PD-1 Inhibitor Therapy

Consensus statement from the faculty of the Melanoma Nursing Initiative on managing adverse events

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BACKGROUND: Programmed cell death protein 1 (PD-1) inhibitor therapies are now a standard treatment for advanced melanoma and other tumor types. The immune-related adverse events (irAEs) associated with PD-1 inhibitor therapy are drastically different from the AEs associated with chemotherapy. Because these irAEs reflect immune system activation rather than side effects of therapy, nurses should be cognizant of the range of organ systems potentially affected as well as likely clinical presentations.

OBJECTIVES: This article presents consensus statements to guide nurses in the recognition and management of irAEs associated with PD-1 inhibitor monotherapy for advanced melanoma.

METHODS: Members of the Melanoma Nursing Initiative discussed the current literature and clinical experience regarding nursing interventions related to irAEs associated with PD-1 inhibitor therapy.

FINDINGS: The care step pathways provided for select irAEs represent a proactive, comprehensive nursing care plan to support optimal outcomes for patients receiving PD-1 inhibitor therapy.

KEYWORDS
nivolumab; pembrolizumab; PD-1; malignant melanoma; adverse events

DIGITAL OBJECT IDENTIFIER
10.1188/17.CJON.S4.42-51

SINCE THEIR RECENT INTRODUCTION IN ONCOLOGY, programmed cell death protein 1 (PD-1) inhibitors have become a common treatment modality for unresectable or metastatic (advanced) melanoma as well as other malignancies, including non-small cell lung cancer, squamous cell carcinoma of the head and neck, Hodgkin lymphoma, renal cell carcinoma, and urothelial carcinoma (Franklin, Livingstone, Roesch, Schilling, & Schadendorf, 2017; Redman, Gibney, & Atkins, 2016). Two PD-1 inhibitor therapies have received approval from the U.S. Food and Drug Administration (FDA) as monotherapies for the treatment of patients with advanced melanoma: pembrolizumab (Keytruda®) and nivolumab (Opdivo®) (Bristol-Myers Squibb, 2017; Franklin et al., 2017; Merck, 2017; Redman et al., 2016). In phase 3 trials conducted in patients with melanoma, both agents significantly improved one-year survival and progression-free survival: nivolumab when compared with dacarbazine and pembrolizumab when compared with ipilimumab (Robert, Long, et al., 2015; Robert, Schachter, et al., 2015). Nivolumab was subsequently approved in the United States in combination therapy with ipilimumab for use in advanced melanoma. Because PD-1 inhibitor therapies were first approved in the melanoma setting, nurses with melanoma expertise have developed a wealth of experience in the identification and management of the unique toxicity profile of these agents. Two PD-L1 inhibitors have been approved by the FDA for the treatment of other cancers: atezolizumab (Tecentriq®) and avelumab (Bavencio®). These will not be discussed in this consensus statement because they are not currently in use for metastatic melanoma (Genentech, 2017; Pfizer, 2017).

An examination of the mechanism of action of PD-1 inhibitors provides insight into the efficacy and immune-related adverse events (irAEs) associated with this immune checkpoint inhibitor (ICI) class. Several irAEs for PD-1 inhibitor therapies are shown in Table 1. Checkpoints are one mechanism by which the immune system regulates itself to prevent too robust of an immune response, which could lead to tissue destruction and autoimmunity, among other consequences (Buchbinder & Desai, 2016; Shimanovsky, Jethava, & Dasanu, 2013; Tentori, Lacal, & Graziani, 2013). Simply put, they are major components of a complex system that functions as a provider of checks and balances to control immune response and prevent autoimmunity. One checkpoint, cytotoxic T lymphocyte-associated antigen 4 (CTLA4), regulates

T-cell proliferation early in an immune response (priming phase), primarily in lymph nodes, whereas PD-1 suppresses T cells later in an immune response (effector phase), primarily in peripheral tissue (Buchbinder & Desai, 2016; Rubin, 2012). Activated T cells perform immune surveillance. They are tasked with recognizing foreign cells, as well as host cells that are functioning improperly, such as cancer cells. PD-1 is a protein that is expressed on activated T cells. When PD-1 binds with its ligands (PD-L1 and PD-L2), T-cell function is inhibited or turned off. These ligands can be expressed by other cells in the immune system, including dendritic cells, or by the tumor itself; this is one mechanism by which cancer cells are able to avoid destruction by a patient's immune system (Buchbinder & Desai, 2016; Rubin, 2012). PD-1 inhibitor therapies bind to PD-1 receptors on T cells, preventing the binding to PD-L1 and, thereby, unleashing the immune system.

Understanding the mechanism of action of ICIs lays the foundation for understanding the associated toxicity profiles. An uninhibited T cell will remain fully and persistently active. CTLA4 acts earlier in T-cell activation, whereas PD-1 acts later. This important distinction underscores the differences in toxicity between CTLA4 inhibitor therapy and PD-1 inhibitor therapy (i.e., PD-1 inhibitor therapy tends to produce fewer and less severe irAEs than ipilimumab). Figure 1 shows helpful analogies for explaining the relationship between the mechanism of action and efficacy and safety profiles of ICIs to patients.

"Understanding the mechanism of action of immune checkpoint inhibitors lays the foundation for understanding the associated toxicity profiles."

Nurses must understand that the irAEs associated with PD-1 inhibitor therapies result from a dramatically different mechanism than AEs stemming from cytotoxic chemotherapy. Although the presenting symptoms may be identical, the difference in the mechanism of development necessitates different strategies to reverse or otherwise minimize their negative impact. These strategies require that nurses be aware of how a manipulated, overly active immune system can affect various organ systems, sometimes in subtle or unanticipated ways. Nurses who anticipate these varied effects and know what to do when they occur will have a critical role in the early recognition and management of these irAEs.

Faculty of the Melanoma Nursing Initiative (MNI) convened to define management challenges associated with the use of PD-1 inhibitor therapies in advanced melanoma. Based on a review of the current literature (Boutros et al., 2016; Dadu, Zobniw, & Diab, 2016; Day & Hansen, 2016; Friedman, Proverbs-Singh, & Postow, 2016; Kähler et al., 2016; Spain, Diem, & Larkin, 2016; Villadolid & Amin, 2015; Weber, Postow, Lao, & Schadendorf, 2016) and clinical experience, they developed consensus recommendations for nursing care of this population. Recommendations are made for the following:

- Administration and dosing, with a focus on dosage holds and schedule adjustments
- irAE recognition and management, with care step pathways (CSPs) developed for high-priority irAEs associated with ICIs for which nursing assessment and care are essential to producing successful outcomes

The text of this article focuses on irAE recognition and management principles specific to PD-1 inhibitor monotherapy.

APPENDIXES A–K.
CARE STEP PATHWAYS

Care step pathways for Appendixes A–K in Madden and Hoffner (2017) and McGettigan and Rubin (2017) can be found on pp. 52–75. A reference list for Appendixes A–K can be found on p. 71.

- **Appendix A:** Care step pathway for management of skin toxicities, p. 52
- **Appendix B:** Care step pathway for management of gastrointestinal toxicity: Diarrhea and colitis, p. 54
- **Appendix C:** Care step pathway for management of mucositis and xerostomia, p. 57
- **Appendix D:** Care step pathway for management of hepatotoxicity: Immunotherapy-induced inflammation of liver tissue, p. 59
- **Appendix E:** Care step pathway for management of hypophysitis: Inflammation of pituitary gland, p. 62
- **Appendix F:** Care step pathway for management of thyroiditis: Inflammation of thyroid gland, p. 64
- **Appendix G:** Care step pathway for management of type 1 diabetes mellitus: Immune destruction of beta cells in pancreas, p. 66
- **Appendix H:** Care step pathway for management of pneumonitis: Inflammation of lung alveoli, p. 67
- **Appendix I:** Care step pathway for management of arthralgias and arthritis, p. 69
- **Appendix J:** Care step pathway for management of neuropathy: Motor or sensory nerve impairment or damage, p. 72
- **Appendix K:** Care step pathway for management of nephritis: Inflammation of the kidneys, p. 74

Testing and Patient Selection

PD-1 inhibitor therapies are used in a range of tumor types. Given the mechanism of action of these agents, selection of patients based on tumor PD-L1 expression would be a reasonable consideration. However, PD-L1 expression status in melanoma remains investigational, given the lack of reliable assays (National Comprehensive Cancer Network, 2016). PD-L1 status or elevated expression is not a prerequisite for PD-1 inhibitor treatment of advanced melanoma, as it is in lung cancer (Bristol-Myers Squibb, 2017; Merck, 2017).

Another aspect of patient selection with PD-1 inhibitor therapy relates to the use of single-agent nivolumab or pembrolizumab versus combination therapy using anti-CTLA4 and PD-1 inhibitors (ipilimumab and nivolumab). Grade 3 or 4 toxicities are typically more common with combination therapy than with either nivolumab or pembrolizumab monotherapies, and should be considered when recommending treatment. Nurses play fundamental roles in assessing patient knowledge, understanding treatment options, and providing support as patients consider these options. Such support includes assessing each patient's fitness for different therapeutic options.

TABLE 1.
PD-1 MONOTHERAPY: SELECTED TREATMENT-RELATED ADVERSE EVENTS BASED ON PHASE 3 TRIAL RESULTS

	NIVOLUMAB						PEMBROLIZUMAB	
	CHECKMATE 037		CHECKMATE 066		CHECKMATE 067[a]		KEYNOTE 006[b]	
ADVERSE EVENT	ALL GRADES (%)	GRADES 3–4 (%)	ALL GRADES (%)	GRADES 3–4 (%)	ALL GRADES (%)	GRADES 3–4 (%)	ALL GRADES (%)	GRADES 3–5 (%)
Cause of discontinuation	2.6		6.8	5.8	7.7	5.1	6.9	
Dermatologic								
Pruritus	16	–	17	0.5	18.8	–	14.1	–
Rash	9.3	0.4	15	0.5	25.9	0.6	13.4	–
Endocrine								
Hyperthyroidism	1.9	–	3.4	–	4.2	–	2.5	–
Hypophysitis	NR	NR	0.5	0.5	0.6	0.3	0.4	0.4
Hypothyroidism	5.6	–	4.4	–	8.6	–	7.6	–
Fatigue	25	0.7	19.9	–	34.2	1.3	19.1	0.4
Gastrointestinal								
Colitis	1.1	0.7	1	0.5	1.3	0.6	2.9	1.8
Diarrhea	11.2	0.4	16	1	19.2	2.2	14.4	1.1
Hepatic								
Elevated ALT/AST	6.7	1.1	2.4	1.5	7.7	2.2	3.6	0.7
Hepatitis	NR	NR	NR	NR	NR	NR	1.8	1.8
Pneumonitis	1.9	–	1.5	–	1.3	0.3	1.8	0.4
Total	67.5	9	74.3	11.7	82.1	16.3	72.9	10.1

[a] These numbers reflect only those obtained in the nivolumab monotherapy arm of the study. (The study also included a nivolumab and ipilimumab arm and an ipilimumab monotherapy arm.)
[b] Based on pembrolizumab dosing regimen of 10 mg/kg every three weeks
ALT—alanine transaminase; AST—aspartate transaminase; NR—not reported; PD-1—programmed cell death protein 1
Note. Based on information from Larkin et al., 2015; Robert, Long, et al., 2015; Robert, Schachter, et al., 2015; Weber et al., 2015, 2016.

Dosing and Administration

Pembrolizumab is given as an IV infusion every three weeks; the dosage has been modified to a fixed dosage of 200 mg administered over 30 minutes versus a weight-based dosing regimen (Merck, 2017). Nivolumab is given as an IV infusion every two weeks; the dosage has been modified to a fixed dose of 240 mg administered over 60 minutes rather than a weight-based dose (Bristol-Myers Squibb, 2017). Specific holds and discontinuation instructions for irAEs are discussed in the CSPs. No definitive standardized treatment duration exists for PD-1 inhibitor therapy. Although the labeling indicates continuation of PD-1 inhibitor monotherapy to disease progression or unacceptable toxicity, institutions (and even different clinicians within a given institution) often vary in how long therapy will continue if a patient achieves a state of no evidence of disease and continues to tolerate treatment well.

Management

Each CSP for the management of notable irAEs associated with PD-1 inhibitor therapy incorporates essential components of the nursing assessment specific to that AE. Look, listen, and recognize categories within the nursing assessment section direct the nurse to a specific set of symptom-related queries to ask the patient and/or caregiver as well as highlight additional information to be considered and reviewed as part of the nursing assessment. Data obtained from this assessment will guide appropriate management strategies. Wherever possible, grading for the specific AE is provided within the pathway based on the National Cancer Institute's (2010) Common Terminology Criteria for Adverse Events (CTCAE). However, for the CSPs for thyroiditis and type 1 diabetes mellitus (DM), the CTCAE guidance was not used. Instead, Melanoma Nursing Initiative members agreed that, for these irAEs, diagnosis and management were better informed by laboratory value criteria from an individual's institutional norms (such as thyroid stimulating hormone, free T3, and T4 for thyroiditis and serum glucose levels for DM).

