Supportive Care and Management of Treatment-Related Adverse Effects From Immune Checkpoint Inhibitors and Targeted Therapies in Melanoma

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Molecularly targeted agents, and notably, the immune checkpoint inhibitors, are now considered standard therapies for the treatment of advanced melanoma and have forever changed the treatment paradigm for this difficult-to-treat disease. The adverse event profile associated with each class stems from the respective mechanism of action and varies considerably from traditional chemotherapy. By possessing a thorough understanding of the side effects of each agent, oncology advanced practitioners are in pivotal positions to positively influence treatment outcomes. Awareness, vigilant screening, early identification and prompt intervention, as well as providing comprehensive patient and caregiver education are key strategies of toxicity management and enable patients the greatest chance of treatment continuation. This article provides an overview of the spectrum of toxicities associated with immune checkpoint inhibitors. It focuses on the most commonly encountered toxicities and will describe the less common but clinically challenging toxicities. The molecularly targeted agents, including BRAF and MEK inhibitors, will also be reviewed, along with an overview of management strategies for common toxicities. Patient and caregiver resources are included as a reference.

Melanoma has historically been one of most difficult-to-treat cancers, with standard therapies, including chemotherapy and radiotherapy, having never demonstrated a survival advantage. Effective therapies were limited, and most patients diagnosed with advanced melanoma would succumb to their disease. Survival was measured in months and treatments were purely palliative with few exceptions. Prior to the advent of modern immunotherapy, half of the patients who presented with meta-

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static stage IV disease would succumb within a year, and those patients unlucky enough to develop brain metastasis had an even poorer prognosis of only 12 weeks.

REDEFINING TREATMENT STRATEGIES

From this abysmal background arose paradigm-changing therapies on both the immunotherapy and molecular pathway–targeted therapy fronts. It is likely that no other disease has benefitted more from the decades-long research resulting in effective therapies that have redefined the treatment strategies for melanoma. Along the immunotherapy front, discovery of checkpoint pathways within the immune system, combined with the fact that melanoma tumors exploit these very same pathways to evade immunosurveillance, have led to anticheckpoint therapies that derepress these inhibitory pathways, thereby exposing tumors to the full brunt of the body's immune system. Along the targeted therapy front, the discovery of the *BRAF* V600 mutation as a critical driver in the oncogenic process that transforms melanocytes into their malignant phenotype has led to the development of small-molecule inhibitors of the mutant *BRAF*, along with downstream effectors.

Each of these therapies provides highly significant benefit to both the progression-free and overall survival of patients suffering from melanoma. For the first time, response to initial therapy and long-term control of the disease have become a matter of routine expectation instead of the extraordinary event that one would have expected in the past.

TOXICITY COSTS

There are toxicity costs to these benefits. Because of their divergent mechanisms of action, the toxicities associated with these agents not only differ among themselves but differ from traditional chemotherapy and previous immunotherapies. The presentation can be protean, may exhibit a waxing and waning course, and can be confused with disease progression. These effects and the patient's ability to tolerate these effects will have tremendous influence on the course of therapy and the patient's quality of life.

Management is often complex and time consuming, with some patients requiring significant support (Lomax et al., 2017). Care of patients receiving these therapies is unique and requires the expertise of highly educated and skilled providers who possess a thorough understanding of the mechanistic effects associated with these therapies. Moreover, clinicians caring for patients receiving immunotherapies should have a ready assemblage of resources, offering tools, strategies, and interventions to maximize patient care; this includes best practices for telephone triage, a necessary and critical skill when caring for patients receiving immunotherapy. Patient and caregiver education is a major component of care, along with ongoing assessment of adherence and understanding.

SUPPORTING PATIENTS RECEIVING IMMUNOTHERAPY

The current immune checkpoint inhibitors (ICIs) approved for use in patients with advanced melanoma (Table 1) include ipilimumab, nivolumab, pembrolizumab, and a combination regimen of ipilimumab plus nivolumab. Immune checkpoint inhibitors work by blocking pathways called checkpoints. Madden and Hoffner (2017) describe immune checkpoints as "on- or off-regulators." CTLA-4 and PD-1 act as "brakes" for the immune system. Inhibitors of CTLA-4 (ipilimumab) and PD-1 (nivolumab and pembrolizumab) exploit these natural immune pathways. By blocking (inhibiting) the inhibitory action of the immune response, T cells are then able to remain active, enabling immune response. However, this deregulation of the immune system may lead to adverse effects (also referred to as toxicities), which are immune mediated and therefore referred to as immune-mediated adverse events (imAEs) or immune-related adverse events (irAEs). These irAEs are wide ranging in terms of organs affected and severity, and may occur alone or in constellation (Puzanov et al., 2017). Because of the unique mechanism of action of ICIs, overall management differs considerably from other anticancer therapies. For example, unlike chemotherapy, dose reductions are not used; instead, delaying or withholding the agent is advised so as to not potentiate the immune response.

Most toxicities associated with ICIs are mild to moderate in severity and easily managed when identified early (Prieux-Klotz et al., 2017; Puzanov et al., 2017; Roberts, Culleton, Lwin, O'Byrne, &

Table 1. Approved Immune Checkpoint Inhibitors for Melanoma

Indication	Agent	Approved regimen
Adjuvant	Ipilimumab[a]	10 mg/kg IV every 21 days × 4 doses
	Nivolumab[b]	240 mg IV every 14 days **or** 480 mg IV every 28 days until disease recurrence or unacceptable toxicity, for a maximum of 1 year
	Pembrolizumab[b,c]	200 mg IV every 21 days until disease recurrence or unacceptable toxicity, for a maximum of 1 year
Metastatic or unresectable	Ipilimumab	3 mg/kg IV every 21 days × 4 doses
	Nivolumab	240 mg IV every 14 days **or** 480 mg IV every 28 days until disease progression or unacceptable toxicity
	Ipilimumab + nivolumab	3 mg/kg IV every 21 days × 4 doses (ipilimumab) + 1 mg/kg IV every 21 days × 4 doses (nivolumab) followed by nivolumab monotherapy at 240 mg IV every 14 days **or** Nivolumab monotherapy at 480 mg IV every 28 days until disease progression or unacceptable toxicity

Note. IV = intravenously.
[a]Anti–CTLA-4 antibody.
[b]Anti–PD-1 antibody.
[c]Not yet FDA-approved; expected approval by 2019.

