Immunotherapy for Advanced Melanoma: The Emerging Role of Therapeutic Antibodies Against CTLA-4 for Metastatic Melanoma

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The anticytotoxic T-lymphocyte antigen-4 (CTLA-4) monoclonal antibody ipilimumab was approved recently by the U.S. Food and Drug Administration for the treatment of patients with unresectable or metastatic melanoma. Anti-CTLA-4 treatment yields tumor responses or stable disease that may last months or years. Antitumor responses can occur within the first few weeks or even months after initiation of treatment, even as the disease appears to be progressing or new lesions are detected. Most side effects are immune related, consistent with the immune-based mechanism of action, and generally manageable with supportive measures and steroids. With anti-CTLA-4 therapy, patient response differs (both clinically and psychologically) to that generally observed with chemotherapy or other agents used to treat advanced cancer. Patients and caregivers require education about the likely patterns of response to treatment to help them understand why beneficial clinical outcomes may require weeks or months to occur and why continued treatment may be advisable, even when the disease may appear to be progressing. At the author’s institution, the staff have noted that patients also need increased psychological support as a result of these clinical features and decisions. Patients and caregivers require instruction on recognition of potential side effects, the importance of reporting them in a timely manner, and their management.

The incidence of melanoma has increased since the 1980s at a faster rate than that observed with any other cancer (Ries et al., 2007), and an expected 70,230 new cases of melanoma will be diagnosed and 8,790 deaths will be attributed to melanoma in the United States in 2011 (Siegel, Ward, Brawley, & Jemal, 2010). Patients with metastatic melanoma (stage IV) have an extremely poor prognosis, with one-year survival rates ranging from 41%-59%, depending on the extent of metastases (Balch et al., 2001).

In the face of limited efficacy with conventional cytotoxic therapy for advanced melanoma, much effort has been made to develop new therapeutic options for this disease. With increased understanding of the complex factors and pathways involved in tumor biology, targeted therapies against specific molecules have been developed to target the immune system for more effective responses against solid tumors, such as advanced melanoma. These therapies include anti-CTLA-4 antibodies (ipilimumab), anti-programmed death receptor 1 (PD-1) antibodies (nivolumab, pembrolizumab), and anti-programmed death-ligand 1 (PD-L1) antibodies (atezolizumab, durvalumab).

At a Glance

- Anticytotoxic T-lymphocyte antigen-4 immunotherapy aids the immune system in mounting an effective immune response against solid tumors, such as advanced melanoma.
- Responses and stable disease resulting from ipilimumab treatment often are long lasting and may occur weeks to months after the start of treatment or after apparent progressive disease or new lesions.
- The side effects of ipilimumab are mainly immune-related adverse events and generally are responsive to supportive treatment or immunosuppressive steroids.

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involved in tumor pathogenesis and immune evasion have been developed. Cytotoxic T-lymphocyte antigen-4 (CTLA-4) is found on T cells and plays a critical role in regulating natural immune responses; inhibition of CTLA-4 has demonstrated antitumor activity (Melero, Hervas-Stubbs, Glennie, Pardoll, & Chin, 2007). Ipilimumab is a fully human monoclonal antibody directed against CTLA-4 and was approved by the U.S. Food and Drug Administration (FDA) in March 2011 for the treatment of patients with unresectable or metastatic melanoma.

This review will present the rationale for anti-CTLA-4 treatment, examine the key differences between the efficacy and safety profiles for ipilimumab and those for more conventional compounds in the treatment of advanced melanoma, and review outcomes to date at the author’s cancer center with the specific patient care needs with ipilimumab. After reading this article, nurses should be better able to provide the education and support required by patients with malignant melanoma receiving anti-CTLA-4 therapy.

Established Treatments for Melanoma

The National Comprehensive Cancer Network (NCCN) has developed updated clinical practice guidelines for melanoma, summarizing the use of available agents (NCCN, 2011). Until recently, available agents had low levels of activity and little consensus existed regarding treatment approaches (NCCN, 2011).

