Realizing the Promise of Immunotherapy in the Clinic

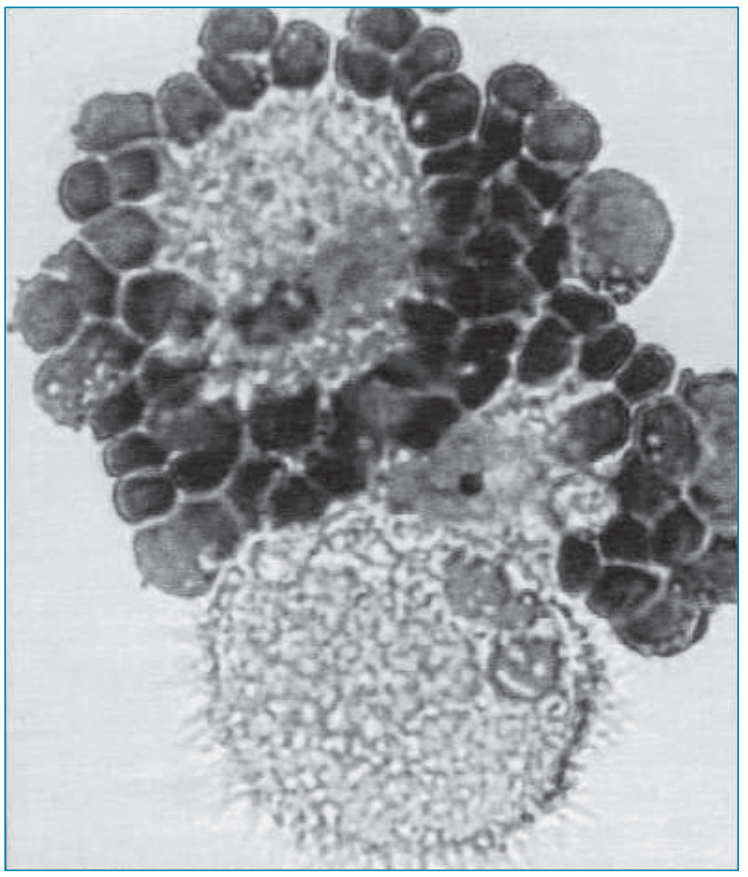
BY PEGGY EASTMAN

Targeted immunotherapies have added an important new treatment approach to oncologists' armamentarium, especially for melanoma, lung cancer, and blood cancers. Cancer immunotherapy is considered such an exciting area that the American Society of Clinical Oncology (ASCO) chose this field as its cancer advance of the year for 2016.

But many challenges remain in bringing treatments that harness the immune system to fight cancer fully into clinical practice, according to speakers at a workshop sponsored by the National Cancer Policy Forum (NCPF) of the National Academy of Medicine (formerly the Institute of Medicine). Issues that may be hampering the development of this field include physician training needs; the need for patient and family education; adverse events in immunotherapy treatment; and the high and escalating costs of these therapies, said workshop planning chair Samir N. Khleif, MD, Director of the Georgia Regents University Cancer Center and the Georgia Health Sciences University Cancer Center. Khleif noted that now, with immunotherapies being used in combination, it could cost up to $1 million per patient with this treatment approach, depending on how long that patient lives.

Studying the Possibilities

A number of groups are studying the challenges of realizing immunotherapy's promise for cancer patients. The Friends of Cancer Research (FOCR) told *OT* it recently brought together a policy work group to develop a strategic plan to accelerate progress in immunotherapy across multiple cancers. The Society for Immunotherapy of Cancer (SITC) has established an immunotherapy biomarkers task force. In addition, the Association of Community Cancer Centers (ACCC) has established the Institute for Clinical Immuno-Oncology to translate immunotherapies into practical application for cancer patients.



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Learning Objectives for This Month's CME Activity: After participating in this CME activity, readers should be better able to recognize the challenges of using targeted immunotherapies in the treatment of patients who have cancer.

