Management of Immune-Related Adverse Effects in Cancer Immunotherapy Patients

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ABSTRACT

Managing immune-related adverse events (irAEs) in patients receiving cancer immunotherapy is a significant and evolving challenge in oncology care.Clinical pharmacists play a crucial role in the early detection of adverse events (irAEs) in patients undergoing Intensive Care Unit (ICU) medication. Their participation in protocol-based pharmacotherapy management (PBPM) improves the rate of required laboratory tests, enabling timely detection of adverse events. The involvement of pharmacists and pharmacologists on expert panels can aid in the interpretation of aberrant test findings produced by ICI and other medications. Regular education and upskilling of pharmacists and clinicians will further promote adaptive care as new drug combinations and rare toxicities emerge.

KEY WORDS: Adverse effects, immunotherapy, clinical pharmacists, cytokine therapy, Cancer.

INTRODUCTION

Managing immune-related adverse events (irAEs) in cancer immunotherapy patients is a significant and evolving challenge in oncology care. This review provides comprehensive insights that although immunotherapy has transformed the treatment of cancer by increasing the immune system's ability to fight tumors, it also causes a wide range of adverse events (irAEs) that impact several organ systems. From mild to life-threatening, these toxicities require early detection and specialized care to protect patients and preserve treatment effectiveness [1]. Applying standardized grading systems like CTCAE, being familiar with organ-specific toxicities, and having a thorough understanding of the underlying immunopathology are all necessary for effective irAE management [2]. To maximize results, a multidisciplinary strategy including clinical pharmacists, oncologists, and other experts is necessary. Clinical pharmacists are essential because they teach patients how to recognize symptoms and facilitate early detection through protocol-based monitoring [3].

IMMUNOTHERAPY AND IMMUNE-RELATED ADVERSE EFFECTS

Immunotherapy is one of the biological therapies that enhances or manipulates the immune system to recognize and combat diseases, particularly cancer, infections, and autoimmune conditions. Managing immune-related adverse events (irAEs) in patients receiving cancer immunotherapy is a significant and evolving challenge in oncology care. This review provides comprehensive insights that, although immunotherapy has transformed the treatment of cancer by increasing the immune system's ability to fight tumours, it also causes a wide range of adverse events (irAEs) that impact several organ systems.From mild to life-threatening, these toxicities require early detection and specialized care to protect patients and preserve treatment effectiveness.Applying standardized grading systems like CTCAE, being familiar with organ-specific toxicities, and having a thorough understanding of the underlying immunopathology are all necessary for effective irAE management. To maximize results, a multidisciplinary strategy including clinical pharmacists, oncologists, and other experts is necessary. Clinical pharmacists are essential because they teach patients how to recognize symptoms, facilitate early detection through protocol-based monitoring,

a) Types of Cancer Immunotherapy

i.Checkpoint Inhibitors:

These drugs blockproteins that prevent T cells from attacking cancer cells, effectively releasing the brakes on the immune system. Checkpoint inhibitors are a class of immunotherapy drugs that block immune checkpoint proteins, which are molecules in the immune system that either turn up a signal (co-stimulatory molecules) or turn down a signal (inhibitory checkpoint molecules). By blocking these checkpoints, checkpoint inhibitors enhance the immune system's ability to recognize and attack cancer cells.

These drugs primarily target molecules such as CTLA-4 (cytotoxic T-lymphocyte–associated antigen 4), PD-1 (programmed cell death protein 1), and PD-L1 (programmed death-ligand 1), which are involved in suppressing the immune response.[1]

i.CAR T-Cell Therapy:

This involves extracting a patient's T cells, genetically modifying them to express chimeric antigen receptors (CARs) that target cancer cells, and reinfusing them into the patient. This therapy was generally used inleukaemia and lymphomas. [2]

ii.Cytokine Therapy:

