Ipilimumab for Advanced Melanoma: A Nursing Perspective

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Melanoma, the most serious type of skin cancer, accounted for an estimated 62,480 new cases of cancer and 8,420 deaths in the United States in 2008 (American Cancer Society, 2008). Melanoma incidence is increasing at a faster rate than any other cancer. The percentage of Americans with melanoma has more than doubled since the late 1970s (Ries et al., 2007). Patients with stage IV melanoma (a cancer considered difficult to control with systemic therapy) have a very poor prognosis; one-year survival rates are dependent on the extent of metastases and are 59% for stage M1a, 57% for stage M1b, and 41% for stage M1c (Balch et al., 2001). Because patients with late-stage melanoma are unlikely to be cured with available treatment options, clinical trial participation is the preferred course of action.

Dacarbazine is the only chemotherapeutic agent for advanced melanoma approved in the United States. Although dacarbazine currently is considered the first-line standard of care, response rates are low (about 7.5%) and survival time is short (less than eight months) (Bedikian et al., 2006). The most common toxicity associated with dacarbazine administration is hemopoietic depression; symptoms of anorexia, nausea, and vomiting are observed in most patients. Temozolomide, another chemotherapeutic agent often used off-label for the treatment of melanoma because of its greater potential to treat brain metastases by penetrating the blood-brain barrier, demonstrated response and survival rates similar to dacarbazine (Quirt, Verma, Petrella, Bak, & Charette, 2007). High-dose interleukin-2 (IL-2) was approved for use in the second-line setting for advanced melanoma based on results from a single-arm trial that yielded an objective response rate of about 16%, with prolonged responses in some patients (Atkins et al., 1999). A 2007 investigation showed a 19% response rate for high-dose IL-2 monotherapy (Tarhini, Kirkwood, Gooding, Cai, & Agarwala, 2007). However, the high toxicity often associated with the treatment (e.g., risk of severe hypotension, cardiac dyshythmias, respiratory impairments) requires administration in the hospital setting and limits the number of patients that can

Purpose/Objectives: To discuss the response patterns and side effects related to ipilimumab, a new immunotherapeutic agent under investigation in the treatment of advanced melanoma and other malignancies.

Data Sources: Published articles, abstracts, research data, and clinical experience.

Data Synthesis: Ipilimumab is a fully human monoclonal antibody that inhibits the activity of cytotoxic T-lymphocyte antigen-4 (CTLA-4), a naturally immunosuppressive molecule. The most common side effects are immune mediated (e.g., inflammatory diarrhea, pruritis) and appear to occur as a direct result of CTLA-4 inhibition and enhanced immune system activation. Side effects generally are grade I or II and resolve with standard treatments. Most grade III or IV events are managed successfully after swift diagnosis and treatment with corticosteroids; steroid-refractory events resolve after treatment with infliximab or mycophenolate.

Conclusions: The response patterns and side effects associated with ipilimumab therapy greatly differ from those common to other advanced melanoma therapies (e.g., chemotherapy, cytokines, vaccines).

Implications for Nursing: Nurses have an important role in educating patients about the differences between anti-CTLA-4 therapy and chemotherapy. In addition, teaching patients to recognize ipilimumab's side effects and report them early can result in fast treatment to prevent symptom progression from grade I or II to III or IV. Communication between nurses and patients throughout the treatment process will help patients benefit maximally from the new therapeutic strategy.

be treated (Atkins et al.). Interferon alpha-2b is approved for use in malignant melanoma in the adjuvant setting, but its administration also can result in significant and potentially life-threatening toxicity (Schering Corporation, 2008), including neutropenia or leukopenia. For the three therapies currently approved for malignant melanoma, the potential therapeutic benefit must be weighed against the toxicity risks before administration. Numerous phase III trials have evaluated dacarbazine with other drugs, but no combination has demonstrated improved survival compared to single-agent dacarbazine (O'Day & Boasberg, 2006). Many vaccines also have been

studied, but none has proven beneficial to date in controlled clinical trials (Rosenberg, Yang, & Restifo, 2004). A new therapeutic option to improve the treatment of advanced melanoma is needed urgently. Understanding of the complex factors and pathways involved in tumor biology has expanded in recent years, leading to the development of targeted therapies against specific molecules involved in tumor pathogenesis and immune evasion. Monoclonal antibody therapy, the focus of much current investigation, may improve clinical outcomes for patients with advanced melanoma.