Hughes, 2017; Rutkowski, 2018). The most common irAEs affect the skin (rash, pruritus), gastrointestinal organs (diarrhea, colitis, hepatitis), and endocrine systems (thyroiditis, hypophysitis, adrenalitis, diabetes). Neurologic and cardiac irAEs occur with less frequency (Roberts et al., 2017) but may have serious consequences if they are not recognized and promptly treated (Kottschade et al., 2016). Notably, patients with low-grade toxicities can also present clinical challenges, particularly when they negatively impact quality of life.

Due diligence warrants a thoughtful assessment of symptoms (Rubin, in press). Evaluating for other etiology is necessary to ensure proper diagnosis and management. Once an irAE has been recognized, appropriate intervention is based on the severity, or grade of the symptom as defined by the most current version of the National Cancer Institute's (2017) Common Toxicity Criteria for Adverse Events (CTCAE), Version 5.0 (accessible at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50).

This process allows for interpretation of subjective symptoms in an objective manner (Rubin, 2017) by employing a grading system from 1 (mild) to 5 (death) to represent symptoms defined by specific parameters based on the organ system involved (National Cancer Institute, 2017). Grading defines appropriate intervention; however, other factors should also be considered when determining appropriate intervention for an individual patient. Barriers to treatment or adherence, such as lack of physical resources including transportation or a telephone (Madden & Hoffner, 2017), may warrant more conservative management for an individual. Comorbid conditions must be considered, especially those with potential to negatively affect treatment outcomes (e.g., current or prior history of serious mental illness, cognitive deficit, substance abuse, underlying autoimmune disease). In the following pages, this article will provide guidance on how to evaluate and manage specific irAEs.

MANAGEMENT OF CUTANEOUS IMMUNE-RELATED ADVERSE EVENTS

Cutaneous toxicity (dermatitis) is common with ICI therapy. Approximately one third of patients receiving anti–PD-1 therapy (pembrolizumab or nivolumab) and half of patients receiving ipilimumab report some form of dermatitis, but the greatest incidence is seen in individuals receiving

combination ipilimumab and nivolumab, with incidence rates nearing 60% (Champiat et al., 2016; Collins, Chapman, Carter, & Samie, 2017; Puzanov et al., 2017). Dermatitis tends to occur earliest in the treatment course (Collins et al., 2017), on an average of 21 to 42 days from the start of treatment (Curry et al., 2017)

Rash and/or pruritus are the most prevalent of the cutaneous effects; however, a broad range of clinical appearances can be seen, including maculopapular, follicular, pruritic, pustular, vesicular, acneiform, and exfoliative lesions. A pruritic morbilliform (maculopapular) rash (Figure 1) on the trunk and extremities is the most common cutaneous presentation with ipilimumab, while lichenoid reactions (Figure 2) are seen more commonly with PD-1 blockade (Collins et al., 2017).

Unique to melanoma, approximately 8% of patients receiving ICIs develop vitiligo (Puzanov et al., 2017). Most cutaneous irAEs are grade 1 or 2, and managed well with conservative measures such as proactive skin care and use of topical corticosteroids and antihistamines. However, severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported (Brahmer et al., 2018; Kottschade et al., 2016; Puzanov et al., 2017). Such severe toxicity is considered a medical emergency and typically requires hospitalization with an intensive level of care. For this reason, ongoing vigilance is imperative for prompt recognition of red flags, such as extensive or rapidly progressive rash, oral involvement, or other indicators of SJS or TEN.

Evaluation

Review of symptoms (ROS) and physical exam are the primary components necessary to decide on the grade of the irAE. However, grading according to CTCAE is a challenge for skin; instead, severity may be based on body surface area, tolerability, morbidity, and duration (Brahmer et al., 2018). Laboratory data may be indicated and should be determined on an individual basis. Review of

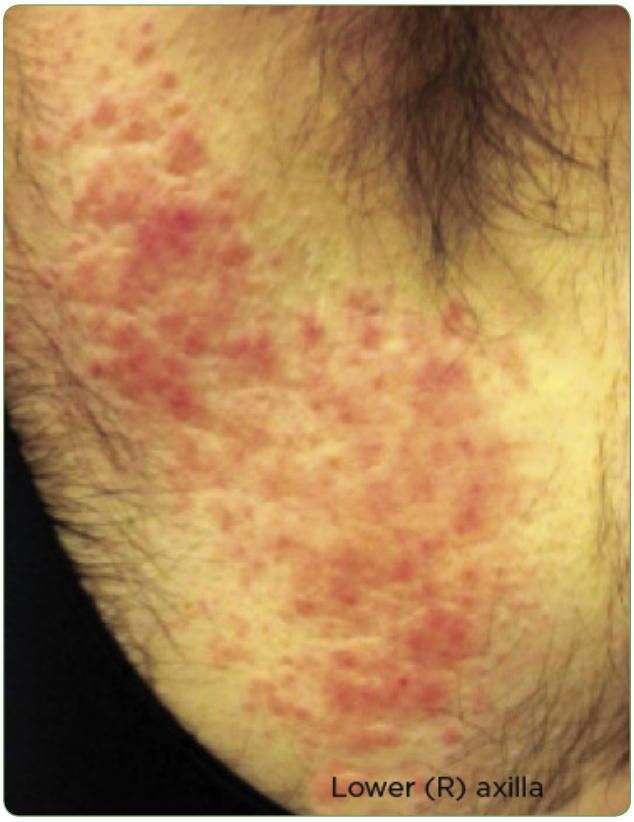

Figure 1. Morbilliform rash from ipilimumab. Photo courtesy of Krista M. Rubin, Massachusetts General Hospital Cancer Center.

