Cancer Immunotherapy, Part 2: Efficacy, Safety, and Other Clinical Considerations

C. Lee Ventola, MS

This is the second in a series of three articles about cancer immunotherapy. The first article, published last month, was an introduction to cancer immunology, immunotherapy strategies, and each of the classes of anticancer therapeutic agents, which will be expounded upon here. The third article, which discusses challenges and future trends, will be published next month.

INTRODUCTION

The understanding of the relationship between cancer and the immune system has progressed rapidly in recent decades.1–3 The efficacy of many cancer immunotherapies, such as monoclonal antibodies, cytokines, cancer vaccines, and cell-based therapies, has been demonstrated, allowing these treatments to be incorporated into clinical practice.1,3–8 However, in some cancers and some patients, the success of cancer immunotherapy agents that target single molecular abnormalities or cancer survival mechanisms has been limited to clinical responses and modestly better survival.1,2 To improve outcomes, combination treatments with cancer immunotherapy agents may be necessary.1–3,6,9,10 This article provides an overview of the efficacy and safety of cancer immunotherapies, including additional clinical considerations regarding immune checkpoint blockers (ICBs).3,11–17

EFFICACY AND SAFETY OF CANCER IMMUNOTHERAPY AGENTS

In the past few decades, knowledge about the relationship between cancer and the immune system has grown quickly.1 The efficacy of many cancer immunotherapies has been demonstrated, causing the rapid integration of these treatments into clinical practice.1,3 One of the most attractive features of many cancer immunotherapies is that they target malignant cells while sparing normal, healthy tissues from the damage often seen with radiation and chemotherapy that contributes to patient morbidity and mortality.2

Previously, cancer immunotherapies had been associated with only a few examples of predictable clinical success, such as the use of high-dose interleukin (IL)-2 to achieve a complete response (CR) in advanced melanoma and renal cell carcinoma (RCC).1 However, further progress has since been made, and cancer immunotherapy is now more often considered to be effective (Table 1).1,3 Positive responses with cancer immunotherapy are reported more frequently—sometimes even complete or long-lasting responses or cures, even in patients with solid tumors or aggressive malignancies.1–3 At present, cancer immunotherapy has been shown to be most beneficial in treating patients with melanoma, RCC, or hematologic malignancies.3 However, emerging data are demonstrating the potentially broader efficacy of immunotherapy in treating many other types of malignancies.3

Among the considerations when selecting a cancer immunotherapy to treat a patient are the treatment goals, patient’s status, type of tumor, speed of disease progression, and potential efficacy and adverse effects (AEs).3 Because patients with cancer often have a limited therapeutic window, the extended time needed to generate certain immunotherapies is another consideration that could eliminate some treatment choices.3 For example, genetically engineered cytotoxic T lymphocytes (CTLs) can take weeks to months to prepare.3,18 AEs associated with cancer immunotherapies can be mild and localized or more severe and systemic, depending on the treatment.3

In general, the AEs that may develop with cancer immunotherapy depend on the treatment modality, route of administration, and mechanism of action.3 Some immunotherapies

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ABBREVIATIONS

AE—adverse effect
Allo-HSCT—allogeneic hematopoietic stem cell transplant
AML—acute myeloid leukemia
APC—antigen-presenting cell
CAR—chimeric antigen receptor
CLL—chronic lymphocytic leukemia
CR—complete response
CRC—colorectal cancer
CRS—cytokine release syndrome
CTL—cytotoxic T lymphocytes
CTLA-4—cytotoxic T-lymphocyte-associated protein 4
GvHD—graft-versus-host disease
GM-CSF—granulocyte-macrophage colony-stimulating factor
HER-2—human epidermal growth factor receptor 2
HLA—human leukocyte antigen
ICB—immune checkpoint blocker
irAE—immune-related adverse event
IFN—interferon
IL-2—interleukin-2
MM—metastatic melanoma
mAb—monoclonal antibody
NSCLC—non–small-cell lung cancer
ORR—objective response rate
OS—overall survival
PR—partial response
PD—programmed death
PAP—prostatic acid phosphatase
rhIL-2—recombinant interleukin-2
RCC—renal cell carcinoma
TBI—total body irradiation
TIL—tumor-infiltrating lymphocyte
broadly activate the immune system, while others precisely target distinct tumor antigens. Vaccines that are administered locally may have a potent effect in stimulating an immune response at the injection site, while the AEs observed with cytokines and ICBs (both which induce the broad activation of the immune system) can produce symptoms that are often observed during high levels of immune activity, such as those accompanying a systemic infection. Another important consideration with respect to some cancer immunotherapies is the possibility of long-term antitumor effects due to “immune memory.” Although this effect can be beneficial, it can also be a double-edged sword because it can lead to long-lasting toxicities, such as those seen with allogeneic hematopoietic stem cell transplant (allo-HSCT), which can potentially cause a broad, prolonged immune response against normal tissue.

A brief overview of the efficacy and safety of various cancer immunotherapy agents follows.

### MONOCLONAL ANTIBODIES

The ability to identify and characterize proteins associated with tumors has led to the development of targeted therapies, such as therapeutic monoclonal antibodies (mAbs). In 1997, the first therapeutic mAb demonstrated sufficient efficacy to receive approval from the Food and Drug Administration (FDA), and rituximab (Rituxan, Genentech/Biogen Idec) was approved for the treatment of relapsed or refractory CD20+, B-cell, low-grade or follicular non-Hodgkin’s lymphoma. Since then, many other therapeutic mAbs have been granted FDA approval for use in a wide range of clinical indications, including: cetuximab (Erbitux, Eli Lilly) for head and neck cancer and colorectal cancer (CRC); trastuzumab (Herceptin, Genentech) for human epidermal growth factor receptor 2 (HER-2)-positive breast cancer and gastric and gastroesophageal cancer; ofatumumab (Arzerra, Novartis) for chronic lymphocytic leukemia (CLL); alemtuzumab (Campath, Genzyme) for B-cell CLL; panitumumab (Vectibix, Amgen) for CRC; and bevacizumab (Avastin, Genentech) for CRC, nonsquamous non–small-cell lung cancer (NSCLC), glioblastoma, RCC, cervical cancer, and recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. Over the past 20 years, therapeutic mAbs have become mainstays of cancer treatment for a variety of malignancies, including breast cancer, lymphoma, and CRC. Notably, rituximab and trastuzumab have demonstrated such significant utility in treating lymphomas and HER-2/neu-positive breast cancer, respectively, that they have become important components of curative regimens for these malignancies.

