interrupted, and infusions should be discontinued in the event of severe or life-threatening infusion reactions. Patients should be advised of the potential for fetal harm and the need for effective contraception during and after treatment. Ipilimumab and nivolumab are marketed as Yervoy and Opdivo, respectively, by Bristol-Myers Squibb.[3,4]

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Venetoclax approved to treat CLL patients regardless of genotype

The approval of Bcl-2 inhibitor venetoclax was expanded by the US Food and Drug Administration in June 2018 to include the treatment of patients with chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL), regardless of their genotype, who have received at least 1 prior therapy.[1] It was previously approved in 2016 for the treatment of patients who had a chromosome 17p deletion, which leads to loss of the tumor-suppressor gene *TP53*.

Approval was based on the positive results of the phase 3, randomized, multicenter, open-label MURANO trial in which 389 patients were randomized 1:1 to receive a combination of venetoclax and the CD20-targeting monoclonal antibody rituximab (venetoclax–rituximab) or bendamustine in combination with rituximab (bendamustine–rituximab).

Eligible patients were 18 years of age or older, had been diagnosed with relapsed/refractory CLL that required treatment, had received 1-3 prior therapies (including at least 1 chemotherapy regimen), had an Eastern Cooperative Oncology Group performance status of 0 or 1 (on a 5-point scale, with 5 indicating the greatest level of disability), and had adequate bone marrow, renal, and hepatic function.

Patients who had received prior bendamustine treatment were eligible for the trial provided they had experienced a duration of response of 24 months or longer. However, patients with transformed CLL, central nervous system involvement, prior treatment with allogeneic or autologous stem cell transplant, major organ dysfunction, other active malignancy, or who were pregnant or breastfeeding, were excluded from the study.

Patients in the venetoclax arm received a 5-week ramp-up schedule, followed by a dose of 400 mg once daily for 24 months. Rituximab treatment started at the end of the venetoclax ramp-up period and was administered at a dose of 375 mg/m^2 intravenously on cycle 1 day 1 and 500 mg/m^2 on day 1 of cycles 2-6. In the control arm, patients received 6 cycles with the same rituximab dosing and schedule as the study group and bendamustine at a dose of 70 mg/m^2 on days 1 and 2 of each 28-day cycle.

The primary endpoint was progression-free survival (PFS), as assessed by an independent review committee over a median follow-up of 23 months. Median PFS

What's new, what's important

The significant improvement in PFS demonstrated in the MURANO trial in patients with CLL or SLL who were treated with the venetoclax-rituximab combination is highly encouraging for clinicians and patients alike. The findings were the basis for the approval of venetoclax for patients with previously treated relapsed/refractory CLL, regardless of genotype, in which patients were randomized to receive either the venetoclax–rituximab or bendamustine–rituximab combinations.

Patients in the venetoclax arm received a 5-week ramp-up schedule, then 400 mg daily for 24 months. Rituximab was initiated at the end of the venetoclax ramp-up (375 mg/m2 IV on day 1 of cycle 1, and 500 mg/m2 on day 1 of cycles 2-6). Controls received bendamustine at 70 mg/m2 on days 1 and 2 of each 28-day cycle, and 6 cycles with the same rituximab dosing and schedule as the study patients.

The primary endpoint was PFS assessed over a median follow-up of 23 months. Median PFS was significantly improved in the venetoclax arm (not yet reached vs 18.1 months in the bendamustine arm) and ORR and EFS were also better in the study group compared with controls (ORR: 92% and 72%, respectively; 2-year EFS: 84.9% and 34.8%). A trend toward improved 24-month OS rate (91.9% vs 86.6%) did not achieve statistical significance, nor did median OS.

The most common AEs with venetoclax were neutropenia, diarrhea, upper-respiratory tract infection, fatigue, cough, and nausea (grade 3/4 neutropenia: 64% of patients; serious AEs: 46%). Serious infections occurred in 21% of patients; there were 10 treatment-related deaths in the venetoclax arm, and 11 in the bendamustine arm.

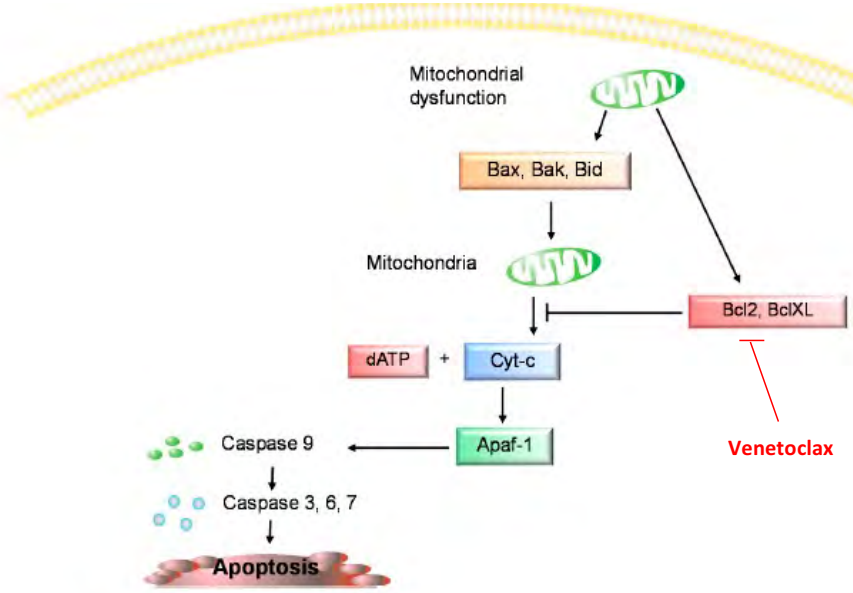
Warnings and precautions relate to the risk of tumor lysis syndrome, which is higher in patients with higher tumor burden or reduced renal function, or who receive strong or moderate CYP3A inhibitors or P-gp inhibitors during ramp-up. Preventive strategies would include hydration and antihyperuricemics, monitoring of blood chemistry and timely management of abnormalities, or dose interruption or adjustment as needed. Other warnings relate to neutropenia, immunization, and embryofetal toxicity.

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

Report prepared by Jane de Lartigue, PhD. JCSO 2018;16(5):e185-e187. ©2018 Frontline Medical Communications. doi: https://doi.org/10.12788/jcso.0422

Mechanism of action: venetoclax

Blocking the cancer hallmark of avoiding apoptosis. Venetoclax is a small-molecule inhibitor of the Bcl-2 protein, the eponymous member of a family of proteins that play a central role in apoptosis, a form of cell death that clears unwanted or damaged cells and maintains tissue homeostasis. There are 2 major pathways involved in regulating apoptosis – the intrinsic and extrinsic pathways, which are triggered by signals that come from inside and outside the cell, respectively.



Venetoclax is an inhibitor of Bcl-2, a key protein in the intrinsic pathway of apoptosis that is often overexpressed in cancer cells to permit them to grow unchecked even in the presence of cancer-induced DNA damage or cellular stress that should trigger cell death. Reproduced under a Creative Commons Attribution license. Musumeci G, et al. Biomarkers of chondrocyte apoptosis and autophagy in osteoarthritis. Int J Mol Sci. 2015;15:20560-20575.

The Bcl-2 family of proteins predominantly regulate the intrinsic pathway and contain both anti-apoptotic and pro-apoptotic members that interact with one another to finely tune the signals that govern cell fate. In healthy cells, pro-apoptotic Bcl-2 family proteins are bound by anti-apoptotic members (Bcl-2 among them), which helps to keep their activity in check.

In response to stimuli, such as DNA damage or defects in mitosis, some of the pro-apoptotic proteins (known as BH3-only proteins) are activated and bind to the anti-apoptotic proteins. This relieves their suppression on other pro-apoptotic proteins (known as effector proteins), particularly BAK and BAX. These proteins are then free to partner up and form small complexes that insert themselves into the mitochondrial membrane, creating holes through which cytochrome c is able to escape.

In the cytoplasm, cytochrome c drives the formation of the apoptosome, a protein complex that activates a family of protease enzymes – the caspases, which are key effectors of apoptosis, breaking down intracellular proteins.

The ability to evade apoptosis and thus continue to proliferate unchecked is a hallmark of cancer cells and, as a central regulator of apoptosis, Bcl-2 is overexpressed in several different malignancies, including CLL and SLL. Thus, it represents a key therapeutic target.

was significantly improved in the venetoclax arm (not yet reached versus 18.1 months in the bendamustine arm [HR, 0.19; $P < .001$]). In addition, objective response rate (ORR) and event-free survival (EFS) also favored the venetoclax arm; ORR was 92% compared with 72%, respectively, and 2-year EFS was 84.9% compared with 34.8%. There was also a trend toward improved 24-month overall survival (OS) rate (91.9% vs 86.6%), however this did not achieve statistical significance, nor did median OS.

The most common adverse events (AEs) in patients treated with venetoclax were neutropenia, diarrhea, upper-respiratory tract infection, fatigue, cough, and nausea. Grade 3/4 neutropenia occurred in 64% of patients, and serious AEs in 46% of patients. Serious infections occurred in 21% of patients, most commonly pneumonia. Ten deaths in the venetoclax arm were attributed to treatment, compared with 11 deaths in the bendamustine arm.[2]

The prescribing information details warnings and precautions relating to the risk of tumor lysis syndrome, which is increased in patients with higher tumor burden, reduced renal function, or in receipt of strong or moderate CYP3A inhibitors or P-gp inhibitors during the ramp-up stage. Patients should receive appropriate preventive strategies, including hydration and antihyperuricemics, blood chemistry should be monitored and abnormalities managed promptly, and dosing should be interrupted or adjusted as necessary.

Other warnings relate to neutropenia (complete blood counts should be monitored throughout treatment and

venetoclax treatment interrupted or dose reduced for severe neutropenia, alongside possible use of supportive measures), immunization (live vaccines should not be administered before or during treatment or after treatment until B-cell recovery, and patients should be advised of the potentially reduced efficacy of vaccines), and embryofetal toxicity (patients should be advised of the risks and the need for effective contraception during and after treatment). Venetoclax is marketed as Venclexta by Genentech.[3]

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Effect of time of admission to treatment initiation on outcomes of patients with acute myeloid leukemia: a tertiary care referral center experience

Sami Ibrahimi, MD,[a] Sarbajit Mukherjee, MD,[a] Michael G Machiorlatti, MS,[b] Hossein Maymani, MD,[a] Sara K Vesely, PhD,[b] Samer A Srour, MB, ChB, MS,[a] and Mohamad Cherry, MD[a]

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Background The time from diagnosis of acute myeloid leukemia (AML) to initiation of treatment could affect patient outcomes, but findings from previous studies have been mixed.
Objective To analyze the impact of the time from admission to treatment initiation (TAT) on overall survival (OS) and event-free survival (EFS) in patients who are newly diagnosed with AML.
Methods A retrospective review of the records of all newly diagnosed AML patients treated at the Oklahoma University Health Sciences Center from January 2000 through June 2015 was conducted. Inclusion criteria also included age ≥18 years and available insurance data. Data on patient characteristics, laboratory values, pathology, treatment, response, and survival were obtained from the electronic medical records.
Results In all, 154 patients were divided into 2 groups: those with a TAT of 0-4 days (n = 109) and those with a TAT of >4 days (n = 45). The median OS of the TAT 0-4 days group and the TAT >4 days group was 1.3 years and 0.57 years, respectively (P = .0207), and the median EFS for the groups was 1.21 years and 0.57 years, respectively (P = .0392). That association remained significant in a multivariate analysis adjusting for age, white blood cell count, molecular risk group, and undergoing allogeneic stem cell transplant.
Limitations Study limitations include a small sample size and a short median follow-up time.
Conclusion Patients with AML who are treated more than 4 days after admission have a lower OS and EFS compared with patients treated within 0-4 days of admission.
Funding/sponsorship None

Acute myeloid leukemia (AML) is the most common acute leukemia in adults in the United States.[1] In 2018, the estimated annual incidence of AML is 19,520 (32.4% of all new leukemia cases), with 10,670 projected deaths (43.8% of all leukemia deaths).[1] New molecularly targeted treatments are increasingly being used in treating AML, and some of them have shown improved health outcomes. In general, age, white blood cell (WBC) count at presentation, cytogenetics, and molecular characteristics are the major determinants of prognosis and treatment outcome. Studies analyzing the Surveillance Epidemiology and End Results database have also shown racial differences in outcomes.[2] It is well known to the oncology community that patients with similar characteristics may respond differently to treatment and that outcome is not uniformly related to the well-defined clinical and laboratory characteristics. Issues related to health care disparities and access to health care are also known to affect the outcome in patients with cancer.[3-9]

AML is generally considered by the medical community as a time-sensitive condition. Treatment of patients with AML usually consists of induction chemotherapy followed by consolidation treatment

Accepted for publication September 13, 2018. Correspondence: Sami Ibrahimi, MD; Sami-Ibrahimi@ouhsc.edu.
Disclosures: Dr Cherry is on the advisory board of Gilead. The remaining authors report no disclosures or conflicts of interest. JCSO 2018;16(5):e188-e193. doi: https://doi.org/10.12788/jcso.0428

TABLE 1 Baseline characteristics based on group

Variable	Overall no. of patients (%) (N = 154)	Time from admission to treatment initiation		χ^2 *P*-value
		0-4 days (n = 109)	>4 days (n = 45)	
Age, y				
<60	107 (69.5)	81 (74.3)	26 (57.8)	.0427
≥60	47 (30.5)	28 (25.7)	19 (42.2)	
Gender				
Male	99 (64.3)	67 (61.5)	32 (71.1)	.2560
Female	55 (35.7)	42 (38.5)	13 (28.9)	
WBC count at diagnosis, μ/L				
<50 x 10^3	121 (78.6)	80 (73.4)	41 (91.1)	.0148
≥50 x 10^3	33 (21.4)	29 (26.6)	4 (8.9)	
Race				
White	118 (77.3)	85 (78.0)	34 (75.6)	.0805[a]
Black	17 (11.0)	10 (9.2)	7 (15.6)	
Hispanic	5 (3.3)	2 (1.8)	3 (6.7)	
Other	13 (8.4)	12 (11.0)	1 (2.2)	
Cytogenetic/ molecular risk				
Favorable	26 (16.9)	18 (16.5)	8 (17.8)	.6214
Intermediate	44 (28.6)	34 (31.2)	10 (22.2)	
Unfavorable	39 (25.3)	25 (22.9)	14 (31.1)	
Unknown	45 (29.2)	32 (29.4)	13 (28.9)	
Health insurance				
Insured	123 (79.9)	87 (79.8)	36 (80.0)	.9794
Uninsured	31 (20.1)	22 (20.2)	9 (20.0)	
AlloSCT[b]				
No	117 (77.0)	81 (75.7)	36 (80.0)	.5655
Yes	35 (23.0)	26 (24.3)	9 (20.0)	
Induction therapy[c]				
7+3	117 (79.6)	88 (83.8)	29 (69.0)	.0448
Other	30 (20.4)	17 (16.2)	13 (31)	
Day of admission				
Monday-Thursday	115 (74.7)	89 (81.7)	26 (57.8)	.0014
Friday-Sunday	39 (25.3)	20 (18.3)	19 (42.2)	

7 + 3, 7 days cytarabine and 3 days anthracycline; AlloSCT, allogeneic stem cell transplant; WBC, white blood cell

[a]Fisher exact test used. [b]Missing 2 observations. [c]Missing 7 observations.

with consideration for stem cell transplant. The duration of time from admission to treatment (TAT) of AML with induction chemotherapy is dependent on multiple factors. These may include the assessment of comorbid conditions and the availability of molecular studies at the time of treatment, which can be time consuming. The effect of treatment delays after AML diagnosis has been investigated, but with conflicting results. One study showed that time from diagnosis to treatment initiation affects survival in younger patients, and another showed it has no effect on survival regardless of patient age.[10,11] We describe here the results of a retrospective analysis evaluating the impact of

TABLE 2 Median overall survival and event-free survival (unadjusted) based on TAT and day of admission group (N = 154)

	Overall survival		Event-free survival	
Group	**Months (95% CI)**	***P*-value**	**Months (95% CI)**	***P*-value**
0-4 days TAT	15.6 (9.1-24.1)	.0207	14.5 (8.9-21.1)	.0392
>4 days TAT	6.8 (4.7-13.8)		6.8 (4.7-12.5)	
Monday-Thursday	13.8 (8.6-17.8)	.9334	10.9 (8.3-15.6)	.9162
Friday-Sunday	12.5 (6.8-21.1)		9.6 (6.8-21.1)	

TAT, time from admission to treatment initiation

TAT and day of admission on outcomes of patients with AML who received treatment at a tertiary care referral center.

Methods and materials

We did a retrospective medical record review of all newly diagnosed AML patients at the Oklahoma University Health Sciences Center (OUHSC). Our sample was composed of 154 adult patients. Our inclusion criteria were an age of 18 years or older with complete insurance data, a diagnosis of AML, and having received treatment at our institution from January 2000 through June 2015. Data were obtained on laboratory values at diagnosis, pathology data including cytogenetics, molecular data, and bone marrow biopsies. Data on patient characteristics such as age, race and/or ethnicity, and comorbidities were obtained from the electronic medical records. Treatment data on type and dose of chemotherapy during induction, subsequent treatment phases, and number of treatments to achieve complete response (CR) as well as response data of CR achievement, relapse, date of CR, date of relapse, stem cell transplantation data, date of death, and date of last follow-up visit were recorded retrospectively from the electronic medical record. The study was approved by the OUHSC Institutional Review Board.

Statistical analysis

TAT was analyzed categorically (0-4 days vs >4 days), and day of admission was analyzed categorically (Monday to Thursday vs Friday to Sunday). Descriptive statistics were calculated overall and by TAT group. The chi-square test was used to compare the association between our covariates and TAT. Kaplan-Meier estimates (with a log-rank test) were used to assess the unadjusted effect of TAT with overall survival (OS) and event-free survival (EFS). Median OS and EFS and 95% confidence intervals (CIs) were also calculated. We used the Cox proportional hazards regression modeling to evaluate the relationship between OS and TAT. The initial model was built by including covariates, with $P < .25$ for the association between the covariates with OS. TAT was maintained in the final model because it was the primary variable of interest, whereas age and risk group were also included in the final model because those covariates are known prognostic risk factors in AML. Among the set of variables screened in, all 2-way interactions were assessed using $P < .05$. No significant interactions were found. Backward elimination was then performed. During the backward elimination, confounding was deemed to have been present if the measure of association of significant variables in the model changed by more than 20% and the *P*-value of the confounding variable was less than .30. Variables with *P*-values of less than .05 or deemed a confounder would then be retained. A similar modeling approach was used to examine EFS and CR. To evaluate the association between CR with potential predictors, binary logistic regression was used, whereby day of admission and time to treatment were explored unadjusted and then adjusted for age, WBC count, risk group, and undergoing allogeneic stem cell transplant (AlloSCT). SAS version 9.4 (SAS Institute Inc, Cary, North Carolina) was used for all analyses. A final alpha of 0.05 was used unless otherwise noted.