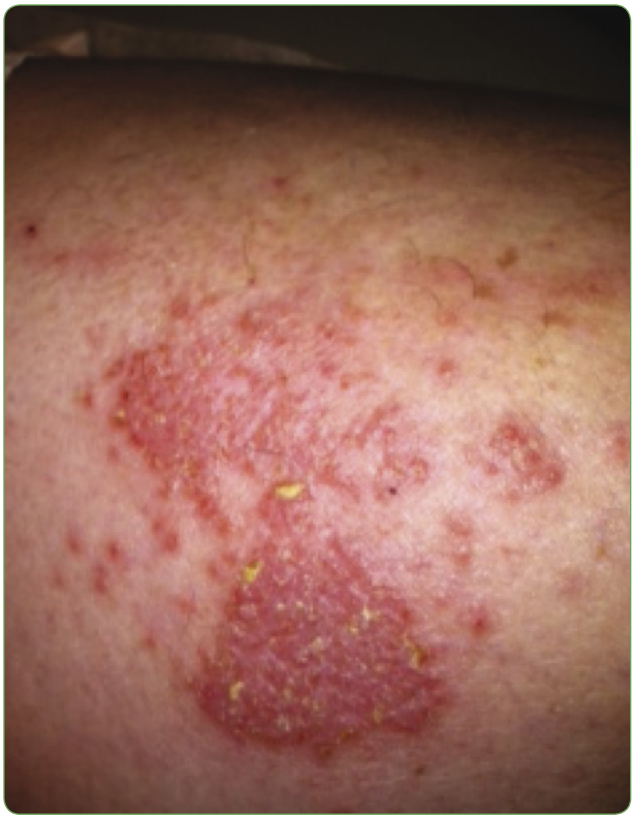

Figure 2. Lichenoid rash from nivolumab. Photo courtesy of Krista M. Rubin, Massachusetts General Hospital Cancer Center.

symptoms should include the impact of symptoms on quality of life, including factors such as the ability to perform activities of daily living, impact on body image (in the case of rash), and ability for an individual to self-manage. Physical exam should include a description of rash or skin lesion(s), extent of body surface area involved, skin integrity, and importantly, whether there is oral involvement (Brahmer et al., 2018).

Management

Proactive prevention strategies should be advised for all patients and should encompass a skin hygiene regimen that promotes hydration, protects from ultraviolet (UV) radiation, and treats any underlying xerosis (Madden & Hoffner, 2017; McGettigan & Rubin, 2017). Prospectively identifying at-risk individuals, including those with preexisting skin or mucosal disorders (psoriasis, eczema, severe xerosis), those with dermatitis from prior immunotherapy, and xerostomia from prior radiation or surgery, is crucial.

Grade 1 toxicity can be managed with topical corticosteroids and/or topical or oral antipruritics. Treatment need not be withheld; however, close surveillance is necessary (Kottschade et al., 2016; Puzanov et al., 2017).

Grade 2 toxicity involves more aggressive management of symptoms and may necessitate withholding treatment. Patients should be monitored weekly. When the toxicity improves to grade 1, treatment can then be considered. Higher grade toxicity or any patient with blisters covering ≥ 1% BSA, a rash with mucosal involvement, a rash involving ≥ 30% BSA, or a rash with skin pain with or without blisters (excluding dermatomal varicella zoster) warrants urgent dermatologic evaluation (Puzanov et al., 2017).

Grade 3 dermatitis warrants holding treatment and starting moderate-dose oral or intravenous (IV) corticosteroids.

Grade 4 symptoms require high-dose IV steroids (methyl)prednisolone (or equivalent) at 1 to 2 mg/kg/day and hospitalization with specialty care. When toxicity improves to grade 2 or less, steroid taper can begin and should extend over at least 4 weeks (Puzanov et al., 2017; Roberts et al., 2017). A grade 4 irAE warrants permanent discontinuation ICIs.

MANAGEMENT OF GASTROINTESTINAL IMMUNE-RELATED ADVERSE EVENTS

The primary gastrointestinal-related irAEs are diarrhea and colitis. Diarrhea is one of the most frequently reported irAEs in patients receiving ICIs (Puzanov et al., 2017). Just as nausea and vomiting are distinct entities, so are diarrhea and colitis. When diarrhea is accompanied by abdominal pain or the presence of mucus and/or blood in the stool, or rectal bleeding, symptoms are suggestive of colitis (Madden & Hoffner, 2017; Prieux-Klotz et al., 2017; Puzanov et al., 2017). However, it is imperative for advanced practitioners to recognize that colitis can occur in the absence of diarrhea, and it is important to distinguish among these two often distinct entities.

The CTCAE Version 5 defines diarrhea as a "disorder characterized by an increase in frequency and/or loose or watery bowel movements," while the definition of colitis is "a disorder characterized by inflammation of the colon." In many patients, diarrhea is the only presenting symptom and may be self-limiting; however, diarrhea may also be just a part of ICI-induced colitis (Wang et al., 2018). Because colitis can progress to severe or life-threatening forms, hospitalization is often required with gastrointestinal consultation, and surgical consultation is needed if peritoneal signs are noted (e.g., poor appetite, nausea, abdominal pain or tenderness aggravated by movement, distension) and perforation is suspected (Madden & Hoffner, 2017).

Rates of diarrhea and colitis are higher in patients treated with ipilimumab (23%–33%) compared to rates seen with anti–PD-1 blockade (≤ 19%), yet the highest rates are seen with the combination anti–CTLA-4 and anti–PD-1 regimen (44%; Kottschade et al., 2016; Prieux-Klotz et al., 2017; Puzanov et al., 2017; Roberts et al., 2017). Diarrhea and colitis are the most common reasons for immunotherapy treatment discontinuation (Roberts et al., 2017); therefore, directed and focused assessments to pick up seemingly insignificant patient reports may also uncover additional symptoms suggestive of early toxicity (McGettigan & Rubin, 2017). Diarrhea and colitis occur with a median of 6 weeks into ICI treatment, but can start much later, which is why suspicion for

immune-mediated colitis should remain high for the first several months (Prieux-Klotz et al., 2017). Early management of ICI-induced diarrhea may prevent severe complications and decrease rates of hospitalization (Prieux-Klotz et al., 2017; Roberts et al., 2017) .

Evaluation

Infectious etiology should be ruled out for all patients, regardless of grade, with stool sample screening for *Clostridium difficile* toxin and other enteric pathogens and serum cytomegalovirus polymerase chain reaction (PCR) stool ova and parasites. Inflammatory markers (fecal leukocytes or lactoferrin, fecal calprotectin) and fecal occult blood testing may help indicate whether there is an inflammatory process underlying the diarrhea (Kottschade et al., 2016; Puzanov et al., 2017). Differential diagnoses such as ICI-induced celiac disease and immune hyperthyroidism should also be considered (Prieux-Klotz et al., 2017). Assessing severity in side-effect graduation during immune-mediated colitis is based on a patient's general condition (Eastern Cooperative Oncology Group performance status), increase in number of stools per day over baseline, presence of nocturnal stools, incontinence, rectal bleeding, abdominal pain, intensity, and the use of antidiarrheal therapy (Prieux-Klotz et al., 2017).

