Atypical Clinical Response Patterns to Ipilimumab: Four Case Studies of Advanced Melanoma

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Patients with advanced melanoma have few treatment options, and survival is poor. However, improved understanding of how the immune system interacts with cancer has led to the development of novel therapies. Ipilimumab is a monoclonal antibody that inhibits cytotoxic T-lymphocyte antigen–4 (CTLA-4), a key negative regulator of host T-cell responses. This article presents cases of patients receiving ipilimumab in clinical trials along with a discussion of their significance and relevance to nursing practice. The patients showed different response patterns to ipilimumab and also had various typical immune-related adverse events (irAEs), which were managed successfully. The atypical response patterns produced by ipilimumab likely reflect its mechanism of action, which requires time for the immune system to mount an effective antitumor response. Meanwhile, lesions may appear to enlarge as a consequence of enhanced T-cell infiltration, although this may not necessarily be true disease progression. Patients receiving ipilimumab may respond very differently compared to how they might react to chemotherapy. Responses can take weeks or months to develop; therefore, clinicians should not terminate treatment prematurely, providing the patient’s condition allows for continuation. Early recognition of irAEs combined with prompt management will ensure that events are more likely to resolve without serious consequences.

At a Glance

- Treatment of advanced melanoma with ipilimumab has demonstrated promising results with respect to one- and two-year survival.
- During ipilimumab treatment, lesions may appear to enlarge as a result of the immune system mounting an effective antitumor response with enhanced T-cell infiltration.
- Nurses should understand ipilimumab’s mechanism of action and possible response patterns and educate patients and their caregivers to prevent premature treatment withdrawal.

Prompt diagnosis and surgery are effective for early-stage melanoma, with almost 100% of patients with resected localized stage I or II tumors surviving to five years after diagnosis (Horner et al., 2009); however, melanoma continues to be an ongoing challenge in its advanced stages. Only 15% of patients with metastases will still be alive five years after diagnosis (Horner et al., 2009), and survival rarely exceeds 12 months (Eggermont, 2006). Since dacarbazine (also known as DTIC) was first introduced in the 1970s, survival has remained fundamentally unchanged in patients with advanced melanoma (Serrone, Zeuli, Sega, & Cognetti, 2000), underscoring an urgent need for new treatment strategies.

The arrival of cytokine- and vaccine-based immunotherapies in the early 1990s was promising, but those therapies have delivered...
little to date. Interferon-α (approved as adjuvant monotherapy or in various combination regimens) and interleukin-2 (IL-2) (approved as monotherapy) have produced only modest survival benefits offset by limited utility because of toxicity, and vaccines have been largely ineffective (Hauschild, 2009; Hauschild et al., 2008; Riley & Agarwala, 2008; Schadendorf et al., 2009). DTIC and IL-2 remain the reference therapies, and innovation has stayed within the confines of clinical trials (National Comprehensive Cancer Network, 2010).

High doses of IL-2 produce durable responses in about 5%–15% of patients with melanoma; therefore, targeting the patients’ immune systems instead of their cancer has remained at the forefront of new developments (Atkins et al., 1999). Tumors often are highly antigenic and, therefore, can be recognized as foreign by the immune system. However, IL-2’s ability to elicit an immune response declines over time as the cancer progresses (Swann & Smyth, 2007). Essentially, tumors learn how to escape from immune control (Drake, Jaffee, & Pardoll, 2006). This happens through a series of tumor-driven effects that begin at the tumor site but extend regionally in time, resulting in a complex and as yet incompletely understood interplay between the tumor itself and the host immune system, collectively called *immunoediting* (Dougan & Dranoff, 2009; Dunn, Old, & Schreiber, 2004; Kim, Emi, Tanabe, & Arihirok, 2006). The patient’s immune system eventually can no longer mount an effective response against the tumor, and the cancer progresses. Treatment strategies that help the patient’s immune system to mount a more effective antitumor response are being pursued, with much work involving patients with advanced melanoma.