Results

Baseline characteristics are presented in Table 1. Treatment was initiated within 4 days for 71% (109/154) of patients. Most patients in our study were younger than 60 years (70%), male (64%), and white (77%). Most patients were admitted to the hospital for treatment between Monday and Thursday (75%). A higher proportion of patients in the 0-4 days TAT group were <60 years of age compared with patients in the >4 days TAT group ($P = .0427$). A higher proportion of patients in the 0-4 days TAT group had a WBC count of ≥50 x 10^3 μ/L compared with patients in the >4 days TAT group (27% vs 9%, respectively; $P = .0148$). A higher proportion of patients were admitted Friday to Sunday in the TAT >4 days group. Insured and uninsured patients were equally distributed between the 2 groups ($P = .0014$). Cytogenetic and/or molecular risk was not statistically different between the 0-4 days and >4 days TAT groups (unfavorable risk, 25% vs 23%, respectively; $P = .6214$). A higher proportion of patients received 7 + 3 induction chemotherapy (7 days cytarabine and 3 days anthracycline) in the TAT 0-4 days group compared with

the >4 days TAT group (84% vs 69%, respectively; $P = .0448$). The most common intensive chemotherapy regimen used was 7 + 3 (80%). The rest of the patients (20%) received high-dose cytarabine clofarabine-based chemotherapy, hypomethylating agents, or other treatments. The proportion of patients who received an AlloSCT did not differ between the 0-4 days and >4 days TAT groups (24% vs 20%, respectively; $P = .5655$).

The median OS for all patients was 10.9 months (95% CI, 8.3-15.1), and the median EFS was 9.1 months (95% CI, 7.4-13.8). Median follow-up time was 8.6 months (95% CI, 6.7-11). We found a significant association between TAT and both OS and EFS without any adjustment (Table 2). The median OS for the TAT 0-4 days group was 15.6 months, and for the TAT >4 days group, it was 6.8 months ($P = .0207$; Figure 1). The median EFS for the TAT 0-4 days group was 14.5 months, and for the TAT >4 days group, it was 6.8 months ($P = .0240$; Figure 2). We found no association between the day of admission to hospital (Monday-Thursday vs Friday-Sunday) and either OS or EFS. After adjusting for age, WBC count, molecular risk status, and undergoing AlloSCT, the OS was shorter for those who received treatment >4 days after admission compared with those who received treatment within 0 to 4 days, with a hazard ratio (HR) of 1.59 (95% CI, 1.02-2.49; $P = .0427$; Table 3). There was no association between day of admission with OS in the multivariable analysis. Similarly, after adjusting for age, WBC count, molecular risk status, and undergoing AlloSCT, EFS was shorter in patients who received treatment >4 days after admission compared with those who received treatment within 0 to 4 days (HR, 1.64; 95% CI, 1.06-2.54; $P = .0268$). There was no association between day of admission with EFS in the multivariable model. Although there was a trend for a higher CR rate with earlier treatment, this was not statistically significant (Table 4).

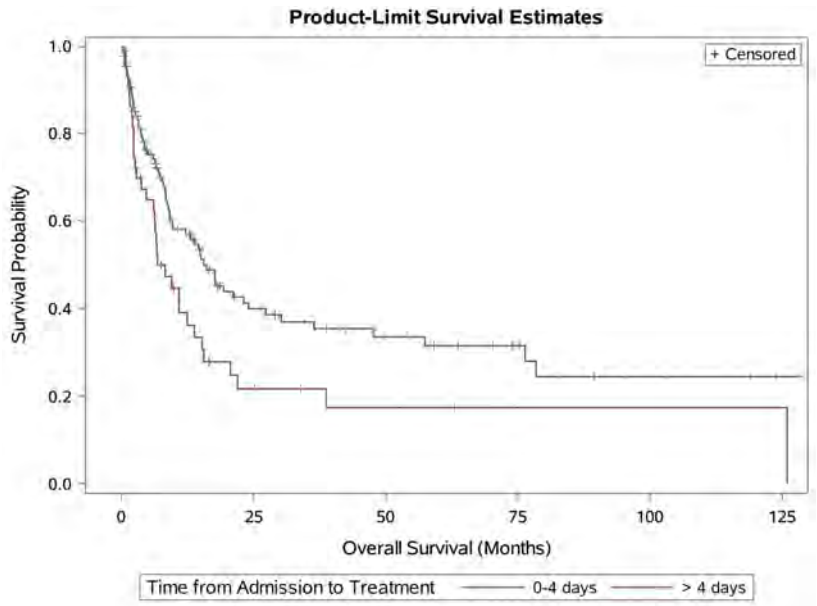

FIGURE 1 Overall survival in months of time to treatment – unadjusted ($P = .0207$)

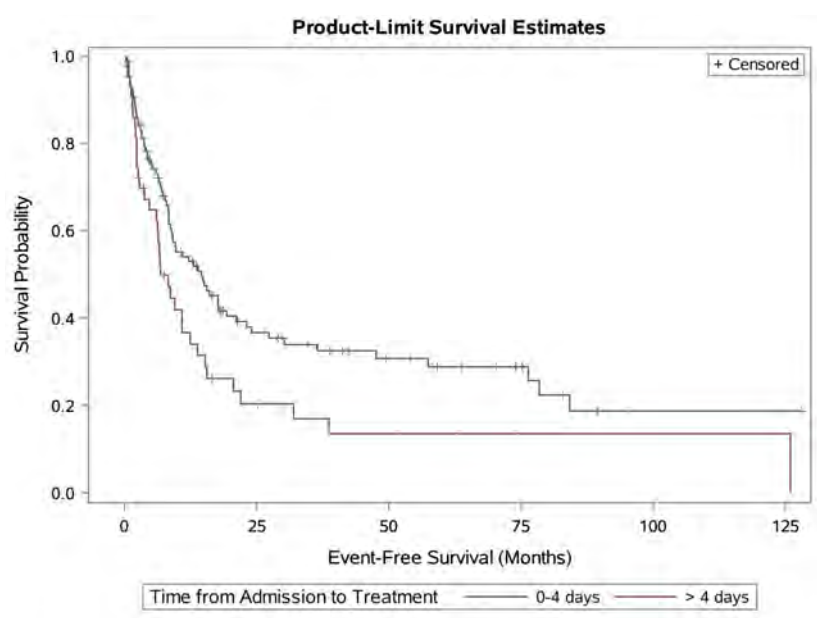

FIGURE 2 Event-free survival in months of time to treatment – unadjusted ($P = .0392$)

Discussion

Treatment outcomes for patients with AML are known to be affected by several patient- and disease-related factors. Patient-related factors can include age, performance status, comorbidities, and availability of a stem cell donor. Examples of disease-related factors include molecular alterations and site of disease involvement. Little is known about whether the timing of treatment initiation affects patient outcomes. Short-term treatment delays after the diagnosis of leukemia are not uncommon. Generally, patients are treated with anthracycline-based induction chemotherapy, but the response rate and survival are particularly poor in the older age group.[12] Moreover, increasing comorbidities with aging are expected to lead to lower treatment tolerability.[13] Therefore, elderly patients are particularly prone to treatment delays while providers await the results of the molecular studies to guide the use of less intensive targeted therapies.[10] Other reasons for treatment delays may also include transfers between hospitals, sus-

TABLE 3 TAT adjusted for age, white blood cell count, molecular risk status, and having an AlloSCT (N = 152, 2 missing AlloSCT)

		Overall survival		Event-free survival	
Parameter	**Group**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
TAT	>4 days vs 0-4 days	1.59 (1.02-2.49)	.0427	1.64 (1.06-2.54)	.0268

AlloSCT, allogeneic stem cell transplant; TAT, time from admission to treatment initiation

TABLE 4 Unadjusted and adjusted (age, white blood cell count, risk group, allogeneic stem cell transplant) association between complete response and TAT

Variable	**Group (>4 days vs 0-4 days)**	**OR (95% CI)**	***P*-value**
TAT	Unadjusted (n = 154)	0.54 (0.27-1.11)	.0944
	Adjusted (n = 152)	0.67 (0.29-1.52)	.3369

TAT, time from admission to treatment initiation

pected or documented infections, and evaluation of chronic illnesses. Our analysis also indicates that admission to the hospital on the weekend contributes to a delay in therapy compared with admission on a weekday.

We found a decreased OS and EFS in patients who received treatment >4 days after admission to the hospital compared with patients who received treatment within 0 to 4 days of admission. This association was statistically significant in a bivariate analysis as well as in a multivariable analysis with adjustment for age, WBC count on presentation, molecular risk group, and undergoing AlloSCT. A previous large retrospective study showed that the time from diagnosis to treatment initiation predicts survival in younger, but not older, patients with AML.[10] This remained true after adjusting for age, performance status, WBC count, and the type of AML in a multivariable analysis. In our study, the declines in overall survival and event-free survival were evident after a delay of more than 4 days.

Another retrospective study that included 599 newly diagnosed AML patients, with a median time from diagnosis to treatment of 8 days, did not show any impact of treatment delay on overall survival, early death, or response rate.[11] These differences in the effect of treatment delay on outcomes could be related to the differences in baseline characteristics of patients in these studies. Our study had a higher proportion of patients younger than 60 years, for example. We hypothesize that treatment delays, especially in patients with a high WBC count on presentation, might lead to further organ compromise and poorer outcomes with chemotherapy.

In our study, a higher proportion of patients were admitted over the weekend in the >4 days TAT group, but when we analyzed the day of admission to hospital separately, it was not associated with OS or EFS. Admission over the weekend was also not associated with clinical outcomes including 30-day mortality in a larger study that included 422 patients treated at a large teaching referral hospital.[14]

Limitations of our study include a small sample size and a short median follow-up time. Most of our patients were young and white, which may not be representative of the general population.

In conclusion, we found that treatment delays are associated with inferior outcomes in AML patients. It remains to be elucidated whether the benefit gained from using targeted and less-intensive chemotherapy, especially in elderly patients, outweighs the potential harm from delaying treatment. Additional studies are needed to confirm our findings in different settings and patient populations.

Acknowledgment

Statistical support was provided by the Stephenson Cancer Center Biostatistics and Research Design Shared Resource.

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Marriage predicts for survival in patients with stage III non–small-cell lung cancer

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Background Comprehensive analysis of prognostic significance of marital status in patients with stage III non–small-cell lung cancer (NSCLC) when adjusted for patient-, disease-, and treatment-specific factors, including the interaction with racial, nutritional, and immunologic status, is lacking.

Objective To evaluate whether marital status is an independent predictor of clinical outcomes in patients with stage III NSCLC who are treated uniformly with curative intent.

Methods The Kaplan-Meier method and Cox proportional hazards model were used to estimate the overall survival and freedom from recurrence (FFR) in 355 patients with stage III NSCLC who were treated during 2000-2013.

Results 52% of patients in the cohort were married and were more likely to self-identify as white ($P < .0001$), reside in zip codes with a higher household median income ($P < .0001$), have Eastern Cooperative Oncology Group Performance Status of 0 ($P = .001$), have higher pretreatment albumin ($P = .009$), undergo surgery ($P = .001$), and have insurance ($P = .029$). On multivariate analysis, marital status remained an independent predictor of survival and was associated with a 40% decreased risk of death ($P < .0001$), further stratifying outcomes beyond gender and stage grouping. FFR was comparable between the 2 groups ($P = .108$).

Limitations Retrospective analysis; information on individual support system beyond the marital and insurance status and zip code income was not available.

Conclusions In a cancer such as NSCLC, in which modern therapeutic approaches have yielded only modest survival improvements despite considerable treatment-related toxicity, marital status remains an independent predictor for survival. Marriage is likely a surrogate for better psychosocial support; the scale of survival improvements seen justifies investments into supportive care interventional strategies to help advance overall outcomes.

Funding/sponsorship None

Non–small-cell lung cancer (NSCLC) remains the leading cause of cancer death in the United States, where 29% of patients will present with stage III disease.[1,2] Ongoing research efforts seek to improve these outcomes using novel systemic therapy options or modern radiation techniques. However, there have also been recent studies showing the importance of marital and/or partner status on clinical outcomes.[3-7] For example, in a large Surveillance, Epidemiology, and End Results (SEER) analysis of 734,889 patients diagnosed with several types of cancer (including lung cancer), patients identified as married were less likely to present with metastatic disease, more likely to receive definitive therapy, and had superior cancer-related mortality even after adjusting for other variables such as cancer stage and treatment when compared with single patients.[3] Population-based assessments are important in relaying information about trends and general outcomes based on marital status, but because they are large, they often lack patient-specific information such as nutrition, immunologic status, and variability in treatment paradigms, all of which can independently have an impact on overall survival (OS) in stage III NSCLC.[8-10] In addition, population analyses have typically included patients of all cancer stages and hence involved a multitude of treatment approaches ranging from curative to palliative. There are limited well-annotated institutional

Accepted for publication September 6, 2018. Correspondence: Melissa AL Vyfhuis, MD, PhD; mvyfhuis@umm.edu or Josephine L Feliciano, MD; jfelici4@jhmi.edu. Disclosures: The authors report no disclosures or conflicts of interest. JCSO 2018;16(5):e194-e201. doi: https://doi.org/10.12788/jcso.0427

data on the association of marital status on nonmetastatic, locally advanced (LA-NSCLC) in the setting of National Comprehensive Cancer Network-guided, standard-of-care definitive treatment.

The objective of this analysis is to evaluate the effect of marital status on OS and freedom from recurrence (FFR) in patients with stage III NSCLC who were treated at a National Cancer Institute–designated cancer center with curative intent from 2000 through 2013. We performed a detailed multivariate analysis (MVA) of patient-, disease-, and treatment-specific factors, including the interaction with racial, nutritional, and immunologic status, which to our knowledge has not been previously reported, to comprehensively evaluate the benefit of marital status in patients with LA-NSCLC.

Methods

Patient population and treatment

From January 2000 through December 2013, 355 patients diagnosed with clinical stage III NSCLC (American Joint Committee on Cancer 7th edition) were definitively treated at the University of Maryland in Baltimore, Maryland. Their clinical data were retrospectively analyzed under internal review board approval (GCC 1175, Thoracic Oncology Database). All of the patients were evaluated before treatment by a multidisciplinary team consisting of thoracic surgeons and medical and radiation oncologists. Before treatment, the patients underwent standard work-up, which included systemic imaging with positron-emission (PET), computed-tomographic (CT), PET–CT, and/or bone scan, brain imaging consisting of magnetic-resonance imaging or CT with contrast, and routine blood. Patients had documentation of mediastinal disease by either imaging, mediastinoscopy, or endobronchial ultrasound biopsy.

Definitive therapy was administered using the backbone of chemoradiation therapy (CRT) with (trimodality) or without (bimodality) surgical resection. Concurrent CRT was typically administered with weekly carboplatin–paclitaxel (areas under the curve [AUCs], 2 and 50 mg/m^2, respectively) and was generally followed with 2 cycles of consolidative treatment with definitive doses of carboplatin–paclitaxel (AUCs, 5-6 and 200-225 mg/m^2, respectively) as tolerated. The entire cohort was also assessed for possible trimodality therapy at the time of initial diagnosis, and patients who were potential surgical candidates were reassessed for mediastinal nodal clearance following repeat radiographic staging after full-dose CRT. Patients who experienced pathologic mediastinal clearance of disease underwent resection followed by consolidative chemotherapy. Unless there was evidence of disease progression, patients who did not have mediastinal lymph node clearance or who were found not to be a surgical candidate proceeded directly to consolidative chemotherapy. The details of patient selection for trimodality therapy and the oncological outcomes have been previously reported.[10] For follow-up, patients were normally followed with serial CT or PET–CT scans as clinically indicated every 3 months for the first year, 4 to 6 months for the next 2 to 5 years, and then yearly thereafter.

For the analysis, patients were categorized as being either married or single based on self-reporting. As a surrogate for nutrition status, patients were stratified into 4 pretreatment body mass index (BMI) cohorts based on the following World Health Organization criteria: underweight, <18.5 kg/m^2; normal weight, 18.5 to <25 kg/m^2; overweight, 25 to <30 kg/m^2; and obesity, ≥30 kg/m^2. Pretreatment albumin was also evaluated as a continuous variable. For assessment of immunological status, neutrophil-to-lymphocyte ratio (NLR) was calculated at the time of diagnosis by dividing the absolute neutrophil count by the absolute lymphocyte count.

Statistics

We used the Pearson chi-square test to compare categorical variables. OS was calculated from the date of diagnosis (by biopsy of either primary tumor or mediastinal nodes) to the time of death or date of last follow-up. Patients were only censored if they were lost to follow-up. FFR was determined by the date of diagnosis to the time of first failure, with either distant or locoregional disease progression. For this analysis, patients were censored at the time of their last follow-up or death. The Kaplan-Meier product limit method was used to estimate OS and FFR, and we applied the log-rank test to compare outcomes between the 2 cohorts.

We conducted the multivariate analyses using Cox regression with forward model selection. Variables analyzed included age (<60 vs ≥60 years), sex, race (black vs non-black), median household income, insurance status (Yes vs No), Eastern Cooperative Oncology Group Performance Status (ECOG PS) (range: 0-3; 0 = fully active and 3 = capable of limited self-care, confined to bed/chair >50% of day) at time of diagnosis (0 vs ≥1), pre-CRT BMI, smoking (pack-years), chronic obstructive pulmonary disorder (Yes vs No), Charlson Comorbidity Index score (≤6 vs >7; range, 3-15; this score takes into consideration age, cardiovascular disease, malignancy, and other chronic conditions to calculate 1-year mortality), histology, calculated pretreatment NLR (as a continuous variable), pretreatment albumin (as a continuous variable), T stage, N stage, overall stage (IIIA vs IIIB), radiation technique (3D-CRT vs intensity-modulated radiation therapy [IMRT]), date of diagnosis (divided into quartiles based on proportion diagnosed by years: 2000-2002, 2003-2005, 2006-2009, 2010-2013), use of trimodality therapy, and consolidation chemotherapy. SPSS software (version 23.0) was used for statistical analysis (IBM Corp, Armonk, NY).

