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DANIEL C. MCFARLAND, DO, ON **Decisional Capacity Determination in Patients With Cancer**

‘Time specific and decision specific’

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Lung Cancer FDA Approvals

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Ensuring Decisional Capacity

Patients with cancer often face difficult, life-changing decisions and encounter clinical situations that may impair or threaten their ability to make those decisions. Determining decisional capacity in patients is often the responsibility of oncologists, but meaningful relationships and familiarity with their patients can sometimes cause the process of assessing cognitive ability and decisional capacity to be overlooked.

In this issue of *ONCOLOGY*®, Daniel C. McFarland, DO, and colleagues discuss the importance of properly assessing decisional capacity in patients with cancer. “Decisional capacity may fluctuate and requires a variable amount of decisional ability depending on the clinical situation,” writes McFarland. “Hence, it is time-specific and decision-specific.

“Close and deliberate follow-up is a necessary part of managing a patient’s decisional incapacity and capacity,” McFarland continues, when discussing the keys to properly evaluating patients. “Clinicians should resist the temptation to use a single interview...or point in time as a template for future care, since decisional capacity fluctuates and needs to be determined for all decisions where patient engagement and cooperation are appropriate.”

Also in this issue, you will read an article from Christopher R. Flowers, MD, and colleagues from the University of Texas MD Anderson Cancer Center on strategies for

overcoming disparities for patients with hematologic malignancies. Flowers and colleagues discuss the differences in incidence, prevalence, and burden of disease in both minority and rural populations compared with the rest of the United States. They propose that among other solutions, improving enrollment in clinical trials can help to alleviate these disparities.

For this month’s clinical quandary, you will read about the case of a 57-year-old man with a diagnosis of stage IVB hypopharynx squamous cell carcinoma. What is the best treatment strategy for larynx preservation? Read on to find out.

Within these pages, you will also find a case study discussing hereditary and familial pancreatic cancers, a roundup of some of the recently released abstracts from the American Urological Association 2020 Virtual Meeting, and a summary of the FDA’s recent approvals of atezolizumab (Tecentriq) and nivolumab (Opdivo) plus ipilimumab (Yervoy), both as frontline therapies for metastatic non-small cell lung cancer.

I hope you find our journal helpful in caring for your patients through what is likely one of the most challenging times in their lives. As always, thank you for reading.

Mike Hennessy Sr

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Clinical Trials Are Needed—Now More Than Ever

Howard S. Hochster, MD

*Distinguished Professor of Medicine, Rutgers Robert Wood Johnson Medical School
Associate Director for Clinical Research, Rutgers Cancer Institute of New Jersey
Director of Oncology Research, RWJBarnabas Health*

Never in the history of this country has the mainstream media spent more time speaking about clinical trials than in the past few months. A search for “clinical trials” in the *New York Times* cites 857 articles since the beginning of this year alone.

With the onset of the coronavirus disease 2019 (COVID-19) outbreak in the United States, President Donald J. Trump announced on March 19 that he “hears good things about hydroxychloroquine” and it could be a “game changer,” rather than concentrating on a federal strategy to deal with millions of infected individuals. And on April 4, he gave his considered recommendation of “What do you have to lose?” The FDA gave emergency approval in days, and the federal government purchased millions of doses, rather than needed personal protective equipment, based on biased anecdotal reports of a 100% cure rate at the *Instituts Hospitalo-Universitaires* in France (*New York Times*, May 5). At the same time, Anthony Fauci, MD, climbed out on a limb to suggest that the efficacy had not been proved and that appropriately controlled clinical trials were lacking. Placebo-controlled trials, such as one being conducted at Rutgers, are still pending results, looking at viral clearance on day 5 as the primary end point.

It was therefore with great dis-

appointment that I read about the underwhelming results of the remdesivir SIMPLE trial, which sent Gilead stock soaring and the Dow Jones average bounding upward. In a randomized trial of 640 patients treated with 5 versus 10 days of the drug, the time to discharge was about the same (median, 10-11 days), although patients treated within 10 days of symptom onset seem to have been discharged sooner, and more than 60% of patients were discharged by day 14. However, without a control group, we really do not know the meaning of any of this. Fortunately, the National Cancer Institute followed up shortly with the interim analysis of the ACTT trial, which randomized 1063 patients to remdesivir or placebo. The results demonstrated a moderate effect of 31% shorter time to recovery (median, 11 vs 15 days, respectively) and lower mortality (8.0% vs 11.6%). These results have been issued by press release and have not been published with actual data for review.

At the time of this writing, we now have more than 2 million cases of proven COVID-19 infection in the United States and possibly 10 times that many individuals who have actually been infected. And we are rapidly approaching 115,000 deaths.

Despite these crushing numbers, we do not have a single appropriately conducted randomized clinical trial result in the public domain. Just 1

trial of approximately 3000 patients, randomized 2:1, to either receive remdesivir or any appropriate drug versus placebo would give us hard information on the hazard ratios for viral clearance, duration of hospitalization, time to recovery, and which subgroups benefit the most, whether they are distinguished by age, ethnicity, or severity of illness. We can never develop these data without appropriate control groups, and therefore we are left to proceed in ignorance when tending to millions of those afflicted for the lack of having the moral courage to conduct a randomized controlled trial.

As physicians, we must bring the message to our patients that the control group in such a trial is not receiving inadequate or inferior treatment because they did not receive a drug having uncertain toxicity and efficacy. These several thousand volunteers are necessary to define the use of any treatment before it is unleashed on the public. It is only through this process that we will be able to treat the millions to come in the next year with this disease, and to render care with appropriate medical knowledge and certainty. Now, more than ever, we need properly controlled, randomized clinical trials to show us the way. We must educate and treat the clinical trial subjects as the *heroes* they are for their voluntary assistance in proving the benefit of these treatments. ■

Hereditary vs Familial Pancreatic Cancer: Associated Genetic Syndromes and Clinical Perspective

Mehmet Sitki Copur, MD; Geoffrey A. Talmon, MD; Whitney Wedel, MD; Johnathan D. Hart, MD; Shaheed Merani, MD, PhD; and Luciano M. Vargas, MD

ABSTRACT: Pancreatic ductal adenocarcinoma (PDAC) is a disease marked by high rates of mortality; it is mostly incurable at the time of diagnosis. Only about 7% of patients survive 5 years after diagnosis. Diagnosis at a late stage and rapid progression with minimal response to available treatments are the main reasons for this poor outcome. It is crucial to identify individuals at high risk of developing PDAC so preventive and early detection measures can be employed.

Approximately 10% to 15% of PDAC cases have a hereditary or familial basis. In the majority of PDAC cases, no main causative gene has been identified, but several known germline pathogenic mutations have been shown to be related to an increased risk of this cancer. The presence of 2 or more patients with pancreatic cancer within the circle of first-degree relatives, without the presence of a causative germline mutation, is defined as familial pancreatic cancer; this accounts for 4% to 10% of PDAC. Based on the growing evidence supporting the benefit of germline genetic testing in patients with PDAC, both the American Society of Clinical Oncology and the National Comprehensive Cancer Network recently updated their guidelines to include recommendations around genetic testing for patients with pancreatic cancer. However, there is no general consensus on the group of patients and individuals who should be studied and screened. We present a demonstrative case and review the available data on hereditary and familial PDAC.

KEYWORDS: pancreatic ductal adenocarcinoma, hereditary, familial, mutation, screening, prevention

Introduction

Pancreatic ductal adenocarcinoma (PDAC) has one of the worst prognoses among major cancers. In 2020 in the United States, it is expected to be the third-leading cause of cancer mortality, following lung and colorectal cancer, with 47,050 deaths in both genders combined (**Table 1**).¹

The average lifetime risk of pancreatic cancer is about 1 in 65 (1.5%), with a 5-year survival rate of 7%.² Although incidence is roughly equal in both genders, African Americans have a higher incidence than any other racial group.³

Older age is among the main risk factors for the development of PDAC; median age at diagnosis is 71 years.⁴ Apart from family history, which can influence the likelihood of PDAC development, other risk factors include tobacco and alcohol abuse, chronic pancreatitis, dietary factors, obesity, and type 2 diabetes mellitus.⁵⁻⁸ The incidence of PDAC in the United States has increased in recent years, possibly due to the aging population and the increasing prevalence of obesity.

First-degree relatives of patients with PDAC have at least a 2-fold increased

risk of developing the disease. The risk increases proportionally to the number of affected first-degree relatives.⁹⁻¹¹ In nearly 10% to 15% of all PDAC cases, a hereditary cancer predisposition syndrome can be implicated. Among the genetic syndromes associated with PDAC are Peutz-Jeghers,¹² hereditary pancreatitis,¹³⁻¹⁶ familial atypical multiple mole melanoma,^{17,18} hereditary breast-ovarian cancer,¹⁹⁻²² and hereditary nonpolyposis colorectal cancer (Lynch) syndromes^{23,24} (**Table 2**). However, in the remaining 85% to 90% of cases with familial aggregation of PDAC,

there is a lack of such a defined hereditary cancer predisposition component.²⁵ The presence of 2 or more patients with pancreatic cancer within the circle of first-degree relatives without an association to a known hereditary cancer genetic syndrome has been defined as familial pancreatic cancer, which accounts for 4% to 10% of PDAC. In the majority of families with PDAC, a responsible gene mutation cannot be identified.²⁶

Case

A Caucasian male, aged 74 years, was incidentally found to have a pancreatic mass during a surveillance imaging positron emission tomography (PET) scan for his prior malignant melanoma. The PET scan detected a suspicious uptake in the pancreatic tail corresponding to a subtle 2.6 cm x 1.8 cm region of low attenuation with a standardized uptake value of 7.5 (**Figure 1**). A CT scan of the abdomen revealed this to be a hypodense mass in the distal body/tail portion of the pancreas measuring 3.4 cm x 2.5 cm (**Figure 2**). Further work-up with upper endoscopy and endoscopic ultrasound biopsy revealed invasive PDAC. Family history was significant; his father and paternal grandfather had both received a diagnosis of PDAC around age 70 years and died from it. A genetic counseling visit and germline multigene hereditary pancreatic cancer panel testing detected no pathogenic sequence variants or deletions/duplications in the analyzed genes; these included *APC*, *ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *PMS2*, *STK11*, and *TP53* (sequencing and deletion/duplication), and *EPCAM* (deletion/duplication only).

The medical history was significant for a diagnosis of malignant melanoma in his right lower extremity, diagnosed and treated with curative intent 3 years earlier. It had a Breslow's depth of 1.45 mm, Clark's level IV, and ulcerated superficial spreading. He was initially treated with wide local excision and a sentinel

TABLE 1. Estimated Deaths by Cancer Type, Both Sexes Combined American Cancer Society, 2020

Lung and bronchus

135,720

Colorectum

53,200

Pancreas

47,050

Breast

42,690

Prostate

33,330

Liver and intrahepatic bile duct

30,160

Figure 1 Positron emission tomography (PET) CT scan 8/1/19: small focus of increased fluorodeoxyglucose (FDG) activity within the pancreatic tail, suspicious for pancreatic malignancy measuring approximately 26 x 18 mm.

TABLE 2. Hereditary/Familial Syndromes Associated With Pancreatic Ductal Adenocarcinoma

Syndrome	Identified genes	Clinical presentation	Cumulative risk of PDAC	Relative risk of PDAC
Peutz-Jeghers syndrome	<i>STK11/LKB1</i>	Gastrointestinal hamartomatous polyps; mucocutaneous pigmentation; high-risk gastrointestinal, breast, ovarian, endometrial, and lung cancers	Up to 36% lifetime risk	132-fold
Familial pancreatitis syndrome	<i>PRSS1, SPINK1, PRSS2, CFTR</i>	Recurring acute pancreatitis and chronic pancreatitis	Up to 53% at age 75 years	26- to 87-fold
Familial malignant melanoma syndrome	<i>P16/CDKN2A</i>	Multiple atypical nevi and history of melanoma and other tumors such as breast, lung, endometrium	Up to 17% at age 75 years	13- to 46.6-fold
Lynch syndrome	Colorectal, endometrial, stomach, small intestine, urinary tract, brain cancers	<i>MLH1, MSH2, MSH6, PMS2</i>	3.7% at age 70 years	8.6-fold
Hereditary breast-ovarian cancer syndrome	<i>BRCA1, BRCA2, PALB2</i>	Breast and ovarian cancer	1.5%-4.0% at age 70 years; more in <i>BRCA2</i>	<i>BRCA1</i> : 4- to 6-fold <i>BRCA2</i> : 3- to 22-fold <i>PALB2</i> : 6-fold
Familial pancreatic cancer	2 or more first-degree relatives with PDAC	Unknown in most families	3 or more first-degree relatives with PDAC: up to 16%-40% 2 first-degree relatives with PDAC: up to 12%	3 or more first-degree relatives with PDAC: 32-fold 2 first-degree relatives with PDAC: 6-fold 1 first-degree relative with PDAC: 2- to 5-fold

PDAC; pancreatic ductal adenocarcinoma

node procedure, which revealed 1 positive lymph node without extracapsular extension. Further surgery with radical superficial groin dissection showed no further evidence of melanoma. He was treated with adjuvant immunotherapy with nivolumab (Opdivo) for 1 year, and he currently had no evidence of malignant melanoma.

For his newly diagnosed locally advanced PDAC, the patient was treated with 6 cycles of a neoadjuvant FOLFIRINOX chemotherapy regimen, which reduced his pancreatic mass from 3.4 cm x 2.5 cm to 1.5 cm x 1.2 cm on imaging studies (Figure 3). He underwent a successful partial pancreatic body/tail pancreatectomy and splenectomy. Pathology revealed a 2.4-cm (pT2) residual invasive moderately differentiated PDAC arising in association with a low-grade intraductal papillary mucinous tumor at the proximal margin. While

there was some perineal invasion, there was no lymphovascular invasion or any involved lymph nodes, of 14 removed (pN0). All resection margins were negative (R0 resection) (Figures 4, 5, 6). Spleen was without diagnostic abnormality. Immunostaining for DNA mismatch repair proteins (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) revealed retained nuclear staining for all 4 antigens. Results of the next-generation sequencing of tumor tissue revealed a microsatellite-stable tumor with a tumor mutational burden of 3 mutations per megabase. Genomic findings showed *CDKN2A/B* loss and presence of *KRAS*-Q61H, *SGK1*-K138fs13, *SMAD4*-P18fs17, and *TP53*-R273H, with no reportable therapeutic or clinical trial options.

Discussion

In most cases, the genetic basis of inherited PDAC is not well understood. Several

large epidemiological studies have established the fact that a family history of pancreatic cancer increases the risk of developing the disease. However, as many as 80% of patients with a family history of pancreatic cancer have no identifiable genetic cause.²⁷ A prospective registry study revealed that having 1 first-degree relative with PDAC increased the risk of developing the disease up to 2- to 5-fold, and having 2 first-degree relatives with the disease increased the risk to 6.4-fold.¹⁰ Early-onset (<50 years) pancreatic cancer in the family is associated with an even greater risk. The lifetime PDAC risk increases as the age of family members with the disease decreases.

Peutz-Jeghers syndrome is an autosomal dominant disorder characterized by hamartomatous polyps in the gastrointestinal tract; by pigmented macules of the lips, buccal mucosa, and digits; and increased risk of gastrointestinal can-

cers, including pancreatic cancer. Germline mutations of the *STK11/LKB1* gene have been attributed to Peutz-Jeghers syndrome, which results in risk of PDAC increasing by as much as 132-fold. Inactivation of *STK11/LKB1*, by homozygous deletions or by somatic sequence mutations coupled with loss of heterozygosity, has been demonstrated in 4% to 6% of sporadic pancreatic cancer cases; this indicates a possible causal role in the carcinogenesis for both sporadic and inherited forms of PDAC.²⁸

Hereditary/familial pancreatitis syndrome is a rare cause of chronic pancreatic inflammation. Its onset is early, usually during childhood. It often starts with recurrent episodes of acute pancreatitis, and the clinical phenotype is not very different from other etiologies of the disease. The long-lasting inflammation generates a tumor-promoting environment predisposing to carcinogenesis. Several genes have been implicated with the familial form of pancreatitis, including *PRSS1*, *SPINK1*, and *CFTR*. The increased risk of developing PDAC has been estimated as between 26- and 87-fold.^{15,16,29,30}

Familial malignant melanoma syndrome, also known as melanoma-pancreatic cancer syndrome or familial atypical multiple mole melanoma syndrome, is an autosomal dominant disease characterized by the familial occurrence of malignant melanoma of the skin and multiple atypical precursor lesions. Germline mutations in the *p16 (CDKN2A)* gene have been reported in at least a quarter of such families and associated with pancreatic cancer.³¹ In an analysis of 521 patients who met criteria for familial pancreatic cancer, 2.5% had germline mutations in *CDKN2A*, while patients with a family history of pancreatic cancer and melanoma had germline mutations of *CDKN2A* in 7.8% of cases.³² Familial malignant melanoma syndrome is associated with a 20- to 47-fold increased risk of pancreatic cancer.¹⁸ Patients with this syndrome have an earlier onset of pancreatic cancer compared with the general population.³³

■ **Figure 2** Axial contrast enhanced CT (arterial phase) demonstrates pancreatic tail lesion with relative hypoenhancement, corresponding to the focus of uptake on the recent positron emission tomography (PET) imaging. There was dilatation of the pancreatic duct distal to this finding (not shown), which did not show fluorodeoxyglucose (FDG) uptake on PET.

■ **Figure 3** 12/6/19. Axial contrast enhanced CT (arterial phase) again demonstrates the subtle hypoenhancing lesion in the pancreatic tail. Decreased from 34 x 25 mm to 15 x 12 mm.

■ **Figure 4** Distal pancreatectomy showing invasive, moderately differentiated adenocarcinoma (H&E, 200X magnification).

■ **Figure 5** Perineural invasion (H&E, 200X magnification).

■ **Figure 6** The tumor arose in association with a low-grade papillary mucinous neoplasm (H&E, 40X magnification).

Lynch syndrome is an inherited cause of colorectal cancer caused by mutations of DNA mismatch repair genes *MLH1*, *MSH2*, *MSH6*, or *PMS2*. A number of extracolonic tumors have been associated with this disorder, including pancreatic cancer. The risk for pancreatic cancer can be as high as 9- to 11-fold greater than average in affected patients.^{34,35} Mutations in germline mismatch repair genes result in the lack of repair of errors that are introduced during DNA replication; these errors shorten or lengthen microsatellites, leading to their persistence on somatic cells. These can be tested on somatic tumor tissue samples. Microsatellite instability is also a prognostic factor for survival. The accumulated risk of pancreatic cancer in patients with Lynch Syndrome is around 3.7%. Pancreatic tumors developing in patients with Lynch Syndrome often present with a characteristic medullary appearance and prominent lymphocytic infiltration. Individuals with Lynch syndrome have an 8.6-fold increase in risk of pancreatic cancer development compared with the general population.^{36,37}

Hereditary breast-ovarian cancer syndrome represents another genetic syndrome in which an excess of pancreatic incidence has been reported. In families harboring *BRCA1/2* mutations, the risk of pancreatic cancer is increased by 2- to 6-fold, and the age of onset is younger than the average in the general population. *BRCA1/2* mutations occur in 4% to 7% of all patients with pancreatic cancer.^{21,38,39}

Familial pancreatic cancer is defined as having at least 2 first-degree relatives with pancreatic cancer that occurs in association with none of the genetic cancer syndromes described above. Although this syndrome does not seem to follow a specific Mendelian pattern of inheritance, research is under way to better understand this cohort of patients. Hereditary/familial syndromes associated with PDAC are listed in **Table 2**.