Dacarbazine is the only approved chemotherapeutic agent for advanced melanoma in the United States and represents the standard of care. However, dacarbazine achieves only limited efficacy, with a median overall survival (OS) of less than eight months (Avril et al., 2004; Falkson et al., 1998; Middleton et al., 2000). Numerous phase III trials have evaluated dacarbazine in combination with other drugs to increase efficacy, but no combination has yet demonstrated improved survival compared with single-agent dacarbazine (O’Day & Boasberg, 2006). The alkylation agent temozolomide frequently is used off-label for the treatment of melanoma (Agarwala, 2009). The increased temozolomide penetration of the central nervous system compared with dacarbazine, however, suggests that temozolomide may be a viable alternative to dacarbazine in patients with advanced melanoma and central nervous system disease.

As conventional systemic chemotherapy generally is associated with limited success in patients with advanced melanoma, alternative therapeutic approaches have been widely explored. Biologic response modifiers can act passively by enhancing the immunologic response to tumor cells or actively by altering the differentiation or growth of tumor cells. Active immunotherapy with cytokines, such as interferons (IFNs) and interleukins (ILs), is a form of nonspecific active immune stimulation. IL-2 was approved by the FDA for the treatment of relapsed, advanced melanoma based on results from a single-arm trial, which demonstrated an objective response rate of about 16% with prolonged responses in some patients (Atkins et al., 1999). That clinical activity was confirmed (Tarhini, Kirkwood, Gooding, Cai, & Agarwala, 2007), but the considerable associated toxicity (e.g., risk of severe hypotension, cardiac arrhythmias, respiratory impairments) requires that the agent is administered in a hospital setting and, therefore, limits the number of patients who can be treated (Atkins et al., 1999). IFNz-2b is approved for use in malignant melanoma (stage III) in the adjuvant setting, but its administration also can result in toxicity, including fatigue and neutropenia (Eggermont et al., 2008; Merck & Co., Inc., 2008).

The use of vaccines also has been explored in melanoma, but none has proven beneficial to date in controlled clinical trials (Rosenberg, Yang, & Restifo, 2004). Therefore, the data highlight the need for new approaches in the treatment of patients with melanoma.

Cytotoxic T-Lymphocyte Antigen-4 Antibodies: Enhancing the Innate Antitumor Immune Response

All tumor cells express antigens on their cell surfaces—proteins that can be recognized by the immune system as foreign and thereby trigger immune responses (Boon, Cerottini, Van den Eynde, van der Bruggen, & Van Pel, 1994). However, most human tumors are poorly immunogenic and have developed methods for avoiding the immune system, allowing the tumor cells to proliferate and spread unchallenged. The aim of cancer immunotherapy, including anti-CTLA-4 antibodies, is to improve the effectiveness of the immune system in detecting and destroying tumor cells.

The first step in an antitumor immune response is when peptide antigens, in association with major histocompatibility complex molecules, are presented by antigen-presenting cells (APCs) to T cells via their T-cell receptors (Egen, Kuhns, & Allison, 2002) (see Figure 1A). However, that step is not sufficient in itself to trigger an immune response. Separate stimulatory molecules on the T-cell surface (e.g., CD28 molecule) also must bind to receptors on the APC surface (e.g., B7 molecule). As a result of that costimulatory signal, T cells proliferate and release cytokines, which may lead, in turn, to infiltration and subsequent destruction of the tumor.

The role of the CTLA-4 molecule is to limit the immune response and to prevent overactivation of the immune system and consequent autoimmune attacks on healthy cells and tissue. CTLA-4 is expressed by T cells several days after initiation of the immune response and binds to the APC receptors with high affinity, thereby blocking the essential costimulatory signal and preventing additional immune activation (see Figure 1B). As CTLA-4 expression acts as a negative feedback mechanism that dampens the immune response, inhibition of CTLA-4 reverses immune system suppression and thereby enhances tumor-specific T-cell responses (see Figure 1C). In this way, the body can potentially mount a more effective and sustained immunologic attack against the tumors.

