Advances in the understanding of the immunogenicity of tumors have provided the basis for immuno-oncology, the development of immunotherapeutic agents that augment the patient’s antitumor immunity and disrupt the immune-regulatory circuits that allow tumors to evade the immune system. Two immunomodulatory agents recently have been introduced for the treatment of malignancy: sipuleucel-T and ipilimumab. Unlike cytotoxic chemotherapy, immunotherapies stimulate the patient’s immune system to mount or augment existing endogenous antitumor immune responses. Both agents have demonstrated significant improvements in long-term overall survival in patients. Like other immunotherapies, sipuleucel-T and ipilimumab also are characterized by adverse events that manifest as immune-related inflammatory conditions that typically are low grade. Management guidelines have been developed and emphasize early recognition of the signs and symptoms of immune-related adverse events and treatment with corticosteroids. Because these events can manifest even after the cessation of therapy, patients treated with immunotherapies should continue to be followed by their oncology team and other healthcare providers.

Rajni Kannan, BS, MS, RN, ANP-BC, and Kathleen Madden, RN, BSN, MSN, FNP-BC, AOCNP®, and Stephanie Andrews, MS, ANP-BC

Cancer immunotherapy was observed over 100 years ago when the remission of tumors was generally associated with acute infections, leading to the realization that activated immunity in response to an underlying infection was responsible for the observed tumor regression (Coley, 1891; Thomas & Bandini, 2011). Since then, advances in the understanding of molecular interactions between tumors and the immune system have provided the basis for development of immunostimulatory and inhibitory monoclonal antibodies, cancer vaccines, immune adjuvants, and cytokines (see Table 1), which all aim to augment protective antitumor immunity and disrupt the immune-regulatory circuits that allow tumors to evade the immune system (Dougan & Dranoff, 2009).

Two immunomodulatory agents, sipuleucel-T and ipilimumab, have recently received regulatory approval for the treatment of malignancy (Pazdur, 2013; Witten, 2013). Sipuleucel-T is a dendritic cell (DC)–based vaccine approved by the U.S. Food and Drug Administration (FDA) in 2010 for the treatment of asymptomatic or minimally symptomatic metastatic prostate cancer (Witten, 2013). Ipilimumab, an anticytotoxic T lymphocyte–associated antigen (CTLA)-4 monoclonal antibody that augments T-cell activation and proliferation, was approved by the FDA in 2011 for the treatment of advanced or metastatic melanoma (Pazdur, 2013).

This article provides an overview of tumor immunology supporting the rationale for the development of these new immunotherapeutics and the patterns of response seen with them. Common adverse events (AEs) are discussed, together with practical management strategies. The aim of this article is to provide oncology nurses with the knowledge and tools for clinical management of patients treated with these new immunotherapies.

Overview

Classic hallmarks of cancer include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating...
Immune defense against tumors is multifaceted, initially mediated by innate immune system and, later, by the adaptive immune system (Bhawan, 2007) (see Figure 1). The innate immune system is the body's initial defense against foreign pathogens. This is a nonspecific defense mechanism in which phagocytes, natural killer cells, and complement proteins respond to chemical properties common to certain pathogens (Abbas & Lichtman, 2006). Adaptive immune responses, on the other hand, develop later and are mediated by lymphocytes and their products in response to specific proteins that are recognized as foreign (antigens).

Two types of adaptive immunity exist, cell-mediated and humoral (antibody-mediated). Cell-mediated immunity is mediated by T-lymphocytes (T cells) that either induce death in cells that express antigens (cytotoxic T cells) or activate cells implicated in innate immunity or humoral immunity. Humoral immunity is mediated by antibodies that are secreted by transformed B-lymphocytes (plasma cells) following antigen exposure. When these antibodies bind to antigenic proteins expressed on cells, the cells are flagged for destruction. In contrast, activation of the adaptive immune response allows the immune system to "remember" an encounter with a specific antigen and swiftly respond at a subsequent encounter by means of activated B and T cells (Abbas & Lichtman, 2006).

In the cancer setting, tumor cells may express tumor-associated antigens (TAAs), which are not present on normal cells and can induce an adaptive immune response if they are recognized as foreign (Rivoltini et al., 2002). Antibodies and activated T cells specific to TAAs have been found in blood or tumor samples from numerous types of cancer (Nagorsen, Scheibenbogen, Marincola, Letsch, & Keilholz, 2003), suggesting that, in these cases, an antitumor immune response has been mounted but has not completely eradicated the tumor.