Cytotoxic T-Lymphocyte Antigen-4 and the Immune System

The goal of cancer immunotherapy is to harness the body's own immune system to fight cancer (Peggs, Quezada, Korman, & Allison, 2006). The immune system can mount an antitumor response by recognizing specific proteins (or antigens) on the surface of the tumor as foreign and sending signals to initiate T-lymphocyte activation, resulting in proliferation and cytokine release. The cytokines, in turn, stimulate the generation of effector immune T lymphocytes that infiltrate and destroy the tumor. The cytotoxic T-lymphocyte antigen-4 (CTLA-4) molecule, a negative feedback mechanism, limits the developing immune response to keep it from becoming overactivated and possibly causing nonspecific tissue damage. CTLA-4's inhibition effect allows for increased immune system activation against tumor antigens, making the molecule a target for cancer immunotherapy.

Anti-CTLA-4 therapy can help the immune system generate and maintain an effective antitumor immune response that can destroy tumors that have developed as a result of successful immune system evasion. The approach uses a mechanism different from chemotherapy (direct cytotoxic effect on tumor cells), cytokines (nonspecific signaling molecules used by lymphocytes), or vaccines (education of the immune system to tumor-derived signals).

Two fully human anti-CTLA-4 monoclonal antibodies, ipilimumab and tremelimumab, are under investigation in clinical trials in patients with advanced melanoma and other malignancies. Ipilimumab and tremelimumab specifically bind to CTLA-4, thereby blocking the negative regulation of T lymphocytes. Anti-CTLA-4 may be an effective therapy for multiple tumor types because, unlike other monoclonal antibodies that target tumors, anti-CTLA-4 monoclonal antibodies target the immune system, so direct access to the tumor is not required. In addition, patients using the therapy have a low possibility of developing an anaphylactic reaction because the antibodies are fully human.

The results of several phase I and II studies of ipilimumab administered in varying dosing regimens either alone (Fischkoff et al., 2005; Maker et al., 2006; Weber et al., 2007) or in combination with dacarbazine (Fischkoff et al.) or vaccine (Attia et al., 2005) have indicated preliminary objective response rates ranging from 5.8%–15.8% (Hamid et al., 2008; O'Day et al., 2008; Weber et al., 2008). Ipilimumab in combination with IL-2 yielded slightly higher response rates, but concomitant toxicities associated with IL-2 therapy also were observed (Maker et al., 2005). In a pooled analysis of early ipilimumab studies (356 patients), the duration of objective response ranged from three months to greater than four years (Hamid et al., 2007). In addition, 24% of patients achieved stable disease as their best response, and the response was durable (24 weeks or more) in more than 25% of patients with stable disease (Hamid et al., 2007). When treated with 10 mg/kg ipilimumab induction dosing, more than 30% of patients achieved stable disease as their best overall response; stable disease endured longer than 24 weeks in all but one of the patients (Weber et al., 2008).

At the Angeles Clinic and Research Institute in Santa Monica, CA, more than 100 patients with advanced melanoma have received ipilimumab; about 30% of the patients were treatment naive and the other 70% received ipilimumab as a second-line therapy. The response patterns and side effects associated with ipilimumab therapy are very different from other therapies for advanced melanoma, highlighting the need for increased awareness and attention to specific patient care needs with ipilimumab therapy. An overview of the clinical profile associated with ipilimumab therapy and a potential explanation for these observations are presented in Table 1.