Ipilimumab

Clinical Activity and Survival

Patients in the first phase III clinical trial (MDX010-20) received 3 mg/kg of ipilimumab in a regimen that started with an induction phase (Hodi et al., 2010). The induction phase began with the
first infusion on day 1 and continued for three additional doses. Patients received ipilimumab 3 mg/kg in single, 90-minute IV infusions every three weeks for four doses (weeks 1, 4, 7, and 10). The long induction phase is aimed at allowing the immune system sufficient time to build an antitumor response. The first assessment point was at week 12 so as to allow sufficient time for ipilimumab to demonstrate clinical activity. In the author’s experience, tumor responses have been noted before week 12, but most occur at or beyond this date.

Whereas most chemotherapy regimens typically cause rapid responses of short duration or short-lived periods of disease stability, the author’s experience and that of other investigators is that ipilimumab administration causes long-term (months to years) tumor responses and stable disease in many treated patients. In a pooled analysis of various early studies of ipilimumab at various doses (mostly 3 mg/kg) and regimens (single and multiple dosing) in 356 treated patients with advanced melanoma, the duration of tumor responses and stable disease ranged from two months to more than five years (Hamid et al., 2007; Maio et al., 2010; Ottensmeier et al., 2010). The extended durations of response and stable disease most likely reflects the chronic activation of the immune system rather than the pharmacokinetics of ipilimumab. Data reported in the past few years have shown that apparent progressive disease can occur prior to tumor response, indicating that such responses are not unique to the author’s institution (Hamid et al., 2007; Harmankaya et al., 2008; Hodi et al., 2008). It should be emphasized that stable disease of this duration in this poor-prognosis population is very beneficial and uncommon with currently available therapies.

A second phase III, randomized controlled trial (CA184-024) has been completed recently (Robert et al., 2011). The study compared dacarbazine alone with dacarbazine plus ipilimumab at an investigational dose of 10 mg/kg in previously untreated patients (N = 502) with metastatic melanoma. Dacarbazine plus ipilimumab demonstrated a statistically significant increase in OS in patients compared to dacarbazine alone (11.2 months versus 9.1 months; hazard ratio [HR] = 0.72, p < 0.01). Among all randomly assigned patients with a complete or partial response, the median duration of response was 19.3 months (95% confidence interval [CI] [12.1, 26.1]) in the dacarbazine-ipilimumab group compared with 8.1 months (95% CI [5.19, 10.9]).

Figure 1. Mechanism of Action of CTLA-4 Inhibition With Ipilimumab

A. APC—antigen-presenting cell; CTLA-4—cytotoxic T-lymphocyte antigen-4; MHC—major histocompatibility; TCR—T-cell receptor

Note. For Figure 1A, APCs process tumor-associated peptide antigens and present them in association with MHC molecules to the TCR on the surface of T cells. A costimulatory signal is triggered by the binding of B7 molecules expressed by APCs to CD28 molecules expressed by T cells. These two signals combined promote T-cell activation and proliferation, which contribute to an antitumor immune response.

Note. For Figure 1B, CTLA-4 is expressed by T cells several days after initiation of the immune response and binds to B7 molecules on APCs with high affinity, thereby blocking the essential costimulatory signal and preventing further immune activation.

Note. For Figure 1C, blocking CTLA-4 using ipilimumab may activate or enhance the tumor-specific immune response.
In the dacarbazine group (p = 0.03) (Robert et al., 2011). The most common safety events were inflammatory in nature and consistent with the types of events observed in previous studies. However, the rates of specific events differed from those observed when ipilimumab was used as monotherapy in clinical studies. Gastrointestinal perforations and hypophysitis (inflammation of the pituitary gland), for example, were observed in previous studies (Hodi et al., 2010), but none were reported in the phase III study (Robert et al., 2011).