Because they are targeted, the side effects that occur with therapeutic mAb treatment are generally considered to be mild compared with other types of cancer treatment. Side effects that can occur with mAbs include chills, diarrhea, fever, headache, low blood pressure, nausea, rash, weakness, and vomiting. Toxicity associated with a therapeutic mAb may also relate to its specific pharmacological activity. Although targeted, therapeutic mAbs may also cause toxicity by interacting with the target antigen where it is present in places other than the intended tissue. For example, the skin toxicity observed with cetuximab (approved for head and neck cancer) is believed to occur because the target antigen, epidermal growth factor receptor (most often known simply as EGFR), is also present on human keratinocytes. Although many AEs seen with mAbs are antigen-/target-related, off-target, nonspecific toxicity can also be observed; for example, hypersensitivity reactions are common and are thought to be related to the immunogenicity of mAbs. Fully human mAbs generally have reduced immunogenicity compared with chimeric or humanized mAbs. This is because mAbs composed of a high proportion of nonhuman sequences are more likely to be identified as “foreign,” thereby inducing a host immune response. This can result in reduced efficacy and more AEs, due to greater clearance and an increase in infusion- or injection-site reactions.

Although the use of “naked” (unconjugated) therapeutic mAbs (those that work by themselves) has significantly impacted cancer treatment, efficacy can often be improved by linking them to a biologically active cytotoxic drug or a radioisotope (radioimmunoconjugate). Brentuximab vedotin (Adcetris, Seattle Genetics), for example, is an antibody–drug conjugate that was generated by conjugating a humanized anti-CD30 mAb, SGN-30, to the cytotoxic agent monomethyl auristatin E. It is approved for the treatment of classical Hodgkin’s lymphoma and systemic anaplastic large cell lymphoma. Another antibody–drug conjugate, ado-trastuzumab emtansine (Kadcyla, Genentech), which is conjugated to the maytansinoid DM1, a cytotoxic agent, has been approved for the treatment of HER-2-positive metastatic breast cancer. An example of a mAb that is conjugated to a radioisotope is ibritumomab tiuxetan (Zevalin, Spectrum Therapeutics).
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Pharmaceuticals), which has demonstrated encouraging results in treating patients with non-Hodgkin’s lymphoma. It should be noted that while conjugated antibodies can be more effective than “naked” mAbs, they can also cause more side effects, depending on the substance attached to them.15

Because of the heterogeneity of tumors, it has been recognized that for treatment to succeed, it may be necessary to employ a combination of targeted therapies.10 Therefore, during the past few years, attention has turned to developing mAbs that target a variety of tumor-associated antigens, such as surface glycoproteins.10 More information regarding FDA-approved therapeutic and ICB mAbs is presented in Table 2. Numerous new mAbs are in phase 3 clinical trials or are already being reviewed by regulatory authorities.5

Immune Checkpoint Blockers

ICBs are a type of mAb that have rapidly emerged as a promising cancer immunotherapy. They are becoming more broadly used, particularly in advanced cancer when standard chemotherapy has not been effective or is not a promising treatment option.7 Currently approved ICBs block immune checkpoints such as the cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) receptor or the interaction between programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1). Among others, the ICBs approved by the FDA have included ipilimumab (Yervoy, Bristol-Myers Squibb), nivolumab (Opdivo, Bristol-Myers Squibb), and pembrolizumab (Keytruda, Merck Sharp & Dohme Corp.), each for different indications such as melanoma, RCC, NSCLC, Hodgkin’s lymphoma, head and neck squamous cell carcinoma (HNSCC), and urothelial carcinoma.2,6,9

Evidence for clinical response with ICBs is accumulating in many different types of cancer, so treatment indications for these agents are expected to expand.6 Indeed, clinical trial data have shown that approximately 15% to 25% of patients (and sometimes more) with various types of cancer respond to ICBs.7,16 Positive objective response rates (ORR) following ICB treatment have been reported in many malignancies, including gastric cancer