Colonoscopy is the most accurate means of evaluating the extent and severity of colitis and is recommended in appropriate cases since recent data suggest that the presence of ulceration on endoscopy predicts steroid-refractory disease (Puzanov et al., 2017); however, in some instances, rectosigmoidoscopy is appropriate and offers the advantage of minimal preparation, minimal sedation, and more rapid diagnosis (Prieux-Klotz et al., 2017).

Management

Management of ICI-induced colitis is varied, with no established standard of care and significant variation in practice (Mir, Shaw, & Nathan, 2017). In general, current management initially involves CTCAE assessment of toxicity with exclusion of contributing causes, such as infection or bowel perforation. In cases of abdominal symptoms suggesting peritonitis, or any grade 3 or 4 diarrhea, abdominal computed tomography scanning seeking colonic perforation must be performed. If there is no argument for gastrointestinal perforation, endoscopic assessment should be performed within a short period of time to rule out any other differential diagnosis. Mild symptoms are managed conservatively and in most cases treatment with the ICI can continue. Alternatively, the ICI can be held temporarily, and if symptoms do not progress, treatment can resume (Brahmer et al., 2018; Prieux-Klotz et al., 2017). Patients should be encouraged to follow a low fiber, bland diet, and adequate hydration should be encouraged (Prieux-Klotz et al., 2017; Roberts et al., 2017). Recommendation for use of antidiarrhea medications such as loperamide is limited to patients with grade 1 diarrhea and only *after* infections etiology (e.g., *C. difficile*) is ruled out (Brahmer et al., 2018; Prieux-Klotz et al., 2017; Roberts et al., 2017). In fact, Prieux-Klotz and colleagues (2017) discourage the use of any antidiarrheal agents even in the absence of infection, claiming such use has the potential to mask higher-grade toxicities and could be dangerous in the case of severe colitis.

Grade 2 symptoms warrant withholding the ICI until symptoms resolve to ≤ grade 1 (Brahmer et al., 2018) and initiating symptomatic management as described for grade 1. Patients should be monitored closely, with at least weekly (if not more frequently) phone call updates or weekly clinic visits. For grade 2 diarrhea, treatment should be held and oral corticosteroids initiated (e.g., 0.5–1 mg/kg/day prednisolone or equivalent). Gastroenterology consult should also be considered (Brahmer et al., 2018; Kottschade et al., 2016). High-grade toxicity requires higher doses of corticosteroids (e.g., 1–2 mg/kg/day prednisone or equivalent). Generally, these patients require hospitalization, intravenous hydration, and close monitoring. In case of deterioration despite corticosteroids, infliximab (anti-TNFα) should be considered with a single dose of 5 mg/kg. Once symptoms begin to improve, corticosteroids can begin to be tapered (or changed from IV to oral route and then tapered over a period of at least a month). Once tapered to 10 mg/day of prednisone or equivalent, and if the patient remains symptom-free, restarting treatment could be con-

sidered. Grade 4 requires permanent discontinuation of the ICI.

MANAGEMENT OF HEPATITIS FROM IMMUNOTHERAPY

Hepatotoxicity, specifically inflammation of liver tissue (autoimmune hepatitis), has been reported with ICIs. Presentation is typically an asymptomatic elevation of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), and is less frequently accompanied by fever and malaise (Hassel et al., 2017; Puzanov et al., 2017; Roberts et al., 2017). Hepatotoxicity has been reported to occur in 2% to 10% of patients treated with ipilimumab, nivolumab, and pembrolizumab monotherapy, and notably, the incidence with combination ipilimumab and nivolumab is reported as 25% to 30% for all-grade hepatitis, with about half of the cases being grade 3. The onset of symptoms occurs within the first 6 to 12 weeks from treatment start (Brahmer et al., 2018; Hassel et al., 2017; Robert et al., 2015).

Evaluation

Asymptomatic elevations in liver function tests (LFTs) are often noted on routine bloodwork. However, patients may also present with vague abdominal pain, increased fatigue, and jaundice.

Management

Liver function tests should be obtained at baseline and prior to each infusion, including AST, ALT, and bilirubin. Treatment can continue for grade 1 LFT elevations. Patient counseling should include minimizing hepatoxic agents such as alcohol and acetaminophen, and LFTs should be monitored closely with serial LFTs once or twice weekly. Other causes of liver damage such as viral infection, alcohol, other medications, or cancer progression should be excluded, and other thromboembolic and outflow obstructive etiology should also be excluded through imaging (Puzanov et al., 2017). Grade 2 or higher LFT abnormality in which progressive and/or new liver disease has been ruled out warrants withholding the immunotherapy and initiating low- to moderate-dose corticosteroids (0.5 to 1 mg/kg/daily prednisone or equivalent; Brahmer et al., 2018; Kottschade et al., 2016). The frequency of LFT monitoring should increase with the grade.

MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS IN THE ENDOCRINE SYSTEM

Endocrine-related toxicities, referred to as endocrinopathies, are a distinct set of treatment-related adverse events that are unique and outside of the typical side-effect profile of chemotherapies. They occur in up to one third of patients treated with ICIs (Alessandrino, Shah, & Ramaiya, 2018) and include thyroid dysfunction, hypophysitis, primary adrenal insufficiency, and autoimmune type 1 diabetes mellitus. Endocrinopathies tend to appear after the sixth or seventh week of treatment, with a median time to onset of 7 to 20 weeks (González-Rodriguez & Rodriguez-Abreu, 2016). Awareness is key. Moreover, if not identified and managed promptly, symptoms may progress and pose serious, possibly life-threatening consequences as in the cases of adrenal insufficiency or adrenal crisis. Unique from other irAEs, endocrinopathies typically do not resolve because the function of the gland rarely recovers. As such, lifelong hormone replacement of the affected organ is required.