Nurses should be excited by the durable responses and stable disease achieved with ipilimumab therapy, as most patients gained little benefit from the agents offered historically. The nurses in the author's institution who use ipilimumab therapy use personal anecdotes when counseling patients, describing others who have had robust clinical benefit in terms of durable responses and stable disease to help new patients understand the potential benefits of this new immunotherapeutic agent. Those anecdotes encourage patients and their caregivers and provide them with a chance at prolonged survival.

**New Patterns of Response**

Conventional response guidelines (e.g., World Health Organization, Response Evaluation Criteria in Solid Tumors) do not recognize all patterns of ipilimumab activity that are likely to contribute positively to patient outcome (Miller, Hooogstraten, Staquet, & Winkler, 1981; Therasse et al., 2000). Progressive disease conventionally prompts the discontinuation of treatment, but in the case of ipilimumab therapy, new lesions may not always indicate treatment failure, particularly in patients with decreasing or stable lesions when new lesions appear. Careful evaluation of patients with apparently progressing tumors is therefore needed to avoid premature treatment cessation. Criteria that may capture the unique clinical patterns of anti-CTLA-4 response have been developed (Harmankaya et al., 2008; Hodi et al., 2008; Wolchok et al., 2009). The four main patterns of clinical response to ipilimumab are:

- **Response in baseline lesions**
- **Stable disease with a slow, steady decline in total tumor burden**
- **Response after initial increase in total tumor burden (response after progressive disease)**
- **Response in total tumor burden in the presence of new lesions (response after progressive disease)**

Although the first two responses may be considered classical responses to therapy, the latter two responses appear to be new to immunotherapies. A number of cases have noted progression on scan and on physical examination at week 12 (after four doses of treatment) before a response became apparent (Wolchok et al., 2009). In addition, results show that ipilimumab-treated patients with advanced melanoma who developed new lesions can go on to achieve responses with subsequent shrinkage of the new lesions. For that reason, patients in the author’s institution are asked to wait for four more weeks after apparent disease progression at week 12 before they discontinue ipilimumab treatment. In one case, a patient had very aggressive liver metastasis that increased by week 12, but subsequent scans at weeks 16 and 20 showed a significant decrease in liver metastasis (Wolchok & Saenger, 2008), and the patient reported feeling “more like himself.” That patient has gone on to show additional response on scans and on physical examination. In situations such as this one, patients often require substantial support and education from the nursing team.

The mechanisms underlying these clinical activity patterns have not been conclusively demonstrated, but differences between the immune systems of individual patients are likely to contribute to the varying time to response. Responses occurring weeks to months after ipilimumab therapy also likely reflect a combination of the indirect action of ipilimumab, accumulation of sufficient available antigen for immune recognition, and the chronic nature of the immune response. In addition, progressive disease observed during ipilimumab therapy, as determined by radiographic analysis, may result from lymphocytic infiltration or edema during an inflammatory response causing an increase in tumor volume, which would not be distinguishable, radiographically, from a growing tumor (Wolchok et al., 2009). Shrinkage and/or eradication of new lesions after they appear has not been described with any other substance in oncology and, consequently, is an unfamiliar concept to healthcare professionals and patients alike.

Patients receiving this type of targeted immunotherapy, therefore, require a different approach to education and management. At the author’s institution, the staff have found that patients require extensive education about the differences between traditional chemotherapy and anti-CTLA-4 therapy for advanced melanoma. Specifically, because the clinical benefit may not be observed right away, patients need to be reminded of how anti-CTLA-4 works and told that responses to anti-CTLA-4 therapy take weeks to become noticeable. During initial visits...
and throughout the course of treatment, patients should be informed that they may not see improvement during the first 12 weeks and reminded that most patients do not see a response until after 16–20 weeks. Moreover, their cancer symptoms may appear to get worse before they improve. In addition to education, patients should receive psychological support and reassurance, particularly during the first 12 weeks of treatment. At the author’s institutions, patients respond positively to reports of previous patients who have done well on anti-CTLA-4 therapy, reinforcing the fact that cases of progression before complete response have been observed. It should be stressed to patients that they should continue their anti-CTLA-4 therapy. However, progression of disease is confirmed if scans continue to show progression beyond week 16 and if patients’ cancer symptoms are increasing. Figure 2 provides key recommendations for nurses regarding anti-CTLA-4 therapy and the unique patterns of response.