TABLE 1 Baseline patient, disease, and treatment characteristics (N = 355)

Characteristic	Marital status: Married, no. patients (%) (n = 185)	Marital status: Not married, no. patients (%) (n = 170)	*P*-value
Age, y			
Median [range]	61 [30-86]	59.5 [38-84]	.960
≥60	100 (54.1)	86 (51.2)	.590
Sex			
Male	113 (55.7)	90 (53.9)	.122
Race			
White	126 (68.1)	72 (42.4)	
Black	53 (28.6)	97 (57.1)	<.0001
Other	6 (3.2)	1 (0.5)	
Above median income[a]			
≥$43,723	117 (63.6)	55 (33.3)	<.0001
Insurance status			
Yes	161 (87)	137 (80.6)	
No	16 (8.6)	28 (16.5)	.029
Unknown	8 (4.4)	5 (2.9)	
ECOG Performance Status[b]			
0	102 (55.1)	63 (37)	
≥1	81 (43.8)	105 (61.8)	.001
Unknown	2 (1.1)	2 (1.2)	
Pretreatment BMI[c]			
Median, kg/m^2 [range]	26.3 [16.1-41.3]	24.4 [11.2-43.9]	.050
Obese	42 (22.7)	35 (20.6)	
Overweight	53 (28.6)	34 (20)	
Normal	49 (26.5)	58 (34.1)	.095
Underweight	7 (3.8)	12 (7.1)	
Unknown	34 (18.4)	31 (18.2)	
Smoking, pack-years			
Median [range]	40 [0-180]	40 [0-212]	.818
COPD diagnosis			
Yes	49 (27)	51 (30)	.477
Charlson Comorbidity Index score[d]			
≤6	99 (53.5)	90 (52.9)	
>7	86 (46.5)	79 (46.5)	.961
Unknown	-	1 (0.6)	
Histology			
Adenocarcinoma	61 (33)	52 (30.6)	
Squamous cell	48 (25.9)	56 (32.9)	.544
NSCLC (NOS)	62 (33.5)	50 (29.4)	
Other	14 (7.6)	12 (7.1)	

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Characteristic	Marital status: Married, no. patients (%) (n = 185)	Marital status: Not married, no. patients (%) (n = 170)	*P*-value
Pretreatment NLR			
Median [range]	3.22 [0.22-57.9]	3.30 [0.67-37.5]	.393
Pretreatment albumin, g/dL			
Median [range]	3.7 [0.80-5.0]	3.6 [0.70-4.9]	.009
T stage[ef]			
TX	10 (5.4)	8 (4.7)	
≤T2	90 (48.9)	71 (42)	.361
≥T3	84 (45.7)	90 (53.3)	
N stage[eg]			
NX	2 (1.1)	1 (0.6)	
≤N1	31 (16.8)	25 (14.8)	.906
N2	112 (60.9)	106 (62.7)	
N3	39 (21.2)	37 (21.9)	
Overall stage			
IIIA	109 (58.9)	91 (53.5)	.306
IIIB	76 (41.1)	79 (46.5)	
Treatment			
Trimodality	59 (31.9)	29 (17.1)	.001
Bimodality	126 (68.1)	141 (82.9)	
Type of chemoradiation			
Concurrent	175 (94.6)	152 (89.4)	.070
Sequential	10 (5.4)	18 (10.6)	
Radiation dose delivered, Gy[h]			
Median [range]	64.8 [10.8-70.2]	63 [19.8-81.6]	.126
≥60	154 (93.9)	139 (88)	.063
Radiation technique[i]			
3D-confromal	132 (77.6)	103 (69.1)	.098
IMRT	38 (22.4)	46 (30.9)	
Adjuvant chemotherapy[j]			
Yes	121 (73.3)	91 (65.5)	.137

BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; IMRT, intensity-modulated radiation therapy; NLR, neutrophil-to-lymphocyte ratio; NOS, not otherwise specified; NSCLC, non–small cell lung cancer

[a]Data not available for 6 patients. [b]ECOG PS range, 0-3, with 0 = fully active and 3 = capable of limited self-care, spending >50% of the day in a chair or in bed. [c]BMI, normal, 18.5-25 kg/m^2. [d]Charlson Comorbidity Index score range, 3-15 (this score takes into consideration age, cardiovascular disease, malignancy, and other chronic conditions to calculate 1-year mortality). [e]T and N staging not available for 2 patients. [f]T staging is reflected of AJCC 7th edition. [g]N staging is reflected of AJCC 7th edition. [h]Data not available for 33 patients. [i]Data not available for 36 patients. [j]Data not available for 8 patients.

Results

Treatment cohorts

Table 1 compares and summarizes patient demographics, disease, and treatment characteristics for married (n = 185; 52.1%) and nonmarried (n = 170; 47.9%) patients. Married patients were more likely to self-identify as being white ($P < .0001$), reside in zip codes with a higher household median income ($P < .0001$), have an ECOG PS of 0 ($P = .001$), have a higher distribution of pretreatment albumin levels ($P = .009$), and undergo trimodality therapy

(P = .001), and they were twice as likely to have insurance (P = .029). Both cohorts were evenly distributed in terms of T stage, N stage, and overall staging. There was no difference in pretreatment NLR or pretreatment BMI between married and single patients. Concurrent CRT was used in more than 85% of patients in both groups, with approximately two-thirds also receiving consolidation chemotherapy (Table 1). Median delivered radiation dose was 64.8 Gy (range, 10.8-81.6 Gy). There was no statistically significant difference in radiation dose delivered to either group, with nearly 90% of the cohort receiving ≥60 Gy.

OS and FFR

With a median follow-up of 15 months for all patients and 89 months for surviving patients (range, 1-184 months), married patients had improved OS when compared with the single cohort, with a median survival of 29.6 and 18.4 months, respectively (unadjusted hazard ratio [HR] of married vs nonmarried, .640; 95% confidence interval [CI], 0.502-0.816; P < .0001; Figure 1A). The estimated 2- and 5-year OS for married and single patients were 56% and 31% and 38.6% and 15%, respectively. When stratified by stage, married patients with stage IIIB disease (median survival, 25 months; Figure 1B) had a similar survival to unmarried patients with stage IIIA disease (median survival, 24 months; Figure 1B). In stage IIIA patients, marital status was associated with an unadjusted HR of .696 (95% CI, 0.497-0.974; P = .035), with a larger OS benefit seen in the IIIB group (unadjusted HR, .601; 95% CI, 0.422-0.856; P = .005).

Survival as it pertains to marital status was further stratified by sex (Figure 2A) and race (Figure 2B). Married men had an improved estimated median survival of 30 months when compared with single men, whose median survival was 16 months (unadjusted HR, .541; 95% CI, 0.392-0.746; P < .0001). On the other hand, marital status had no statistically significant effect on OS when comparing married women with their single counterparts (unadjusted HR, .717; 95% CI, 0.491-1.048; P = .085; Figure 2A), with an overall median survival of approximately 28 months for the entire female cohort. Stratification by race also showed similar results, with married nonblack patients demonstrating better OS when compared with single nonblack patients (HR, .586; 95% CI, 0.420-0.820; P = .002; Figure 2B), with a median survival of 29 and 17 months, respectively. Black patients also had a similar improvement in survival when comparing the married (median survival, 30 months) and nonmarried groups (median survival, 19.6 months; unadjusted HR, .676; 95% CI, 0.457-1.000; P = .050; Figure 2B).

FFR did not differ between the 2 groups, with a median time to failure of 17 and 15 months for married and nonmarried patients, respectively (unadjusted HR, .799; 95% CI, 0.607-1.051; P = .108; Figure 3). Estimated 2- and 5-year FFR for married and nonmarried patients were 39.4% and 27% and 31.5% and 18.5%, respectively (Figure 3).

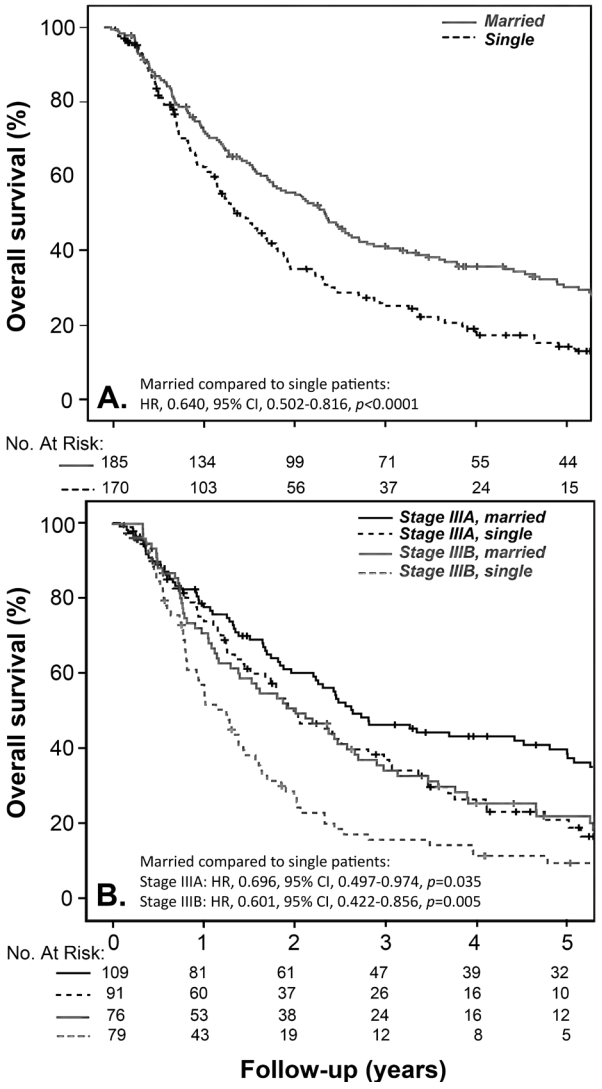

FIGURE 1 Kaplan-Meier plot of overall survival of stage III NSCLC patients based on **A,** marital status and **B,** marital status stratified by overall stage. Unadjusted hazard ratios are reported in each figure.

Clinical predictors of survival

On MVA, factors that were independent predictors for OS are summarized in Table 2. Risk of death was reduced by approximately 65% and 45% in patients who underwent trimodality treatment (P < .0001) or were able to undergo consolidative chemotherapy (P = .004) when compared with those who were treated definitively with bimodality treatment or did not undergo systemic doses of adjuvant chemotherapy, respectively. Having insurance (P = .048) and use of IMRT over 3D-CRT (P = .008) was

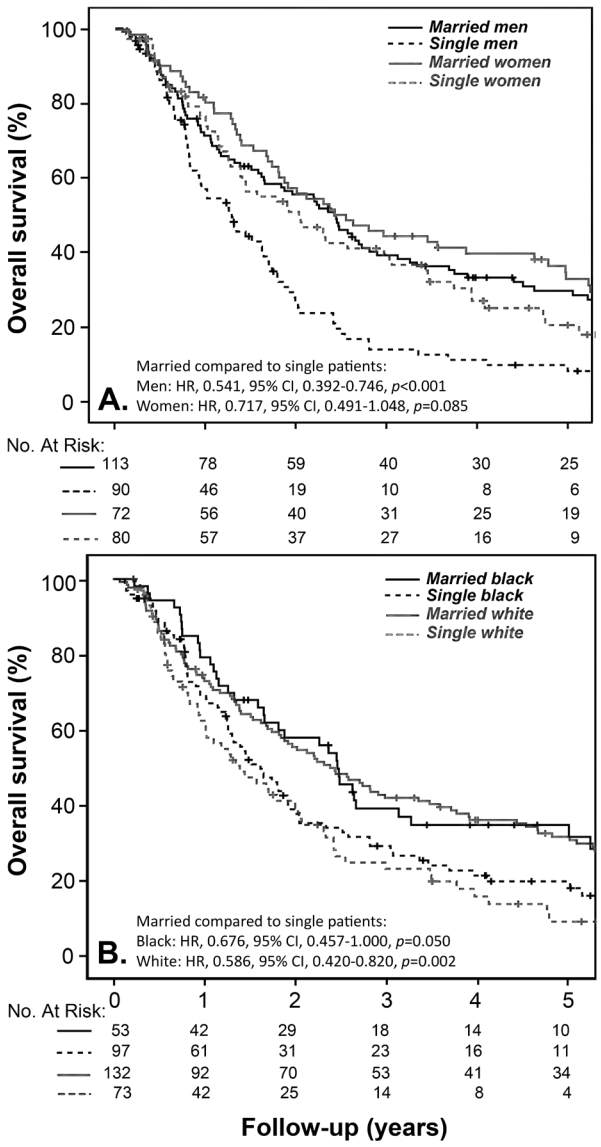

FIGURE 2 Kaplan-Meier plot of overall survival of stage III NSCLC patients based on **A,** marital status stratified by sex or **B,** marital status stratified by race. Unadjusted hazard ratios are reported in each figure.

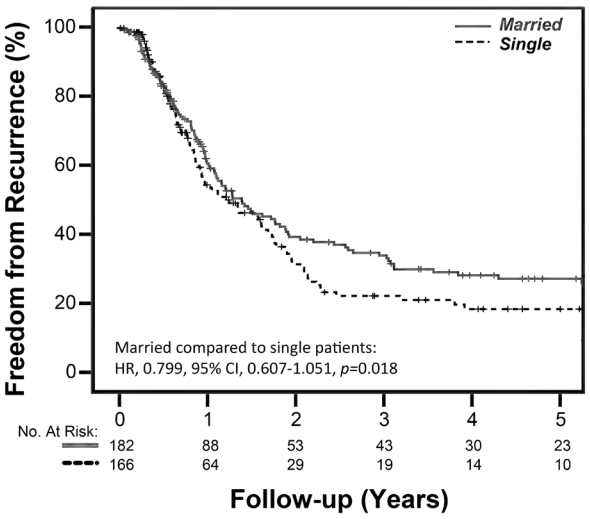

FIGURE 3 Kaplan-Meier plot of freedom from recurrence of stage III NSCLC stratified by marital status. Unadjusted hazard ratios are reported.

associated with a reduction of mortality by about half in this cohort. Both gender (improved OS with female sex; $P = .004$) and marital status (improved OS with marriage; $P = .006$) were associated with a decreased the risk of death by 40% (Table 2). By contrast, a higher NLR resulted in a 1.1-times increased risk of death ($P = .001$).

Discussion

Our study continues to support the notion that marital status is an independent indicator of survival in stage III NSCLC (adjusted HR, .59; 95% CI, 0.404-0.859; $P = .006$). The benefit of marriage in this population seems to be better than that reported in the SEER analysis for all stages, wherein the HR for death of married patients compared with their single counterparts was .85 (95% CI, 0.83-0.87). In their analysis, the investigators hypothesized that this survival advantage could partially be explained by better access to health care and adherence to therapy, as was supported by the higher likelihood of married patients presenting with localized disease and receiving definitive treatment.[3] Another population-based study using the Florida Cancer Data System identified 161,228 lung cancer patients (NSCLC and small-cell lung histology included), and on MVA, marital status remained an important prognostic indicator for OS when compared with never-married patients (HR, .86; $P = .001$).[6] In addition to typically including patients with all stages of diseases, population-based studies often include patients who receive a heterogeneous combination of treatment modalities, possibly confounding the analysis. Furthermore, large population analyses typically do not report on patient-specific variables such as nutrition (ie, BMI and albumin) or immunologic status (ie, NLR), both of which have been shown to be independent predictors of survival in LA-NSCLC.[8,9]

In contrast, some other studies have failed to demonstrate an OS advantage with marital status in patients with NSCLC. For example, in a meta-analysis that evaluated the influence of race, gender, and marital status on 1,365 nonoperative NSCLC patients who were enrolled in 9 Radiation Therapy Oncology Group (RTOG) trials, the investigators did not find marital status to be independently predictive of survival.[11] In addition, for the 5,898 patients who were prospectively enrolled in a Mayo Clinic

Lung Cancer Cohort (MCLCC), marital status was also found not to be prognostic for NSCLC outcomes when all stages of the disease were analyzed together.[4] There are some possible confounding factors in these studies. Patients recruited for clinical trials tend to be healthier with a better performance status and have a support system (including close monitoring by the study team) when compared with the general population diagnosed with lung cancer. About 70% to 76% of the patients in both the RTOG and MCLCC studies were married, which is significantly higher than both the national average (51%) and our group (52.1%). Like other population-based studies, the MCLCC included patients with all stages getting a variety of treatments. Although no overall impact on survival was noted, the investigators noted that single, divorced, and widowed patients were more likely to not receive cancer therapy ($P < .0001$). The marital status also influenced the choice of therapy, with subgroup analysis revealing inferior outcomes in widowed and divorced patients with stage IA, IIB, or IIIB disease. The authors also recognized an inherent referral bias from patients, with support system being typically seen at the Mayo clinics, which may have played an additional role. All of the patients in our analysis were appropriately staged and received curative-intent treatment by a team of physicians using essentially identical therapeutic strategies, thus minimizing some of these confounding factors. This allowed us to explore the impact of marital status while a patient was undergoing stage-appropriate treatment. We demonstrated a strong association with marital status and survival that even overcame the effects of stage (IIIA vs IIIB) on clinical outcomes (Figure 1B).

Furthermore, our analysis allowed us to explore the interaction of race and marital status more definitively because the demographics of the patients in the RTOG and MCLCC included 14% and less than 3% of patients identified as being nonwhite, respectively, in contrast to our analysis in which 41% of the patients self-identified as black.[12] In our black population, marital status was associated with an observable improvement in OS, similar to our nonblack, predominantly white (97%) cohort (Figure 2B). Also, the results of our analysis may be a more accurate representation of the general population living in large urban or semiurban settings and further implies that an intact social support system could have a greater influence on clinical outcomes.

The current analysis is unique when compared with previous published studies in that beyond conventional demographic and treatment-related factors, we have comprehensively explored potential mechanisms that may explain the survival advantage seen in married patients by evaluating additional factors, such as functional status (ECOG and Charlson's scores), nutritional status (BMI and albumin), immunologic characteristics (NLR), and other social factors (race, income, insurance status). Although married patients were more likely to have a higher BMI and albumin at diagnosis, when controlling for these factors in the multivariable analysis, marital status remained strongly prognostic (Table 2), suggesting that nutrition alone does not fully account for the observed survival advantage demonstrated. A similar conclusion can be drawn about immunologic status. NLR has previously been shown to be prognostic in a number of cancers,[13-16] including in our own cohort.[8] Although immune status remains an important predictor for OS in our locally advanced NSCLC population, when we take NLR into consideration in our analysis, marital status continues to be a strong indicator for survival (Table 2). In terms of other variables analyzed, insurance status was a significant predictor of OS in the MVA, though functional status and other social factors including race were not significant.

We also explored cancer control outcomes in the form of FFR. Married patients had an observable, although not statistically significant, improvement in FFR when compared with the single cohort (Figure 2). In our study, married patients were more likely to undergo trimodality therapy (Table 1), which has likely translated to the improvement of FFR seen in our group. In this case, marriage may serve as a surrogate for availability of a support system to undergo aggressive, potentially toxic treatment.[3,17,18] Even in the setting of bimodality therapy, the RTOG 0617 study noted

TABLE 2 Factors associated with overall survival in the final Cox regression model[a]

Characteristic	Hazard ratio	95% confidence interval	*P*-value
Trimodality	.440	0.292-0.662	<.0001
Insurance status	.491	0.243-0.994	.048
Radiation technique	.502	0.302-0.837	.008
Consolidation chemotherapy	.560	0.380-0.827	.004
Marital status	.590	0.404-0.859	.006
Sex	.598	0.421-0.849	.004
NLR	1.051	1.020-1.082	.001

NLR, neutrophil-to-lymphocyte ratio

[a]Cox regression with forward model selection was used for multivariate analysis.

about 17.5% treatment interruptions because of adverse effects or illness, with more than 30% of patients experiencing grade 3 or more esophagitis, irrespective of radiation technique.[19] In these scenarios, in addition to receiving better attention to nutrition and care, significant others often provide emotional and social support that, in turn, can lead to better compliance. Social supports and sociodemographic factors are especially critical in patient populations in which access to health care is challenging.

Despite the compelling outcomes presented, our study suffers from the common limitations of retrospective analyses. Marital status, in this setting, most likely correlates with improved socioeconomic status and greater support, which have resulted in improved survival. Furthermore, although patients were self-classified as married or single, our data were not able to capture whether patients were single but lived with another adult or had other types of social support. However, even if there was a proportion of the unmarried cohort that had an alternate support system, separating them out is likely to further expand the differences. Quantifying the amount of social, emotional, or even spiritual support was not possible to accomplish in our analysis, though we know that all 3 can play a role in cancer outcomes.[20,21] Further prospective studies would have to be done to completely understand how marital status can influence clinical decisions. Understanding whether marital status is a proxy for social provisions may help to identify populations at risk for inferior outcomes. These at-risk patients may benefit from targeted clinical interventions, such as closer physician follow-up, more aggressive supportive care, access to support groups, or nurse navigator visits.