At the NCPF workshop, speakers stressed that years of building on advances in science have brought immunotherapy to the point of becoming another pillar in cancer treatment. "If you can induce a complete response, it is very likely to be durable," said pioneering immunotherapy researcher Steven A. Rosenberg, MD, PhD, Chief of Surgery at the National Cancer Institute (NCI). Rosenberg has achieved exactly that kind of durable regression in patients who have metastatic melanoma by using the technique of autologous tumor-infiltrating lymphocytes (TILs). He also has seen marked tumor regression in patients with advanced sarcomas and lymphomas using this technique, which involves the adoptive transfer of genetically modified, cancer-fighting lymphocytes extracted from patients' tumors and grown to very large numbers *in vitro*.

While "cell transfer therapy can mediate durable regressions in patients with metastatic cancer refractory to other treatments," said Rosenberg, he acknowledged that "the problems are daunting." In effect, each treatment is unique to each patient, so each patient is getting an individualized immunotherapy based on his or her own mutation profile. "The final common pathway of immunotherapy is the recognition of cancer mutations," noted Rosenberg.

Now, said Rosenberg, these anti-tumor cells can be identified in peripheral blood as well as in the tumor tissue itself, which could lead to mechanization of TILs and a broader use of this technique of adoptive cell transfer therapy. "The key is to get those antigens from peripheral blood; that's going to help get this into the clinic," NCPF member Otis Brawley, MD, Chief Medical Officer and Executive Vice President of the American Cancer Society, told *OT*.

Several speakers stressed the promise of chimeric antigen receptor (CAR) T cell therapy to treat cancer patients. This therapy involves collecting T cells from a cancer patient, genetically programming them in the laboratory and infusing them back into the patient; the CAR cells are reprogrammed to make proteins which attack cancer cells. "This is a living drug," said David L. Porter, MD, the Jodi Fisher Horowitz Professor in Leukemia

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Care Excellence and Director of Blood and Marrow Transplantation at the Hospital of the University of Pennsylvania, Philadelphia.

Porter said patient responses to CAR cells can be modified, responses can last for a long time because the cells remain biologically active and CAR cell therapy can eradicate even bulky disease. In one study of relapsed, refractory acute lymphoblastic leukemia (ALL), 90 percent of patients achieved a complete remission with CAR T cell therapy. However, said Porter, as of yet he and his team have not been able to determine why some patients respond and some do not—a recurring theme at the NCPF workshop. Also, Porter cautioned that toxicity and side effects can be significant, and may include tumor lysis syndrome, cytokine release syndrome, high fever, nausea, hypotension, and hypoxia. Some patients may require admission to the ICU.

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Regulatory Trials

Speakers from the FDA stressed that cancer immunotherapies can present regulatory challenges for the agency. In preclinical studies, "even more frequently than with therapeutic antibodies targeting non-immune associated targets (for example, VEGFR and EGFR), species relevance can be an issue," said Whitney S. Helms, PhD, Supervisory Pharmacologist in FDA's Office of Hematology and Oncology Products. Basically, an investigational immunotherapy can behave quite differently in another species than in humans.

Combination immunotherapies can also present a regulatory challenge. "In general, combination toxicology studies are not required," said Helms. But, she added, "If a first-in-human study where there was no clinical experience with either product was proposed, then a combination study might be warranted. In cases where there is limited clinical experience with one or both products, then combination pharmacology studies are often recommended."

The regulatory challenges for autologous cell therapies include tracking, stability, and safety concerns, said Peter F. Bross, MD, Medical Review Officer with FDA's Office of Cellular, Tissue and Gene Therapy, Center for Biologics Evaluation and Research (CBER). Also, he noted, there are regulatory issues related to clinical trials with very small patient numbers, which may require new regulatory paradigms. The FDA has grappled with regulation of cellular therapies with the approved therapies sipuleucel-T (Provenge) for prostate cancer and talimogene laherparepvec (T-Vec) for melanoma.