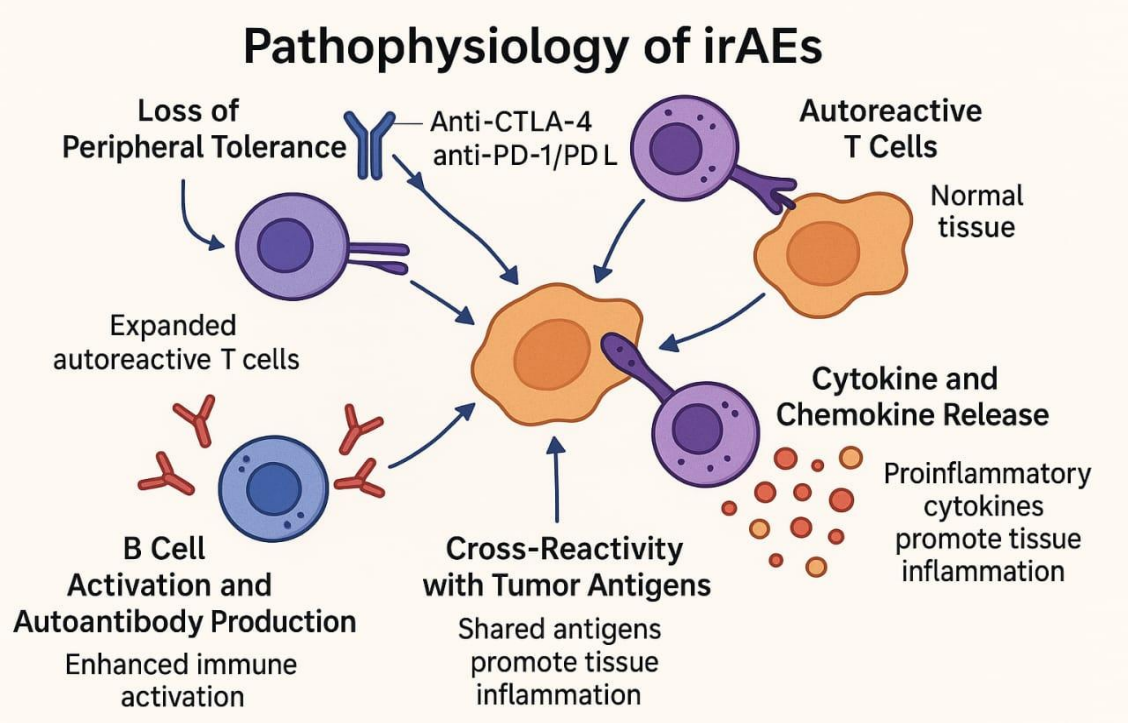
Utilizes cytokines like interleukins and interferons to boost the immune system's response against cancer. While effective, they can have significant side effects.

Commonly Used Immunotherapy Drugs: PD-1 Inhibitors**:** Nivolumab, Pembrolizumab, PD-L1 Inhibitors: Atezolizumab, CTLA-4 Inhibitors**:** Ipilimumab, Tremelimumab

These drugs are administered via intravenous infusion and are approved for treating various cancers, including melanoma, non-small cell lung cancer, and renal cell carcinoma. [3]

b) Pathophysiology of Immune-Related Adverse Events (irAEs)

irAEs occur when the activated immune system attacks normal tissues, leading to inflammation in organs such as the skin, intestines, liver, endocrine glands, and lungs. The mechanisms include, Enhanced activity of T and B cellsIncreased production of cytokines and autoantibodies. Cross-reactivity between tumor antigens and normal tissue antigen. [4]



Classification and Spectrum of irAEs

Immune-related adverse events (irAEs) are unintended immune-mediated toxicities resulting from immune checkpoint inhibitors (ICIs), such as anti-CTLA-4, anti-PD-1, and anti-PD-L1 antibodies. They are classified based on the organ system involved and the severity of presentation.

a) Organ Systems Affected

i. **Dermatologic**: Dermatologic irAE is the most common one, occurring in 30–50% of patients, this may include red spots and bumps called maculopapular rash, pruritus (comes with other skin diseases), and vitiligo(more common in melanoma patient) and other severe skin conditions such as Stevens-Johnson syndrome and Toxic epidermal Necrolysis[5].