Because of the low incidence of PDAC

in the general population, with a lifetime risk of 1.5%, screening is not feasible. It should, however, be considered in high-risk individuals, especially those with 5- to 10-fold or higher increased risk for PDAC. This scenario includes hereditary syndromes associated with increased risk of PDAC and members of families with familial pancreatic cancer. The purpose of screening is to detect precursor lesions or early cancer. Identification of PDAC at an early stage can be essential to improved survival, as demonstrated by the small proportion of patients with localized cancers who reach the 5-year survival mark at a rate of 31.5%. Moreover, recent data suggest that some specific germline mutations (mainly related to homologous repair) could be therapeutically targetable and guide personalized therapy. Identifying patients with predisposing genetic factors can improve clinical outcomes.

Outcome of the Case

The patient had a successful curative-intent treatment and currently has no evidence of cancer. His personal history of pancreatic cancer and malignant melanoma and a strong family history of pancreatic cancer—including 1 first-degree relative (father) and 1 second-degree relative (paternal grandfather)—put him and his family at an increased risk for future cancers, although that increased risk

is not yet well defined. His current clinical presentation does not match any of the above-mentioned hereditary cancer syndromes. There seems to be a familial form of vertically inherited pancreatic cancer susceptibility in his family, despite the absence of clinically significant mutations in his germline multigene hereditary pancreatic cancer panel testing. Possible explanations for this presentation may include an alteration in a gene that cannot be currently detected with available technology, or there may be an entirely different, as-yet-undiscovered cancer-risk gene involved for which testing is not yet available. As no mutation was detected, his assessed risk to develop another cancer will be mostly based upon his medical and family history.

The patient's first-degree relatives may remain at an elevated risk to develop pancreatic cancer. He was asked to notify us if any new cancers developed in his family, so we could assess if other testing would be appropriate. He and his family members were also encouraged to consider surveillance options and to potentially participate in screening, early detection, and prevention clinical trials.

Conclusions

Patients who receive a diagnosis of PDAC should undergo evaluation for hereditary syndromes known to be associated with increased risk for PDAC.

Similarly, individuals with a family history of PDAC—whether they themselves are affected yet by cancer or not—who meet the criteria for familial pancreatic cancer, or those with 3 or more diagnoses of pancreatic cancer on the same side of their family, have an increased risk for pancreatic cancer and should be candidates for genetic testing, as should individuals who meet criteria for other genetic syndromes associated with increased risk for pancreatic cancer. Such genetic testing should include a comprehensive review of family history of cancer, preferentially with the help of a genetic counselor. Germline genetic testing for cancer susceptibility may be discussed with individuals with a pancreatic cancer diagnosis, even if family history is unremarkable. Benefits and limitations of pancreatic cancer screening should be discussed with individuals whose family history meets criteria for familial PDAC and/or genetic susceptibility to pancreatic cancer. ■

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For full reference list, visit:
cancernetwork.com/PDAC_casestudy

Merani

is assistant professor, transplantation surgery, University of Nebraska.

Wedel

is a staff pathologist at Mary Lanning Healthcare.

Vargas

is assistant professor, transplantation surgery, University of Nebraska.

Copur

is a medical oncologist/hematologist at Morrison Cancer Center, Mary Lanning Healthcare in Hastings, Nebraska, and is a professor at the University of Nebraska Medical Center. He is also editor-at-large and a Community Oncology Advisory Board member at *ONCOLOGY*®.

Hart

is a radiologist at Mary Lanning Healthcare.

Talmon

is a professor in the Department of Pathology and Microbiology at the University of Nebraska Medical Center, specializing in gastrointestinal, renal, and placental pathology.

FDA Approves 2 Therapies for Treatment of Metastatic Non–Small Cell Lung Cancer

Kevin Wright

The FDA approved 2 new therapies, each with its own companion diagnostic, for the treatment of patients with metastatic non–small cell lung cancer (mNSCLC).

Atezolizumab Approved as Frontline Monotherapy

Atezolizumab (Tecentriq) was granted approval as a frontline monotherapy to treat adults with mNSCLC whose tumors have high PD-L1 expression (PD-L1–stained $\geq 50\%$ of tumor cells [TCs] or PD-L1–stained tumor-infiltrating cells [ICs] covering $\geq 10\%$ of the tumor area), as determined by an FDA-approved test, with no *EGFR* or *ALK* genomic tumor aberrations.¹

The Ventana PD-L1 (SP142) assay (Roche) was granted approval as a companion diagnostic device for selecting patients with NSCLC for treatment with atezolizumab.

Approval for atezolizumab, the first and only single-agent cancer immunotherapy with 3 dosing options, was based on an interim analysis from the phase 3 IMpower110 study. IMpower110 is a randomized, open-label trial evaluating the efficacy and safety of atezolizumab monotherapy compared with cisplatin or carboplatin and pemetrexed or gemcitabine in PD-L1–selected, chemotherapy-naïve patients with stage IV nonsquamous or squamous

NSCLC.

The study enrolled 572 participants, of which 554 were in the intent-to-treat TC3/IC3–wild-type population. Participants were randomized 1:1 to receive either atezolizumab monotherapy or platinum-based chemotherapy. Treatment continued until disease progression, unacceptable toxicity, or death.

Data analysis showed that atezolizumab monotherapy improved overall survival (OS) by 7.1 months compared with chemotherapy (median OS, 20.2 months vs 13.1 months; HR, 0.59; 95% CI, 0.40–0.89; $P = .0106$) in individuals with high PD-L1 expression.

Treatment-related adverse events (AEs) were reported in 12.9% of patients receiving atezolizumab, compared with 44.1% of those receiving chemotherapy. No new safety signals were reported for atezolizumab, which has already received 4 approvals across various NSCLC indications, either as a single agent or in combination with other targeted therapies and/or chemotherapies. Atezolizumab is also approved in combination with carboplatin and etoposide as a first-line treatment for adult patients with extensive-stage small cell lung cancer.²

The primary end point for the study was OS by PD-L1 subgroup, as determined by the SP142 assay test. Median progression-free survival (PFS), a

secondary end point for the study, was 8.1 months (95% CI, 6.8–11.0) in the atezolizumab arm and 5.0 months (95% CI, 4.2–5.7) in the chemotherapy arm (HR, 0.63; 95% CI, 0.45–0.88). Confirmed overall response rates (ORRs) were 38% (95% CI, 29%–48%) and 29% (95% CI, 20%–39%), respectively.

The recommended atezolizumab dosage for treatment of NSCLC is 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks, administered intravenously over 60 minutes.

Nivolumab Plus Ipilimumab Approved With Companion Diagnostic

The FDA also approved the combination of nivolumab (Opdivo) plus ipilimumab (Yervoy) as a first-line treatment for patients with mNSCLC whose tumors express PD-L1 ($\geq 1\%$), as determined by the PD-L1 IHC 28-8 pharmDx companion diagnostic (Agilent), with no *EGFR* or *ALK* genomic tumor aberrations. The diagnostic tool was newly approved by the FDA as well.³

Approval was based on results of the CheckMate 227 trial, which was designed to evaluate the combination treatment in patients with metastatic or recurrent NSCLC and no prior anticancer therapy.

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Decisional Capacity Determination in Patients With Cancer

Daniel C. McFarland, DO¹; Liz Blackler, MBE, LCSW-R²; Fay J. Hlubocky, PhD, MA³; Rebecca Saracino, PhD¹; James Masciale, PhD²; Martin Chin, MD^{1,2}; Yesne Alici, MD^{1,2}; and Louis Voigt, MD^{2,4,5}

¹Department of Psychiatry and Behavioral Sciences, Memorial Sloan Kettering Cancer Center, New York, NY; ²Ethics Committee, Memorial Sloan Kettering Cancer Center, New York, NY; ³Section of Hematology/Oncology, Department of Medicine, University of Chicago, Chicago, IL; ⁴Department of Anesthesiology and Critical Care Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; ⁵Department of Anesthesiology, Weill Cornell Medical College, New York, NY

ABSTRACT: Patients with cancer face many difficult decisions and encounter many clinical situations that undermine decisional capacity. For this reason, assessing decision-making capacity should be thought of at every medical encounter. The culmination of variable disease trajectories, following patients to the end of life, use of high-risk treatments, and other weighty personal decisions require attention to patients' ability to engage in decisions. Oncologists develop meaningful relationships with their patients. This familiarity may lead to forgoing the process of diligently assessing a patient's cognitive ability and/or decisional capacity when important decisions need to be made. While the process may feel like it takes place spontaneously, many subtle and overt details are involved with the decisions around cancer care that require pointed questioning and probing. Thus, there are many ways to fall short in determining decisional capacity. Clinicians are inconsistent in their decisional capacity determinations and generally assume more decisional capacity than the patient has. Consult and referral services such as ethics and psychiatry can help with treatment decisions and with assessing underlying psychosocial and psychiatric conditions. Decisional capacity may fluctuate and requires a variable amount of decisional ability depending on the clinical situation; hence, it is time-specific and decision-specific. This review is intended to provide a summary of key components of decisional capacity while highlighting areas in need of clinical refinement.

Introduction

Decisional capacity assessment should be an integral part of routine clinical care with patients, and it is especially important in oncology settings.¹ Cancer care is dynamic. It involves the coordination of multiple teams of clinicians whose decisions affect patients, families, and communities.² While some decisions in oncology may seem straightforward or procedural, others are clearly more complicated or entail higher risk for patients. Each of these clinical decisions requires the consent of a patient who is able to engage in reviewing multiple potential options with their clinicians; assessing and weighing complicated information as it becomes available; and

deciding for themselves based on life experience, values, and an idiosyncratic approach to novelty. In other words, the context of a clinical decision for patients is often much more complex than the actual decision the patient is being asked to make. There is a temptation to simplify decisions to their clinical parts and apply the "reasonable person" standard to all patients. This approach is inherently flawed and will lead to inadvertently compromised clinical care. Therefore, clinicians should be curious about decisional capacity during all clinical encounters in which patient engagement is required. An assessment could vary from minimal (no questions) to

formal, depending on the situation; the latter requires specific documentation.

Unfortunately, the assessment of patients' decision-making abilities is not routinely taught in a methodological way throughout medical training and into practice.³ Many patients with cancer face periods of cognitive impairment or compromise due to a multiplicity of risk factors and medical situations.⁴ The ability to think clearly and consistently can be compromised by polypharmacy, metabolic disturbances, infection, high rates of brain metastasis (especially nearing the end of life), sleep dysregulation, emotional distress, and other premorbid conditions that may impair decisional capacity.⁵ A review

of psychiatric consultations for decisional capacity among hospitalized patients with cancer found that refusal of treatment was the most common reason for consult requests.⁶ Also, patients with personality disorders tended to retain decisional capacity, while patients with delirium and dementia did not, and decisional capacity of patients with mood disorders was more variable.⁶

An approach to patients that integrates the assessment of decisional capacity should be the cornerstone of personalized medicine, because clinicians are able to align care in accordance with a patient's ability to validate their choices. Ultimately, responsible care in which physicians consider a patient's ability to make decisions that are consistent with their values leads to a more coordinated practice that honors patients as autonomous partners in a truly therapeutic alliance.

Decisional capacity is often thought of as a prerequisite for consent to treatment, but it actually pervades all aspects of medical care and should be an inherent aspect of clinician–patient interactions. At the very least, decisional capacity is required for the provision of informed consent.

Historical Account of Decisional Capacity

The idea of informed consent originates from a series of ethically charged medical cases from the mid-1950s through the 1970s, after which the American Medical Association published, in 1981, an official policy on informed consent.⁷ Informed consent was preceded by an era of “simple consent,” in which the doctor was presumed to know what was best for the patient; the role of the patient was to either accept or refuse the expert recommendation provided by the physician, not to evaluate the necessary elements of a medical decision. The goal of simple consent was to protect patients from “battery” (unwanted touching, usually surgical) in the spirit of self-determination regarding a procedure, but not necessarily to protect patient autonomy. It was not uncommon for physicians to deceive patients in an effort to

protect them, and to do “what’s best” for the patient. A disclosure about what was to be done to the patient (eg, a procedure) along with a nod from the patient was all that was needed for simple consent in accordance with accepted medical practice. There was no need to assess the patient's ability to engage in the decision-making process because the physician determined what was best for the patient and all the patient had to do was agree or disagree.⁸

The legal evolution of informed consent began with patients being allowed to determine what would happen to their bodies regardless of understanding (*Schloendorff v Society of New York Hospital*, 1914) and eventually evolved into a right to understand the medical decision affecting them.⁷ In this famous case, Justice Benjamin Cardozo stated, “Every human being of adult years and sound mind has a right to determine what shall be done with his own body, and a surgeon who performs an operation without his patient's consent commits an assault.”⁷ Patients' rights for informed decision-making and consent were brought forth in 1957 by a court proclamation that “physicians have a duty to disclose any facts which are necessary to form the basis of an intelligent consent by the patient to the proposed treatment” (*Salgo v Leland Stanford Jr University Board of Trustees*). While “intelligent” or informed consent is now the standard of care, courts deferred to the medical professional standards at that time to decide how much information was necessary for informed consent. Therefore, the level of understanding required for informed consent was not universal or quantified, and it relied on professional responsibility alone to determine patients' ability to make decisions.

In oncology, significant and life-altering decisions require a sophisticated level of intelligent, informed consent. A demonstration of adequate decisional capacity often becomes more difficult for patients as diseases progress. Cognitive processing may become slowed because of medications, biochemical changes, or the emotional weight of cancer. These factors and significant rela-

tionship strains impair the patient's ability to process information, placing a greater pressure on clinicians to appropriately assess decisional capacity.⁹ An overestimation of decisional capacity is common, but this can be disastrous for some patients and undermine the care of others.¹⁰

Assessing Decisional Capacity Case

A man with metastatic lung cancer, aged 57 years, has undergone 3 lines of therapy over the last 2 years with partial but long durations of response. He has no other significant medical comorbidities but has a significant history of depression that was reported on initial evaluation. He has remained on sertraline at the same dose over the last couple of years. You are not sure whether he's seen a psychiatrist since he received the lung cancer diagnosis. His lung cancer has progressed, and a recent biopsy has revealed a potentially actionable mutation. He is in good condition physically despite progression of disease. He may be eligible for an early-stage clinical trial targeting this mutation that requires a heavy patient commitment (eg, 12-hour days for pharmacokinetic data, frequent follow-up, and substantial adverse effect burden). The patient asks only simple logistic questions about the trial when you review it with him, but he agrees to participate because you feel it is the next best treatment. In reviewing even some of the basic information with him, he is unable to recall significant details, but he seems to “get it” once prompted. He is clearly more withdrawn than he has been in the past, but you attribute this to learning about the latest progression of disease. Upon reviewing his history, it becomes even more apparent that his cognitive ability is compromised. While his demeanor had always been somewhat reserved and hesitant, at this meeting he also lacked his usual conversational tempo. You were also surprised by his inability to recall basic facts of the trial because this was not consistent with his usual presentation.

This scenario presents the oncologist

TABLE. Evaluation of 4 Core Dimensions of Decisional Capacity^{16,29,a}

Dimension	Skill	Questions
Understanding	State the meaning of relevant information	"Can you tell me in your own words?" "What is your understanding of your condition?" "What are the options for your specific situation?" "What are the risks of treatment and the odds of having adverse effects?" "What will happen if nothing is done?"
Appreciation	Ability to explain the relevance of information as it applies to themselves	(a) Diagnosis: "Tell me what you really believe about your medical condition." "Why do you think your doctor recommended X?" "Do you think it is the best treatment for you?" "What do you think will happen if you accept the treatment? Or not?" (b) Benefit: "Do you think it is possible the medicine can benefit you? Can you elaborate more?" (c) Risk: "Do you think this procedure can harm you? Can you explain why?"
Reasoning	Ability to compare information and infer consequences of choices	"What factors/issues are most important to you in deciding about your treatment? Are you considering other options?" "How are you balancing the differences?" "How could drug X affect your daily activities?"
Expressing a choice	Ability to state a decision	"Based on what you've heard, what would be your best choice?" "We have discussed several options. What do you want to do?"

^aAdapted from Karlawish et al 2017 and Tunzi 2001.

with a difficult situation, especially when it involves a patient they may have known for some time and for whom they feel an experimental treatment holds promise. The patient's newly advancing disease may be presenting in the central nervous system; a clinical depression may be resurfacing, causing pseudodementia; or he may just be distracted given his clinical situation. The oncologist should begin with an assessment of decision-making capacity, determining whether appropriate referrals and testing are necessary before deciding to move on with trial participation (**Table**).^{16,29}

The ability to make competent treatment decisions is generally organized around 4 commonly used medico-legal standards: (1) ability to understand information relevant to the treatment decision; (2) ability to appreciate the relevance of the decision; (3) ability to reason/describe the information about the risks and benefits of the decision in light of individual goals and values; and (4) ability to express a consistent choice.¹¹

UNDERSTANDING. The patient should demonstrate the ability to communicate the primary facts of the situation. The patient demonstrates that they know the purpose and meaning of the information that has

been provided. Several different aspects of the decisional landscape must be probed to ensure that key components of the decision are understood by the patient. It is also imperative that the evaluator has a clear understanding of the actual medical decision so that the patient's understanding of their medical condition can be adequately examined. Understanding might include the purpose of the proposed intervention (eg, diagnostic or therapeutic), the rationale for the intervention, typically hoped-for benefits, the most important risks and their likelihood of occurrence, the alternatives to the proposed intervention (including doing nothing at all), and the associated benefits and risks of each alternative. The assessment must also vet a patient's discernment of courses of action that are not options due to safety, logistics, or limitations of science. A patient's ability to communicate does not need to be ideal, but an understanding of the essential facts relevant to the situation should be demonstrated.

In severely symptomatic or life-limiting illness, as may be the case for cancer, the patient may be unhappy with the options available. Sometimes patients would persist in choosing a cure with return to a prediagnosis state of health when that

option is not available. In this case, the patient may persevere between toxic treatment or a comfort-focused plan and fail to "make a decision" because neither option is desirable. This failure to "choose" may not indicate an impaired decisional capacity. Simply put, a decision is not required if there are no options and only a single course of action is possible. Reframing the situation from one requiring a decision to one requiring acknowledgment may allow resolution of the impasse.

