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Review Article

Adverse Drug Reactions Associated with Cancer Immunotherapy: Mechanisms, Clinical Spectrum, and Management Strategies

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ABSTRACT

Cancer immunotherapy has substantially reshaped contemporary oncology by improving survival outcomes across solid tumours and haematological malignancies. Immune Checkpoint Inhibitors (ICIs) and Chimeric Antigen Receptor T-cell (CAR-T) therapies enhance antitumor immune activity but are associated with a distinctive spectrum of immune-mediated adverse drug reactions, collectively termed immune-Related Adverse Events (irAEs). These toxicities may involve virtually any organ system and range from mild, self-limiting manifestations to severe, life-threatening complications requiring aggressive immunosuppression.

This review provides a structured synthesis of the mechanisms, clinical manifestations, grading systems, and evidence-based management strategies for immunotherapy-associated adverse reactions, with particular emphasis on ICIs and CAR-T therapies. Updated international consensus recommendations are incorporated to support standardized clinical practice. Structured pharmacovigilance frameworks and multidisciplinary collaboration-including formal integration of clinical pharmacists-are emphasized as critical components to improve early detection, optimize toxicity management, and enhance patient safety outcomes.

Keywords: Cancer immunotherapy, CAR-T therapy, Immune checkpoint inhibitors, Immune-related adverse events, Pharmacovigilance.

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INTRODUCTION

Immunotherapy has become integral to the management of multiple malignancies. Agents targeting Programmed Death-1 (PD-1), Programmed Death Ligand-1 (PD-L1), and Cytotoxic T-Lymphocyte-Associated antigen-4 (CTLA-4) restore antitumor immune responses by inhibiting regulatory checkpoints that suppress T-cell activation (Ribas and Wolchok, 2018).

Chimeric antigen receptor T-cell therapies involve *ex vivo* genetic modification of autologous T cells to express tumor-specific receptors, enabling targeted cytotoxicity (Neelapu *et al.*, 2018).

Unlike cytotoxic chemotherapy, these agents alter immune homeostasis and may provoke immune-mediated inflammation in normal tissues (Postow *et al.*, 2018). The incidence and severity of irAEs vary depending on drug class, dosage, and combination regimens (Xu *et al.*, 2020). As immunotherapy indications expand, structured recognition and standardized toxicity management have become essential components of oncology practice.

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METHODOLOGY

Mechanisms of Immunotherapy-Related Adverse Drug Reactions

Checkpoint inhibition disrupts peripheral immune tolerance and enhances autoreactive T-cell activity, forming the immunologic basis of most irAEs (Postow *et al.*, 2018; Martins *et* al., 2019). Blockade of PD-1/PD-L1 and CTLA-4 signaling enhances effector T-cell proliferation, cytokine production, and loss of regulatory T-cell-mediated suppression, thereby promoting autoreactive inflammatory responses in non-malignant tissues (Postow *et al.*, 2018; Martins *et* al., 2019) (Table 1).

CAR-T therapies may induce Cytokine Release Syndrome (CRS) due to rapid immune activation and cytokine amplification (Neelapu *et al.*, 2018). Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS) is attributed to endothelial activation and altered blood-brain barrier permeability (Lee *et al.*, 2019).

Host-related factors, including genetic predisposition and pre-existing autoimmune disease, may further influence

susceptibility to toxicity (Martins *et al.*, 2019; Kennedy *et al.*, 2019).

Organ-Specific Immune-Related Adverse Events

Immunotherapy toxicities may involve nearly any organ system (Postow *et al.*, 2018; Martins *et* al., 2019) (Table 2).

Dermatologic: Rash and pruritus are frequent early manifestations (Postow *et al.*, 2018; Eigentler *et al.*, 2016).

Gastrointestinal: Immune-mediated colitis ranges from mild diarrhea to severe inflammatory colitis requiring systemic corticosteroids (Postow *et al.*, 2018; Martins *et* al., 2019).

Endocrine: Thyroid dysfunction and hypophysitis are common and may necessitate long-term hormone replacement therapy (Postow *et al.*, 2018; Haanen *et al.*, 2022).

Pulmonary: Immune-related pneumonitis may present with dyspnoea, cough, and radiologic infiltrates and can be life-threatening if untreated (Barlesi *et al.*, 2019; Schneider *et al.*, 2022).

Cardiac: Immune checkpoint inhibitor-associated myocarditis, although uncommon, is associated with significant morbidity and mortality (Palaskas *et al.*, 2020; Wang *et al.*, 2018).

Hepatic: Immune-mediated hepatitis may manifest as asymptomatic transaminase elevation or severe hepatic dysfunction requiring corticosteroid therapy and treatment interruption (Postow *et al.*, 2018; Martins *et* al., 2019).

Severity Grading

The Common Terminology Criteria for Adverse Events (CTCAE) provides a standardized framework for grading toxicities from Grade 1 (mild) to Grade 5 (death) (Brahmer *et al.*, 2021). This grading system informs therapeutic decision-making and reporting (Table 3).

For CAR-T-related toxicities, the ASTCT consensus grading system standardizes CRS and ICANS assessment (Lee *et al.*, 2019).

Detection and Guideline-Based Management

Baseline clinical evaluation and periodic laboratory monitoring facilitate early toxicity detection (Brahmer *et al.*, 2021) (Table 4).

International consensus guidelines provide structured management algorithms (Brahmer *et al.*, 2021; Haanen *et al.*, 2022; Schneider *et al.*, 2022).