This resistance to immune attack has been postulated to occur, at least in part, through immunoediting, the process by which immune-mediated tumor cell destruction inadvertently selects residual tumor cells that are resistant to immune attack, resulting in a tumor that grows in spite of an ongoing immune response (DuPage et al., 2012). In a murine sarcoma model, tumors not subject to T-cell-mediated immunoediting in mice lacking cytotoxic T cells were highly susceptible to rejection when transplanted into wild-type, immune-competent animals. In contrast, tumors that developed in mice with a full complement of T cells exhibited reduced expression of TAAs and grew rapidly when transplanted into wild-type mice, presumably through the selective outgrowth of cells that escaped immune attack (DuPage, Mazumdar, Schmid, Cheung, & Jacks, 2012).

In addition to altering expression of TAAs, evidence suggests that tumors also leverage immune-checkpoint pathways as a mechanism of immune resistance. Immune-checkpoint pathways are naturally occurring regulatory mechanisms that limit the extent of antigen-specific immune activation. Under physiological conditions, these checkpoints maintain self-tolerance and prevent immune-mediated damage to normal tissue; however, in
the cancer setting, these checkpoints may become dysregulated (Peggs, Segal, & Allison, 2007). One of the most well-studied immune-checkpoint pathways is that of CTLA-4. A T cell recognizes a specific antigen through cell surface interaction with an antigen-presenting cell (APC), such as a scavenger DC, via the T cell receptor (TCR). Translation of TCR stimulation into full T-cell activation requires a second signal, in which B7 molecules on the APC surface bind with CD28 receptors on the T cell surface (Anassi & Ndefo, 2011; Boasberg, Hamid, & O’Day, 2010; Hoos, Ibrahim, et al., 2010; Medzhitov et al., 2011; Melero, Hervas-Stubbs, Glennie, Pardoll, & Chen, 2007; Salama & Hodi, 2011; Weber, 2010). To limit the immune response, TCR stimulation also triggers cell surface expression of CTLA-4, which competes with CD28 for binding to B7 on APCs (see Figure 2). This process attenuates the costimulatory signal and blunts T cell activation and proliferation. The most direct experimental evidence came from studies of CTLA-4–deficient mice, which showed massive expansion of autoreactive T cells followed by death; conversely, CTLA-4 antibody blockade in mice prevented B7 interactions while preserving CD28 signaling, and expansion and activation of T cells were observed. Additional in-vitro melanoma and animal model studies confirmed the anti-tumor effects of anti–CTLA-4 antibodies (Hoos et al., 2010a).

Immunotherapeutic treatment of cancer is designed to stimulate, strengthen, or restore endogenous responses to tumors. A study of immunotherapeutic mechanisms stimulated the antitumor response by inhibiting suppressor mechanisms or increasing the immunogenicity of tumor cells (Mellman, Cuocos, & Dranoff, 2011).

The slow growth of many prostate cancers makes immunotherapy an attractive therapeutic intervention (Drake & Antonarakis, 2012). Therefore, antigen-specific and antigen-independent immunotherapeutic treatments for prostate cancer have been explored. Sipuleucel-T is a prostate cancer vaccine consisting of autologous peripheral-blood mononuclear cells, including APCs, which have been activated ex vivo with a recombinant fusion protein consisting of a prostate antigen (prostatic acid phosphatase [PAP]) fused to an immune-cell activator (Kantoff et al., 2010). PAP is a TAA that is highly expressed in prostate cancer cells, but not on other tissue (Anassi & Ndefo, 2011). Although its mechanism of action has not been fully elucidated, it has been proposed that sipuleucel-T activates T cells, which proliferate as part of the cell-mediated immune response and attack PAP on prostate cancer cells. In contrast, the anti–CTLA-4 antibody, ipilimumab, approved as therapy for advanced melanoma and currently in phase 3 investigation for advanced prostate cancer, targets a systemic immune-suppressor pathway instead of one specific TAA. The ipilimumab binding of CTLA-4 may allow the immune system to maintain responsiveness against many TAAs (Kirkwood et al., 2008, 2012; Pandolfi et al., 2011; Weber, 2010).