**Background**

**Role of Cytotoxic T-Lymphocyte Antigen–4 in Host Antitumor Immunity**

Cytotoxic T-lymphocyte antigen–4 (CTLA-4) is a key checkpoint in the immune system cascade and the main negative regulator of T-cell-mediated antitumor immune responses (Robert & Ghiringhelli, 2009). Therefore, this molecule has been identified as a target for cancer therapy. During the process of T-cell priming, specialized antigen-presenting cells deliver tumor-associated antigens attached to major histocompatibility complex I or II to T-cell receptors, initiating activating signal 1 (Peggs, Quezada, Korman, & Allison, 2006; Robert & Ghiringhelli, 2009; Weber, 2009) (see Figure 1). A second costimulatory signal required for completing T-cell activation is initiated by B7 molecules (CD80 and CD86) on the surface of the antigen-presenting cell binding with CD28 receptors on the T-cell surface. The resulting dual-cell signaling activates T cells that then can proliferate and assume an effector-cell phenotype, rendering them immunologically active.

Alongside T-cell activation, a process of negative regulation is essential to restrict T-cell responses to areas of inflammation or injury, maintaining peripheral tolerance and preventing nonspecific response.

![Figure 1. Priming, Activation, and Subsequent Homeostatic Inactivation of T Cells](image-url)

tissue damage from unwanted autoimmunity. T-cell activation up-regulates CTLA-4 expression; CTLA-4 then competes with CD28 for binding to B7 on antigen-presenting cells, but with higher affinity, interrupting activation signal 2 and inactivating the T cell (Peggs et al., 2006; Robert & Ghiringhelli, 2009; Weber, 2009). Chronic T-cell stimulation by tumor-associated antigens has been proposed to result in persistently higher levels of CTLA-4 expression and produce a population of immune cells that are primed but “switched off” (Peggs et al., 2006). Theoretically, targeting CTLA-4 and thereby interrupting negative immune regulation would help to restore T-cell activation and support the patient’s immune system in mounting an effective antitumor immune response.

**Ipilimumab: A New T-Cell Potentiator**

Ipilimumab (YERVOY™) is a first-in-class fully human monoclonal antibody directed against CTLA-4, approved by the U.S. Food and Drug Administration in March 2011 for patients with advanced melanoma (Bristol-Myers Squibb, 2011a). Ipilimumab has been studied in an extensive program of clinical trials involving more than 3,000 patients with advanced stage IV melanoma and has shown durable complete responses and prolonged survival, even in heavily pretreated patients (Hodi et al., 2003, 2008; Maker et al., 2005; O’Day et al., 2010; Phan et al., 2003; Robert et al., 2011; Weber et al., 2009; Wolchok et al., 2010). In a phase III study, ipilimumab significantly improved overall survival; some patients who progressed after initially responding had durable responses on reinduction (Hodi, O’Day, McDermott, Haanen, et al., 2010; Hodi, O’Day, McDermott, Weber, et al., 2010). Ipilimumab is a T-cell potentiator that acts by competing with B7 ligand molecules on antigen-presenting cells for binding to CTLA-4 on T cells (Weber, 2009) (see Figure 2). Therefore, ipilimumab interrupts CTLA-4 cell signaling and reverses or prevents T-cell inactivation, prolonging and augmenting the T-cell-mediated antitumor immune response (Peggs et al., 2006; Robert & Ghiringhelli, 2009).

In a large phase II clinical trial of treatment naïve and pretreated patients with unresectable stage III-IV melanoma (N = 115), ipilimumab resulted in median overall survival of up to 19.3 months and durable disease control in almost 14% of patients; in addition, about 40% of patients were still alive after two years (Weber et al., 2009). Overall and two-year survival has been reported to be slightly lower in heavily pretreated patients (O’Day et al., 2010; Wolchok et al., 2010). Notable throughout those studies was the range of treatment responses, with some being very different from the patterns observed with chemotherapy. Responses to ipilimumab were seen during, at the end of, and beyond the 12-week induction period (Saenger & Wolchok, 2008). The responses fell into four distinct patterns: (a) response in baseline (index) lesions corresponding to complete response or partial response similar to chemotherapy responses; (b) durable stable disease, in some cases followed by a slow, steady decline in tumor burden; (c) response after an increase in tumor burden (i.e., after apparently progressive disease by standard response criteria); and (d) response in index and new lesions accompanied by the appearance of other new lesions (a mixed response but overall decrease in total tumor burden) (Weber et al., 2009; Wolchok et al., 2009). Patterns c and d are not recognized in standard response criteria such as the World Health Organization (WHO) guidelines or Response Evaluation Criteria in Solid Tumors (RECIST) (Therasse et al., 2000), and oncology nurses who usually care for patients receiving chemotherapy or traditional immunotherapy are not familiar with those patterns. Remarkably, all four patterns were associated with favorable effects on survival.