Ipilimumab Therapy: A Nursing Perspective

Administration and Time to Response

Patients at the Angeles Clinic and Research Institute receive 10 mg/kg ipilimumab in a single, 90-minute IV infusion every three weeks for 12 weeks (four doses). Premedication to prevent an anaphylactic reaction is not required because ipilimumab is a fully human monoclonal antibody. The induction phase of administration is designed to block CTLA-4 suppression of the immune system, enabling the immune system to mount a response against the tumor. In some trials, patients with stable disease or better (complete or partial response) after the induction phase are eligible to continue treatment with maintenance ipilimumab (10 mg/kg every 12 weeks) until disease progression or toxicity (Hamid et al., 2008; O'Day et al., 2008; Weber et al., 2008). Some patients at the Angeles Clinic have been treated with ipilimumab for up to 1.5 years.

Unlike chemotherapy, in which direct cytotoxic activity results in a response that is evident within the first few cycles of treatment, the time to patient response for ipilimumab can vary greatly, presumably because the

Table 1. Treatment Parameters Associated With Ipilimumab Therapy

Parameter	Profile	Rationale and Hypotheses
Administration	Induction phase: every three weeks for four doses (until week 12) Maintenance phase: every 12 weeks until disease progresses or significant toxicities develop	Induction phase: initially blocks CTLA-4 activity, providing time to build an antitumor immune response Maintenance phase: ensures immune system is active continually through CTLA-4 inhibition; existing tumors and new metastases destroyed
Time to response	Varied • At week 12 • Slow and steady after week 12 • Preceded by stable or apparent progressive disease	Time is required to build an antitumor response. Variations in patient immune systems (e.g., inherent activation levels) indicate that different levels of additional activation through CTLA-4 inhibition are required.
Tumor assessment	First assessment at week 12	Because of the time required to mount an antitumor immune response, patients may demonstrate early apparent progressive disease.
Durability of response	Months to years post-treatment initiation in some patients	Targeting the immune system rather than the tumor allows for clearance of existing lesions.
Side effects	Immune related	Likely caused by ipilimumab's effects on the immune system; T-lymphocyte activation is enhanced with CTLA-4 inhibition and may cause nonspecific peripheral tissue damage.
Therapy discontinuation	Patients should complete induction dosing (all four doses) until obvious progressive disease or severe toxicity is observed or until week 12 and proceed with maintenance dosing.	Because of the time required to build an antitumor immune response, patients may demonstrate early apparent progressive disease or the development of new lesions prior to response; removing patients prematurely from treatment may result in missed clinical benefit. Therefore, disease progression should be confirmed several weeks later (e.g., four weeks).

CTLA-4—cytotoxic T-lymphocyte antigen-4

human immune system varies from patient to patient. A clinical response is evident in some patients within the first few weeks of therapy; for example, visually monitoring dermal tumors has shown evidence of regression around the time of the third infusion (week 9). However, many have had a slow and steady response. For example, most patients do not achieve the full extent of the antitumor response by the end of the induction phase (week 12); objective responses generally start around weeks 16 or 20. Complete responses tend to occur after a prolonged partial response. Patients have been observed with extended periods of stable disease before achieving a partial or complete response (Hamid et al., 2007; Weber et al., 2007).

Other patients appear to have progressive disease before responding; in some patients, subcutaneous disease seems to worsen (i.e., increased growth and discomfort) after about the third ipilimumab dose (week 9). Patients who progressed before responding have been described previously (Hamid et al., 2007). Although some patients' scans at week 12 appeared to show classical signs of increased disease (e.g., increased size on computed tomography [CT] and activity on positron emission tomography [PET]), subsequent histopathologic analysis of tumor biopsy samples indicated tumor necrosis and lymphocytic infiltration.

Some patients have had a variable response at week 12 or 16, with some lesions increasing in size and oth-ers shrinking or disappearing. At the Angeles Clinic, discrepancies have been observed between the CT and PET scans; some week 12 or 16 CT scans demonstrated apparent increased disease (e.g., increased lesion size), but PET scans showed a lower standard uptake value than pretreatment scans. In addition, week 20 and 24 CT scans may show visible disease that is no longer PET-positive. Some ipilimumab-treated patients have developed new lesions while their target lesions were regressing; in most cases, the new lesions ultimately respond to treatment. Unlike other therapies (particularly cytotoxic chemotherapy), the appearance of new lesions during ipilimumab treatment is not necessarily indicative of treatment failure. Based on the observations regarding the unique and varied time to response to ipilimumab, week 12 is the first protocol-defined point of tumor assessment scans in ongoing ipilimumab clinical trials.