<table>
<thead>
<tr>
<th>Generic Name (Brand, Manufacturer)</th>
<th>FDA Approval</th>
<th>Target</th>
<th>Structure/Description</th>
<th>Indication(s)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab (Campath, Genzyme)</td>
<td>2001</td>
<td>CD52</td>
<td>Humanized IgG1</td>
<td>B-cell CLL</td>
</tr>
<tr>
<td>Atezolizumab* (Tecentriq, Genentech)</td>
<td>2016</td>
<td>PD-L1</td>
<td>Humanized IgG1</td>
<td>Locally advanced or metastatic UC; metastatic NSCLC</td>
</tr>
<tr>
<td>Avelumab* (Bavencio, EMD Serono)</td>
<td>2017</td>
<td>PD-L1</td>
<td>Human IgG1</td>
<td>Merkel cell carcinoma; UC</td>
</tr>
<tr>
<td>Bevacizumab (Avastin, Genentech)</td>
<td>2004</td>
<td>VEGF</td>
<td>Humanized IgG1</td>
<td>Metastatic CRC and RCC; NSCLC; glioblastoma; cervical cancer; epithelial ovarian, fallopian tube, or primary peritoneal cancer</td>
</tr>
<tr>
<td>Blinatumomab (Blinlyto, Amgen)</td>
<td>2014</td>
<td>CD19/CD3</td>
<td>BITE</td>
<td>B-cell ALL</td>
</tr>
<tr>
<td>Brentuximab vedotin (Adcetris, Seattle Genetics)</td>
<td>2011</td>
<td>CD30</td>
<td>Chimeric IgG1 conjugated with mitotic toxin MMAE</td>
<td>HL; systemic anaplastic large cell lymphoma</td>
</tr>
<tr>
<td>Cetuximab (Erbitux, Eli Lilly)</td>
<td>2004</td>
<td>EGFR</td>
<td>Chimeric IgG1</td>
<td>CRC; HNSCC</td>
</tr>
<tr>
<td>Daratumumab (Darzalex, Janssen Biotech)</td>
<td>2015</td>
<td>CD38</td>
<td>Humanized IgG1</td>
<td>MM</td>
</tr>
<tr>
<td>Durvalumab* (Imfinzi, AstraZeneca)</td>
<td>2017</td>
<td>PD-L1</td>
<td>Human IgG1</td>
<td>UC</td>
</tr>
<tr>
<td>Ibritumomab tiuxetan (Zevalin, Spectrum Pharmaceuticals)</td>
<td>2002</td>
<td>CD20</td>
<td>Mouse IgG1 conjugated with radionuclide Y90</td>
<td>B-cell NHL</td>
</tr>
<tr>
<td>Ipilimumab* (Yervoy, Bristol-Myers Squibb)</td>
<td>2011</td>
<td>CTLA-4</td>
<td>Human IgG1</td>
<td>Metastatic melanoma</td>
</tr>
<tr>
<td>Nivolumab* (Opdivo, Bristol-Myers Squibb)</td>
<td>2014</td>
<td>PD-1</td>
<td>Human IgG4</td>
<td>Metastatic melanoma; metastatic NSCLC; advanced RCC; HL; HNSCC; advanced or metastatic UC</td>
</tr>
<tr>
<td>Obinutuzumab (Gazyva, Genentech)</td>
<td>2013</td>
<td>CD20</td>
<td>Glycoengineered IgG1</td>
<td>CLL; follicular lymphoma</td>
</tr>
<tr>
<td>Ofatumumab (Arzerra, Novartis)</td>
<td>2009</td>
<td>CD20</td>
<td>Human IgG1</td>
<td>CLL</td>
</tr>
</tbody>
</table>

Table continues
ICB treatment can be durable compared with that seen with chemotherapy or other targeted therapies. In some cases the toxicity observed in more than 10% of patients have been arthralgia, rash, and vomiting. With anti-PD-1/PD-L1 agents, the toxicities observed in more than 10% of patients have been anorexia, abdominal pain, diarrhea, fatigue, nausea, pruritus, rash, and vomiting. With anti-CTLA-4/PD-L1 agents, the toxicities observed in more than 10% of patients have been arthralgia, diarrhea, fatigue, nausea, pruritus, and rash. In addition, the AE

**Table 2  Therapeutic and Immune Checkpoint Blocker Monoclonal Antibodies Approved for Cancer Treatment**

<table>
<thead>
<tr>
<th>Generic Name (Brand, Manufacturer)</th>
<th>FDA Approval</th>
<th>Target</th>
<th>Structure/Description</th>
<th>Indication(s)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaratumab (Lartruvo, Eli Lilly)</td>
<td>2016</td>
<td>PDGFR-α</td>
<td>Human IgG1</td>
<td>Soft tissue sarcoma</td>
</tr>
<tr>
<td>Panitumumab (Vectibix, Amgen)</td>
<td>2006</td>
<td>EGFR</td>
<td>Human IgG2</td>
<td>Metastatic CRC</td>
</tr>
<tr>
<td>Pembrolizumab* (Keytruda, Merck Sharp &amp; Dohme)</td>
<td>2014</td>
<td>PD-1</td>
<td>Humanized IgG4</td>
<td>Metastatic melanoma; NSCLC; metastatic HNCC; HL; UC; MSI-H or dMMR CRC</td>
</tr>
<tr>
<td>Pertuzumab (Perjeta, Genentech)</td>
<td>2012</td>
<td>HER-2</td>
<td>Humanized IgG1</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Rituxumab (Rituxan, Genentech)</td>
<td>1997</td>
<td>CD20</td>
<td>Chimeric IgG1</td>
<td>NHL; CLL</td>
</tr>
<tr>
<td>Ramucirumab (Cyramza, Eli Lilly)</td>
<td>2014</td>
<td>VEGFR2</td>
<td>Human IgG1</td>
<td>NSCLC; gastric cancer; metastatic CRC</td>
</tr>
<tr>
<td>Siltuximab (Sylvant, Janssen Biotech)</td>
<td>2014</td>
<td>IL-6</td>
<td>Chimeric IgG1</td>
<td>Multicentric Castleman’s disease</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin, Genentech)</td>
<td>1998</td>
<td>HER-2</td>
<td>Humanized IgG1</td>
<td>Breast cancer; metastatic gastric or gastro-esophageal junction adenocarcinoma</td>
</tr>
<tr>
<td>Trastuzumab emtansine (Kadcyla, Genentech)</td>
<td>2013</td>
<td>HER-2</td>
<td>Humanized IgG1</td>
<td>Metastatic breast cancer</td>
</tr>
</tbody>
</table>

* Immune checkpoint blocker monoclonal antibodies.
† Please see the approved label for complete prescribing information regarding these agents.