**Safety and Tolerability**

Most side effects associated with anti-CTLA-4 immunotherapy are immune related, consistent with activation of the immune system, and are different from those associated with commonly used agents in advanced melanoma (Ledezma, 2009) (see Figure 3). The most common adverse events observed with ipilimumab treatment were immune-related adverse events, which were typically mild to moderate in severity but, left unrecognized and untreated, could become severe and life threatening (Hodi et al., 2010; O’Day et al., 2010; Robert et al., 2011; Weber et al., 2009; Wolchok et al., 2010). In clinical trials of ipilimumab therapy involving patients with melanoma, the most common adverse events (all grades of severity) were gastrointestinal (diarrhea, colitis, or enterocolitis) and dermatologic (dermatitis and pruritus [with or without rash]), which is not surprising as the immune system is particularly active in the skin and gastrointestinal tract (Chin et al., 2008; Hodi et al., 2010; O’Day et al., 2010; Weber et al., 2009; Wolchok et al., 2010). Hypophysitis and hepatitis occurred infrequently (Attia et al., 2005; Beck et al., 2006; Blansfield et al., 2005; Bulanhagui et al., 2006; Chin et al., 2008; Fischkoff et al., 2005; Hamid et al., 2007; Hodi et al., 2010; Maker et al., 2005, 2006; O’Day et al., 2010; Phan et al., 2003; Ribas et al., 2005, 2007; Robert et al., 2011; Weber et al., 2009; Wolchok et al., 2010).

As those side effects have been observed with both ipilimumab and tremelimumab, they are most probably class effects (i.e., ipilimumab and tremelimumab are in a class of monoclonal antibodies known as immunomodulatory antibodies). However, product-specific treatment guidelines have been developed for the management of immune-related adverse events (Bristol-Myers Squibb, 2011; Weber, 2007). The side effects of ipilimumab are medically manageable with early detection and treatment, often with high-dose oral corticosteroids (Attia et al., 2005; Beck et al., 2006; Bulanhagui et al., 2006; Fischkoff et al., 2005; Hodi et al., 2010; Maker et al., 2005, 2006; O’Day et al., 2010; Phan et al., 2003; Ribas et al., 2005, 2007; Robert et al., 2011; Weber et al., 2009; Wolchok et al., 2010). No evidence exists to suggest that using immunosuppressive corticosteroids affects the antitumor action of ipilimumab (Attia et al., 2005; Beck et al., 2006; Maker et al., 2005, 2006; Ron et al., 2008; Weber et al., 2009); however, mild-to-moderate side effects typically resolve with standard supportive measures alone (e.g., with gastrointestinal events, changes in diet and motility reducers are used; for dermatologic events, topical steroids or oral antihistamines may be used). As ipilimumab is a fully human monoclonal antibody, no premedication is required to prevent anaphylactic shock.

Based on patients treated at the author’s institution, of the side effects associated with ipilimumab therapy, diarrhea represents the biggest challenge. Guidelines have been developed for the treatment and management of ipilimumab-induced diarrhea (Bristol-Myers Squibb, 2011; Weber, 2007). Diarrhea should be treated early (i.e., first day of onset). With early grade 1 diarrhea (less than four stools per day over baseline), for instance, changes in diet and increased oral fluids should be encouraged. Nurses should instruct patients to initiate a bland diet and increase oral fluids. Bland diet instructions should eliminate spicy or fried foods, raw vegetables, and limit caffeine, alcohol, and dairy products. Carbohydrates such as white bread, pasta, crackers, and non-whole grain cereals should be encouraged (Roman, 2010).