Durability of Response

Response to ipilimumab treatment appears to be durable for months to years in some patients. Patients who have achieved stable disease as their best overall response continue to be monitored with scans. Disease can continue to shrink and demonstrate less activity on PET scans even a year after the patient's last infusion (Attia et al., 2005; Fischkoff et al., 2005; Hamid et al., 2007; Ribas et al., 2005; Weber et al., 2007).

Immune-Related Side Effects

Ipilimumab inhibits CTLA-4, leading to enhanced T-lymphocyte activation. Highly active T lymphocytes may cause nonspecific damage to host tissues, resulting in immune-related side effects unique to this new drug class. Immune-related side effects associated with ipilimumab therapy mostly occur in areas that already contain significant resident T-lymphocyte populations, such as the gastrointestinal tract (e.g., diarrhea, enterocolitis) or the skin (e.g., rash, dermatitis). Less frequently occurring side effects include hepatitis, hypophysitis, uveitis, and nephritis (Attia et al., 2005; Fischkoff et al., 2005; Maker et al., 2005, 2006). Immune-related side effects generally are grade I or II and resolve with standard treatments. For example, grade I or II diarrhea often resolves with changes in diet, increased hydration, and motility reducers (e.g., diphenoxylate, atropine, loperamide) (Weber, 2007). However, grade III or IV diarrhea must be treated with corticosteroids to reduce immune response and prevent damage to normal host tissue caused by anti-CTLA-4 therapy. Although steroid use may be common in certain situations with patients with cancer (e.g., treating brain edema caused by brain metastases), using steroids to treat diarrhea is uncommon; the treatment strategy is similar to the management of autoimmune diseases, such as Crohn disease. Therefore, nurses should be trained to treat the familiar symptom of grade III or IV diarrhea in a very different way.

Nonspecific clinical symptoms (e.g., headache, tiredness, decreased libido) may indicate endocrinopathies. Patients usually present with the following symptoms: severe headache or pressure behind the eyes that is not relieved with over-the-counter medications, severe fatigue, decreased libido, and decreased appetite. Magnetic resonance imaging often reveals an enlarged pituitary. High-dose steroids are given to decrease the swelling, and symptoms usually resolve immediately. The steroids are then tapered and the deficient hormones are supplemented. Patients are then referred to and monitored closely by an endocrinologist.

Although less common, immune-related hepatitis can present in asymptomatic patients as an increase in liver function tests, and must be treated with corticosteroids if severe (grade III or IV) (Weber, 2007). In a minority of cases, steroids may be insufficient and patients will require alternative immunosuppressive drugs, such as infliximab (an anti-inflammatory monoclonal antibody directed against tumor necrosis factor-α) for colitis or mycophenolate (an inhibitor of immune cell growth) for hepatitis (Chin et al., 2008).

An association between the development of immune-related side effects and the efficacy of anti-CTLA-4 therapy has been observed (Antonia et al., 2007; Attia et al., 2005; Beck et al., 2006; Reuben et al., 2006; Weber,

2007); however, patients have responded to anti-CTLA-4 without experiencing such immune-related toxicities. Therefore, immune-related side effects cannot be used to predict response yet, and additional studies to investigate the relationship are warranted.

The side-effect symptom profile and management approach associated with anti-CTLA-4 monoclonal antibodies differs from the profile traditionally observed in chemotherapy. Side effects associated with ipilimumab require more thorough education of healthcare professionals and their patients as well as frequent communication between them. A greater appreciation and urgency for early management of diarrhea or immune hepatitis are required because the intervention and prompt side-effect management may change the outcome successfully and prevent rare but serious complications, such as bowel perforation. Treatment algorithms for the early management of diarrhea have been implemented (Weber, 2007). Clinical nurses should be aware of the management guidelines. At the Angeles Clinic, the number of bowel perforations has decreased as a result of early implementation of the treatment algorithms; however, additional, extensive studies to prove their efficacy are warranted.