Friends of Cancer Research Recommendations

The immunotherapy policy work group recently convened by the Friends of Cancer Research recommends focusing on these areas to advance the field of cancer immunotherapy and realize its promise for patients:

- aligning oncology review functions within the FDA;
- developing consensus around specific alternate immuno-oncology endpoints and definitions that are appropriate to immuno-oncology and have sufficient rigor to be acceptable to regulatory agencies;
- promoting opportunities to collect patient-reported outcomes, including symptoms and quality-of-life issues from real-world patients;
- promoting novel trial designs in immuno-oncology, such as basket-type studies that attempt to match cancer patients with a rare mutation, regardless of tumor histology, to a drug expected to work through the mutated pathway;
- promoting a virtual bio-bank/common data platform that encourages and fosters data-sharing; and
- developing an education initiative for the full spectrum of care providers in a patient's team within the community setting.

Collaboration Needed

To realize the promise of immunotherapy for cancer patients, partnerships between industry and academic centers are vital, said several speakers. Porter noted such a partnership exists between the University of Pennsylvania and Novartis. These relationships are valuable as manufacturers try to operationalize and standardize immunotherapies for widescale use. Richard C. Woodman, MD, Novartis Senior Vice President and Head of North America Oncology Clinical Development & Medical Affairs, seconded Porter's view. "We need partnerships," Woodman told *OT*.

Agreeing was Richard Simon, DSc, Chief of the Biometric Research Branch at the NCI. "There is a need for companies to make immune-modulating agents available to academics for discovery studies," said Simon. Not having these agents available to academia, especially for studies of immunotherapy combinations, constitutes "a major roadblock," he said.

While manufacturing immunotherapy agents on a large scale seems daunting because these agents are personalized, there are ways to streamline the process, said Harpreet Singh, PhD, Managing Director, Founder and Chief Scientific Officer of Immatics Biotechnologies. He told *OT* that manufacturing peptide vaccines is cost-effective using a warehouse approach in which the peptides are stored on shelves in powder form. "Peptides when lysolized last a long time," Singh said. He said it now takes about three months to create an individualized peptide vaccine for a cancer patient, a process which he wants to reduce to two weeks.

Access to Data

In addition to cost, educational, regulatory and large-scale manufacturing issues, moving the clinical use of immunotherapies forward is going to require prudent use of large amounts of data, especially the data in a cancer patient's electronic health record (EHR), stressed Amy P. Abernethy, MD, Chief Medical Officer and Senior Vice President for Oncology at Flatiron Health, Professor in the Division of Medical Oncology at Duke University School of Medicine, Director of the Center for Learning Health Care at Duke and a member of the NCPF.

"The EHR is a massive file cabinet for the patient" with valuable data, but much of the data are unstructured, said Abernethy. "A dataset is an amalgamation of patient stories," she added. Leveraging the valuable material in these patient-story datasets to advance the science of immunotherapy will require organized data processing and linkage and—most of all—interoperability, said Abernethy. "Policy solutions should demand interoperability," she emphasized.

To that end, ASCO recently made a pledge to the U.S. Department of Health and Human Services (HHS) to improve health information sharing. "Big data initiatives and future cancer care will depend on the ability to electronically share clinical information between practitioners," said ASCO President Julie M. Vose, MD, MBA, the Neumann M. and Mildred E. Harris Professorial Chair and Chief of the Oncology/Hematology Division in the Department of Internal Medicine at the University of Nebraska Medical Center, in a statement.

"However, EHRs often contain data that cannot easily be shared among physicians or contribute to quality improvement, public health reporting, or analytics," said Vose. She noted that ASCO is actively working to develop interoperability standards and treatment plans for sharing cancer information, has outlined steps Congress should take to advance EHR interoperability and prevent information blocking, and leads the development of CancerLinQ, ASCO's cutting-edge health information technology platform. OT

Peggy Eastman is a contributing writer for OT.