Thyroid dysfunction occurs commonly in patients treated with ICIs with rates, including subclinical dysfunction, occurring in up to 50% of patients (Morganstein et al., 2017). It is seen more frequently in patients treated with anti–PD-1 agents and is more common in females (Alessandrino et al., 2018; González-Rodriguez & Rodriguez-Abreu, 2016). However, the greatest incidence is reported in patients treated with combination anti–PD-1 plus anti–CTLA-4 regimens. Thyroiditis manifests most commonly as hypothyroidism and less commonly as hyperthyroidism. The median onset of hypothyroidism ranges from 1 to 5 months, sometimes following a brief period of hyperthyroidism. Treatment of hypothyroidism involves replacing thyroid hormone (e.g., levothyroxine), while hyperthyroidism is managed with β-blockers in symptomatic cases, followed by levothyroxine for hypothyroidism that develops later (Sznol et al., 2017). Notably, immunotherapy-induced thyroid dysfunction has been associated with improved outcomes (Iglesias, 2018).

Evaluation

Physical exam, ROS, and laboratory data aid in the diagnosis. Baseline thyroid-stimulating hor-

mone (TSH) should be obtained on all patients. Because thyroid endocrinopathies are most commonly asymptomatic and detected by routine laboratory surveillance, regular testing for thyroid dysfunction (TSH and free thyroxine [FT4]) should be performed every 4 to 6 weeks (Brahmer et al., 2018). A high TSH and low FT4 is indicative of primary hypothyroidism, while a low TSH in the setting of high FT4 indicates thyrotoxicosis (Barroso-Sousa et al., 2018). Thyroiditis is usually transient and resolves in a few weeeks to primary hypothyroidism or, in some instances, back to normal (Brahmer et al., 2018). Thyroiditis can present with sore throat, tachycardia, palpitations, and other symptoms of hyperthyroidism (Sznol et al., 2017). Risk factors for hyperthyroidism include male sex and age > 64 (Morganstein et al., 2017) .

Management

Immune checkpoint inhibitor–associated hypothyroidism is treated with thyroid replacement. For patients without risk factors, full replacement can be estimated with an ideal body weight–based dose of approximately 1.2 to 1.6 µg/kg/day (Brahmer et al., 2018; Kottschade et al., 2016), and for the elderly, those with cardiac disease, or fragile patients with multiple comorbidities, a starting dose of 25 to 50 µg is advised, and can be titrated upwards based on repeat TSH and FT4 (Barroso-Sousa et al., 2018; Brahmer et al., 2018). Asymptomatic thyrotoxicosis generally does not require treatment; however, patients with symptomatic thyrotoxicosis may require treatment with a β-blocker or other agent to block peripheral thyroid hormone action until the thyroiditis converts over a period of weeks to a euthyroid or hypothyroid state (Sznol et al., 2017). Importantly, it is not necessary to routinely discontinue ICI therapy in patients who develop ICI-related thyroid disorders (Barroso-Sousa et al., 2018).

MANAGEMENT OF HYPOPHYSITIS FROM IMMUNOTHERAPY

Inflammation of the pituitary gland is reported primarily with ipilimumab and appears to be dose dependent (Iglesias, 2018). Hypophysitis with anti–PD-1 monotherapy is exceedingly rare, and when anti–CTLA-4 and anti–PD-1 are combined, the incidence increases; yet interestingly, the severity is less (Igesias, 2018). The time to onset is early at approximately 2 months (Iglesias, 2018). The main risk factor for developing hypophysitis in patients treated with ipilimumab are male sex and age > 60 (Faje et al., 2014), and the mean time to onset for nivolumab is 5.5 months and 3.5 months for pembrolizumab (Torino, Corsello, & Salvatori, 2016).

Hypophysitis can be challenging to recognize as signs and symptoms are often subtle and nonspecific in presentation (Alessandrino et al., 2018). Key presenting symptoms include headache, weakness, and fatigue (Alessandrino et al., 2018; Faje et al., 2014; Kottschade et al., 2016; Sznol et al., 2017; Torino et al., 2016); however, it is vital for the advanced practitioner to recognize that ICI-induced hypophysitis can present as either panhypopituitarism or isolated anterior pituitary hormone deficiency, with or without pituitary enlargement (Barroso-Sousa et al., 2018). As such, presenting symptoms can vary based on location and degree of pituitary involvement reflecting specific hormonal deficiency (Alessandrino et al., 2018), including neuropsychiatric symptoms (confusion, hallucinations, memory loss, and labile mood), visual impairment, insomnia, anorexia, diarrhea, cold intolerance, chills, erectile dysfunction, and loss of libido (Torino et al., 2016). Hyponatremia is commonly seen, most likely secondary to adrenal insufficiency (Barroso-Sousa et al., 2018).

Evaluation

For all patients treated with ICIs, especially if the regimen includes ipilimumab, if the patient presents with headaches, fatigue, and hyponatremia, and especially if it is between the second and fourth doses, autoimmune hypophysitis should be ruled out. Furthermore, hypophysitis should be suspected when a patient presents with central hypothyroidism (low FT4 with low or inappropriately normal levels of TSH; Barroso-Sousa et al., 2018; Kottschade et al., 2016).

Bloodwork measuring pituitary hormones as well as target tissue hormones should be obtained, including: cortisol, adrenocorticotropic hormone (ACTH), follicle-stimulating hormone,

luteinizing hormone, FT4, free triiodothyronine, prolactin, testosterone in men, and estradiol in women (Brahmer et al., 2018; González-Rodriguez & Rodriguez-Abreu, 2016). Magnetic resonance imaging is the modality of choice to evaluate for enlargement of the pituitary, which can be seen in approximately 75% of cases (Kottschade et al., 2016). It is important to note that some patients with hypophysitis can present with signs of adrenal crisis, a life-threatening endocrine disturbance resulting from either primary or secondary adrenal insufficiency (Barroso-Sousa et al., 2018).

Management

When hypophysitis is suspected, ICI therapy should be withheld during the initial inflammatory period. Treatment of the acute inflammatory phase of hypophysitis includes steroids (usually at 1–2 mg/kg) until the acute symptoms have resolved. Discontinuing treatment is typically not necessary, and usually treatment can be reinstated when the patient recovers from the acute symptoms and is on physiologic replacement dosing of steroids (Kottschade et al., 2016).