ii. **Gastrointestinal**:Diarrhea is the first and most common symptom and then the colitis with abdominal pain and mucus or blood in stools. Enteritis, Gastritis and Esophagitis are the other gastrointestinal irAEs. [6].

iii. **Hepatic:** These are less common than dermatologic or GI irAEs. Mostly it occurs as asymptomatic. This causes elevation of ALT, AST, ALP and bilirubin. So should monitor LFT once a week [7].

iv. **Endocrine:** EndocrineirAEs are common and permanent complications of Immune checkpoint inhibitors. It Includes hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, and type 1 diabetes mellitus [8].

v. **Pulmonary**: It includes Pneumonitis the condition of inflammation of lung parenchyma by overactivation of T cell due to inhibition of checkpoint. Prior lung disease, thoracic radiation history, combination immunotherapy and smoking history are the risk factors[9].

vi. **Cardiovascular**: They can affect multiple cardiac structures such as Myocarditis, pericarditis, arrhythmias, and vasculitis.[10] These may be severe or fatal. Pre-existing cardiovascular disease, combination ICI therapy, concurrent use of other cardiac agents, older age are the risk factors.

vii. **Neurological**: These can be severe or rapidly progressive affecting central, peripheral and autonomic nervous system. Can present as myasthenia gravis, Guillain-Barré syndrome, encephalitis, or peripheral neuropathy [11]. And present with wide variety of symptoms.

viii. **Hematologic**: Rare events include autoimmune hemolyticanemia, thrombocytopenia, and aplastic anemia. It is rare. But It may be life threatening and involve autoimmune destruction or suppression of various blood cells. [12]

b)Grading Severity (CTCAE Criteria)

The Common Terminology Criteria for Adverse Events (CTCAE) is used to grade irAEs:

Grade 1: Mild; asymptomatic or mild symptoms; no intervention needed.

Grade 2: Moderate; minimal, local or non-ninvasive intervention indicated; may limit instrumental ADL.

Grade 3: Severe; hospitalization indicated; limits self-care ADL.

Grade 4: Life-threatening; urgent intervention required.

Grade 5: Death related to irAE[13].

Common Immune-Related Adverse Effects and Their Clinical Manifestations

Immune-related adverse events (irAEs) reflect immune system dysregulation caused by immune checkpoint inhibitors (ICIs). They can affect virtually any organ system and vary in presentation from mild to life-threatening.

a) Dermatologic Toxicities

These are among the earliest and most common irAEs.

Clinical manifestations include: Maculopapular rash, pruritus, eczema-like lesions, and vitiligo.

Severe forms: Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN).

Typically appear within 2–6 weeks of ICI initiation and are more common with anti-CTLA-4 therapies [14].

b)Gastrointestinal Toxicities

Symptoms: Diarrhea, abdominal pain, and hematochezia.

Severe cases: Colitis with ulceration and perforation risk.

Onset typically within 6–8 weeks, earlier with anti-CTLA-4 than anti-PD-1 agents.

Histology mimics inflammatory bowel disease [15].

c)Hepatotoxicity

Most commonly presents as asymptomatic elevation in transaminases.

Severe: Autoimmune hepatitis-like picture with histologic lobular inflammation.

Occurs in 1–10% of patients, more common in combination ICI therapy [16].

d)Endocrine

i. **Thyroid dysfunction:** Hypothyroidism is most frequent, preceded sometimes by transient hyperthyroidism. The clinical maifestations are TSH level, Anti TPO antibodies, Anemia, Hair thinning, facial puffiness, Goiter, Cold intolerance, Constipation, Menstrual irregularities and weight gain.
ii. **Hypophysitis:** More common with ipilimumab, presents with fatigue, hypotension, headache, weakness, constipation, weight gain, Amenorrhea, decreased libido infertility in men and women, visual disturbances and diabetes insipidus.
iii. **Type 1 diabetes mellitus**: Can present with DKA as first sign. Other symptoms include polyuria, polydipsia, polyphagia, weight loss, fatigue, weakness, blurred weakness, and recurrent infections.

iv. **Primary adrenal insufficiency:** It is a rare Rare condition but serious. The clinical manifestations include fatigue, weakness, weight loss, anorexia, malaise, dizziness, hyperpigmentation, hypotension, salt craving, hyponatremia, hyperkalemia, GI symptoms, depression, and confusion. These are often irreversible, requiring lifelong hormone replacement [17].

e)Pulmonary Toxicities

Manifestations: Dry cough, dyspnea, wheezing, hemoptysis, malaise, fatigue, weight loss, crackles, clubbing, and hypoxia.