The assessment of understanding may begin with disclosing information to the patient and assessing their ability to repeat it. Memory and the ability to retain information is a prerequisite to a patient's ability to understand. Patients need to retain information long enough to provide a consistent, stable setting for effective implementation of the chosen option. Memory or cognitive impairment does not necessarily preclude decisional capacity. Understanding precedes the ability to demonstrate appreciation of the information; therefore, understanding needs to be assessed prior to gauging appreciation.

APPRECIATION. The patient should be able to apply the known facts to their own life situation, such that the personal impli-

FIGURE. Threshold Determination^{29,a} ^aAdapted from Tunzi 2001

cations of the choice are clear. A lack of an ability to appreciate how facts of the situation are relevant to the patient may stem from impaired insight or delusional beliefs; for example, a patient might not believe that the diagnosis of cancer is correct. While the ability to demonstrate appreciation will vary from patient to patient based on education and health literacy, the patient simply needs to demonstrate how the information is relevant to their medical needs. After asking for an explanation of what the patient has absorbed, the clinician may follow up with, “What do you think about what I’ve told you? Can you tell me what it means for your situation?”

Impaired ability to appreciate the decision may stem from a thought disorder that is psychiatric in nature, such as a fixed belief or psychotic thinking that is out of touch with reality. This may stem from one of several psychiatric conditions (eg, bipolar disorder, serious major depression with psychotic thinking, delusional disorder, paranoia); however, the presence of such a condition, in less severe form or when treated, may not impair a patient’s ability to appreciate the decision. More commonly, patients without a psychiatric disorder exhibit a narrowed “field of vision” that

may be a distortion of their own values (ie, premorbid values and beliefs). Perversion of values or thoughts can be difficult to ascertain. For example, a depressed patient who is not psychotic may display a rigid pessimism and not be able to “see” other options. Similarly, a patient’s acceptance of death may be a manifestation of their own choosing or influenced by underlying depressive symptoms. At the same time, some patients simply lack insight into their own situation, which may be due to a reason or condition such as underlying cognitive impairment, brain injury, stroke, seizure, etc.

A gentle, nonthreatening approach to probing appreciation is paramount because patients often do not want to disclose beliefs or thoughts that they may know will be perceived as odd or controversial. A confidential, trusting environment that communicates the desire to provide patients with purposeful care is helpful in obtaining their cooperation and openness.

REASONING. The patient should be able to compare options and infer consequences of each choice (ie, consequential reasoning). Reasoning may draw on a patient’s core values and beliefs, which should be demonstrated in a conversation and be consistent with what is known about the

patient. A careful and curious interviewer will elicit elements of ability to reason throughout an interview. Reasoning ability can be simply probed by the question, “Can you tell me *why* you are refusing/asking for treatment X?” At the same time, an attempt should be made to understand whether the choice is consistent with the patient’s known values and/or historical choices, ie, “Why is this choice better than that choice?”

Clinicians should be attentive to cultural or religious bias in assessing reasoning. They must be both deliberate in their efforts to appraise patients’ reasoning objectively (eg, uncovering personal biases that disfavor certain styles of thought expression) and nimble in accepting some degree of relativism. Patients may hold to convictions regarding the use of blood products, end-of-life care, or other medical interventions that may seem unreasonable to the examiners or other individuals who do not share the patient’s cultural context. However, cultural determinants of reasoning are not immutable and are often imbued with “mosaicism.”

EXPRESSING A CHOICE. The patient should be capable of clearly communicating a choice when presented with multiple treatment options. A frequent change in choice may indicate a lack of decisional capacity; therefore, it may be helpful to ask the patient to communicate a choice more than once during an interview: “Now that we have talked about your condition and the recommended treatment, what would you like to do?” A communication of choice frequently leads to the clinical questioning of decisional capacity. Thus, attempting to gain an understanding of the choice enhances rapport and can lead to an assessment of the patient’s understanding, appreciation, and reasoning around the decision.

Each of these areas needs to be assessed and to form a convincingly integrated whole that is woven into the understanding of the decision at hand. The clinician should consider the level of scrutiny or threshold of determination that must be

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Telehealth Is the Future — and the Future Has Arrived

Bill Dacey, MHA, MBA, CPC-I

For several years, we've seen Medicare and the American Medical Association's Current Procedural Terminology (CPT) manual slowly approach the age of telehealth. Despite a lot of discussion and many headlines during each of the last few years, the codes and coverage embracing the modern age of medicine have lagged far behind the technology.

This isn't limited to telehealth, or even to coding and payments. The degree of penetration and utilization of the electronic health record in the last decade has left many of the regulations intended to deal with the business of medicine in the dust. Rules written to govern the paper chart don't really jibe with reality anymore. The old consult language of "communicated by written report" hasn't changed since those

notes were typed on a typewriter and envelopes addressed by hand.

The federal documentation guidelines, a standard for the last 25 years and a physician's daily confinement of compliance, are the latest to show up in the rearview mirror.

Fast-forward to the future in a matter of weeks, at least temporarily. Since the public health emergency that is coronavirus disease-19 (COVID-19) came to America in January 2020, the Centers for Medicare & Medicaid Services (CMS) has unleashed a series of changes intended to allow the codes and coverage to catch up with the newly imposed reality of telehealth.

Although specific e-service and telehealth-type codes were in their infancy, both the CPT and CMS systems are equipped to allow for telehealth services

and claims to be clearly identified, coded and billed. CPT had introduced the star symbol next to certain codes that were eligible for telehealth. Modifier 95 has been around for some time and identifies services performed via synchronous telemedicine with real-time audio and video communication.

The place of service (POS) codes, as CMS now uses them since March 31, allow the agency to determine whether or not the service rendered was a traditional remote originating site (POS 2) or the new temporary version using office, hospital, or other POS codes (11, 22, etc.).

Until March, the single largest obstacle to widespread adoption of telehealth for office services was the geographic limitation imposed by Medicare's originating site requirement—that the originating site be outside a major metropolitan area. That was the elephant in the room, effectively blocking the use of the codes for any urban and many suburban areas, regardless of the practicality.

COVID-19 moved the elephant, at least for now. Welcome to the future.

Since late March, CMS has taken extraordinary steps to allow providers to do what needs to be done, and to pay them for it. Among those steps:

- As of March 6, Medicare will pay for office, hospital and other visits furnished via telehealth, including those in a patient's place of residence, across the country. A range of providers, such as doctors, nurse

Codes for Diagnosing COVID-19:

For diagnosis coding, consider the following:

Code B34.2: coronavirus infection, in addition to manifestation

Code B97.29: for COVID-19 diagnosis

- Possible exposure to COVID-19 ruled out: **Z03.818**
- Exposure to person with confirmed COVID-19: **Z20.828**
- Pneumonia: **J12.89**
- Acute bronchitis: **J20.8**
- Respiratory infection NOS: **J98.8**
- Acute respiratory distress syndrome: **J80**

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Telehealth Codes to Know

There are numerous options when it comes to reporting visits that are not the traditional face-to-face office visit. This varies somewhat by payer, of course.

Medicare has temporarily relaxed some of the geographic and security/privacy restrictions on telehealth visits, including the office visit codes. This will allow patients to call your office, and as long as there is some type of combined audio/video communication between the provider and the patient, these "visits" can be billed with the 99201-99215 series codes, adding the 95 modifier.

For Medicare there are numerous options:

Office Codes (99201-99215)

The new visit codes to the extent the 1135 waiver requires an established relationship. The US Department of Health and Human Services (HHS) will not conduct audits to ensure that such a prior relationship existed for claims submitted during this public health emergency.

Any new visit codes 99201-99205 would likely need to be coded based on time given the limitations of the exam. The established patient codes 99211-99215 could be billed by counseling time or by documenting the level of history and medical decision-making associated with a given code level.

Virtual Check-Ins (G2012)

A brief (5-10 minutes) check-in with your practitioner via telephone or other telecommunications device to decide whether an office visit or other service is needed. This is provided to an established patient, not originating from a related evaluation and management (E/M) service provided within the previous 7 days nor leading to

an E/M service or procedure within the next 24 hours or soonest available appointment.

E-Visits (G2061-G2063)

Online digital E/M service, for an established patient, for up to 7 days, cumulative time during the 7 days. For Medicare these are:

- G2061: for up to 7 days, cumulative time during the 7 days; 5 to 10 mins.
- G2062: for up to 7 days, cumulative time during the 7 days; 11 to 20 mins.
- G2063: for up to 7 days, cumulative time during the 7 days; 21 or more minutes.

Private Payers

For private payers and some Medicare Replacement plans, you can use:

- 99421: 5-10 minutes
- 99422: 11-20 minutes
- 99423: 21 or more minutes

Those are the mainstream codes to consider here. Reimbursement varies, with the office visit codes typically paying the most. Visit the websites for UnitedHealthcare, BCBS, Aetna, CIGNA, Humana, and others for specific policy changes. To document your visit, be sure to note in your EHR the date, time, and duration of the encounter. Also record the relevant history, and exam, decision-making, and other management elements as you would for any other visit.

practitioners, clinical psychologists, and licensed clinical social workers, are able to offer telehealth services to their patients. Additionally, the Department of Health and Human Services Office of Inspector General is providing flexibility for health care providers to reduce or waive cost sharing for telehealth visits paid by federal health care programs.

- Medicare, after some back and forth, has settled on paying physicians the standard (POS) office rate for services provided via telehealth and not applying the site-of-service differential associated with hospital clinic-type encounters.
- HIPAA and privacy standards have been temporarily relaxed to allow the use of FaceTime, Zoom, Skype and certain real-time 2-way

telecommunications with patients for office visits.

- The April 6 *Federal Register* included details on relaxed documentation requirements for COVID-19 telehealth office visit documentation: "On an interim basis, we are revising our policy to specify that the office/outpatient evaluation and management (E/M) level selection for these services when furnished via telehealth can be based on medical decision making (MDM) or time, with time defined as all of the time associated with the E/M on the day of the encounter; and to remove any requirements regarding documentation of history and/or physical exam in the medical record."

It's truly a back-to-the-future moment as this is the documentation stan-

dard that the CMS and CPT manuals are moving to on January 1, 2021. The items above are just some of the larger moves. There are many more, including new ones such as payment for certain phone calls. The CMS website has the latest updates, which have been posting every few days.

So, although all of this activity is unfortunately in response to COVID-19, it is heartening to see CMS respond so appropriately and relatively quickly. Who knew an elephant could move so quickly? But once we are through this health care crisis, CMS will face another challenge, perhaps a more difficult one: how to get the telehealth genie back in the bottle. ■

Dacey is principal at The Dacey Group Inc.

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Review Article: Decisional Capacity Determination

Continued from page 206

used when investigating each of these 4 components. An in-depth investigation of 1 or more of these components may be required, depending on the specific situation, to call into question the patient's decisional capacity. That is, clinical interventions that involve high risk for minimal benefit require substantially more ability to manipulate the information beyond a basic understanding, so a higher threshold for reaching decisional capacity is needed. Clinical interventions that carry little risk for a large clinical benefit require a less nuanced or sophisticated level of understanding, and a lower threshold for decisional capacity may be sufficient. This risk/benefit approach can be used to guide the frequency and rigor of decisional capacity determinations (**Figure**).²⁹ This is referred to as a "sliding scale" approach to decisional capacity assessments. This approach is ethically appropriate because an incapacitated patient cannot exercise autonomy, so it is the clinician's fiduciary responsibility to ensure that the best interest or reasonable person standards or the ethical principle of beneficence is followed. Health care institutions also have a fiduciary responsibility to patients to care for them in a way that prioritizes their interests.

In an effort to respect a patient's dignity and autonomy, the assessment should identify the proximal cause of decisional incapacity. Potential interventions (eg, decreasing sedation, treating infection) and prognosis for restoring decisional capacity should also be listed if appropriate. Likewise, the potential for fluctuation in capacity, eg, delirium or evolving sepsis, should be documented.

Decisional capacity should be assessed for each significant clinical decision. That is, one determination of decisional incapacity does not extend to all other diagnostic or therapeutic interventions because the knowledge or understanding that needs to be demonstrated is unique for each clinical decision.

Clinicians' Roles in Decisional Capacity Determination

Decisional capacity should be documented and form part of the patient record. A licensed clinician (eg, physician or nurse practitioner) providing medical care can legally perform a determination of decisional capacity, but acceptable surrogate decision makers vary across jurisdictions.¹² Decisional capacity assessments are best when made and documented by the clinicians who will perform the procedure or treatment. For most decisions, medical considerations are best addressed by clinicians who are experts in the proposed interventions. Psychiatrists and bioethicists are frequently called upon to help make determinations regarding decisional capacity. Ethicists can speak to the underlying ethical principles and their applicability to a particular decision. Psychiatrists and mental health clinicians are experts in mental status evaluations and can assist in capacity assessments when psychiatric symptoms that may interfere with decisional capacity are present. In some jurisdictions, assessment by a psychiatric practitioner is required when severe mental illness, such as schizophrenia, is present. In the current case scenario, a referral to psychiatry may be appropriate especially if the patient has a significant clinical history of depression requiring ongoing psychiatric care (eg, hospitalizations, suicide attempts, etc).

Risk Factors for Limited Decisional Capacity

The most common reasons for lack of decisional capacity are cognitive impairment and altered mental status. Any illness or treatment that compromises cognition may be associated with reduced decisional capacity. The likelihood of diminished capacity is related to the severity of the cognitive impairment, although brief measures of overall cognition such as the Mini-Cog or the Mini Mental Status Ex-

amination (MMSE) are not substitutes for an assessment of capacity.¹³ High scores on these instruments are not always correlated with intact capacity to make decisions, although decisional incapacity does increase in patients with lower MMSE scores (eg, dementia).¹⁴ The presence of illness associated with cognitive impairment, or of a thought disorder such as dementia or schizophrenia, is insufficient for the determination of decisional capacity or incapacity and should not substitute for an assessment of capacity that is explicitly documented.¹⁵ Decision-making incapacity due to cognitive impairment is not static, as cognition may be impaired by reversible factors such as fleeting delirium or medications. Mitigation of these factors may restore a patient's decision-making capacity.

The groups with the highest risk for decisional incapacity are patients with neurodegenerative diseases, of which dementia is the most common.¹⁶ Psychiatric disorders that affect thought content and processing such as psychotic disorders (eg, schizophrenia), severe depression, bipolar episodes, or substance-abuse disorders also increase risk of decisional incapacity, but they do not necessarily compromise decisional capacity. Disease severity and domain of dysfunction are important correlates of impaired capacity. Patients with psychosis may retain capacity for some decisions if there is overall minor executive dysfunction.¹⁷ Finally, patients with a history of traumatic brain injury, cognitive developmental delay, or protracted hospitalization, as well as those approaching the end of life, are all at elevated risk of decisional incapacity.¹⁸

Patients with cancer who receive surgery, radiation, and systemic therapies will experience physical, mental, psychological, and neuropsychological adversity. Therefore, decisional capacity variability and fluctuation are common and should be assessed routinely. Decisional capacity should certainly be reassessed with changes in clinical status and as new decision points arise. In general, hospitalized patients more commonly exhibit decision-

al incapacity due to their increased risk factors for limited decisional ability and cognitive impairment.¹⁰ Similarly, patients with primary or secondary central nervous system involvement demonstrate a 25% to 50% rate of decisional incapacity.¹⁹ At the same time, patients who might be assumed to lack decisional capacity may demonstrate surprisingly high rates of insight and ability to discriminate among various choices.²⁰ Performance status (eg, Karnofsky or ECOG) is not helpful, as many patients with an elevated Karnofsky performance score of 90 to 100 do not demonstrate decisional capacity; conversely, decisional capacity may be variable with a lower score.²¹ Neuropsychological testing in patients with advanced cancer may not be informative due to lack of significant correlations between specific domains of neuropsychological dysfunction and decision-making incapacity.²² While neuropsychological dysfunction lessens decisional capacity, the mechanism is more or less global, rather than affecting domain-specific abilities. In one study, about one-third of patients with advanced cancer had decisional incapacity that was associated with impaired verbal ability and cognitive function, but not with depression or anxiety.²³

Cancer often affects an aging population; independent of their disease, patients may demonstrate differences in decisional style.²⁴ Elderly patients may prefer to agree with treating clinicians, but they are also at higher risk for cognitive impairment. Therefore, formal screening tools, such as the MacArthur Competency Tool for Treatment, informal interview techniques, and clear ideas of when to assess for decisional capacity, are all important.²⁵ While age is a consideration, biological age does not always follow chronologic age linearly. The nuances and complexities of determining decisional capacity for elderly patients with cancer may warrant an evaluation by geriatric, psychiatric, or ethics consultants, especially when the risk/benefit ratio of the proposed intervention is high.²⁶

Standards of Formal Capacity Assessments

The prevalence of decisional incapacity is much higher than the rate at which consult services (eg, psychiatry and ethics) are called to provide a formal assessment. A rate of decisional incapacity in the hospital has been reported in 25% to 35% of inpatients, yet only 0.2% to 0.4% of admissions prompted a decisional capacity consultation.^{27,28} Of those consultations, half the patients were found to not have decisional capacity. The rest of the time, clinical decisions are made either tacitly or more conscientiously by busy clinicians.

There are 4 clinical scenarios that should regularly trigger decisional capacity assessments by either the treating clinical team or consultation services: (1) an abrupt change in mental status or cognitive ability, which may be secondary to infection, hypoxia, metabolic disturbances, or an acute neurologic or psychiatric process; (2) refusal of recommended treatments, especially when unwilling to discuss the refusal or when the basis of refusal seems illogical or inconsistent with the patient's history; (3) consent to invasive or high-risk treatments without careful consideration by the patient of the risks, benefits, and alternatives; and (4) risk factors for limited or fluctuating decisional capacity, eg, neurologic diseases, chronic psychiatric conditions, limited health literacy, or barriers due to language or culture.²⁹

These formal scenarios certainly require attention to decisional capacity, but impairment can occur unpredictably in many situations. Therefore, every clinical encounter should include a minimum assessment of decisional capacity, especially in ongoing cancer treatment during which the risks of therapeutic misestimation and treatment-related toxicity can be substantive (eg, first-in-human studies).^{30,31} Impairment in cognitive ability and its influence on decisional capacity can be subtle and requires a high degree of suspicion to detect.³² In patients with cancer, especially patients undergoing treatments, cognitive ability should be assessed regularly.

Role of the Mental Status Examination

Cognitive assessment is not akin to a determination of decisional capacity. These 2 exercises have different goals. However, they often go hand-in-hand because cognitive impairment is frequently the underlying cause of decisional incapacity. Also, understanding a patient's cognitive status or ability helps the clinician personalize decision-making questions according to the patient's cognitive level. A complete Mental Status Exam (MSE) assesses multiple domains of neuropsychiatric functioning, including appearance, behavior, mood, affect, thought content, thought process, cognition, insight, and judgment. Each domain includes many components; for example, the examination of thought process may include logic, abstraction, and practical judgment. MSE can be used in addition to the 4 components of capacity to understand a patient's underlying cognitive capacity, which may fluctuate in very ill patients.