Grade 2 diarrhea (an increase of 4–6 stools per day over baseline) can be managed symptomatically with motility reducers (e.g., loperamide, diphenoxylate, atropine). However, if grade 2 diarrhea symptoms do not subside, an oral steroid (budesonide or prednisone) should be added and a diagnostic endoscopy may be performed. It should be explained to patients that use of corticosteroids does not appear to negatively impact ipilimumab efficacy (Ron et al., 2008; Weber et al., 2009). These patients will be monitored closely with telephone follow-up to ensure the symptoms do not advance. Bloody diarrhea and severe colitis detected with endoscopy, as well as grade 3 or
4 diarrhea (an increase of seven or more stools per day over baseline or diarrhea resulting in life-threatening consequences), require hospitalization and immediate initiation of high-dose IV steroid therapy. After discharge, these patients may be put on high-dose corticosteroids tapered over a month on an outpatient basis, with frequent telephone follow-up by the nurse. Unless contraindicated, infliximab (5 mg/kg) should be administered to patients with diarrhea or colitis not responding to steroid therapy within one week of initiation or relapse following a steroid taper. If necessary, infliximab therapy may be repeated within two weeks. According to the guidelines, prolonged diarrhea not responding to steroid therapy, bowel rest, total parenteral nutrition, and infliximab therapy is an indication for either a diverting ileostomy or partial/complete colectomy. The patient must inform his or her nurse of symptoms right away so that management can be implemented and symptom progression from grade 1 or 2 to grade 3 or 4 can be prevented (Bristol-Myers Squibb, 2011; Ledezma, 2009).

Because of the risk of hypophysitis (Blansfield et al., 2005), all patients receiving ipilimumab should be closely monitored for autoimmune endocrinopathies according to published guidelines (Bristol-Myers Squibb, 2011; Chin et al., 2008). Although inflammation involving the eye (uveitis) has been observed following administration of anti-CTLA-4 therapy, ophthalmic monitoring during a study of tremelimumab revealed no adverse effect of anti-CTLA-4 therapy on vision (Stratma et al., 2007).

It has been shown that effective and prompt implementation of the guidelines for management of the ipilimumab-associated side effects (e.g., diarrhea, endocrinopathy, skin toxicities, liver toxicities) results in reduced frequency of serious or life-threatening side effects (Chin et al., 2008). However, to permit prompt implementation of these guidelines, patients need to be told the importance of reporting the first signs of a side effect (e.g., diarrhea, rash) so that they may be treated appropriately. Patients should be informed about the symptoms that may occur and how these symptoms may be related to therapy. These points must be highlighted to patients and reinforced at each office visit or other point of patient contact, such as telephone calls. When a patient is scheduled to begin treatment, nurses must spend a considerable amount of time with the patient going over the potential side effects that may occur. Patients should be given written materials at the initiation of therapy that outlines the symptoms of side effects and how to manage each individually as well as health provider contact information. Patients also should be instructed on the mechanism of action of anti-CTLA-4 therapy to better understand the need for prompt reporting of side effects.

Conclusion

Anti-CTLA-4 therapy is an exciting new form of cancer therapy with the potential to extend life in advanced melanoma, one of the more difficult to treat forms of cancer. By harnessing and activating physiologic tumor-directed T-cell responses, intense immunologic attacks may be focused against specific tumors. Nurses have an important role in educating patients and caregivers on the key differences between cancer treatments, what to expect during treatment, and how to ensure the best possible clinical outcome. Patients respond, both clinically and psychologically, to anti-CTLA-4 therapy very differently than they do to chemotherapy. As such, patients receiving anti-CTLA-4 immunotherapy require a different approach to education and management. Patients and caregivers require education on the patterns of response to better understand the details of drug administration and the reason behind clinical outcomes that may require weeks or months to occur. In addition, patients will need increased psychological support, particularly during the time when their disease may not seem to be improving. Lastly, patients and caregivers need to be instructed on how to recognize potential side effects and the importance of reporting them as soon as possible. Nurses will otherwise play a key role in educating patients and caregivers on the differences in cancer therapies and helping patients to ensure that they have the best possible clinical outcome.

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