Ipilimumab is associated with a novel range of adverse events, termed immune-related adverse events (irAEs) because of their association with the immune-related action mechanism of the drug (O’Day et al., 2010; Robert et al., 2011; Weber et al., 2009; Wolchok et al., 2010). Most oncology nurses are unfamiliar with irAEs because they differ significantly from the adverse events generally associated with chemotherapy and other oncology drugs. Response and tolerability vary; therefore, patients treated with ipilimumab may need to be managed differently than those receiving other types of anticancer treatment.

At the authors’ center, four patients presented with advanced metastatic melanoma that had progressed following prior treatment and then responded to treatment with ipilimumab in different ways, representing variations of the four response patterns described previously. This article discusses the management of those patients in the context of their differing responses and irAEs associated with therapy. In addition, the...
broader implications of those observations for future oncology nursing practice will be considered.

Case Studies

Case 1: Partial Response Leading to Complete Response

E.L., an older man, had completed initial surgery for melanoma successfully and remained disease free for 11 months. He then presented with metastatic spread (see Figure 3) and was enrolled in a clinical trial of IV ipilimumab (10 mg/kg every three weeks for four cycles). E.L. originally presented with a left prehilar lymph node and multiple liver lesions, which were followed and tracked when he was placed on the ipilimumab trial. E.L. tolerated the initial infusions well, complaining only of minor itching, and at the week 10 infusion he had shaking chills that resolved with nonsteroidal anti-inflammatory drug treatment. At week 12, E.L. had a partial response accompanied by extensive vitiligo on the neck and chest, progressing to the face, back (including the site of initial disease), and lower extremities (see Figure 4). He also had intense fatigue requiring 12–14 hours of sleep daily. Further investigation revealed an adrenocorticotropic hormone level of 8 pg/ml (normal range = 6–48 pg/ml), a serum thyroid-stimulating hormone level of 1.9 mIU/L (normal range = 0.5–6 mIU/L), a T3 level lower than 8 ng/dl (normal range = 85–205 ng/dl), and a T4 level of 3.8 ug/dl (normal range = 0.75–1.54 ug/dl). Those findings were consistent with E.L. trending toward hypothyroidism and adrenal insufficiency, which could lead to serious consequences; therefore, prompt management was required. E.L. was started on levothyroxine with corticosteroids, resulting in a resolution of symptoms. Week 24 scans showed a complete response. He continued to receive levothyroxine, and although his vitiligo became more widespread after two years, E.L. has maintained a complete response. To date, E.L. is still alive more than three years since he started ipilimumab and is scheduled for ongoing clinic follow-up.

E.L.’s case highlights durable partial response detectable after completion of the induction course of ipilimumab, which developed into a complete response that was maintained for more than three years since the start of treatment. Development of the partial response coincided with effects related to irAEs: hypopituitarism and adrenal insufficiency, hypothyroidism, and vitiligo. Hypophysitis, an inflammation of the pituitary gland, may contribute to or result in hypothyroidism, which has been reported previously (Attia et al., 2005; Maker et al., 2006). In the authors’ experience and as evidenced by this case, symptoms such as fatigue, erectile dysfunction, myalgia, constipation, and mental status changes should be investigated early to establish the source because hypophysitis, hypothyroidism, and primary adrenal insufficiency can be effectively managed with replacement therapy. E.L.’s hypothyroidism responded well to levothyroxine, and he continues to receive medication to date.

