Article

Understanding Immune Checkpoint Inhibitors for Effective Patient Care

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Background: Immune checkpoint inhibitors represent a paradigm change in the treatment of melanoma and other advanced cancers. These agents manipulate key immune-regulating pathways to restore immune responses against tumors. The success of this approach is demonstrated by ipilimumab (Yervoy®) for the treatment of advanced melanoma, with improvement in three-year survival rates of about 20%. Newer checkpoint inhibitors targeting the programmed death-1 (PD-1) pathway have been approved and may have higher response rates and improved tolerability.

Objectives: This article aims to educate nurses and increase their comfort level with these new therapies.

Methods: The mechanism of action of immune checkpoint inhibitors is reviewed, and insight is provided on how nurses can use this knowledge to more effectively care for patients receiving these therapies.

Findings: The use of immuno-oncology agents is increasing. Oncology nurses must understand the basic immune mechanism of action responsible for the novel toxicity profile characterized by immune-related adverse events (irAEs) and clinical response patterns. Managing irAEs with immune checkpoint inhibitors is not necessarily more difficult than with conventional agents, but a difference does exist. Nurses and other healthcare providers must consider the underlying cause of toxicity with immune checkpoint inhibitors when making management decisions.

Metastatic melanoma has historically been considered an incurable cancer. However, the treatment landscape for metastatic or unresectable melanoma and other advanced malignancies is undergoing rapid change. New immunotherapies, termed immune checkpoint inhibitors, work by reactivating an immune response against tumors (Pardoll, 2012). Immune checkpoint inhibitors for treating melanoma include ipilimumab (Yervoy®), pembrolizumab (Keytruda®), and nivolumab (Opdivo®). The checkpoint inhibitor ipilimumab, which targets the cytotoxic T-lymphocyte antigen 4 (CTLA-4) pathway, was approved for use in 2011 (Bristol-Myers Squibb, 2015b). Agents targeting the programmed death-1 (PD-1) pathway (i.e., pembrolizumab and nivolumab) are approved for the treatment of patients with unresectable or advanced melanoma that has progressed after ipilimumab (and, if positive for BRAF V600 mutation, a BRAF inhibitor). Nivolumab was recently approved for the treatment of non-small cell lung cancer (NSCLC) with progression after platinum-based chemotherapy or after targeted therapy (Bristol-Myers Squibb, 2015a), and pembrolizumab was also recently approved for the same indication, but for those whose tumors express PD-L1 (a biomarker) (Merck & Co., 2015). In addition, the U.S. Food and Drug Administration approvals included the combination of nivolumab and ipilimumab as a first-line treatment for patients with metastatic melanoma and wild-type BRAF, as well as the approval of ipilimumab as an adjuvant therapy for stage III melanoma following surgery (Bristol-Myers Squibb, 2015b). Most oncology nurses will likely be caring for patients receiving these agents in the near future. To optimize patient care, nurses must have a basic understanding of immune checkpoint inhibitors and their mechanisms of action.
B7 molecules, expressed by immune cells
Can be rapid or delayed; often prolonged
Activated T-cells, after prolonged stimulation
Melanoma, NSCLC, malignant mesothelioma
Limits T-cell activation; down-regulates acti
PD-L1 and PD-L2, expressed by immune cells, tumor
PD-1 Pathway

Understanding of these immuno-oncology agents and their associated toxicity profile.

Immune Checkpoint Pathways

The inhibitory cytotoxic CTLA-4 and PD-1 pathways dampen T-cell responses to minimize tissue damage (see Table 1). Figures 1 and 2 illustrate how the CTLA-4 and PD-1 checkpoint pathways operate in a successful antiviral immune response compared with an unsuccessful antitumor immune response. These two pathways have nonredundant roles in stopping T-cell functions.