Conclusions

In patients with locally advanced NSCLC treated with curative-intent following uniform treatment algorithms, marital status was linked with improvement in survival even when adjusted for other key variables, with the second highest HR (after insurance status) among pretreatment demographic variables. Although marriage is an unmodifiable factor in itself, it is most likely a surrogate for better psychosocial support. The scale of these positive survival improvements emphasizes the need to institute targeted supportive care strategies to help advance overall outcomes in a tumor for which modern therapeutic approaches (novel systemic therapy and radiation) have yielded only modest improvement in outcomes yet come at the cost of considerable treatment-related toxicity.

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Primary renal synovial sarcoma – a diagnostic dilemma

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Soft tissue sarcomas are rare mesenchymal tumors that comprise 1% of all malignancies. Synovial sarcoma accounts for 5% to 10% of adult soft tissue sarcomas and usually occurs in close association with joint capsules, tendon sheaths, and bursa in the extremities of young and middle-aged adults.[1] Synovial sarcomas have been reported in other unusual sites, including the head and neck, thoracic and abdominal wall, retroperitoneum, bone, pleura, and visceral organs such as the lung, prostate, or kidney.[2] Primary renal synovial sarcoma is an extremely rare tumor accounting for <2% of all malignant renal tumors.[3] To the best of our knowledge, fewer than 50 cases of primary renal synovial sarcoma have been described in the English literature.[4] It presents as a diagnostic dilemma because of the dearth of specific clinical and imaging findings and is often confused with benign and malignant tumors. The differential diagnosis includes angiomyolipoma, renal cell carcinoma with sarcomatoid differentiation, metastatic sarcoma, hemangiopericytoma, malignant solitary fibrous tumor, Wilms tumor, and malignant peripheral nerve sheath tumor. Hence, a combination of histomorphologic, immunohistochemical, cytogenetic, and molecular studies that show a unique chromosomal translocation t(X;18) (p11;q11) is imperative in the diagnosis of primary renal synovial sarcoma.[4] In the present report, we present the case of a 38-year-old man who was diagnosed with primary renal synovial sarcoma.

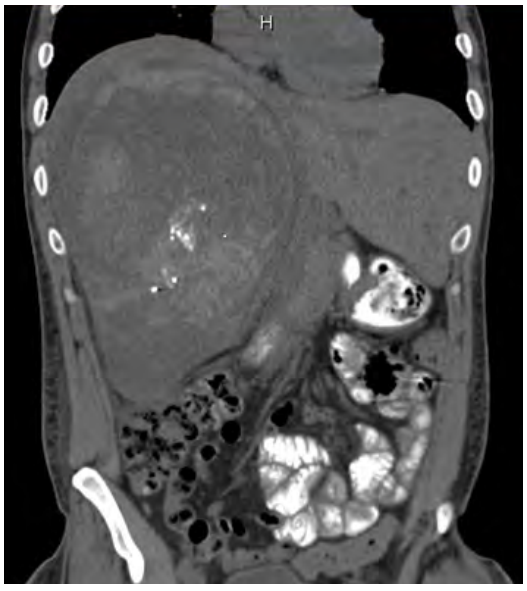

FIGURE 1 Coronal section of a computed-tomographic scan of the abdomen and pelvis, showing large right retroperitoneal hematoma with indwelling punctate calcifications, raising concern for underlying retroperitoneal or renal neoplasia and mass. Right kidney is displaced antero-inferiorly.

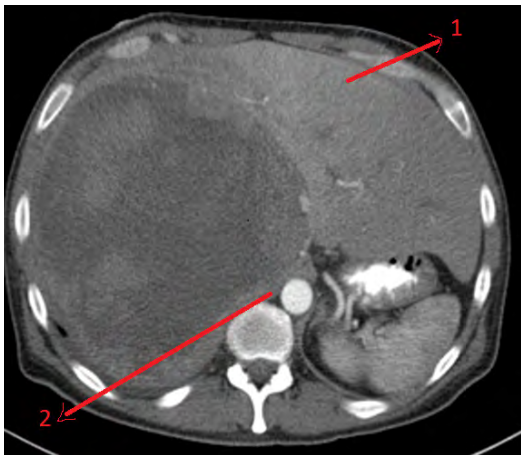

FIGURE 2 Cross-section of the abdomen and pelvis with contrast, showing the liver displaced to the left (1) and the inferior vena cava displaced anteriorly and to the left (2).

Accepted for publication October 5, 2018. Correspondence: Yellala Amulya, MD; amulya.yellala@ahn.org. Disclosures: The authors report no disclosures or conflicts of interest. JCSO 2018;16(5):e202-e205. ©2018 Frontline Medical Communications. doi: https://doi.org/10.12788/jcso.0426

Case presentation and summary

A 38-year-old man with a medical history of gastroesophageal reflux disease and Barrett's esophagus presented to our hospital for the first time with persistent and progressive right-sided flank and abdominal pain that was aggravated after a minor trauma to the back. There was no associated hematuria or dysuria.

Of note is that he had experienced intermittent flank pain for 2 years before this transfer. He had initially been diagnosed at his local hospital close to his home by ultrasound with an angiomyolipoma of 2 × 3 cm arising from the upper pole of his right kidney, which remained stable on repeat sonograms. About 22 months after his initial presentation at his local hospital, the flank pain increased, and a computed-tomographic (CT) scan revealed a perinephric hematoma that was thought to originate from a ruptured angiomyolipoma. He subsequently underwent embolization, but his symptoms recurred soon after. He presented again to his local hospital where CT imaging revealed a significant increase in the size of the retroperitoneal mass, and findings were suggestive of a hematoma. Subsequent angiogram did not reveal active extravasation, so a biopsy was performed.

Before confirmatory pathologic evaluation could be completed, the patient presented to his local hospital again in excruciating pain. A CT scan of his abdomen and pelvis demonstrated a massive subacute on chronic hematoma in the right retroperitoneum measuring 22 × 19 × 18 cm, with calcifications originating from an upper pole right renal neoplasm. The right kidney was displaced antero-inferiorly, and the inferior vena cava was displaced anteriorly and to the left. The preliminary pathology returned with findings suggestive of sarcoma (Figures 1 and 2).

The patient was then transferred to our institution, where he was evaluated by medical and surgical oncology. A CT scan of the chest and magnetic-resonance imaging (MRI) of the brain did not reveal metastatic disease. He underwent exploratory laparotomy that involved the resection of a 22-cm retroperitoneal mass, right nephrectomy, right adrenalectomy, partial right hepatectomy, and a full thickness resection of the right postero-inferior diaphragm followed by mesh repair because of involvement by the tumor.

In its entirety, the specimen was a mass of 26 × 24 × 14 cm. It was sectioned to show extensively necrotic and hemorrhagic variegated white to tan-red parenchyma (Figure 3). Histology revealed a poorly differentiated malignant neoplasm composed of round cells with scant amphophilic cytoplasm arranged in solid, variably sized nests separated by prominent thin-walled branching vascular channels (Figure 4). The mitotic rate was high. It was determined to be a histologically ungraded sarcoma according to the French Federation of Comprehensive Cancer Centers system of grading soft tissue sarcomas; the margins were indeterminate. Immunohistochemistry was positive for EMA, *TLE1*, and negative for AE1/AE3, S100, *STAT6*, and *Nkx2.2*. Molecular pathology fluorescent in situ hybridization (FISH) analysis demonstrated positivity for *SS18* gene rearrangement (*SS18-SSX1* fusion).

After recovering from surgery, the patient received adjuvant chemotherapy with doxorubicin and ifosfamide. It has been almost 16 months since we first saw this patient. He was started on doxorubicin 20 mg/m^2 on days 1 to 4, ifosfamide 2,500 mg on days 1 to 4, and mesna 800 mg on days 1 to 4, for a total of 6 cycles. He did well for the first 5 months, after which he developed disease recurrence in the postoperative nephrectomy bed (a biopsy showed it to be recurrent synovial sarcoma) as well as pulmonary nodules, for which he was started on trabectedin 1.5 mg/m^2 every 3 weeks. Two months later, a CT scan showed an increase in the size of his retroperitoneal mass, and the treatment was changed to pazopanib 400 mg daily orally, on which he remained at the time of publication.

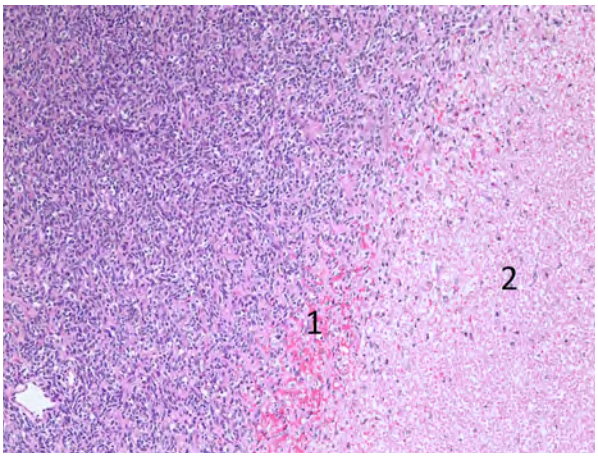

FIGURE 3 Histology of the tumor showing hemorrhage (1) and gross necrosis (2) (H&E, 10×).

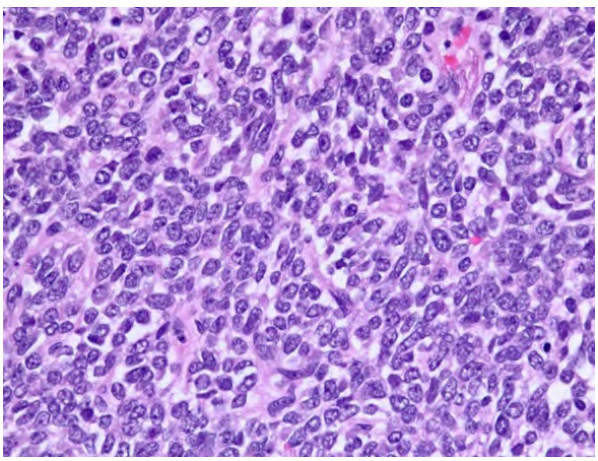

FIGURE 4 Tumor composed of round cells with scant amphophilic cytoplasm arranged in solid nests separated by prominent thin-walled branching vascular channels (H&E, 40×).

Discussion

Synovial sarcoma is the fourth most common type of soft tissue sarcoma, accounting for 2.5% to 10.5% of all primary soft tissue malignancies worldwide. It occurs most frequently in adolescents and young adults, with most patients presenting between the ages of 15 and 40 years. Median age of presentation is 36 years. Despite the nomenclature, synovial sarcoma does not arise in intra-articular locations but typically occurs in proximity to joints in the extremities. Synovial sarcomas are less commonly described in other sites, including the head and neck, mediastinum, intraperitoneum, retroperitoneum, lung, pleura, and kidney.[4,5] Renal synovial sarcoma was first described in a published article by Argani and colleagues in 2000.[5]

Adult renal mesenchymal tumors are classified into benign and malignant tumors on the basis of the histologic features and clinicobiologic behavior.[6,7] The benign esenchymal renal tumors include angiomyolipoma, leiomyoma, hemangioma, lymphangioma, juxtaglomerular cell tumor, renomedullary interstitial cell tumor (medullary fibroma), lipoma, solitary fibrous tumor, and schwannoma. Malignant renal tumors of mesenchymal origin include leiomyosarcoma, rhabdomyosarcoma, angiosarcoma, osteosarcoma, fibrosarcoma, malignant fibrous histiocytoma, solitary fibrous tumor, and synovial sarcoma.

Most of these tumor types cause the same nonspecific symptoms in patients – abdominal pain, flank pain, abdominal fullness, a palpable mass, and hematuria – although they can be clinically silent. The average duration of symptoms in synovial sarcoma is 2 to 4 years.[8] The long duration of symptoms and initial slow growth of synovial sarcomas may give a false impression of a benign process.

A preoperative radiological diagnosis of primary renal synovial sarcoma may be suspected by analyzing the tumor's growth patterns on CT scans.[9] Renal synovial sarcomas often appear as large, well-defined soft tissue masses that can extend into the renal pelvis or into the perinephric region.[9] A CT scan may identify soft tissue calcifications, especially subtle ones in areas where the tumor anatomy is complex. A CT scan may also reveal areas of hemorrhage, necrosis, or cyst formation within the tumor, and can easily confirm bone involvement. Intravenous contrast may help in differentiating the mass from adjacent muscle and neurovascular complex.[9,10] On MRI, renal synovial sarcomas are often described as nonspecific heterogeneous masses, although they may also exhibit heterogeneous enhancement of hemorrhagic areas, calcifications, and air-fluid levels (known as "triple sign") as well as septae. The triple sign may be identified as areas of low, intermediate, and high signal intensity, correlating with areas of hemorrhage, calcification, and air-fluid level.[9,10] Signal intensity is about equal to that of skeletal muscle on T1-weighted MRI and higher than that of subcutaneous fat on T2-weighted MRI.

In the present case, the tumor was initially misdiagnosed as an angiomyolipoma, the most common benign tumor of the kidney. Angiomyolipomas are usually solid triphasic tumors arising from the renal cortex and are composed of 3 major elements: dysmorphic blood vessels, smooth muscle components, and adipose tissue. When angiomyolipomas are large enough, they are readily recognized by the identification of macroscopic fat within the tumor, either by CT scan or MRI.[11] When they are small, they may be difficult to distinguish from a small cyst on CT because of volume averaging.

On pathology, synovial sarcoma has dual epithelial and mesenchymal differentiation. They are frequently multilobulated, and areas of necrosis, hemorrhage, and cyst formation are also common. There are 3 main histologic subtypes of synovial sarcoma: biphasic (20%-30%), monophasic (50%-60%), and poorly differentiated (15%-25%). Poorly differentiated synovial sarcomas are generally epithelioid in morphology, have high mitotic activity (usually 10-20 mitoses/10 high-power field; range is <5 for well differentiated, low-grade tumors), and can be confused with round cell tumors such as Ewing sarcoma. Poorly differentiated synovial sarcomas are high-grade tumors.

Immunohistochemical studies can confirm the pathological diagnosis. Synovial sarcomas usually stain positive for Bcl2, CD99/Mic2, CD56, Vim, and focally for EMA but negatively for desmin, actin, WT1, S-100, CD34, and CD31.[5] Currently, the gold standard for diagnosis and hallmark for synovial sarcomas are the t (X;18) translocation and *SYT-SSX* gene fusion products (*SYT-SSX1* in 67% and *SYT-SSX2* in 33% of cases). These can be detected either by FISH or reverse-transcription polymerase chain reaction. This genetic alteration is identified in more than 90% of synovial sarcomas and is highly specific.

The role of *SYT-SSX* gene fusion in the pathogenesis of synovial sarcoma is an active area of investigation. The fusion of SYT with SSX translates into a fusion protein that binds to the transcription activator SMARCA4 that is involved in chromatin remodeling, thus displacing both the wildtype SYT and the tumor suppressor gene *SMARCB1*. The modified protein complex then binds at several super-enhancer loci, unlocking suppressed genes such as *Sox2*, which is known to be necessary for synovial sarcoma proliferation. Alterations in *SMARCB1* are involved in several cancer types, implicating this event as a driver of these malignancies.[12] This results in a global alteration in chromatin remodeling that needs to be better understood to design targeted therapies.

The clinical course of synovial sarcoma, regardless of the tissue of origin, is typically poor. Multiple clinical and pathologic factors, including tumor size, location, patient age, and presence of poorly differentiated areas, are thought to have prognostic significance. A tumor size of more than 5 cm at presentation has the greatest impact on prognosis, with studies showing 5-year survival rates of 64%

for patients with tumors smaller than 5 cm and 26% for patients with masses greater than 5 cm.[13,14] High-grade synovial sarcoma is favored in tumors that have cystic components, hemorrhage, and fluid levels and the triple sign.

Patients with tumors in the extremities have a more favorable prognosis than those with lesions in the head and neck area or axially, a feature that likely reflects better surgical control available for extremity lesions. Patient age of less than 15 to 20 years is also associated with a better long-term prognosis.[15,16] Varela-Duran and Enzinger[17] reported that the presence of extensive calcifications suggests improved long-term survival, with 5-year survival rates of 82% and decreased rates of local recurrence (32%) and metastatic disease (29%). The poorly differentiated subtype is associated with a worsened prognosis, with a 5-year survival rate of 20% through 30%.[18,19] Other pathologic factors associated with worsened prognosis include presence of rhabdoid cells, extensive tumor necrosis, high nuclear grade, *p53* mutations, and high mitotic rate (>10 mitoses/10 high-power field). More recently, the gene fusion type *SYT-SSX2* (more common in monophasic lesions) has been associated with an improved prognosis, compared with that for *SYT-SSX1*, and an 89% metastasis-free survival.[20]

Although there are no guidelines for the treatment of primary renal synovial sarcoma because of the limited number of cases reported, surgery is considered the first choice. Adjuvant chemotherapy with an anthracycline (doxorubicin or epirubicin) combined with ifosfamide has been the most frequently used regimen in published cases, especially in those in which patients have poor prognostic factors as mentioned above.

Overall, the 5-year survival rate ranges from 36% to 76%.[14] The clinical course of synovial sarcoma is characterized by a high rate of local recurrence (30%-50%) and metastatic disease (41%). Most metastases occur within the first 2 to 5 years after treatment cessation. Metastases are present in 16% to 25% of patients at their initial presentation, with the most frequent metastatic site being the lung, followed by the lymph nodes (4%-18%) and bone (8%-11%).

Conclusion

Primary renal synovial sarcoma is extremely rare, and preoperative diagnosis is difficult in the absence of specific clinical or imaging findings. A high index of suspicion combined with pathologic, immunohistochemical, cytogenetic, and molecular studies is essential for accurate diagnosis and subsequent treatment planning. The differential diagnosis of renal synovial sarcoma can be extensive, and our experience with this patient illustrates the diagnostic dilemma associated with renal synovial sarcoma.

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Prolonged survival in adenocarcinoma of unknown primary treated with chemoradiotherapy

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Cancer of unknown primary (CUP) represents 3% to 5% of all cancer malignancies in the world.[1] Since 2003, CUP has been divided into 2 subsets – favorable (20% of the cases) and unfavorable (80% of the cases) – based on histopathologic and clinical manifestations.[2] The impact of locoregional therapies, such as surgery and radiation, in addition to systemic chemotherapy in adenocarcinomas of unknown primary is not well described in the literature. We report here the case of a patient with adenocarcinoma of unknown primary with lymph-node–only metastases who has remained free of tumor progression for 2 years since completion of systemic multiagent chemotherapy followed by consolidation chemoradiotherapy (CRT).

Case presentation and summary

A 37-year-old Bengali woman born and raised in Bangladesh, with a history of gallstones diagnosed in 2010, presented to the emergency department at an outside community hospital in New York in the fall of 2014 with right upper-quadrant pain that was more severe after meals during the previous 3 to 6 months. Her past medical history was significant for hypertension, gastroesophageal reflux disease, and kidney stones. She had no past surgical procedures. On family history, both her parents were deceased, and her mother had been diagnosed with hypertension. Her 4 siblings and 2 daughters had no known medical conditions. She did not smoke or drink alcohol and lived with her husband in Queens, New York. On physical exam, her abdomen was soft, nontender, and with normal bowel sounds. An ultrasound on November 10, 2014, showed a shadowing stone measuring 1.5 x 0.9 cm in the gallbladder fundus. She therefore underwent a cholecystectomy at an outside community hospital in December 2014 and was found to have gallstones and a metastatic adenocarcinoma of a pericholecystic lymph node. No mass was found in the gallbladder. A positron-emission and computed-tomographic (PET-CT) scan in January 2015 showed hypermetabolic activity in the porta hepatis. She was scheduled for an upper endoscopy that was cancelled because the results of her beta human chorionic gonadotropin (hCG) test were elevated.