**Patterns of Response**

Unlike cytotoxic chemotherapy, immunotherapies stimulate the patient’s immune system to mount an endogenous antitumor immune response (Dougan & Dranoff, 2009). The nature of this immune-based response means clinically observed changes can be very different from the typical response patterns.
observed in patients on conventional cytotoxic treatment. In fact, clinical response patterns with immunotherapies have been noted to extend beyond those of cytotoxic agents and can manifest after an initial increase in tumor burden or after the appearance of new lesions, conventionally defined as progressive disease (Wolchok et al., 2009). To date, ipilimumab provides the most characterized example of the four most common patterns (Wolchok et al., 2009). First, as with chemotherapy, patients treated with immunotherapy may demonstrate an immediate response in baseline lesions without the presence of new lesions. Second, immunotherapy can yield durable, stable disease, which may be followed by a slow, steady decline in total tumor burden. Third, immunotherapy can occasionally result in a response in the presence of development of new lesions, which may have been present at baseline, but were radiographically undetectable. Lastly, treatment with immunotherapy may rarely yield a response following an increase in total tumor burden. Each of these patterns of response has been described following treatment of metastatic melanoma with ipilimumab (Hoos, Eggermont et al., 2010) (see Figure 3).

The most appropriate endpoints for evaluation of response to immunotherapies such as sipuleucel-T (Thara et al., 2012) and ipilimumab (Hoos, Eggermont, et al., 2010; Wolchok et al., 2009) remain debatable. Because patterns of response differ to those observed with chemotherapy or radiotherapy, conventional Response Evaluation Criteria in Solid Tumors or World Health Organization criteria, designed to detect early effects of cytotoxic agents, may not provide a complete assessment of immunotherapeutic agents. Therefore, novel criteria for the evaluation of antitumor responses with immunotherapeutic agents, termed immune-related response criteria (irRC), have been proposed (Hoos, Eggermont, et al., 2010; Wolchok et al., 2009).

Although most agree that traditional response criteria may not capture all responses to immunotherapies, irRC and other proposed alternatives have not yet been studied in prospective trials. The most appropriate measures of immunotherapeutic response in patients remain an evolving concept for future studies.

### Immune-Related Adverse Events

Immunotherapies are commonly characterized by AEs that manifest as inflammatory conditions, known as immune-related AEs (irAEs). Typically, irAEs are low grade and manageable. In the next section, the authors discuss the management of AEs commonly experienced by patients administered either sipuleucel-T or ipilimumab.

#### Sipuleucel-T

Sipuleucel-T is administered as three, one-hour IV infusions at about two-week intervals for treatment of metastatic prostate cancer. Patients should be premedicated with oral acetaminophen and an antihistamine, such as diphenhydramine, to minimize infusion-related reactions (Dendreon, 2011). Each infusion is

![FIGURE 2. The Two Signals Required for T-Cell Activation](image)


![FIGURE 3. Total Tumor Burden Followed by Response With Ipilimumab Treatment in Metastatic Melanoma](image)

preceeded by a standard leukapheresis procedure, which is commonly performed at a blood center, to collect peripheral blood mononuclear cells about three days prior to treatment.

In the registrational phase 3 IMPACT study performed in patients with castration-resistant prostate cancer, chills, pyrexia, headache, influenza-like illness, myalgia, hypertension, hyperhidrosis, and groin pain occurred more frequently with sipuleucel-T than with placebo (Kantoff, 2010; Kantoff et al., 2010). Other AEs commonly seen with sipuleucel-T include back pain, nausea, joint ache, and headache. Most of these events were grade 1 or 2 in intensity and occurred within one day of infusion and resolved after one or two days (Dendreon, 2011).

In the event of an acute infusion reaction to sipuleucel-T, the infusion rate may be decreased or the infusion may be stopped, depending on the severity of the reaction. In controlled clinical trials, symptoms of acute infusion reactions were treated with acetaminophen, IV H1 and/or H2 blockers, and low-dose IV meperidine (Dendreon, 2011). If the infusion must be interrupted, the infusion should not be resumed if the infusion bag has been held at room temperature for more than three hours. If a patient is unable to receive a scheduled infusion, the patient will need to have an additional leukapheresis procedure before treatment can be continued (Bristol-Myers Squibb, 2011).

**Ipilimumab**

For treatment of metastatic melanoma, ipilimumab (3 mg/kg) is administered as a 90-minute IV infusion every three weeks for a total of four cycles (Bristol-Myers Squibb, 2011). The most frequent irAEs with ipilimumab are diarrhea, rash, fatigue, pruritus, and colitis. These events may be a consequence of an ipilimumab-induced T cell attack on normal tissues (Lemech & Arkenau, 2012). Regardless of organ system, most irAEs experienced with ipilimumab are grade 1 or 2 in severity and are manageable and reversible; however, some can be severe and life-threatening (Lemech et al., 2012; Verschaeren, 2012; Bristol-Myers Squibb, 2011). Although the onset of irAEs may vary depending on the patients and the organ system involved, the majority develop early in treatment (Ibrahim et al., 2011). However, irAEs may develop weeks or even months after initiation of therapy (Dummer et al., 2010), which highlights the need for vigilant follow-up, even after completion of all infusions.