Endocrine consultation and comanagement is recommended for long-term management due to the fact that, in a manner unique from other irAEs, endocrinopathies typically do not resolve because the function of the gland rarely recovers. Lifelong hormone replacement is therefore required (Iglesias, 2018; Sznol et al., 2017). Patient counseling must be provided regarding "sick day rules" of steroid dosing for medical procedures or acute illness (fever, or cases of nausea, vomiting, and diarrhea), and patients should be encouraged to obtain a medical alert necklace or bracelet (Sznol et al., 2017). In most cases, providing patients with a prescription and instructions for use of hydrocortisone emergency injections may be beneficial (González-Rodriguez & Rodriguez-Abreu, 2016). It is also prudent to assess for barriers to medication adherence (e.g., inability to take oral medication, cognitive dysfunction, lack of caregiver resources, and financial problems that may impact inability to afford medication). Due to the risk of adrenal crisis, medication adherence is critical (González-Rodriguez & Rodriguez-Abreu, 2016).

MANAGEMENT OF PRIMARY ADRENAL INSUFFICIENCY FROM IMMUNOTHERAPY

Primary adrenal insufficiency associated with ICIs is rare, with a reported incidence of 0.7%; however, the reported rate among patients treated with combination anti–PD-1 and anti–CTLA-4 is much higher, at 4.2% (Barroso-Sousa et al., 2018). It is important to recognize that adrenal insufficiency may be either primary or secondary, related to hypopituitarism with reduced levels of ACTH, and possible involvement of multiple pituitary axes (Alessandrino et al., 2018). Clinically, primary adrenal insufficiency is usually manifested as asthenia (Iglesias, 2018) and may occasionally cause chronic hyponatremia. Acutely ill patients with symptoms or signs suggestive of primary adrenal insufficiency, including volume depletion, hypotension, hyponatremia, hyperkalemia, fever, abdominal pain, hyperpigmentation, or hypoglycemia, should have diagnostic tests performed to establish this diagnosis (Barroso-Sousa et al., 2018).

Evaluation

The preferred method with which to assess the pituitary-adrenal axis is to measure morning fasting paired ACTH and cortisol (Barroso-Sousa et al., 2018). Unless the serum cortisol is very low (< 3 µg/dL), an ACTH stimulation test can be performed to confirm the diagnosis of primary adrenal insufficiency. It also is recommended to monitor serum glucose and electrolytes (Barroso-Sousa et al., 2018). Although primary adrenal insufficiency presents with low cortisol and high ACTH levels, central pituitary disorders result in low serum levels of both cortisol and ACTH. Imaging presentation can be subtle, and careful inspection of adrenal glands should be performed in any patient treated with ICIs (Barroso-Sousa et al., 2018; Iglesias, 2018; Sznol et al., 2017).

Management

Treatment with hydrocortisone and fludrocortisone controls symptoms, reverses hyponatremia, and allows continued immunotherapy treatment. It should be noted that if adrenal dysfunction is present, cortisol must always be replaced before thyroid hormone therapy is initiated. As noted above, patient education and assessing compli-

ance with medication regimens is a must, given the life-threating risk of adrenal crisis.

LESS COMMON BUT SERIOUS IMMUNE-RELATED ADVERSE EVENTS

While irAEs can affect any tissue or organ system, there are select and rare but potentially serious or life-threatening irAEs that warrant mentioning. This article will not provide a comprehensive description; instead, they will be highlighted in an effort to increase advanced practitioner awareness.

Cardiac Immune-Related Adverse Events

Immune checkpoint inhibitor–associated myocarditis appears to be a class effect, and the risk of myocarditis seems to be higher with combination checkpoint inhibitor regimens (Neilan et al., 2018). The true incidence of ICI-associated myocarditis may be underestimated due to the wide range of clinical presentations, challenges in diagnosis, general lack of awareness of this condition (Neilan et al., 2018), and minimal cardiac monitoring (including obtaining troponin, a sensitive and specific marker of cardiotoxicity; Varricchi et al., 2017). For patients with any suspicion of myocarditis, initial workup should include troponin, electrocardiography, N-terminal pro B-type natriuretic peptide (NT-proBNP), and possibly an echocardiogram. Urgent cardiology consult is warranted. Further assessment with cardiac magnetic resonance imaging, stress test, and even a cardiac biopsy may be required. Management for myocarditis remains consistent with the management of other irAEs and should include corticosteroids and other recommendations as set forth by cardiology (Varricchi et al., 2017). Immune checkpoint inhibitor treatment should be withheld during evaluation and may require permanent discontinuation depending on the severity (Rubin, in press).

Pulmonary Immune-Related Adverse Events

Although uncommon, pneumonitis is a potentially fatal irAE and is a significant cause of treatment discontinuation (Roberts et al., 2017). The overall incidence is < 5%, with high-grade (≥ grade 3) events occurring in 1% to 2% of patients. As with other irAEs, incidence is greater in patients receiving combination PD-1 and CTLA-4 inhibitors (Brahmer et al., 2018; Puzanov et al., 2017; Roberts et al., 2017). The onset of symptoms varies widely from 1 month to nearly 2 years from treatment start; however, the majority of cases occur at around 3 months (Roberts et al., 2017).

Presentations vary considerably from asymptomatic radiologic changes, consistent with interstitial lung infiltrates, to fulminant respiratory failure (Kottschade et al., 2016). Because many cases are asymptomatic, incidence rates are likely underreported. Evaluation for pneumonitis should occur in any patients with reports of chronic cough, dyspnea on exertion, or chest pain (Kottschade et al., 2016). Initial evaluation should include cross sectional imaging (chest CT scan), as pneumonitis may be missed in as many as 25% of the cases with plain chest x-ray (Kottschade et al., 2016). Additionally, pulmonary function testing and/or bronchoscopy may be helpful in guiding diagnosis and management. As patients can decompensate quickly with pneumonitis, prompt intervention with corticosteroids is imperative.

Ocular Immune-Related Adverse Events

Eye toxicities can range from "dry eye" syndrome to uveitis. Left untreated, this can lead to pain, ulceration, and permanent vision loss. Patients who are experiencing dry eyes can be managed conservatively with lubricating eye drops twice daily (Brahmer et al., 2018; Kottschade et al., 2016). Any patient who presents with eye pain, reddened sclera, or visual changes should be immediately evaluated by an ophthalmologist. Topical steroid drops and/or intraocular steroid injections are the usual forms of treatment for this condition, and rarely are systemic steroids required (Brahmer et al., 2018; Kottschade et al., 2016).