The patient was frustrated by the lack of diagnosis and extensive work-up and decided to travel to Bangladesh for several months. Upon her return in May 2015, the patient underwent dilation and curettage at an outside tertiary care center because of her persistently elevated beta-hCG levels (>500 mIU/mL; reference range for nonpregnant woman, <5 mIU/mL) that found no products of conception and excluded a malignant process. Endoscopy and colonoscopy at that time failed to reveal a primary tumor.

She was then referred to our institution. Her level of beta-hCG remained elevated, and another transvaginal ultrasound was performed but failed to reveal any masses or evidence of pregnancy. Mammogram and a breast ultrasound showed left breast lesions. Biopsy of the breast lesions was performed, and the pathology demonstrated fibrocystic changes.

Because the lymph node was located near the liver, we also measured the patient's alpha fetoprotein (AFP), which is a marker for hepatocellular carcinoma. It was found to be elevated at 1,800.7 ng/mL (reference range, 0.0-9.0 ng/mL). Elevated

Accepted for publication September 6, 2018. Correspondence: Sofya Pintova, MD; sofya.pintova@mssm.edu. Disclosures: The authors report no disclosures or conflicts of interest. JCSO 2018;16(5):e206-e209. doi: https://doi.org/10.12788/jcso.0424

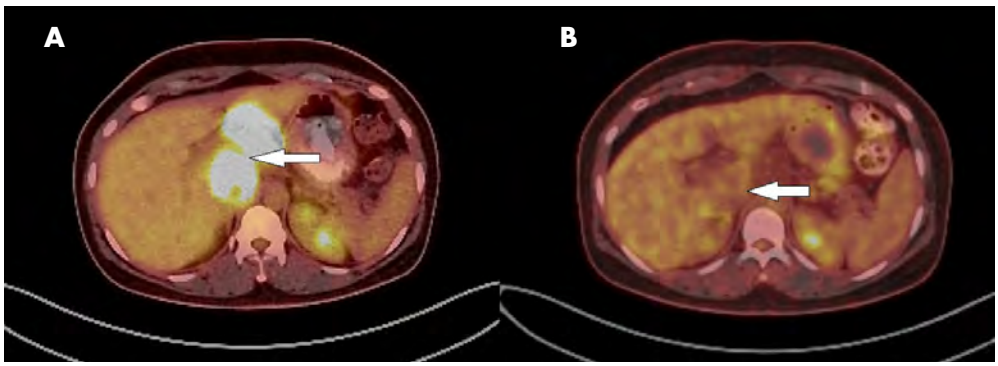

FIGURE 1 A, Baseline PET-CT scan before any therapy, with porta hepatis lymphadenopathy, with an SUV of 14. **B**, PET-CT after 4 months of chemotherapy, with porta hepatis lymphadenopathy, with an SUV of 3.5.

PET-CT, positron-emission and computed-tomographic; SUV, standardized uptake value

serum AFP occurs in pregnancy, nonseminatous germ cell tumors, hepatocellular carcinoma, and other gastrointestinal tumors. The test for AFP has a low sensitivity, so an elevated AFP is not clinically useful in helping identify the origin of the primary tumor. The patient's level of lactate dehydrogenase (LDH), a tumor marker for germ cell tumors, was also elevated at 296 U/L (reference range, 100-220 U/L). CA 19-9, CA 125, and carcinoembryonic antigen, tumor markers of gastrointestinal carcinomas, did not demonstrate elevated levels at 19.8 U/mL (reference range, 0.0-35.0 U/mL), 16 U/mL (reference range, 0-35 U/mL), and 0.7 ng/mL (reference range, 0.0-3.0 ng/mL), respectively. No hepatitis serologies were measured at the time of diagnosis.

The results of a PET-CT scan in August 2015 showed a lobulated abdominal mass of 5.7 x 3.7 cm, consisting of multiple periportal necrotic lymph nodes with a standardized uptake value (SUV) of 14 (Figure 1A) and a 2.0-cm hypermetabolic retroperitoneal lymph node at the aortic bifurcation level with an SUV of 8.6. The SUV is a ratio of activity per unit volume of a region of interest to the activity per unit whole body volume. An SUV of 2.5 or higher is generally considered to be indicative of malignant tissue. We conducted a detailed review of the lymph node pathologic specimen. Immunohistochemical (IHC) studies were positive for CK7, CDX2, and EMA; focally positive for PR and mammaglobin; and negative for CK20, ER, TTF-1, and WT-1. Nonspecific staining was seen with BRST2, and there was no staining with GATA3. IHC stain for HER2-NEU was equivocal. Molecular analysis did not detect *BRAF*, *KRAS*, *NRAS*, and *PIK3CA* mutations, but did find a *CTNNB1* mutation. The IHC pattern suggested pancreatobiliary origin of the tumor.[3]

Although serum tumor marker pattern of elevated beta-hCG, AFP, and LDH can be seen in germ cell tumors, the pathology evaluation did not favor a germ cell tumor. No site of origin was evident on radiographic evaluation, and the patient was diagnosed with CUP. Based on tumor metastatic distribution and the elevated beta-hCG level,[4] we suspected that an undetected pancreatic primary was possible, and we therefore chose the folinic acid, fluorouracil, irinotecan, oxaliplatin (FOLFIRINOX) chemotherapy regimen for its evidence in prolonging survival in metastatic pancreatic cancer.[5] At the initiation of treatment, the patient's elevated tumor markers were beta-hCG 953.6 mIU/mL (reference for nonpregnant woman, <5 mIU/mL) and AFP 1,800.7 ng/mL (reference range, 0.0-9.0 ng/mL). The patient began FOLFIRINOX chemotherapy in August 2015 and after 1 month of treatment, her beta-hCG and AFP levels declined notably to 1.7 mIU/mL and 11.2 ng/mL, respectively. She completed a total of 8 cycles of FOLFIRINOX in November 2015. After completion of chemotherapy, the PET-CT scan showed a decrease in fluoro-D-glucose (FDG) uptake in the porta hepatis and retroperitoneal lymph nodes (Figure 1B). SUV in the porta hepatis lymph nodes declined from 14 to 3.5. The patient's case was presented to our institution's multidisciplinary tumor board, and the members deemed the risk of possible lymph node dissection surgery would outweigh the benefit. It was recommended that we proceed with radiotherapy to the residual lymph node stations.

During December 2015 through February 2016, the patient underwent a course of consolidative chemoradiation therapy to the intra-abdominal lymph nodes to a dose of 5,400 cGy in 30 fractions, with concurrent capecitabine as radiosensitizer, using intensity-modulated radiation therapy. During both chemotherapy and CRT, the patient experienced nausea, vomiting, fatigue, and anorexia, which were treated with antiemetics. She completed therapy without major complications and recovered completely from the adverse effects.

Five weeks after completion of chemoradiation, a restaging PET-CT scan showed a persistent small FDG uptake in the periportal region (SUV, 4.2). After CRT, tumor markers beta-hCG and AFP declined to less than 1.2 mIU/mL and less than 2.0 ng/mL, respectively.

Three and a half years after diagnosis and 2.5 years after completion of the treatment course, the patient remains free of cancer progression without any therapy. Restaging CT scans of the chest, abdomen, and pelvis every 3 to 6 months continue to show an amorphous soft tissue density in the porta hepatis, which has remained unchanged throughout the last 2 years since chemoradiation

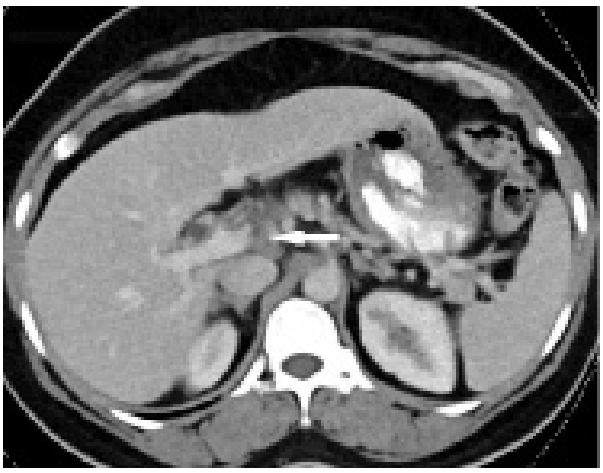

FIGURE 2 Computed-tomographic scan of the patient's chest, abdomen, and pelvis 24 months after chemoradiation therapy showing amorphous soft tissue density in the porta hepatis.

(Figure 2). The levels of the patient's tumor markers AFP and beta-hCG remain normal.

Discussion

CUP is divided into favorable and unfavorable subsets.[1] The favorable subset includes women with adenocarcinoma involving axillary lymph nodes, women with papillary adenocarcinoma of peritoneal cavity, and adenocarcinoma with a colon profile. The unfavorable subset includes moderate to poorly differentiated adenocarcinomas (64%) and undifferentiated tumors (36%). It involves the liver in 40% to 50% of the cases, followed by lymph nodes (35%), lungs (31%), bones (28%), and the brain (15%).[1,2,6] Although data suggest that CUP with lymph-node–only metastases generally fall into an unfavorable prognosis group, our patient's survival and progression-free survival have been especially prolonged. Remarkably, our patient is still alive 44 months after the diagnosis.

The combined platinum–paclitaxel-based regimens are the treatment of choice in this unfavorable subset of CUP,[7,8] with patients showing 16% to 38% response rates and median overall survival times of 6.5 to 13 months.[7] Platinum–gemcitabine combinations can also be used as an alternative first-line regimen, with an overall response rate of 55% and a median survival of 8 months.[9] The addition of the targeted agents bevacizumab and erlotinib to the carboplatin–paclitaxel combination, followed by bevacizumab and erlotinib maintenance, has been shown to yield a median survival of 12.6 months but was not meaningfully superior to historical studies with chemotherapy alone.[10]

We chose the FOLFIRINOX regimen for our patient. Conroy and colleagues reported a notably improved survival of 11.1 months with that combination chemotherapy in patients with metastatic pancreatic cancer compared with 6.8 months with gemcitabine alone.[5] Given the possible pancreatobiliary site of tumor origin on IHC, the lymph node pattern of spread, and the patient's young age and robust performance status, we felt that this multiagent systemic therapy would offer the best chance of prolonged survival. FOLFIRINOX includes a platinum agent, oxaliplatin, and platinum agents are recommended to be included in chemotherapy combinations for CUP.[9,10] Although there is no data to suggest the superiority of a triplet regimen over a doublet regimen in a CUP, a triplet chemotherapy regimen may be considered in select cases.

There have been only a few reports showing the effectiveness of radiotherapy in the treatment of adenocarcinomas of unknown primary outside of the head and neck. Kubisch and colleagues have reported a case of a woman with hepatic adenocarcinoma of unknown primary that was treated with chemotherapy and surgery. Upon recurrence, the patient was then treated with selective internal radiation therapy (SIRT). She was still alive 3 years after diagnosis, and there had been no tumor relapse 21 months after SIRT.[11] Shiota and colleagues have reported a case of a mediastinal lymph node CUP that was treated with docetaxel and cisplatin with concurrent thoracic radiation therapy.[12] The patient remained free of symptoms without regrowth of the primary site 22 months after disease onset, and exploration of the body with enhanced and PET-CT scan showed no further abnormalities.

Other reports suggest that locoregional therapy such as surgery and radiation may be of benefit to select patients with CUP. A retrospective study by Löffler and colleagues reported that patients with a limited local involvement who received radical surgery had a median overall survival of 52.7 months compared with those who received radiation (median overall survival, 19.4 months) and those who received chemotherapy alone (median overall survival, 16 months).[13] A case of a metastatic undifferentiated CUP also reported a long-term (>5 years), disease-free survivor after pancreaticoduodenectomy and systemic adjuvant chemotherapy.[14]

Our case further demonstrates that a multidisciplinary approach to CUP may lead to excellent clinical outcomes. Chemotherapy followed by chemoradiation in our patient increased local tumor control and survival. Our patient's 44-month survival was superior to the historic 6.5- to 13-month median survival in CUP patients treated with chemotherapy alone. Consolidation chemoradiation treatment may therefore be a viable and more effective therapy in the treatment of adenocarcinoma of unknown primary, in which anatomical disease concentration is amenable to radiotherapy following control with systemic chemotherapy. Nevertheless, it is difficult to draw conclusions from select cases. Another case of mediastinal adenocarcinoma, favoring a colorectal primary but with no evidence of a

primary lesion on endoscopy, had a poorer outcome than did our patient, with the cancer recurring 6 months after completion of chemotherapy, surgical excision, and adjuvant radiotherapy.[15]

Adenocarcinomas of unknown primary cases should involve management by a multidisciplinary team. Clinical trials incorporating locoregional therapies for CUP in addition to systemic therapy are warranted.

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Game changers in pediatric cancer

Jane de Lartigue, PhD

Although there have been significant improvements in patient outcomes for some forms of pediatric cancer, progress has been painfully slow for others. An increasing understanding of pediatric cancers is highlighting the unique molecular drivers and challenging the assumption that drugs developed in adults can be applied to children and young adults. Here, we discuss game-changing therapeutic advances and a shifting view of childhood cancers.

Unique genomic background

Although pediatric cancers are rare, representing just 1% of all new cancers diagnosed annually in the United States, they are the second leading cause of death in children aged 1 to 14 years. There are many different histological tumor types under the umbrella of childhood cancers, of which the most common are leukemias, central nervous system tumors, and lymphomas (Figure 1).[1,2]

Significant progress has been made in the treatment of certain pediatric cancers in recent decades, exemplified by pediatric acute lymphoblastic leukemia (ALL), which has been transformed from a virtually incurable cancer to one in which 5-year survival rates now reach up to 90%. In other forms of pediatric cancer, however, survival rates have stagnated and little progress has been made in the development of effective new therapies.[3]

Because of their rarity, pediatric cancers are difficult to study and adequate enrollment of children in clinical trials can be challenging. Pharmaceutical companies are often hesitant to test drugs in the pediatric population in patients who often cannot advocate for themselves. As a result, the activity of drugs developed in adult patients has often been inferred in pediatric patients with the same tumor type or molecular aberrations. However, as researchers have gathered more information about pediatric cancers, there has been increasing recognition of their unique attributes and the need for dedicated clinical trials in this patient population.

Pediatric cancers tend to be found in the developing mesodermic tissue, whereas adult cancers are more prevalent in the epithelial tissues. Genome sequencing studies have revealed a much lower

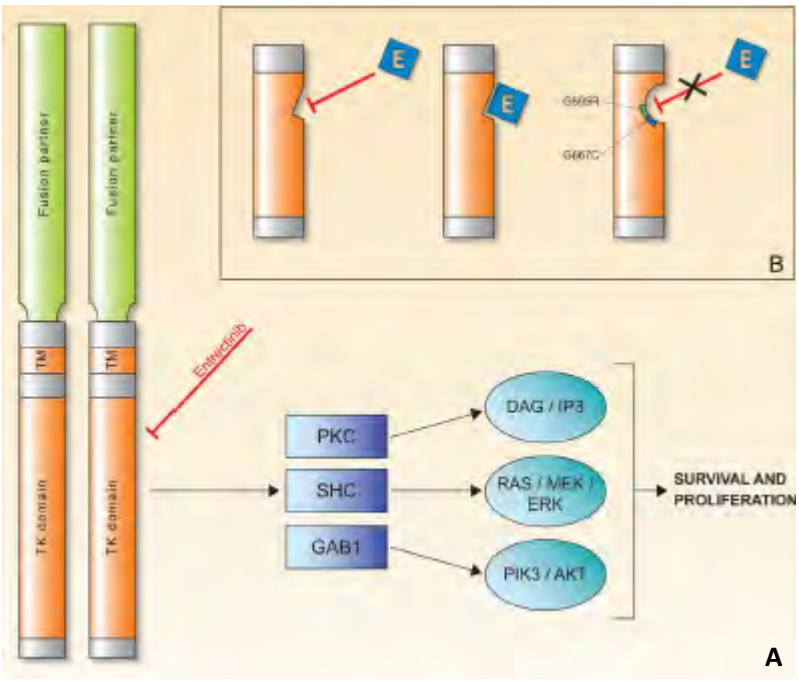

FIGURE 1 Targeting TRK fusions.[16] The tropomyosin receptor kinases are a family of transmembrane proteins, highly expressed in neuronal tissue, which control many cancer hallmark processes through the activation of several downstream signaling pathways. Gene fusions involving the *NTRK* genes are being identified in an ever-growing list of tumor types. The fusions drive constitutive activation of these tyrosine kinases and the cellular processes they regulate. A number of TRK inhibitors have been developed that are designed to block the activity of TRK fusions, including entrectinib (A). Several mechanisms of resistance to TRK inhibitors have already been identified (B).

JCSO 2018;16(5):e210-e216. ©2018 Frontline Medical Communications. doi: https://doi.org/10.12788/jcso.0430

TABLE 1 Recent US Food and Drug Administration approvals in pediatric cancer

Drug	Manufacturer	Mechanism of action	Approved pediatric indication
Tisagenlecleucel (Kymriah)	Novartis	CD19-targeted CAR T-cell therapy	Relapsed/refractory B-cell ALL after 2 or more prior treatments
Pembrolizumab (Keytruda)	Merck	PD1-targeted mAb	Relapsed/refractory cHL after 3 or more prior treatments Relapsed/refractory dMMR/MSI-high solid tumors Relapsed/refractory PMBCL after 2 or more prior treatments
Nivolumab (Opdivo)	Bristol-Myers Squibb	PD1-targeted mAb	Relapsed/refractory dMMR/MSI-high mCRC after failure of chemotherapy (alone or in combination with ipilimumab)
Ipilimumab (Yervoy)	Bristol-Myers Squibb	CTLA4-targeted mAb	Metastatic melanoma
Blinatumomab (Blincyto)	Amgen	CD19-targeted BiTE	Relapsed/refractor B-cell ALL regardless of Philadelphia chromosome status
Dasatinib (Sprycel)	Bristol-Myers Squibb	Multitargeted kinase inhibitor	Chronic phase Philadelphia chromosome-positive CML
Nilotinib (Tasigna)	Novartis	Multitargeted kinase inhibitor	Chronic phase Philadelphia chromosome-positive CML
Gemtuzumab ozogamicin (Mylotarg)	Pfizer	CD33-targeted ADC	Relapsed/refractory CD33-positive AML
Dinutuximab (Unituxin)	United Therapeutics	GD2-targeted mAb	High-risk neuroblastoma

ADC, antibody-drug conjugate; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BiTE, bispecific T-cell engager; CAR, chimeric antigen receptor; cHL, classical Hodgkin lymphoma; CML, chronic myeloid leukemia; CTLA-4, cytotoxic T lymphocyte antigen-4; dMMR, defective mismatch repair; mAb, monoclonal antibody; mCRC, metastatic colorectal cancer; MSI, microsatellite instability; PD-1, programmed cell death protein-1; PMBCL, primary mediastinal large B-cell lymphoma

mutational burden in pediatric cancers and the mechanisms of oncogenesis are also quite different; adult tumors can develop from a series of acquired gene mutations, but pediatric tumors tend to develop from a single catastrophic event.[4,5]

Even the same type of cancer in a pediatric and adult patient can be quite different, with very different underlying molecular mechanisms. In a recent genomic analysis of different types of pediatric cancer by researchers at St Jude's Children's Research Hospital, less than half of the identified mutated genes were found to be similar to those found in adult patients.[6]

A 'magic bullet'?

