



Nursing Management of Patients With Metastatic Melanoma Receiving Ipilimumab

Jane Bryce, MSN, AOCNS®, and Claudia Passoni, RN

A 46-year-old Caucasian male named N.M. was diagnosed in March 2002 with melanoma of the trunk. The melanoma was resected and a left axillary sentinel lymph node biopsy was negative for malignant cells. Three years later, melanoma recurred to the left axillary lymph nodes, which were subsequently dissected. No adjuvant therapy was administered. In November 2007, a computed tomography (CT) scan showed multiple lesions (2–6 cm) in the abdomen wall, peritoneum, and small bowel, and a mass of 10 cm in the left axillary region. N.M. was enrolled into a phase III trial and received 850 mg/m² dacarbazine plus 10 mg/kg ipilimumab at weeks 1, 4, 7, and 10, followed by dacarbazine alone every three weeks through week 22.

Tumor assessment at week 12 showed a reduction in size of all lesions in the abdomen wall, peritoneum, and small bowel, with only one lesion remaining measurable at 15 mm. However, the mass in the left axillary region had increased more than 20% in size, with associated pain and functional limitation. N.M. was diagnosed with progressive disease by RECIST (Response Evaluation Criteria in Solid Tumors).

For reasons of pain and function, the accessible mass in the left axillary region was surgically removed. Histologic examination of the mass confirmed melanoma; however, massive infiltration of lymphocytes also occurred, which was suggestive of an antitumor immune response. Postoperative CT scan demonstrated no change to other lesions, and N.M. continued with maintenance therapy, receiving 10 mg/kg ipilimumab every 12 weeks. N.M. remained progression free until January 2009 when cerebral metastases were observed.

Before the third induction dose of ipilimumab, N.M. reported grade 2 macu-

lopapular rash of the trunk, hands, and feet with associated grade 1 pruritus. A topical 0.1% hydrocortisone cream was prescribed, and the patient was advised about skin care, using moisturizer, and avoiding sun exposure. Following an increase in pruritus from grade 1 to grade 2, N.M. was prescribed an antihistamine (diphenhydramine) to be used on an as-needed basis. One week later, the rash had lessened and the pruritus had resolved.

Prior to the fourth dose of ipilimumab, N.M. reported an increased number of bowel movements and was prescribed loperamide. A bland diet with increased oral hydration was recommended and N.M. was advised to attend the clinic or emergency room in the case of a painful or distended abdomen or the presence of blood in his stools. One week later, the diarrhea had stopped and clinical examination revealed normal bowel sounds and serum electrolytes. In addition, N.M.'s skin rash had almost completely resolved. The fourth ipilimumab dose was delayed by one week to monitor for any additional gastrointestinal symptoms.

Throughout treatment, vigilant monitoring by N.M. and his healthcare providers ensured that diarrhea and rash associated with ipilimumab treatment were identified quickly and managed appropriately. In this case, advice given to the patient with regard to monitoring ongoing adverse reactions minimized disruption to the ipilimumab treatment schedule.

The incidence of malignant melanoma, the most serious type of skin cancer, has been increasing steadily. An estimated 76,250 cases of melanoma were reported in the United States in 2012 compared to 62,480 in 2008 (Jemal et al., 2008; Siegel, Naishadham, & Jemal, 2012). A similar trend has been noted in

Europe, where an estimated 50,000 cases of melanoma were diagnosed in 2004, rising to 84,000 cases in 2008 (Boyle & Ferlay, 2005; Ferlay, Parkin, & Steliarova-Foucher, 2010). Patients diagnosed with metastatic melanoma are faced with poor survival rates and limited treatment options. The latest versions of clinical practice guidelines for melanoma from the National Comprehensive Cancer Network ([NCCN], 2013) and the European Society for Medical Oncology clinical practice guidelines (Dummer, Hauschild, Guggenheim, Keilholz, & Pentheroudakis, 2012) recommend treatment with ipilimumab, a novel immunotherapy, for all patients.

Mechanism of Action

Ipilimumab is a human monoclonal antibody that blocks cytotoxic T-lymphocyte antigen-4 (CTLA-4) (Fong & Small, 2008). CTLA-4 normally acts to block the activation of cytotoxic CD8 T cells. With ipilimumab, blockade of the inhibitory signal from CTLA-4 potentiates T-cell activation, proliferation, and infiltration into tumors, which may lead to tumor cell death (Fong & Small, 2008; Melero, Hervas-Stubbs, Glennie, Pardoll, & Chen, 2007; O'Day, Hamid, & Urba, 2007; Robert & Ghiringhelli, 2009).