General Management Principles

Grade	Recommended Approach
Grade 1	Continue immunotherapy with close monitoring
Grade 2	Temporarily withhold therapy; initiate corticosteroids
Grade ≥3	Discontinue therapy (in most cases); initiate high-dose intravenous corticosteroids with gradual taper

For grade ≥3 toxicities, permanent discontinuation is generally recommended for CTLA-4 inhibitors (Brahmer *et al.*, 2021). Rechallenge decisions for PD-1/PD-L1 inhibitors require individualized risk-benefit assessment (Haanen *et al.*, 2022; Dolladille *et al.*, 2020).

Steroid-refractory cases may require additional immunosuppressive agents such as infliximab or mycophenolate mofetil (Brahmer *et al.*, 2021; Thompson *et al.*, 2021).

CAR-T-associated CRS is managed according to ASTCT grading criteria, with early administration of tocilizumab in moderate-to-severe cases (Lee *et al.*, 2019).

Early multidisciplinary intervention and adherence to consensus-based algorithms have been associated with reduced treatment interruptions and improved continuation of effective immunotherapy in selected patients (Brahmer *et al.*, 2021; Brahmer *et al.*, 2021).

Role of the Clinical Pharmacist

The integration of clinical pharmacists into oncology care pathways strengthens medication safety and institutional pharmacovigilance systems (Table 5).

Structured oncology pharmacy involvement has been associated with improved adherence to consensus-based irAE management protocols and earlier corticosteroid initiation (Puzanov *et al.*, 2017; Hwang *et al.*, 2020). Published practice models also report enhanced documentation accuracy and increased adverse drug reaction reporting rates (Poudel and Nissen, 2021; Liekweg *et al.*, 2012).

Pharmacists contribute through medication reconciliation, drug interaction screening, laboratory review, patient counselling on early symptom recognition, and structured adverse drug reaction documentation (Hwang *et al.*, 2020; Poudel and Nissen, 2021). Standardized pharmacist-led monitoring may reduce variability in real-world toxicity management and support safer immunotherapy continuation when clinically appropriate (Puzanov *et al.*, 2017).

DISCUSSION

Although most irAEs are manageable with early intervention, severe toxicities such as myocarditis or pneumonitis require urgent recognition and aggressive treatment (Postow *et al.*, 2018; Palaskas *et al.*, 2020).

Table 1: Types of Cancer Immunotherapy and Mechanisms of Action.

Type of immunotherapy	Examples	Mechanism of action	Common adverse events
PD-1 inhibitors	Nivolumab, Pembrolizumab	Block PD-1 receptor, restoring T-cell activation	Rash, colitis, pneumonitis
PD-L1 inhibitors	Atezolizumab, Durvalumab	Block PD-L1 ligand on tumor cells	Hepatitis, dermatitis
CTLA-4 inhibitors	Ipilimumab	Enhance T-cell priming and activation	Colitis, hypophysitis
CAR-T therapy	Tisagenlecleucel	Genetically engineered T cells targeting tumour antigens	Cytokine release syndrome, neurotoxicity

Table 2: Organ-Specific Immune-Related Adverse Events.

Organ system	Common Manifestations
Skin	Rash, pruritus
Gastrointestinal	Diarrhoea, colitis
Endocrine	Hypothyroidism, hypophysitis
Pulmonary	Pneumonitis
Hepatic	Hepatitis
Cardiac	Myocarditis

Table 3: CTCAE-Based Severity Grading.

Grade	Description
1	Mild; asymptomatic or mild symptoms
2	Moderate; limiting instrumental activities
3	Severe; hospitalization indicated
4	Life-threatening consequences
5	Death

Table 4: Management Strategy Based on Severity.

Severity grade	Recommended management
Grade 1	Continue therapy with monitoring
Grade 2	Withhold therapy; initiate corticosteroids
Grade ≥3	Discontinue therapy; high-dose intravenous corticosteroids

Combination immunotherapy regimens are associated with increased rates of high-grade adverse events compared with monotherapy (Xu *et al*., 2020; Wang *et al*., 2018). Therefore, individualized treatment selection should consider patient comorbidities, baseline immune status, and institutional capacity for toxicity management.

Emerging biomarkers-including baseline autoantibody profiles, circulating cytokine levels, and T-cell repertoire diversity-are being investigated to predict irAE susceptibility; however, validated predictive models remain limited. Prospective risk stratification strategies are required to personalize immunotherapy safety monitoring and optimize patient outcomes.

Table 5: Role of Clinical Pharmacists in Immunotherapy Safety.

Domain	Responsibilities
Monitoring	Laboratory review and early toxicity identification
Medication review	Drug interaction screening and supportive care optimisation
Patient education	Counselling on early symptom recognition
Pharmacovigilance	Adverse drug reaction documentation and reporting
Coordination	Participation in multidisciplinary oncology care teams

CONCLUSION

Immunotherapy-associated adverse drug reactions represent a central challenge in contemporary oncology practice. Early recognition, CTCAE-based grading, and adherence to established consensus guidelines are essential to reduce morbidity and mortality (Brahmer *et al*., 2021; Haanen *et al*., 2022). Structured multidisciplinary collaboration-including formal integration of clinical pharmacists-enhances pharmacovigilance systems and strengthens patient safety.

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ABBREVIATIONS

ADR: Adverse Drug Reaction; **ASTCT:** American Society for Transplantation and Cellular Therapy; **CAR-T:** Chimeric Antigen Receptor T-cell; **CRS:** Cytokine Release Syndrome; **CTCAE:** Common Terminology Criteria for Adverse Events; **CTLA-4:** Cytotoxic T-Lymphocyte-Associated Antigen-4; **ESMO:** European Society for Medical Oncology; **ICANS:** Immune Effector Cell-Associated Neurotoxicity Syndrome; **ICI:** Immune Checkpoint Inhibitor; **irAE:** Immune-Related Adverse Event; **NCCN:** National Comprehensive Cancer Network; **PD-1:** Programmed Death-1; **PD-L1:** Programmed Death Ligand-1.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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