T-cells are initially stimulated by antigens, including viral or tumor antigens, in lymph nodes. Up-regulation of CTLA-4 (a cell surface receptor) on T-cells is used to turn off T-cells that may inadvertently respond to self-antigens and, therefore, cause autoimmunity. PD-1 (also a T-cell surface receptor) has two key ligands, PD-L1 and PD-L2. During the course of the immune response, tissues and other infiltrating immune cells begin to express PD-L1 and/or PD-L2, and responding T-cells begin to express PD-1. When these T-cells encounter PD-L1 and/or PD-L2, they are turned off. This step is important for ending an ongoing immune response so as not to damage healthy tissues and to allow healing (Topalian, Drake, & Pardoll, 2012).

Tumors can up-regulate PD-L1 and/or PD-L2 to inhibit activated antitumor T-cells (Zou & Chen, 2008). Checkpoint blockade works by reactivating T-cells that lead to enhanced antitumor response. CTLA-4 inhibitors (ipilimumab, tremelimumab) are designed to allow more T cells to become activated and to stay activated longer, thereby more effectively targeting tumor cells. One potential explanation for their anticancer effects is that CTLA-4 blockade supports the development of a larger number of activated antitumor T-cells (Tivol et al., 1995). PD-1 pathway inhibitors are designed to prevent activated antitumor T-cells from being turned off. In theory, they prolong and enhance ongoing antitumor immune responses (Pardoll, 2012). Anti-PD-1 agents (nivolumab, pembrolizumab, and pidilizumab) block PD-1 from binding both its ligands, PD-L1 and PD-L2. Anti-PD-L1 agents durvalumab (MEDI4736) and atezolizumab (MPDL3280A) block PD-L1 and PD-L1 binding, whereas PD-1 and PD-L2 binding remains intact (Topalian, Drake, et al., 2012).

Immune Checkpoint Blockade in Practice

The power of immuno-oncology approaches was initially demonstrated by interleukin-2 (IL-2), a cytokine that promotes T-cell growth and proliferation. A proportion (7%) of patients who received high-dose IL-2 in early trials survived more than five years (Atkins, Kunkel, Sznol, & Rosenberg, 2000). IL-2 was approved for the treatment of metastatic melanoma in 1998; however, the significant toxicities associated with IL-2 treatment limited its widespread use (National Comprehensive Cancer Network [NCCN], 2015). Instead of the broad T-cell activation by IL-2, immune checkpoint inhibitors are designed to stimulate subsets of T-cells. Meaningful and durable responses occur in about 11% of ipilimumab-treated patients with advanced disease, in contrast to more transient responses, which occur in 12%–20% of patients.

### TABLE 1. Comparison of CTLA-4 and PD-1 Pathways and Inhibition

<table>
<thead>
<tr>
<th>Biologic Characteristic</th>
<th>CTLA-4 Pathway</th>
<th>PD-1 Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptor expression and timing of expression</td>
<td>Activated T-cells, shortly after activation</td>
<td>Activated T-cells, after prolonged stimulation</td>
</tr>
<tr>
<td>Ligands and expression pattern</td>
<td>B7 molecules, expressed by immune cells</td>
<td>PD-L1 and PD-L2, expressed by immune cells, tumor cells, and inflamed tissues</td>
</tr>
<tr>
<td>Role in immune regulation</td>
<td>Limits T-cell activation; down-regulates activated T-cells early in the immune response</td>
<td>Down-regulates activated T-cells later in the immune response</td>
</tr>
</tbody>
</table>

**Inhibition Via Immune Checkpoint Inhibitors**

| Agents approved or in late-stage clinical development | CTLA-4 inhibitors: ipilimumab (Yervoy®) | PD-1 inhibitors: nivolumab (Opdivo®), pembrolizumab (Keytruda®), pidilizumab; PD-L1 inhibitors: durvalumab (MEDI4736) and atezolizumab (MPDL3280A) |
| Mechanism of action | Prevents CTLA-4–mediated T-cell inactivation | Prevents PD-1–mediated T-cell inactivation |
| Clinical activity in cancer types | Melanoma, NSCLC, malignant mesothelioma | Melanoma, NSCLC, renal cell carcinoma, hematologic malignancies, ovarian cancer |
| Clinical responses | Can be rapid or delayed; often prolonged (Median response duration was 16 months in one case series.) | Can be rapid or delayed; often prolonged (Median response duration was 1.9 years with nivolumab).* |

*Data with PD-1 immune checkpoint inhibitors are preliminary.