Cognitive assessment involves formal and specific questioning that exercises specific domains of thought processing. Cognitive examination tools vary in the emphasis placed on each domain, resulting in different characteristics. The Folstein MSE has high sensitivity but low specificity, and the Montreal Cognitive Assessment demonstrates higher specificity and lower sensitivity.³³ These tools are insufficient for diagnosis of cognitive disorders, but they can precede more formal neuropsychological testing that can require several hours.³⁴ An assessment of cognitive ability should formally test specific cognitive skills such as attention, abstraction, orientation, and reasoning, while a decisional capacity interview should be tailored to the specific decision of concern.

Meaning of Incapacity: Clinical Implications

Decisional capacity is distinct from competency, which is a judicial determination that is binding; it is neither decision specific nor temporal.³⁵ On the other hand, deci-

sional capacity assessments are time and decision specific. Each situation is unique and combines patient factors with clinical factors. Every opportunity should be afforded to the patient to participate in their treatment, which means that causes for decisional incapacity should be identified, prognosticated, and mitigated to the extent possible. A capacity determination should include probability of either regaining decisional capacity or the tenuousness of the patient's decisional capacity.

While a clear yes-or-no outcome of an evaluation of decisional capacity is desirable, for some patients this may not be possible. Decisional capacity presents a spectrum in which a patient may retain decisional capacity for some less-weighty decisions, eg, dietary restrictions or refusal of blood work, yet lack decisional capacity for more substantial decisions, eg, code status or enrollment into a clinical trial. The situation may be more complex when the capacity to refuse a procedure is different from the capacity to consent to the same procedure. Careful consideration will reveal that consenting to a life-preserving procedure, such as initiating hemodialysis, is distinct from refusing that same procedure, and that the capacity to consent to a procedure may not imply that the capacity to refuse the same procedure is also intact. The gravity of the consequences of refusing versus consenting—eg, death—may warrant a much higher level of scrutiny of the decision to refuse. The patient must demonstrate higher levels of understanding, appreciation, and reasoning that may lead to the conclusion that while the patient retains the ability to consent, the patient lacks the decisional capacity to refuse. In practice, this is illustrated by the relative lack of ethics or psychiatric consult requests when patients consent to procedures compared with when patients refuse.

In many cases, the patient cannot demonstrate sufficient levels of understanding, appreciation, and reasoning to conclude that their decisional capacity is intact, yet the patient may be able to

express a preference. Therefore, patients should still be included in clinical decisions to the extent possible given the medical situation. Consideration of the patient's preferences by surrogate decision makers may be important in obtaining the patient's assent.

Assent is a bridge between simple consent and informed consent. Assent is a concept that is frequently used in pediatric populations; it occurs when a patient who is too young to provide informed consent agrees to and cooperates with a procedure. Informed consent is obtained from a parent. The same principle may be used with patients who have impaired decisional capacity but have identified surrogate decision makers. In most cases, agreement and cooperation, or assent, by the patient is required for safe and effective performance of procedures. Careful consideration should be given in situations where assent from the patient is not expected, especially when there is no humane way to compel adherence to the procedure. If a patient is legally incompetent, clinicians can attempt to pursue assent, but they should recognize that beneficence is the *prima facie* rationale for decision-making, particularly in emergent situations.

If incapacity is determined, a surrogate decision maker should be identified and enlisted to make the decision on the patient's behalf. Ideally, the patient would have already selected an agent through a health care proxy, power of attorney, living will, or advance directive. If a health care agent or power of attorney has not been previously identified, is unavailable, or is unable or unwilling to decide, the clinician must locate a reasonable surrogate to act on behalf of the patient. While a patient may lack decisional capacity to consent, the patient may possess decisional capacity to select a surrogate or may express a preference for a surrogate. Therefore, the patient should be asked about surrogate decision makers, especially if circumstances of decisional incapacity can be foreseen.

If the patient is not able or refuses to select a surrogate decision maker, then

a reasonable surrogate must be sought. Usually the order of reasonable surrogates starts with spouse and then extends to other immediate family and other interested parties, even friends in some instances, depending on the municipality, state, or country. In most jurisdictions, a formal application to a court for a determination of incompetency and assignment of a guardian to act on the patient's behalf is required. This can be a lengthy process, and many urgent clinical decisions compete with the protracted time required for a court-appointed guardian. In such instances, other mechanisms may be available for surrogate decision-making. In some circumstances, ethics committees, patient advisory committees, or health care providers are permitted to make time-sensitive decisions on behalf of a patient who lacks both decisional capacity and a surrogate decision maker. Again, this process varies by jurisdiction, and consultation with knowledgeable legal counsel may be helpful in clarifying the local approach. To avoid delays in care due to lengthy court processes, every measure should be undertaken to identify suitable surrogates in advance and to ensure that appropriate documents are completed and easily retrievable in the medical record. Communication with any potential surrogate should be very deliberate, and clinical information should not be shared until all parties are in agreement that the surrogate has been chosen and is willing to use the responsibility.

A patient's autonomy and right to self-determination should be the first consideration. Therefore, decisions made by surrogates must be guided by the standard of substituted judgment.³⁶ In other words, surrogates should be asked to make a decision based on what the patient would have wanted under the circumstances. Surrogates should be coached to use the patient's wishes and values based on the surrogate's knowledge of the patient's previous actions and statements, or on other experiences with the patient. If the patient lacks decisional

capacity but can state a preference, the surrogate must consider the patient's preferences in making the decision.

If the surrogate is not able to opine on the wishes or values of the patient, the decision should be based on what any reasonable person would select under the circumstances. The best-interest standard does not necessarily reflect the wishes or values of the individual and is therefore a less preferred standard for surrogate decision-making.

Patients are entitled to know the outcomes of decisional capacity determinations that apply to them. This information should be provided by the primary or consultant clinicians. However, treating clinicians can decide whether and/or when disclosing that information would be detrimental to the patient (eg, risk of agitation and treatment disruption). Management of a patient who objects to the findings should be respectful and commensurate with the patient's level of understanding to the extent possible. Considerations may be made for the necessity of the intervention (postponement), reason for decisional incapacity (eg, reversibility), and goals of care. Recruitment of and communication with individuals who are close to the patient are essential. Despite decisional incapacity, treating clinicians should continue to identify and treat underlying causes of decisional incapacity and offer comfort

and support, as the patient may be undergoing a procedure or intervention that they do not understand.

Treating clinicians should exercise a low threshold for escalating any clinical situation that may jeopardize a patient's autonomy to their relatives and friends, the ethics committee, hospital administration, and/or legal counsel. The process of soliciting outside, objective evaluation ensures that various perspectives are sought, considered, and utilized to guide a potentially contentious treatment decision, to protect the patient's welfare, and to shield clinicians and health care organizations against potential conflicts of interests.

Close and deliberate follow-up is a necessary part of managing a patient's decisional incapacity (and capacity), especially given clinical factors that influence the reversibility or tenuousness of the determination. Clinicians should resist the temptation to use a single interview (eg, a consult) or point in time as a template for future care because decisional capacity fluctuates and needs to be determined for all decisions where patient engagement and cooperation are appropriate.

Summary

The need for decisional capacity determinations is inevitable when treating patients with cancer. From genomic investigations to choosing among 2 or more diagnostic or

treatment options, clinical decisions in oncology are complex. Cancer and its treatments impact many aspects of patients' lives and mingle with premorbid factors that may compromise decisional capacity. Patients with cancer may be willing to try risky interventions out of desperation. Decisional capacity must be integrated into all patient encounters and with each clinical decision. Clinicians generally overestimate patients' abilities to make decisions, and they should avoid assumptions about patients' understanding, appreciation, and reasoning. Ultimately, to preserve the patient's autonomy, it is essential to ensure that the patient's decisions are properly and appropriately informed, particularly when they seem aligned with their physicians' recommendations. ■

CONTACT INFORMATION:

Daniel C. McFarland, DO
Department of Psychiatry and Behavioral Sciences
New York, NY 10034
Mcfarld1@mskcc.org

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➤ For full reference list, visit
cancernetwork.com/decisionalcapacity

Alici

is the clinical director, psychiatry service, Memorial Sloan Kettering Cancer Center, New York, NY.

Saracino

is a clinical psychologist at Memorial Sloan Kettering Cancer Center in New York, NY.

Hlubocky is a clinical health psychologist, section of Hematology/Oncology, Department of Medicine, University of

Chicago, Chicago, IL.

Blackler

is program manager & clinical ethics consultant, Ethics Committee at Memorial Sloan Kettering Cancer Center, New York, NY.

McFarland

is an oncologist, psycho-oncology investigator, and instructor, Department of Psychiatry and

Behavioral Sciences, Memorial Sloan Kettering Cancer Center, New York, NY.

Voigt

is chair of the Ethics Committee and a member of the Department of Psychiatry and Behavioral

Sciences, Memorial Sloan Kettering Cancer Center, New York, NY.

Chin

is a psychiatrist, Memorial Sloan Kettering Cancer Center, New York, NY.

Masciale is a member of the Ethics Committee at Memorial Sloan Kettering Cancer Center.

SERIES EDITORS
E. David Crawford, MD
Maria T. Bourlon, MD

Which Larynx-Preservation Strategy Would Be Best for a Patient With Resectable, Locally Advanced, Hypopharynx Squamous Cell Carcinoma?

Nora Sobrevilla-Moreno, MD¹; Javier I. Altamirano-Garcia, MD²; Martín Granados-Garcia, MD³; Alexandra Garcilazo-Reyes, MD¹; Marytere Herrera-Martínez, MD¹; and Miguel A. Alvarez-Avitia, MD¹.

¹Department of Medical Oncology, Instituto Nacional de Cancerología, Mexico City, Mexico; ²Department of Radiation Oncology, Instituto Nacional de Cancerología, Mexico City, Mexico; ³Department of Surgical Oncology, Instituto Nacional de Cancerología, Mexico City, Mexico

THE CASE

A 57-year-old man with a heavy smoking and alcohol consumption history, but no comorbidities, presented with pharyngeal pain to his primary care physician's office. He received empirical treatment with oral antibiotics and experienced partial improvement. A couple of months later, he developed a left cervical mass with progressive growth. A head and neck CT scan revealed a hypopharyngeal tumor. Results of a tumor biopsy indicated an ulcerated, moderately differentiated squamous cell carcinoma (SCC) with lymphovascular invasion. The patient was sent to our institution for treatment.

At the first visit, the patient complained of pharyngeal pain, hoarseness, mild pain of the bilateral cervical matted lymph nodes, mild dysphonia, and no swallowing issues. He did not mention dysphagia or weight loss, and he had quit smoking 2 months before evaluation. In the physical examination, he was found to have COG 1, with bilateral cervical matted lymph nodes; the largest one, measuring 7 cm x 6 cm, was located on the right side of the neck.

The nasofibrolaryngoscopy described a tumor at the hypopharynx that invaded the epiglottis and the posterior pharyngeal wall, with fixation of the right hemilarynx. An endoscopy ruled out extension to the esophagus. The CT scan described the presence of a tumor at the hypopharyngeal level with transglottic extension. It also revealed bilateral cervical matted lymph nodes (**Figure 1a**). Chest CT scan ruled

Figure 1A. Basal contrast enhanced CT scan shows a tumor with heterogeneous enhancement located in the pharyngomucosal space (hypopharynx) with lost interface with the lateral portion of the glottis (left). Right cervical matted nodes in level IIA and multiple left cervical nodes (right).

In this patient, which LP treatment option(s) could be considered?

- A. Definitive chemoradiotherapy.
- B. Definitive bioradiotherapy with cetuximab.
- C. Induction chemotherapy with cetuximab followed by chemoradiotherapy.
- D. Induction chemotherapy and then,

➔ **TURN TO PAGE 212** for the answer and a discussion of this case by experts.

CORRECT ANSWER: [A] Definitive chemoradiotherapy and [D] induction chemotherapy and then, according to response, consider chemoradiotherapy vs surgery.

Continued from page 211

out distant metastases; the complete blood count and blood chemistry were normal. The patient was given a diagnosis of a stage IVB (T3N3M0) hypopharynx SCC.

The case was discussed in a multidisciplinary board. Considering the characteristics of the patient and the disease, both a total laryngectomy with neck dissection and a larynx preservation (LP) strategy were proposed. The options were discussed with the patient, who refused to have the surgical treatment.

Discussion

Head and neck squamous cell carcinoma (HNSCC) represented 705,781 of new cancer cases and caused 358,144 deaths worldwide in 2018.¹ HNSCC varies in incidence according to anatomical site.¹ Stage distribution also varies among anatomical sites^{2,3} and by geographical location, with some countries describing an incidence of locally advanced (LA) disease in up to 70% of their HNSCC patients.⁴ Depending on the site of the primary tumor, recurrence rates in LA disease are between 25% and 50%.⁵

Hypopharynx SCC is a rare disease that accounts for 3% to 5% of all HNSCC. Consequently, treatment decisions are frequently based on data from other sites (ie, larynx). Most of these patients will receive a diagnosis of LA disease and have a poor prognosis.⁶

Patients with SCC of the larynx and/or hypopharynx can be treated with combinations of chemotherapy and radiotherapy (RT) instead of surgery, in cases when the tumor is resectable but resection would involve losing a crucial organ or function. The definition of LP has changed over time. The first trials evaluating this procedure focused on preserving “the larynx in place.” With time, function preservation was also considered, including the avoidance of such

procedures as long-term tracheotomy or feeding-tube placement.⁷

Chemoradiotherapy for Resectable LA SCC of Larynx and Hypopharynx

Definitive chemoradiotherapy (CRT) is considered a standard treatment for LA HNSCC. In the Chemotherapy in Head and Neck Cancer meta-analysis, concurrent treatment with RT and chemotherapy was shown to be the most effective treatment option, compared with induction chemotherapy (IC)-RT or RT alone, with a decrease in the risk of death of 19% and an absolute benefit in overall survival (OS) of 6.5% at 5 years,⁸ which persisted when analyzed by tumor site.⁹

In terms of LP, the RTOG 91-11 trial randomized patients with stage III and IV (low-volume T4 tumors) SCC of the larynx to receive IC-RT, CRT, or RT alone. Only patients with a complete response (CR) or partial response (PR) after 3 cycles of IC were treated with RT. The control arm was the IC-RT arm.¹⁰ After a 10-year follow-up, there was no difference between the IC-RT and CRT arms in terms of laryngectomy-free survival (HR, 1.05; 95% CI, 0.83-1.34; $P = .68$). The rates of laryngeal preservation, local control (LC), and locoregional control (LRC) were superior for the CRT arm compared with the IC-RT arm, and they were not different when comparing the IC-RT and the RT-alone arms. There were no differences in distant disease control, disease-free survival (DFS), or OS between IC-RT and CRT, although a tendency for better survival in the IC-RT arm compared with the CRT arm was observed (HR, 1.25; 95% CI, 0.98-1.61; $P = .08$). In terms of impaired speech and swallowing dysfunction, rates remained similar between the groups.¹¹

To our knowledge, the only random-

ized phase 3 study that has compared CRT with IC in SCC of the hypopharynx was conducted by Prades et al¹²; it compared CRT with cisplatin to IC with cisplatin plus 5-fluorouracil (PF) followed by conventional RT in patients with stage T3 disease with a fixed hemilarynx. The rates of LP at 2 years were 67.5% for IC and 92.0% for CRT ($P = .016$). There was no difference between the arms in terms of DFS or OS.

It must be taken into account that associated toxicity is always greater when chemotherapy is given concurrently with RT than when RT alone is given. Nevertheless, with modern radiotherapy techniques, acute G4 mucositis occurs in less than 5% of the patients; chronic G3 toxicity in the esophagus and mucosa, and xerostomia, each occur in about 4%.¹³

A caveat of these studies is that, until the 2000s, they all utilized outdated RT techniques, with heterogeneous fractionation. Modern RT techniques have demonstrated an impact on LC rates in treating nasopharynx and oropharynx SCC,^{13,14} as well as an impact on tolerance; furthermore, reduced long-term complications associated with modern RT techniques could be associated with decreased rates of nononcological deaths, which were seen in patients treated with older RT techniques.¹⁵ The use of modern techniques could lead to better survival with CRT than with IC-RT, but no prospective data are yet available.

Induction Chemotherapy for Resectable LA HNSCC of the Larynx and Hypopharynx

Clinical guidelines recommend surgery or CRT (for LP purposes) as treatment options for resectable disease; nevertheless, most of the guidelines do not consider IC as a standard treatment.¹⁶⁻¹⁸

Several studies have explored the use of IC for LP purposes, all evaluating response after a certain number of IC cycles. A PR, defined as reduction of the primary tumor by at least 50%, was considered as a cutpoint to decide whether

Figure 1B. Post induction chemotherapy (IC) contrast enhanced CT scan shows a partial response of the tumor located in the hypopharynx (left). Decrease in size of the right matted lymph nodes and the left lymph nodes (right).

a patient could receive RT or should be treated with surgery.

The first randomized trial that evaluated IC for LP was the Department of Veterans Affairs Laryngeal Cancer study.¹⁹ Patients with resectable stage III/IV SCC of the larynx were randomized to total laryngectomy or to PF IC; after 2 cycles of IC, patients with a PR were treated with 1 more cycle of IC followed by RT. Of the patients in the PF IC arm, 85% achieved a PR and were treated with RT. The larynx was preserved in 64% of patients treated with IC. Stage IV disease and T4 were both associated with greater odds of a total laryngectomy after IC-RT. There was no difference between the arms in terms of OS or DFS. Patterns of recurrence differed between the groups: Patients receiving IC-RT had significantly more local recurrences than those in the surgery arm (12% vs 2%; $P = .001$) but fewer distant recurrences (17% vs 12%, respectively; $P = .001$).