Chromosomal rearrangements are common in pediatric cancers. This type of molecular abnormality can result in a fusion of 2 different genes when the chromosome breaks apart and the pieces join back together in a muddled order. If the genetic code fuses in a manner that is "readable" by the cell, then it can drive aberrant activation of one or both genes.[7] Gene fusions often involve kinase enzymes that are essential players in cell signaling pathways regulating hallmark cancer processes, such as unchecked cell proliferation. The fusion drives the constitutive activation of the kinase and, thus, these downstream signaling pathways.

One of the first chromosomal rearrangements linked to cancer, BCR-ABL1 – more commonly known as the Philadelphia chromosome – results in aberrant activation of the ABL1 kinase. It is present in nearly all cases of chronic myeloid leukemia (CML) and 3% to 5% of patients with ALL, and thus became the central focus of targeted drug development. Imatinib was initially approved by the US Food and Drug Administration (FDA) in 2001 for the treatment of adult patients with CML and had such a significant impact on the treatment landscape that it made the cover of Time magazine as a "magic bullet" in the war on cancer.[8]

Approval was expanded into pediatric patients in 2006 and for pediatric patients with ALL in 2013. However, as with the use of most kinase inhibitors, tumors can evolve under the selective pressure of treatment, developing additional molecular abnormalities that drive resistance.[9]

Next-generation multikinase inhibitors that more potently inhibit the BCR-ABL1 fusion protein have been developed to provide additional treatment options for patients who become resistant to imatinib. Dasatinib and nilotinib are among several drugs that have recently been approved for pediatric cancer therapy (Table 1). Both therapies were approved to treat children with Philadelphia chromosome-positive CML in the chronic phase in either the front- or second-line setting after failure of imatinib.

The approval of dasatinib was based on data from 97 patients across 2 trials, 51 of whom were newly diagnosed and 46 previously treated with imatinib. Most of the patients were treated with dasatinib 60 mg/m^2 once daily. After 2 years of follow-up, more than 95% of newly diagnosed patients and 82.6% of relapsed/refractory patients had complete cytogenetic response.[10]

TABLE 2 Ongoing clinical trials of targeted therapies in pediatric cancers

Drug	Developer	Mechanism of action	Most advanced stage of clinical development in the pediatric setting (ClinicalTrials.gov identifier)
Larotrectinib (LOXO-101)	Loxo	TRK inhibitor	Phase 1/2 in relapsed/refractory solid or primary CNS tumors (NCT02637687)
Entrectinib (RXDX-101)	Ignyta	TRK inhibitor	Phase 1 in relapsed/refractory solid or primary CNS tumors (NCT02650401)
LOXO-195	Loxo	TRK inhibitor	Phase 1/2 in relapsed/refractory NTRK fusion-positive cancers (NCT03215511)
Vemurafenib (Zelboraf)	Genentech	BRAF inhibitor	Phase 1 in relapsed/refractory BRAF-mutant gliomas (NCT01748149)
Dabrafenib (Tafinlar)	Novartis	BRAF inhibitor	Phase 2 + trametinib in relapsed/refractory glioma (NCT02684058)
Trametinib (Mekinist)	Novartis	MEK inhibitor	Phase 2 in relapsed/refractory glioma or neurofibroma (NCT03363217)
Selumetinib (AZD6244)	AstraZeneca	MEK inhibitor	Phase 1/2 in relapsed/refractory BRAF-mutant glioma (NCT01089101)
Erdafitinib	Janssen	Pan-FGFR inhibitor	Phase 2 in relapsed/refractory solid tumors, NHL, or histiocytic disorders with FGFR mutations (NCT03210714)
Crizotinib (Xalkori)	Pfizer	ALK/MET/ROS1 inhibitor	Phase 2 + combination chemotherapy in newly diagnosed ALCL (NCT01979536)
Ceritinib (Zykadia)	Novartis	ALK inhibitor	Phase 1/2 + brentuximab vedotin in ALK-positive ALCL (NCT02729961)
Lorlatinib	Pfizer	ALK/ROS1 inhibitor	Phase 1 in relapsed/refractory ALK-positive neuroblastoma (NCT03107988)
Dasatinib (Sprycel)	Bristol-Myers Squibb	Multi-targeted kinase inhibitor	Phase 3 in newly diagnosed ALL (NCT03020030)
Nilotinib (Tasigna)	Novartis	Multi-targeted kinase inhibitor	Phase 1/2 + vinblastine in relapsed/refractory low-grade glioma (VINILO; NCT01884922/NCT01887522)

ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; ALL, acute lymphoblastic leukemia; CNS, central nervous system; FGFR, fibroblast growth factor receptor; MEK, mitogen-activated protein kinase; NHL, non-Hodgkin lymphoma; TRK, tropomyosin receptor kinase

Nilotinib was approved on the basis of findings from 2 clinical trials including 69 patients – 1 trial involving patients who were refractory to or relapsed after dasatinib and imatinib treatment, and 1 that included both relapsed/refractory and newly diagnosed patients. Patients received nilotinib 230 mg/m^2 twice daily, rounded to the nearest 50-mg dose, in 28-day cycles. By cycle 12, the cumulative major molecular response rate (MMR) was 47.7% in patients with relapsed/refractory disease, and 64% in newly diagnosed patients.[11] Clinical trials of both drugs in the pediatric setting are ongoing.

Other prominent gene fusions

Gene fusions involving the anaplastic lymphoma kinase (ALK) occur in patients with non–small-cell lung cancer and ALK inhibitors have provided an effective new treatment option for patients whose tumors display this abnormality.

ALK fusions are also a prominent feature of several kinds of pediatric cancers and ALK inhibitors offer promise in this setting.[7,12] An *NPM-ALK* fusion is found in 90% of pediatric anaplastic large cell lymphoma (ALCL) cases,[13] whereas a variety of ALK fusions are found in up to half of patients with inflammatory myofibroblastic tumor (IMT), a rare form of soft tissue sarcoma.[14] ALK inhibitors are being tested in a variety of clinical trials in pediatric patients (Table 2).

The results of a small phase 1 study of crizotinib in pediatric patients with ALK-positive ALCL (n = 26) or IMT (n = 14) were recently published. ALCL patients received crizotinib at a dose of 165 mg/m^2, while IMT patients were given 100, 165, or 280 mg/m^2. For the latter, the results were presented as a pooled cohort since safety and efficacy data were similar across dose levels. The overall response rate (ORR) was 83% for patients with ALCL and 86% for those with IMT. Grade 3/4 adverse events occurred in 83% and 71% of patients, respectively, and most commonly involved reduced neutrophil count.[15]

Most recently and perhaps most promisingly, fusions involving the neurotrophic tropomyosin receptor kinase (*NTRK*) gene have generated significant buzz. There are 3 *NTRK* genes, *NTRK1, 2,* and *3,* which encode the TRKA, TRKB, and TRKC proteins, respectively.

To date, 22 different partner genes have been identified that can fuse with the *NTRK* genes and, as with other kinase fusions, drive constitutive activation of the receptor proteins and downstream oncogenic signaling pathways, including the mitogen-activated protein kinase (MAPK) pathway (Figure 2).

NTRK fusions are being identified in an ever-growing number of cancer types, but are typically found in a small percentage of patients. However, in certain rare pediatric tumors, including congenital infantile fibrosarcoma and papillary thyroid cancer, they are found at much higher frequencies.

TRK inhibitors have been developed to target the fusion proteins and, given the spread of *NTRK* fusions across different types of cancers, they offer the most substantial promise as the next tumor agnostic cancer therapy – to treat patients based on the shared presence of a molecular aberration, irrespective of the type of cancer.[16]

The ongoing SCOUT trial is evaluating larotrectinib (LOXO-101) in pediatric patients. Among 24 patients (17 with *NTRK* fusions and 7 without) with infantile fibrosarcoma (47%), soft tissue sarcoma (41%) or papillary thyroid cancer (12%), the ORR was 93%, including complete response (CR) in 13% of patients.[17]

Preliminary results from an ongoing phase 1/2 study of entrectinib in pediatric patients with extracranial solid tumors were also recently presented at the annual meeting of the American Society for Clinical Oncology (ASCO). Among 15 evaluable patients enrolled to date, 3 have *NTRK* fusions and all experienced an objective response, with 1 (a patient with IMT) ongoing at 10 months.[18]

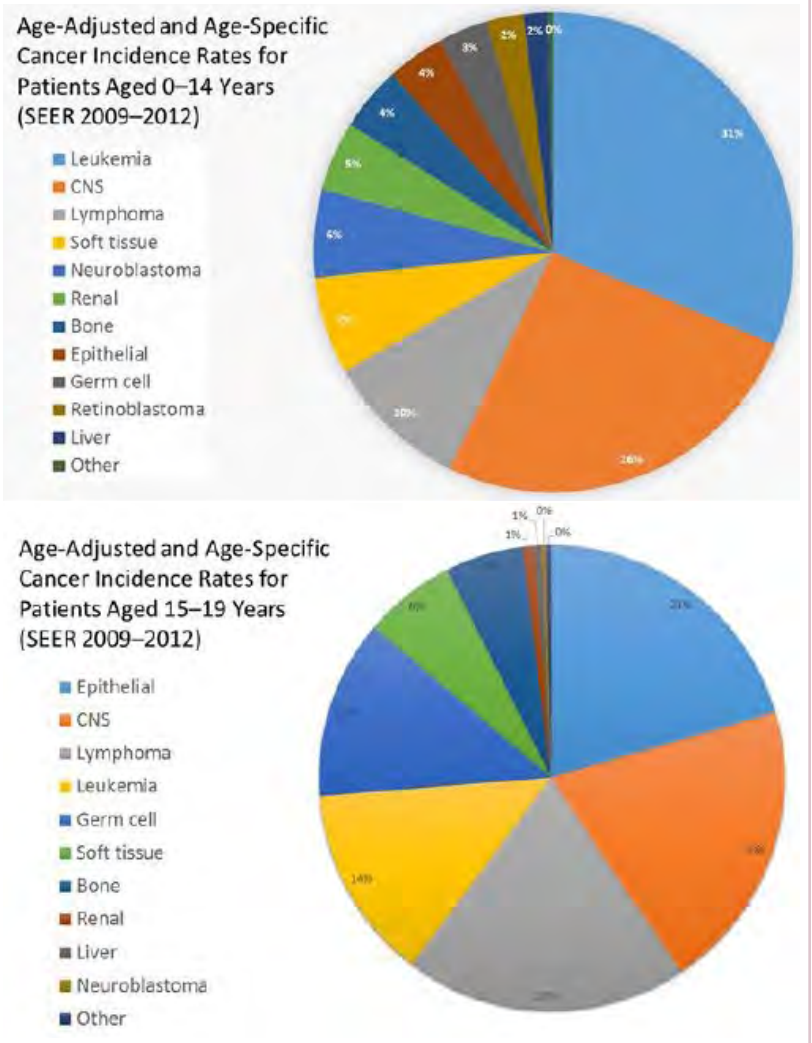

FIGURE 2 Pediatric cancer incidence.[2] Age-adjusted and age-specific Surveillance, Epidemiology and End Results data (2009-2012), showing cancer incidence rates by International Classification of Childhood Cancer group for patients aged 0-14 and 15-19 years. Leukemias and central nervous system (CNS) tumors represent the largest proportion of cases for the former and epithelial and CNS tumors and lymphomas are most prevalent in the latter.

CAR T cells transformative in ALL

A variety of different types of immunotherapy have been tested in patients with pediatric cancers. In general, immunotherapy has proved less effective than in adult cancers, possibly because of the lower tumor mutation burden in pediatric cancers, which means there are likely fewer cancer antigens to provoke an antitumor immune response.

There are notable exceptions among the disappointments, however, and most exciting is the development of chimeric antigen receptor (CAR) T cells. CAR T cells fall into a category of immunotherapy known as adoptive cell therapy (ACT), in which immune cells are harvested from a patient and grown outside the body to increase their numbers before being reinfused into the patient.

In the case of CAR T-cell therapy, the cells are genetically engineered to express a CAR that endows them with tumor-targeting capabilities. To date, the development of CAR T cells has focused on the use of the CD19 antigen as a target, which is highly expressed on a variety of B-cell malignancies, including several of the most common forms of pediatric cancer. ASCO shined the spotlight on CAR T-cell therapy this year, naming it the Advance of the Year for 2018, saying that the treatment is "poised to transform childhood ALL."[19]

Two CD19-targeted CAR T-cell therapies – tisagenlecleucel and axicabtagene ciloleucel – were brought to market in 2017. Only tisagenlecleucel is approved in the pediatric ALL population, however, having been awarded approval for the treatment of patients aged up to 25 years whose disease is refractory to or relapsed after receiving at least 2 prior therapies. In the pivotal trial, complete responses were observed in more than 60% of patients.[20]

TABLE 3 Select ongoing clinical trials of immunotherapy in pediatric cancers

Drug	Developer	Mechanism of action	Most advanced stage of clinical development in the pediatric setting (ClinicalTrials.gov identifier)
Ibrutinib (Imbruvica)	Pharmacyclics/ Janssen	BTK Inhibitor	Phase 3 in relapsed/refractory NHL (NCT02703272)
Blinatumomab (Blincyto)	Amgen	CD19-targeted BiTE	Phase 1 + immune checkpoint inhibitors in B-cell leukemias/ lymphoma (NCT02879695, NCT03605589)
Brentuximab vedotin (Adcetris)	Seattle Genetics	CD30-targeted ADC	Phase 3 + combination chemotherapy in high-risk cHL (NCT02166463)
Inotuzumab ozogamicin (Besponsa)	Wyeth	CD22-targeted ADC	Phase 3 + chemotherapy in newly diagnosed B-cell ALL (NCT03150693)
Pembrolizumab (Keytruda)	Merck	PD1-targeted mAb	Phase 3 in metastatic melanoma (KEYNOTE-716; NCT03553836)
Nivolumab (Opdivo)	Bristol-Myers Squibb	PD1-targeted mAb	Phase 2 +/- ipilimumab in high-grade primary CNS malignancies (NCT03130959)
Durvalumab (Imfinzi)	AstraZeneca	PDL1-targeted mAb	Phase 1 in relapsed/refractory solid tumors, lymphoma and CNS tumors (NCT02793466)
Tisagenlecleucel (Kymriah)	Novartis	CD19-targeted CAR T-cell therapy	Phase 2 in NHL (BIANCA; NCT03610724)
Axicabtagene ciloleucel (Yescarta)	Kite	CD19-targeted CAR T-cell therapy	Phase 2 in B-cell ALL (ZUMA-4; NCT02625480)
CD22 CARs	Various	CD22-targeted CAR T-cell therapy	Phase 2 in relapsed/refractory B-cell NHL (NCT03196830)
Bispecific CARs	Various	CD19 and CD22 dual-targeting CAR T-cell therapy	Phase 1/2 in relapsed/refractory B-cell malignancies (NCT03289455, NCT03287817, NCT03468153, NCT03098355, NCT03185494, NCT03614858)
GD2 CARs	Various	GD2-targeted CAR T-cell therapy	Phase 2 in neuroblastoma (4SCAR-GD2; NCT02765243)
GD2-targeting NK CARs	Baylor College of Medicine	NK cells expressing CARs targeting GD-2	Phase 1 in neuroblastoma (GINAKIT2; NCT02765243)
CD30 CARs	UNC Lineberger Comprehensive Cancer Center	CD30-targeted CAR T-cell therapy	Phase 1/2 in relapsed/refractory CD30-positive HL and NHL (NCT02690545)
HER2 CARs	Seattle Children's Hospital	HER2-targeted CAR T-cell therapy	Phase 1 in relapsed/refractory CNS tumors (NCT03500991)
EGFR CARs	Seattle Children's Hospital	EGFR806-targeted CAR T-cell therapy	Phase 1 in relapsed/refractory solid and CNS tumors (NCT03638167, NCT03618381)
Glypican-3 CARs	Baylor College of Medicine	Glypican-3-targeted CAR T-cell therapy	Phase 1 in solid tumors (NCT02932956)
Dinutuximab (Unituxin)	United Therapeutics	Anti-GD2 mAb	Phase 2 + 131I-MIBG in relapsed/refractory neuroblastoma (NCT02932956)
Hu3F8	Y-mAbs Therapeutics	Anti-GD2 mAb	Phase 1/2 in high-risk neuroblastoma (NCT02650648, NCT01757626)
NK cells	Various	Adoptive cell therapy using donor NK cells	Phase 1/2 in relapsed/refractory AML (NCT03068819, NCT02763475), solid tumors (NCT01807468*, NCT03420963, NCT02100891), neuroblastoma (NCT02573896)

ADC, antibody-drug conjugate; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BiTE, bispecific T-cell engager; BTK, Bruton's tyrosine kinase; CAR, chimeric antigen receptor; cHL, classical Hodgkin lymphoma; CNS, central nervous system; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; mAb, monoclonal antibody; MIBG, meta-iodobenzylguanidine; NH, non-Hodgkin lymphoma; NK, natural killer; PD-1, programmed cell death protein-1

Clinical trials of both CAR T-cell therapies in pediatric ALL and non-Hodgkin lymphoma are ongoing (Table 3).

CD19 has also proven to be a promising target for other forms of immunotherapy, including a new type of antibody known as a bispecific T-cell engager (BiTE). In 2014, blinatumomab became the first BiTE to receive regulatory approval, for the treatment of adult patients with relapsed/refractory ALL. Blinatumomab also targets the CD3 protein on T cells and helps to bring cancer cells and cytotoxic immune cells into close enough proximity that an immunological synapse can be formed between the two, facilitating tumor cell killing.[21]

In 2016, the approved indication was expanded into the pediatric population based on the results of a phase 1/2 study in which the safety and efficacy of blinatumomab were evaluated in 93 pediatric patients with relapsed/refractory ALL. Among the 70 patients who received the recommended dose of 5µg/m^2 a day for the first 7 days, followed by 15µg/m^2 a day thereafter, 51% achieved complete remission within the first 2 cycles, 52% of whom achieved minimal residual disease (MRD).[22] Most recently, the FDA expanded the indication for blinatumomab to include patients (both adults and children) who are in remission, but MRD positive.[23]

Despite the dramatic responses, many patients relapse after treatment with CD19-targeted CAR T cells, and researchers have uncovered numerous mechanisms of resistance. Among them is the loss of the CD19 antigen on the surface of target cells, such that a CD19-positive tumor becomes CD19-negative after treatment, driving relapse.[24-26]

Several strategies for overcoming CD19-negative relapse are already being investigated, including the development of CD22-targeted CAR T cells and bispecific CAR T cells that target both CD19 and CD22. The results of a first-in-human trial of anti-CD22 CAR T-cell therapy were recently published. Among 21 pediatric and adult patients with relapsed/refractory B-cell ALL who were treated with either 3 x 10^5 cells/kg, 1 x 10^6 cells/kg, or 3 x 10^6 cells/kg, complete responses were observed in 57%.[27]

Results from 15 pediatric patients enrolled in a trial evaluating CD22-targeted CAR T cells as salvage therapy for those who relapse after CD19-targeted CAR T cell therapy were presented at the recent Congress of the European Hematology Association in Stockholm, Sweden. Patients who had undergone a stem cell transplant received the CAR T cells at a dose of 0.9 x 10^5 cell/kg and those who had not undergone a transplant received a dose of 8.2 x 10^5 cells/kg. At 30 days after CAR T cell infusion, the CR rate was 80% and the treatment was well tolerated.[28]

More immunotherapy approvals

The immune checkpoint inhibitors, which work by blocking inhibitory receptors on the surface of T cells, have also had recent approvals in pediatric patient populations. Pembrolizumab and nivolumab, inhibitors of the programmed cell death receptor 1 (PD-1) protein, have both been approved for use in adult and pediatric patients (older than 12 years) with relapsed/refractory metastatic colorectal cancer (and other solid tumors in the case of pembrolizumab) that display defects in the mismatch repair pathway that fixes damaged DNA or in patients that have high levels of microsatellite instability. Both deficient mismatch repair and microsatellite instability–high can indicate a high mutation burden in a tumor, which may predict increased sensitivity to immunotherapy.[29]

The approval in pediatric patients in both of those instances, however, was not based on data in pediatric patient populations but extrapolated from adult patients. Pembrolizumab is also approved for the treatment of adults and pediatric patients with classical Hodgkin lymphoma (cHL) after 3 or more previous treatments, but once again efficacy in the pediatric population was inferred from clinical trials performed in adults. Most recently, pembrolizumab was approved for the treatment of adult and pediatric patients with relapsed or refractory primary mediastinal large B-cell lymphoma.[30]

Ipilimumab, which targets a different T cell receptor – cytotoxic T lymphocyte antigen-4 (CTLA-4) – has been approved for the treatment of pediatric patients aged 12 years and older with metastatic melanoma. This expanded indication, following on from its approval in adult patients in 2011, was based on data from 2 trials in which objective responses were observed in 2 out of 17 patients, including 1 partial response that lasted 16 months.[31]

Finally, antibody-drug conjugates (ADC), in which tumor antigen-targeting monoclonal antibodies are conjugated to cytotoxic payloads to combine the specificity of an antibody with the cell-killing potency of chemotherapy, have also generated some recent successes in pediatric cancers.