Case 2: Complete Response Following Apparent Progression

C.M., a 53-year-old man, had received surgery for a locally metastasized melanoma and his disease subsequently recurred,
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Case 2: Progression on Standard Therapy

C.M., a 58-year-old male, presented in February 2007 with progressive metastatic melanoma. He had a history of severe diarrhea (grade 3), controlled with loperamide and high-dose (1 mg/kg) oral prednisone; his viral hepatitis work-up was negative, and no new disease or life threatening masses were found; therefore, the authors decided not to change his therapy and monitor his disease. He had surgery with associated T-cell infiltrate comprised an approximately equal mixture of CD8+ (cytotoxic) and CD4+ (helper) T cells, and no residual melanoma was seen in smaller lesions. Therefore, C.M. demonstrated a complete pathologic response. Nine months after starting ipilimumab, C.M. remained in complete remission and was tapered off all immunosuppressive medication. Unfortunately, C.M. died of disease progression in October 2008, one year and 11 months after first receiving ipilimumab.

C.M.’s case was unusual, as he appeared to have progressive disease at the initial week 12 assessment on ipilimumab treatment. However, most of the increase in tumor volume could have been caused by T-cell infiltration and not tumor cell proliferation, given the histopathology. C.M. went on to have stabilization of tumor burden for five months, as well as after resection, demonstrating an ongoing surgical complete response. This outcome was significant given C.M.’s metastatic disease and progression on standard therapy.

Case 3: Partial Response, Then Progression Followed by a Complete Response

R.J., a 68-year-old man, had successful resection of a primary melanoma lesion but subsequently relapsed and developed metastatic disease while not receiving treatment. He had surgery with adjuvant radiotherapy, but his cancer recurred, necessitating further surgery and repeat cycles of an experimental biochemotherapy regimen. Despite therapy, R.J.’s disease progressed with several lesions to his liver, left supravacular lymph node, and chest. R.J. subsequently was enrolled in an ipilimumab trial and received an induction course (10 mg/kg every three weeks for four cycles) followed by a maintenance phase starting at week 24 (10 mg/kg every 12 weeks). R.J. received the first three induction doses of ipilimumab with a minor complaint of diarrhea (grade 2), controlled with loperamide and diphenoxylate and atropine. After the fourth dose of ipilimumab (week 10), R.J. had severe diarrhea (grade 3, not controlled by the previous treatment), tenesmus, and abdominal pain. Biopsy confirmed grade 3 immune-related colitis refractory to budesonide, loperamide, Lomotil, and high-dose (1 mg/kg) oral prednisone; ipilimumab was stopped.

R.J.’s colitis ultimately resolved within one week of receiving one dose of infliximab; he continued on oral prednisone,
which was tapered slowly. At week 12, R.J. had progressive disease with no new sites of metastatic disease. R.J.’s colitis worsened during prednisone tapering, requiring hospital admission, IV steroids, and methylprednisolone enemas, which improved his symptoms. At week 24, R.J.’s scans showed progressive disease with an increasing suprasternal soft tissue nodule and an obstructive left lung mass. He underwent resection of the remaining disease sites, resulting in a surgical complete response. To date, R.J. remains in surgical complete response more than three and a half years after his enrollment in the ipilimumab clinical trial. He still has occasional diarrhea, which is controlled by loperamide, and intermittent pruritus. R.J. demonstrated a positive outcome with ipilimumab after biochemotherapy failure. In this case, ipilimumab resulted in a partial response that converted to apparent progressive disease and then was managed successfully to a durable complete response by surgery.

**Case 4: Mixed Response**

T.R., a 70-year-old Caucasian man, initially presented with stage III melanoma postresection with high risk of recurrence. He received adjuvant therapy with four cycles of an experimental biochemotherapy (regimen containing temozolomide, vinblastine, cisplatin, IL-2, and interferon) followed by 12 cycles of maintenance biotherapy (regimen containing IL-2 and granulocyte macrophage-colony-stimulating factor) before he was found to have disease progression with lesions in his bones, spleen, and liver.

T.R. then was enrolled in a clinical trial of ipilimumab in which the planned treatment was an induction course of ipilimumab (10 mg/kg every three weeks for four cycles). Five splenic lesions and a portacaval lymph node were used to evaluate T.R.’s disease during the trial. He had other lesions within the liver and spleen that were present but nonevaluable. T.R. only received three of the four scheduled doses of ipilimumab in the trial. Subsequently, he was enrolled in an ipilimumab compassionate use trial (ipilimumab 10 mg/kg every 12 weeks) and received an additional four maintenance doses of ipilimumab starting at week 24.