The European Organisation for Research and Treatment of Cancer conducted a similar trial in patients with hypopharyngeal SCC. This trial randomized patients with T1-T4, N0-N2b, and operable N3 disease to receive IC with PF followed by RT or surgery. Re-

sponse rates were evaluated after each cycle of IC. Only patients who achieved a CR after 2 or 3 cycles of IC were treated with RT; this condition was met by 61% of patients and they received RT.²⁰ In a 10-year follow-up, there were no differences in first progression, locoregional failures, or distant metastases between the RT and surgery arms. The 5- and 10-year disease-specific survival rates with preserved larynx for the IC arm were 40.5% and 26.97%, respectively. Noninferiority of OS (2.1 years for surgery vs 3.7 years for IC; HR, 0.88; $P = .002$) was achieved.²¹

The addition of a taxane to the IC regimen (TPF) was analyzed in the GORTEC 2000-01 trial. Patients with resectable LA larynx and hypopharynx patients with stage III or IV disease were randomly assigned to receive TPF or PF, followed by RT in those patients with a CR or a PR and recovery of normal cordal mobility. Rates of PR and CR were higher in the TPF arm. Subsequently, 76.4% and 61.2% of patients in the TPF and PF arms, respectively, received RT. The 3-year LP, the primary end point, was 70.3% for the TPF arm and 57.5% for the PF regimen ($P = .03$) and was pre-

served long-term.²² The 10-year larynx dysfunction-free survival rates (death, local relapse, total or partial laryngectomy, tracheotomy at 2 years or later, or feeding tube at 2 years or later) were 63.7% (95% CI, 0.52-0.74) and 37.2% (95% CI, 0.24-0.52; $P = .001$), in the TPF and PF arms, respectively. No differences in OS, DFS, or LRC rates were detected between the arms. These results were confirmed with a meta-analysis, which described a survival benefit for the TPF regimen over PF.²³

With these data, we conclude that IC-RT can be an option as a LP strategy for resectable LA HNSCC in the larynx and/or hypopharynx, increasing the rate of LP and function, without negatively affecting OS, DFS or LRC. Achieving a PR with IC seems to be a predictor of response to RT. The regimen of choice for the IC-RT strategy is TPF.

Nevertheless, several questions remain: Is IC-RT better than or equal to CRT alone? Which is the best strategy for patients with a good response after IC: RT alone or CRT? If so, what is the best drug to combine with RT in CRT: cisplatin, carboplatin, or cetuximab?

Our patient began induction chemotherapy based on the TPF regimen. He received 2 cycles and experienced grade 2 toxicities that did not require treatment delays. A subsequent CT scan indicated decreases of the primary tumor and the cervical matted nodes, equivalent to a PR with a greater than 50% reduction in tumor size (**Figure 1b**).

The patient was reevaluated in the tumor board, and it was decided to continue treatment with CRT as definitive therapy. The patient was treated with conventional fractionation, sequential, intensity modulated RT, 70 Gy (46 Gy/23 fractions + 24 Gy/12 fractions) for 7 weeks. Concurrent chemotherapy consisted of 3 cycles of high-dose cisplatin (100 mg/m²) every 3 weeks. The patient developed G2 dysphonia, dysgeusia, xerostomia, nausea, and radioepithelitis, as well as grade 1 mucositis and dysphagia.

Figure 1C. Post chemoradiotherapy (CRT) contrast enhanced CT scan shows postradiotherapy changes in the hypopharynx, no evidence of the primary tumor (left). Right cervical matted nodes (right).

IC Followed by CRT in Resectable HNSCC of the Larynx and Hypopharynx

Little prospective evidence exists for this treatment approach. In fact, to our knowledge, no prospective randomized phase 3 trials directly compare IC-CRT with CRT for LP.

The TREMPIN trial is a phase 2 randomized trial that compared CRT vs bionradiotherapy with cetuximab, after 3 cycles of IC with TPF, in patients with resectable LA SCC of the larynx. A total of 76% of patients completed 3 cycles of TPF; 24% dropped out after IC, mostly due to toxicity. Of the patients randomized to the CRT arm, 84% received at least 2 cycles of cisplatin, and 71% of those in the cetuximab arm completed 7 doses. There was no difference in G3/4 toxicity between cisplatin and cetuximab in respect to mucositis; skin reactions were more frequent with cetuximab. Patients in the cisplatin arm required more dose modifications due to acute toxicities. Local failures were less frequent with cisplatin (8.3% vs 14.3%). Because of the number of dropouts, the primary end

point of LP at 3 months was not evaluable. The analysis did not show a difference between the 2 arms, and the LP rate at 3 months was very similar to that of patients treated with IC-RT alone in the GORTEC 2000-01 trial (LP for CRT, 95%; 95% CI, 86%-98%; LP for RT-cetuximab, 93%; 95% CI, 83%-97%).²⁴

Other studies have focused on using 1 cycle of IC to identify patients who would be good candidates for CRT. A prospective 1-arm trial evaluated this strategy in patients with resectable SCC of the larynx. After 1 cycle of PE, 75% of patients achieved greater than 50% response, and 70% achieved LP after cisplatin-based CRT.²⁵ In a cohort at the University of Michigan, patients who were treated with IC for 1 cycle followed by CRT had better disease-specific survival compared with those treated with CRT alone (HR, 0.48; 95% CI, 0.29-0.80).²⁶ These studies suggest that just 1 cycle of IC may be enough to select patients for CRT, compared with 3 cycles, and the strategy may improve tolerance and adherence to treatment.

Ten weeks after the patient finished CRT, a CT scan reported persistence of cervical adenopathies and CR of the primary tumor (**Figure 1c**). A laryngoscopy described edema of the lateral walls of the hypopharynx, base of the tongue, and uvula, without evidence of tumor. The pathological findings revealed unspecific chronic inflammatory changes.

Due to the persistence of lymph node disease with a complete primary response and without evidence of metastatic disease, a bilateral selective neck dissection, levels II to IV, was performed. The pathology findings were metastatic SCC in 3 of 12 dissected right lymph nodes and in 4 of 13 left lymph nodes.

Planned or Complementary Surgery on the Neck

When a PR, versus a CR, is reached after a nonsurgical CRT approach in LA HN-SCC, surgery undoubtedly improves locoregional control; in fact, most patients in studies of IC-RT who had a PR experienced a resection of persistent disease. But even with a CR, which includes negative imaging studies, planned neck dissections have been used to optimize control. In both circumstances, planned or complementary surgery improves locoregional control, prolongs OS, and possibly cures the patient.²⁷ The specific evidence for hypopharynx SCC is limited.

N2 and N3 disease are now often treated with initial chemotherapy and RT, but planned or complementary neck dissection is used when the original lymphadenopathy was greater than 3 cm, and the primary lymph node disease has been controlled.²⁸ Lending support to this strategy is the fact that patients with N2/N3 involvement at diagnosis who reach a CR after a CRT approach show residual tumor in up to 22% of surgical specimens.²⁹

Two large retrospective trials evaluated the benefit of a modified radical node dissection in documented CR patients treated with chemotherapy and RT. Compared with observation, this procedure has demonstrated a benefit in

LC, LRC, metastasis-free survival, and OS for N2/N3 patients.^{30,31}

The introduction of 18-FDG-PET-CT has changed the method of evaluating CR in patients with LA HNSCC who have been treated with CRT. Compared with CT scan or MRI, PET scan has been found to be superior for neck evaluation in patients with HNSCC; it has a negative predictive value (NPV) of 97.7% at 5 years.^{32,33} In patients who have oropharynx SCC positive for human papillomavirus (HPV) with bulky lymphadenopathy and are undergoing CRT, observation is appropriate if CR is confirmed with a post-treatment evaluation of the neck with ultrasonography and PET scan because this combination brings the highest NPV.^{34,35} Nevertheless, the surveillance for patients evaluated with this technique may not be cost-effective³⁶ and is recommended only in HPV-positive oropharynx SCC.

After surgery, the patient presented with neck stiffness, which remitted with rehabilitation exercises. He continued with surveillance visits. He continued to experience long-term grade 1 xerostomia and also developed hypothyroidism, for which he received hormonal substitution. Importantly, no swallowing or voice alterations persisted, and to date, after 5 years of follow-up, he has no clinical or radiological signs of tumor activity.

The most important steps in choosing an LP strategy involve being as sure as possible that the treatment is right for the particular patient. The decision should be weighed by a multidisciplinary team, and numerous factors must be taken into account. First, the characteristics of the

tumor should be evaluated. Patients with stage III/IV resectable disease and, ideally, with a functional larynx, should be considered. Physicians must also consider the patient's baseline characteristics. The TALK score (which considers tumor size, performance status, alcohol intake status, and baseline blood albumin) can be a good tool for discriminating whether a patient might or might not tolerate CRT.³⁷ Another very important factor is the patient's preference: All therapeutic options should be discussed with the patient before treatment, and they must have an active role in the decision.

In terms of the type of LP treatment to be offered, CRT is considered the current standard of care because it has shown better LP, LC, and LRC compared with IC-RT. While no difference in OS has been shown in any individual clinical trial, a large meta-analysis has indicated that CRT has an advantage in OS over IC-RT in patients with LA HNSCC. There is no standard drug to combine with RT in CRT; in our center, high-dose cisplatin is preferred.

The main advantage of IC-RT is that it can help distinguish patients who will benefit from RT from those who will need surgery. It also avoids the added toxicity generated by CRT. Response to treatment must be evaluated early, preferably after 2 cycles of IC, to define the subsequent treatment. TPF regimen is preferred over PF.

In our patient, an approach incorporating IC followed by CRT was chosen. IC followed by CRT seems to increase toxicity, and it has been difficult to prove its advantage in terms of LP, LRC, DFS, or OS. Although our patient has experienced

Key Points

- LP strategies should be considered only in patients with resectable stage III/IV larynx and hypopharynx SCC, ideally those who have a functional larynx.
- The choice of treatment must be discussed by a multidisciplinary team, and the patient must have an active role in making the decision.
- CRT and IC-RT are both approved larynx-preservation approaches.
- IC-RT has demonstrated high rates of LP without decreasing DFS or OS, compared with surgery.
- CRT has demonstrated better LP rates, as well as local control and LRC, compared with IC-RT, and it should be considered a standard of care.

excellent long-term control of disease, this strategy should be used only in the setting of a clinical trial. Since the publication of the results of the TREMPIN trial, our standard of care for LP has become CRT with high-dose cisplatin.■

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➤ For full reference list, visit cancernetwork.com/headandneck_CQ

Altamirano-García staff physician
Radiation Oncologist; Department of Radiation Oncology,
Head & Neck Cancer; Instituto Nacional de Cancerología,
Mexico City, México

Sobrevilla-Moreno Staff Physician; Medical
Oncologist; Department of Medical Oncology, Head & Neck
Cancer; Instituto Nacional de Cancerología

Granados-García Head of the Head & Neck
Surgical Department; Surgical Oncologist; Department
of Surgical Oncology, Head & Neck Cancer; Instituto
Nacional de Cancerología

Garcilazo-Reyes Medical Oncology Fellow;
Department of Medical Oncology; Instituto Nacional de
Cancerología

Strategies for Overcoming Disparities for Patients With Hematologic Malignancies and for Improving Enrollment on Clinical Trials

Stephanie Williams, MD; Amy A. Ayers, MPH; Michelle A. T. Hildebrandt, PhD; Lorna H. McNeill, PhD; and Christopher R. Flowers, MD

Background

A multitude of factors contribute to cancer disparities, including, but not limited to, differences in diet, lifestyle, environmental exposures, cultural beliefs, genetic and biological factors related to ancestry, socioeconomic status (SES), and access to health care. More investigation is needed in evaluating these factors in less common cancers and hematological malignancies. Addressing disparities in cancer incidence, prevalence, burden of disease, mortality, and survivorship that have been documented among racial/ethnic minority populations with blood cancers will require multilevel models of the interactions between relevant factors and performance of translational research that uses knowledge of cancer biology to develop and test the feasibility of interventions that can impact human end points. Such work must address a wide range of research areas, including prevention, early detection, diagnosis, treatment, epidemiology, cancer control, treatment, and survivorship. To be effective, efforts should be made to advance these research findings to applications that can transform clinical practice and

health care delivery. We reviewed the literature to define a framework for overcoming disparities for patients with hematologic malignancies and to improve patient enrollment on clinical trials.

A Patient Example

A 47-year-old African man moved from Kenya to the United States to find work, having to leave his family behind. In the months after moving, he developed progressive fatigue, general malaise, and right upper quadrant abdominal pain that prompted a visit to the county hospital's emergency department. His work-up revealed an initial CD4 count of 6 and an HIV viral load nearing 1 million copies, while his CT scan showed more than 20 subcentimeter lesions within the liver. Unfortunately, because of lack of insurance, it took approximately 1 month to establish an interventional radiology appointment, and yet another month to finally biopsy one of the liver lesions. The results of the biopsy revealed diffuse large B-cell lymphoma (DLBCL), germinal center B-cell–like type without BCL-2, BCL-6, or MYC rearrangements. He was started on treatment 2 weeks after

the diagnosis. Given that his lymphoma was related to underlying HIV, he was given aggressive chemotherapy in the form of dose-adjusted rituximab (Rituxan), etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin.¹ This treatment typically involves inpatient admission every 3 weeks, but given limited hospital bed availability in the chemotherapy unit and difficulty with patient transportation to his scheduled appointments, there were multiple delays and reduced adherence to this timeline. Despite displaying both clinical and radiological evidence of improvement, the patient inexplicably stopped coming to his lab and clinic appointments. By the time cycle 4 was due of his planned 6 cycles, he was no longer reachable via telephone or letter. The reason for his decision to stop treatment remains unclear.

This patient's situation highlights multiple disparities in health care delivery and cancer care that exist within a resource-limited setting. First, we see that patients without insurance often experience a delay in diagnosis. The delay in biopsy led to significant anxiety and frustration for the patient, even before

starting treatment. Next, we see how the lack of beds in the chemotherapy ward of an underresourced hospital negatively impacted timely administration of chemotherapy. Coupled with the lack of social support, financial constraints, and the emotional burden of his underlying malignancy in a system with limited resources, the timeliness of delivering potentially curative therapy and the outcome for this patient were challenged. His opportunities to participate in observational studies and therapeutic clinical trials were also limited.

Disparities in Hematologic Malignancies

The National Cancer Institute (NCI) defines cancer disparities as differences in cancer measures (including incidence, prevalence, number of cancer cases, cancer-related deaths, and cancer-associated health complications) across population groups. Observed differences in cancer outcomes are often described in medically underserved populations, including racial and ethnic minorities and individuals with lower SES and lower health literacy.² The Minority Health and Health Disparities Research and Education Act declared that a population experiences a health disparity “if there is a significant disparity in the overall rate of disease incidence, prevalence, morbidity, mortality, or survival rates in the population as compared with the health status of the general population.”³ Our review will focus on defining, summarizing, and suggesting strategies to overcome these disparities in patients with hematologic malignancies, with a specific focus on clinical research.

According to the American Cancer Society (ACS), there will be an estimated 1,806,590 newly diagnosed cancer cases and an estimated 606,520 cancer deaths in the United States in 2020. Of these new cancer diagnoses, approximately 178,522 will be in patients with hematologic malignancies, including lymphoma (~85,270 new cases; 20,910

deaths), multiple myeloma (~32,270 new cases; 12,830 deaths), and all forms of leukemia (~60,530 new cases; 23,000 deaths).⁴ Despite these numbers, data regarding racial differences in patients with hematologic malignancies are more limited than in those with solid tumors. To address this, Kirtane et al⁵ published a review examining the racial and ethnic disparities in incidence, survival, and outcomes across patients with various hematologic malignancies, as described below.

An analysis of 39,000 patients in the Surveillance, Epidemiology, and End Results (SEER) database from 1999 to 2008 showed that black and Hispanic patients with acute myeloid leukemia (AML) had increased risk of death by 12% and 6%, respectively, compared with non-Hispanic whites. This observation occurred despite the higher prevalence of favorable cytogenetics and younger age at diagnosis among the minority groups.⁶ Another analysis of the SEER database for patients with multiple myeloma revealed that novel myeloma therapies disproportionately benefited white patients of higher SES.⁷ After the introduction of these novel therapies, white patients had double the observed survival improvements compared with black patients. For example, controlling for sociodemographic factors, black patients with multiple myeloma in the United States were 21% less likely to be treated with bortezomib, an effective agent used during that treatment era.⁸

Disparities in incidence, age at diagnosis, and survival rates have also been identified for Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) subtypes.^{5,9-13} In one study, patients with HL in the lowest SES category had a 64% increased risk of death related to HL compared with those in the highest SES category.¹⁴ Among adolescent and young-adult patients with NHL, blacks and Asian/Pacific Islanders were more likely to be given a diagnosis at a later stage than other groups.¹⁵ For patients

with DLBCL diagnosed between 1992 and 2005, racial differences in survival varied according to stage.¹⁶ For stage I disease, non-Hispanic whites had the best 5-year survival rate (67%), whereas blacks had the worst (60%). Asian/Pacific Islanders had the worst survival rate for stage IV disease (35%), and non-Hispanic whites had the best survival rate (41%). In other studies, black patients received a diagnosis at a mean age more than 10 years younger than whites, and they more commonly had advanced-stage disease.¹⁷ Furthermore, these patients were less likely to be insured, less commonly received standard-of-care therapy, and experienced worse overall survival (OS).¹⁵⁻¹⁷

Across leukemias, multiple myeloma, and lymphomas, there are also racial disparities seen in hematopoietic cell transplantation (HCT). Given that HCT requires numerous resources to be both safe and effective, HCT can be associated with disparities in access and outcomes for minority populations. Analysis of the California Cancer Registry found that black and Hispanic patients with AML had a decreased likelihood of stem cell transplantation compared with white patients (odds ratio [OR], 0.64; 95% CI, 0.46-0.87; vs OR, 0.74; 95% CI, 0.62-0.89, respectively).^{9,18} SEER-Medicare data revealed that age-adjusted relative rates of autologous HCT for patients with myeloma were significantly higher in non-Hispanic whites than in blacks, Hispanics, and Asians.^{10,19} In another myeloma study, black patients were found to be 49% less likely to receive stem cell transplantation than white patients.¹¹

Ancestry and Disparities

With the established differences in incidence, clinical features, and outcomes by race for many hematologic malignancies, there is increased interest in understanding the role of genetic factors and genetic ancestry in influencing differences among populations. Genome-wide association studies (GWAS) have identified

common germline genetic variations associated with susceptibility to lymphomas, leukemias, and multiple myeloma, primarily in populations of European descent.¹²⁻³⁸ GWAS studies in other population groups are slowly emerging and are enabling investigation into shared and unique genetic risk factors. For example, analysis of GWAS data from African Americans identified stronger loci for several of the established susceptibility regions for multiple myeloma, while failing to replicate several of the other regions identified in populations of European descent.^{35,39} Similarly, studies of DLBCL susceptibility loci in Asian populations have found shared and race-specific associations.³⁶⁻⁴¹ However, larger genetic studies are needed in more diverse populations to continue to identify the genetic basis of disparities. Currently, there is a lack of genome-wide genetic studies in Hispanics for adult hematologic malignancies, leaving a gap in our understanding of this rapidly growing patient population.