Each CSP describes overall management strategies as well as nursing-specific interventions. Where applicable, strategies specific to each AE grade are listed, including dose holds and discontinuations. Patient counseling, along with recommendations for additional care and referral to specialty or ancillary care providers, are included in the management section, as appropriate.

General Education

Patients should be educated as a first step in early recognition and management of irAEs. A key point to emphasize is that any change from baseline health, no matter how subtle or seemingly insignificant, may be a sign of an irAE and should be reported immediately to the oncology healthcare provider (HCP). This is an

FIGURE 1.
CHECKPOINT INHIBITOR ANALOGIES: EXPLANATIONS FOR PATIENTS

THE ARMY ANALOGY TO EXPLAIN HOW IMMUNE CHECKPOINT INHIBITORS WORK

Courtesy of Jill Maria Weberding, MPH, BSN, RN, OCN®

- Anti-CTLA4 therapy helps us build the bigger army. CTLA4 is the first brake on the immune response; it's the down regulator turning the immune response off. It essentially tells the T-cell army to go back to base—mission complete. When we block that brake, we can build a bigger army made up of activated T cells on constant surveillance looking for bad guys and foreign invaders, like cancer cells.
- PD-1 inhibitor therapy helps us kill the cancer cells that are faking out our immune system. While that T-cell army is out patrolling, looking for foreign invaders, it's bound to run into normal, healthy cells, too. But we don't want it to attack those normal cells. So, normal cells raise their PD-L1 and PD-L2 flags to signal to the T cell, "Hey, I'm a good guy—don't attack me!" The PD-L1 and PD-L2 flags bind to the PD-1 receptor on the T cell and deactivate it. Unfortunately, tumor cells are sneaky and quite greedy, as we know. They will do anything to keep growing and multiplying and avoid detection from our immune system. In fact, some tumor cells have figured out a way to mimic being a normal, healthy cell by raising the same flag, PD-L1. So, a tumor cell can raise its PD-L1 flag and bind with the PD-1 receptor on the T cell and deactivate it, just like a normal cell. The immune response is suppressed, and the tumor can continue to grow. By blocking the PD-1 pathway, we can expose these cancer cells to being attacked.
- Sometimes building a bigger army doesn't work because, down the road, T cells can be turned off by a pig wearing lipstick (i.e., a tumor cell faking out the T cell). Sometimes, however, combining anti-CTLA4 and PD-1 inhibitor therapy can lead to better outcomes, because you can ensure an adequate army (anti-CTLA4) and the ability to recognize those tumor cells (PD-1 inhibitor therapy).

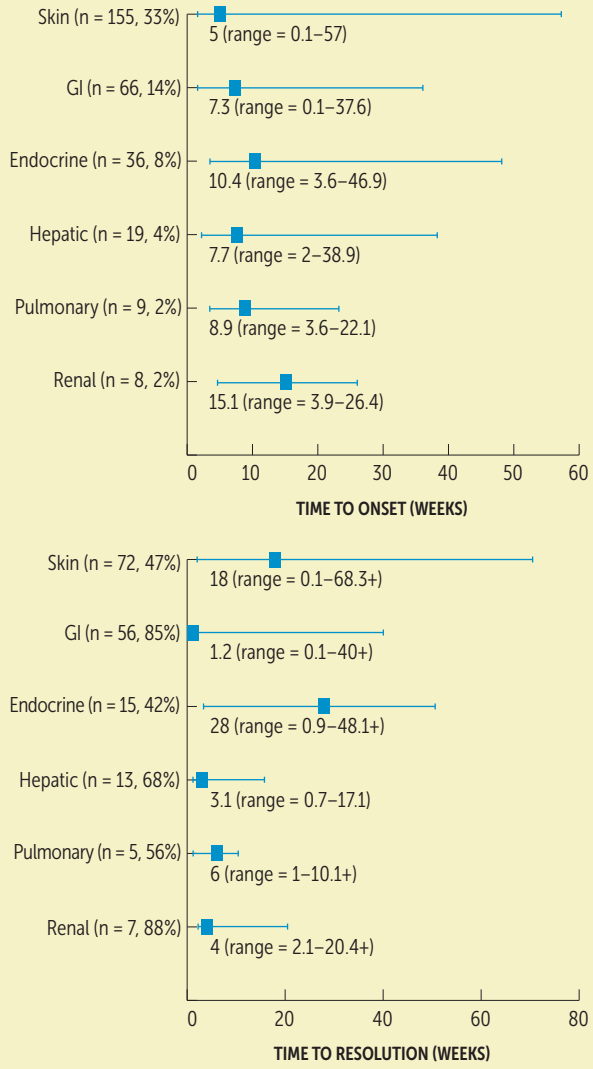
THE MATURING CHILDREN ANALOGY TO EXPLAIN DIFFERENCES IN IMMUNE-RELATED ADVERSE EVENTS

Courtesy of Krista M. Rubin, RN, MS, FNP-BC

- CTLA4 inhibitors are like toddlers; they have a lot of energy but are not very focused in their actions. Their nonspecific action can lead to more immune-related adverse events.
- PD-1 inhibitors are more mature, more like teenagers; they are (generally) more focused and careful in their actions. They can still cause immune-related adverse events, but those adverse events generally occur less frequently and are less severe than they are with anti-CTLA4.

CTLA4—cytotoxic T lymphocyte-associated antigen 4; PD-1—programmed cell death protein 1

FIGURE 2.
TIME TO ONSET AND RESOLUTION OF irAEs ASSOCIATED WITH NIVOLUMAB MONOTHERAPY



GI—gastrointestinal; irAE—immune-related adverse event
Note. Squares show medians, and bars indicate ranges.
Note. From Weber, J.S. et al.: "Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma," *Journal of Clinical Oncology, 35*(7), 2017: 785–792. Adapted with permission. © (2017) American Society of Clinical Oncology. All rights reserved.

important communication point for patients who may be hesitant to report a change for fear that treatment may be discontinued. Such patients may feel the need to persist with treatment, which may result in more severe toxicity. Forming a strong partnership with patients and their caregivers, encouraging open and honest communication, and reassuring patients that reporting symptoms will increase the likelihood of staying on therapy are strategies that should ensure early reporting of symptoms. In addition, patients and their family members must be counseled that irAEs may occur at any time after initiating treatment, even months later (see Figure 2) (Champiat et al., 2016). Within this framework, the importance and rationale for obtaining baseline and follow-up testing to aid in irAE detection and diagnosis should be emphasized (Champiat et al., 2016). Counseling women with childbearing potential to avoid pregnancy is important because of the potential embryo-fetal toxicity (Friedman et al., 2016).

Oncology nurses can help to ensure that patients are aware of educational and financial resources for their therapies and how to access such resources (see Figure 3). Particularly useful are drug-specific patient wallet cards that identify signs and symptoms that should be immediately reported to the treating oncologist or other members of the healthcare team. Patients should be encouraged to carry the card with them at all times. One strategy discussed by the MNI was a recommendation to patients to paperclip their insurance cards to their wallet card. Consequently, whenever they need to show their insurance card, they can share information about their immunotherapy regimen. Wallet cards not only serve as ready guides for notable signs and symptoms potentially reflective of an irAE, but also provide relevant information to other HCPs (such as emergency department personnel) to improve patient care (Chae, Chae, Isaacson, & James, 2009; Institute for Healthcare Improvement, 2011).

Overall Approach

Some general principles inform management strategies across all the CSPs. Many of the irAEs with PD-1 therapies are either grade 1 (mild; asymptomatic or mildly symptomatic) or grade 2 (moderate; moderately symptomatic, with some impact on activities of daily living). For grade 2 irAEs, ICIs are generally withheld and not resumed until toxicity is reduced to grade 1 or less. Corticosteroids are usually initiated if symptoms do not resolve within a week. For some grade 3 (severely symptomatic or having a large impact on activities of daily living) or grade 4 (life-threatening) irAEs, the ICI is often permanently discontinued, and high doses of corticosteroids are given. These high dosages are often split into two daily doses. Corticosteroids are slowly tapered (over at least a month) to avoid rebound symptoms. Methylprednisolone dosepaks are used by some providers, but are often not sufficient to reduce the inflammatory reactions resulting from the ICIs. Gastric prophylaxis with a proton pump inhibitor or H_2 blocker should be considered when initiating high-dose corticosteroids. Patients should be educated to take their corticosteroid dose with food. In addition, antimicrobial prophylaxis is a consideration for patients prescribed high-dose corticosteroids, particularly those patients requiring extended therapy (more than 20 mg per day for more than one month) (Limper et al., 2011).

Dermatologic Toxicities

Appendix A provides a detailed CSP for cutaneous toxicities. Maculopapular rash and pruritus are the most common irAEs associated with PD-1 inhibitor therapy and are typically the first to develop (at 9 weeks to 2.8 months in trials) (Dadu et al., 2016; Friedman et al., 2016). These toxicities can have a detrimental impact on quality of life. Pruritus can be particularly distressing and distracting to patients. The nurse plays a crucial role in counseling and in providing individualized interventions, particularly in high-risk patients, as well as in assessing skin integrity and symptom distress. Mild to moderate cases are typically well managed with skin care, oral antihistamines, and, if necessary, topical or oral corticosteroids. Severe rash cases require dermatology consultation, hospitalization, treatment with systemic corticosteroids, and discontinuation of PD-1 inhibitor therapy.

Gastrointestinal Toxicities

Appendixes B and C provide detailed CSPs for gastrointestinal toxicities. Diarrhea and colitis are the second most frequently encountered irAEs observed with PD-1 inhibitor therapy (Larkin et al., 2015; Robert, Long, et al., 2015; Robert, Schachter, et al., 2015;

FIGURE 3.
NURSE AND PATIENT/CAREGIVER RESOURCES ON PD-1 INHIBITOR THERAPY

ADVERSE EVENTS AND MANAGEMENT AIDS (NIVOLUMAB)

Downloadable resources (treatment journal, patient alert card)
- http://bit.ly/2uuUQkf

Patient wallet card
- http://bit.ly/2sUDKLa

ADVERSE EVENTS AND MANAGEMENT AIDS (PEMBROLIZUMAB)

Information about serious and common side effects, and links to patient wallet card and what to expect while being treated
- www.keytruda.com/melanoma/keytruda-side-effects

Medication guide
- www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_mg.pdf

Tips on self-monitoring and immediately reporting symptoms to healthcare team and having discussions about healthy eating and physical activity (for patients and caregivers)
- www.keytruda.com/melanoma/treatment-tips

DRUG ACCESS AND FINANCIAL RESOURCES (NIVOLUMAB)

Oncology support services (benefit investigation, prior authorization, claims appeal, patient financial assistance, charitable foundation lookup tool, access to care services; for nurses)
- www.bmsaccesssupport.bmscustomerconnect.com

Understanding the reimbursement process, determining coverage, and investigating options for financial support (for patients and caregivers)
- www.bmsaccesssupport.bmscustomerconnect.com/patient

DRUG ACCESS AND FINANCIAL RESOURCES (PEMBROLIZUMAB)

Merck Access Program (coverage and reimbursement support, coding and billing resources; for nurses)
- www.merckaccessprogram-keytruda.com/hcp

Programs for copay and patient assistance, list of Merck Access Program representatives, and list of independent copay assistance foundations (for patients and caregivers)
- www.merckaccessprogram-keytruda.com/hcc

GENERAL PRODUCT INFORMATION (NIVOLUMAB)

Clinical trial results
- www.opdivo.com/metastatic-melanoma/about-opdivo/clinical-trial-results

Dosing and administration
- www.opdivo.com/metastatic-melanoma/about-opdivo/getting-an-infusion

Mechanism of action
- www.opdivo.com/metastatic-melanoma/about-opdivo/how-opdivo-works

GENERAL PRODUCT INFORMATION (PEMBROLIZUMAB)

Clinical trial results, dosing and treatment schedule, immunotherapy treatment (mechanism of action), and what to expect while being treated
- www.keytruda.com/melanoma
- www.keytruda.com/static/pdf/guide-for-keytruda.pdf

GENERAL SUPPORT (NIVOLUMAB)

Downloadable resources (patient information, questions to ask healthcare provider, caregiving guide)
- http://bit.ly/2sRmVQm

Links to cancer and melanoma resources
- http://bit.ly/2tud313

Living with melanoma
- http://bit.ly/2uP9sdq

GENERAL SUPPORT (PEMBROLIZUMAB)

General treatment support resources
- www.keytruda.com/melanoma/keytruda-support-program

Links to cancer and melanoma resources
- www.keytruda.com/melanoma/melanoma-resources

PATIENT ADVOCACY AND NURSE SUPPORT

Nurse on Call (for patients and caregivers)
- www.aimatmelanoma.org/living-with-melanoma/nurse-on-call
- 1-877-246-2635

Resources (for patients and caregivers)
- http://bit.ly/2spYXyW

Symposiums (for patients and caregivers)
- http://bit.ly/2sAyFZ9

Toolkits for promoting adherence and managing adverse events, downloadable patient materials, and community nurse portal (for nurses)
- www.themelanomanurse.org

PD-1—programmed cell death protein 1

Weber et al., 2015). The time of onset for diarrhea and colitis in clinical trials was 3.4 months for pembrolizumab and 5.6 months for nivolumab (Dadu et al., 2016). Nurses play an essential role in the early recognition and management of diarrhea. Key to management is establishing a patient's baseline bowel pattern, including frequency and consistency of stools. Determining severity of symptoms is based on change from patient's baseline. For example, CTCAE grading of diarrhea is determined based on the increase of bowel movements above baseline, not the absolute number of stools. Therefore, depending on the baseline stool output, one patient with five stools a day may have mild diarrhea, whereas another with the same number of stools per day could have moderate diarrhea. Colitis can occur in the absence of diarrhea and may lead to serious sequelae, including death, if not identified promptly and managed appropriately.