During induction therapy, the first two doses of ipilimumab were associated with a minor complaint of rash (grade 2) and pruritus (grade 1) to T.R.’s chest and upper extremities. After the second induction dose of ipilimumab, T.R. developed fever, fatigue, diarrhea that was controlled with loperamide, elevated liver function tests (all grade 1), and thrombocytopenia (grade 2). A panhypopituitary panel was drawn and found to be normal, and liver function tests were monitored twice a week until they resolved. After the third induction dose of ipilimumab, T.R. developed grade 3 thrombocytopenia and grade 4 disseminated intravascular coagulation with a fibrinogen less than 60 mg/L (normal range = 190–400 mg/L) and D-dimer of 8.5 mcg/ml (normal range = 0.4 mcg/ml or lower). T.R. also had grade 2 elevated liver function tests and hyperbilirubinemia. He was admitted to a local hospital, where he received supportive care until the symptoms resolved.

The fourth and final induction dose of ipilimumab was not given, and scans at week 12 showed disease progression per standard RECIST criteria (Therasse et al., 2000) with an overall increase in tumor burden of 55%. Analysis of the scans showed that T.R.’s lesions, which were not being used as target lesions, had either decreased in size or remained stable. In addition, his liver lesions were stable, his lymphadenopathy and splenic lesions had increased in size, and he had developed new splenic lesions. Four weeks later, T.R. had repeat scans, which showed that his disease was stable. T.R. then was enrolled in a compassionate use trial, 16 weeks after his last induction dose of ipilimumab and the complete resolution of all side effects. After two doses on the compassionate use trial, T.R. developed grade 2 vitiligo, which is ongoing to date, and he continues to experience an intermittent grade 1 rash and pruritus. During the last follow-up at week 84, T.R.’s scans showed a partial response using the new response criteria (immune-related partial response) (Wolchok et al., 2009), an overall decrease in target lesion size of 41%, and no new disease. T.R.’s case shows how disease status categorized as ongoing progressive disease by conventional response criteria may, in fact, result in a prolonged decrease in overall tumor burden associated with improved survival.

**Figure 5. Scans Before and After Ipilimumab Treatment and Resection of a Lesion**

*Note. Images courtesy of the Angeles Clinic and Research Institute. Used with permission.*
Discussion

Although conventional objective responses (e.g., tumor shrinkage soon after treatment initiation) can be observed in patients receiving ipilimumab, the patterns of response are variable and may take weeks or months to develop (Hamid et al., 2007; Saengger & Wolchok, 2008; Wolchok et al., 2009, 2010). In addition, a response sometimes can be preceded by progressive disease (by conventional definition) or prolonged stable disease. Those patterns of responses differ from responses to traditional cytotoxic chemotherapy; they are proposed to be a result of the time needed for CTLA-4 blockade to “educate” and expand the cellular arm of the immune system and for the infiltrating effector T cells to exert a clinically detectable effect (Wolchok et al., 2009). The adverse event profile associated with ipilimumab therapy also differs from that of chemotherapy, primarily as a result of the overactivation of the immune system. From a scientific perspective, irAEs may be a result of self-reactive T cells uncovered by CTLA-4 blockade (O’Day, Hamid, & Urba, 2007). The irAEs are well characterized, manageable, and reversible by applying established irAE management guidelines in most cases.

Ipilimumab in the Case Studies

The four cases presented in this article illustrate many of the key differences between ipilimumab and conventional chemotherapy in relation to responses and adverse event profiles. Case 1 shows that responses can develop in a conventional way, with a partial response occurring soon after treatment, then developing into a complete response. Case 2 illustrates that, as reported previously, disease stabilization following ipilimumab induction therapy may arise several weeks or even months after initial administration. In addition, stable disease occurred four months after the start of treatment in C.M. despite apparent early progression, which led the authors to consider the nature of the progressive disease observed in C.M. at week 12. This phenomenon has been proposed to represent the time needed for the immune system to develop and effectively control the tumor. However, it actually may be a transient increase in tumor volume caused by the infiltration of immune effector cells (Ribas, Chmielewski, & Glaspy, 2009). The latter hypothesis was supported by the histologic analysis of C.M.’s resected lesions, which showed infiltration of T cells and macrophages and extensive inflammation and necrosis.