A small number of analyses based on genetic ancestry of patients, instead of self-reported ancestry, have been conducted to better define the role of genetics and disparities. In an analysis of survival following allogeneic stem cell transplant, increased African ancestry in the recipient increased risk of overall mortality by more than 2-fold (HR, 2.26; 95% CI, 1.28-3.96) and increased by 3.3-fold (HR, 3.09; 95% CI, 1.7-5.64) for increased levels of African ancestry in the donor. These increased risks were independent of clinical variables, and most striking, independent of self-reported race/ethnicity.^{38,42} Multiple myeloma is the most frequent hematologic malignancy diagnosed in blacks. In genetic ancestry analyses, specific subtypes—(11;14), t(14;16), and t(14;20)—were more frequent in individuals with higher degrees of African ancestry, while other cytogenetic abnormalities, such as trisomies and monosomy 13/13q deletion, were less prevalent.^{39,43} For

DLBCL, analysis has shown that recurrent somatic mutations in known driver genes (*ATM*, *MGA*, *SETD2*, *TET2*, *DNMT3A*, and *MLL3*) were more common in patients with African ancestry, and that the spectrum of mutations differed from that in patients of European ancestry.⁴⁰ Together, these studies provide evidence that many of the observed disparities in incidence, clinical features, and outcomes among hematologic malignancies may have a genetic underpinning. Future research in this area will be necessary to fully elucidate these relationships.

Disparities by Insurance Status

Understanding how genetic factors influence cancer outcomes among different patient populations is one basis for health disparities research. Other key components for evaluation include residence, education level, SES, and insurance status. The National Cancer Database (NCDB) is a national oncology database across more than 1500 facilities accredited by the Commission on Cancer that includes information on more than 70% of newly diagnosed cancer cases. This database helps record patient-specific factors important in disparities research. Studies utilizing the NCDB have shown that patients without insurance commonly experience a delay from symptom onset to diagnosis.⁴¹ This delay affects the nearly 27.5 million Americans (8.5%) who were uninsured as of 2018. While the Affordable Care Act established in January 2014 has significantly improved the percentage of insured Americans, Hispanics and blacks continue to be the most likely to be uninsured (18% and 10%, respectively); for non-Hispanic whites, the rate is 5%.⁴ Without insurance, minority patients often lack access to optimal health care, leading to delayed diagnosis, delayed treatment initiation, and disparities in OS.

In 2014, the ACS published a study linking lack of insurance with inferior survival rate among patients with DLBCL. Using the NCDB, authors analyzed ap-

proximately 4000 patients with DLBCL in 2004, categorized into those with private insurance, Medicaid, or no insurance. Of note, many of the patients involved in this study enrolled in Medicaid after their diagnosis of DLBCL. Approximately 80% of the full cohort had private insurance (higher than the general insurance rate among Americans at that time), 10% were uninsured, and 10% had Medicaid insurance. The uninsured and Medicaid patients were, on average, younger, more likely to be members of a racial/ethnic minority, receive a diagnosis at an advanced stage, and less likely to receive standard-of-care chemoimmunotherapy. After controlling for sociodemographic factors but not adjusting for prognostic factors or specific treatment, this study found that uninsured patients and Medicaid-insured patients with DLBCL had a lower survival rate compared with those with private insurance (HR, 1.39, vs HR, 1.48, respectively). The OS rates at 5 years' follow-up for privately insured, Medicaid-insured, and uninsured patients were 75%, 64%, and 66%, respectively. The authors postulated that uninsured patients had inferior OS rates because of more advanced-stage disease at diagnosis, less use of standard-of-care chemoimmunotherapy, and scarce enrollment on clinical trials.⁴¹ The association between insurance status and OS in other lymphoma subtypes has been studied as well. Utilizing the NCDB for patients with follicular lymphoma (FL) and Burkitt lymphoma, those without insurance or with Medicare or Medicaid had significantly worse OS rates when compared with patients with private insurance.^{42,43} Even worse, a large national cohort study published in 2012 showed that uninsured patients with DLBCL were less likely to receive any treatment at all.⁴⁴

Disparities in Rural and Lower-SES Patients

Authors of past studies have argued that patients' zip codes may supersede their genetic codes when it comes to access to

quality health care.⁴⁵ To test this concept as it relates to lymphoma outcomes, Ritter et al investigated the influence of a patient's residence and household income on OS. Using the NCB, the authors examined 83,000 patients with DLBCL and 43,000 patients with FL based on geographic population density (rural, urban, or metropolitan). Rural was defined as a county with a population less than 2500; urban, a county with a population of at least 2500 that does not meet criteria for a metropolitan area based on the United States Department of Agriculture Office of Management and Budget parameters; and metropolitan, a county with at least 1 densely settled urban area with a population of at least 50,000. In the Ritter study, 1.7% of patients lived in rural areas, 13.1% in urban areas, and 85.2% in metropolitan areas (population percentages that reflect the general population).

When controlling for other patient demographic information, there was a significant decrease in OS for both rural and urban populations compared with metropolitan populations with DLBCL (HR, 1.09, vs HR, 1.08, respectively) and FL (HR, 1.2 vs HR, 1.11). Both urban and rural patients were less likely to have private insurance and were more likely to fall into the low SES class. Furthermore, those with household income less than \$38,000 had an inferior survival rate (HR, 1.22).⁴⁶ The results highlight that although patients from rural populations comprise a significant percentage (approximately 14.9%) of the United States, they may often face more obstacles to ideal health care than their metropolitan area-based counterparts.⁴⁷

Barriers to Minority Enrollment on Clinical Trials

Clinical trials are key components of cancer research and continually enhance treatment options for patients across all tumor types. However, fewer than 5% of adult patients with cancer in the United States are estimated to enroll on

Figure 1. Age-Adjusted Mortality Rates for NHL in African American Patients by County. *Data generated from <https://statecancerprofiles.cancer.gov/> NHL, non-Hodgkin lymphoma.

cancer clinical trials, while about 70% of Americans are willing to participate.^{48,49} In an analysis by the ACS Cancer Action Network and Unger et al, the overall trial participation rates average 15.9% at academic centers and 7% at community centers.⁵⁰ Unfortunately, in both kinds of settings and across most studies, African Americans, Hispanics, and patients older than 65 years were underrepresented on clinical trials, as were patients from urban/rural communities, who had limited access to them.

Many reasons have been proposed for this situation, including both structural (absence of available clinical trials based on tumor type and stage) and clinical (patient eligibility) barriers.⁵⁰ The largest obstacles to enrollment on trial for rural patients seem to be both the physical distance and the lack of communication between large centers and small clinics,

ultimately leading to unfamiliarity with clinical trial opportunities. This indicates a need to examine and address recruitment barriers by catchment area. Two examples of assessing disparities in patients with hematological malignancies for a catchment are described below.

Sample Catchment Area Results on Cancer Disparities for Applying Strategies Locally

While documentation of cancer disparities has mostly occurred at the national level, successful implementation of strategies to overcome disparities are likely to be more successful when they are customized to the local environment. This requires an assessment of disparities in a local cancer catchment area. We provide 2 examples that can be replicated to address disparities that exist for hematological and other cancers.

■ **Figure 2.** Age-Adjusted Mortality Rates for NHL in Hispanic Patients by County.

*Data generated from <https://statecancerprofiles.cancer.gov/>
NHL, non-Hodgkin lymphoma.

Georgia

An estimated 50,000 residents of the state of Georgia receive a new cancer diagnosis annually, and more than 16,000 Georgians succumb to cancer each year; the leading causes of these deaths are lung, breast, colon, and pancreatic cancers. Georgia residents experience disparities in cancer incidence and cancer outcomes for several malignancies as compared with national outcomes. In addition, disparities in outcomes also exist within the state, both among specific ethnic and racial groups, and based on factors related to geography and socioeconomic status. A 2019 Emory University study analyzed all NHL cases diagnosed in Georgia from 2001 to 2015 using the Surveillance, Epidemiology, and End Results (SEER) database, to better classify racial disparities found among patients with NHL in the state.⁵¹ Results indicated that the age-adjusted incidence rate for NHL in

Georgia increased 1.03% per year for all patients.

However, African American patients had a higher annual percent change (APC) in NHL incidence when compared with whites (APC, 1.72 vs 0.84, respectively). This results also revealed racial disparities when analyzing different characteristics of disease presentation within DLBCL and FL subtypes. African American patients with DLBCL or FL received a diagnosis at a younger age and were more likely to present with B symptoms when compared with white patients with DLBCL or FL. Furthermore, African American patients with DLBCL were more likely to present with advanced-stage disease. Not only did African American patients with DLBCL and FL have differing characteristics at baseline, but 5-year relative survival rate was worse in African American patients with DLBCL when compared with white patients with DLBCL (58.8% vs 62.3%,

respectively). This study acknowledged the racial disparities in patients with NHL at the state level in Georgia both in incidence rate and in disease presentation, and in 5-year relative survival within NHL subtypes. This analysis and others have also examined the distributions of new lymphoma diagnoses across the state of Georgia to identify targeted regions for interventions and to characterize rural areas where outreach is needed.

A qualitative study based in rural Georgia gathered information on lymphoma survivors who sought treatment at a university research hospital.⁵² The overall goal of the study was to understand barriers to participation in university hospital-based clinical research among these patients living in rural Georgia. Individual, semistructured telephone interviews identified the main barriers to accessing such research opportunities as being distance to larger clinics, transportation difficulties, and less time with their clinician at university clinics. The use of patient portals to enhance communication between providers and patients was suggested as the potentially most significant contributor to better understanding of research opportunities. These authors also piloted an epidemiological questionnaire based on the findings of the InterLymph DLBCL Subtype Study to examine the behavioral and lifestyle characteristics among 50 African-American and 50 white patients with DLBCL in Georgia using a resource-constrained recruitment protocol that involved a single initial mailing. The questionnaire was composed of 30 items organized into 4 domains: (1) lifestyle and habits, (2) medical history, (3) family history, and (4) demographic background. Response rates differed significantly between African American patients (24%) and white/other race patients (48%) with DLBCL ($P = .013$). Overall, lifestyle, occupation, and medical histories were similar among African Americans and whites who returned the questionnaire. However, 75% of the African American individuals in this study

■ **Figure 3.** Social, Biologic, and Environmental Factors That Contribute to Disparities in Lymphoma Survival
CBC, complete blood count; LDH, lactic acid dehydrogenase; NFKB, nuclear factor kappa-B

were given a diagnosis of DLBCL before age 60 years, compared with 38% of the white population ($P = .024$). Approaches like this, which utilize geospatial analyses of disparities in cancer incidence to inform the sample selection and enrich the study with patients from high-incidence regions, provide examples of future strategies that will enhance efforts to customize strategies to local populations.

Texas

Utilizing data gathered and analyzed from statecancerprofiles.cancer.gov, we generated maps representing the age-adjusted NHL mortality rates per 100,000 in Hispanics and African Americans by county in Texas. The highest rates of mortality for NHL in African American patients were found in Fort Bend and Jefferson counties, with age-adjusted mortality rates of 6.2 (95% CI, 3.9-9.3) and 5.4 (95% CI, 3.4-8.2), respectively (Figure 1). The overall age-adjusted mortality rate is 3.9 (95% CI, 3.6-4.3) in African American patients with NHL for the entire state of Texas. The highest rates of mortality for NHL in Hispanic

patients were found in Travis and Starr counties, with age-adjusted mortality rates of 6.9 (95% CI, 4.9-9.3) and 6.4 (95% CI, 3.7-10.3), respectively (Figure 2). Overall, Texas has an age-adjusted mortality rate of 5.0 (95% CI, 4.8-5.3) for Hispanic patients with NHL. Only 12 of 254 counties for Hispanic patients and 7 counties for African American patients had reported age-adjusted mortality rates. Because of the majority of counties having fewer than 3 average annual NHL deaths, rates for those counties were suppressed to ensure patient confidentiality and rate stability.

In 2016, the Texas Cancer Registry data documented 5172 newly diagnosed cases of lymphoma within the state of Texas: 61% non-Hispanic white, 26% Hispanic, 9% African American, 3% Asian. Women constitute 45% of all patients with lymphoma in Texas. These data can be utilized to identify how institutional populations and clinical trial enrollment compared with local population demographics for a cancer catchment area. Future approaches can assess the factors that mediate these disparities and determine strategies to overcome them: specifically, an increased

focus on clinical trial awareness, education, and care coordination. Identifying these disparities can aid in defining institutional changes that will ultimately result in improved participation across all clinical trials.

Research Strategies to Address Cancer Disparities

Proposed strategies to address cancer disparities involve accurately defining patient factors that increase one's risk of poor outcome. Specifically, many studies do not have standardized definitions or categories of race versus ethnicity. Both the NCI and SEER database have recoded their definition of race to include the following categories: white, black, American Indian/Alaskan Native, Asian, or Pacific Islander. Ethnicity is defined as Hispanic or non-Hispanic, but in many studies, a person is identified as Hispanic without identification of his or her race. Notably, the SEER race codes have changed over the years. Prior to 2005, terms like *all other races*, *unknown*, or *other* were used, which can complicate the way we analyze data.⁵³ Similarly, issues exist with

■ **Figure 4.** *Proposed Framework to Design a Clinical Trial Without Health Disparities*

correctly quantifying SES or identifying those with low health literacy. Once we apply standard definitions of race and ethnicity, as well as of other sociodemographic factors, we can use these measures in cancer registries and research protocols to create better representations of the populations in need. Additionally, once clear definitions are established, we can further clarify etiologies to explain these disparities, including individual, biologic, and operational factors.

The information that was gathered utilizing the strategies above can be shared with stakeholders to inform real-world health policy and to encourage increased funding. These findings constitute possible mechanisms that may account for the racial disparities in DLBCL survival, which will require substantially divergent approaches to overcome. These studies have informed a multilevel model for understanding disparities in outcomes for lymphoma (**Figure 3**), which can be extended to other cancers in our catchment area. However, having a direct impact on the outcomes for the population of patients with hematologic cancers in our catchment area will first require an examination of knowledge gaps and behavioral factors that may influence

outcomes within local communities, and then performance of geospatial analyses that characterize the cancer recurrence risk and mortality across various regions of the state.

Strategies for Improving Minority Enrollment on Clinical Trials

Biological, environmental, and social/institutional factors ultimately lead to cancer care disparities. As **Figure 3** highlights, lymphoma-specific outcomes can be influenced by various institutional factors (eg, population demographics, health care system, economic/legal systems, public health policies), environmental factors (eg, residential exposure), individual factors (eg, age, socioeconomic status, health status, education, race/ethnicity, health literacy), and biological factors (eg, treatment response, genetic ancestry). Understanding that these themes can be applied broadly across hematologic malignancies, we developed a stepwise approach to design a clinical trial ideally without health disparities (**Figure 4**). The first step in addressing cancer disparities involves the establishment of national statistics on disparities, as well as an in-depth review of prior successful interventions.

These data are then analyzed at a local level to assess whether enrollment on trials is proportionate to the number of patients observed in the catchment area. Ongoing awareness of past national disparity levels, along with an active assessment of current enrollees, will lead to a strategy that increases minority enrollment on clinical trials.

There have been other published strategies across US cancer centers that aim to analyze these factors and optimize the recruitment process for minorities in cancer research. For instance, Regnante and colleagues conducted qualitative research in the form of interviews with multiple US cancer centers that are actively involved in increasing accrual rates for racial and ethnic minorities.⁵⁴ From 2016 to 2018, the percentage of minority participation accrued in cancer clinic trials for all 8 cancer centers included in the study ranged from 10% to 40%. The results of this study led to the identification of 5 broad themes to increase participation in clinical trials: commitment from center leadership, investigator training and mentoring, community engagement, patient engagement, and operational practices.

The first theme, the need for commitment from cancer center leaders to

ensure inclusion of minorities in clinical research, involves a primary emphasis on identifying any discrepancy within one's institution and using that information to engage with providers. Efforts must be made to establish a diverse faculty, create broad outreach programs for both staff and patients, and form an active presence in the community to create an informed population. Next, an investment must be made in educating the workforce, including trainees, ancillary staff, and physicians, with the goal of cultural competency across the system and a better understanding of the issues that need to be addressed. Once hospital staff are informed, the focus can shift to engagement and education of the community. This entails forming partnerships with community clinics to create a system for inclusion of all potentially appropriate patients in clinical research. Patient-specific information must be adapted and tailored toward the needs of the community in a manner that is both culturally and linguistically understandable. All these best practices must work together to remove any potential barriers and create a system that allows for equal access on clinical trials.

While the need to actively recognize these barriers still exists, some strategies are currently in place and others are emerging to address these issues. Historically, many clinical trials have had strict criteria that can inadvertently exclude those minorities or individuals with lower SES. For example, trials may have exclusion criteria of comorbidities (such as diabetes and hypertension) that

are more prevalent in African American patients, or have requirements for reading consents in English, which can exclude patients who are not fluent or face barriers in the translation of medical terminology. However, organizations such as the Communities Working Group are striving to adjust certain aspects of the clinical trial design, including inclusion/exclusion criteria that can ameliorate this issue. Furthermore, the National Institutes of Health (NIH) Revitalization Act of 1993 requires the NIH to establish guidelines for inclusion of women and minorities in clinical research,⁵⁵ with the goal of ensuring that these subgroups are proportionately represented.

Unique strategies to address health disparities have developed amid the climate of coronavirus disease 2019 (COVID-19). The pandemic has created both challenges and innovations in the way health care is delivered universally. More clinics are connecting to patients and colleagues via video conferencing, telephone visits, remote monitoring, and electronic consultations than ever before. According to the American Hospital Association, in 2017, 76% of US hospitals used telehealth in some capacity, typically only as an exception to the traditional in-person patient-physician visit.⁵⁶ However, the use of telehealth has dramatically increased in response to COVID-19.⁵⁷ These systemwide changes are due to the need to preserve health care access when in-person visits are not possible. This concept can be applied to vulnerable populations like the underserved and elderly patients in the post-COVID-19 era who will continue

to have difficulty attending in-person visits. The accelerated implementation of telehealth due to COVID-19 ideally can reduce access barriers to cancer expertise in the future. In turn, this will provide opportunities to increase awareness of clinical trial options, facilitate care in home environments, and enhance appointment adherence for underserved patient populations.

We have aimed in this review to identify a variety of factors that contribute to survival rate among patients with hematologic malignancies, highlighting possible reasons why patients without insurance, those who live in rural/urban communities, and those with lower individual-level SES tend to have inferior survival. Recognition of these factors, however, is only the first step: Institutions and health care leaders must work to educate both their staff and the surrounding communities in a proactive manner to remove these barriers. Using our proposed framework, we hope to disseminate a comprehensive method to address these factors at a local level, with the goal of overcoming disparities nationally and of transforming our cancer health care delivery systems to improve outcomes for all patients. ■

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➤ For full reference list, visit cancernetwork.com/patient_disparities

Ayers

is a clinical research coordinator at the Emory University School of Medicine.

Williams

is a hematology/oncology fellow at The University of Texas MD Anderson Cancer Center.

Hildebrandt

is an associate professor at The University of Texas MD Anderson Cancer Center.

McNeill

is chair of the Department of Health Disparities Research at The University of Texas MD Anderson Cancer Center.

Flowers

is chair of the Department of Lymphoma/Myeloma at The University of Texas MD Anderson Cancer Center.

MEET OUR EXPERT

Meisel is an assistant professor in the Department of Hematology and Medical Oncology at Emory University School of Medicine.