Currently, the response observed with ICBs is most often a partial response (PR), at rates comparable to other targeted agents or chemotherapy. However, the degree of response observed with ICBs can be extreme (i.e., 80% to 90% tumor shrinkage), as well as durable. Until recently, surgeons were reluctant to operate on a patient with advanced metastatic cancer because doing so was unlikely to lengthen the patient’s life. However, in some of these patients, ICBs have been able to eliminate or shrink the tumors to sizes and locations where they can be surgically removed. Furthermore, even a PR to ICB treatment can durable compared with that seen with chemotherapy or other targeted therapies. In some cases the prolonged benefit that has been observed with ICB treatment can be considered a functional cure.
profile for anti-PD-1/PD-L1 agents is considered to be milder than that of anti-CTLA-4 ICBs; the rate of grade 3 or 4 toxicities with anti-CTLA-4 agents has been observed to be 20% to 30% versus 10% to 15% for anti-PD-1 agents.6,16 Importantly, although severe irAEs occur in a small minority of patients receiving ICB treatment, they can become life-threatening if not anticipated and appropriately managed.6 The main life-threatening toxicities with anti-CTLA-4 treatment and PD-1/PD-L1 agents are dysimmune colitis and interstitial pneumonitis, respectively.6 However, other severe toxicities associated with ICB treatment have been reported, including autoimmune anemia, infusion reactions, type-1 diabetes with ketoacidosis, Guillain–Barré syndrome, Stevens–Johnson syndrome, and thrombocytopenia with bleeding complications.6

Figure 1 provides a representation of the types of AEs that have been reported with ICBs.6

**CYTOKINES**

**Interferons**

In 1996, interferon (IFN)-α2b was approved by the FDA for the treatment of advanced melanoma.3,5 Since then, IFN-α2b has become the standard treatment for patients with stage III (resected node-positive) melanoma, and it is also strongly considered for patients with high-risk stage IIB or IIC melanoma.3,5 The ORR for IFN-α2b in patients with advanced melanoma has been reported as 22%; however, response has been limited to patients with a small disease burden.21

Once IFN-α2b was observed to have antitumor activity against metastatic melanoma (MM), the Eastern Cooperative Oncology Group conducted a study in stage II and III high-risk melanoma patients who were assigned to receive either a year-long treatment of high-dose IFN-α2b or standard chemotherapy.22 This study showed that high-dose IFN-α2b increased median relapse-free survival by nine months and overall survival (OS) by one year, and had also improved both of these measures by nearly 10% at five years.22 This study also found that IFN-α2b treatment improved patient quality of life and was cost-effective.22 Studies that have investigated the timing and dosing of IFN-α2b as an adjuvant therapy for advanced melanoma have not agreed on the best method of administration.3

IFN-α has also been used to treat patients with RCC or hematologic malignancies.3,5 The use of IFN-α for the treatment of patients with RCC has demonstrated small benefits, improving survival by about four months.23 However, this use has decreased due to the availability of therapeutic mAbs, such as axitinib (Inlyta, Pfizer), sorafenib (Nexavar, Bayer...
HealthCare Pharmaceuticals), and sunitinib (Sutent, Pfizer) and the ICB nivolumab for the treatment of RCC, which do not have the toxicities associated with IFN-α treatment. In hematologic malignancies, IFN-α2b has also been used to treat hairy cell leukemia with some success, but other agents are preferred for the treatment of this disease. The most common AEs observed with IFN-α treatment are flu-like symptoms, including chills, fever, headache, and myalgias. These effects may be severe and have been associated with the withdrawal of a significant proportion of patients enrolled in IFN-α trials. Additional toxicities associated with IFN-α treatment include anorexia, depression, hepatic dysfunction, and thyroid abnormalities. However, these effects usually reverse rapidly upon treatment cessation.

Interleukins
High-dose recombinant IL-2 (rhIL-2) was first approved for the treatment of metastatic RCC by the FDA in 1992 and then received approval for MM in 1998. For RCC, a high-dose of rhIL-2 (600,000–720,000 IU/kg) is administered as an intravenous bolus over consecutive days. This regimen is repeated for several cycles depending on tumor response. A similar treatment regimen of high-dose rhIL-2 therapy is followed for the treatment of MM.

A longitudinal study spanning 20 years showed that high-dose intravenous rhIL-2 treatment of RCC produced an ORR of 20% and a CR in 8.9% of patients. During follow-up visits ranging from 24 to 221 months after therapy, 83% of the patients in CR remained recurrence free at last follow-up visit. In MM, high-dose intravenous rhIL-2 treatment is expected to achieve lower ORR and CR, which were observed in 16% and 6% of patients, respectively. Nonetheless, because durable responses have been observed in patients with MM who had achieved a CR following rhIL-2 treatment, this treatment is considered a valid option for these patients.

AEs observed with rhIL-2 treatment include anemia, cardiac arrhythmia, chills, confusion, diarrhea, eosinophilia, fever, hypotension, lethargy, metabolic acidosis, nausea, thrombocytopenia, and organ failure (including hepatic and renal failure). Because of potential organ toxicity, patients who are expected to be treated with rhIL-2 are routinely screened for organ function prior to its use, and extra caution is taken when patients with organ failure are treated. Even in patients who have normal organ function, toxicities can occur with high-dose rhIL-2 therapy that require treatment cessation to allow the patient to recover. Fortunately, although they can be severe, most AEs occurring with high-dose rhIL-2 treatment tend to be rapidly reversible.

This therapy may also cause a severe, potentially life-threatening reaction due to the stimulation of proinflammatory cytokines, leading to vasopermeability, vascular leak, and a sepsis-like syndrome. Because of the potential for these severe toxicities, administration of rhIL-2 is often restricted to treatment centers with established protocols and experienced clinicians. In some institutions, rhIL-2 is administered only in the intensive care setting.