Recognizing and Managing Immune-Related Side Effects and Symptoms: Case Illustrations

The following case examples document the recognition and subsequent management of several common ipilimumab-mediated immune-related side effects. Based on the examples and general experience with ipilimumab at the Angeles Clinic, several fundamental commonalities have been identified regarding side-effect management (Antonia et al., 2007; Attia et al., 2005; Beck et al., 2006; Blansfield et al., 2005; Weber, 2007) (see Figure 1). The case studies can be used to train nurses who are new to ipilimumab therapy to administer the drug, identify and treat side effects, and educate patients.

Case 1: Rash, Pruritus, and Hypophysitis Management

Overview: P.N., a 56-year-old Caucasian woman with melanoma, responded to ipilimumab with stable disease at her 12-week scan. Her disease continued to regress, with scans at week 20 showing ongoing stable disease. P.N. developed grade II rash and pruritus and grade III hypophysitis (inflammation of the pituitary gland that inhibits its function) during treatment that were managed successfully with several topical and systemic anti-inflammatory drugs and hormone replacement therapy.

Rash and pruritus: P.N. presented in September 1998 with a skin lesion located on the right shoulder. The lesion subsequently was resected. The patient's pathology

- Common symptoms include diarrhea and skin rash.
- Most side effects are mild to moderate (grade I or II).
- Mild to moderate side effects are manageable with standard treatment (e.g., motility reducers for diarrhea), but patients should be monitored closely for their occurrence, and corticosteroid therapy should be initiated promptly when indicated.
- Early treatment of symptoms is mandatory and improves the likelihood of managing toxicity successfully; nurses should educate patients to report diarrhea, skin rash, and other nonspecific symptoms immediately.
- Hepatitis and hypophysitis are observed infrequently (Attia et al., 2005); common, nonspecific symptoms include fatigue, headaches, and impotence.
- Patients treated with steroids for immune-related side effects have maintained efficacy; aggressive treatment with anti-inflammatory (immunosuppressant) drugs does not affect antitumor response after initial dosing with ipilimumab (Antonia et al., 2007; Attia et al., 2005; Beck et al., 2006; Blansfield et al., 2005).
- Treatment guidelines from clinical trials will help identify, treat, and manage immune-related side effects (Weber, 2007).
- As the most frequent point of patient contact, nurses can help patients recognize early signs of immune-related side effects and ensure that they advise the clinical team accordingly.

Figure 1. Overview of Immune-Related Side Effects

report revealed compound proliferation with atypical melanocytes. In November 2003, the lesion recurred and was consistent with malignant melanoma. She developed a recurrent mass in the right shoulder scar in March 2004 that was excised and found positive for melanoma. In August 2005, PET and CT scans demonstrated multiple areas of bone metastases within the axial skeleton at L3-L4 and lymph node metastases to right axilla. P.N. had not yet received any systemic treatment for advanced melanoma.

P.N. underwent cyber knife radiation to the lumbar spine between August 2005 and March 2007. She started ipilimumab therapy in March 2007 and received a total of three doses of ipilimumab in a randomized, double-blind, phase II study. She received either 3 mg/kg or 10 mg/kg. After the first dose, P.N. developed a grade I macular, papular, and erythematous rash on her arms and legs. After the second dose of ipilimumab, the rash worsened to grade II with grade II pruritus; both conditions initially were managed with Eucerin® (Beiersdorf, Inc.) and diphenhydramine (1%) creams. Hydrocortisone cream (1%) and cetirizine (10 mg) were added, and topical fluticasone (0.005%) later replaced the hydrocortisone. The creams were administered BID for Eucerine, hydrocortisone, and fluticasone, and PRN for diphenhydramine and cetirizine. The rash was controlled by the treatments and P.N.'s itching symptoms diminished. P.N. was instructed to take lukewarm baths or showers and was cautioned against using any new products, such as lotions, perfumes, soaps, or detergents, that might exacerbate the rash.