Studies to clarify the nature of clinically apparent progressive disease are needed. However, in the absence of a substantially increased tumor burden, patients may benefit from an extended period of observation without receiving a new therapy. At minimum, clinically significant progressive disease should be confirmed by repeat scan at least four weeks after initial scans demonstrating disease progression before starting a new treatment.

In case 3, ipilimumab-enhanced immune activity may have prevented recurrence after resection. In the authors’ experience, alternative systemic treatment should be considered only if evidence shows clinically significant disease progression, an increase in overall tumor burden, or a decrease in performance status. However, whether the growing lesions would have regressed without resection in R.J.’s case is unclear. Studies are warranted that follow the natural history of new lesions in patients receiving ipilimumab with the aim of preventing invasive surgery. R.J. also had apparent progressive disease after initial partial response, eventually developing a complete response. The tumor growth after partial response may have reflected lesion enlargement because of T-cell infiltration; that is, the tumor growth was a consequence related to the mode of action of ipilimumab and not caused by tumor cell proliferation. This possibility was supported by R.J.’s eventual complete response.

Case 4 was perhaps the most challenging. The definition of progressive disease by RECIST or WHO criteria relies on the monitoring of measurable index lesions at baseline and after therapy (Therasse et al., 2000). Those criteria may underestimate efficacy and lead to premature treatment withdrawal because of ipilimumab’s novel action mechanism. As a result, novel response criteria, known as immune-related response criteria, have been developed and validated (Wolchok et al., 2009). As with RECIST and WHO guidelines, immune-related response criteria are based on total disease burden at baseline. However, the first disease assessment typically occurs later, and progressive disease is noted only after a 25% increase in total disease burden has been exceeded twice and at least four weeks apart (irrespective of individual lesion sizes or the appearance of new lesions) (Weber, 2009; Wolchok et al., 2009). According to immune-related response criteria, T.R. in case 4 had an irPR to ipilimumab because his total disease burden decreased after treatment, although he had apparent growth in some lesions and new lesions appeared. The increases in lesion growth may
be attributable to T-cell infiltration in response to ipilimumab and not true tumor growth (Ribas et al., 2009). In addition, some seemingly new lesions actually may be established lesions that became measurable as a result of T-cell infiltration (Wolchok et al., 2009).

Immune-related adverse effects: Vitiligo is an interesting irAE that could be a visual indicator of therapy efficacy. No studies have examined the etiology of specific irAEs; however, a correlation has been observed between depigmentation (either spontaneous or after treatment) and good prognosis and outcome in patients with malignant melanoma (Wankowicz-Kalinska, Le Poole, van den Wijngaard, Storkus, & Das, 2005). Of interest, E.L.’s vitiligo in case 1 was apparent particularly at the initial site of disease, as well as at more distant locations.

In patients treated with ipilimumab, vitiligo likely is caused by the immune-mediated destruction of melanocytes. A correlation may exist with antitumor efficacy because of the potential for cross reactivity between immune-effector cells specific for melanoma and melanocytes (depending on the tumor antigens expressed) (Phan et al., 2003; van Elias, Hurwitz, & Allison, 1999; Wankowicz-Kalinska et al., 2003). However, vitiligo could simply be caused by nonspecific immune-cell overactivity. Identifying vitiligo as a visual, noninvasive measure of antitumor immune status would help optimize therapy; therefore, additional research is needed. No effective treatment for vitiligo is available to date, but healthcare providers should advise patients that it is a known side effect of ipilimumab therapy and likely is related to the way the drug works.

Case 2 illustrated the management and complete resolution of grade 3 hepatitis, a relatively uncommon irAE. C.M. was treated in accordance with guidelines used in the authors’ institution (O’Day et al., 2007), which also were a component of the trial protocol. Early diagnosis and prompt management are important success factors, and patients should be tapered off steroid therapy slowly using symptoms and laboratory values to determine the time required (minimum of four to six weeks). The relationships of this irAE to CTLA-4 inhibition and treatment outcome are unclear, although histologic investigation of hepatitis in two clinical trials showed extensive hepatic lymphocyte infiltration (Phan et al., 2003), suggesting a causative relationship with immune cells nonspecifically activated through ipilimumab mediated CTLA-4 inhibition. Secondary, stronger immunosuppressive agents (e.g., mycophenolate mofetil, infliximab) may be necessary in steroid-refractory cases.