Because of the severe toxicity seen with rhIL-2 treatment, studies were conducted to determine the efficacy of alternative dosing regimens. These studies involved a change in the route of administration and dose, or the administration of rhIL-2 with other treatments. In a phase 3 study by the National Cancer Institute, standard high-dose rhIL-2 treatment was compared to low-dose treatment (72,000 IU/kg) in the treatment of RCC. High-dose rhIL-2 achieved a response rate of 21%, compared with 13% for low-dose treatment \((P = 0.048)\). In addition, the duration of response and survival in patients who had achieved a CR was determined to be higher in those who had received a high dose rather than a low dose \((P = 0.04)\). As expected, a higher incidence of AEs was seen in the high-dose group, but there was no difference in the incidence of death attributable to rhIL-2 treatment between the two groups.

CANCER VACCINES
Cancer vaccines have been studied in a wide variety of tumor types, but to date they have yielded mostly discouraging results. The overall outcomes of treating established tumors with vaccines have been suboptimal, with clinical benefit in the majority of patients being prolonged survival rather than remission. However, one vaccine, sipuleucel-T (Provenge, Dendreon), has been approved for the treatment of men with prostate cancer.

Preclinical models have demonstrated that once tolerance is established in poorly immunogenic tumors, treatment with vaccines alone is ineffective at reducing a significantly established tumor burden. Only a limited activation and expansion of tumor-specific T cells occurs in response to treatment with a vaccine, which is likely a consequence of: 1) tumor-mediated immune suppression; 2) low affinity of autologous T cells to self-antigens; and 3) patient immune system suppression due to other treatments, such as systemic chemotherapy administration. Although many newer-generation vaccines can activate dendritic cells, T-cell tolerance remains a barrier that is difficult to overcome by vaccination alone. Some researchers have suggested that the inability of cancer vaccine treatment to induce a remission is due to “suboptimal design.” They suggest that better results may be obtained with improvement in the choice of antigen, and with combination therapy using other agents (such as ICBs) that reverse immunosuppressive mechanisms.

Polyvalent cell-based cancer vaccines (such as dendritic-cell or tumor-cell vaccines) can include a wide range of tumor-associated antigens and are considered promising; however, technical difficulties impede their clinical use. With respect to antigen choices, neoantigens that appear as a result of tumor-specific mutations have been considered particularly relevant to therapeutic cancer vaccination because T cells for these antigens are not deleted by central tolerance mechanisms, which renders them inactive. However, the process of identifying tumor neoantigens is labor intensive and time consuming, so few have been found. This is a major limitation for this technique because most known tumor antigens are tumor-associated and not tumor-specific. Although these antigens are broadly expressed by malignant cells, they are also expressed by normal tissues, so cancer treatments targeting tumor-associated antigens can potentially cause irAEs. Therefore, the ideal goal of therapeutic vaccination is to induce an immune response that targets antigens that are only expressed by cancer cells.
Peptide-Based Vaccines

Peptide-based vaccines have two major limitations in cancer treatment. First, knowledge of the immunogenic tumor-specific proteins, their presence in different tumors, and identification of the peptide sequence within these proteins that elicit the immune response is necessary. Second, because these peptide-based vaccines are human leukocyte antigen (HLA)-restricted, prior knowledge of the patient’s HLA type is also required. Most tumor antigens are proteins that are structurally homologous among different individuals; however, small nine- to 14-amino-acid peptides are expressed on the tumor cell surface in association with HLA molecules that must also be identified. Despite these limitations, initial clinical studies have shown that peptide vaccines can stimulate antigen-specific immune responses and have highly favorable toxicity profiles, so there is interest in further investigating these agents.

The use of peptide vaccines targeting three well-characterized melanoma antigens (MART-1, gp100, and tyrosinase) has been investigated. These antigens were targeted individually, as well as in a multi-epitope approach, in order to broaden the immune response elicited against melanoma. In a phase 3 clinical trial, 185 patients (identified as type HLA-A2+) with locally advanced stage III or IV cutaneous melanoma were randomly assigned to receive rhIL-2 alone or gp100 peptide vaccine followed by rhIL-2. The clinical response was found to be greater in the group who had also received the gp100 peptide vaccine, compared with those receiving rhIL-2 alone (16% versus 6%, respectively; \( P = 0.03 \)). Patients who had received the vaccine also experienced significantly longer progression-free survival (2.2 months versus 1.6 months; \( P = 0.008 \), as well as longer OS (17.8 months versus 11.1 months; \( P = 0.06 \)). The AEs experienced by patients in this study were determined to result primarily from rhIL-2.

Peptide vaccines have also been investigated in clinical trials involving patients with breast cancer. The most studied immunogenic peptide that has been observed in breast cancer is E75, which is an HLA-A2/A3-restricted, nine-amino-acid peptide derived from the HER-2 protein. A phase 1/2 study investigated E75 given in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) in an adjuvant setting to prevent disease recurrence in high-risk node-negative and node-positive breast cancer patients. Administration of the E75 peptide vaccine resulted in increased disease-free survival of 94.3% in vaccinated patients, compared with 86.8% in control patients.

In this trial, the E75 peptide vaccine was associated with only mild local and systemic toxicities. The local toxicities were judged to be grade 1 in 81% and grade 2 in 19% of patients, the most common being erythema or pruritus at the injection site. Systemic toxicities were judged as grade 0 to 2, fever (grade 1), and pruritus (grade 1 or 2). The AEs experienced by patients in this study were determined to result primarily from rhIL-2.