Gemtuzumab ozogamicin is an ADC that targets the CD33 protein, which is highly expressed on 85%-90% of cases of acute myeloid leukemia (AML). In 2000, it was the first ADC to be brought to market in the United States, but it was subsequently voluntarily withdrawn by the manufacturer in 2010 after confirmatory trials failed to show a survival benefit.

Recently, a meta-analysis of gemtuzumab ozogamicin trials suggested that the drug likely does improve long-term overall survival (OS) and reduce the risk of relapse and researchers developed an intermittent dosing schedule to help mitigate toxicity.[32] This new dosing regimen received FDA approval in 2017 for the treatment of pediatric patients aged 2 years and older on the basis of 2 clinical trials.

In the MyloFrance-1 trial, 57 patients were administered 3 mg/m^2 gemtuzumab ozogamicin on days 1, 4, and 7 followed by cytarabine consolidation therapy and demonstrated a 26% CR rate and median recurrence-free survival of 11.6 months. In the phase 3 AML-19 trial, 237 patients received gemtuzumab ozogamicin at a dose of 6 mg/m^2 on day 1 and

3 mg/m^2 on day 8 or best supportive care. Gemtuzumab ozogamicin improved OS from 3.6 to 4.9 months.[33,34]

Inotuzumab ozogamicin is a CD22-targeting ADC that has been FDA approved for the treatment of adult patients with relapsed/refractory B-cell precursor ALL since last year. The therapy has been available to pediatric patients through a compassionate access program, but it has not been extensively evaluated in this population. The results of a retrospective analysis of pediatric patients who received at least 1 dose of inotuzumab ozogamicin were presented at ASCO in 2017. Among 29 patients with heavily pretreated disease the CR rate was 62%, 72% of whom achieved MRD negativity.[35]

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Collaboration is key to bridging the AYA cancer care divide

Sharon Worcester

A range of efforts and collaborations aim finally to correct the disparities in survival improvements among adolescents and young adults with cancer.

Survival gains among adolescents and young adults (AYAs) with cancer continue to lag behind outcomes for children and older adult patients. It's a trend that spans decades, but clinicians and researchers are finally getting serious about trying to understand the underlying causes and are re-examining prevailing practices in an effort to address the discrepancies.

"This is a very heterogeneous group of disorders," Rabi Hanna, MD, a pediatric hematologist and oncologist at Cleveland Clinic Children's Hospital, Ohio, said in an interview. He's specifically referring to the cancers that affect AYAs, who are broadly defined as patients aged 15 through 39 years. "A few cancers, such as [acute lymphoblastic leukemia], are more common in children, and others, such as breast cancer, are more common in adults. The biology may be different in the adolescent and young adult patients, which may lead to different outcomes."


DR HANNA

In addition, the psychosocial needs in this age group differ vastly from those in other groups. "Many of these patients are in college or have just started their families, so we have to pay more attention to [issues related to] financial toxicity and fertility, for example," said Dr Hanna, who is the director of pediatric bone marrow transplantation at the clinic. (The term "financial toxicity" describes the cumulative negative impact of the high cost of care, lost work time, and delays in reaching educational and career goals on patients with cancer and their families.)

Another factor that likely contributes to the outcome disparities between AYAs and other populations with cancer is the relative lack of clinical trial involvement among AYAs.

A recent series of articles published in the journal Blood addressed these and other issues, among them, whether AYAs with acute lymphoblastic leukemia (ALL)[1] or aggressive B-cell non-Hodgkin lymphomas (NHLs) [2] should be treated as children or adults; treatment strategies for those with acute myeloid leukemias (AMLs); [3] management of Hodgkin lymphoma;[4] and psychosocial challenges and health-related quality of life (QoL) in AYAs with hematologic malignancies.[5]


DR CORTES

In the introduction to the series, Jorge Cortes, MD, an assistant editor on the journal, wrote that hematologic malignancies in AYAs "represent a unique challenge because of their special biological features and distinctive therapeutic requirements, as well as the unique medical, social, and psychological characteristics of this patient population."[6]

He noted, however, that "not much has been done to explore unique molecular and biological features of AYA hematologic malignancies. The discussion on the management of AYAs often centers on whether these patients should be treated in a pediatric setting or an adult setting, or with regimens designed for children or for adults," noted Dr Cortes, professor and chair of the chronic myeloid leukemia section in the department of leukemia at the University of Texas MD Anderson Cancer Center, Houston.

Therapeutic options: pediatric or adult protocols?

In their article on ALL in AYAs, Nicolas Boissel, MD, and André Baruchel, MD, note that the use of "fully pediatric protocols" in patients aged 15 through 20 years is supported by findings from numerous studies. In young adults, evidence increas-

JCSO 2018;16(5):e217-e220.

ingly supports "pediatric-inspired or even fully pediatric approaches" because they have been shown to significantly improve outcomes, with long-term survival rates nearing 70%.[1] Patients in these age groups require specific programs that factor in access to care and to trials, an increased risk of acute toxicities, and treatment adherence, which can be particularly problematic in AYAs, they concluded.

However, Kristen O'Dwyer, MD, and colleagues, argue in an article on AML treatment in AYAs that neither the pediatric nor adult approaches are ideally suited for AYAs because of the "distinguishing characteristics of AYAs with AML." Rather, they conclude that AYA-specific approaches merit consideration.[3]

Similarly, Kieron Dunleavy, MD, and Thomas G Gross, MD, note in an article on managing aggressive B-cell NHLs in AYAs that there is a "remarkable divide" in the treatment of patients younger than 18 years with lymphoma compared with their young adult counterparts, and that it underscores the need for collaboration in developing consensus regarding treatment of AYAs.[2]

Clinical setting: pediatric or adult?

Consideration is also being given to the clinical setting in which AYA patients receive their treatment. Lori Muffly, MD, MS, and colleagues have reported that survival was superior for AYA patients with ALL who were treated in pediatric cancer settings,[7] and other researchers have reported similar findings.

However, those improved outcomes in the pediatric setting might be offset by a higher use of resources and therefore higher costs, based on recent findings in a Canadian study by Paul C Nathan, MD, and colleagues.[8] Among 1,356 patients aged 15-17 years who were diagnosed with cancer between 1996 and 2010, the authors found that the cost of care was higher when treatment took place in a pediatric setting compared with in an adult institution, and that it was driven in part by higher hospitalization rates and longer hospital stays. These findings were true across different diagnoses, including leukemias, lymphomas, sarcomas, and germ cell tumors, but only during the initial treatment phase.

In an accompanying editorial, Helen M Parsons, PhD, and her co-authors wrote that adolescents who receive treatment in the pediatric setting "tended to seek more [emergency department (ED)] care immediately before diagnosis and during the initial treatment phase; these adolescents also used more home care services during initial treatment and survivorship.[9] They pointed out that the findings of higher inpatient days in the pediatric setting was not surprising given that induction therapies for pediatric ALL tend to be more complex and intensive than therapies commonly used in adults with ALL, and that pediatric cancer hospitals tend to have a wider array of services, including psychosocial and family support services.

"What is less clear is why individuals seen in pediatric settings have higher rates of ED care directly before diagnosis and during the initial treatment phase," they wrote, adding that further investigation was needed on this topic to better understand those trends. "The finding that adolescents treated in pediatric institutions had higher resource use across diagnostic groups demonstrates that resource utilization may be driven just as much by care setting as diagnosis."[9]

The authors of the editorial emphasized that because of the differences in health care delivery and payment structures between the United States and Canada, where the Nathan study was done, it was important that similar studies are done in the United States to confirm these findings.

Disease and developmental biology

As Dr Hanna noted, biological differences and changes over time suggest that different age groups need varying approaches to treatment and that they may have different outcomes with the same treatments.

For example, the biology of AML is known to change with age, Dr O'Dwyer and her colleagues noted,[3] citing a recent European study of 5,564 patients with de novo AML that showed that the frequency of favorable cytogenetics was low in infants (13.7%), increased in children (25%) and young adults (44%), and decreased again in middle age and older patients.[10]

"Most unfavorable cytogenetic abnormalities are rare across all age groups, though complex cytogenetics are relatively more frequent in infants, decrease in frequency in AYAs, and then increase in frequency beyond AYA," Dr O'Dwyer and her colleagues wrote.[3] It was also becoming more apparent that age influences the presence of AML-related molecular abnormalities, and recognition of age-related differences in disease biology "will provide the best opportunity to improve the clinical outcomes that have been static for decades."

Dr Boissel and Dr Baruchel also noted in their report that light was finally being shed on the "black hole" of understanding ALL biology in AYAs, and research has shown that there is a continuum between childhood and adult ALL.[1] They concluded that "risk stratification based on recent biology findings and sequential [minimum residual disease] evaluations should now be implemented, as well as new therapeutic options including immunotherapy and targeted therapies, at best within the setting of integrated pediatric and AYA protocols."

Psychosocial factors

"Cancer is a non-normative event for AYAs. It is extremely disruptive to them physically, psychologically, and vocationally ... and this poses significant challenges," John Salsman, PhD, director of clinical research in AYA oncology at Wake Forest University, Winston-Salem, NC, said in an interview.

These patients have 5-year survival rates that haven't improved in tandem with those in pediatric and adult populations over the last 3 decades, and in addition to the financial toxicity and strain, they also have higher rates of depression and anxiety, including fear of recurrence, he added. "Quality of life is incredibly important, and these things need to be addressed because of the developmental changes AYAs are navigating; there are issues of positive body image, family and career decisions ... these are challenging for anyone, and when you throw a cancer diagnosis into the mix they become disproportionately so."


DR SALSMAN

In a 2014 study, Dr Salsman and his colleagues found that AYAs with cancer had poorer physical and emotional quality of life when compared with matched controls, but better social quality of life.[11] The latter finding was surprising and highlights the importance of the social dimension in the lives of AYAs. "Patient after patient will say 'I found out who my real friends are,' " he said. "There's this refinement and deepening of the social network among some posttreatment survivors."

Dr Salsman and his colleagues are using those findings to develop interventions that can maximize self-care in posttreatment survivorship – a time when AYAs may feel they have a new lease on life and may be more motivated to adhere to recommendations and take care of themselves. For example, a randomized controlled pilot study that incorporates social media apps and other technologies to build on the positive social components of their lives in promoting physical activity interventions is underway.

Another intervention targets emotional well-being through the use of web-based tools to increase positive affect. A proof-of-concept study showed that the approach was feasible and well received, and a larger-scale randomized controlled trial is being planned, he said.

Dr Salsman also praised the PRISM (Promoting Resilience in Stress Management) tool developed by researchers at Seattle Children's Hospital. It was created to help AYAs with cancer and other illnesses learn coping skills to manage stress after their diagnosis and to boost quality of life beyond treatment. A digital app has also been developed to be used in conjunction with the program.

Trial enrollment

In his editorial introducing the Blood series on AYAs and cancer, Dr Cortes noted a paucity of clinical trials specifically designed for this population. "At the time of this writing, I could identify four therapeutic trials registered at www.clinicaltrials.gov that appeared to be somewhat specifically designed for AYAs (some included children also)," he wrote, describing AYA enrollment in clinical trials in cancer as "suboptimal at best."[6]

Dr Salsman said these dismal enrolment numbers could in part be related to treatment setting. Data suggest that most AYAs with cancer are treated in community-based practices rather than comprehensive cancer centers where the bulk of research is being done, he explained.

Dr Hanna agreed that more research involving AYAs was needed as is a better understanding of why enrollment is so much lower in this population. He pointed out that in 2017 the American Society of Clinical Oncology and Friends of Cancer Research released a statement recommending that pediatric patients be considered for enrollment in later-phase trials for cancer types that span both adults and children.[12] The organizations said that individuals aged 12 years and older should routinely be included in such trials because their drug metabolism is similar to adults, and inclusion of younger patients may also be appropriate if they are part of the population affected by the disease, depending on specific disease biology, action of the drug, and available safety information.

Officials at the Food and Drug Administration are considering that possibility, Dr Hanna said.

Dr Salsman added there has been an increase in recent years in the attention paid to disparities in survival improvements and trial involvement among AYAs with cancer, compared with other age groups. For example, about 5 years ago, the National Clinical Trials Network formed a working group that developed a number of specific objectives for incorporating more AYAs into cancer trials and finding better ways to study this population;[13] the Institute of Medicine held a forum on the care of AYAs with cancer;[14] and the National Cancer Institute held a state-of-the-science meeting that focused on identifying strategic priorities for AYA oncology,[15] he noted.

Dr Hanna added that "scientific groups such as Southwest Oncology Group (SWOG) and Children's Oncology Group (COG) also have AYA committees now. One of the success stories of working together between SWOG and COG was the intergroup study C10403 for patients with ALL. And now there are efforts for an intergroup AYA-AML task force to include representatives from each of the cooperative groups that historically coordinated myeloid disease clinical trials – COG, SWOG, Alliance, and ECOG-ACRIN," he said.

In fact, all of the National Clinical Trials Network groups have some initiative in place to address AYA concerns, said Dr Salsman, who chairs the ECOG-ACRIN AYA oncology subcommittee.

Despite these efforts, and many others, long-term survival improvements among AYAs with cancer still fall short, compared with those of other age groups.[16]

Next steps

Among the recommendations from authors in the AYA series in Blood is a call for assessing AYA-specific therapy in future clinical trials, as well as improved collaboration between adult and pediatric teams and the involvement of multidisciplinary teams in care for this population.

Many centers are already working on models for collaborative care, Dr Salsman said, citing the Fort Worth AYA Oncology Coalition led by medical director Karen Albritton, MD, as an example of a program that has been successful in helping clinical and supportive caregivers and their AYA patients "have a shared vision" as they work to maximize improvements in outcomes.

Patients are also taking the lead in demanding better care and attention to their psychosocial needs, Dr Hanna said. In the case of the community-powered advocacy organization Critical Mass, members have succeeded in getting lawmakers to introduce a bill in the US House of Representatives that would allow college students to defer loan payments while undergoing cancer treatment.

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Advances in precision medicine help refine – and redefine – cancer care

Among the groundbreaking findings presented at this year's annual meeting of the American Society of Clinical Oncology were those showing that most women with HR-positive, HER2-negative, early-stage breast cancer who have an intermediate recurrence score can safely skip adjuvant chemotherapy, and that upfront pembrolizumab for patients with NSCLC expressing PD-L1 on at least 1% of tumor cells can not only significantly improve overall survival, but do so with less toxicity than standard chemotherapy.

TAILORx marks major advance for precision medicine in breast cancer

Key clinical point The majority of women with HR-positive, HER2-negative, node-negative early-stage breast cancer who have an intermediate recurrence score can safely skip adjuvant chemotherapy. **Major finding** In women with an Oncotype DX Recurrence Score in the midrange (11-25), invasive DFS with endocrine therapy alone was not inferior to that with chemotherapy plus endocrine therapy (HR, 1.08; $P = .26$). **Study details** A phase 3 trial in 10,273 women with HR-positive, HER2-negative, node-negative, early-stage breast cancer, with a noninferiority randomized component in the 6,711 women with a midrange recurrence score (TAILORx trial). **Funding** This study received funding primarily from the National Cancer Institute, National Institutes of Health. Additional support was provided by the Breast Cancer Research Foundation, Komen Foundation, and US Postal Service Breast Cancer Stamp. **Disclosures** Dr Sparano disclosed that he has a consulting or advisory role with Genentech/Roche, Novartis, AstraZeneca, Celgene, Lilly, Celldex, Pfizer, Prescient Therapeutics, Juno Therapeutics, and Merrimack; has stock or other ownership interests with MetaStat; and receives research funding (institutional) from Prescient Therapeutics, Deciphera, Genentech/Roche, Merck, Novartis, and Merrimack. **Source** Sparano et al. ASCO 2018 Abstract LBA1: https://meetinglibrary.asco.org/record/161490/abstract

Use of the 21-tumor gene expression assay (Oncotype DX Recurrence Score) allows nearly 70% of women with hormone receptor-positive, HER2-negative, node-negative, early-stage breast cancer to safely forgo adjuvant chemotherapy, sparing them adverse effects and preventing overtreatment, TAILORx trial results show.

The findings, which were reported in the plenary session at the meeting and simultaneously published in the New England Journal of Medicine (N Engl J Med. 2018; 379:111-121; [behind paywall]), mark a major advance in precision medicine.

"The rationale for the TAILORx precision medicine trial is that we are really trying to 'thread the needle,'" lead study author Joseph A Sparano, MD, commented in a press briefing. Oncologists typically recommend adjuvant chemotherapy for the half of all breast cancers that are hormone receptor positive, HER2 negative, and node negative, even though its absolute benefit in reducing recurrences in this population is small. "This results in most patients being overtreated because endocrine therapy alone is adequate. But some are undertreated: They do not receive chemotherapy although they could have benefited from it," he noted.

DR SPARANO

The recurrence score is known to be prognostic and predictive of benefit from adding chemotherapy to endocrine therapy, Dr Sparano said. "But there was a major gap: There was uncertain benefit for patients who had a midrange score, which is about two-thirds of all patients who are treated," said Dr Sparano, the associate director for clinical research at Albert Einstein Cancer Center and Montefiore Health System in New York, and vice-chair of the ECOG-ACRIN Cancer Research Group.

The phase 3 TAILORx trial registered 10,273 women with hormone receptor-positive, HER2-negative, node-negative, early-stage breast cancer, making it the largest adjuvant breast cancer trial to date. Analyses focused on the 6,711 evaluable women with a midrange recurrence score (defined as 11 through 25 in the trial), who were randomized to receive endocrine therapy alone or adjuvant chemotherapy plus endocrine therapy, with a noninferiority design. Of note is that contemporary drugs and regimens were used.