Hypophysitis: After her third dose of ipilimumab, P.N. developed headaches that initially were grade I but quickly escalated to grade III and were not alleviated by over-the-counter medications. She experienced pressure behind the eyes, a heavy sensation in her head, and fatigue. Ipilimumab administration was discontinued temporarily after the third dose. She immediately had a magnetic resonance imaging scan of the brain and pituitary that revealed mild-to-moderate diffuse enlargement of the pituitary gland (12 mm). P.N.'s laboratory results showed low levels of cortisol (3.6 mcg/dl [normal range = 6–23]), free T4 (0.42 mcg/dl [normal range = 4.5–11.2]), and thyroid-stimulating hormone (0.492 mIU/L [normal range = 0.4–4]). No baseline values were recorded. A one-time dexamethasone 20 mg IV infusion was administered in the clinic, and oral levothyroxine was started at 75 mcg per day. The following day, all of her symptoms significantly improved, and her laboratory values returned to normal several weeks after daily oral supplementation with 75 mcg levothyroxine. P.N.'s symptoms resolved quickly, and she was started on oral prednisone 60 mg, which was tapered slowly over two months to 20 mg per day. P.N. now is maintained with 75 mcg levothyroxine and hydrocortisone (15 mg every morning and 5 mg hydrocortisone every afternoon). She currently is being followed by an endocrinologist and will continue on levothyroxine. P.N. was advised to call the clinic immediately if her headaches resumed or if she had excessive fatigue or loss of appetite or weight.

Case 2: Diarrhea Management

Overview: M.B., a 73-year-old Caucasian woman, responded to ipilimumab therapy for advanced melanoma with a partial response at week 24 and a complete response at week 28. She remained in complete remission 15 months after her first dose of ipilimumab. During treatment, the patient developed grade III diarrhea, which was managed successfully with motility reducers and steroids.

Diarrhea: M.B. presented in September 2005 with a skin lesion on the upper left arm that initially was treated with cryotherapy and antibiotics. The lesion persisted and was excised with inconclusive pathology. In January 2006, a lesion was found on her upper right arm. A routine follow-up CT scan in February 2006 revealed subcutaneous nodules to the chest and pelvic/lower abdominal region. In May 2006, M.B. participated in a clinical trial in which she received a dendritic cell vaccine for melanoma and fludarabine, but she progressed.

In July 2006, M.B. was enrolled in a randomized, phase II study in which ipilimumab 10 mg/kg was administered every three weeks for four doses, followed by every 12 weeks with or without prophylactic oral budesonide, a corticosteroid commonly used to treat Crohn disease; the budenoside was placebo-controlled, and both study arms were blinded. After the induction-dosing phase (36 weeks, average daily ipilimumab dose was 570 mg) and two maintenance doses of ipilimumab,

M.B. abruptly developed grade III diarrhea for the first time. Colitis was confirmed by colonoscopy and biopsy. Diphenoxylate and atropine (as needed) and budesonide (9 mg orally) were started to treat the diarrhea (about four episodes per day), but the symptom persisted. Daily prednisone (80 mg orally) was added to the patient's drug regimen. Prednisone taper was started after one week (decreased by 10 mg increments until 5 mg was reached; 5 mg was maintained for one week, then 5 mg was given on alternate days for one week) and discontinued when the diarrhea symptoms resolved. M.B. was encouraged to increase oral hydration, particularly by drinking sports drinks containing electrolytes (e.g., Powerade®, Gatorade®). She also was advised to eliminate dairy products and spicy and caffeinated foods, and was encouraged to increase her carbohydrate intake. Her diarrhea recurred during prednisone taper, so the prednisone was increased to 80 mg and then tapered over a longer period of time, after which the diarrhea resolved. M.B. showed no evidence of disease more than a year after her last ipilimumab infusion. She received education about the signs and symptoms that may occur with diarrhea (e.g., abdominal pain, bloody stools) and was encouraged to immediately communicate all information to the clinic to prevent a bowel perforation if the symptoms recur.

