Immune-Related Adverse Events (irAEs) in Cancer, with Inputs from a Nursing Expert: A Review

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Abstract

Immune checkpoint inhibitors (ICPis) belong to a group of immunotherapeutic agents that act on different immune cells and tumor cells and reactivate the suppressed immune system of the host. The emergence of immunotherapy has resulted in the successful management of many malignancies. High success rates with certain advanced cancers have attributed wide importance and relevance to the use of immunotherapy. Although ICPis have gained huge popularity, their use often leads to side effects that can affect almost any system; immune-related adverse events (irAEs). These adverse events occur due to unrestrained T cell activity that unsettles the immune homeostasis of the host. Although close monitoring for toxicities controls the events on most of the occasions, the inability to diagnose them early may prove fatal on some occasions due to their subtle and nonspecific symptoms. This review summarizes in brief the usual irAEs and their management, besides a very important nursing perspective, from a nursing expert about an overall insight into the routine irAEs.

Keywords
- immune-related adverse events
- immune checkpoint inhibitors
- immunosuppressant
- cytotoxic T lymphocyte antigen 4
- programmed cell death protein 1

Introduction

Advances in the treatment of cancer have led to the development of immune checkpoint inhibitors (ICPis) that reinforce the immune system to target tumor cells. The agents, cytotoxic T lymphocyte antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), and PD-1 ligand 1 (PD-L1) inhibitors, have contributed for the effective treatment of advanced cancers in the recent times. The beneficial clinical responses of such agents against various malignancies have resulted further in U.S. Food and Drug Administration approval of checkpoint inhibitors, pembrolizumab, nivolumab, cemiplimab, atezolizumab, durvalumab, and avelumab. These agents are approved for several malignancies including melanoma, renal cell carcinoma, lung cancer (small and nonsmall cell types), bladder cancer, and Hodgkin disease. Currently several clinical trials are further investigating the combination therapies involving checkpoint inhibitors, targeted therapy, radiotherapy, chemotherapy, and various antiangiogenic agents, with few of these combinations already approved and used in clinical practice. ICPis are generally well tolerated and less toxic than the cytotoxic chemotherapy. These agents, however, function by

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recalibrating the immune cell functions by blocking the internal down-regulators of the immune system, resulting in a distinctive group of side effects referred to as immune-related adverse events (irAEs). These are different from the side effects seen with conventional cancer therapy.\textsuperscript{9,10} The adverse events can be seen in most of the organs due to the heightened immune system, and thus organs like liver, skin, bowels, kidneys, endocrine tissues, and the central nervous system are affected (\textsuperscript{\textbullet}) Fig. 1.\textsuperscript{11} The irAEs are diverse and range from a mild dermatitis to fatal pneumonitis and myocarditis. Higher rates of irAEs are seen with ICPis targeting CTLA-4 than those acting on PD-1.\textsuperscript{12,13} Most irAEs develop during the initial 3 to 4 months of immunotherapy use, although the events can manifest any time during the course of treatment or sometimes even after the conclusion of immunotherapy treatment. The initial events often include nonspecific symptoms like fatigue and malaise. Patients often presume them to be anticipated with the disease process, and if not documented could result in delayed diagnosis. Therefore, careful observation of patients under ICPis becomes important for the differential diagnosis, and effective management of any events.

CTLA-4 and PD-1/PD-L1 negatively regulate and maintain the balance in the immune system under normal conditions. T cell surfaces express CTLA-4 and CD28 that compete on the surface of antigen presenting cells (APCs) with the same binding sites as CD80/CD86. The activation signal for T cells is achieved when CD28 integrates with CD80/CD86.\textsuperscript{14} The activation of T cells is obstructed with down-regulation of their responses when CTLA-4 combines with CD80/CD86.\textsuperscript{15,16} PD-1 and its ligand PD-L1 are expressed on the surface T cells, and the surface of APCs, respectively. The down-regulation of the T cell response also occurs when PD-1 and PD-L1 integrate on the tumor cell surface thereby enabling tumor cells to evade immune response of the host.\textsuperscript{17,18} These immune inhibitor molecules are up-regulated by the tumor cells to escape the immune response. This ultimately facilitates the initiation of the tumor, followed by the stages of progression and metastasis. The uses of ICPis in cancer treatment block PD1/PD-L1 or CTLA-4 and thus stimulate the body’s antitumor immunity disrupting immune homeostasis and also make patients susceptible for irAEs. The class of ICPis used dictates the incidence and extent of these irAEs. The use of ipilimumab that inhibits CTLA-4 caused irAEs in up to 60 to 70\% of patients,\textsuperscript{1} while the incidence of irAEs is seen in 30\% of patients under PD-1 inhibitors. The combination of ipilimumab and another PD-1 inhibitor nivolumab has shown the highest incidence of irAEs.\textsuperscript{19}