Upper gastrointestinal–related irAEs, such as mucositis or xerostomia, have also been noted with these regimens. Although not common or medically significant, they can have a major negative impact on quality of life. Little to no data support best practices or interventions for oral irAEs. Interventions and management approaches were developed based on the clinical experience of the members of the MNI. Esophagitis and gastritis have also been reported with PD-1 inhibitor therapies.

Hepatotoxicity (Hepatitis)

Appendix D provides a CSP for hepatotoxicity. PD-1 inhibitor therapies may cause inflammation of liver tissue (autoimmune hepatitis) that commonly presents as an asymptomatic elevation in alanine transaminase (ALT) and/or aspartate transaminase (AST) and, less frequently, elevated bilirubin (Dadu et al., 2016; Friedman et al., 2016). Although ALT and AST elevations occur less often with PD-1 inhibitor monotherapy than do skin and gastrointestinal toxicities (Larkin et al., 2015; Robert, Long, et al., 2015; Robert, Schachter, et al., 2015; Weber et al., 2015, 2016), hepatic irAEs can be severe and even life-threatening if not recognized early and managed effectively (Dadu et al., 2016). Onset of hepatic irAEs has been reported at 1.2 months and at 3.7 months with pembrolizumab and nivolumab monotherapy, respectively (Dadu et al., 2016). Because liver function tests (LFTs) play an essential role in the detection and monitoring of changes in ALT and AST levels during treatments, oncology nurses should ensure that LFTs are obtained prior to each infusion and as directed (Dadu et al., 2016; Friedman et al., 2016). If LFTs are elevated, other possible causes of elevations (e.g., drug-induced toxicities, tumor progression, infectious causes) should be investigated (Dadu et al., 2016; Friedman et al., 2016; Weber et al., 2016).

Endocrinopathies

Various endocrinopathies have been associated with PD-1 inhibitor therapy, including hypophysitis (inflammation of the pituitary gland), thyroid dysfunction (including hypothyroidism, hyperthyroidism, and, rarely, acute thyroiditis), adrenal insufficiency, and type 1 DM (Dadu et al., 2016; Friedman et al., 2016; Weber et al., 2016). Diagnosing endocrinopathies can be difficult because they often present with fatigue or other nonspecific symptoms. Because endocrinopathy is outside of the typical side-effect profile of chemotherapies, nurses should be particularly diligent in monitoring for these toxicities when assessing patients receiving immunotherapy. Using the look, listen, and recognize categories of the CSPs for thyroiditis and hypophysitis will assist oncology nurses in homing in on specific questions to ask at each patient visit and during triage calls, as necessary. Unique from other irAEs, endocrinopathies do not usually resolve because the function of the gland rarely recovers. In those cases, appropriate hormone replacement will be lifelong, but the irAE does not typically require treatment discontinuation. Oncology nurses should educate patients about the possibility of the requirement for lifelong hormone replacement before starting therapy, as well as reassure patients about the ability to live high-quality lives with replacement therapy. In general, management of endocrinopathies related to PD-1 inhibitors warrants endocrinology consultation for initial diagnosis and ongoing treatment (Dadu et al., 2016; Friedman et al., 2016; Weber et al., 2016).

Endocrinopathies associated with PD-1 inhibitor therapy are relatively common, with as many as 20% of patients developing an endocrine-related irAE in clinical trials. Hypothyroidism is the most prevalent irAE, followed by hyperthyroidism, then thyroiditis. In most instances, severity is rarely higher than grade 2. Thyroid disorders are more frequent in women, which is akin to the higher incidence observed in the general population (González-Rodríguez & Rodríguez-Abreu, 2016). Inflammation of the thyroid gland (thyroiditis) may also produce hypothyroidism or, less commonly, hyperthyroidism. Hyperthyroidism commonly precedes hypogonadism (Dadu et al., 2016; Weber et al., 2016). The most severe endocrinopathy related to PD-1 inhibitors is acute adrenal insufficiency, a life-threatening toxicity that often requires hospitalization for monitoring and the administration of stress-dose corticosteroids. PD-1 inhibitor therapy should be held and may have to be discontinued, depending on the severity of symptoms (Friedman et al., 2016; Weber et al., 2016).

Appendixes E and F provide detailed CSPs for PD-1 inhibitor–emergent hypophysitis and thyroiditis, respectively. High-dose systemic corticosteroid therapy is sometimes used during the acute phase of hypophysitis to reverse the inflammatory process, restore function, and prevent the need for permanent hormone replacement (Dadu et al., 2016; Friedman et al., 2016). However, most patients with hypophysitis and hypothyroidism will require long-term supplementation of affected hormones. Rare but notable cases of type 1 DM have been reported (Chae et al., 2017; Friedman et al., 2016). This irAE is characterized by an absolute insulin deficiency caused by autoimmune destruction of pancreatic beta cells, implying dependence on insulin (González-

Rodríguez & Rodríguez-Abreu, 2016). The CSP for type 1 DM is shown in Appendix G.

Pneumonitis

Appendix H provides a detailed CSP for pneumonitis, which is a rare but serious and potentially life-threatening irAE associated with PD-1 inhibitor therapy, typically emerging several months after treatment initiation (although it can occur at any time) (Dadu et al., 2016; Friedman et al., 2016; Weber et al., 2016). Signs and symptoms can be innocuous. Patients who have received prior radiation therapy to the lung and/or have large or multiple lung metastases may be at greater risk. Clinical presentations can vary, making accurate diagnosis difficult. Patients may be asymptomatic, with lung infiltrates seen on routine restaging scans. Imaging findings can also be variable, and no characteristic radiographic findings of ICI-related pneumonitis exist (Teply & Lipson, 2014). Symptomatic patients may report new or worsening respiratory symptoms, including dyspnea, shortness of breath, cough, pleuritic chest pain, and hypoxia. Lack of prompt recognition and proper treatment may result in increased morbidity or possibly mortality. Nurses play a significant role in the early

TABLE 2.
MANAGEMENT OF AEs ASSOCIATED WITH PD-1 INHIBITOR THERAPY

VARIABLE	COMMON SYMPTOMS	AGENT	COMMON MANAGEMENT AND ANTICIPATORY GUIDANCE
Allogeneic hematopoietic stem cell transplantation	Hepatic veno-occlusive disease; steroid-requiring febrile syndromes	Nivolumab, pembrolizumab (for hematologic malignancies)	Advise patients of potential complications; monitor patients.
Anorexia	Decreased appetite	Nivolumab, pembrolizumab	Monitor weight; query patients about appetite and eating; advise dietary modification if necessary. Anticipate standard dose holds and discontinuations[a].
Constipation; abdominal pain	Infrequent stools; difficulty stooling; abdominal pain	Nivolumab, pembrolizumab	Increase fluid, fiber, and laxatives; consider appropriate testing to evaluate bowel obstruction. Anticipate standard dose holds and discontinuations for grade 3 or 4 (constipation with manual evacuation indicated, severe abdominal pain, or life-threatening consequences)[a].
Embryo-fetal toxicity	–	Nivolumab, pembrolizumab	Advise women of reproductive potential of risk to fetus and to use effective contraception during treatment and for five months after nivolumab and four months after pembrolizumab is discontinued. Advise patients to immediately notify healthcare provider if they suspect pregnancy while undergoing therapy.
Encephalitis	Headache; fever; tiredness; confusion; memory problems; sleepiness; hallucinations; seizures; stiff neck	Nivolumab	For new-onset (grade 2 or 3) moderate to severe symptoms, rule out infectious or other causes, consult neurologist, and obtain brain magnetic resonance imaging and lumbar puncture. Withhold nivolumab for new-onset grade 3 or 4 moderate to severe neurologic symptoms; permanently discontinue for immune-mediated encephalitis.
Fatigue	Feeling tired; lack of energy	Nivolumab, pembrolizumab	Query patients regarding energy level; evaluate possible contributory factors, including infection, disease progression, and hematologic and biochemical abnormalities; provide standard supportive care. Anticipate standard dose holds and discontinuations[a].
Infusion reaction	Chills and shaking; itch; flushing; difficulty breathing; hypotension; fever	Nivolumab, pembrolizumab	With nivolumab, for mild to moderate symptoms (grade 1 or 2), interrupt or slow rate of infusion, and monitor to recovery; for severe to life-threatening symptoms (grade 3 or 4), discontinue nivolumab, manage anaphylaxis via institutional protocol, and monitor. With pembrolizumab, monitor patients; for grade 3 (severe) or grade 4 (life-threatening) symptoms, stop infusion, and permanently discontinue pembrolizumab.
Nausea and vomiting	Vomiting; queasiness; left or right upper quadrant pain	Nivolumab, pembrolizumab	May indicate hepatotoxicity; check liver function tests, as well as lipase and amylase; provide standard supportive care. Anticipate standard dose holds and discontinuations[a].
Upper respiratory tract infection	Cough; runny nose; sore throat; nasal breathing	Nivolumab	Provide standard supportive care. Anticipate standard dose holds and discontinuations[a].

[a] For nivolumab and pembrolizumab, withhold for any grade 3 (severe) AEs, and permanently discontinue for any grade 4 (life-threatening) AEs, persistent grade 2 or 3 AEs, or any grade 3 AE that recurs, or when 10 mg or more prednisone or equivalent is required for 12 weeks. Resume treatment when AE returns to grade 0 or 1.
AE—adverse event; PD-1—programmed cell death protein 1
Note. Based on information from Bristol-Myers Squibb, 2017; Merck, 2017; National Cancer Institute, 2010.

IMPLICATIONS FOR PRACTICE

- Advise patients receiving programmed cell death protein 1 (PD-1) inhibitor therapy to immediately report any changes in their health, including subtle changes in the way they feel, to their healthcare team.
- Support patients receiving PD-1 inhibitor therapy by providing educational and adverse event (AE) management resources.
- Provide comprehensive nursing assessment and care for immune-related AEs associated with PD-1 inhibitor therapy.

identification of pneumonitis by checking patients' pulse oxygen saturation at rest and on exertion at every visit, as well as assessing for a decrease, possibly indicating an early finding of pneumonitis.

Performing directed and focused assessments to pick up seemingly insignificant patient reports may also uncover additional symptoms suggestive of early toxicity. For example, during a prior visit, a patient may have reported that he or she could climb a set of stairs without difficulty. However, during the current visit, he or she may have reported becoming slightly "winded" with the same activity. A nurse with knowledge of the spectrum of toxicities with PD-1 inhibitor therapy would recognize these subtle signs, further evaluate the symptoms as potential red flags for pneumonitis, and intervene accordingly. These simple nursing interventions are paramount to early recognition of a possible irAE and may make the difference in a patient's ability to continue on therapy.

Specialty care from a pulmonologist is often needed for management of immune-mediated pneumonitis. Moderate pneumonitis is managed with corticosteroids while withholding PD-1 inhibitor therapy. Severe pneumonitis is managed with prompt initiation of high-dose corticosteroids and PD-1 inhibitor discontinuation. Mycophenolate mofetil, cyclophosphamide, or infliximab may be indicated for corticosteroid-resistant symptoms. Because of the possibility of respiratory compromise, patients may require oxygen (grade 3) or urgent intubation and ventilatory support (grade 4).

Other Immune-Related Adverse Events

Appendix I presents a CSP for arthralgias and arthritis, less-common irAEs that often remain underrecognized or untreated, negatively affecting patient quality of life. The clinical presentations of these irAEs vary, and they typically require higher doses of corticosteroids for management than is used in the general population. Appendix J presents a CSP for neuropathy, sensory and motor. A wide variety of neurologic conditions can result from ICIs, including Guillain-Barré syndrome, myasthenia gravis, posterior reversible encephalopathy syndrome, and other forms of neuropathy. These conditions require neurology or neuromuscular consultation and, ideally, comanagement. Appendix K presents a CSP for nephritis. Nephritis is another rare complication associated with PD-1 inhibitor therapy; however, if unrecognized or misdiagnosed, it can lead to serious sequelae. Early recognition and aggressive management, ideally provided collaboratively with a nephrologist, is the best approach.