Case 3: Immune-Related Hepatitis Management

Overview: B.R., a 60-year-old Caucasian man, responded to ipilimumab therapy for advanced melanoma with a 73% reduction in tumor volume at the week-12 scan. His week-54 scan showed an additional decrease to a 92% overall reduction. His disease continued to show regression at every scanning visit. During treatment, he developed immune-related hepatitis, which was managed successfully with systemic corticosteroids.

Hepatitis: With no significant medical history, B.R. presented in 1999 with melanoma of the posterior rectal area. He did well with only a wide excision until July 2004 when he developed metastases to the left parotid gland and left lung, which were treated surgically. His disease recurred in the left lung in March 2005 with additional metastasis to the third left rib. He progressed further with lung disease, liver disease, a brain metastasis, and subcutaneous disease; he received gamma-knife radiotherapy for the brain lesion. In June 2005, B.R. was treated with biochemotherapy (a drug regimen consisting of dacarbazine, vinblastine, cisplatin, IL-2, and interferon), but his disease continued to progress. He received carboplatin and paclitaxel in August 2005, but the disease continued to progress.

B.R. was enrolled in a study of ipilimumab with or without prophylactic oral budesonide in May 2006. The primary outcome measure of the study was a rate of grade II or higher diarrhea. He received a total of three doses of ipilimumab (10 mg/kg every three weeks). After the first dose, he developed a grade I rash and grade I increased liver function tests (see Table 2). After the second dose, the rash remained unchanged, but the liver function tests elevated to grade II. After the third dose, the rash was unchanged but the patient experienced fatigue and mild confusion, and his laboratory values were again elevated. B.R. also developed hypophysitis and vitiligo (skin depigmentation).

The patient was hospitalized and treated with IV methylprednisolone at 2 mg/kg (60 mg every eight hours). He responded to the steroids in the first 12–24 hours, and his laboratory tests significantly improved: alanine aminotransferase = 805 units/L, aspartate aminotransferase = 279 units/L, alkaline phosphatase = 494 units/L, and bilirubin = 0.06 mg/dl. The patient was discharged after four days. His liver function tests were within the normal range, and he was placed on a daily dose of 60 mg of prednisone, which was tapered slowly by decreasing the dose in 10 mg increments each week.

B.R. was treated for ipilimumab-related hepatitis before treatment guidelines were implemented in all ipilimumab clinical trials. Checking liver function test levels before every ipilimumab dose, even if the patient is asymptomatic, and early intervention with steroids when warranted now are routine.

Patient Education

Nurses often are patients' first point of contact and spend more time with them than any other healthcare provider. Nurses should educate patients about the new drug class because patients must understand the clinical decisions made by their healthcare team and how the therapy may affect them. Caregivers need appropriate advice about recognizing and reporting immune-related side effects and education to understand how ipilimumab differs from other therapies for advanced melanoma and educate their patients (Levy, 2007). At the Angeles Clinic,

Table 2. Laboratory Test Results of a Patient Receiving Ipilimumab Therapy

Ipilimumab Treatment	Test Results			
	ALT (units/L)	AST (units/L)	AP (units/L)	Bilirubin (mg/dl)
First dose	26	23	128	–
Second dose	108	63	231	–
Third dose	1,450	955	653	2.6

Note. Normal ranges: ALT = 0–41, AST = 10–34, AP = 44–147, bilirubin = 0.3–1.9

ALT—alanine aminotransferase; AP—alkaline phosphatase; AST—aspartate aminotransferase

clinical trial nurses have developed several strategies to ensure that appropriate communication is established and maintained between patients and the clinical team (see Figure 2). Patients often become nervous and anxious when they see and feel tumors growing or experience increased discomfort. Nurses should assure patients that the symptoms may be the result of effective ipilimumab therapy; ipilimumab may be initiating an inflammatory response around the disease, which can cause some pain and make the tumor appear to be growing. Certain medications commonly used in oncology practice to control pain (e.g., narcotics) can mask serious side effects (e.g., symptoms of intestinal perforation, peritonitis). Patients who receive narcotics for pain control should be evaluated and monitored closely to ensure that serious complications do not develop.