To see the full video with Dr. Meisel, scan the code

Assessing the Impact of TAILORx on Breast Cancer Management

How results from TAILORx validates and informs the care of patients with breast cancer

The landmark TAILORx trial has dramatically changed the way patients with estrogen receptor-positive cancer are treated. Continued analyses from the trial have further stratified clinical risk for a subset of women who are 50 years or younger, based on their OncotypeDX Breast Recurrence Score.

ONCOLOGY® recently sat down with Jane L. Meisel, MD, of Emory University School of Medicine in Atlanta, Georgia, to discuss how these data from the TAILORx trial validate and inform the current and future care of patients with breast cancer.

Q: Can you give us some background on the TAILORx trial?

MEISEL: It helps to talk first about what oncoproteins are. Essentially, it's a genomic test that takes a woman's tumor after it's been removed from her body and analyzes it to look at the levels of expression of different genes. If you have high levels of expression of high-risk genes, genes that portend a poor prognosis or a high risk of recurrence, then your oncoprotein score is higher. And if you have higher levels of expression of low-risk genes, your score will typically come back lower. The score is on a continuum.

The test has been validated for

a long time, and we've known for a long time, as a clinical community, based on large studies, that if you have a very low oncoprotein score—like 10 or below, then you really don't benefit from chemotherapy. If you've got an early-stage, lymph node-negative breast cancer, you can get away with antiestrogen therapy alone and not get chemotherapy and still have a great outcome. Conversely, if you have a high-risk score, typically defined as 26 or higher, then you do benefit from chemotherapy in addition to endocrine therapy.

This has been really helpful. You know that if you have a high-risk score, you need chemo, and if you have a low-risk score, you don't need chemo. However, the vast majority of scores fall in the intermediate-risk category, between 11 and 25. [In these cases,] you have to take into account the patient's preferences, the doctor's estimation of risk, and [many other factors] to make a decision about chemo or no chemo. The TAILORx trial was designed to take a closer look at that intermediate-risk group. It randomized those women to receiving chemo in addition to endocrine therapy, or to receiving just endocrine therapy, and looked at outcomes to try to answer, essentially: Can those women get away without having chemotherapy? Do they all need

chemotherapy? Or can many of them get away without it? Is there perhaps a subset of women who might benefit from more aggressive treatment?

Q: What were the main findings?

MEISEL: This was a landmark trial that has changed our practice [to a substantial degree. The results showed] that the vast majority of women who have risk scores between 11 and 25 did not benefit from chemotherapy. They did just as well when they received antiestrogen therapy alone.

However, the primary results of the trial, when the initial trial was published, showed that a group of women under 50 years who had scores between 16 and 25 may benefit from chemotherapy in addition to endocrine therapy. So, when these data were first presented, and then subsequently when additional analyses were done, a lot of thought was put into [pinpointing] who [exactly] are these women under 50 who might still benefit from some chemotherapy? How do we determine who they are, as best as possible, so that we give the right treatment to the right woman? You don't want to withhold chemotherapy for someone who needs it, and for whom it might make the difference between cure and not

cure. But you also don't want to give chemotherapy to a lot of people who don't need it. I think those challenges, particularly in the current coronavirus [disease 2019] era that takes into consideration other risks, really highlight the need to make these decisions.

Q: Can you discuss the trial's impact some more?

MEISEL: The fact that this study looked at thousands of women prospectively, meaning it randomized large numbers of women to one treatment or another, allows you to really have faith in the integrity of the data. This trial was looking at noninferiority: trying to make sure that the regimen of withholding chemo [and giving] endocrine therapy alone was not inferior to a regimen including chemotherapy. The fact that the results were so unequivocal for this large group of women, especially postmenopausal women over 50 years—that they did not need chemotherapy anymore—has really made a huge difference.

Q: Do you have any specific examples of that impact, patients who were directly affected by the results?

MEISEL: When this trial was presented at the American Society of Clinical Oncology (ASCO) 2018 Annual Meeting, I had a woman in my practice in Atlanta who had an intermediate-risk score—in the low 20s, I think—and she was just over 70 [years] and really did not want to do chemotherapy. Before the TAILORx trial, a score in the low 20s for women, even for a woman of 70 who was in good

shape, would be a situation in which we talked about benefits and said, “Well, you could withhold chemo, but we don't really know yet because we're waiting for the results of this trial.” So, I said to this patient, because I knew we were going to have these answers in a few weeks, “Why don't I call you after ASCO and I'll let you know what these results show?” [She agreed,] and when I called her the day after that presentation and told her, “You don't need chemotherapy,” it was the happiest day of her life.

She [ended up being] the subject of a layperson's piece in the *Atlanta Journal-Constitution*, which my patient loved, but it really was a meaningful moment for her. And there are so many other women like her who [are] now going to make this decision to withhold chemotherapy in very good faith based on data from thousands of patients. And I think we can talk lots and lots about data and hazard ratios and *P* values, but, you know, for each woman who gets to make a treatment decision, and can do so without having to look back, this can mean the world.

Q: How have the results affected treatment decisions when it comes to the patient-physician conversation?

MEISEL: Before TAILORx, we were telling many, many women who had intermediate-risk scores that we were all anxiously awaiting the results of this huge trial, but that until we [had those results], we really had to think about risks and benefits, your preferences, all these things, as we make this decision about whether to give chemo or withhold it. Once we

“The fact that this study looked at thousands of women prospectively, meaning it randomized large numbers of women to one treatment or another, allows you to really have faith in the integrity of the data.”

—Jane L. Meisel, MD

had the study results, though, for many women, particularly those over 50, that decision became a lot more crystal-clear. For women under 50 [with an] oncotype score of 15 or less it also provided a lot of clarity, because those women also do not need chemo. For those women who still remain in a gray zone—women under 50 with scores between 16 and 25—the question wasn't answered unequivocally, but the results did give us a lot of data with which to enhance our conversation.

Q: For women under 50 years, what was the importance of this kind of exploratory analysis?

MEISEL: We know from lots of experiences and lots of studies that, unfortunately, younger women who get breast cancer tend to have more aggressive breast cancers. So this finding in the initial TAILORx trial data that in the overall population [generally, women] with a risk score under 25 don't need chemotherapy, but that a subset under 50 may benefit, underscores the fact that maybe we do not want to be so quick

to withhold chemo from all of these women. A subset of the population may actually get benefit from it. So, we've got to be careful. To look more closely at that subset of almost 3000 women under 50, the authors divided those women with recurrence scores between 16 and 25 into 2 groups: clinically high-risk versus clinically low-risk. They then looked at their Oncotype scores along with that and tried to determine whether [that should] impact the decision making at all. That's something that we were doing in clinic anyway, because as we take into account the recurrence score, we're also looking at other factors: Was their tumor, for instance, 7 mm or 3 cm? Was it grade 3 or grade 1? But, now [we have some codification] by defining clinically high-risk and clinically low-risk. It was found that women with an Oncotype score between 16 and 20 who were clinically high-risk actually did benefit from the addition of chemotherapy. Those with the same score but who were clinically low-risk didn't benefit from the chemo. So that further identified a group of women

under 50 years, with that high intermediate score, who may not need the chemotherapy.

Q: Can you cite another case where the impact of these findings has emerged in clinical practice?

MEISEL: Absolutely. We use these data all the time in practice; they are a wonderful tool to have at our disposal. For example, a patient I had was 45 years old and came to me with a 1.6-cm tumor, grade 2. Her recurrence score was 22, and she really did not want to do chemotherapy—come in for infusions, lose her hair, [none of it]. Her mother had had chemotherapy for a different type of cancer and had had a horrible experience. [On the other hand,] this patient had 2 young children, a job, lots of things she wanted to do in life, and she wanted to reduce

the risk of her breast cancer as much as she could.

So, we talked. I presented a few different options for chemotherapy regimens to her because in the TAILORx trial, the women who received chemotherapy got actually a variety of regimens: About a third received anthracycline, and just more than 50% received docetaxel cyclophosphamide, and there was no difference seen [in outcomes] in terms of the chemotherapies provided. She still was not [happy] about it and asked what other options she had beyond tamoxifen. So, I talked to her about the fact that she was still menstruating regularly, and that we thought that some of the benefit of chemotherapy might be in the form of ovarian suppression.

We discussed probably being able to give her some benefit just by ovarian suppression if she wasn't willing to do the

chemotherapy. I felt ovarian suppression made absolute sense for her, if we were going to withhold the chemotherapy and still be as aggressive as possible. So, she started leuprolide acetate (Lupron) and tamoxifen, and then after 3 months she transitioned from the tamoxifen to an aromatase inhibitor. She's been doing really well with that combination and I think she feels good about the decision she made, being true to herself and her desire to not receive chemotherapy if she did not have to. We were able to do the ovarian suppression and tailor the treatment plan to be as aggressive as she wanted it to be, with data to support it.

Q: From a clinical standpoint, what is one of the most important points physicians can take away from these data?

MEISEL: I think the big plus

is that these data add a lot of clarity for this population. For women who have an early-stage, node-negative, estrogen-positive breast cancer, the data give us a lot of good information about what should we do for these patients in terms of chemotherapy versus no chemotherapy. And as I mentioned in the previous patient case, if people don't want to do chemotherapy, we can do more in terms of antiestrogen therapy to help them. Even for the women who are still in that gray zone, a lot of meat has been added to the substance of that treatment conversation. ■

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Drug Overview: FDA Approvals

Continued from page 202

In part 1a of the trial, 793 participants were randomized to either nivolumab plus low-dose ipilimumab (n = 396) or platinum-doublet chemotherapy (n = 397).

The study results demonstrated an improvement in OS for patients with PD-L1 tumor expression 1% or greater receiving the combination of nivolumab plus ipilimumab compared with those in the chemotherapy arm. Median OS was 17.1 months (95% CI, 15.0-20.1) versus 14.9 months (95% CI, 12.7-16.7) (HR, 0.79; 95% CI, 0.67-0.94; P = .0066).

Median PFS, per blinded independent central review (BICR),

was 5.1 months (95% CI, 4.1-6.3) in the combination arm and 5.6 months (95% CI, 4.6-5.8) in the chemotherapy arm (HR, 0.81; 95% CI, 0.69-0.97). ORRs as assessed by BICR were 36% (95% CI, 31%-41%) and 30% (95% CI, 26%-35%), respectively.

Median duration of response for patients receiving nivolumab plus ipilimumab was 23.2 months, compared with 6.2 months for those receiving chemotherapy.

Fatigue, rash, decreased appetite, musculoskeletal pain, diarrhea/colitis, dyspnea, cough, pruritus, nausea, and hepatitis were the most commonly

observed AEs, with 20% or greater participants reporting these toxicities.

The FDA-recommended dosages for metastatic NSCLC treatment are 3 mg/kg of nivolumab every 2 weeks and 1 mg/kg of ipilimumab every 6 weeks until disease progression or unacceptable toxicity, or up to 2 years in patients without disease progression. ■

FINANCIAL DISCLOSURE: The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

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RADICAL PROSTATECTOMY AS PRIMARY TREATMENT FOR PROSTATE CANCER LEADS TO BETTER SURVIVAL

Wayne Kuznar

Compared with local radiation therapy (RT), radical prostatectomy (RP) as primary treatment for prostate cancer may result in a lower risk of castrate-resistant disease and superior overall survival (OS) from the time of metastasis.

In a retrospective analysis of a nationwide database of men who had received prior RT or surgery for localized prostate cancer, those who received RT were found to have a 32% adjusted higher risk of developing castrate-resistant disease compared with the RP group, reported Mohammed Shahait, MD, in a poster presented at the American Urological Association 2020 virtual meeting.

On multivariable analysis, after developing metastatic disease, mortality was significantly higher among the men who received RT alone versus those who underwent RP ($P = .0013$).

The findings come from an examination of the database derived from the Flatiron Health electronic health record, which includes about 2.5 million patients with cancer.

“Metastatic prostate cancer is a heterogeneous disease. [Patients] include men with de novo metastases upon presentation [and men] who [originally] presented with local disease, underwent a local treatment, and then progressed to metastases,” said Shahait, who was clinical instructor in urology at the University of Pennsylvania in Philadelphia at the time of the study. “Most of the data in the literature mix these patient groups when assessing

outcomes, and we believe that it’s wrong from a biologic point of view. Therefore, to have a more homogeneous cohort, we aimed to study only patients who received local treatment and progressed to metastases.”

The cohort consisted of 664 patients who had received prior RP with or without adjuvant RT ($n = 310$) or RT alone ($n = 354$) for local disease and had progressed to metastatic disease between 2010 and 2018.

At the time of metastasis, the RP group was younger (63.8 ± 7.25 vs 69.3 ± 7.67 years; $P < .0001$), had a lower prostate-specific antigen (PSA) level at prostate cancer diagnosis (7.8 vs 10.9 ng/mL; $P < .0001$), and were more likely to have a Gleason score of 8 or higher (64.5% vs 54.5% ; $P = .0089$). The RP group also had a lower PSA level at the time of metastasis compared with the RT group (6.4 vs 17.2 ng/mL; $P < .0001$). The group treated with RT was more likely to receive androgen deprivation therapy (ADT) before metastasis compared with the RP group (76.0% vs 60.7% ; $P < .0001$).

The association between prior local treatment and progression to castrate-resistant disease and OS was tested, adjusting for age, race, PSA level, Gleason score, castrate-resistant disease, administration of ADT before metastasis, and treatment year.

“As urologists and radiation therapists, we don’t know what happens to all patients after metastasis because most of the

management is led by medical oncologists. The focus here is to see what would happen after metastasis,” said Shahait, who is currently a consultant of urology at King Hussein Cancer Center, Amman, Jordan.

Median follow-up from the date of metastasis was 30.0 months for the RP group and 29.4 months for the RT group. The unadjusted hazard ratio for castrate-resistant disease in the group who received RT was 1.45 ($P < .001$). The association remained significant upon adjusting for patient- and disease-specific parameters (HR, 1.326; $P = .0259$).

On multivariable analysis, men who received RT alone had 77% higher overall mortality after developing metastatic disease ($P = .0013$) compared with men who underwent RP.

Notwithstanding the inherent selection bias at the time of choosing the type of local treatment because of unmeasured confounding variables, the results add to a growing body of evidence that supports the benefit of extirpation of the primary disease on OS after developing metastatic disease, the investigators concluded in their poster.

One theory for the finding is that early use of ADT as well as RT may potentiate epithelial-mesenchymal transition, which mediates tumor invasion, metastasis, and the development of castrate resistance, leading to worse outcomes, said Shahait. ■

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CONTINUING MEDICAL EDUCATION (CME)

Overcoming T Cell Exhaustion as a Resistance Mechanism in Immuno-Oncology

FACULTY

Jason J. Luke, MD

Director of the Cancer Immunotherapeutics Center
Associate Professor of Medicine
UPMC Hillman Cancer Center and
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

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LEARNING OBJECTIVES

Upon successful completion of this activity, you should be better prepared to:

- Explain differences between mechanisms of immune activation and suppression in cancer.
- Describe the mechanisms by which T cell exhaustion arises in patients with cancer.
- Assess different immunotherapeutic strategies to overcome T cell exhaustion.
- Evaluate novel and investigational approaches for treating cancer with T cell exhaustion

RELEASE DATE: June 1, 2020

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Introduction

Molecular and Cellular Mechanisms of T Cell Exhaustion

T cell exhaustion is a type of T cell dysfunction caused by chronic antigen exposure. Initially elucidated in murine models of chronic viral infection, T cell exhaustion can also occur in cancer and affect tumor response to certain therapies.^{1,2} Exhausted T cells undergo progressive and hierarchical loss of effector functions and primarily have a decreased ability to produce cytokines and increased expression of inhibitory receptors.^{1,3} Upregulated inhibitory receptors then downregulate effector functions upon binding to inhibitory ligands or soluble factors in the tumor microenvironment (TME).²

Acute and intermittent antigen exposure allows T cells to fully differentiate into memory T cells, but persistent antigen exposure can prevent recovery to normal memory differentiation.³ The overexpression of immune checkpoints and inhibitory molecules is characteristic of T cell exhaustion.^{3,4} These overexpressed molecules include programmed cell death protein 1 (PD-1), lymphocyte-activation gene 3 (LAG-3), CD160, cytotoxic T lymphocyte antigen 4 (CTLA-4), T cell immunoglobulin domain and mucin domain-containing protein 3 (TIM-3), and T cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT). Typically, the higher the number of co-expressed inhibitory receptors, the greater the level of exhaustion.³

Loss of effector function via

upregulation of inhibitory receptors during T cell exhaustion is typically progressive, with the ability to produce some cytokines usually lost prior to others. Loss of production of interleukin (IL)-2 often occurs earlier in the process, whereas an inability to produce interferon (IFN)- γ is characteristic of severe, potentially irrevocable exhaustion.⁴ These results imply T cell exhaustion is a distinct lineage fate for T cells.

Transcriptional analyses of T cell exhaustion have yielded additional insights into the molecular mechanisms of this state. Results from genomic studies provide additional support for the role of inhibitory receptors in T cell exhaustion and further indicate changes in the T cell receptor pathway, cytokine signaling, metabolic pathways, regulation of migratory abilities, and chemokine expression.^{4,5} Furthermore, transcriptional changes associated with T cell exhaustion involve alterations in the expression patterns of several transcription factors, including Forkhead box protein O1 (Foxo1) and PR domain zinc finger protein 1 (Blimp-1).⁶

An immunosuppressive TME is another factor modulating T cell exhaustion.⁵ One contributor to the progression of T cell exhaustion in the TME is myeloid-derived suppressor cells (MDSCs). MDSCs are M2-like pathologically activated immature myeloid cells that suppress normal T cell function and growth and promote T cell exhaustion through the release of several compounds.⁵ Tumor-associated macrophages and soluble me-

diators, such as Transforming growth factor beta (TGF- β) and IL-10, can also contribute to an immunosuppressive TME and to the development of T cell exhaustion.⁵ Exposure to inflammatory cytokines increases PD-L1 in the TME, which in turn binds to PD-1. Similarly, TIGIT's ligands, CD155 and CD112, are almost continuously expressed in the TME.⁶ Overall, the TME can promote inhibitory receptor-mediated modulation of T cells, which promote T cell exhaustion.