PD-1 inhibitor therapy has been associated with several other AEs. Table 2 lists these, along with recommended management strategies. With the exception of the infusion reaction, these AEs generally reflect the widespread impact of the immune system on various body systems, although some may have a different etiology. For example, low-grade fatigue and other constitutional symptoms are the most common of all AEs associated with PD-1 inhibitor therapy, but whether these are irAEs is unclear. In some cases, they may be caused by nonspecific cytokine release or undiagnosed endocrinopathies related to PD-1 inhibitor therapy use (Day & Hansen, 2016).

Implications for Nursing

The incidence of irAEs is generally lower with PD-1 inhibitor therapy than with ipilimumab, with no notable differences between nivolumab and pembrolizumab (Day & Hansen, 2016; Friedman et al., 2016; Weber et al., 2016). Also, the onset of grade 3 or 4 irAEs is typically later in the treatment course with PD-1 inhibitor therapy versus ipilimumab-based therapy. For oncology nurses familiar with ipilimumab, some irAEs do tend to occur more frequently with PD-1 antibodies than with ipilimumab, including thyroid dysfunction, some dermatologic toxicities (rash, vitiligo), arthralgias, myalgias, and pneumonitis (Day & Hansen, 2016; Spain et al., 2016).

Conclusion

PD-1 inhibitor therapy has become a standard approach for the treatment of advanced melanoma. The unique mechanism of action affords improved outcomes in terms of higher response rates and more durable responses, but accompanying that is the vast array of immune toxicities, including dermatitis, colitis, hepatotoxicity, hypophysitis, thyroiditis, diabetes, pneumonitis, arthralgia, nephritis, and neuropathy. Oncology nurses familiar with irAEs are ideally positioned to optimize care via patient education about the importance of early detection and reporting of new or worsening signs or symptoms, regular and ongoing patient assessments, and prompt intervention when toxicity is identified. Nurses can also help patients access additional sources of support and financial assistance. By becoming familiar with the CSPs highlighted in this article, nurses will be better prepared to provide the comprehensive nursing care so critical to improving irAE management and outcomes with PD-1 inhibitor therapy.

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The authors gratefully acknowledge Jill Maria Weberding, MPH, BSN, RN, OCN®, for reviewing the manuscript from the community oncology nursing perspective.

The authors take full responsibility for this content. This supplement was funded by the AIM at Melanoma Foundation, with support via unrestricted grants from Amgen, Array Biopharma, Bristol-Myers Squibb, Incyte Corporation, Merck and Co., and Novartis Pharmaceuticals. Writing and editorial support was provided by Michael L. Coco, PhD, of Coco Communications, Inc., Lisa A. Tushla, PhD, H(ASCP), of Terranova Medica, and Marjorie Joyce, BA. McGettigan serves on speakers bureaus for Bristol-Myers Squibb, Genentech, Merck and Co., and Novartis Pharmaceuticals. Rubin has previously consulted for Merck and Co., and has received support from EMD Serono, Merck and Co., and Novartis Pharmaceuticals. The article has been reviewed by independent peer reviewers to ensure that it is objective and free from bias. Mention of specific products and opinions related to those products do not indicate or imply endorsement by the Oncology Nursing Society.

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APPENDIX A.
CARE STEP PATHWAY FOR MANAGEMENT OF SKIN TOXICITIES

NURSING ASSESSMENT

Look
- Does the patient appear uncomfortable?
- Does the patient appear unwell?
- Is there an obvious rash?
- Is the patient scratching during the visit?
- Is skin integrity intact?
- Are there skin changes?
  - ☐ Xerosis
  - ☐ Changes in skin pigment or color
- Is there oral involvement of the rash?

Listen
- Does the patient have pruritus with or without rash? Is there a rash with or without pruritus?
- Are symptoms interfering with ADLs? With sleep?
- Have symptoms worsened?

Recognize
- Is there a history of dermatitis, preexisting skin issues (e.g., psoriasis), and wounds?
- Laboratory abnormalities consistent with other etiologies (e.g., eosinophils on complete blood count, liver function abnormalities)

GRADING TOXICITY: MACULOPAPULAR RASH (MORBILLIFORM RASH)

A disorder characterized by the presence of macules (flat) and papules (elevated); frequently affects the upper trunk, spreading centripetally, and associated with pruritus

Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (potentially life-threatening)	Grade 5 (death)
■ Macules and papules covering less than 10% BSA, with or without symptoms (e.g., pruritus, burning, tightness)	■ Macules and papules covering 10%–30% BSA, with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADLs	■ Macules and papules covering more than 30% BSA, with or without associated symptoms; limiting self-care ADLs; skin sloughing covering less than 10% BSA	■ Papules and pustules covering any percentage of BSA, with or without symptoms, and associated with superinfection requiring IV antibiotics; skin sloughing covering 10%–30% BSA	

GRADING TOXICITY: PRURITUS

A disorder characterized by an intense itching sensation

Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (potentially life-threatening)	Grade 5 (death)
■ Mild or localized; topical intervention indicated	■ Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing or crusts); limiting instrumental ADLs	■ Intense or widespread; constant; limiting self-care ADLs or sleep		

MANAGEMENT

Overall strategy
- Assess for other etiology of rash: Ask patient about new medications, including herbals, supplements, alternative or complementary therapies, and lotions.

ADLs—activities of daily living; BSA—body surface area

Note. Based on information from Bristol-Myers Squibb, 2017a, 2017b; Champiat et al., 2016; Dadu et al., 2016; Fecher et al., 2013; Friedman et al., 2016; Kähler et al., 2016; Kumar et al., 2017; Merck, 2017; Naidoo et al., 2015; National Cancer Institute, 2010; Spain et al., 2016; U.S. Food and Drug Administration, 2012.

MANAGEMENT BY GRADE

Intervention (at-risk patients)

- Advise gentle skin care.
  - ☐ Avoid soap. Instead, use nonsoap cleansers that are fragrance- and dye-free; use mild soap on the axillae, genitalia, and feet.
  - ☐ Daily applications of nonsteroidal moisturizers or emollients containing humectants (urea, glycerin)
  - ☐ Apply moisturizers and emollients in the direction of hair growth to minimize development of folliculitis.
- Advise sun-protective measures.
- Assess patient and family understanding of prevention strategies and rationale.
  - ☐ Identify barriers to adherence.

Grade 1 (mild)

- Immunotherapy to continue
- Oral antihistamines will be used in some patients.
- Topical corticosteroids will be used in some patients.
- Advise vigilant skin care.
  - ☐ Increase to twice daily applications of nonsteroidal moisturizers or emollients applied to moist skin.
  - ☐ Moisturizers with ceramides and lipids are advised; however, if cost is an issue, petroleum jelly is also effective.
  - ☐ Soothing methods (cool cloth applications; topicals with cooling agents, such as menthol or camphor; refrigerating products prior to application)
  - ☐ Avoid hot water; bathe or shower with tepid water.
  - ☐ Keep fingernails short.
  - ☐ Cool temperature for sleep
- Advise strict sun protection.
- Monitor vigilantly. Instruct patient and family to call clinic with any sign of worsening rash or symptoms. Anticipate office visit for evaluation.
- Assess patient and family understanding of skin care recommendations and rationale.
  - ☐ Identify barriers to adherence.

Grade 2 (moderate)

- Ipilimumab will be withheld for any grade 2 event.
- Oral corticosteroids (0.5–1 mg/kg per day) and oral antihistamines and oral antipruritics to be used
- Consider dermatology consultation.
- Patient education
  - ☐ Proper administration of oral corticosteroids (take with food and early in the day; concomitant medications may be prescribed, including H_2 blocker and antimicrobial prophylaxis)
- Advise vigilant skin care.
  - ☐ Gentle skin care
  - ☐ Tepid and oatmeal baths
- Advise strict sun protection.
- Assess patient and family understanding of toxicity and rationale for treatment hold.
  - ☐ Identify barriers to adherence.

Grades 3–4 (severe or life-threatening)

- Nivolumab to be withheld for grade 3 rash or confirmed Stevens-Johnson syndrome or toxic epidermal necrolysis
- Ipilimumab to be discontinued for any grade 3 or 4 event, and nivolumab for grade 4 rash or confirmed Stevens-Johnson syndrome or toxic epidermal necrolysis
- Pembrolizumab or nivolumab to be discontinued for any grade 3 or 4 event that recurs or persists for 12 or more weeks, or for inability to reduce steroid dose to 10 mg or less prednisone or equivalent within 12 weeks
- Anticipate hospitalization and initiation of IV corticosteroids (1.5–2 mg/kg per day; divided doses).
- Anticipate dermatology consultation with or without biopsy.
- Provide anticipatory guidance.
  - ☐ Rationale for hospitalization and treatment discontinuation
  - ☐ Rationale for prolonged steroid taper
  - ☐ Side effects of high-dose steroids
  - ☐ Risk of opportunistic infection and need for antibiotic prophylaxis
  - ☐ Effects on blood sugars and muscle atrophy
- Assess patient and family understanding of toxicity and rationale for treatment discontinuation.
  - ☐ Identify barriers to adherence, specifically compliance with steroids when transitioned to oral corticosteroids.

RED FLAGS

- Extensive rash (more than 50% BSA) or rapidly progressive
- Oral involvement
- Concern for suprainfection

APPENDIX B.

CARE STEP PATHWAY FOR MANAGEMENT OF GASTROINTESTINAL TOXICITY: DIARRHEA AND COLITIS

NURSING ASSESSMENT

Look

- Does the patient appear weak?
- Has the patient lost weight?
- Does the patient appear dehydrated?
- Does the patient appear in distress?

Listen

- Quantity and quality of bowel movements (e.g., change in or increased frequency over baseline): solid, soft, or liquid diarrhea; dark or bloody stools; stools that float
- Fever
- Abdominal pain or cramping
- Increased fatigue
- Upset stomach, nausea, or vomiting
- Abdominal pain or cramping
- Bloating or increased gas
- Decreased appetite or food aversions

Recognize

- Serum chemistry and hematologic abnormalities
- Infectious versus immune-related adverse event causation
- Peritoneal signs of bowel perforation (e.g., pain, tenderness, bloating)

GRADING TOXICITY: DIARRHEA (INCREASED FREQUENCY, LOOSE, LARGE VOLUME, OR LIQUIDY STOOLS)

Grade 1 (mild)

- Increase of less than four stools per day over baseline
- Mild increase in ostomy output compared to baseline

Grade 2 (moderate)

- Increase of four to six stools per day over baseline
- Moderate increase of output in ostomy compared to baseline

Grade 3 (severe)

- Increase of seven or more stools per day over baseline; incontinence
- Hospitalization indicated
- Severe increase in ostomy output compared to baseline
- Limiting self-care ADLs

Grade 4 (potentially life-threatening)

- Life-threatening (e.g., perforation, bleeding, ischemic necrosis, toxic megacolon)
- Urgent intervention required

Grade 5 (death)

GRADING TOXICITY: COLITIS (INFLAMMATION OF THE INTESTINAL LINING)

Grade 1 (mild)

- Asymptomatic; clinical or diagnostic observation only; intervention not indicated

Grade 2 (moderate)

- Abdominal pain; blood or mucus in stool

Grade 3 (severe)

- Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs

Grade 4 (potentially life-threatening)

- Life-threatening (e.g., hemodynamic collapse); urgent intervention indicated

Grade 5 (death)

MANAGEMENT

Overall strategy

- Rule out infectious, noninfectious, and disease-related etiologies.

MANAGEMENT BY GRADE

Grade 1 (mild)

- May continue immunotherapy
- Diet modifications (very important)
  - ☐ Institute bland diet; decrease fiber, uncooked foods and vegetables, red meats, fats, dairy, oil, caffeine, alcohol, and sugar.

Grade 2 (moderate)

- Send stool sample for *Clostridium difficile* testing, culture, and ova and parasite examination.
- Immunotherapy to be withheld until grade 0 or 1 or patient's baseline (ipilimumab, pembrolizumab, nivolumab)
- Provide antidiarrheals: loperamide (Imodium®) or diphenoxylate and atropine (Lomotil®).
- If upper or lower gastrointestinal symptoms persist for more than five to seven days, oral steroids should be started (prednisone or equivalent 0.5–1 mg/kg per day).
  - ☐ After control of symptoms, a steroid* taper of four or more weeks will be initiated.
- Immunotherapy to be discontinued if grade 2 symptoms persist for six or more weeks (ipilimumab) or for 12 or more weeks (pembrolizumab, nivolumab), or for inability to reduce steroid dose to 7.5 mg or less (ipilimumab) or 10 mg or less prednisone or equivalent (pembrolizumab, nivolumab) within 12 weeks
- Diet modifications
  - ☐ Institute bland diet low in fiber, residue, and fat (BRAT [Bananas, Rice, Applesauce, Toast] diet).
  - ☐ Decrease fiber, uncooked foods and vegetables, red meats, fats, dairy, oil, caffeine, alcohol, and sugar.
  - ☐ Avoid laxatives or stool softeners.
  - ☐ Advance diet slowly as steroids are tapered*, and assess for loose or liquid stool for several days or longer.
- (Moderate) persistent or relapsed symptoms with steroid* taper
  - ☐ Consider gastroenterology consultation for possible intervention (flexible sigmoidoscopy, colonoscopy, endoscopy).
  - ☐ IV steroids* to be started at 1 mg/kg per day
  - ☐ Immunotherapy to be held until grade 0 or 1
  - ☐ Control symptoms, then steroid* taper of four or more weeks
  - ☐ Recurrent diarrhea is more likely when treatment is restarted.