Nurses can remind patients that the response to this new method of treatment may not be seen immediately because ipilimumab works indirectly through the immune system, unlike chemotherapy, which acts directly on tumor cells. Nurses at the Angeles Clinic advise patients that immune-related side effects can be positive, indicating that the body may be responding favorably to treatment. As a result, patients my be more attentive to symptoms and become more involved in their own

management. When patients are treated with immunosuppressants for immune-related side effects, they require reassurance that successfully managing their symptoms does not negate the effect of ipilimumab; the corticosteroids used to treat ipilimumab side effects are immunosuppressive. Patients often are comforted by hearing accounts of previous patients who ultimately responded to ipilimumab. In addition, patients at the Angeles Clinic have appreciated having the patient education repeated and reviewed at the clinic or over the telephone when they were anxious.

Conclusions

Nurses have an important role in educating patients about the differences between ipilimumab anti-CTLA-4 therapy and chemotherapy and working with them to achieve a positive clinical outcome. Developing a relationship with patients and helping them understand ipilimumab therapy will help ensure timely and accurate reporting of any side effects, leading to effective management.

Nurses should monitor and question patients regarding the presentation of immune-mediated side effects and help them understand the negative consequences of failing to immediately report symptoms. For example, diarrhea and the resulting dehydration that emerge in ipilimumab-treated patients require prompt treatment and cannot be left unattended for several days. Nurses also should instruct patients to immediately contact their physician or nurse when symptoms occur; failure to manage mild-to-moderate diarrhea may rapidly result in a severe and potentially life-threatening event. Patients must understand that a delay in reporting and obtaining appropriate treatment for diarrhea may lead to a bowel perforation, which requires emergency treatment. In addition, nonspecific clinical symptoms, such as headaches, tiredness, and decreased libido may indicate endocrinopathies.

Healthcare professionals also require education about how ipilimumab works as well as how to recognize and treat immune-related side effects. Some symptoms well known to nurses (e.g., diarrhea) must be treated in a completely different manner (i.e., with steroids) when they emerge during an ipilimumab treatment regimen. Receiving education on how ipilimumab works will help oncology nurses support patients and provide rationale for continuing the treatment course through at least week 12 or longer before considering alternate therapies. Relaying the information to patients also will help reduce unnecessary anxiety and prevent patients from asking to stop therapy if treatment does not seem to be working. Ensuring that patients understand and support ipilimumab treatment may allow the agents to be used to full potential, thus maximizing patient benefit.

Immune System, CTLA-4, and Ipilimumab
- Provide a basic and brief lesson on how the patient's immune system can fight tumors.
- Emphasize how ipilimumab stimulates the patient's immune system.
- Describe how ipilimumab and anti-CTLA-4 therapy differ from chemotherapy.

Immune-Related Side Effects
- Review possible side effects and symptoms with the patient and family members when introducing the patient to the study, at time of consent, and during each clinic visit.
- Instruct the patient and family members to have over-the-counter medications (e.g., loperamide, acetaminophen or ibuprofen, hydrocortisone or Eucerin® cream [Beiersdorf, Inc.], antihistamines) on hand should the patient experience any immune-related symptoms or side effects related to ipilimumab before the first ipilimumab dose.
- Ask the patient whether he or she has experienced nausea, rash, itching, diarrhea (or any changes in bowel movements), headaches, excessive fatigue, lower abdominal pain, or visual changes during every clinical visit.
- Encourage the patient to keep a diary and document the date and time of symptoms, even if they do not appear to be treatment related.
- Encourage the patient and family members to call nurses and physicians at the onset of any symptoms or to ask questions.
- Initiate phone contact with the patient if he or she begins to experience symptoms of ipilimumab side effects; call either daily or every other day, depending on symptom severity.
- Have a nurse readily available via phone or in the clinic to reassure the patient, who may find waiting for a response difficult.

CTLA-4—cytotoxic T-lymphocyte antigen-4

Figure 2. Approaches to Patient Education

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