CTLA-4—cytotoxic T-lymphocyte antigen 4; NSCLC—non-small cell lung cancer; PD-1—programmed death-1; PD-L1/L2—programmed death-1 pathway ligand 1 or ligand 2.

Note. Based on information from Armand et al., 2013; Atkins et al., 2014; Blank, 2014; Calabro et al., 2013; Hamanishi et al., 2014; Hamid et al., 2013; Hodi et al., 2010; Horn et al., 2013; Lynch et al., 2012; Pardoll, 2012; Prieto et al., 2012; Robert et al., 2014; Robert, Long, et al., 2015; Topalian, Hodi, et al., 2012; Wherry, 2011; Wolchok et al., 2009; Zou & Chen, 2008.
receiving chemotherapy (Shah & Dronca, 2014). Of note, unlike chemotherapy, response rates with immune checkpoint inhibitors do not appear to decrease in patients who have had more lines of prior treatment. Targeted agents, such as BRAF and MEK inhibitors, have higher response rates (22%–50%) than ipilimumab; however, most tumors eventually develop resistance.

Phase I trials of PD-1 inhibitors in patients with previously treated melanoma have reported very promising response rates of 26%–38% (Hodi et al., 2014; Robert et al., 2014) and supported the fast-track approval of pembrolizumab in September 2014 and nivolumab in December 2014. A randomized phase III trial compared nivolumab versus dacarbazine in patients with treatment-naïve metastatic melanoma; the overall response rate was 40% with nivolumab and 14% with dacarbazine (Robert, Long, et al., 2015). When two checkpoint inhibitors (ipilimumab and nivolumab) were used together in a phase I trial of patients with advanced melanoma, the response rate was 43%–53% at the maximum tolerated dose, higher than when either agent was used alone (Sznol et al., 2014). This combination also showed preliminary one- and two-year survival rates of 85% and 79%, respectively. Based on these results, healthcare providers can expect combination or sequential therapies in the future.

Long-term survival of greater than three years has been reported in about 20% of patients receiving ipilimumab, with reports of some patients from early trials surviving 10 years (Olszanski, 2014; Schadendorf et al., 2015). Initial reports of phase I melanoma trials of PD-1 reported one-year survival rates of 58%–69% (pembrolizumab and nivolumab) and two-year survival rates of 48% (nivolumab) (Hodi et al., 2014; Robert et al., 2014). Overall, one-year survival in the phase III trial in treatment-naïve patients was significantly higher with nivolumab versus dacarbazine (73% versus 42%, p < 0.001) (Robert, Long, et al., 2015).

Adverse Events With Immune Checkpoint Inhibitors

Checkpoint inhibitors are associated with a novel toxicity profile that is inflammation-based and, therefore, are termed immune-related adverse events (irAEs). The key to toxicity management is to understand the concept of an immune-based etiology and subsequent treatment plan. Because T-cells are dispersed throughout the body, any organ can be affected. Patients can present with fast, sometimes nonspecific symptoms, which may be life threatening if not promptly recognized. When caring for patients receiving immunotherapy, nurses must be cognizant that these therapies and their associated toxicities differ from chemotherapy and targeted agents.

irAEs commonly include rash, pruritus, diarrhea/colitis, endocrinopathies, elevated liver enzymes, pneumonitis, nephritis, dermatitis, hepatitis, hypophysitis, thyroiditis, and uveitis. Differences in the side effect profiles of CTLA-4 and PD-1 checkpoint inhibitors are likely caused by differences in mechanism of action (MOA). PD-1 inhibitors such as nivolumab and pembrolizumab appear to have a more tolerable safety profile than ipilimumab (Larkin et al., 2015; Robert, Schachter, et al., 2015). The rate of grade 3–4 treatment-related AEs also was lower with nivolumab than with dacarbazine (DTIC-Dome®) in a phase III trial (12% versus 18%) (Robert, Long, et al., 2015).

