Immunotherapy May Need to Have Its Own Value Model

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The average release price of a new therapeutic agent in oncology “is north of $10,000 a month,” Peter P. Yu, MD, the physician-in-chief of the Hartford Healthcare Cancer Institute, in Hartford, Conn, told attendees at the SITC meeting. There are multiple models to assess the value of a cancer treatment, including the American Society of Clinical Oncology’s Value Framework, the European Society of Medical Oncology’s Magnitude of Clinical Benefit Scale (ESMO-MCBS), the National Comprehensive Cancer Network Evidence Blocks, Memorial Sloan Kettering Cancer Center’s Drug Abacus, and the Institute for Clinical and Economic Review Value Assessment Framework, Dr. Yu said. While they all look at cost, effectiveness and population health impact, none are perfect to apply to immunotherapy or are really easy to use, he said. However, he noted that they could be used as a basis to develop a new value framework for immunotherapy.

The models also underestimate the benefits of immunotherapy not only for patients and their families but for society, he added. The annual benefit of curing just 1% more cancers is estimated to be $500 billion, he said.

With respect to overestimating toxicity, Dr. Atkins said that while approximately 50% of patients getting the nivolumab–ipilimumab combination develop serious immune toxicities involving the skin, liver, colon or endocrine organs, approximately 80% of adverse events resolve in four to six weeks with immune-modulating treatments such as steroids. In addition, he said, these side effects do not interfere with ultimate response to therapy.

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The hallmark of immunotherapy, Dr. Atkins said, is the “tail of the Kaplan-Meier survival curve,” referring to long-term survival. In melanoma over the past few years, survival rates have increased from 10% to 20% with ipilimumab (Yervoy, Bristol-Myers Squibb) treatment, to 35% to 40% with anti-PD-1 [programmed cell death protein 1] agents, to potentially higher than 50% with combination ipilimumab/nivolumab (Opdivo, Bristol-Myers Squibb), Dr. Atkins noted. This “means melanoma—a disease that had a median survival of six to nine months in 2011—now has no median survival,” he said.

Immunotherapy, along with targeted therapy, also has helped transform the treatment of lung cancer over the past 10 to 15 years, said Roy S. Herbst, MD, PhD, a professor of medicine and chief of medical oncology at Yale Cancer Center, in New Haven, Conn. “Are we curing people?” he asked. “I think we’re getting pretty close.”

He described the findings of the KEYNOTE-024 trial presented at the ESMO 2016 Congress (N Engl J Med 2016 Oct 8. [Epub ahead of print], PMID: 27718467), which demonstrated significant progression-free and overall survival benefits for patients with advanced lung cancer and high programmed death ligand 1 (PD-L1) expression taking pembrolizumab (Keytruda, Merck) compared with those taking platinum chemotherapy. These findings have “changed the way we think about lung cancer,” Dr. Herbst said.

Anti-PD-1 agents are effective for several other cancers, Dr. Atkins said, noting, “We probably have had no single treatment that was so broadly relevant in oncology.”

**Patient-Reported Outcomes**

In addition to incorporating the benefits shown via these positive clinical trial results, good value frameworks have to include patient-reported outcomes (PROs), according to Heather S. Jim, PhD, an associate member at Moffitt Cancer Center and Research Institute, in Tampa, Fla.; and Adam P. Dicker, MD, PhD, a senior vice president and chief of radiation oncology, and a professor of radiation oncology, pharmacology and experimental therapeutics at Thomas Jefferson University, in Philadelphia, who also spoke at the SITC meeting. PROs can help show clinical benefit in reducing disease-related symptoms, provide more accurate estimates of toxicity, enhance value frameworks, help model treatment costs and help improve symptom management, they said. The National Cancer Institute has developed the PRO-Common Terminology Criteria for Adverse Events (PRO-CTCAE), offering a menu of symptoms such as rash, fatigue or itching to select clinical trials or targeted therapies that are more useful for immunotherapy than measures like the ECOG health-related quality of life questionnaire.

In the CheckMate 025 trial, a Phase III study of nivolumab versus everolimus (Afinitor, Novartis) in previously treated patients with advanced or metastatic renal cell carcinoma, investigators included a measure of kidney cancer-specific symptomatology, Dr. Jim said. Symptoms in patients taking nivolumab showed improvements as soon as four weeks into treatment, she said, and continued through two years of follow-up data, “showing that not only could nivolumab improve overall survival but could improve the quality of survival,” she said, noting that this information is “important not only for patients but also for regulatory agencies and payers.”
Using PROs in Assessing Cost of Toxicity

A study from Moffitt investigators, presented at the 2016 annual meeting of the American Society of Clinical Oncology, used PROs to model treatment toxicity costs. They looked at patients treated with ipilimumab, nivolumab and pembrolizumab and estimated patient toxicity from billing records. Then they searched public databases to estimate the added costs of these toxicities to the total cost of treatment, determining among other findings that colitis adds about $8,500 and fever adds $3,300, increasing the costs of ipilimumab by 6%, nivolumab by 18% and pembrolizumab by 16%. “These toxicities really do have costs, and it’s important to model those in the value frameworks so patients have an idea of how much out-of-pocket costs they might incur,” Dr. Jim said.

PROs also can help improve symptom management, which can help patients stay on treatment longer with potential survivor benefits, she added. In a recent clinical trial, 766 patients treated with chemotherapy for metastatic breast, genitourinary, gynecologic or lung cancer filled out tablet-based questionnaires about their symptoms (J Clin Oncol 2016;34[24]:2925-2934, PMID: 27247218). The program’s software triggered email alerts to nurses when patients reported severe or significantly worsening symptoms for common conditions in the PRO-CTCAE, and the nurses reached out to these patients to offer help in managing the symptoms. Of the patients receiving this intervention, 34% demonstrated improved quality of life compared with 18% of those receiving usual care; 21% of those in the intervention group had clinically significant improvements in quality of life compared with 11% in usual care. Patients receiving interventions also had fewer ER visits at one year and spent more median months on chemotherapy.

Technology such as smartphone applications or activity trackers may offer ways to better monitor PROs, Dr. Dicker said. “There’s a lot that happens between patient visits that’s not always being captured. We also appreciate white coat syndrome—patients may not want to report toxicities because they want to stay on therapy.”