Various IrAEs and Their Management

Skin

The most common ICPis induce dermatological reactions that include rash, vitiligo, and pruritus. The dermatologic toxicities are the earliest irAEs encountered, appearing at an average of 3.6 weeks after ICPis initiation.\textsuperscript{20} It is recommended to undertake a thorough clinical examination of the mucocutaneous surfaces to determine the type and spread of the lesions,\textsuperscript{21} for the purpose of differential diagnosis.\textsuperscript{22} Topical emollients and topical steroids are the mainstay for the mild rashes secondary to the use of ICPis. Cold packs and oatmeal baths have been successfully used for relieving pruritus.\textsuperscript{23} Moderate cases affecting quality of life are treated with oral antihistamines along with medium to high potency topical corticosteroids; the treatment continues until lesions
return to grade 1. If the lesions continue unabated despite the interventions, ICPis are withheld and patients are referred for dermatology consultations to determine recovery prospects from irAEs.

**Respiratory**

ICPis therapy can lead to pneumonitis (interstitial lung disease) on rare occasions. The various clinical trials have reported a pneumonitis incidence of 1% due to ipilimumab, 3 to 5% with anti PD-1 and anti-PD-L1 monotherapy. The incidence soars up to 10% in combination therapy with anti PD-1 or anti-PD-L1 and CTLA-4 inhibitors. The main investigations required for the diagnosis of immune-mediated pneumonitis include pulse oximetry, chest X-ray, and computed tomography (CT). Radiographic evidence is used to evaluate grade 1 pneumonitis and the disease progression is assessed by a CT at 3 to 4 weeks. In moderate-to-severe cases, ICPis are terminated till recovery or until reversal to grade 1 toxicity, with administration of prednisone in grade 2 pneumonitis. In addition to aborting of ICPis, it is recommended to administer appropriate antibiotics and prednisolone if the toxicity is progressing to either grade 3 or to grade 4. ICPis-related pneumonitis has four patterns, organizing pneumonia, nonspecific interstitial pneumonia, hypersensitivity pneumonitis, and diffuse alveolar damage (Table 1).

**Gastrointestinal Tract**

The most common gastrointestinal (GI) adverse reaction to ICPis is watery diarrhea. Gastrointestinal tract (GIT) signs may also present as bloody diarrhea, mucus in the stool, and abdominal discomfort. The combination therapy of CTLA-4 and PD-1 inhibitors may lead to severe diarrhea or colitis, as compared with minor symptoms associated with the single agent therapy of anti PD-1 or ipilimumab. Additionally, CTLA-4 inhibitors may lead to oral ulcers, anal lesions (fissures/fistulas/abscesses), and some extraintestinal manifestations. ICPis-induced colitis may mimic other infections or may be itself related to the underlying cancer; therefore, it is important to establish a differential diagnosis. To rule out any underlying infection, a stool test should be performed to check for any bacterial pathogens, parasitic infection, or *Clostridium difficile*. It is recommended to use clinical correlation, thorough medical history, and additional imaging to rule out other conditions like irritable bowel syndrome, disseminated melanoma, and associated GI metastasis if any. Endoscopic evaluation with biopsy constitutes the gold standard for a definite diagnosis of colitis due to irAEs. Supportive care with antidiarrheals, maintaining electrolyte balance usually suffices for grade 1 colitis/mild diarrhea, without disrupting the use of ICPis. Grade 2 colitis requires additional therapy with oral corticosteroids, with the dosage being 0.5 to 1 mg/kg/day. Immune therapy is withheld and diagnosis should be confirmed by endoscopy and biopsy. Hospital admission is advised for grade 3 colitis with prompt intravenous (IV) corticosteroids at a dose of 1 to 2 mg/kg/day and the immunotherapy is withheld until improvement. If the patients do not respond to the IV corticosteroid treatment, infliximab 5mg/kg is recommended. Some patients may require a second dose of infliximab 2 weeks after the first dose.