Radiographic findings: Ground-glass opacities, organizing pneumonia, interstitial lung disease.Occurs in 3–5% of patients; higher risk with anti-PD-1/PD-L1 agents.Severe pneumonitis can be fatal if not treated promptly [18].

f) Cardiotoxicity

Myocarditis is the most seriousirAEs, where the early mortality rate is high. The Other cardiac diseases include Arrhythmias, pericarditis, vasculitis, Takotsubo-like syndrome. It typically occurs within 30 days of treatment.ECG, troponin, and cardiac MRI are critical in diagnosis [19].

e) Neurological Toxicities

i. **Central:** Encephalitis, aseptic meningitis, transverse myelitis.
ii. **Peripheral:** Myasthenia gravis, Guillain–Barré syndrome, sensory neuropathy.

Neuromuscular irAEs often have overlapping features and can be rapidly progressive [20].

f) Hematologic and Other Rare Toxicities

These include Autoimmune hemolyticanemia, aplastic anemia, immune thrombocytopenia, neutropenia.[12]The Rare irAEs are Nephritis, uveitis, pancreatitis, and sarcoid-like reactions.These require high suspicion and early immunosuppressive therapy [21].

CLINICAL PHARMACIST'S ROLE IN IRAE MONITORING AND MANAGEMENT

Pharmacists' knowledge of immune-related adverse events (irAEs) associated with these medicines is more important than ever. Pharmacists have a critical role in recognizing irAEs early, monitoring their progression, and effectively managing them to reduce severe consequences and avoid premature withdrawal from ICI treatment. Pharmacists play a key role

in educating patients about irAEs and their treatments, assessing risk factors, and coordinating with specialists to monitor high-risk patients. [22][23]

a) **Early Detection and Assessment of irAEs:** Clinical pharmacists play a crucial role in the early detection of adverse events (irAEs) in patients undergoing Intensive Care Unit (ICU) medication. Their participation in protocol-based pharmacotherapy management (PBPM) improves the execution rate of required laboratory tests, allowing for the timely detection of adverse events. The involvement of pharmacists and pharmacologists on expert panels can aid in the interpretation of aberrant test findings produced by ICI and other medications. However, advice for early detection and optimal laboratory tests are scarce. While early irAE diagnosis is critical for outcomes and quality of life, guidelines do not provide clear recommendations on test time and frequency. Routine testing every 2-3 weeks is still burdensome. This research recommends critical laboratory and functional testing to improve early detection and management of irAE. [24][25]

b) **Patient Education on Symptom Recognition and Self-Monitoring:** Educating patients about possible immune-related adverse events (irAEs) empowers them to identify early warning signs and seek timely medical care. Pharmacists play a key role by delivering personalized education about the specific side effect profiles of immune checkpoint inhibitors (ICIs), which promotes patient involvement and supports adherence to recommended monitoring protocols.[1] Patients and their caregivers should receive accurate and up-to-date education on immunotherapy covering its mechanism of action and possible immune-related adverse events (irAEs) before treatment begins and continuously throughout therapy and survivorship.[26]

c) **Medication review and monitoring for potential drug interactions:** Pharmacists are essential in performing thorough medication reviews to detect and prevent drug interactions that may intensify immune-related adverse events. Their assessments help ensure the safe and appropriate use of supportive therapies, such as corticosteroids and immunosuppressants, reducing the likelihood of adverse interactions. [27][28]

d) **Dosage adjustments and therapy modifications:** optimizing treatment by recommending adjustments in response to immune-related adverse events (irAEs), helping to improve patient outcomes and reduce therapy interruptions. As integral members of the oncology care team, they contribute to the early identification, patient education, and effective management of irAEs, ultimately supporting safer and more effective treatment. [29]