Grades 3–4 (severe or life-threatening)

- Onset
  - ☐ Continued diet modification, antidiarrheals, and steroid titration
- Immunotherapy
  - ☐ Grade 3: Pembrolizumab or nivolumab to be withheld when used as single agent; ipilimumab to be discontinued as single agent and nivolumab when given with ipilimumab
  - ☐ Grade 4: Ipilimumab and/or PD-1 inhibitor to be discontinued
- Doses of steroids* to be increased
  - ☐ 1–2 mg/kg prednisone or equivalent per day; methylprednisolone (Solu-Medrol®) 1 g IV daily (divided doses)
- Hospitalization
- Gastrointestinal consultation
- Assess for peritoneal signs and perforation (nothing by mouth and abdominal x-ray, surgical consultation when necessary).
- Use caution with analgesics (opioids) and antidiarrheal medications.
- Steroid* refractory (if not responsive within 24–72 hours to high-dose IV steroid* infusion)
  - ☐ Infliximab (Remicade®) 5 mg/kg infusion may be considered.
  - ☐ May require one or more infusions to manage symptoms (may readminister at weeks 2 and 6)
  - ☐ Avoid with bowel perforation or sepsis.
  - ☐ Tuberculin testing not required in this setting
  - ☐ Infliximab infusion delay may have life-threatening consequences.
- Diet modification
  - ☐ Very strict with acute symptoms; clear liquids; very bland, low fiber, and low residue (BRAT diet)
  - ☐ Advance diet slowly as steroids* reduced to low doses
  - ☐ Steroids* to be tapered for at least four weeks
  - ☐ Supportive medications for symptomatic management
    - Loperamide 2 capsules at the onset and 1 with each diarrhea stool thereafter, with maximum of 6 tablets per day
    - Diphenoxylate and atropine, 1–4 tablets per day; simethicone when necessary

Continued on the next page

APPENDIX B. *(CONTINUED)*

CARE STEP PATHWAY FOR MANAGEMENT OF GASTROINTESTINAL TOXICITY: DIARRHEA AND COLITIS

NURSING IMPLEMENTATION

- Compare baseline assessment; grade and document bowel frequency.
- Early identification and evaluation of patient symptoms
- Grade symptom, and determine level of care and interventions required.
- Early intervention with laboratory work and office visit if colitis symptoms are suspected

Steroid taper instructions and calendar as a guide but not an absolute *

- Taper should consider patient's current symptom profile.
- Close follow-up in person or by telephone, based on individual need and symptomatology
- Anti-acid therapy daily as gastric ulcer prevention while on steroids
- Review steroid medication side effects: mood changes (anger, reactive, hyperaware, euphoric, mania); increased appetite; interrupted sleep; oral thrush; fluid retention)
- Be alert to recurring symptoms as steroids taper down and report them (taper may need to be adjusted).

Long-term high-dose steroids

- Consider antimicrobial prophylaxis (sulfamethoxazole and trimethoprim double dose Monday, Wednesday, and Friday; single dose if used daily) or alternative if sulfa-allergic (e.g., atovaquone [Mepron®] 1,500 mg by mouth daily)
- Consider additional antiviral and antifungal coverage.
- Avoid alcohol and acetaminophen, as well as other hepatoxins.

RED FLAGS

- Change in gastrointestinal function; decreased appetite
- Bloating; nausea
- More frequent stools; consistency change from loose to liquid
- Abdominal pain
- Fever

ADLs—activities of daily living; PD-1—programmed cell death protein 1

Note. Based on information from Bristol-Myers Squibb, 2017a, 2017b; Champiat et al., 2016; Dadu et al., 2016; Fecher et al., 2013; Kähler et al., 2016; Kumar et al., 2017; Merck, 2017; Naidoo et al., 2015; National Cancer Institute, 2010; Spain et al., 2016; U.S. Food and Drug Administration, 2012; Weber et al., 2016.

APPENDIX C.

CARE STEP PATHWAY FOR MANAGEMENT OF MUCOSITIS AND XEROSTOMIA

NURSING ASSESSMENT

Look

- Does the patient appear uncomfortable?
- Does the patient appear unwell?
- Difficulty talking?
- Licking lips to moisten often?
- Weight loss?
- Does the patient appear dehydrated?
- Does the patient have thrush?

Listen

- Does the patient report any of the following?
  - ☐ Mouth pain (tongue, gums, buccal mucosa)
  - ☐ Mouth sores
  - ☐ Difficulty eating
  - ☐ Waking during sleep to sip water
  - ☐ Recent dental-related issues
  - ☐ Dental work need (root canal, tooth extraction)
- Have symptoms worsened?

Recognize

- A history of mouth sores
- Does patient smoke?
- Concomitant medications associated with causing dry mouth?
- Reports of dry mouth often accompany mucositis.
- Other reports of dry membranes (e.g., eyes, nasal passages, vagina)

GRADING TOXICITY: ORAL MUCOSITIS

A disorder characterized by inflammation of the oral mucosa

Grade 1 (mild)

- Asymptomatic or mild symptoms; intervention not indicated

Grade 2 (moderate)

- Moderate pain; not interfering with oral intake; modified diet indicated

Grade 3 (severe)

- Severe pain; interfering with oral intake

Grade 4 (potentially life-threatening)

- Life-threatening consequences; urgent intervention indicated

Grade 5 (death)

GRADING TOXICITY: XEROSTOMIA (DRY MOUTH)

A disorder characterized by reduced salivary flow in the oral region

Grade 1 (mild)

- Symptomatic (e.g., dry or thick saliva); without significant dietary alteration; unstimulated saliva flow of more than 0.2 ml per minute

Grade 2 (moderate)

- Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva flow of 0.1–0.2 ml per minute with oral intake

Grade 3 (severe)

- Inability to adequately aliment orally; tube feeding or total parenteral nutrition indicated; unstimulated saliva of less than 0.1 ml per minute

Grade 4 (potentially life-threatening)

- Life-threatening consequences; urgent intervention indicated

Grade 5 (death)

MANAGEMENT

Overall strategy

- Assess for other etiology of mucositis or dry mouth: candidiasis; ask patient about new medications (particularly antihistamines), including herbals, supplements, and alternative and complementary therapies.

Intervention (at-risk patients)

- Advise basic oral hygiene.
  - ☐ Tooth brushing (soft toothbrush, avoid toothpaste with whitening agents)
  - ☐ Use of dental floss daily
  - ☐ More than one mouth rinse per day to maintain oral hygiene (avoid commercial mouthwashes or those with alcohol)
- If patient wears dentures, assess for proper fit and areas of irritation.
- Dental referral if necessary
- Assess patient and family understanding of prevention strategies and rationale.
  - ☐ Identify barriers to adherence.

Continued on the next page

APPENDIX C. *(CONTINUED)*

CARE STEP PATHWAY FOR MANAGEMENT OF MUCOSITIS AND XEROSTOMIA

MANAGEMENT BY GRADE

Grade 1 (mild)

- Anticipate immunotherapy to continue.
- Advise ongoing basic oral hygiene.
- Advise avoidance of hot, spicy, acidic foods.
- Anticipate possible alternative treatment(s).
  - ☐ Zinc supplements or 0.2% zinc sulfate mouthwash
  - ☐ Probiotics with *Lactobacillus*
  - ☐ Benzydamine hydrochloride
- Assess patient and family understanding of recommendations and rationale.
  - ☐ Identify barriers to adherence.

Grade 2 (moderate)

- Ipilimumab to be withheld for any grade 2 event (resume when grade 0 or 1)
- Immunotherapy to be discontinued for grade 2 events persisting six or more weeks (ipilimumab) or 12 or more weeks (pembrolizumab, nivolumab)
- Assess for Sicca syndrome and Sjögren syndrome.
- Encourage vigilant oral hygiene.
- Xerostomia
  - ☐ Advise moistening agents (saliva substitute, synthetic saliva, oral lubricants).
  - ☐ Advise secretagogues, both nonpharmacologic (sugarless gum and hard candies, natural lemon) and pharmacologic (pilocarpine, cevimeline hydrochloride).
- Mucositis
  - ☐ Vigilant oral hygiene
    - Increase frequency of brushing to every four hours and at bedtime. If unable to tolerate brushing, advise chlorhexidine gluconate 0.12% or sodium bicarbonate rinses (1 tsp baking soda in 8 ounces of water or ½ tsp salt and 2 tbsp sodium bicarbonate dissolved in 4 cups of water).
  - ☐ Encourage sips of cool water or crushed ice.
  - ☐ Encourage soft, bland, nonacidic foods.
  - ☐ Anticipatory guidance regarding use of pharmacologic agents (as applicable)
    - Analgesics (Gelclair® and Zilactin®; 2% viscous lidocaine applied to lesions 15 minutes prior to meals; 2% morphine mouthwash; 0.5% doxepin mouthwash; "miracle mouthwash" of diphenhydramine, lidocaine, and simethicone)
    - Corticosteroid rinses (dexamethasone oral solution)
  - ☐ Monitor weight and hydration status.
  - ☐ Nutrition referral, if appropriate
  - ☐ Assess patient and family understanding of toxicity and rationale for interventions, as well as treatment hold.
    - Identify barriers to adherence.

Grades 3–4 (severe or life-threatening)

- Nivolumab to be withheld for first occurrence of grade 3 event; immunotherapy to be discontinued for any grade 4 event or for a grade 3 event persisting 12 or more weeks (ipilimumab, pembrolizumab, nivolumab) or any recurrent grade 3 event (pembrolizumab, nivolumab)
- Anticipate hospitalization if unable to tolerate oral solids or liquids.
- Unclear role of systemic corticosteroids
- Anticipate need for supplemental nutrition.
  - ☐ Enteral
  - ☐ Parenteral
- Anticipatory guidance regarding use of pharmacologic agents
  - ☐ Analgesics (systemic opioids may be indicated)
- Oral care
- Assess patient and family understanding of toxicity and rationale for interventions, as well as treatment discontinuation.
  - ☐ Identify barriers to adherence.

Note. Based on information from Bristol-Myers Squibb, 2017a, 2017b; Dadu et al., 2016; Friedman et al., 2016; Lalla et al., 2014; Merck, 2017; National Cancer Institute, 2010; Van Sebille et al., 2015.

APPENDIX D.

CARE STEP PATHWAY FOR MANAGEMENT OF HEPATOTOXICITY: IMMUNOTHERAPY-INDUCED INFLAMMATION OF LIVER TISSUE

NURSING ASSESSMENT

Look

- Does the patient appear fatigued or listless?
- Does the patient appear jaundiced?
- Does the patient appear diaphoretic?
- Does the patient have any ascites?

Listen

- Change in energy level?
- Change in skin color? Yellowing?
- Change in stool color (paler)?
- Change in urine color (darker or tea-colored)?
- Abdominal pain, specifically in the right upper quadrant?
- Bruising or bleeding more easily?
- Fevers?
- Change in mental status?
- Increased sweating?

Recognize

- Elevation in LFTs
  - ☐ AST/SGOT
  - ☐ ALT/SGPT
  - ☐ Bilirubin (total and direct)
- Alteration in gastrointestinal function
- Symptoms such as abdominal pain, ascites, somnolence, and jaundice
- Other potential causes (viral, drug toxicity, disease progression)

GRADING TOXICITY: ULN

Grade 1 (mild)

- AST/ALT: Greater than ULN, less than or equal to 3 times ULN
- Bilirubin: Greater than ULN, less than or equal to 1.5 times ULN

Grade 2 (moderate)

- AST/ALT: Greater than 3 times ULN, less than or equal to 5 times ULN
- Bilirubin: Greater than 1.5 times ULN, less than or equal to 3 times ULN

Grade 3 (severe)

- AST/ALT: Greater than 5 times ULN, less than or equal to 20 times ULN
- Bilirubin: Greater than 3 times ULN

Grade 4 (potentially life-threatening)

- AST/ALT: Greater than 20 times ULN
- Bilirubin: Greater than 10 times ULN

Grade 5 (death)

MANAGEMENT

Overall strategy

- LFTs should be checked and results reviewed prior to each dose of immunotherapy.
- Rule out infectious, noninfectious, and malignant causes. Consider assessing for new onset or reactivation of viral hepatitis, medications (acetaminophen, statins, other hepatotoxic medications, supplements or herbals), and recreational substances (alcohol); consider disease progression.
- Infliximab infusions are not recommended because of potential hepatotoxic effects.

Continued on the next page

APPENDIX D. *(CONTINUED)*

CARE STEP PATHWAY FOR MANAGEMENT OF HEPATOTOXICITY: IMMUNOTHERAPY-INDUCED INFLAMMATION OF LIVER TISSUE

MANAGEMENT BY GRADE

Grade 1 (mild)

- Immunotherapy may be withheld if LFTs are trending upward; recheck LFTs within approximately one week.