Dosing and Administration

Ipilimumab is indicated in the United States and Europe (pretreated patients only) for the treatment of advanced (unresectable or metastatic) melanoma in adults (Bristol-Myers Squibb, 2011). The recommended induction regimen of ipilimumab is 3 mg/kg administered via IV for a 90-minute period, every three weeks, for a total of four doses. Patients should receive all four doses as

tolerated, regardless of the appearance of new lesions or growth of existing lesions. Assessment of tumor response should only be conducted after completion of the induction period, 12 weeks after treatment initiation.

In cases of severe infusion reaction, the ipilimumab infusion must be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive ipilimumab with close monitoring. Premedication with antipyretic medication and an antihistamine may be considered. Signs or symptoms of immune-related adverse reactions (IrARs), including diarrhea and colitis, must be continuously assessed, and liver function tests and thyroid function tests should be evaluated at baseline and before each dose of ipilimumab.

Ipilimumab Responses Versus Conventional Chemotherapies

The direct cytotoxic mechanism of action of chemotherapeutic agents often translates into meaningful measurable effects within the first few weeks of treatment. By contrast, response dynamics with immunotherapies reflect the time taken to activate and build an immune response (Pennock, Waterfield, & Wolchok, 2012). Clinically measurable antitumor effects, mediated by activated immune cells, can occur over weeks or months, and may be observed after the appearance of new lesions, after an initial increase in tumor volume, or in the form of a delayed, slow, and steady decline in total tumor volume (Hoos et

al., 2010; Robert et al., 2011; Wolchok et al., 2009). Given the novel response patterns observed with immunotherapy, withdrawal from treatment at that stage may be premature and underestimate the true efficacy of the treatment.

The patient should understand the differences between responses to chemotherapy and immunotherapy. Patients who see their lesions increasing in size will naturally have concerns about the efficacy of their treatment. In such cases, the nurse can offer education and advice to address those concerns, thereby ensuring that treatment is continued long enough, as tolerated, for a response to occur.

Side Effects

Ipilimumab treatment is associated with inflammatory adverse reactions that occur because of the enhanced action of the immune system (Bristol-Myers Squibb, 2011). IrARs can be severe or life threatening, and most commonly affect the dermatologic and gastrointestinal organ systems. Toxicities affecting the liver or endocrine system also have been reported, but occur less frequently than dermatologic and gastrointestinal toxicities (Boasberg, Hamid, & O'Day, 2010; Ibrahim et al., 2011).

Early diagnosis and appropriate management are essential to minimize life-threatening complications. Management of IrARs may require the omission of a dose of ipilimumab, or permanent discontinuation of treatment. Administration of systemic high-dose corticosteroids, or in some cases the addition

of other immunosuppressive therapy, may be required. The use of steroids should be avoided before starting ipilimumab because they can interfere with the ipilimumab. Steroids or other drugs that suppress the immune system can be used after starting ipilimumab to treat reactions in the skin, colon, liver, and other organs. This does not appear to affect the activity of ipilimumab when steroids are given later (Boasberg et al., 2010; Harmankaya et al., 2011). Dose reduction of ipilimumab is not recommended, and doses that are omitted because of an adverse reaction must not be replaced.

Nursing Management

Teaching the patient how to recognize any symptoms associated with IrARs is important so he or she can report them to a healthcare professional immediately. Some side effects can quickly worsen if not treated promptly, whereas most rapidly improve or disappear if treated early. Patients should be advised to watch for adverse reactions such as diarrhea, an increased number of bowel movements than usual, pain or tenderness in the stomach area, blood or mucus in stools, jaundice, skin rash with or without itching, muscle weakness, numbness or tingling in hands or feet, loss of consciousness, difficulty waking up, tiredness, headaches, decreased sexual drive, behavioral changes, redness or pain in the eye, and vision problems or blurred vision (Bristol-Myers Squibb, 2011). Under no circumstances should patients attempt to treat symptoms

Clinical Highlights

Ipilimumab: Management Guidance for Immune-Related Adverse Reactions (IrARs)

Dermatitis

- If mild, treat symptomatically (e.g., with antihistamines).
- Persistent mild rash or pruritus (lasting 1–2 weeks) can be treated with topical or oral corticosteroids and antihistamines.
- Oatmeal colloidal baths such as Aveeno® and urea-containing moisturizers may help.
- For mild to moderate rash or pruritus that persists 1–2 weeks, oral corticosteroid therapy should be initiated (e.g., prednisone 1 mg/kg per day or equivalent). If severe, refer to the note at the end.