OTHER IMMUNE-RELATED ADVERSE EVENTS

There are several other rare irAEs of interest that have been reported, including hematologic (e.g., thrombocytopenia, hemolytic anemia), neurologic (e.g., encephalitis, aseptic meningitis, acute inflammatory demyelinating polyneuropathy), renal (e.g., acute interstitial nephritis), and rheumatologic (e.g., inflammatory arthritis, scleroderma, sicca syndrome, systemic lupus erythematous) irAEs (Brahmer et al., 2018; Puzanov et al., 2017;

Roberts et al., 2017). Symptoms can range from asymptomatic lab abnormalities to life-threatening symptoms. The appropriate specialists should be consulted for assistance in management.

Additional Resources for Advanced Practitioners

Recently, several groups have released multidisciplinary guidelines on the management of irAEs from ICI therapy. Both the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) worked collaboratively to develop guidelines both on the treatment of irAEs but also on when it is appropriate to rechallenge patients with ICI therapy vs. those irAEs that require permanent discontinuation of ICI therapy. The Society of Immunotherapy in Cancer (SITC) has also published guidelines for the management of irAEs. The AIM at Melanoma Foundation through the Melanoma Nurse Initiative published nurse-centric care pathways for toxicity management. All of these resources are available online and are free to those who access them (Table 2).

SUPPORTING PATIENTS RECEIVING TARGETED THERAPY

Molecularly targeted agents have also earned a place in the therapeutic landscape for melanoma in both the adjuvant and metastatic arenas. Inhibitors of v-Raf murine sarcoma viral oncogene homolog B (BRAF) and MAP kinase (MEK) have dramatically improved outcomes for patients with *BRAF*-mutant melanoma. Combination BRAF and MEK therapy is considered a standard treatment option for patients with unresectable or metastatic melanoma with an identified *BRAF* V600E or V600K mutation (Daud & Tsai, 2017). Currently, there are three approved combination regimens: dabrafenib and trametinib, vemurafenib and cobimetinib, and most recently, encorafenib and binimetinib. Combination dabrafenib and trametinib is also available as an adjuvant treatment option for patients with resected stage III disease.

Targeted therapies are oral medications taken daily. They are generally well tolerated and share several common adverse events with traditional cancer therapies (e.g., fatigue, nausea, diarrhea). However, there are novel, class-specific adverse events of BRAF inhibitors, MEK inhibitors, and those specific to combination BRAF and MEK inhibitor therapy (Rubin, 2017), including pyrexia and cutaneous toxicities such as rash, photosensitivity, and development of new primary skin cancers, specifically squamous cell carcinoma and its variant, keratoacanthoma. Other notable adverse events include arthralgias, ocular toxicities, and cardiac events. Of the adverse events, pyrexia is by far identified as a characteristic and challenging adverse event associated with BRAF inhibitor–based therapy, and is primarily seen with combination dabrafenib and trametinib (Rubin, 2017). In this section, the management of adverse events of targeted therapies is discussed.

MANAGEMENT OF PYREXIA FROM TARGETED THERAPY

Pyrexia with or without chills is a very common and distressing side effect for patients undergoing therapy with a regimen that includes BRAF inhibitors. In both of the pivotal phase III trials in the metastatic and adjuvant settings, the incidence of pyrexia was around 60% (Long et al., 2017; Robert et al., 2015). Pyrexia is particularly common with the dabrafenib and trametinib combination, but can be seen to a lesser extent with the other BRAF and MEK inhibitor combinations (Array Biopharma Inc., 2018; Genentech,

Table 2. Guidelines on the Management of Immune-Related Adverse Events From Immune Checkpoint Inhibitor Therapy

Organization	Website
American Society of Clinical Oncology and National Comprehensive Cancer Network	ASCO: doi.org/10.1200/JCO.2017.77.6385 NCCN: nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf
Society of Immunotherapy in Cancer	sitcancer.org/research/cancer-immunotherapy-guidelines
AIM at Melanoma	aimatmelanoma.org
Melanoma Nursing Initiative	themelanomanurse.org

2017). Pyrexia is one of the most common reasons for dose reduction and interruption, as compared with any other adverse event with combination BRAF and MEK inhibitor therapy.

Evaluation

As targeted therapy is an oral regimen and patients may not be seen in the clinic as often, patient education is key. Patients should be encouraged to report any symptoms of chills with or without fever (> 100°F) to the treating oncology team immediately (Czupryn & Cisneros, 2017). Intervention is of utmost importance in preventing significant and serious consequences from pyrexia.

Management

For patients with grade 1 pyrexia (< 101°F), symptomatic management is key and involves the use of antipyretics (acetaminophen or ibuprofen), assuring adequate hydration, and ruling out any infectious process (if appropriate). In this way, agents can be continued with caution (Czupryn & Cisneros, 2017). Patients experiencing grade 2 pyrexia should have the BRAF inhibitor held with aggressive symptom management, while those who are refractory or not responding to antipyretics should be treated with low-dose corticosteroids (i.e., 10 mg prednisone or equivalent; Czupryn & Cisneros, 2017; Lee et al., 2014; Menzies et al., 2015).

For those experiencing grade 3 or 4 pyrexia, holding of both agents should be done with aggressive management (including possible hospitalization) with antipyretics and fluids (Czupryn & Cisneros, 2017; Lee et al., 2014; Menzies et al., 2015). Additionally, all patients should have renal function followed and monitored for signs of dehydration. Once the fever has recovered to < grade 1, resumption or dose reduction of agents should occur according to the manufacturer's recommendations. In the metastatic setting, providers could consider switching to a different BRAF or MEK inhibitor in an attempt to lessen the pyrexia (Czupryn & Cisneros, 2017).