Results at a median follow-up of 7.5 years showed that the trial met its primary endpoint: the risk of

JCSO 2018;16(X):e221-e225.

invasive disease-free survival (DFS) events (invasive disease recurrence, second primary cancer, or death) was not inferior for women given endocrine therapy alone compared with counterparts given chemotherapy plus endocrine therapy (hazard ratio [HR], 1.08; *P* = .26), Dr Sparano reported.

The groups were also on par, with absolute differences of no more than 1% between rates, with respect to a variety of other efficacy outcomes: freedom from distant recurrence and any recurrence, and overall survival (OS).

Findings were similar across most subgroups. But analyses suggested that women aged 50 years and younger and who had a recurrence score of 16-25 fared better when they received chemotherapy. "Though exploratory from a statistical perspective, this is a highly clinically relevant observation," Dr Sparano said. "It suggests ... that chemotherapy should be spared with caution in this subgroup, after a careful discussion of potential benefits and risks in a shared decision process."

In other findings, analyses of the trial's nonrandomized groups confirmed excellent outcomes in women with a low recurrence score (0-10) who were given endocrine therapy alone, and at the other end of the spectrum, there was need for a more aggressive approach, including chemotherapy, in women with a high recurrence score (26-100).

Ultimately, application of the recurrence score allowed 69% of the trial population to skip chemotherapy: all of the women with a score of 0-10 (16% of the trial population), those older than 50 years with a score of 11-25 (45%), and those aged 50 years or younger with a score of 11-15 (8%).

An ongoing companion phase 3 trial, RxPONDER, is assessing the benefit of applying the recurrence score in women who are similar but ihave node-positive disease.

Study details

All of the women with hormone receptor-positive, HER2-negative, node-negative, early-stage breast cancer enrolled in TAILORx met National Comprehensive Cancer Network guidelines for receiving adjuvant chemotherapy. About 69% had an intermediate recurrence score (11-25) and were randomized. All of the 17% with a low recurrence score (0-10) were given only endocrine therapy, and all of the 14% with a high recurrence score (26-100) were given both adjuvant chemotherapy and endocrine therapy.

Of note, the recurrence scores used to define midrange were adjusted downward from those conventionally used to account for exclusion of patients with higher-risk HER2-positive disease and to minimize potential for undertreatment, Dr Sparano explained.

In the women with midrange scores who were randomized, the hazard ratio of 1.08 for invasive DFS with endocrine therapy alone compared with chemotherapy plus endocrine therapy fell well within the predefined hazard ratio for noninferiority (1.322). The 9-year rate of invasive DFS was 83.3% with endocrine therapy and 84.3% with chemotherapy plus endocrine therapy.

The groups had similar rates of freedom from distant recurrence (94.5% vs 95.0%; HR, 1.10; *P* = .48) and distant or locoregional recurrence (92.2% vs 92.9%; HR, 1.11; *P* = .33), and similar OSs (93.9% vs 93.8%; HR for death, 0.99; *P* = .89).

In exploratory analyses, there was an interaction of age and recurrence score (*P* = .004) whereby women aged 50 years or younger derived some benefit from chemotherapy if they had a recurrence score of 16-20 (9% fewer invasive DFS events, including 2% fewer distant recurrences) or a recurrence score 21-25 (6% fewer invasive DFS events, mainly distant recurrences). "This is information that could drive some younger women who have a recurrence score in this range to accept chemotherapy," Dr Sparano said.

The 9-year rate of distant recurrence averaged 5% in women with midrange scores overall. It was 3% in those with a low recurrence score given endocrine therapy alone, but it was still 13% in those with a high recurrence score despite receiving both endocrine therapy and chemotherapy. The latter finding may "indicate the need to explore potentially more effective therapies in this setting," he proposed.

Tailoring treatment: 'not too much and not too little'

"These are important data because this is the most common form of breast cancer in the United States and other developed countries, and the most challenging decision we make with these patients is whether or not to recommend adjuvant chemotherapy with all its side effects and potential benefits," said ASCO expert Harold Burstein, MD, PhD, FASCO. "The data show that the majority of women who have this test performed on their tumor can be told that they don't need chemotherapy, and that can be said with tremendous confidence and reassurance."

DR BURSTEIN

The recurrence score has been used for a decade, but the trial was necessary because the score was originally developed in patients who were receiving older chemotherapy regimens and older endocrine therapies, and because there have been few data to guide decision making in the large group of patients with midrange scores, he said. "Now we can say with confidence ... that the patients got contemporary chemo regimens and still saw no benefit from chemotherapy.

"This is not so much about de-escalation ... the goal of this study was not to just use less treatment but to tailor treatment. The investigators chose the title very aptly," said Dr Burstein, a medical oncologist at the Dana-Farber Cancer Institute and associate professor of medicine at the Harvard Medical School, Boston.

"This is extraordinary data for breast cancer doctors and women who have breast cancer. It allows you to individualize treatment based on extraordinary science, which now has tremendous prospective validation," he said. Overall, "women with breast cancer who are getting modern therapy are doing well, and this test shows us how to tailor that management so that they get exactly the right amount of treatment – not too much and not too little."

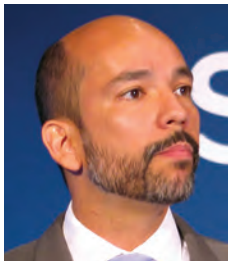
— Susan London

First-line immunotherapy boosts survival in NSCLC patients

Key clinical point Many patients with previously untreated NSCLC could benefit from first-line therapy with the checkpoint inhibitor pembrolizumab. **Major finding** In all patients with expression of PD-L1 on 1% or more of tumor cells, OS was 16.7 months with pembrolizumab, compared with 12.1 months for chemotherapy. **Study details** Randomized phase 3 trial of 1,274 patients with advanced or metastatic NSCLC. **Funding** Merck, the maker of the study drug, funded the study. **Disclosures** Dr Lopes disclosed institutional research funding from Merck Sharp & Dohme, EMD Serono, and AstraZeneca. Dr Heymach disclosed stock/ownership in Bio-Tree and Cardinal Spine, a consulting or advisory role for Abbvie, ARIAD, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Calithera Biosciences, Genentech, Medivation, Novartis, Oncomed, and Synta, and institutional research funding from AstraZeneca. Dr Gandhi reported having no relevant disclosures. **Source** Lopes G et al. ASCO 2018, abstract LBA4. https://meetinglibrary.asco.org/record/165950/abstract

Pembrolizumab as first-line treatment of advanced non–small-cell lung cancer (NSCLC) offered longer OS with better tolerability compared with chemotherapy, results of the Keynote-042 phase 3 randomized trial show.

In 1,274 patients with advanced, previously untreated NSCLC with expression of the PD-L1 on 1% or more of tumor cells, median OS after a median follow-up of 12.8 months was 16.7 months for patients treated with pembrolizumab monotherapy, compared with 12.1 months for patients treated with either paclitaxel or pemetrexed plus carboplatin, reported lead author Gilberto Lopes, MD, of the Sylvester Comprehensive Cancer Center at the University of Miami.



DR LOPES

The survival benefit for immunotherapy was even greater for patients with higher levels of PD-L1 expression: 20 versus 12.2 months for patients with PD-L1 expression of 50% or greater, and 17.7 versus 13 months for patients with PD-L1 expression of 20% or greater, Dr Lopes noted.

For all 3 PD-L1 expression groups, the median duration of response was 20.2 months, compared with 10.8-8.3 months for patients in the chemotherapy arm.

"These are responses that are unlike anything that we have seen with chemotherapy in the past for non–small-cell lung cancer," Dr Lopes said at a briefing before his presentation. "In addition to that, and probably more importantly, patients had fewer adverse events [with pembrolizumab]. Overall, about 60% had any treatment-related adverse event with pembrolizumab, versus 90% with chemotherapy," he added.

'A true milestone'

ASCO expert John Heymach, MD, PhD, of the University of Texas MD Anderson Cancer Center in Houston, said at the briefing that the study was "a true milestone for the field, because now, for the first time, we can say that in non–small-cell lung cancer patients receiving first-line therapy, the vast majority can receive immunotherapy with pembrolizumab instead of chemotherapy."

DR HEYMACH

He noted that an earlier study, Keynote-024, showed that pembrolizumab significantly improved progression-free survival in patients with tumors expressing PD-L1 on at least 50% of cells compared with standard platinum-based chemotherapy (10.3 vs 6 months).

"This more than doubles that population that can start immunotherapy as a first-line treatment, assuming the [Food and Drug Administration] modifies the label in accordance with this study," he added.

The Keynote-042 investigators enrolled 1,274 patients with locally advanced or metastatic NSCLC, and randomly assigned them to receive either a maximum of 35 cycles of pembrolizumab 200 mg every 3 weeks, or the investigators' choice of not more than 6 cycles of either paclitaxel–carboplatin or pemetrexed–carboplatin, with optional pemetrexed maintenance for patients with nonsquamous histologies only.

The randomization was stratified by region (Asia vs non-East Asia), Eastern Cooperative Oncology Group performance status 0 or 1, squamous versus nonsquamous histology, and PD-L1 expression, or TPS (tumor proportion score) greater than 50% versus 1%-49%.

As noted before, the primary endpoint of OS in all patients with a TPS of 1% or greater was met, with respective median OS in the pembrolizumab versus chemotherapy groups of 16.7 and 12.1 months, translating into an HR favoring pembrolizumab of 0.81 (P = .0018). Respective hazard ratios for the TPS 20% or greater and TPS 50% or greater groups were 0.77 (P = .0020) and 0.69 (P = .0003).

At 12.8 months of median follow-up, 13% of patients assigned to pembrolizumab were still on the drug, and

4.3% of patients were receiving maintenance pemetrexed.

Treatment-related adverse events of any grade occurred in 399 of 636 patients assigned to pembrolizumab (62.7%), compared with 553 of 615 patients assigned to chemotherapy (89.9%). Grade 3 or greater events occurred in 17.8% and 41% of patients, respectively. There were 13 deaths related to therapy in the pembrolizumab arm (2.0%), and 14 in the chemotherapy arm (2.3%). Adverse events leading to discontinuation were similar between the groups, at 9% and 9.4%, respectively.

There were more immune-mediated adverse events in the pembrolizumab arm than in the chemotherapy arm (27.8% vs 7.2%, respectively), and of those, grade 3 or higher events occurred in 8% and 1.5% of patients. There was 1 immune-mediated death, from pneumonitis, in the immunotherapy arm; there were no deaths related to immune-mediated side effects in the chemotherapy arm.

"I really view this as a 'double whammy' for patients," Dr Heymach said at the briefing. "Often advances in survival for our lung cancer patients come at the cost of significant toxicities. Here, by contrast, not only are patients living longer and having a much higher likelihood of prolonged survival in years, often instead of months, but they're also receiving a treatment that has substantially less toxicity across virtually all measures, and this really impacts the day-to-day life of these patients."

Leena Gandhi, MD, PhD, of the Perlmutter Cancer Center at New York University, the invited discussant at the plenary, agreed that pembrolizumab improves survival, compared with chemotherapy patients with PD-L1 expression levels greater than 1%, but noted that most of the benefit – as also seen in Keynote-024 – was in those patients whose tumors had high levels of PD-L1 expression.

She emphasized that although PD-L1 is an imperfect biomarker, it should still be used to help select patients for therapy and it may be complementary with tumor mutational burden for more precise treatment selection.

"What we know, and what this study adds to, is that PD-L1 really does define a patient population that could receive benefit from pembrolizumab over chemotherapy. Patients with low or no PD-L1 expression likely should get some type of combination therapy," she said. "This study extends what we've seen from other recent studies, which is that chemotherapy alone is no longer a first-line standard of care in non–small-cell lung cancer."

— Neil Osterweil

Better survival with maintenance chemo in youth with rhabdomyosarcoma

Key clinical point 6 months of maintenance chemotherapy improves survival in youth with high-risk rhabdomyosarcoma. **Major finding** Patients given maintenance low-dose vinorelbine and cyclophosphamide had better 5-year OS compared with those not receiving any additional treatment (86.5% vs 73.7%; HR, 0.52). **Study details** A phase 3 randomized controlled trial in 371 patients aged 0-21 years with high-risk rhabdomyosarcoma who had had a complete response to standard intensive therapy. **Funding** The study received funding from Fondazione Città della Speranza, Italy. **Disclosures** Dr Bisogno disclosed that he has a consulting or advisory role with Clinigen Group, and receives travel, accommodations, and/or expenses from Jazz Pharmaceuticals. **Source** Bisogno et al. ASCO 2018, Abstract LBA2. https://meetinglibrary.asco.org/record/161695/abstract

Six months of maintenance chemotherapy prolongs OS in youth with high-risk rhabdomyosarcoma, finds a phase 3 randomized controlled trial of the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG).

Rhabdomyosarcoma is a rare but highly aggressive tumor, lead study author Gianni Bisogno, MD, PhD, a professor at the University Hospital of Padova, Italy, and chair of the EpSSG, noted in a press briefing at the meeting, where the findings were reported. In pediatric patients who achieve complete response to standard therapy, "we know that after 1 or 2 years, one-third of these children relapse, and most of them die," he said.

The EpSSG trial, which took about 10 years to conduct, enrolled 371 patients aged 0-21 years with high-risk rhabdomyosarcoma who had had a complete response to standard intensive therapy. They were randomized evenly to stop treatment or to receive 6 months of maintenance treatment consisting of low-dose vinorelbine and cyclophosphamide.

DR BISOGNO

Results reported in the meeting's plenary session showed that giving maintenance chemotherapy improved the 5-year OS rate by an absolute 12.8%, which translated to a near halving of the risk of death. And the maintenance regimen used was generally well tolerated.

"At the end of this long, not-easy study, we concluded that maintenance chemotherapy is an effective and well tolerated treatment for children with high-risk rhabdomyosarcoma," Dr Bisogno said.

There are three possibilities for its efficacy, he speculated. "It may be the duration, the type of drugs used, or the metronomic approach. Maybe altogether, these three different actions have a benefit to increase survival.

"Our group has decided this is the new standard treatment for patients. At least in Europe, we give standard intensive therapy and then we continue with 6 more months of low-dose chemotherapy," Dr Bisogno concluded. "We think that this approach – a new way of using old drugs – can be of interest also for other pediatric tumors."

The trial is noteworthy in that it shows "how to successfully conduct large and important trials in rare diseases," said ASCO expert Warren Chow, MD.

The standard therapy for rhabdomyosarcomas is somewhat different in the United States, typically a regimen containing vincristine, actinomycin D, cyclophosphamide, and (more recently) irinotecan, he noted. "We have not been traditionally using maintenance chemo for any of the pediatric sarcomas, so this is a paradigm shift. These results will need to be tested with US-based protocols before becoming standard of care in the United States. Also, we will need to determine if these results are applicable to patients older than 21 years of age who are considered high risk based solely on their age.

DR CHOW

"Even with these caveats, this is the first significant treatment advance in this rare cancer in more than 30 years," concluded Dr Chow, a medical oncologist and clinical professor at City of Hope, Duarte, Calif. "No doubt, this trial was a home run."

Study details

Patients enrolled in the EpSSG trial had had a complete response to the standard intensive therapy used in Europe: high-dose chemotherapy (ifosfamide, vincristine, and actinomycin D, with or without doxorubicin), radiation therapy, and surgery.

The maintenance chemotherapy consisted of a combination of low-dose intravenous vinorelbine given weekly and oral cyclophosphamide given daily. The 6-month duration was somewhat arbitrary, according to Dr Bisogno. "We had to start somewhere. So when we started, we decided to use 6 months because there was some evidence in the past for regimens that long. In our next European trial, we are going to test different kinds and durations of maintenance because this is very important."

The maintenance regimen was well tolerated compared with the regimen given during standard intensive therapy, with, for example, lower rates of grade 3 and 4 anemia (8.9% vs 48.9%), neutropenia (80.6% vs 91.6%), and thrombocytopenia (0.6% vs 26.0%), which translated to less of a need for transfusions, and a lower rate of grade 3 or 4 infection (29.4% vs 56.4%), Dr Bisogno reported. There were no cases of grade 3 or 4 cardiac, hepatobiliary/pancreatic, or renal toxicity.

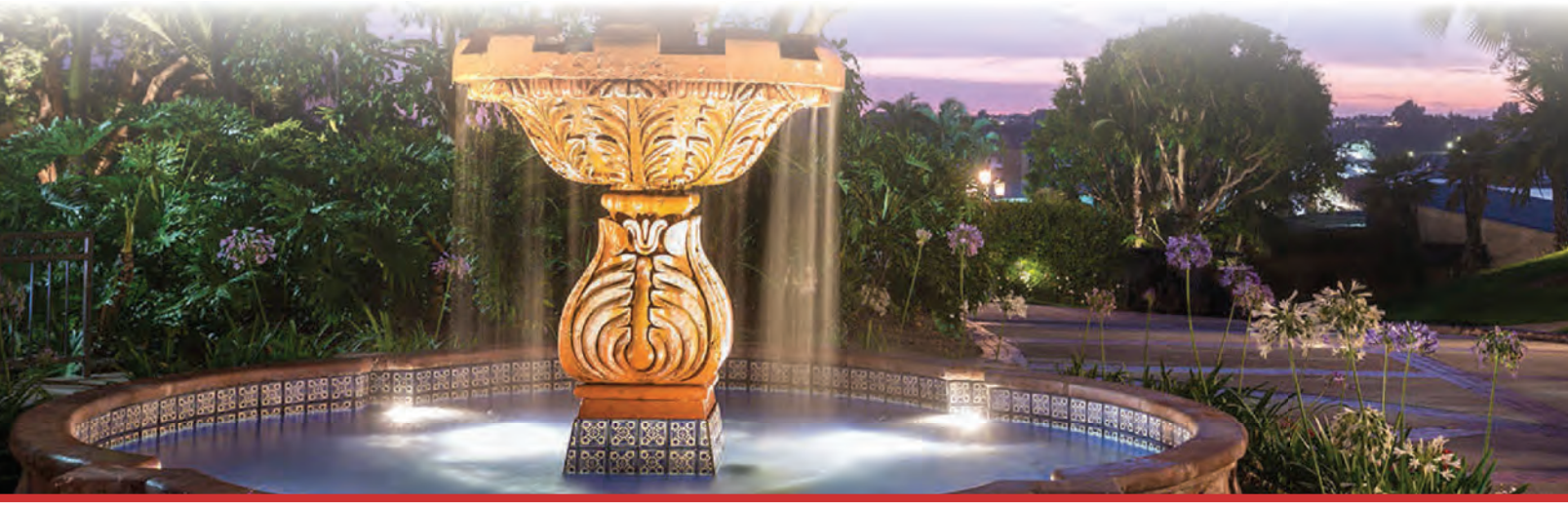
Relative to peers who stopped treatment after standard intensive therapy, patients who received maintenance treatment tended to have better DFS (77.6% vs 69.8%; HR, 0.68; $P = .0613$) and had significantly better OS (86.5% vs 73.7%; HR, 0.52; $P = .0111$).

— Susan London

Acute Leukemia FORUM 2019

April 11–12, 2019

Hyatt Regency Newport Beach
Newport Beach, CA



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Hematologists, oncologists, and other healthcare providers who manage or treat patients with leukemia.

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