TREATMENT AND MANAGEMENT STRATEGIES

a) **General Principles of irAE Management**: The management of immune-related adverse events (irAEs) necessitates prompt recognition, accurate grading, and appropriate intervention to mitigate toxicity while preserving the efficacy of immune checkpoint inhibitors (ICIs). Utilization of standardized criteria, such as the Common Terminology Criteria for Adverse Events (CTCAE), facilitates consistent assessment of irAE severity. A multidisciplinary approach, involving oncology, gastroenterology, endocrinology, dermatology, and other relevant specialties, ensures comprehensive care tailored to the affected organ system. Clinical decisions should balance the need for treatment interruption or discontinuation with patient safety and quality of life. Patient education and vigilant monitoring are essential to enable early detection and management of irAEs.[30]

b) **Mild (Grade 1) Toxicities**: Supportive Care and Symptomatic Treatment Grade 1 irAEs are typically mild and do not necessitate discontinuation of ICIs. Management focuses on symptomatic relief and supportive care. For instance, mild dermatologic reactions may be treated with topical corticosteroids and antihistamines, while low-grade diarrhea can be managed with dietary modifications and anti-diarrheal agents. Continued immunotherapy is generally appropriate, provided patients are closely monitored for any progression of symptoms.

c) **Moderate (Grade 2) Toxicities**: Corticosteroids Initiation and Dose Modification Grade 2 irAEs often require temporary suspension of ICIs and initiation of systemic corticosteroid therapy. Prednisone, or its equivalent, is typically administered at a dosage of 0.5 to 1 mg/kg/day. Patients should be monitored for symptom resolution and potential side effects of corticosteroids. Once the irAE improves to Grade 1 or less, a gradual tapering of corticosteroids over 4–6 weeks is recommended. Resumption of immunotherapy may be considered after the irAE is adequately controlled and corticosteroids have been tapered to a minimal dose.

d) **Severe (Grade 3–4) Toxicities:** High-dose corticosteroids, Immunosuppressants, and Permanent Discontinuation of Immunotherapy are severe and potentially life-threatening, necessitating immediate intervention. Management includes permanent discontinuation of ICIs and initiation of high-dose corticosteroids, such as prednisone at 1 to 2 mg/kg/day. If there is no improvement within 48 to 72 hours, escalation to additional immunosuppressive agents like

infliximab or mycophenolate mofetil may be required. These interventions are critical to prevent irreversible organ damage and ensure patient safety. Long-term monitoring and multidisciplinary coordination are essential components of care in these scenarios. [26]

CORTICOSTEROID THERAPY IN IRAES

a) **Guidelines for Steroid Initiation and Tapering:** Corticosteroids are the first-line treatment for moderate to severe irAEs from ICI therapy. Grade 2 irAEs require temporary ICI suspension and prednisone at 0.5–1 mg/kg/day. For Grade 3–4 irAEs, initiate high-dose corticosteroids (1–2 mg/kg/day) and withhold or discontinue ICIs based on severity. Once symptoms improve to Grade 1 or less, taper steroids over 4–6 weeks. If no response occurs within 48–72 hours, consider additional immunosuppressants like infliximab or mycophenolate. [30][31]

b) **Monitoring Steroid-Related Side Effects**

Long-term corticosteroid use can lead to **osteoporosis** in up to 40% of patients due to increased bone breakdown and reduced bone formation. Bone mineral density should be assessed with DEXA scans before starting treatment and monitored regularly. Preventive measures include calcium and vitamin D supplementation, lifestyle modifications, and bisphosphonate therapy for those at high risk. [31] [32]

c) Corticosteroids can lead to **hyperglycemia**, even in patients without a prior history of diabetes. Regular blood glucose monitoring is important, particularly during the initial phase of treatment. If necessary, antidiabetic medications should be adjusted to maintain appropriate glucose levels. [29]

d) Corticosteroid-induced immunosuppression raises the risk of **infections**, including opportunistic ones. Close monitoring for infection signs is essential, and prophylactic measures like Pneumocystis jirovecii pneumonia [PJP] prevention should be considered for high-risk patients.[33]

