Cancer Immunology, Success Without Sequencing

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After I playfully told him I’d play a game with him sometime in the future, my 8-year-old son Jack said, “That won’t work. The future never gets here. The present just keeps going and going. So you can’t just say ‘the future,’ you have to give me a time.”

In sharing this funny story with patients in my leukemia and bone marrow transplant practice, I thought about it more and more in a medical context. I remembered something I heard Dr. Daniel Van Hoff, pioneer in clinical cancer research and current head of the Translational Genomics Research Institute, say in a lecture several years ago. He set a goal to provide novel therapy for “the person sitting in front of me.” Every week, new gene mutations important in cancer are discovered. Advances based on a better understanding of mutated genes and genomes are coming, faster and with exciting frequency, but most patients with cancer currently in the clinic can only be offered sequencing and not sequencing-informed therapy. No doubt, the work of Dr. Van Hoff and the community of cancer investigators like him around the world will increasingly realize the lofty goal of personalized therapy, both today (for some) and “sometime in the future” (for many more). Yet, the past year has also seen exciting advances in a different area, harnessing the immune response to kill cancer cells, making several treatments available for patients in the present. In fact, cancer immunology was named the 2013 breakthrough of the year by Science.

Recently, we received sad news of the passing of a giant in clinical cancer immunology, Dr. John Goldman. Dr. Goldman developed autologous and allogeneic hematopoietic cell transplantation (alloHCT) for chronic myelogenous leukemia before imatinib arrived on the scene. On his shoulders, and those of many others, we stand and look ahead at new opportunities to use and modify the immune response to cure patients with cancer.

Several novel immunotherapies have shown great promise in the past year. Chimeric antigen receptor (CARs) T cells have had astounding early success for patients with refractory B-cell chronic lymphocytic leukemia (CLL) or acute lymphoblastic leukemia (ALL). Preclinical studies by Dr. Carl June and others led to these and subsequent clinical trials with ex vivo gene engineering of autologous T cells, directing the cells to target tumor-associated antigens such as CD19 on B cells. In several trials on CARs presented at the annual American Society of Hematology (ASH) meeting in December 2013, more than 80% of patients with relapsed/refractory B-cell ALL, including children and adults, experienced remission. Severe toxicities related to cytokine release are also now more clearly understood and manageable. Questions such as in vivo expansion of CARs, loss of target antigen expression in tumor cells, and the feasibility of large-scale manufacture remain. Whether the clinical success can be extended into larger trials will be one of the most important questions of the next few years. Likewise, the question of whether this technology can be applied to other cancers is also an ongoing concern. Currently, this approach for treating lymphomas has not shown the same rousing success, and new CARs targeting myeloid (eg, CD33, CD123) or solid tumor antigens have not yet been seen successfully driving on our scientific roads. Currently, ClinicalTrials.gov lists more than 40 CAR CAR T-cell trials.

Fame (and fortune) in cancer immunology really began with monoclonal antibodies (mAbs), namely FDA approval of the chimeric anti-CD20 antibody rituximab in 1997 followed by trastuzumab in 1998. Treatment advances in this area are seemingly endless, including the recent success of “enhanced” antibodies like...
obinutuzumab (GA101), a third-generation anti-CD20 antibody with higher binding affinity for human Fc receptor. The year 2014 started with a bang, as obinutuzumab plus chlorambucil improved progression-free survival and response compared with rituximab plus chlorambucil (and both were superior to chlorambucil alone) in previously untreated patients with CLL with medical comorbidities.\(^4\)

Among other mAbs, exciting responses in solid tumors have been seen with agents that target T-lymphocyte immune checkpoint blockade. Foremost among these is ipilimumab, an mAb-targeting cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), previously shown to improve survival in metastatic melanoma.\(^5\) Combining ipilimumab with nivolumab (targeting programmed death [PD]-1) improved the response rate even further.\(^6\) Subsequent data with these agents in melanoma suggested that each might still be active even when the other has already failed.\(^7\) Not surprisingly, the number of mAbs targeting T-cell checkpoint blockade is increasing rapidly. Lambrolizumab (targeting PD-1, formerly known as MK-3475) showed single-agent activity in melanoma, including in patients who experienced progression on ipilimumab.\(^8\) Antibody-mediated blockade of PD-L1 (PD-1 ligand) on tumor cells induced tumor regression in a range of solid tumors, including non–small cell lung cancer, melanoma, and renal cell cancer.\(^9\) Further, targeting of not just CTLA-4 or PD-1 but also lymphocyte activation gene-3 (LAG-3) and other checkpoints is increasing. Preclinical evidence for synergistic activity when these agents are combined abounds.

Next, antibodies that bind 2 targets simultaneously are finding their way into clinical practice. Among these are the bispecific T-cell engager BiTE (blinatumomab) for CD19/CD3 in ALL and the so-called dual affinity-retargeting (DART) molecule reported by Dr. John DiPersio and colleagues at ASH 2013 for CD123/CD3. Finally, novel mAbs designed to enhance natural killer cell anticancer immunity are also showing promising results in the clinic. A natural killer immunoglobulin-like receptor (KIR) targeting mAb (anti-KIR) showed activity in early trials for patients with acute myeloid leukemia (AML), myeloma, and lymphoma.

Not to be forgotten in a celebration of advances in cancer immunology are those based on extending the curative potential of alloHCT in hematologic malignancies. KIR mismatching between donor and recipient appears to reduce relapse risk for patients with AML.\(^10\) The National Marrow Donor Program is leading an ongoing trial investigating whether selection of a KIR mismatched donor can improve outcomes. Also, reduced-intensity conditioning has extended the availability of alloHCT and improved disease-free survival for older patients with AML in first remission. Similarly, use of alternative sources of stem cells, such as haploidentical donors or umbilical cord blood, is increasingly becoming part of mainstream practice, even for patients in first remission.

The pharmaceutical industry also recognizes the potential in cancer immunotherapy; a highlight among innumerable transactions is the exclusive global partnership established by Novartis and the University of Pennsylvania to commercialize CARs for all types of cancer. Another example is the redefining of “start-up funds.” Juno Therapeutics has a record-breaking $120 million in such funds to develop immunotherapies for cancer in cooperation with the Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance and Memorial Sloan-Kettering Cancer Center.

Of course, no real summary of cancer immunotherapy is truly possible in a short commentary. I will have to write a longer article “sometime in the future.”
References