Ipilimumab treatment guidelines recommend that unless an alternative etiology has been identified, signs or symptoms of inflammation should be considered immune-related and managed by close adherence to a specific Risk Evaluation and Mitigation Strategy (REMS) (Bristol-Myers Squibb, 2012). Unlike

### TABLE 2. Guidelines for Recommended Management of Immune-Related Adverse Events

<table>
<thead>
<tr>
<th>Site</th>
<th>Signs and Symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine</td>
<td>Nonspecific symptoms include: fatigue, headache, changes in mental status, abdominal pain, unusual bowel habits, and hypotension</td>
<td>Moderate reactions or symptomatic endocrinopathy: Withhold ipilimumab until complete resolution or stable on hormone replacement therapy Patient unable to have corticosteroid dose reduced to 7.5 mg prednisone or equivalent per day: Permanently discontinue ipilimumab Consider long-term hormone replacement therapy as necessary.</td>
</tr>
<tr>
<td>GI</td>
<td>Assess patients for changes in bowel habits and for the following signs and symptoms: diarrhea, abdominal pain, blood or mucus in stool with or without fever, peritoneal signs consistent with bowel perforation, and ileus.</td>
<td>Low-grade events: Symptomatic management (dietary modifications and loperamide) High-grade events: Corticosteroid therapy may be required More than 7 stools per day over baseline, signs consistent with perforation, or patients with a fever: Administer 1 to 2 mg/kg prednisone or equivalent, and then move forward with ensuring differential diagnosis. Withhold ipilimumab for moderate reactions until improvement to mild severity or complete resolution; for severe reactions, discontinue ipilimumab.</td>
</tr>
<tr>
<td>Liver</td>
<td>Evaluate LFT before each infusion or more frequently if possible. Monitor patients for any signs of hepatitis.</td>
<td>Moderate AST or ALT greater than 2.5 times but 5 times or less the ULN, or if moderate total bilirubin elevation is greater than 1.5 times but 3 or less times ULN: Withhold ipilimumab dose. Severe AST or ALT elevations more than 5 times ULN, total bilirubin elevations of 3 or more times ULN, or failure to complete full treatment course within 16 weeks from administration of first dose: Permanently discontinue ipilimumab. Grade 3 or higher hepatitis: Consider corticosteroid therapy.</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Encourage report of changes in muscle weakness or sensory alterations.</td>
<td>New onset or worsening symptoms: May require permanent discontinuation of ipilimumab</td>
</tr>
<tr>
<td>Ocular</td>
<td>Assess patients for uveitis, iritis, or episcleritis.</td>
<td>Administer corticosteroid drops.</td>
</tr>
<tr>
<td>Skin</td>
<td>Evaluate patients for signs and symptoms of pruritus, vitiligo, or maculopapular rash.</td>
<td>Mild to moderate: Symptomatic management; topical moisturizers and oatmeal baths may help relieve mild cases. Moderate to severe: Topical or systemic corticosteroids may be required; withhold ipilimumab dosing. Permanently discontinue ipilimumab in patients with Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration or necrotic, bullous, or hemorrhagic manifestations.</td>
</tr>
</tbody>
</table>

**Note.** This table serves as a guide; please also consult the full prescribing information when managing immune-related adverse events.

**Note.** Based on information from Bristol-Myers Squibb, 2012.
Key Communication Objectives That Oncology Nurses Should Relay to Patients Treated With Novel Immunotherapies

- Response patterns can differ from cytotoxic therapy. Apparent progression prior to response is not unusual.
- Delay in response compared with chemotherapy is normal and expected and not a cause for concern or anxiety that treatment is ineffective. Responses have been seen months after treatment.
- Treatment with immunotherapy may result in durable response and long-term survival.
- If treated with sipuleucel-T for prostate cancer, prostate-specific antigen changes or decreases may not be observed despite an effective immune response to therapy.
- Adverse events of immunotherapy differ from those observed with cytotoxic chemotherapy and reflect the mechanism of action of these agents.
- Vigilance and prompt reporting of all symptoms is key to prompt management of immune-related adverse events (irAEs) to enable patients to complete planned treatment.
- Like response, irAEs also can occur late in the treatment course; therefore, maintaining vigilance and regular follow-up are important.
- Although a link may exist between severe irAEs and improved response to therapy, this is not absolute and patients with mild irAEs also may respond to therapy.