FIGURE 1. Role of Immune Checkpoint Pathways in Viral Infection

Note. (a) Antigen-presenting cells display viral antigens to T-cells in lymph nodes. T-cells that recognize viral antigens become activated. Some T-cells up-regulate CTLA-4 and are inactivated, but they can recognize viral antigens. (b) Activated T-cells move to the site of infection where they release inflammatory cytokines and cytolytic granules to eliminate the infected cells. Other immune cells enter the infected site to participate in the immune response and/or facilitate the repair of damaged tissue. (c) As a result of inflammatory cytokines, tissues and other infiltrating immune cells express PD-L1 and/or PD-L2. With prolonged activation and exposure to viral antigens, T-cells begin to express PD-1. When these T-cells encounter PD-L1/PD-L2, they are inactivated. (d) After eliminating the infected cells, the immune response ends and the tissue can heal.

Note. Images courtesy of Ashfield Healthcare Communications. Used with permission.
Fatigue and mild rash are among the most commonly reported AEs with PD-1 inhibitors (Hamid et al., 2013; Larkin et al., 2015; Ribas et al., 2015; Robert, Long, et al., 2015; Topalian et al., 2014; Topalian, Hodi, et al., 2012). Ipilimumab is associated with gastrointestinal AEs. Any grade diarrhea occurred in 33% of patients in clinical trials, with grade 3–5 diarrhea or enterocolitis occurring in 6% of patients (Larkin et al., 2015). Diarrhea of any grade in clinical trials of PD-1 inhibitors was less common, occurring in 16%–18% of patients with melanoma, and grade 3 or higher diarrhea in less than 2% of patients (Larkin et al., 2015; Ribas et al., 2015; Robert et al., 2014; Robert, Long, et al., 2015; Topalian et al., 2014). In contrast, pneumonitis (any grade) may be more common with PD-1 inhibitors compared with ipilimumab, but is still rare—less than 4% of patients in clinical trials (Larkin et al., 2015; Ribas et al., 2015; Robert et al., 2014; Robert, Long, et al., 2015). Endocrinopathies resulting from PD-1 inhibitors include thyroiditis, hypophysitis, and hypopituitarism (Fecher, Agarwala, Hodi, & Weber, 2013; Hamid et al., 2013; Hodi et al., 2010; Topalian et al., 2014; Weber, Kähler, & Hauschild, 2012) (see Table 2).

PD-1 inhibitors are administered as an IV infusion every two or three weeks depending on the agent and continued until confirmed progression or unacceptable toxicity (Bristol-Myers Squibb, 2015a, 2015b; Merck & Co., 2015; Topalian et al., 2014). Ipilimumab is administered every three weeks for a total of four doses (Bristol-Myers Squibb, 2015b). Infusion-related hypersensitivity reactions are rare with both types of agents, and typically mild (Fecher et al., 2013; Hamid et al., 2013; Topalian et al., 2014; Weber et al., 2013). Caring for patients receiving immune checkpoint inhibitors is best derived from the experiences of treating patients with ipilimumab (Fecher et al., 2013; Rubin, 2012; Weber et al., 2012). Clinical trials of PD-1 inhibitors, therefore, adopted irAE management strategies that were developed for ipilimumab. irAEs typically occur within the first few months of therapy, and prolonged exposure does not appear to increase their incidence (Fecher et al., 2013; Topalian et al., 2014). Onset of irAEs can be rapid and typically observed during the induction period of ipilimumab treatment (Tarhini, 2013); however, irAEs can occur at any time during therapy or even after completion or discontinuation; therefore, ongoing monitoring is necessary. In general, treatment of moderate or severe irAEs requires interruption of the checkpoint inhibitor and the use of corticosteroid immunosuppression.