Immune or Dendritic Cell-Based Vaccines

In 2010, sipuleucel-T was the first cancer vaccine to obtain FDA approval for the treatment of asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer. Sipuleucel-T is an autologous cell-based vaccine designed to use the patient’s own immune system to generate antitumor immunity to extend patient OS. To develop this vaccine, the patient must undergo leukapheresis to obtain peripheral blood containing antigen-presenting cells (APCs), including dendritic cells. The APCs are exposed to recombinant antigen PA2024 (which includes prostatic acid phosphatase [PAP], a protein expressed in approximately 95% of prostate cancers) and GM-CSF, which they take up, resulting in the generation of mature PAP-specific APCs that can activate patient T cells to target the PAP expressed on prostate cancer cells.

The efficacy of sipuleucel-T was demonstrated in the double-blind, placebo-controlled IMPACT trial, which enrolled 512 patients. In this study, 341 patients who received sipuleucel-T had a median OS of 25.8 months, compared with 21.7 months for the 171 patients receiving placebo. Time to disease progression was similar in both groups (14.6 weeks versus 14.4 weeks). Endpoints used to measure immune response (T-cell levels and antibody titers) were higher in patients who received the vaccine, confirming immune-system stimulation. Despite modest efficacy, sipuleucel-T has a low toxicity profile, which may make it an attractive option for the treatment of patients with metastatic castration-resistant prostate cancer.

The most commonly reported AEs, occurring in 10% to 50% of patients, included anemia, back pain, chills, fatigue, fever, headache, and nausea. These AEs usually resolve within one to two days after infusion. Less frequent side effects, observed in less than 10% of patients, included hematuria, cerebrovascular events, hypertension, hypokalemia, rash, and respiratory symptoms.

Tumor Cell-Based Vaccines

The efficacy and safety of tumor cell-based vaccines have also been studied in the treatment of cancer. MVax (AVAX Technologies, Inc.), an investigational autologous tumor-cell vaccine, was developed using melanoma tumors. The treatment of melanoma with MVax was investigated in a phase 2 clinical
Oncolytic Virus-Based Vaccines

Oncolytic viruses can selectively infect cancer cells to cause direct lysis, can disrupt the tumor vasculature, and can induce an antitumor immune response.35 The association between immune activation and oncolytic virus efficacy has led to interest in viruses that encode immunostimulatory agents.35 One such virus, talimogene laherparepvec (T-VEC), received FDA approval in 2015 as Imlygic (Amgen) for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in melanoma that recur after initial surgery.36 T-VEC is an intratumoral injection of herpes simplex virus type 1 genetically modified to produce GM-CSF in the tumor microenvironment, causing tumor lysis.36 In a phase 3 trial, 436 patients with advanced unresectable melanoma received periodic intralesional injections of T-VEC or administration of GM-CSF.36 Patients receiving T-VEC had an improved durable response rate (a CR or PR maintained for at least six months), but no statistically significant improvement in OS compared with patients given GM-CSF.36

CELL-BASED IMMUNOTHERAPY

Autologous Cell Transfer

In the late 1980s and early 1990s, Rosenberg and colleagues first utilized tumor-infiltrating lymphocytes (TILs) concomitantly with rhIL-2 to treat MM patients.1,3,37 In a study enrolling 86 patients, 34% (n = 29) of those receiving this treatment exhibited a CR or PR; however, only five of these patients had achieved a CR.38 One of the major obstacles that was identified was the transient survival of the transferred cells.39 After one week, only 0.1% of the total cells in the body were found to be transferred cells, despite 80% of the patients having received more than 10^11 cells.38 The transient survival of the TILs led to subsequent studies that investigated lymphodepleting chemotherapy combined with autologous cell transfer.39 These studies successfully demonstrated the persistent clonal repopulation of the infused TILs following lymphodepletion.39

After this technique was discovered, a study was conducted to better characterize the efficacy of various methods of lymphodepletion.40 This study evaluated two approaches—chemotherapy and total body irradiation (TBI).40 Ninety-three patients were enrolled; 43 received chemotherapy and 50 received TBI at a dose of 2 Gy (n = 25) or 12 Gy (n = 25).40 Both chemotherapy and TBI were administered in combination with rhIL-2 therapy.40 The study reported ORRs of 49%, 52%, and 72% for chemotherapy, 2 Gy TBI, and 12 Gy TBI, respectively.40 A follow-up study found that 22% of patients receiving treatment had achieved CR.40 Furthermore, the patients who had achieved CR had three- and five-year survival rates of 100% and 93%, respectively.19 The three- and five-year survival rates reported for the entire group were 36% and 29%, respectively.19 In these studies, the AEs associated with TIL treatment were minimal, with most attributed to rhIL-2 therapy and TBI.3 However, despite promising results, limitations remain regarding the use of TIL treatment.3 The time and cost required for TIL production is a major challenge.18 Obtaining a sufficient number of TILs is also difficult because of cell loss during TIL purification.3 Because of the limitations involved in generating autologous TILs, nonautologous approaches are being investigated.3,5

One of the most promising developments with respect to the use of autologous cell transfer to treat cancer has been the development of chimeric antigen receptors (CARs).3,5,11 In a seminal study, CAR-modified T cells successfully targeted the B-cell antigen CD19 in a patient with CLL.3 Evaluation of the patient’s bone marrow found no evidence of CLL 28 days after the initial CAR injection.3 There were also no acute AEs; the only significant toxicity was grade 3 tumor lysis, which had been expected due to a large disease burden.3 In another study, patients with B-cell acute lymphoblastic leukemia and CLL were treated with CAR-based immunotherapy treatments that targeted the surface antigen CD19.19 The CAR T cells that had been infused persisted for more than one year in some patients, and the antitumor effect was associated with depletion of B-lymphopoiesis.3 The most frequently occurring serious AE associated with CAR T-cell therapy was cytokine release syndrome (CRS).3 Other types of cancer, such as carcinomas or AML, have been treated with CAR T-cell–based therapy without significant success.3 Further studies are ongoing to determine the efficacy of CAR T cells in treating a number of malignancies.3,5