Grade 2 (moderate)

- Immunotherapy to be withheld; recheck LFTs daily for three days or every three days; resume when complete or partial resolution of adverse reaction (grade 0 or 1).
- Immunotherapy to be discontinued for grade 2 events lasting six or more weeks (ipilimumab) or 12 or more weeks (pembrolizumab, nivolumab), or for inability to reduce steroid dose to 7.5 mg prednisone or equivalent per day
- Consider starting steroids* 0.5–1 mg/kg prednisone or equivalent per day (IV methylprednisolone 125 mg total daily dose) and an anti-acid.
- Consider hospital admission for IV steroids*.
- If LFTs are normalized and symptoms resolved, steroids* to be tapered for four or more weeks when function recovers
- Once patient returns to baseline or grades 0–1, consider resuming treatment.

Grade 3 (severe)

- Steroids* to be initiated at 2 mg/kg prednisone or equivalent daily (oral).
- Nivolumab to be withheld for first occurrence of grade 3 event. Ipilimumab to be discontinued for any grade 3 event, and nivolumab or pembrolizumab for any recurrent grade 3 event or grade 3 event persisting 12 or more weeks
- Admission for IV steroids*
- Rule out hepatitis infection (acute infection or reactivation).
- Daily LFTs
- If sustained elevation is significant and/or refractory to steroids*, potential for adding to steroid regimen immunosuppressive agent
  - ☐ Mycophenolate mofetil (CellCept®) 500–1,000 mg by mouth every 12 hours, or
  - ☐ Antithymocyte globulin infusion (Atgam®, Thymoglobulin®)
- Hepatology and gastroenterology consultation
- Consider liver biopsy.
- If LFTs are stable or declining daily for five consecutive days, decrease LFT checks to every three days, then weekly.
  - ☐ If LFTs are normalized and symptoms resolved, steroids* to be tapered for four or more weeks

Grade 4 (life-threatening)

- Immunotherapy to be discontinued
- Hospital admission
- Steroids* to be initiated at 2 mg/kg prednisone or equivalent daily via IV
- Rule out hepatitis infection.
- Daily LFTs
- If sustained elevation and refractory to steroids*, potential for adding to steroid regimen
  - ☐ Mycophenolate mofetil 500–1,000 mg by mouth every 12 hours, or
  - ☐ Antithymocyte globulin infusion
- Hepatology or gastroenterology consultation
- Consider liver biopsy.
- If LFTs are stable or declining daily for five consecutive days, decrease LFT checks to every three days, then weekly.
- If LFTs are normalized and symptoms resolved, steroids* to be tapered slowly for four or more weeks.

NURSING IMPLEMENTATION

- Review LFT results prior to administration of immunotherapy.
- Early identification and evaluation of patient symptoms
- Early intervention with laboratory work and office visit if hepatotoxicity is suspected
- Grade LFT results and any other accompanying symptoms.

Steroid taper instructions and calendar as a guide but not an absolute *

- Taper should consider patient's current symptom profile.
- Close follow-up in person or by telephone, based on individual need and symptomatology
- Anti-acid therapy daily as gastric ulcer prevention while on steroids
- Review steroid medication side effects: mood changes (anger, reactive, hyperaware, euphoric, mania); increased appetite; interrupted sleep; oral thrush; fluid retention)
- Be alert to recurring symptoms as steroids taper down and report them (taper may need to be adjusted).

Long-term high-dose steroids

- Consider antimicrobial prophylaxis (sulfamethoxazole and trimethoprim double dose Monday, Wednesday, and Friday; single dose if used daily) or alternative if sulfa-allergic (e.g., atovaquone [Mepron®] 1,500 mg by mouth daily)
- Consider additional antiviral and antifungal coverage.
- Avoid alcohol and acetaminophen, as well as other hepatoxins.

RED FLAGS

- Severe abdominal pain; ascites; somnolence; jaundice; mental status changes

ALT—alanine aminotransferase; AST—aspartate aminotransferase; LFT—liver function test; SGOT—serum glutamic oxaloacetic transaminase; SGPT—serum glutamic pyruvic transaminase; ULN—upper limit of normal

Note. Based on information from Bristol-Myers Squibb, 2017a, 2017b; Champiat et al., 2016; Dadu et al., 2016; Fecher et al., 2013; Friedman et al., 2016; Kähler et al., 2016; Kumar et al., 2017; Merck, 2017; Naidoo et al., 2015; Spain et al., 2016; U.S. Food and Drug Administration, 2012; Weber et al., 2016.

APPENDIX E.

CARE STEP PATHWAY FOR MANAGEMENT OF HYPOPHYSITIS: INFLAMMATION OF PITUITARY GLAND

NURSING ASSESSMENT

Look

- Does the patient appear fatigued?
- Does the patient look listless?
- Does the patient look ill?
- Does the patient look uncomfortable?

Listen

- Does the patient report the following:
  - ☐ Change in energy?
  - ☐ Headache?
  - ☐ Dizziness?
  - ☐ Nausea or vomiting?
  - ☐ Altered mental status?
  - ☐ Visual disturbances?
  - ☐ Fever?

Recognize

- Low levels of hormones produced by pituitary gland (ACTH, TSH, FSH, LH, GH, prolactin)
- Brain MRI with pituitary cuts; enhancement and swelling of the pituitary gland
- DDX adrenal insufficiency (low cortisol and high ACTH)
- DDX primary hypothyroidism (low free T4 and high TSH)

GRADING TOXICITY: OVERALL

Grade 1 (mild)

- Asymptomatic or mild symptoms; clinical or diagnostic observation only (headache, fatigue)

Grade 2 (moderate)

- Moderate symptoms; limiting age-appropriate instrumental ADLs (headache, fatigue)

Grade 3 (severe)

- Severe or medically significant symptoms; limiting self-care ADLs (sepsis, severe ataxia)

Grade 4 (potentially life-threatening)

- Urgent intervention required (sepsis, severe ataxia)

Grade 5 (death)

MANAGEMENT

Overall strategy

- Ipilimumab to be withheld for any symptomatic hypophysitis and discontinued for symptomatic reactions persisting six or more weeks or for inability to reduce steroid dose to 7.5 mg or less prednisone or equivalent per day
- Nivolumab to be withheld for grade 2 or 3 hypophysitis and discontinued for grade 4 hypophysitis; pembrolizumab to be withheld for grade 2 hypophysitis and withheld or discontinued for grade 3 or 4 hypophysitis
- 1 mg/kg methylprednisolone or equivalent IV to be given daily
  - ☐ If given during acute phase, may reverse inflammatory process
- To be followed with prednisone 1–2 mg/kg daily and slowly taper over at least four weeks*
- Long-term supplementation of affected hormones is often required.
  - ☐ Secondary hypothyroidism requiring levothyroxine replacement
  - ☐ Secondary hypoadrenalism requiring replacement hydrocortisone (typical dose of 20 mg in the am and 10 mg in the pm)
- Assess risk of opportunistic infection based on duration of steroid taper (and consider antimicrobial prophylaxis if needed).
- Collaborative management approach with endocrinology (particularly if permanent loss of organ function)

NURSING IMPLEMENTATION

- ACTH and thyroid panel should be checked at baseline and prior to each dose of ipilimumab.
- Ensure that brain MRI is ordered with pituitary cuts or via pituitary protocol.
- Anticipate treatment with corticosteroid and immunotherapy hold.
- Review proper administration of corticosteroid.
  - ☐ Take with food.
  - ☐ Take in am.
- Educate patient regarding possibility of permanent loss of organ function (pituitary and possibly others if involved, including thyroid and adrenal glands).
- Sick-day instructions and vaccinations

Steroid taper instructions and calendar as a guide but not an absolute *

- Taper should consider patient's current symptom profile.
- Close follow-up in person or by telephone, based on individual need and symptomatology
- Anti-acid therapy daily as gastric ulcer prevention while on steroids
- Review steroid medication side effects: mood changes (anger, reactive, hyperaware, euphoric, mania); increased appetite; interrupted sleep; oral thrush; fluid retention)
- Be alert to recurring symptoms as steroids taper down and report them (taper may need to be adjusted).
- Avoid alcohol and acetaminophen, as well as other hepatoxins.

Long-term high-dose steroids

- Consider antimicrobial prophylaxis (sulfamethoxazole and trimethoprim double dose Monday, Wednesday, and Friday; single dose if used daily) or alternative if sulfa-allergic (e.g., atovaquone [Mepron®] 1,500 mg by mouth daily)
- Consider additional antiviral and antifungal coverage.
- Avoid alcohol and acetaminophen, as well as other hepatoxins.

RED FLAGS

- Symptoms of adrenal insufficiency

ACTH—adrenocorticotropic hormone; ADLs—activities of daily living; DDX—differential diagnosis; FSH—follicule-stimulating hormone; GH—growth hormone; LH—luteinizing hormone; MRI—magnetic resonance imaging; TSH—thyroid stimulating hormone

Note. Based on information from Bristol-Myers Squibb, 2017a, 2017b; Byun et al., 2017; Champiat et al., 2016; Dadu et al., 2016; Fecher et al., 2013; Friedman et al., 2016; Kähler et al., 2016; Kumar et al., 2017; Merck, 2017; Naidoo et al., 2015; National Cancer Institute, 2010; U.S. Food and Drug Administration, 2012; Weber et al., 2016.

APPENDIX F.

CARE STEP PATHWAY FOR MANAGEMENT OF THYROIDITIS: INFLAMMATION OF THYROID GLAND

NURSING ASSESSMENT

Look

- Does the patient appear unwell?
- Changes in weight since last visit?
- Changes in hair texture or thickness?
- Appearing hot or cold?
- Does the patient look fatigued?

Listen

- Appetite or weight changes?
- Hot or cold intolerance?
- Change in energy, mood, or behavior?
- Palpitations?
- Increased fatigue?
- Bowel-related changes?
  - ☐ Constipation or diarrhea
- Skin-related changes?
  - ☐ Dry or oily

Recognize

- Ensure that patient undergoes TFTs prior to first dose, every 12 weeks while on PD-1 therapy, and every three weeks with ipilimumab
- High TSH with low free T4 consistent with primary hypothyroidism
- DDX: secondary hypothyroidism because of hypophysitis; low TSH and low free T4
- Occasionally thyroiditis with transient hyperthyroidism (low TSH and high free T4) may be followed by more longstanding hypothyroidism (high TSH and low free T4).
- Other immune-related toxicity?
- Prior thyroid dysfunction?

TYPE OF THYROID ABNORMALITY

TSH low (less than 0.01 mIU/L) with normal or high free T3 or T4

- Acute thyroiditis
- Rarely Graves'-like disease

TSH greater than 5 and less than 10 mIU/L with normal free T4 or T3

- Subclinical hypothyroidism

TSH greater than 10 mIU/L with normal or low free T4 and T3

- Primary hyperthyroidism

TSH low (less than 0.01 mIU/L) with high free T4 or T3

- Hyperthyroidism

MANAGEMENT BY GRADE

TSH low (less than 0.01 mIU/L) with normal or high free T3 or T4

- Consider measuring antithyroid antibodies and/or TSH-receptor autoantibodies to establish autoimmune etiology.
- If patient has not received IV iodinated contrast within two months, can consider a diagnostic thyroid uptake and scan
- Acute thyroiditis usually resolves or progresses to hypothyroidism; consequently, can repeat TFTs in four to six weeks
- If TSH-receptor antibodies high, obtain a thyroid uptake scan and refer to endocrinology.
- Short period of 1 mg/kg prednisone or equivalent per day may be helpful in acute thyroiditis.
- Consider use of beta blockers and immunotherapy hold for symptomatic patients (e.g., beta blockers for tachycardia or murmur and immunotherapy holds for patients who have acute thyroiditis threatening an airway). Therapy is often restarted when symptoms are mild or tolerable.

TSH greater than 5 and less than 10 mIU/L with normal free T4 or T3

- Repeat TFTs in four to six weeks.

TSH greater than 10 mIU/L with normal or low free T4 and T3

- Begin thyroid replacement if symptomatic.
- May consider repeating levels in two to four weeks if asymptomatic
- Levothyroxine dose 1.6 mcg per weight (kg) or 75–100 mcg daily
- Repeat TSH in four to six weeks, and titrate dose to reference range TSH.

TSH low (less than 0.01 mIU/L) with high free T4 or T3

- Consider radioactive iodine therapy or methimazole treatment.
- Consider use of beta blockers for symptomatic patients (e.g., for tachycardia or murmur).

NURSING IMPLEMENTATION

- Educate patient that hypothyroidism is generally not reversible.
- Assess medication compliance with oral thyroid replacement or suppression.
- History of thyroid disorders does not increase or decrease risk of incidence.
- Consider collaborative management with endocrinologist, particularly if the patient is hyperthyroid and if a thyroid scan is needed.