In the author’s clinic, the staff found the majority of irAEs associated with checkpoint inhibitors to be recognizable and manageable. When patients present with toxicity, nurses should evaluate for and rule out noninflammatory causes. As an example, when a patient presents with diarrhea, investigate for possible infectious etiologies, such as Clostridium difficile. Presuming other causes have been ruled out, treatment courses can be pursued (see Figure 3). Of note, steroid use does not appear to diminish the clinical efficacy of ipilimumab in patients who have demonstrated a clinical response (Fecher et al., 2013; Harmankaya et al., 2011). Whether or not the use of steroids adversely affects the efficacy of PD-1 inhibitors is unknown.

FIGURE 2. Role of Immune Checkpoint Pathways and Inhibitors in Cancer

Note. Images courtesy of Ashfield Healthcare Communications. Used with permission.
Dose reductions of immune checkpoint inhibitors are not used to manage irAEs, unlike traditional cancer treatments. Some irAEs are more difficult to diagnose, such as hepatitis or early thyroiditis, both of which can be asymptomatic. For this reason, thyroid and liver enzyme levels should be monitored prior to commencing treatment (Bristol-Myers Squibb, 2015a, 2015b; Fecher et al., 2013; Weber et al., 2012), with ongoing periodic monitoring during and after treatment (Bristol-Myers Squibb, 2015a, 2015b; Merck & Co., 2015). In many patients, treatment can resume following the near or complete resolution of mild or moderate irAEs.

**Treatment Responses With Immune Checkpoint Inhibitors**

Traditional chemotherapeutic agents work nonselectively on dividing cells to promote cell death, and both healthy and tumor cells can be affected (see Table 3). These agents are effective at killing tumor cells rapidly, and toxicity results from the untoward effects on the healthy cells causing anemia, leukopenia, diarrhea, rash, and other side effects (Chapman et al., 2011; Flaherty, Robert, et al., 2012; Florea & Büsselberg, 2011; Marchesi et al., 2007; Sosman et al., 2012). Targeted agents are designed to inactivate specific mutations that are overexpressed in tumor cells, or restrict blood flow to the tumor. Some mutated proteins confer growth advantages to the tumor, and inactivating them inhibits tumor cell growth (Olszanski, 2014). Responses to targeted agents often are rapid (days to weeks) and have a more favorable safety profile than chemotherapy. However, responses with targeted agents often are short-lived, and most patients develop resistance within five to seven months (Luke & Hodi, 2013; Olszanski, 2014).

Restarting effective immune responses using checkpoint inhibitors can take time and is dependent on the individual patient’s immune system. Therefore, it may be weeks to months after treatment initiation before a clinical or radiologic response is seen, and tumor progression often occurs prior to response (Kannan, Madden, & Andrews, 2014; Wolchok et al., 2009). In clinical trials of PD-1 inhibitors in patients with melanoma, the majority of responding patients showed responses by 12–16 weeks; however, responses as early as five weeks and as late as 30 weeks after treatment initiation have been reported (Hodi et al., 2014; Robert et al., 2014; Robert, Long, et al., 2015; Weber et al., 2013). Importantly, ongoing durable responses with checkpoint inhibitors can last much longer compared with those seen with conventional agents and provide a more meaningful remission.

The most mature data with PD-1 inhibitors are from a trial of nivolumab in patients with melanoma. The median duration of response was 99 weeks, and 56% of responses were ongoing at the time of analysis; however, the data are preliminary (Hodi et al., 2014). The long-lived responses support the theory that the immune system is keeping the tumor contained and, in some patients, complete responses have been reported (Ribas et al., 2015; Robert et al., 2014; Robert, Long, et al., 2015; Topalian et al., 2014). Survival curves for ipilimumab suggest that death from disease progression tends to decrease once patients have survived two to three years. After reaching this milestone, some patients may have long-term survival (Olszanski, 2014; Prieto et al., 2010).