MANAGEMENT OF CUTANEOUS ADVERSE EVENTS FROM TARGETED THERAPY

Rash is another common side effect seen with BRAF and MEK inhibition. However, there are several other cutaneous toxicities seen with this class of drugs, including photosensitivity, palmar-plantar erythrodysesthesia, as well as secondary skin cancers (Daud & Tsai, 2017; Rubin, 2017). Additionally, there have been reported cases of severe SJS and TEN. Vemurafenib-associated photosensitivity can be a particularly difficult cutaneous toxicity to manage as patients can have severe reactions with minimal sun exposure. This can be particularly detrimental to patient qualify of life as well. Assessment of patient ability to comply with UV protection is essential prior to embarking with therapy regimens that include vemurafenib.

Evaluation

Patient education remains fundamental to appropriate management. Early self-reporting is critical to early intervention and effective management of cutaneous toxicities to minimize severe toxicity. Patients should undergo skin assessment at each office visit, with formal dermatologic evaluation every 3 to 6 months while on therapy.

Management

For patients with acneiform-type rash, management can include minocycline at 100 mg twice a day. For patients with severe rash, treatment should be held and therapy with corticosteroids initiated (Daud & Tsai, 2017; Rubin, 2017). Additionally, patients should be evaluated by dermatology for further management. Patients who have oral lesions, with or without fever, blisters, and/or peeling skin, should be urgently evaluated for SJS and TEN.

Photosensitivity appears to be an isolated adverse event of vemurafenib. Patients should be instructed to minimize UV exposure, including use of effective photoprotection (Daud & Tsai, 2017; e.g., broad-spectrum sunscreen, clothing such as long sleeves, long pants, and/or UV protective clothing). Management of photosensitivity reactions should be based on the severity of symptoms; patients with severe reactions (burns) should be seen urgently given concern for insensible losses.

Development of secondary cutaneous malignancies is an adverse class effect of these agents; therefore, regular dermatologic follow-up for full-body skin evaluations is essential. In patients who

are diagnosed with a secondary skin cancer, treatment can include excision, cryotherapy, or curettage (Czupryn & Cisneros, 2017; Rubin, 2017). Of note, dose reduction or discontinuation are typically not necessary.

MANAGEMENT OF CARDIAC ADVERSE EVENTS FROM TARGETED THERAPY

Cardiomyopathy is a class effect of MEK inhibitors and can manifest as asymptomatic decreases in left ventricular ejection fraction (LVEF) to fulminant congestive heart failure. Additionally, vemurafenib can cause QTc prolongation, which can lead to fatal arrhythmias (Daud & Tsai, 2017; Rubin, 2017).

Evaluation

Prior to patients initiating MEK inhibitor therapy, a cardiac evaluation should include a comprehensive transthoracic echocardiogram. Continued evaluation of LVEF should occur 1 month after therapy is started and every 3 to 4 months throughout therapy. Patients should be counseled to report any peripheral edema, shortness of breath, or chest pain. Additionally, for patients undergoing therapy with vemurafenib, evaluation should include a 12-lead electrocardiography as well as assessment for concurrent medications that can also prolong the QT interval. Electrocardiograms should be repeated at the following intervals while on therapy with vemurafenib: 14 days after therapy initiation, monthly during the first 3 months of treatment, and every 3 to 4 months while on therapy. Extra monitoring should occur anytime additional medications are started that can also prolong the QTc interval.

Management

For patients who experience asymptomatic decreased LVEF of either 10% from baseline or have an LVEF of between 40% to 50%, MEK inhibitor therapy should be held for 2 weeks with a repeat echochardiogram (Daud & Tsai, 2017). If LVEF function has recovered to baseline, patients can be rechallenged with the next lower dose of the MEK inhibitor. In patients who experience symptomatic decreases in LVEF, defined as either a decrease of > 20% in LVEF from baseline or LVEF of between 20% to 39%, the MEK inhibitor should be held for 4 weeks (Daud & Tsai, 2017). If recovery occurs, patients can cautiously resume the MEK inhibitor with more frequent LVEF evaluation for the first few months after treatment is restarted. The MEK inhibitor should be permanently discontinued for any patient with an LVEF of < 20% or in any patient who has previously had deceased LVEF and has not recovered function within 4 weeks (Daud & Tsai, 2017).

In patients experiencing QTc prolongation, vemurafenib should be held for QTc > 500 milliseconds (or > 60 milliseconds over baseline). Additionally, electrolytes should be corrected, and other QTc-prolonging medications discontinued if possible (Genentech, 2017). Once recovery has occurred with QTc < 500 milliseconds (or QTc recovered to baseline), vemurafenib may be restarted at a lower dose (Genentech, 2017). For recurrent QTc prolongations, when other risk factors are controlled for, vemurafenib should be discontinued (Genentech, 2017).

ADDITIONAL RARE BUT SERIOUS ADVERSE EVENTS OF TARGETED THERAPIES

While uncommon, there are several other toxicities that are unique to BRAF inhibitor and MEK inhibitor therapy that can be serious and life-threatening. Although this article will not go into lengthy detail about the management of these rare adverse events, it is important for the advanced practitioner to be aware of and able to recognize them. Serious adverse events include the following: rhabdomyolysis, uveitis, pneumonitis (interstitial lung disease), and clotting issues (both bleeding and thrombosis). Although most of these adverse events will present as a toxicity with no specific monitoring to prevention, rhabdomyolysis often will present initially with asymptomatic elevated creatine kinase (CK) enzymes. It should also be noted that rhabdomyolysis is a unique side effect to cobimetinib and binimetinib, and as such these patients should be monitored with serial CK levels throughout treatment. Appropriate dose reductions should be undertaken based on CK levels and package insert recommendations based on the agent (Array BioPharma Inc., 2018; Genentech, 2015).

CONCLUSION

In the current era of improved therapies for the treatment of high-risk resected and advanced melanoma, oncology advanced practitioners are in a position to significantly influence treatment outcomes. Understanding most irAEs are mild to moderate in severity and easily managed, astute advanced practitioners recognize that successful identification and management of irAEs is achieved via extreme vigilance and maintaining high alertness for even the most subtle sign or symptom of evolving toxicity. Equally important for advanced practitioners is to be aware that most side effects from targeted therapies are easily reversible with dose reductions and/or holding therapy. Often, patients can be successfully rechallenged at a lower dose. Finally, while recognizing that these therapies have significantly accelerated the treatment of melanoma, early recognition and early intervention is of utmost importance in preventing increased morbidity and mortality in this patient population.

Disclosure

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