While toxicities related to CAR T-cell therapy are not fully understood, they may be so severe as to limit the use of this approach.41 CRS, marked by fever, hypotension, tachycardia, and other symptoms, has emerged as a prominent AE.41 A higher disease burden may predict more severe CRS, and patients with limited comorbidities may be better able to tolerate the surge of cytokines.41 After administration of CAR T-cell therapy, close hemodynamic monitoring is vital; hypotension must be managed aggressively.41 Tocilizumab and corticosteroids have been used to treat CRS-related AEs after CAR T-cell therapy.41

Cancer Immunotherapy—Part 2: Efficacy, Safety, and Other Clinical Considerations
Allogeneic HSCT

Allo-HSCT plays a major role in the standard-of-care treatment of patients with AML, acute lymphoblastic leukemia, CLL, Hodgkin’s lymphoma, and non-Hodgkin’s lymphoma.1–3 In AML, patients who lack favorable prognosticators, allo-HSCT has been shown to provide an improvement in four-year OS (40% versus 30%) and disease-free survival (33% versus 17%) compared with patients who have received non-allo-HSCT-based therapies.42–44 Allo-HSCT is also often used to treat patients with relapsed hematologic malignancies following achievement of a second remission or after the first CR if the cancer is associated with high-risk prognostic markers, such as molecular and cytogenetic mutations.3 In relapsed or refractory AML, allo-HSCT has been shown to provide the greatest chance of a cure.3

Although allo-HSCT may be one of the most fundamental immunotherapeutic approaches, it is also one of the most toxic cancer treatments.3 Unlike the AEs that occur with cytokine therapy, which are reversible following cessation of treatment, AEs associated with allo-HSCT are long-lasting due to the memory effects associated with the infused donor graft.3 These toxicities can appear or continue years after allo-HSCT treatment because the infused donor immune cells are repeatedly primed by infectious exposures that can cause autoimmune responses against normal tissues.3 A major AE associated with allo-HSCT is graft-versus-host disease (GvHD), which is classified as either acute (aGvHD) or chronic (cGvHD).3 This classification was initially based on the time of onset after donor-cell infusion, with the 100th day acting as the cutoff for aGvHD.3 However, GvHD is now more accurately classified based on the type of symptoms and the tissue damage that occurs.45

GvHD occurs in almost 50% of patients receiving allo-HSCT, with cGvHD accounting for 22% of treatment-related patient mortality between the second and fifth year after treatment.46 The most common form of GvHD affects the skin, ranging in presentation from a localized, mild skin rash to extensive involvement that includes bullous lesions and sloughing.47,48 However, GvHD can also involve the upper gastrointestinal (GI) tract, manifesting with upper GI symptoms, including nausea and vomiting (which can cause severe anorexia), and/or lower GI symptoms, such as severe diarrhea.3 GvHD can also manifest with hepatic symptoms related to biliary obstruction, which can then progress to fulminant liver failure.47,48 The mainstay of GvHD treatment is immunosuppression, specifically corticosteroids.3 However, long-term corticosteroid treatment is associated with major side effects, including aseptic bone necrosis, adrenal insufficiency, cataract formation, diabetes mellitus, myopathy, opportunistic infections, and osteoporosis.3 In addition, 40% of patients with GvHD are refractory to corticosteroid treatment and have a poor prognosis for long-term survival (5% to 30%).49 Presently, there is no well-defined approach to treating patients with steroid-refractory GvHD (SR-GvHD); however, therapies that inactivate alloreactive donor T cells or proinflammatory cytokines or their receptors have been investigated.49 An analysis of 25 retrospective studies or phase 2 trials concluded that the weighted average six-month survival for patients with SR-GvHD treated with these therapies was 49%.49 Among the agents used were an anti-CD25 monoclonal antibody (basiliximab [Simulect, Novartis]), anti-tumor necrosis factor-alpha (infliximab [Remicade, Janssen] and etanercept [Enbrel, Amgen]), antithymocyte globulin, anti-IL-2α (nilolimomab), anti-CD52 (alemtuzumab [Campath, Genzyme]), and pentostatin, among others.49

COMBINATION CANCER IMMUNOTHERAPY TREATMENTS

In some patients, treatment with a single cancer immunotherapy is sufficient to achieve a prolonged clinical benefit or even a cure.1 This is in accordance with the principles of natural selection, in that if a treatment impedes the chief mechanism by which a cancer has evolved to successfully escape the host immune system, monotherapy may be sufficient to reawaken the body’s anticancer immune response.1 To date, administering agents that target single cancer pathways or molecular abnormalities has achieved good clinical responses and modestly improved survival in some cancers.2 However, this reductionist approach to cancer treatment may be insufficient to overcome the challenges that prevent improved outcomes.2 In some cases, to achieve long-term efficacy, it may be necessary to use drug combinations that target several molecular alterations and other survival mechanisms that specific cancers have adopted.1,2 But for this approach to succeed, researchers must better understand the nascent resistance mechanisms that are clinically relevant to impeding effective immunotherapy.1 For these reasons, combination therapy could potentially be one of the most challenging but most promising cancer treatment strategies in the future.2

Many treatments that combine cancer immunotherapy agents together or with other types of drugs are currently being investigated or are expected to be in clinical trials within the next few years.1 Cancer immunotherapies will be investigated in combination with one another, chemotherapy, and radiation in an effort to block a broader spectrum of cancer-cell signaling and exploit cytoreductive strategies.1 The combination of PD-1 and CTLA-4 ICBs has already demonstrated efficacy in treating malignant melanoma.1 As new ICBs that target additional checkpoints are developed, they will also likely be studied in combination treatments.4 Combination treatments of therapeutic vaccines administered together with ICBs and agonists for costimulatory pathways have also proven capable of generating significant antitumor responses, even in cases of established metastatic cancer.9 Other strategies that are being investigated include combining therapeutic vaccines with novel immune modulators or cytokines.5 The combination of gp100 peptide with rhIL-2 has been very effective in improving clinical outcomes in patients with melanoma; however, this approach has not yet become part of standard treatment.2 Combinations of ICBs with cellular therapies are also being investigated.1