RED FLAGS

- Swelling of thyroid gland causing compromised airway

DDX—differential diagnosis; PD-1—programmed cell death protein 1; TFT—thyroid function test; TSH—thyroid stimulating hormone

Note. Based on information from Bristol-Myers Squibb, 2017a, 2017b; Champiat et al., 2016; Dadu et al., 2016; Fecher et al., 2013; Friedman et al., 2016; Kähler et al., 2016; Kumar et al., 2017; Merck, 2017; Naidoo et al., 2015; National Cancer Institute, 2010; U.S. Food and Drug Administration, 2012; Weber et al., 2016.

APPENDIX G.

CARE STEP PATHWAY FOR MANAGEMENT OF TYPE 1 DIABETES MELLITUS: IMMUNE DESTRUCTION OF BETA CELLS IN PANCREAS

NURSING ASSESSMENT

Look

- Does the patient appear fatigued?
- Does the patient appear dehydrated?
- Does the patient's breath have a sweet or fruity smell?
- Is the patient tachycardic?

Listen

- Frequent urination?
- Increased thirst?
- Increased hunger?
- Increased fatigue?
- Altered level of consciousness may occur with advanced cases.

Recognize

- Symptoms of diabetes
- Serum glucose levels
- Other immune-related toxicity
- Infections

GRADING TOXICITY (BASED ON FASTING GLUCOSE)

Grade 1 (mild)

- Fasting glucose value greater than ULN, less than or equal to 160 mg/dl

Grade 2 (moderate)

- Fasting glucose value greater than 160 mg/dl, less than or equal to 250 mg/dl

Grade 3 (severe)

- Fasting glucose value greater than 250 mg/dl, less than or equal to 500 mg/dl; hospitalization indicated

Grade 4 (potentially life-threatening)

- Fasting glucose value greater than 500 mg/dl; life-threatening consequences

Grade 5 (death)

MANAGEMENT

Overall strategy

- Immunotherapy may be withheld until blood glucose is regulated.
- Insulin therapy
- Hydration
- Endocrine consultation

NURSING IMPLEMENTATION

- Discuss that type 1 diabetes mellitus will likely be permanent.
- Review signs and symptoms of hyperglycemia and hypoglycemia.
- Follow patients closely with checks on blood glucose levels, fruity breath, and other symptoms (e.g., increased infections).
- Ensure early intervention.
- Provide insulin education (or refer).
- Discuss possibility of other immune-related adverse events, including others of endocrine origin.

ULN—upper limit of normal

Note. Based on information from Bristol-Myers Squibb, 2017a, 2017b; Merck, 2017; National Cancer Institute, 2010; U.S. Food and Drug Administration, 2012.

APPENDIX H.

CARE STEP PATHWAY FOR MANAGEMENT OF PNEUMONITIS: INFLAMMATION OF LUNG ALVEOLI

NURSING ASSESSMENT

Look

- Does the patient appear uncomfortable?
- Did the patient have difficulty walking to the examination or going up stairs?
- Does the patient appear short of breath?
- Is the patient tachypneic?
- Does the patient appear to be in respiratory distress?

Listen

- Has the patient noted any change in breathing?
- Does the patient feel short of breath?
- Does the patient note new dyspnea on exertion?
- Does the patient notice a new cough or a change in an existing cough?
- Have symptoms worsened?
- Are symptoms limiting ADLs?
- Associated symptoms?
  - ☐ Fatigue
  - ☐ Wheezing

Recognize

- Is the pulse oximetry low? Is it lower than baseline or compared to last visit? Is it low on exertion?
- Is there a preexisting pulmonary autoimmune condition (e.g., sarcoidosis)?
- Is there a history of prior respiratory compromise (e.g., asthma, chronic obstructive pulmonary disease, congestive heart failure)?
- Has the patient experienced other immune-related adverse events?

GRADING TOXICITY: PNEUMONITIS

A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma

Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (potentially life-threatening)	Grade 5 (death)
■ Asymptomatic; clinical or diagnostic observations only; intervention not indicated	■ Symptomatic; medical intervention indicated; limiting instrumental ADLs	■ Severe symptoms; limiting self-care ADLs; oxygen indicated	■ Life-threatening respiratory compromise; urgent intervention indicated (tracheostomy, intubation)	

GRADING TOXICITY: HYPOXIA

A disorder characterized by a decrease in the level of oxygen to the body

Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (potentially life-threatening)	Grade 5 (death)
	■ Decreased oxygen saturation with exercise (pulse oximetry of less than 88%); intermittent supplemental oxygen	■ Decreased oxygen saturation at rest (pulse oximetry of less than 88%)	■ Life-threatening airway compromise; urgent intervention indicated (tracheostomy, intubation)	

MANAGEMENT

Overall strategy

- Assess for other etiologies, such as infection, pulmonary embolism, progressive lung metastases, and lung disease.
- Early intervention to maintain or improve physical function and impact on quality of life
- Assess pulse oximetry (resting and on exertion) at baseline and at each visit to assist in identifying a decrease at early onset.

Prevention

- No known interventions

Continued on the next page

APPENDIX H. *(CONTINUED)*

CARE STEP PATHWAY FOR MANAGEMENT OF PNEUMONITIS: INFLAMMATION OF LUNG ALVEOLI

MANAGEMENT BY GRADE

Grade 1 (mild)

- Anticipate immunotherapy to continue.
- Continue to monitor via radiology testing (every two to four weeks, as needed).
- Review symptoms to watch for with patient and family, and remember to assess at every subsequent visit.

Grade 2 (moderate)

- Immunotherapy to be withheld for grade 2 events (resume when grade 0 or 1)
- Immunotherapy to be discontinued for recurrent (pembrolizumab, nivolumab) or persistent (ipilimumab, pembrolizumab, nivolumab) grade 2 events
- Anticipate treatment with
  - ☐ Corticosteroids (e.g., prednisone or equivalent 1–2 mg/kg per day) until symptoms improve to baseline, then slow taper for at least one month
  - ☐ If symptoms do not improve within 48–72 hours, corticosteroid dose will be escalated. IV corticosteroids may be considered.
  - ☐ Additional supportive care medications may also be initiated.
- Anticipatory guidance on proper administration
- Anticipate the use of empiric antibiotics until infection is excluded.
- Anticipate that bronchoscopy may be ordered by provider.
- Assess patient and family understanding of recommendations and rationale.
  - ☐ Identify barriers to adherence.

Grades 3–4 (severe or life-threatening)

- Discontinue immunotherapy for grade 3 or 4 events.
- Patient will likely need to be admitted to hospital for further management and supportive care.
- Anticipate the use of high-dose IV corticosteroids (e.g., methylprednisolone or equivalent 2–4 mg/kg per day).
- Once symptoms have resolved to baseline or grade 1, convert to equivalent oral corticosteroid dose, then taper slowly for at least one month.
- Anticipate the use of empiric antibiotics until infection is excluded.
- Anticipate the use of additional immunosuppressive agents if symptoms do not improve in 48–72 hours (e.g., infliximab, mycophenolate, cyclophosphamide).
- Assess patient and family understanding of toxicity and rationale for treatment discontinuation.
  - ☐ Identify barriers to adherence, specifically compliance with medication and physical activity.

NURSING IMPLEMENTATION

- Identify high-risk individuals (e.g., asthma, chronic obstructive pulmonary disease) and those with cardiopulmonary symptoms prior to initiating immunotherapy. Establish a thorough baseline.
- Educate patients that new pulmonary symptoms should be reported immediately.
- Anticipate that the steroid requirements to manage pneumonitis are high (1–4 mg/kg per day) and that the patient will be on corticosteroid therapy for at least one month.
- Educate patients and family about the rationale for discontinuation of immunotherapy in patients who do develop moderate or severe pneumonitis.

RED FLAGS

- Risk of acute onset
- Risk of mortality if pneumonitis treatment is delayed
- The risk of pneumonitis is greater in patients receiving combination immunotherapy regimens.

ADLs—activities of daily living

Note. Based on information from Bristol-Myers Squibb, 2017a, 2017b; Dadu et al., 2016; Fecher et al., 2013; Friedman et al., 2016; Kähler et al., 2016; Kumar et al., 2017; Merck, 2017; Naidoo et al., 2015; National Cancer Institute, 2010; Spain et al., 2016; U.S. Food and Drug Administration, 2012; Weber et al., 2016.

APPENDIX I.

CARE STEP PATHWAY FOR MANAGEMENT OF ARTHRALGIAS AND ARTHRITIS

NURSING ASSESSMENT

Look

- Does the patient appear uncomfortable?
- Does the patient appear unwell?
- Is the patient's gait affected?
- Obvious swollen or deformed joint(s)?
- Is the patient having trouble getting up and down stairs?

Listen

- Have symptoms worsened?
- Are symptoms limiting ADLs?
- Are symptoms increasing the patient's risk for falling? Other safety issues?
- Associated symptoms?
  - ☐ Fatigue (new or worsening)

Recognize

- Is there a preexisting autoimmune dysfunction?
- Is there a history of prior orthopedic injury, degenerative joint disease, osteoarthritis, or rheumatoid arthritis?
- Other immune-related adverse effects
- Three subtypes of inflammatory arthritis associated with checkpoint inhibitors
  - ☐ Polyarthritis, similar to rheumatoid arthritis
  - ☐ True reactive arthritis with conjunctivitis, urethritis, and oligoarthritis
  - ☐ Subtype similar to seronegative spondyloarthritis with inflammatory back pain and predominantly larger joint involvement

GRADING TOXICITY: ARTHRALGIA

A disorder characterized by a sensation of marked discomfort in a joint

Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (potentially life-threatening)	Grade 5 (death)
■ Mild pain	■ Moderate pain; limiting instrumental ADLs	■ Severe pain; limiting self-care ADLs		

GRADING TOXICITY: ARTHRITIS

A disorder characterized by inflammation involving a joint

Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (potentially life-threatening)	Grade 5 (death)
■ Mild pain with inflammation, erythema, or joint swelling	■ Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADLs	■ Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self-care ADLs		

MANAGEMENT

Overall strategy

- Assess for other etiologies, such as lytic or osseous metastasis.
- Early intervention to maintain or improve physical function and impact on quality of life; symptom control through the treatment of inflammation and pain is often achieved with NSAIDs, corticosteroids, and other adjunct therapies.

Prevention

- No known interventions

Continued on the next page

APPENDIX I. *(CONTINUED)*

CARE STEP PATHWAY FOR MANAGEMENT OF ARTHRALGIAS AND ARTHRITIS

MANAGEMENT BY GRADE

Grade 1 (mild)

- ■ Anticipate immunotherapy to continue.
- ■ Encourage physical activity.
  - ☐ 30 minutes of low- to moderate-intensity physical activity five days per week can improve physical conditioning and sleep and decrease pain perception.
  - ☐ For physically inactive patients, advise supervised exercise and resistance training.
  - ☐ Other options: yoga, tai chi, Qigong, Pilates, aquatic exercise, focused dance program
- ■ Anticipate use of analgesia.
  - ☐ Low-dose NSAIDs, topical (diclofenac gel or patch; for localized, limited, superficial joint inflammation or patients who cannot tolerate oral NSAIDs) and oral (ibuprofen, naproxen, celecoxib); provide guidance on proper administration.
- ■ Assess patient and family understanding of recommendations and rationale.
  - ☐ Identify barriers to adherence.

If symptoms do not improve in four to six weeks, escalate to the next level of therapy.

Grade 2 (moderate)

- ■ Ipilimumab to be withheld for any grade 2 event (until grade 0 or 1) and discontinued for events persisting six or more weeks or inability to reduce steroid dose to 7.5 mg prednisone or equivalent per day
- ■ Dose of pembrolizumab or nivolumab to be held to avoid making symptoms worse
- ■ Pembrolizumab or nivolumab to be discontinued for grade 2 events persisting 12 or more weeks
- ■ Continue to encourage physical activity.
- ■ Anticipate use of analgesia.
  - ☐ NSAIDs (oral NSAIDs include ibuprofen, naproxen, celecoxib); provide anticipatory guidance on proper administration.
- ■ Anticipate referral to rheumatology for collaborative management and consideration of adjunct treatment.
- ■ Anticipate previsit assessment: complete blood count, erythrocyte sedimentation rate, C-reactive protein, blood urea nitrogen/creatinine and aminotransferases, antinuclear antibody, rheumatoid factor

Grade 2 *(continued)*

- ☐ Intraarticular steroids to be used for significant symptomatic joint(s)
- ☐ Low-dose corticosteroids (0.5 – 1 mg/kg per day) to be used (anticipatory guidance should be provided on proper administration; duration of corticosteroid therapy is usually limited, lasting about four to six weeks, with possible resolution of symptoms within weeks to months of treatment)
- ■ Assess patient and family understanding of toxicity and rationale for treatment hold (if applicable).
  - ☐ Identify barriers to adherence.

If symptoms do not improve in four to six weeks, escalate to the next level of therapy.