Enterocolitis

- If mild, treat symptomatically (e.g., with loperamide, fluid replacement) with close monitoring.
- If symptoms persist for 5–7 days, the scheduled dose should be omitted and oral corticosteroid therapy should be initiated (e.g., prednisone 1 mg/kg or equivalent). IV fluids and electrolyte replacement may be required.

- If severe, see the note at the end. In addition, an alternative immunosuppressive agent may be considered, such as infliximab 5 mg/kg, but is contraindicated in sepsis or perforation.

Hepatotoxicity

- For mild liver function test (LFT) elevation, omit scheduled ipilimumab dose and monitor.
- Resume ipilimumab at the next scheduled dose after LFTs improve.
- Check liver function prior to each dose of ipilimumab.
- If LFT elevations persist or are grade 3 or 4, see the note at the end and consider additional immunosuppressive therapy such as mycophenolate mofetil.

Note. If IrAR is grade 3 or 4, high-dose corticosteroid therapy (methylprednisolone 2 mg/kg) is administered until symptoms resolve. Once symptoms resolve, taper corticosteroids for one month and permanently discontinue ipilimumab.

Table 1. Patient Education Regarding the Use of Ipilimumab

Question	Answer
What kind of drug is ipilimumab?	Ipilimumab is a medicine that works by activating the immune system so that the immune system can attack tumor tissue.
How does ipilimumab work?	Ipilimumab targets a key molecule found on certain cells of the immune system that prevents the immune system from being overactive. By targeting this molecule, ipilimumab releases the brake on the immune system, freeing up those immune cells so that they can attack tumors and do their job.
Does ipilimumab work like chemotherapy?	No. Chemotherapy has a direct action against cancer cells, whereas ipilimumab stimulates immune cells to attack tumors. Ipilimumab may not work right away like chemotherapy because it takes time for the immune cells to work on the tumor. Sometimes the tumor can grow or appear larger before this medicine starts to work.
What kind of side effects can I expect?	Releasing the brake on the immune system can sometimes cause immune cells to attack healthy cells. This can affect the skin, causing rash and itching, and the colon, causing diarrhea and stomach pain. Less often, side effects include liver toxicity; inflammation of the pituitary, thyroid, or adrenal glands; eye inflammation; and inflammation of nerves. Reporting any side effects right away is important, particularly if side effects get worse while being treated.
Are ipilimumab side effects similar to chemotherapy side effects?	No. Side effects from chemotherapy include infections and fevers, low blood cell counts, nausea and vomiting, and hair loss. Chemotherapy side effects usually occur days after beginning treatment. Most side effects from ipilimumab involve the skin, colon, liver, and other organs and occur during the first 12 weeks of treatment, but some have been reported months after the last dose of ipilimumab.
Are there other important points?	When you have symptoms while on ipilimumab, make sure you talk to a healthcare professional who is familiar with this medication. Do not take any over-the-counter medicines, vitamins, or herbal or dietary supplements without asking your doctor.

Note. Based on information from Bristol-Myers Squibb, 2011; Rubin, 2012.

themselves without seeking appropriate medical assistance. Table 1 outlines important teaching points for nurses when they are educating patients and families about ipilimumab.

Conclusions

Understanding the differences between immunotherapy and conventional chemotherapy is vital to allow healthcare providers to make informed choices (i.e., to ensure that treatment is not terminated prematurely because of early progressive disease) while treating patients with ipilimumab.

Knowledge of the immune-potentiating mechanism of action of ipilimumab will reinforce nurses' understanding behind delays in response and the appearance of new lesions. Nurses must feel confident in communicating those unique response patterns to patients, reassuring them of the treatment-choice strategy and reducing their anxiety. This knowledge also will aid nurses in early diagnosis of IrARs associated with ipilimumab, enabling appropriate management to minimize life-threatening complications. For instance, nurses must be vigilant of mild-to-moderate cases of diarrhea and to instruct patients to immediately contact their physician or nurse if they have

any signs or symptoms associated with IrARs. This will help maximize the full potential of immunotherapeutic agents, such as ipilimumab, in clinical practice.

Jane Bryce, MSN, AOCNS®, is a research nurse in the Clinical Trials Unit of the National Cancer Institute in Naples, Italy; and Claudia Passoni, RN, is a research nurse in the Melanoma and Muscle-Cutaneous Sarcoma Division of the European Institute of Oncology in Milan, Italy. Editorial support for this article was provided by Stem Scientific and funded by Bristol-Myers Squibb. Mention of specific products and opinions related to those products do not indicate or imply endorsement by the *Oncology Nursing Forum* or the Oncology Nursing Society. Bryce can be reached at jane.bryce@usc-intnapoli.net, with copy to editor at ONFEditor@ons.org.

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