**Hepatic**

ICPis can lead to liver toxicity with elevated enzyme levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Hepatitis is the most common irAE that can occur with an incidence of 7% with either anti PD-1 or anti CTLA-4, but the incidence escalates to nearly 30% with combined immunotherapy. A thorough workup should be performed to exclude other infections, viral etiology, liver Table 1 Common manifestations and treatment of various forms of pneumonitis

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical features</th>
<th>Radiology</th>
<th>Histopathology</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>OP</td>
<td>Nonproductive cough</td>
<td>Peripheral areas of ground glass opacities, multiple, solitary, infiltrative alveolar opacities</td>
<td>Distal bronchi and alveoli involvement with granulation tissue Plasma cells and lymphocytes</td>
<td>Mild Spontaneous recovery may occur Close monitoring of pulmonary functions required Progressive/and or persistent Prednisone 0.5–1.0mg/kg/day (3–6 months)</td>
</tr>
<tr>
<td>NSIP</td>
<td>Nonproductive cough, dyspnea, developing over weeks to months. Bibasilar crackles</td>
<td>Reticular markings, traction bronchiectasis, and ground-glass opacities are seen mostly in lower zones</td>
<td>Fibrosis with diffuse infiltrative cell infiltrate, alveolar walls are uniformly and diffusely thickened, alveolar structural integrity is maintained</td>
<td>Mild Pulmonary function observation Moderate 0.5–1.0mg/kg/day prednisone or equivalent (8–12 weeks) Refractory disease IV corticosteroids and/or cytotoxic therapies</td>
</tr>
<tr>
<td>DAD</td>
<td>Quick onset severe dyspnea, cough</td>
<td>Extensive air space opacities, more in the dependent areas</td>
<td>Alveolar thickening with inflammatory infiltrate</td>
<td>Respiratory failure Supportive therapies High-dose IV corticosteroids</td>
</tr>
</tbody>
</table>

Abbreviations: DAP, diffuse alveolar damage; IV, intravenous; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia.
metastasis, and hepatitis secondary to autoimmune dys-
function.\textsuperscript{22,39,40} Ongoing immunotherapy is continued in
grade 1 hepatitis, and close monitoring is advocated. In
grade 3 and severe hepatitis cases, ICPIs are stopped until
recovery to at least grade 1 stage. The mainstay of manage-
ment in grade 2 and higher toxicity hepatitis is administra-
tion of corticosteroids and evaluation for 3 to 5 days. The
treatment with ICPIs should be interrupted when AST/ALT
are elevated more than normal (ULN), and suspended perpetually when AST/ALT
elevations become severe and alarming.

mended before any hormonal replacement therapy if hypo-
incretism becomes severe and alarming.\textsuperscript{22,51} Thyroid irAEs
appear usually 4 to 10 weeks after immunotherapy, but can
manifest up to 3 years after ICPIs treatment, and mainly
occur after anti-PD-1 agents.\textsuperscript{52,53} Inflammatory destruction of the gland is the most common disease process signif-
ied in the literature; the damage is caused by the cytotoxic T cells
that result in either tissue breakdown (surplus thyroid hormones) or insufficient hormone release.\textsuperscript{54} The symptoms
generally resemble thyroid disorders due to various other
etiologies, and include dry skin, excess body weight, lethargy in
hypothyroidism, and anxiety, and palpitations in hyper-
thyroidism. The management of hypothyroidism requires
evaluating for adrenal insufficiency before initiation of hor-
monal replacement therapy to avoid aggravating any cri-
sis.\textsuperscript{53,55,56} The titration of levothyroxine is done based on the
levels of thyroid stimulating hormone in primary hypothy-
roidism, and on the levels of thyroxine in secondary hypo-
thyroidism. Hyperthyroidism is managed adequately by a
symptomatic approach, and mostly the irAEs are self-
limiting.\textsuperscript{52,57}