**TABLE 2. Immune-Related Adverse Events Reported in Patients With Melanoma Receiving Checkpoint Inhibitors**

<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency (All Grades)</th>
<th>Frequency (Grades 3–4)</th>
<th>Typical Timing of First Occurrence</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologic (rash, pruritus, vitiligo)</td>
<td>9%–49%</td>
<td>3% or less</td>
<td>2–3 weeks</td>
<td>Most cases are mild to moderate and managed conservatively.</td>
</tr>
<tr>
<td>Gastrointestinal (diarrhea, colitis)</td>
<td></td>
<td></td>
<td>5–6 weeks</td>
<td>More common with ipilimumab than with PD-1 inhibitors</td>
</tr>
<tr>
<td>Ipilimumab (Yervoy®): 31%–46% PD-1 inhibitors: 17%–20%</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ipilimumab: 6% PD-1 inhibitors: 2% or less</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic (elevated ALT, elevated AST)</td>
<td>2%–9%</td>
<td>2% or less</td>
<td>7–8 weeks</td>
<td>Grade 3–4 AEs can be asymptomatic.</td>
</tr>
<tr>
<td>Endocrine (hypothyroidism, hyperthyroidism, hypophysitis)</td>
<td>4%–13%</td>
<td>1%–2%</td>
<td>7–9 weeks</td>
<td>Hypophysitis may be difficult to diagnose based on symptoms; endocrinopathies may require lifelong hormone replacement therapy.</td>
</tr>
<tr>
<td>Pulmonary (pneumonitis)</td>
<td>4% or less</td>
<td>2% or less</td>
<td>Unknown</td>
<td>More common with PD-1 inhibitors; rare with ipilimumab. Most cases resolve with steroid treatment.</td>
</tr>
<tr>
<td>Neurologic (neuropathy, arthralgia, myalgia)</td>
<td></td>
<td></td>
<td></td>
<td>More common with combination therapy (ipilimumab plus PD-1 inhibitors); can be managed with NSAIDs</td>
</tr>
</tbody>
</table>

*After treatment initiation; individual patient experiences will vary.

ALT—alanine aminotransferase; AST—aspartate aminotransferase; NSAID—nonsteroidal anti-inflammatory drug

Note: Based on information from Fecher et al., 2013; Hamid et al., 2013; Hodi et al., 2010, 2014; Larkin et al., 2015; Robert et al., 2014; Robert, Long, et al., 2015; Tarhini, 2014; Topalian et al., 2014; Weber et al., 2012, 2013; Wolchok et al., 2013.
### Dermatologic
- Dermatology consult
- Consider skin biopsy
- 1–2 mg/kg per day IV methylprednisolone

<table>
<thead>
<tr>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>If improves to grade 1, taper steroids for one month or longer; resume immuno-oncology therapy.</td>
<td></td>
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</tbody>
</table>

### Gastrointestinal
- Gastroenterology consult
- Consider lower endoscopy.
- 1–2 mg/kg per day IV methylprednisolone

<table>
<thead>
<tr>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>If improves, continue steroids until grade 1, then taper steroids for more than one month.</td>
<td></td>
</tr>
<tr>
<td>If it persists for more than 3–5 days or reoccurs, add 5 mg/kg infliximab (Remicade®), unless contraindicated.</td>
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</table>

### Pulmonary
- Hospitalize
- Pulmonary and infectious disease consults
- Consider bronchoscopy, lung biopsy
- 2–4 mg/kg per day IV methylprednisolone

<table>
<thead>
<tr>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>If improves to baseline, taper steroids for more than six weeks.</td>
<td></td>
</tr>
<tr>
<td>If not improving after 48 hours or worsening, add additional immunosuppressants.</td>
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</tbody>
</table>