Grades 3–4 (severe or life-threatening)

- ■ Pembrolizumab or nivolumab to be withheld for first occurrence of grade 3 or 4 event and discontinued if the following occur:
  - ☐ Grade 3 or 4 event recurs
  - ☐ Persists 12 or more weeks
- ■ Ipilimumab to be discontinued for any grade 3 or 4 event
- ■ High-dose steroids (1–1.5 mg/kg per day in divided doses)
  - ☐ Anticipatory guidance on proper administration should be provided.
  - ☐ Onset of action is rapid (typically within days)
- ■ Anticipate referral to rheumatology for collaborative management and consideration of adjunct treatment.
  - ☐ Nonbiologic agents are more likely to be recommended; conventional synthetic DMARDs, which have a delayed effect and take weeks to work, include methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide.

Grades 3–4 *(continued)*

- ☐ Biologic agents are less likely to be recommended; they include biologic DMARDs, tumor necrosis factor inhibitors (infliximab, etanercept, adalimumab, golimumab, certolizumab pegol), and anti B-cell agents, which are CD-20 blocking (rituximab).
- ☐ Agents not advised include the following: interleukin-6 receptor blocking agent (tocilizumab) and Janus kinase inhibitors (tofacitinib) because of risk of colonic perforation; T-cell co-stimulation inhibitor (abatacept) because it directly opposes the mechanism of checkpoint blockade agents
- ■ Assess patient and family understanding of toxicity and rationale for treatment discontinuation.
  - ☐ Identify barriers to adherence, specifically compliance with medication and physical activity.
- ■ Sulfasalazine is associated with rash; do not use in patients with history of or current treatment-related dermatitis.

NURSING IMPLEMENTATION

- Identify high-risk individuals and those with underlying autoimmune dysfunction.
- Educate patients that arthralgias and arthritis are the most commonly reported rheumatic and musculoskeletal immune-related adverse events with checkpoint inhibitors.
- Arthritis-like symptoms can range from mild, which are managed well with NSAIDs and low-dose corticosteroids, to severe and erosive, which require multiple immunosuppressant medications.
- Anticipate that the steroid requirements to manage arthralgias can be much higher (as much as 1.5 mg/kg per day) than typically required to manage classic inflammatory arthritis.
- Educate patients that symptoms can persist beyond treatment completion or discontinuation.

RED FLAGS

- Risk of fall because of mobility issue

ADLs—activities of daily living; DMARD—disease-modifying antirheumatic drug; NSAID—nonsteroidal anti-inflammatory drug
Note. Based on information from Bristol-Myers Squibb, 2017a, 2017b; Cappelli, Naidoo, et al., 2017; Cappelli, Shah, et al., 2017; Durham et al., 2015; Merck, 2017; National Cancer Institute, 2010.

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APPENDIX J.

CARE STEP PATHWAY FOR MANAGEMENT OF NEUROPATHY: MOTOR OR SENSORY NERVE IMPAIRMENT OR DAMAGE

NURSING ASSESSMENT

Look

- Does the patient appear weak?
- Does the patient appear uncomfortable?
- Altered ambulation or general movement?
- If muscular weakness, any respiratory difficulties?

Listen

- Reported weakness (unilateral or bilateral)?
- Reported new or worsened pain, numbness, or tingling?
- Reported difficulty walking or holding items?

Recognize

- Motor deficits
- Sensory deficits
- Mental status changes
- Paresthesias
- Laboratory values
- Does the patient have diabetes mellitus?
- Are there neurologic symptoms?
- Results of prior imaging
  - ☐ Metastases to spinal cord
  - ☐ Other metastases that may cause symptoms

GRADING TOXICITY: NEUROPATHY

Grade 1 (mild)

- Peripheral motor: asymptomatic; clinical or diagnostic observations only; no intervention indicated
- Peripheral sensory: asymptomatic; loss of deep tendon reflexes or paresthesia

Grade 2 (moderate)

- Peripheral motor: moderate symptoms; limiting ADLs
- Peripheral sensory: moderate symptoms; limiting ADLs

Grade 3 (severe)

- Peripheral motor: severe symptoms; limiting self-care ADLs; requires assistive devices
- Peripheral sensory: severe symptoms; limiting self-care ADLs

Grade 4 (potentially life-threatening)

- Peripheral motor: life-threatening, urgent intervention indicated
- Life-threatening; urgent intervention indicated

Grade 5 (death)

MANAGEMENT

Overall strategy

- Rule out infectious, noninfectious, and disease-related etiologies.
- High-dose steroids (1-2 mg/kg prednisone or equivalent per day in divided doses) to be used
- Ipilimumab to be withheld for grade 2 event, nivolumab for first occurrence of grade 3 event, and pembrolizumab based on disease severity; ipilimumab to be discontinued for grade 2 events persisting six or more weeks or inability to reduce steroid dose to 7.5 mg or less prednisone or equivalent per day; pembrolizumab or nivolumab to be discontinued for grade 3 or 4 events that recur or persist 12 or more weeks, or inability to reduce steroid dose to 10 mg or less prednisone or equivalent per day
- Neurology consultation
  - ☐ Consideration of electromyelogram and nerve conduction tests
  - ☐ Immune globulin infusions
  - ☐ Plasmapheresis
- Taper steroids slowly for at least four weeks once symptoms improve.
- If needed, obtain physical therapy or occupational therapy consult (for functional assessment and to evaluate safety of patient at home).
- Supportive medications for symptomatic management

NURSING IMPLEMENTATION

- Compare baseline assessment; grade and document neuropathy and etiology (diabetic, medication, vascular, chemotherapy).
- Early identification and evaluation of patient symptoms
- Early intervention with laboratory work and office visit if neuropathy symptoms suspected
- Steroid taper instructions and calendar as a guide but not an absolute
  - ☐ Taper should consider patient's current symptom profile.
  - ☐ Close follow-up in person or by telephone, based on individual need and symptomatology
  - ☐ Anti-acid therapy daily as gastric ulcer prevention while on steroids
  - ☐ Review steroid medication side effects: mood changes (anger, reactive, hyperaware, euphoric, mania); increased appetite; interrupted sleep; oral thrush; fluid retention)
  - ☐ Be alert to recurring symptoms as steroids taper down and report them (taper may need to be adjusted).
- Long-term high-dose steroids
  - ☐ Consider antimicrobial prophylaxis for pneumocystis pneumonia.
  - ☐ Consider additional antiviral and antifungal coverage.

RED FLAGS

- Guillain-Barré syndrome
- Myasthenia gravis

ADLs—activities of daily living

Note. Based on information from Bristol-Myers Squibb, 2017a, 2017b; Kumar et al., 2017; Merck, 2017; National Cancer Institute, 2010; Spain et al., 2016.

APPENDIX K.

CARE STEP PATHWAY FOR MANAGEMENT OF NEPHRITIS: INFLAMMATION OF THE KIDNEYS

NURSING ASSESSMENT

Look

- Does the patient appear uncomfortable?
- Does the patient look ill?

Listen

- Has there been change in urination?
  - ☐ Urine color
  - ☐ Frequency
- How much fluid is the patient taking in?
- Are associated symptoms present?
  - ☐ Nausea
  - ☐ Headache
  - ☐ Malaise
  - ☐ Lung edema
- Are there symptoms concerning for the following?
  - ☐ Urinary tract infection
  - ☐ Pyelonephritis
  - ☐ Worsening congestive heart failure
- Are symptoms limiting ADLs?
- Current or recent use of nephrotoxic medications (prescribed and over-the-counter) and other agents?
  - ☐ NSAIDs
  - ☐ Antibiotics
  - ☐ Contrast media or other nephrotoxic agents (contrast dye, aminoglycosides, proton pump inhibitor)?

Recognize

- Laboratory abnormalities (elevated creatinine, electrolyte abnormalities)
- Urinalysis abnormalities (casts)
- Abdominal or pelvic disease that could be causing symptoms
- Prior history of renal compromise
- Other immune-related adverse effects
- Presence of current or prior immune-mediated toxicities, including rhabdomyolysis
- Is patient volume depleted?

GRADING TOXICITY: ACUTE KIDNEY INJURY, ELEVATED CREATININE

A disorder characterized by the acute loss of renal function that is traditionally classified as prerenal, renal, and postrenal

Grade 1 (mild)

- Creatinine level greater than 0.3 mg/dl; creatinine greater than 1.5 times ULN but less than or equal to 2 times ULN

Grade 2 (moderate)

- Creatinine greater than 2 times and less than or equal to 3 times ULN

Grade 3 (severe)

- Creatinine greater than 3 times ULN or greater than 4 mg/dl; hospitalization indicated

Grade 4 (potentially life-threatening)

- Life-threatening consequences; dialysis indicated

Grade 5 (death)

MANAGEMENT

Overall strategy

- Assess for other etiologies, such as infection.
- Eliminate potentially nephrotoxic medications.
- Ensure adequate hydration daily.
- Evaluate for progressive kidney, adrenal, and pelvic metastases that may be contributing to kidney dysfunction.
- Early intervention to maintain or improve physical function and impact on quality of life

ADLs—activities of daily living; NSAID—nonsteroidal anti-inflammatory drug; PD-1—programmed cell death protein 1; ULN—upper limit of normal

Note. Based on information from Bristol-Myers Squibb, 2017a, 2017b; Kähler et al., 2016; Kumar et al., 2017; Merck, 2017; National Cancer Institute, 2010; Rassy et al., 2016; Spain et al., 2016.

MANAGEMENT BY GRADE

Mild elevation in creatinine (grade 1)

- Anticipate immunotherapy to continue.
- Perform detailed review of concomitant medications (prescribed and over-the-counter), including herbals and vitamins, anticipating possible discontinuation of nephrotoxic agents.
- Avoid or minimize addition of nephrotoxic agents, such as contrast media for radiology tests.
- Anticipate close monitoring of creatinine (weekly).
- Educate patient and family on importance of adequate daily hydration, and set individualized hydration goals.
- Review symptoms to watch for with patient and family, and remember to assess at subsequent visits.

Moderate elevation in creatinine (grade 2)

- Ipilimumab to be withheld for any grade 2 event (until grade 0 or 1 and discontinued for events persisting six or more weeks or inability to reduce steroid dose to 7.5 mg prednisone per day)
- Pembrolizumab or nivolumab to be withheld for grade 2 events persisting 12 or more weeks or inability to reduce steroid dose to 10 mg or less prednisone or equivalent per day
- Anticipate increase in frequency of creatinine monitoring (every two to three days until improvement).
- Immunosuppressive medications to be initiated to treat immune-mediated nephritis
  - ☐ Systemic corticosteroids (e.g., prednisone) 0.5–1 mg/kg per day until symptoms improve to baseline, followed by slow taper for at least one month
  - ☐ Anticipate increase in corticosteroid dosing (treat as if grade 3 nephritis) if creatinine does not improve within 48–72 hours.
  - ☐ Anticipate use of additional supportive care medications.
- On symptom resolution to patient baseline or grade 1, begin to taper corticosteroid dose slowly for one month.
- Anticipatory guidance on proper administration
- Anticipate the use of IV fluid to ensure hydration.
- Anticipate that nephrology consultation may be initiated by the provider.
- Assess patient and family understanding of recommendations and rationale.
  - ☐ Identify barriers to adherence.

Moderate (grade 3) and severe (grade 4)

- Pembrolizumab or nivolumab to be withheld for first occurrence of grade 3 or 4 event and discontinued if the following occur:
  - ☐ Grade 3 or 4 event recurs
  - ☐ Persists for 12 or more weeks
  - ☐ Requires more than 10 mg prednisone or equivalent per day for more than 12 weeks
- Ipilimumab to be discontinued for any grade 3 or 4 event
- Immunosuppressive medications to be initiated to treat immune-mediated nephritis
  - ☐ Corticosteroids (e.g., prednisone 1–2 mg/kg per day in divided doses) until symptoms improve to baseline, then slow taper for at least one month
  - ☐ If symptoms do not improve within 48–72 hours, additional immunosuppressive medications will be considered.
- Anticipate that nephrology consultation will be initiated by the provider.
- Anticipate that renal biopsy will be considered.
- Hemodialysis may be considered.
- Anticipate possible hospital admission for grade 4 elevations in creatinine or in patients with multiple comorbidities.

NURSING IMPLEMENTATION

- Identify individuals with preexisting renal dysfunction prior to initiating immunotherapy. Ensure baseline creatinine has been obtained.
- Check kidney function prior to each dose of immunotherapy.
- Monitor creatinine more frequently if levels appear to be rising and for grade 1 toxicity.
- Educate patients that new urinary symptoms should be reported immediately.
- Anticipate that the steroid requirements to manage immune-mediated nephritis are high (as much as 1–2 mg/kg per day) and that patients will be on corticosteroid therapy for at least one month.
- Educate patients and family about the rationale for discontinuation of immunotherapy in patients who develop severe nephritis.

RED FLAGS

- Risk of acute onset
- Risk of mortality if unrecognized or treatment is delayed
- The risk of immune-mediated nephritis is greater in patients receiving combination immunotherapy regimens and PD-1 inhibitors.
- In addition to acute interstitial nephritis seen from PD-1 inhibitors, there are case reports of lupus-like nephritis and granulomatous acute interstitial nephritis.