Nervous System
The incidence of neurological irAEs (neurotoxicity) is low
when compared with the other systems like skin and GIT.\textsuperscript{58} Im-
nunotherapy with single agents like CTLA-4 or anti-PD1
results in 4 to 6% neurological irAEs, and the rate increases to
12% with combination immunotherapy.\textsuperscript{59} Neurotoxic irAEs
present as a toxic encephalopathy that begins with features like difficulty in word finding, aphasia, dysphasia, disruption
in fine motor skills, and somnolent behavior.\textsuperscript{60–62} The severe
forms of neurotoxic irAEs may cause seizures, cerebral
edema, motor weakness, and even coma. Neurotoxicity is
usually preceded by a phase of cytokine release syndrome
(CRS), and hence CRS either initiates or acts as a cofactor for
neurotoxic events. CRS and neurotoxicity are both fatal side
effects produced by therapy with chimeric antigenic receptor
T cells, occurring separately within 1 and 3 weeks after the
treatment, respectively.\textsuperscript{63,64} Supportive care with antipyret-
ics is usually sufficient for low-grade CRS, and any coexisting
reasons for fever (Infection) should be ruled out.\textsuperscript{65} Anti-
cytokine treatment in the form of tocilizumab (anti-inter-
leukin-6 [IL6] receptor) or Siltuximab antibody (chimeric
anti-IL6) is used effectively against CRS and neurotoxic-
ity.\textsuperscript{56,67} Corticosteroids being immunosuppressive and able
to cross blood–brain barrier are widely used for the manage-
ment of neurotoxicity.\textsuperscript{68,69} but their clinical efficacy on the
extensivity and duration of neurotoxicity is not well estab-
lished in the literature.\textsuperscript{69} There is always a need for better
understanding of pathophysiology of CRS and neurotoxicity
to come up with novel and effective treatments.

Clinicians need to be observant and instinctive to the
diversity encompassed in irAEs, also to the possibility that
these adverse events can occur late during the course of
therapy, and sometimes even months or years after the
cancer treatment cessation.\textsuperscript{70,71} Consensus recommenda-
tions from the Society for Immunotherapy of Cancer recom-
mand all patients who are advised ICPIs should be subjected
to a pretreatment evaluation and diagnostic workup
(\textsuperscript{72}Table 2). Few of these tests may not be available at all

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Excerpts from a Nursing Expert

Marianne Davies, NP, DNP, MSN, BSN, a lecturer in nursing at the Yale School of Nursing shared her expertise with OncLive, about various aspects of irAEs.

According to Marianne Davies, inappropriate management of irAEs can end up in severe colitis and myocarditis. She stressed upon baseline assessment in understanding actual etiology, and stressed upon further laboratory investigations and stool cultures. Prompt steroids and immunosuppressive agents are vital to manage and keep in check the severe irAEs. Davies recommends use of supportive treatment like loperamide or diphenoxylate atropine for the most common low-grade GI toxicity based on the Common Terminology Criteria for Adverse Events. Steroids should be started for grade 2 irAEs toxicity that is associated with increased frequency of stools/day, which is in conformity with their previous guidelines for the management of irAEs. Davies further reported that while updating their guidelines, it is recommended now to use infliximab or vedolizumab if colitis does not show any improvement after 2 weeks of steroids use. The use of these additional immunosuppressive agents is to assist in steroid tapering and hence to safeguard against complications associated with continuous steroid use.

There are higher chances of cardiotoxicity if more than one ICPis are used, such as the combination of an anti-PD-1 and anti-CTLA-4 agent. The patients with underlying cardiovascular disease are more likely to develop such toxicity. Such patients should be monitored closely for any sign indicating toxicity. The patients should also be undertaken for baseline electrocardiograph and troponin levels, such that baseline levels are familiar in case of any changes in evaluation of potential irAEs. If the patients do not respond to the initial steroid therapy, additional immunosuppressant agents should be started within 2 to 3 days to reduce chances of fatal reactions in such susceptible patients.

Davies further highlights the importance of distinguishing irAEs from other nonrelated signs particularly in patients under concurrent treatment. ICPis and chemotherapy are given simultaneously in certain cases, and such combination can lead to overlapping of toxicities. Since the agents are administered together, it is vital to understand

<table>
<thead>
<tr>
<th>Routine procedural pretreatment</th>
<th>History</th>
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<tbody>
<tr>
<td></td>
<td>▪ Gather information about infectious, autoimmune, endocrine, and any organ specific disease history</td>
</tr>
<tr>
<td></td>
<td>▪ Enquire about baseline bowel habit (frequency and stool consistency)</td>
</tr>
<tr>
<td>Blood tests</td>
<td>CBC</td>
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<td></td>
<td>CMP</td>
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<td></td>
<td>TSH</td>
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<td></td>
<td>FreeT4</td>
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<td></td>
<td>HbA1c</td>
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<td></td>
<td>Total CK</td>
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<tr>
<td></td>
<td>Fasting lipid profile</td>
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<tr>
<td></td>
<td>HBsAg, HBcAb, HBsAb, CMV antibody, hCAb, T-spot test, HIV antigen(p24)</td>
</tr>
<tr>
<td>Dermatological examination</td>
<td>▪ Mucocutaneous examination, with careful observation of the extent and type of the lesion</td>
</tr>
<tr>
<td>Pulmonary test</td>
<td>▪ Baseline oxygen saturation on room air and during ambulation</td>
</tr>
<tr>
<td>Cardiac tests</td>
<td>▪ ECG</td>
</tr>
<tr>
<td></td>
<td>▪ Troponin I or T: baseline and weekly for 6 weeksb</td>
</tr>
</tbody>
</table>