Although combined immunotherapy treatment is a viable strategy for improving efficacy, increased toxicity has been reported when ICBs have been combined or administered with other targeted therapies or conventional chemotherapy.6 As noted earlier, the rate of grade 3 or 4 toxicities has been reported to be 20% to 30% for anti-CTLA-4 and 10% to 15% for anti-PD-1 ICBs.6 However, when ipilimumab and nivolumab were administered in combination, the rate of grade 3 or 4 toxicities was observed to be 55%.6 Similarly, in a study that investigated the combination of ipilimumab with conventional
In elderly patients, the incidence of irAEs is similar to that in younger patients, and the severity of irAEs is comparatively low.6,17 To encourage early identification of irAEs, patients should be urged to promptly report new symptoms to their caregivers or to a healthcare provider, as early detection and prompt treatment of irAEs could limit their severity.5,17 At any time during treatment, patients should be advised to report new symptoms or the worsening of pre-existing symptoms to their healthcare provider.6,17

Before Initiating ICB Cancer Immunotherapy

Before initiating ICB treatment, patients should be informed that chronic viral infection or autoimmune disease should be taken because these agents may potentiate these conditions.6,17 Proposed principles and guidelines are summarized in the following section.

Cancer Immunotherapy—Part 2: Efficacy, Safety, and Other Clinical Considerations
tation, and imaging conducted at baseline should be taken for reference.6,17 Minimal testing for patients should include renal function, serum electrolytes, a complete blood count, liver function tests, and a thyroid evaluation.6,17 Chest imaging should be performed at baseline for reference in case pulmonary toxicity occurs during ICB treatment.6,17 Baseline comorbidities should be properly evaluated both before initiation and during treatment.6,17 During the physical evaluation, the clinician should look in particular for symptoms of gastrointestinal (diarrhea), respiratory (dyspnea, cough), or dermatological (pruritus, rash) issues, as well as nonspecific general signs that may suggest endocrine toxicity, such as thyroid dysfunction.6,17

Monitoring for irAEs in Patients on ICBs

The time to onset and resolution of irAEs occurring with ICBs differs from what is often seen with conventional cancer treatments.6 The majority of irAEs usually occur within the first four months of ICB treatment; however, immune toxicities can occur at any time during therapy, as well as several months after discontinuation.6,17 Therefore, careful monitoring for irAEs throughout treatment and after termination is warranted.6,17 A suspected or diagnosed irAE should always be closely monitored so that any worsening or relapse is detected.6,17 Although new symptoms or worsening of pre-existing symptoms should be considered and investigated as a possible irAE, these symptoms may also be associated with disease progression or intercurrent infection, which must first be ruled out.6,17 Elderly patients should be monitored carefully, as associated comorbidities can more easily worsen.6,17 Laboratory tests to monitor the patient while on ICB treatment should specifically assess hematologic toxicity (thrombocytopenia, anemia), liver function (transaminase elevation), and renal toxicity (increased serum creatinine).6,17 Thyroid-stimulating hormone should be tested routinely every two to three months.6,17 Because irAEs may occur after treatment is discontinued, it has been proposed that patient clinical and laboratory evaluations should be conducted every three to six months for a year after treatment cessation.6,17

Treating irAEs in Patients on ICBs

Once an irAE is detected, it should be closely monitored so that worsening or relapse is detected promptly; practitioners should also inform patients about self-monitoring.6,17 Most irAEs occurring with ICBs are mild and can be treated symptomatically.6,17 Treatment of irAEs may also require immunosuppressive agents, such as steroids, to target a hyperimmune response.6 However, some symptomatic treatments, such as antihistamines for pruritus or corticosteroids, may expose elderly patients to iatrogenic events, such as mental-status disturbance or worsening diabetes.6,17 It should also be considered that the immunosuppressive activity of corticosteroids may attenuate the antitumor immune system stimulation triggered by ICBs.6 Depending on the severity of the irAEs, close monitoring, interruption, or discontinuation of the ICB, introduction of corticosteroid therapy, and in some cases more immunosuppressive medications such as anti-tumor necrosis factor therapy may be required.6,17 Currently, dose reduction for the FDA-approved ICBs is not recommended.6,17

Resolution of irAEs can be highly variable across different types of toxicities—gastrointestinal, renal, and hepatic toxicities usually improve quickly upon the initiation of immunosuppressant treatment, whereas rash and endocrine-related irAEs tend to be more chronic.6,17 Endocrine insufficiencies may require long-term hormonal substitution.6,17 If required, corticosteroid treatment should be tapered gradually over a period of more than one month to avoid the recurrence or worsening of the irAE.6,17 Lastly, to avoid life-threatening opportunistic infections, prolonged immunosuppressive treatment should be properly monitored and prophylactic treatment instituted.6,17

CONCLUSION

The use of cancer immunotherapy agents to stimulate the immune system to recognize and attack malignancies has provided new possibilities for effective cancer treatment.4 The last few decades have seen the development of a range of novel and effective immunotherapies, broadening oncologists’ choice of weapons to fight cancer.5 Many cytokine-based approaches and numerous mAbs have already become the standard of care for treating various malignancies; however, other strategies, including cancer vaccines and cell-based approaches, remain experimental with few exceptions.5 Fortunately, these and other immunotherapy methods are continuing to be investigated in clinical trials and will hopefully provide long-awaited cures for patients with relapsed and refractory malignancies.

The third article of this series, in the August issue of P&T, will discuss challenges and future trends.

REFERENCES