### Hepatic
- Gastroenterology consult
- Monitor levels every 1–2 days.
- 1–2 mg/kg per day IV methylprednisolone

<table>
<thead>
<tr>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>If improves to grade 2, taper steroids for more than one month.</td>
<td></td>
</tr>
<tr>
<td>If not improved after 3–5 days, worsens, or rebounds, consider adding mycophenolate mofetil 1 g (twice daily); if no response, consider other immunosuppressants.</td>
<td></td>
</tr>
</tbody>
</table>

### Neurologic
- Neurology consult
- Treat symptoms per local guidelines.
- 1–2 mg/kg per day IV methylprednisolone

<table>
<thead>
<tr>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>If improves to grade 2, taper steroids for more than one month.</td>
<td></td>
</tr>
<tr>
<td>If worsens or atypical presentation, consider IV immunoglobulin or other immunosuppressants.</td>
<td></td>
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</table>

### Renal (grade 2–4)
- Nephrology consult
- Consider renal biopsy.
- Monitor creatinine every 2–3 days (grades 2–3) or daily (grade 4)
- 0.5–1 mg/kg per day (grades 2–3) or 1–2 mg/kg per day (grade 4) IV methylprednisolone.

<table>
<thead>
<tr>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>If improves to grade 1, taper steroids for more than one month.</td>
<td></td>
</tr>
</tbody>
</table>

### Symptomatic endocrinopathy
- Evaluate endocrine function.
- Consider pituitary scan.
- Abnormal laboratory results/pituitary scan
- 1–2 mg/kg per day IV methylprednisolone
- Initiate appropriate hormone therapy.
- Normal laboratory results/pituitary scan
- Repeat laboratory tests in 1–3 weeks; magnetic resonance image in one month.

<table>
<thead>
<tr>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>If improves (with or without hormone replacement), taper steroids for more than one month; patients with adrenal insufficiency may require continued steroids with mineralocorticoid component.</td>
<td></td>
</tr>
</tbody>
</table>

### Suspected Adrenal Crisis
- Rule out sepsis.
- Endocrinology consult
- Stress dose of IV steroids with mineralocorticoid activity
- IV fluids

<table>
<thead>
<tr>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>General guidelines for managing immune-related adverse events</td>
<td></td>
</tr>
<tr>
<td>Immuno-oncology therapy should be discontinued or delayed.</td>
<td></td>
</tr>
<tr>
<td>Differential diagnoses should be diligently evaluated.</td>
<td></td>
</tr>
<tr>
<td>Noninflammatory etiologies should be considered and appropriately treated.</td>
<td></td>
</tr>
<tr>
<td>Consultation with a medical or surgical specialist is recommended.</td>
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</tr>
<tr>
<td>Consider adding prophylactic antibiotics for opportunistic infections, with the exception of endocrinopathies.</td>
<td></td>
</tr>
<tr>
<td>Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids should be taken into account when switching.</td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 3. Management of Serious Immune-Related Adverse Events (Grades 3 and 4)**

Fatigue, nausea, vomiting, neurotropenia, thrombocytopenia

Median response duration 2–4 months

Adverse events Fatigue, nausea, vomiting, neurotropenia, thrombocytopenia

TABLE 3. Comparison of Chemotherapy, Targeted Therapy, and Immune Checkpoint Therapy for Treating Melanoma

<table>
<thead>
<tr>
<th>Variable</th>
<th>Chemotherapy</th>
<th>Targeted Therapy*</th>
<th>Immune Checkpoint Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Induces death of dividing cells</td>
<td>Interferes with mutated growth and survival signaling pathways in the tumor</td>
<td>Restores antitumor immune responses</td>
</tr>
<tr>
<td>Response rates</td>
<td>11%–14%</td>
<td>Single agent: 22%–56% Combination: 67%–76%</td>
<td>Single agent: 6%–40% Combination: 42%</td>
</tr>
<tr>
<td>Median response duration</td>
<td>2–4 months</td>
<td>Single agent: 5–7 months Combination: 9 months</td>
<td>Single agent: 1.9 years (nivolumab) Combination: unknown</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Fatigue, nausea, vomiting, neurotropenia, thrombocytopenia</td>
<td>Arthralgia, rash, photosensitivity, fatigue, alopecia, edema</td>
<td>Fatigue, immune-related adverse events (diarrhea, colitis, rash/pruritus, endocrinopathies, hepatitis)</td>
</tr>
</tbody>
</table>

*In patients with tumors containing relevant mutation

† Data with programmed death-1 pathway immune checkpoint inhibitors are preliminary.