Overcoming T Cell Exhaustion

Targeting pathways overexpressed in T cell exhaustion can revive immune responses and reverse the exhausted phenotype. Checkpoint inhibitors block either an inhibitory receptor or its ligand with an antibody. Drugs that accomplish this target PD-1 (eg, nivolumab, pembrolizumab), PD-L1 (eg, atezolizumab), and CTLA-4 (eg, ipilimumab).^{2,3} Additionally, understanding co-expression patterns of inhibitory receptors offers potential opportunity to administer a simultaneous blockade to elicit a synergistic reversal of T cell exhaustion.³ Checkpoint inhibitors are FDA-approved for the treatment of numerous solid tumors and hematologic malignancies.⁷

Obstacles to Overcoming T Cell Exhaustion

Not all patients who test positive for PD-L1 respond to therapy, which can be due to T cell exhaustion. Additionally, some patients who do not test posi-

tive for PD-L1 may potentially respond to immune checkpoint blockade with available therapies.⁸ Further complicating the understanding of PD-L1 positivity, variability across studies define PD-L1 positivity as ranging from 1% to 50% of staining, making it difficult to compare across studies and confounding the contribution of factors that might affect response to treatment.⁸

Furthermore, exhausted T cells are heterogeneous, with some populations of exhausted T cells responding to PD-1 blockade and others persistently nonresponsive. The factors that seem to affect this heterogeneity are complex and include the extent and type of inhibitory receptor overexpression, the transcription factors that are upregulated in the population of T cells, and characteristics of the TME.⁶ Identifying whether exhausted T cells would respond to immune checkpoint blockade with one or more therapies could improve treatment outcomes.

Novel Investigational Targets for Overcoming T Cell Exhaustion

Though checkpoint blockade has provided a dramatic clinical benefit, only a subset of patients experiences deep and durable responses, suggesting other mechanisms are involved in limiting the immune response. New targets for immune checkpoint blockade hold promise for overcoming T cell exhaustion, particularly when combined with other immunotherapies. Several agents targeting the inhibitory

receptors LAG-3, TIM-3, and TIGIT are in various stages of clinical development, primarily in advanced solid tumors. Most trials combine these investigational agents with anti-PD-1, anti-PD-L1, and/or anti-CTLA-4 agents.^{9,10}

Novel therapeutic approaches that could overcome T cell exhaustion also include agonistic targeting of checkpoints. In preclinical models, agonistically targeting Inducible Co-Stimulator (ICOS), a co-stimulatory receptor for T-cell enhancement, potentiated the effect of an immune checkpoint blockade. Early-stage clinical trials combine ICOS agonists with anti-PD-1 or anti-CTLA-4 drugs in advanced and/or refractory solid tumors to assess its clinical potential.¹¹ Preclinical research suggests agonism of the inducible co-stimulatory molecule 4-1BB (CD137), which is expressed on T cells that have recognized cognate antigen, re-invigorated exhausted T cells, and early-stage trials are evaluating its clinical potential.¹²

In the interview below, Jason Luke, MD, provides his insights into how to understand and address T cell exhaustion in treating patients with cancer and what novel therapies might hold promise.

Q: In which patients with resistance to treatment would you expect T cell exhaustion might be playing a role?

LUKE: When we consider response and resistance to checkpoint-blocking immunotherapy, a model that has been proposed is one of the T cell inflamed or

non-T cell-inflamed tumor microenvironment, alternatively described as immunogenic vs immune-excluded. The fundamental mechanism at play is that some patients have generated an immune response where antitumor T cells actually infiltrate the tumor, and patients with this tumor-immune biology are those who predominantly respond to PD-1 checkpoint blockade. Those infiltrating T cells make cytokines, notably IFN- γ , that cause an increase in PD-L1 and some of the other tumor microenvironmental effects that we see associated with immunotherapy. Blocking PD-1 is effective when you have those T cells present and they have caused that upregulation of PD-L1. As an extension, when we think about when T cell exhaustion would likely be playing a role, it would be in those tumors where T cells have infiltrated but had not been able to clear the tumor; multiple resistance mechanisms may have limited that response, including PD-L1, regulatory T cells, and other secondary immune checkpoints inducing resistance.^{6,7} That's really where we would be thinking about T cell exhaustion.

To take it one step further, in which patients would this occur? One would generally think that patients who had had some level of either biochemical or clinical manifestations of having had a T cell infiltration phenotype would likely be those where T cell exhaustion might be playing a role. Those patients might have PD-L1 positive tumors and do not respond to PD-1 blockade or patients

who have an initial response to PD-1 antibody treatment but eventually progress. If PD-L1 is present on tumors, then T cells, via IFN- γ , should be upregulating PD-L1. A reason that they might not respond then may be that the effector T cells may be too terminally differentiated or exhausted.^{5,8}

Alternatively, patients with tumors that have initially responded to checkpoint blockade but then lost that response might also have exhausted T cells in the tumor microenvironment, potentially due to the upregulation of other checkpoints, such as LAG-3 or TIM-3, or another mechanism, such as metabolomic changes.^{4,6} Multiple other factors limit the activity of T cells and can drive T cell exhaustion. But broadly speaking, the clinical phenotype would be patients who are PD-L1 positive in their tumor but do not respond to PD-1 blockade and/or those who have some level of benefits from PD-1 blockade and then lose that benefit.

Q: What are the mechanisms by which T cell exhaustion develops in patients with cancer?

LUKE: The mechanisms that mediate T cell exhaustion are multiple. Evaluating T cell exhaustion specifically in cancer adds a bit of complexity, however, because the phenomenon has been elucidated extensively in preclinical models in experiments in which T cells were not able to clear viruses in mice. The extent to which we truly understand what happens in patients with cancer is obvi-

ously extrapolation because we cannot do this kind of primary biology work in people.^{1,2} That being said, to approach this question we can think about T cell intrinsic and T cell external mechanisms.

Intrinsically, T cells have their own internal regulatory pathways in which chronic exposure to antigen will lead to various differentiation programs, enabling T cells to take on different phenotypes.⁴ In a clinical context, we can consider the expression of putative, secondary exhaustion markers. Two of these markers that are under investigation as drug targets are LAG-3 and TIM-3, but there are a host of other secondary checkpoints, such as TIGIT, that also may be relevant.⁶

Extrinsically, other factors in the tumor microenvironment can drive T cell exhaustion as well, and we should be cognizant of these.⁴ These additional factors include secondary immunoregulatory cells such as T-regulatory cells and myeloid cells, especially putative M2-like macrophages. It's becoming clear that some of the other tumor microenvironmental cells, such as endothelial cells or stromal cells, can also make factors, such as TGF- β , that can impact T cell activity in the tumor microenvironment.⁵ One might say there is a cornucopia of ways that the tumor microenvironment can become hostile to active T cells and drive them into a phenotype of exhaustion.

Q: How should clinicians initially assess for the presence of T

cell exhaustion in their patients?

LUKE: We need to consider where T cell exhaustion happens. Clinically speaking, the most relevant way to think about T cell exhaustion is probably via PD-L1 testing, but we should consider it in a more nuanced way. Currently, PD-L1 testing has quite varied roles across different tumor types. In lung cancer, PD-L1 is an integral marker to know whether to treat patients with PD-1 blockade as monotherapy vs being treated with combination approaches. In lung cancer, PD-L1 is obviously an important clinical variable to have to drive clinical decision making.

We do not commonly do this, but if one wanted to know about T cell exhaustion, it would be very interesting to know what PD-L1 status looked like after a patient progressed on frontline immunotherapy. This really could drive a consideration around what one might do in the second line of treatment.

For example, if an initially PD-L1–positive tumor was treated with immunotherapy and there was some clinical benefit but progressed and still retained PD-L1 positivity, that might be an area where T cell exhaustion could be in play. In such a case, one might consider a combination regimen then of multiple immunotherapies together. If you think about that across other tumor types where we maybe do not use PD-L1 testing as much, such as melanoma or kidney cancer, in those settings, knowing whether or not the patient was PD-L1 positive upfront might

be helpful to determine whether that T cell infiltrate was present to consider what combinations could be useful.

For many tumor types, we are now starting to combine anti-PD-1 or anti-PD-L1 with the previous standard of care. The combination is often with chemotherapy, like in lung cancer, but in melanoma it is with BRAF inhibitors, and in kidney cancer it is with VEGF(R) agents. This consideration of T cell exhaustion could help to stratify patients as we think about future combinations where we would look for IO-IO combinations vs continuing to adhere to standards of care.

It is important to point out that not all PD-L1-negative tumors necessarily lack T cells. A fraction of tumors that have an immune infiltrate with upregulation of secondary markers, such as LAG3, do not have PD-L1. However, that has really only been observed in research studies so far, and the clinical applicability of that is still unclear.

Q: What is the rationale for using immune checkpoint inhibitors to overcome T cell exhaustion?

LUKE: The rationale is that T cell exhaustion is not a static phenotype but rather a sort of sliding process. A famous cartoon describes T cell exhaustion looking a little bit like an escalator going down, where T cells, as they become progressively more exhausted, could take on different phenotypes or express different molecules, and those molecules could be targets for drug development.⁴

An exhausted T cell does not necessarily lose its capacity to be a functional T cell. The expression of PD-1 or PD-L1 identifies to some degree this exhausted phenotype, so if we give PD-1 blocking antibodies, we could push those T cells back up the escalator, so to speak. It seems likely that at some point as the T cell descends far enough down the escalator, it cannot come all the way back up, but that process is not well understood at this point.⁴ A lot of work still needs to be done to better understand what the overall landscape of T cells is, how we can try to rescue T cells, and with which kinds of combination approaches we can rescue them.

The rationale is that you can rescue some of these effective antitumor T cells by relieving some of these exhaustion markers (eg, PD-L1 or LAG3).⁹ That gives us hope that as we better understand the immune infiltrate in different tumor types and in different patients, maybe we can design more personalized immunotherapies that can actually rescue the appropriate T cells for a specific patient.

Q: In what cases would you combine immune checkpoint inhibitors vs combining an immune checkpoint inhibitor with chemotherapy, targeted therapy, or other treatment approaches?

LUKE: This is really something that the field will be grappling with over the next several years. There are 2 ways to think about this question. Randomized clinical trials could prove a benefit of combinations in a

population of patients on a median clinical endpoint such as overall survival. This is how we have historically done things in oncology and certainly is not wrong. There is also a more nuanced way to think about the biology in which we might use biomarkers to decide on a treatment option.

If a randomized study shows that a combination regimen is superior, then for the average patient it can make sense to do that. In the example of patients with lung cancer with low PD-L1, it is quite clear that they get a major benefit of combining anti-PD-1 therapy with chemotherapy as opposed to just giving either of the treatments alone. That makes sense if you are thinking about treating patients on the median. That then extrapolates to other therapies, such as renal cell carcinoma, where we see similarly that monotherapies with PD-1 antibodies or VEGF(R) inhibitors were both inferior to giving the combination together, with frontline combination therapy being quite effective.

Deciding on combinations becomes a little more complicated, however, if we start to think about it on a biological level. If we go back to our T cell exhaustion concept, one could imagine that in some populations an IO-IO combination might be at least as effective if not more effective and potentially less toxic than a chemotherapy combination. Over time, we really need to elucidate biomarkers to better understand optimal combinations.

For example, within a population of patients with PD-L1–

high lung cancer, there probably would be a subpopulation with dual-expressed LAG-3. Perhaps in that PD-L1/LAG-3-high population, we might rather give PD-1 plus LAG-3 antibodies as opposed to PD-1 antibody plus chemotherapy.⁶ We are going to need to think about those kinds of questions as we move into the future.

One other example is in melanoma, where we have rapidly moved forward with therapeutics over the last 10 years with BRAF and MEK inhibitors as well as PD-1 and CTLA-4 antibodies. There are now trials with triplet regimens of BRAF, MEK, and PD-1/PD-L1 therapies that have announced positive results, with presentation of results anticipated at AACR 2020.¹³

But the question really remains whether triplet regimens are better than what we might otherwise do. In translational research studies, it is interesting to look at the effects of triplet combinations, specifically in subpopulations of patients. In an analysis of the phase 1/2 portion of the COMBI-I clinical trial of BRAF/MEK/PD-1, it appears that the triplet regimen may augment the responses of those patients that were most likely to have had a benefit from the individual agents in the first place.¹⁴ It is not necessarily the case that the triplet is expanding the population of patients who would not have otherwise responded or might not have otherwise done well. In fact, for patients less likely to respond, it may be the case that giving a combination of CTLA-4 with PD-1 antibodies actually works better for the

patients who are less likely to respond, but more research is needed.

Subpopulations probably exist within every tumor type where combining with the standard of care would be advantageous vs trying to tailor immunotherapy approaches. I think that coming up with better immune-tailored biomarkers to better define subpopulations who are likely to respond to certain combinations to enable better tailored therapies is going to be an important area of research in the field over the next 10 years. Better immune-tailored biomarkers to subset out who is likely to respond (and not) to which of the combinations needs to be a big priority so that we can better tailor treatment combinations. This approach will be a lot like the way it is done in targeted therapy when identifying the mutation to determine which drugs might be effective. In immunotherapy, we need to move to a world where better understanding the immune system could tell us which combinations might be preferentially effective compared to combining with something like chemotherapy.

Q: What considerations affect whether clinicians should use sequential vs combination therapies to overcome T cell exhaustion in their patients?

LUKE: Treating the patient as an individual really is the important consideration. One example is treating melanoma, where we know that PD-1 antibodies are very effective in

the frontline and that adding CTLA-4 blockade increases the response rate and does appear to increase the overall survival over extended periods of time with that combination vs frontline PD-1 monotherapy.

But the more nuanced question is whether to give a PD-1 antibody and then when the patient progresses, whether to give a CTLA-4 antibody. We do not have robust clinical trial data on sequential vs combination therapy. The way my colleagues and I think about it is that the patients who you are concerned that you might not get 2 shots on goal, so to say, are the ones where there is no question that we want to give the combination upfront.

In melanoma, the way we think about it is that there are some patients that are clearly at very high risk, with features such as elevated LDH or liver metastases or brain metastases. In those patients, we reach for combination therapy right away because we have concerns that if the patient progresses rapidly through the frontline therapy, they may actually decline so quickly we do not get the chance to give the combination. And similarly, I think, that has been a rationale in lung cancer and in head and neck cancer for developing chemotherapy and PD-1 antibody combinations. The attrition after first-line therapy, unfortunately, in those diseases is substantial, so you may not actually get an opportunity to give the sequential therapy.

When you think about the potential toxicity profile, almost always combinations will be more toxic than using mono-

therapies, so you also have to consider whether the patient is robust enough to withstand the potential toxicity of that combination compared with the toxicity of monotherapy. But that is how I think about it. If a patient comes to me and is low risk, or if they are not low risk but have metastatic disease without rapid progression and they appear that their disease is going to be iteratively treatable, then sometimes my preference is to use sequential approaches to limit toxicity. However, in those patients who just clearly have really high-risk disease, we want to go aggressively upfront with combination therapy because of the concern that we might not get multiple chances to give immunotherapy.

Q: Does T cell exhaustion impact the rationale for using chimeric antigen receptor (CAR) T-cell therapy?

LUKE: This question addresses multiple concepts of immunology that are important. We do not yet understand well how T cell exhaustion and CAR T-cell therapy are going to be intertwined. When we consider when T cell exhaustion occurs, it happens in tumors that have been infiltrated by T cells but then basically been blocked or put into suspended animation by the tumor microenvironment. We know that those are the tumors in which checkpoint-blocking antibodies tend to be the most effective.

So far, CAR T cells have predominantly been effective in hematologic malignancies. The mechanisms whereby CAR T-cells kill tumor cells

vs how checkpoint-blocking antibodies induce T cells to kill tumor cells are very different. With CAR T-cells, it is thought that the cells go throughout the body in the bloodstream and find predominantly hematologic malignancies and cause direct cell killing, whereas in the TME, the number of T cells relative to the number of tumor cells is many-fold larger, so there just are not enough T cells that they would directly kill the cancer cells.

The mechanisms, therefore, are very different, and for that reason CAR T-cells have been thought of for solid tumors as potentially providing a bridge to overcome the lack of T cell infiltration in non-T cell-inflamed tumors. This is actually the opposite from the T cell exhaustion paradigm we have discussed. So we may be able to overcome T cell exhaustion with checkpoint antibodies, but if no T cells ever came in, then they are not exhausted because they are not present. In those scenarios, perhaps that is a rationale where we could use CAR T-cells to try to infiltrate the tumor.

Now, one clear resistance mechanism to CAR T-cell therapy that has been elucidated is, in fact, T cell exhaustion. Some CAR T-cells will contact the tumor and become exhausted due to things that the tumor can do in response, so CAR T-cells themselves can be exhausted. Checkpoint inhibitors for CAR T-cells predominantly currently address 2 different sets of patients with tumors. Tumors with T-cell infiltration tend to be those where we think checkpoint blockade could be

the most effective, whereas perhaps CAR T-cells could bring T-cells in for those tumors without T-cell infiltration. We might, in fact, then also need to add checkpoint inhibitors to keep those CAR T-cells active.

A study out of Memorial Sloan Kettering last year in mesothelioma showed that if CAR T-cells were delivered into the pleural space of mesothelioma, the treatment was safe but not highly efficacious. However, upon the addition of PD-1 blockade to rescue those CAR T-cells, approximately half the patients had treatment response. Because of T-cell exhaustion, the addition of checkpoint immunotherapy allowed more effectiveness and frequent responses.¹⁵ I think that shows that there is a path forward for combining those therapies, but we are in very early days of thinking about that.

Q: How do you expect emerging and investigational developments (eg, biomarkers), clinical trials, and/or novel agents that address T cell exhaustion to impact the therapeutic landscape?

LUKE: I am very excited and bullish about the idea that in a hypothesis-driven way, finding biomarkers is possible. Biomarkers could help us enhance these therapies and apply them in the most appropriate scenarios.

One biomarker that I have discussed is LAG-3. The development of the anti-LAG-3 drug relatlimab, which is now in a randomized phase 3 trial in melanoma, developed in a

phase 1 trial in patients who had progressed on anti-PD-1 therapy with melanoma and were treated with a combination of nivolumab with relatlimab.^{9,16}

Although the overall response rate in that initial study was modest, the patients who responded were found to have higher levels of tumor LAG-3 staining. As we go forward, we might be able to identify a population of patients whose tumors express high degrees of LAG-3 in which the combination of anti-PD-1 with anti-LAG-3 could be effective.⁶

Somewhat similarly in lung cancer, a TIM-3 antibody has clinical activity in combination with a PD-1 antibody after initial progression on PD-1 antibody. Again, when researchers evaluated the tumors from responding patients, those tumors retained PD-L1 positivity after they had already progressed on PD-1.^{9,17}

When we consider which patients might have T cell exhaustion, the patients who had some level of benefit and lost it are likely to be those where T cell exhaustion would be in play. In those scenarios, we might be able to elucidate which secondary receptors could be appropriate targets. In patients with tumors expressing secondary receptors that might be able to give us a heads up on which patient populations to treat.

As we develop new therapies, we should be able to identify subpopulations in which these approaches are more likely to work. One caution I have is that this approach will be complicated, and it will prob-

ably develop slowly. Currently, our clinical trials have been trying to treat large numbers of patients with combinations, and with limited success so far.

The efficacy of IO combinations is not as robust as people thought it would be 5 years ago, and I think that is because we need to be more judicious in searching for biomarkers and in better characterizing T cell exhaustion in tumors from patients who have progressed on anti-PD-1. But I think it is doable and I am excited about the idea that we may be able to generate long-term responses even in the second-line or later if we can appropriately profile patients. ■

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