RECOMMENDATIONS FOR CLINICAL PHARMACIST IN IrAE MANAGEMENT

Clinical pharmacists play a crucial role in managing immune-related adverse events (irAEs) linked to immune checkpoint inhibitor (ICI) therapy. Their responsibilities include implementing standardized screening processes, developing management protocols,

collaborating with multidisciplinary teams, supporting patient adherence, and providing ongoing education to both patients and healthcare providers.[34][35]

a) Standardized Screening and Risk Assessment Tools: Clinical pharmacists are instrumental in the early detection of immune-related adverse events (irAEs) through structured screening and risk evaluation. They utilize assessment tools such as the Naranjo algorithm to determine the likelihood of adverse drug reactions. Additionally, pharmacists utilize comprehensive symptom checklists and patient-reported outcome (PRO) measures to track immune-related adverse events (irAEs), facilitating timely and effective clinical responses.[34] [40]

b) Protocol Development for irEA Monitoring and Reporting: Pharmacists are actively involved in the development and implementation of protocols for the monitoring and reporting of immune-related adverse events (irAEs). A notable example is the Protocol-Based Pharmacotherapy Management (PBPM) system, where pharmacists review and complement laboratory test orders to ensure comprehensive monitoring. This collaborative strategy has led to higher completion rates of critical lab tests, ultimately improving patient safety during immune checkpoint inhibitor therapy.[36]

c) Effective irAE management relies on multidisciplinary collaboration. Pharmacists partner with oncologists, nurses, and specialists to coordinate care, recommend interventions, adjust therapies, and educate the team on immunotherapy-related toxicities.[33]

d) Enhancing Patient Adherence and Quality of Life: Pharmacists play a key role in supporting adherence to immunotherapy and enhancing patients' quality of life. Through education, counseling, and tools like mobile apps and electronic reminders, they help patients manage treatment schedules more effectively. These efforts are linked to improved adherence and better health-related outcomes.[37]

e) Continuing Education and Training on Immunotherapy Toxicities: Ongoing training is vital for pharmacists to keep up with advances in immunotherapy. Educational programs such as NCCN Pharmacy Updates and the E-PIMUC e-learning platform provide current guidance on treatment indications, toxicity management, and clinical protocols.

Participation in these programs improves pharmacists' knowledge, confidence, and ability to manage immunotherapy-related toxicities.[38][39]

CONCLUSION

This review addresses the ongoing challenge of managing immune-related adverse events (irAEs) in cancer immunotherapy patients, emphasizing that effective, proactive strategies remain crucial for maximizing therapeutic outcomes and minimizing toxicities. Immunotherapy currently transforms cancer care, but irAEs continuously affect multiple organ systems, requiring multidisciplinary attention for optimal patient outcomes.The findings demonstrate that today's irAEs present a broad spectrum—from mild dermatologic issues to severe organ dysfunction—and that standardized grading, regular monitoring, and clinical pharmacist involvement advance early detection, patient education, and safe medication use. By employing collaborative models, healthcare teams increase adherence to safety protocols, streamline interventions, and sustain the benefits of immunotherapy while supporting patient quality of life. Given the dynamic nature of immunotherapy, future strategies will focus on more robust predictive markers, tailored management protocols, and technology-assisted monitoring to improve early identification and response to irAES. Regular education and upskilling of pharmacists and clinicians will further promote adaptive care as new drug combinations and rare toxicities emerge. Future research will close knowledge gaps, strengthen multidisciplinary pathways, and advance precision management techniques to keep pace with evolving therapies.

Overall, the clinical integration of pharmacists continues to drive innovation in irAE management. By maintaining patient-centered, team-based care, oncology professionals ensure that immunotherapy's promise is achieved safely and effectively, both now and in the years ahead.

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