‡ Not reached at the time of analysis (range = 4–29 months of follow-up)

Note. Based on information from Atkins et al., 2014; Chapman et al., 2011; Fecher et al., 2013; Flaherty, Infante, et al., 2012; Flaherty, Robert, et al., 2012; Hauschild et al., 2009, 2012; Hodi et al., 2010, 2014; Long et al., 2014; Marchesi et al., 2007; Middleton et al., 2000; Pardoll, 2012; Prieto et al., 2012; Ribas et al., 2013; Robert et al., 2014; Robert, Long, et al., 2014; Shah & Dronca, 2014; Sosman et al., 2012; Sznol et al., 2014; Topalian et al., 2014.

In addition, patient and caregiver education about immunotherapy and irAEs is important (Davies, 2014; Ledezma & Heng, 2013; Rubin 2012). In many centers, patients receiving ipilimumab, nivolumab, or pembrolizumab will be provided with a drug-specific wallet card detailing symptoms to watch for and when to notify their healthcare provider. The wallet card also provides information useful to other healthcare providers (e.g., emergency department staff) by describing the common and novel immune effects. Symptom checklists also are integrated into the patient visit, either formally (by completion of the checklist by the nurse or possibly even the patient) or informally (with a directed review of systems). Patients are counseled regarding the expected time to response and importance of open and ongoing communication regarding the development of new or worsening symptoms. Patients must understand that, even in the case of apparent initial radiologic tumor progression, improvements in patient symptoms and/or performance status or other clinical parameters may indicate treatment efficacy. It also may be helpful to remind patients that a delayed response is “worth the wait” because many responses last longer than those seen with conventional agents.

Implications for Nursing

Oncology nurses, the healthcare team, patients, and caregivers should have general knowledge that checkpoint inhibitors are designed to solicit immune responses. Antitumor immune responses will vary from patient to patient, and responses can be delayed. However, for some, significant patient benefit may result. The novel toxicity profile of these agents is based on mechanism of action and must be understood by oncology nurses. Managing irAEs requires different interventions (e.g., decreasing the inflammation) than managing irAEs with conventional agents. By following developed algorithms, most grade 3–4 irAEs can be managed with treatment interruption and/or steroids, and, in some cases, a multidisciplinary approach may be needed (e.g., endocrinologist, gastroenterologist, pulmonologist). Often, treatment with checkpoint inhibitors can be resumed after irAE resolution or improvement to baseline. Prompt recognition and early intervention of irAEs is the most effective management strategy.

Implications for Practice

➢ Understand the immune mechanism of action for checkpoint inhibitors to effectively provide care for patients receiving these therapies.

➢ Be aware of the types of immune-related adverse events associated with checkpoint inhibitors, the majority of which can be successfully managed via regular monitoring.

➢ Instruct patients that the timing and extent of antitumor responses can vary with checkpoint inhibitors; however, once responses occur, they often are durable.

Conclusion

The approvals of PD-1 inhibitors for advanced melanoma and NSCLC provide important new treatment options for patients with these malignancies. In addition, in the United States, the approval of nivolumab in combination with ipilimumab for patients with wild-type BRAF provides an additional treatment option to improve clinical outcomes in advanced melanoma. Although these treatment approaches are different than conventional agents, patient management is not more difficult. Nurses with an awareness and understanding of the immune mechanism of action of immuno-oncology agents will be well positioned to manage the toxicities associated with these therapies.
References


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