Note. Based on information from Weber et al., 2012.

Interferon- or interleukin-2–based therapy, the REMS and prescribing information for ipilimumab recommend use of corticosteroids for management of moderate-to-severe events to reduce the risk of more serious complications (Buzaid & Atkins, 2001; Bristol-Myers Squibb, 2012; Hodi et al., 2010). Importantly, such use of corticosteroids does not diminish the clinical efficacy of ipilimumab (Harmankaya et al., 2011). The REMS also contains practical tools for irAE management, including an irAE management guide, patient wallet card, medication guide, and nursing irAE checklist. The nursing checklist within the REMS provides a practical aid to facilitate nurse-patient communication, serving as a guide for nurses when asking questions that distinguish irAE treatment-related symptoms from those that may not be treatment-related (www.hcp.yervoy.com/pdf/rems-nursing-checklist.pdf). The answers to these questions help facilitate decisions on continuation of therapy or postponement of an ipilimumab dose. In particular, the REMS checklist serves as a reminder of the most common potential irAEs. These questions aid clinicians during their assessment to differentiate between treatment- and non-treatment–related symptoms. Nurses have an essential role in educating patients to identify and report actual and potential irAEs early and promptly.

Well-established key management strategies exist for managing ipilimumab-associated irAEs (Thumar et al., 2011; Bristol-Myers Squibb, 2012) (see Table 2). Although bothersome, mild-to-moderate rash can be managed with moisturizing creams free from alcohol-base or fragrance. Antihistamines may be used for pruritus. Patients with rash may benefit from cool or tepid showers and should avoid new perfumes, laundry detergents, or soaps. Patients also should be informed that diarrhea associated with ipilimumab differs from that associated with cytotoxic chemotherapies and may occur as a result of T cell activity. Patients should monitor and report all changes in gastrointestinal habits, including diarrhea. Immune-mediated hepatitis typically has a late onset, but may develop at any time and may be asymptomatic. This highlights the importance of follow-up to ensure that patients are continually monitored once they have completed active treatment. Of note, endocrinopathy, such as hypophysitis, is a rare event associated with ipilimumab, which may be difficult to diagnose because the symptoms for this irAE are generally nonspecific. Prompt reporting of potential irAEs is important for effective management. Oncology nurses play a central role in ensuring that patients are aware of irAEs and alert to those that may require further evaluation.

The Future of Immuno-Oncology

Immuno-oncology research aims to develop novel compounds that harness the body’s intrinsic potential for generating an effective immune response against cancer. After decades of little progress, the field of immuno-oncology is prospering, with about 40 new drugs in clinical development and nearly a dozen of them in phase III studies (Schmidt, 2012). In fact, significant overall survival in pivotal phase III trials with ipilimumab in metastatic melanoma (Hodi et al., 2010) and sipuleucel-T in castration-resistant prostate cancer (Kantoff et al., 2010) led to approval of these agents for these tumor types (Bristol-Myers Squibb, 2011; Dendreon, 2010). The emergence and approval of novel immunotherapies for cancer may impact how cytotoxic therapy is used within the treatment sequence for a range of tumor types (Flaherty, 2011; Paller & Antonarakis, 2012). Future immunotherapeutic approaches are likely to feature combination strategies in a number of tumor types, including immune checkpoint blockade via CTLA-4 inhibition paired with conventional chemotherapy (Lynch et al., 2010) or combined immune checkpoint blockade (Yu, Steel, Zhang, Morris, & Waldmann, 2010). Other approaches include a combination of immunotherapy with radiotherapy (Demaria, Bhandwaj, McBride, & Formenti, 2005), or use of adjuvants to enhance active immunity (Johanson, Hamzah, Payne, & Ganss, 2012). In addition, the use of immunotherapy in the adjuvant setting is an attractive proposition (Tucker, Laguna, Moon, & Singhal, 2012; Tuma, 2011). These novel treatment strategies require effective communication between patients and their healthcare providers to help patients develop an awareness of what can be expected during treatment, including the probability of experiencing novel irAEs. Nurses are champions at so many facets of patient care and are vital to the safety and success of patients’ adherence to therapies. Oncology
nurses must be familiar with immunology and the therapeutics in this rapidly expanding discipline, which is globally sculpting the future landscape of cancer care.

References


(Continued on page 326)