**Table 2** Pretreatment assessment and diagnostic tests to consider before any immune checkpoint inhibitor therapy

<table>
<thead>
<tr>
<th>Additional screening tests in pre-existing organ disease/at risk of organ-specific toxicity</th>
<th>Endocrine tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>▪ Cortisol (8 AM)</td>
</tr>
<tr>
<td></td>
<td>▪ ACTH (8 AM)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>▪ BNP or NT pro-BNP</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>▪ PFTsc</td>
</tr>
<tr>
<td></td>
<td>▪ 6MWTc</td>
</tr>
</tbody>
</table>

**Abbreviations:** 6MWT, 6 minute walk test; ACTH, adrenocorticotropic hormone; BNP, brain natriuretic peptide; CBC, complete blood count; CK, creatinine kinase; CMP, complete metabolic panel; CMV, cytomegalovirus; ECG, electrocardiogram; HbA1c, glycosylated hemoglobin; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; hCAb, hepatitis C antibody; HIV, human immunodeficiency virus; NT pro-BNP, N-terminal pro B-type natriuretic peptide; PFTs, pulmonary function tests; T4, thyroxine; TSH, thyroid-stimulating hormone.

*a*If patients develop irAEs the tests become pertinent and corticosteroids and/or anti-Tumor Necrosis factor-alpha treatment is required

*b*This test may not be cost efficient as a routine test owing to the rarity of cardiac toxicity. In case of any cardiopulmonary symptoms repeated troponin and natriuretic testing is warranted

*c*Pulmonary toxicity being quite rare the tests should be considered only in patients with a pre-existing lung disease
the onset and pattern of the symptoms to differentiate the cause and also the approach to the treatment of such toxicities. Chemotherapy-associated peripheral neuropathy may occur at the same time when irAEs occur. The hepatic and renal dysfunction secondary to irAEs may also occur as a result of chemotherapy. The chemotherapy-associated side effects mostly occur at 7 to 14 days of chemotherapy and further take around 14 days to improve, in line with the next chemotherapy treatment time. The irAEs are generally persistent for weeks, take longer time to improve and more so if corticosteroid treatment is delayed. If careful assessment indicates a chemotherapy-related toxicity, the dose of the corresponding agent can be either reduced or withheld for some time depending upon the severity of the associated toxicities. On the other hand, Davies pointed out that irAEs do not warrant a dose reduction, but can be aborted in certain situations and a need for immediate corticosteroid therapy is discussed.
Furthermore, it is important to assess the pattern and mode of onset of toxicities for their appropriate management. In addition to the concurrent therapy, other factors that contribute to the adverse effects may include over-the-counter medications and simultaneous viral infections. Davies stressed upon a thorough review of systems and adequate physical examination for the differential diagnosis, and to efficiently devise the management approaches.

**Limitations**

The review does not describe the detailed pathogenesis underlying the advent of irAEs.

The management of irAEs is given briefly to accommodate most of the systems description.

**Strengths**

Although brief, attempts were taken to highlight most of the irAEs and a layout of their management given.

An important section is addressed to the nursing fraternity to raise awareness about the basic aspects of irAEs, and how to begin with treatment as part of a multidisciplinary team.

A set of strategies have been suggested due to a compelling need to develop protocols to manage irAEs effectively (> Table 3).

**Conclusions**

The last decade has seen a revolution in cancer management with the advent of ICPis. The agents have an established role in the treatment of various complicated malignancies, but can lead to adverse events in the form of irAEs. Most of these events are mild and controllable by following an early and well-planned treatment. The diagnosis of irAEs becomes challenging sometimes due to their atypical symptoms and any delay can lead to disruptions in the management of various malignancies. Although appreciable progress has been made in understanding and creating effective management protocols, there is always a room for further improvement. Nurses play an impressive role as part of a dependable interdisciplinary management team.

**Source(s) of Support**

None.

**Presentation at a Meeting**

None.

**Conflict of Interest**

None declared.

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