Diarrhea is a common irAE, but occasionally may be a symptom of colitis, as seen in case 3. Therefore, healthcare providers should advise patients to report diarrhea or any other change in bowel habits immediately and evaluate for possible colitis when the symptoms occur. Colitis can become life threatening quickly; therefore, rapid diagnosis and treatment are essential. By following the management guidelines included in the trial protocol (O’Day et al., 2007), the authors usually are able to manage immune-related colitis successfully in their practice. However, that nonimmune-related causes of colitis (e.g., Clostridium difficile infection) should be excluded first. Some patients with diarrhea may have mucosa that appears healthy; therefore, healthcare providers should perform mucosal biopsies to rule out colitis even if gross pathology is not present. In R.J.’s case, the diarrhea and colitis were not managed with budesonide, IV steroids, or steroid enemas, but local steroid treatment often is effective. The use of infliximab, mesalamine, and hydrocortisone enemas has been suggested as an alternative to steroids (Minor, Chin, & Kashani-Sabet, 2009). In addition, the effectiveness of steroid prophylaxis for severe diarrhea has not been proven (Weber et al., 2009).

Recommendations and Implications for Nursing Practice

Conventional response criteria may underestimate a patient’s response to ipilimumab, and some patients experienced premature treatment withdrawal; therefore, new response criteria were developed (Wolchok et al., 2009). The criteria consider the sum total of tumor burden (index plus baseline lesions). In addition to immune-related complete response, the criteria define immune-related partial response as a decrease in tumor burden by greater than 50% and immune-related stable disease, where patients do not have an immune-related complex or partial response but also do not reach the threshold for progression of their disease. When assessing patients with the new criteria, those who develop new lesions but show a response in one or more baseline lesions will not necessarily be considered to have progressive disease, as would be the case with standard response criteria. Such patients could continue to receive ipilimumab and retain the potential for possible long-term benefits. Patients should receive education and counseling regarding those novel patterns of response and their therapeutic implications.

Nurses have an important role in educating patients on what to expect during ipilimumab therapy (see Figure 7). To have realistic expectations, patients should understand the basic distinction between the mechanism of action of cytotoxic drugs and immunotherapy and the length of time needed to...
Difficulty waking up
Headache (rule out endocrine disorder)
Visual changes
Fever
Fatigue or weakness
Confusion

Sensory or motor neuropathy
Muscle weakness
Fatigue
Difficulty waking up
Paresis

Diarrhea
Stomach pain
Nausea, vomiting, and pain
Blood in stool
Constipation

Skin rash or pruritus

ALT—alanine aminotransferase; AST—aspartate aminotransferase

General Management Recommendations
- Mild: Treat symptomatically.
- Persistent mild or moderate: Treat with oral corticosteroids.
- Symptoms worsen, are severe, or are life threatening: Treat with high-dose IV corticosteroids.

Figure 8. Characteristic Spectrum of Immune-Related Adverse Events to Ipilimumab

Conclusions

Treatment of advanced melanoma with ipilimumab has demonstrated promising results with respect to one- and two-year survival (O’Day et al., 2010). Ipilimumab treatment can result in response patterns not typical of treatment with chemotherapeutic agents, as well as the development of irAEs (Wolchok et al., 2009). The four cases presented in this article demonstrate some of the response patterns and irAEs associated with ipilimumab and provide guidance relating to the diagnosis and management of irAEs and the counseling of patients and their caregivers. Responses can occur soon after the first administration or may take weeks to months, with some patients showing progressive tumor growth prior to immune-mediated stabilization or nonclinically significant progression. Unlike with chemotherapy, patients
can experience prolonged stable disease with ipilimumab that eventually may evolve into an objective tumor response. Finally, new lesions may develop while others regress. Ipilimumab has a predictable pattern of irAEs. However, several (albeit uncommon) irAEs may be life threatening. Prompt diagnosis and appropriate management with established guidelines can result in the resolution of all symptoms. Healthcare providers must ensure that patients are educated and aware of the early symptoms and know to contact the clinic as soon as possible when symptoms present.

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