Review Article

TOXICITY PROFILE RELATED TO IMMUNE CHECK POINT INHIBITORS: A COMPREHENSIVE REVIEW

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ABSTRACT:

Immunotherapies are changing the scope of advanced solid tumour treatment. These molecules that increase the endogenous immune response against molecules that increase the endogenous immune response against tumours. They have revolutionized the field of oncology. Immune checkpoint inhibitors are monoclonal antibodies that are used to treat over one in three cancer patients, checkpoint inhibitors, such as CTLA-4 or PD1/PD-L1 monoclonal antibodies, and CSF-1R antibodies. Cancer immunotherapies have unique toxicity profile different from other cancer therapies, which presents difficult for physician in ruling out and addressing adverse effects produced by inflammation brought immune response activation. Any organ or system in the body may have adverse effects; however, GI, dermatologic, hepatic, endocrine, and pulmonary toxicities are the most frequent. Any changes should raise an alert that they are related to the medication. Immune-related adverse effects (irAEs) vary with incidence and onset depending on the type and dosage of Immune check point inhibitors used. Checkpoint inhibitors therapy is frequently continued even in the event of minor irAEs. However, fatal results have been recorded in instances involving moderate to severe irAEs, and these toxicities require early detection along with suitable care. They can additionally lead to life-threatening decreases in organ function and health related quality of life (HRQL).

KEY WORDS: IMMUNOTHERPY, CHECK POINT INHIBITORS, irAEs, CTLA-4 OR PD1/PD-L1

INTRODUCTION:

Cancer is a complex group of diseases characterized by the uncontrolled growth and spread of abnormal cells. Cancer develops due to genetic mutations that accumulate over time, often triggered by factors such as genetic predisposition, environmental exposures, or lifestyle choices. Traditional cancer treatments include surgery, chemotherapy, and radiation. Developments in Immunotherapy have led to targeted therapies with more effective outcomes.

Immunotherapy is a type of cancer treatment that strengthens the immune system of patients. Immunotherapy can alter or strengthen the immune system's function to enable it to recognize and fight cancerous cells.

The immune system identifies and eliminates abnormal cells as part of its normal function, and it probably stops or slows the growth of many malignancies. For example, immune cells have been observed in and surrounding tumours on occasionally.

Tumour-infiltrating lymphocytes, often known as TILs, are cells that indicate the immune system is reacting to the tumour. Individuals with TIL-containing tumours usually have favourable outlooks than those without them.

Several types of Immunotherapies are used to treat cancer these include:

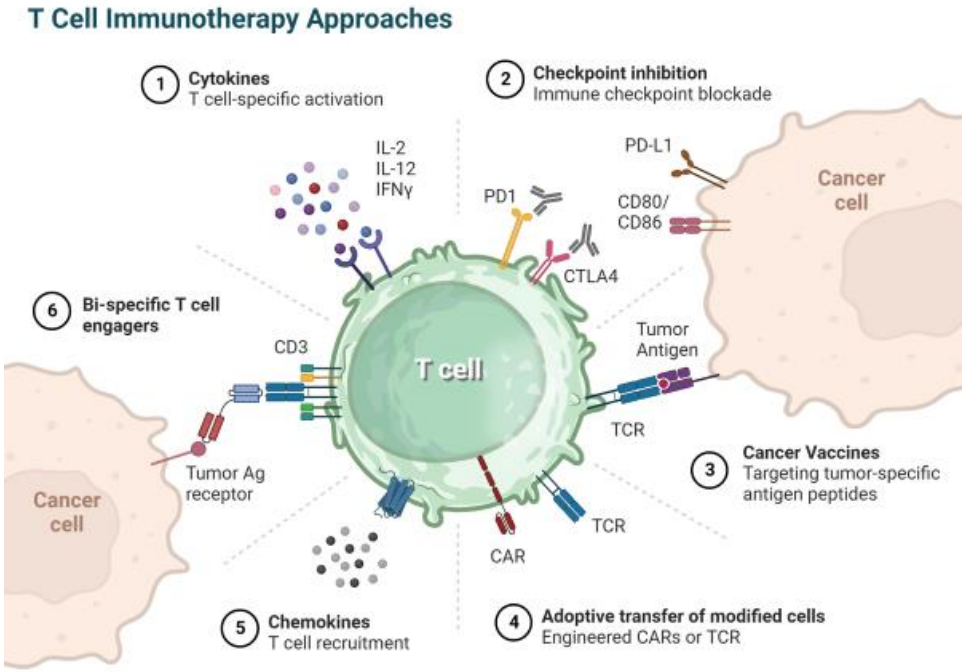
- **Immune checkpoint inhibitors**, which are drugs that block immune checkpoints. These checkpoints are a normal part of the immune system and keep immune responses from being too strong. By blocking them, these drugs allow immune cells to respond more strongly to cancer.

- **T-cell transfer therapy**, which is a treatment that boosts the natural ability of your T cells to fight cancer. In this treatment, immune cells are taken from your tumour. Those that are most active against your cancer are selected or changed in the lab to better attack your cancer cells, grown in large batches, and put back into your body through a needle in a vein. Also be called adoptive cell therapy, Adoptive immunotherapy, or immune cell therapy

- **Monoclonal antibodies**, which are immune system proteins created in the lab that are designed to bind to specific targets on cancer cells. Some monoclonal antibodies mark cancer cells so that they will be better seen and destroyed by the immune system. Such monoclonal antibodies are a type of immunotherapy.

- **Treatment vaccines**, which work against cancer by boosting your immune system's response to cancer cells. Treatment vaccines are different from the ones that help prevent disease

- **Immune system modulators**, which enhance the body's immune response against cancer.[1]



REVIEW MAINLY FOCUSES ON CHECKPOINT INHIBITORS

Immune checkpoints engage when proteins on the surface of immune cells called T cells recognize and bind to partner proteins on other cells, such as tumour cells. These proteins are called immune checkpoint proteins. When the checkpoint and partner proteins bind together, they send an "off" signal to the T cells. This can prevent the immune system from destroying the cancer.

Immunotherapy drugs called immune checkpoint inhibitors work by blocking checkpoint proteins from binding with their partner proteins. This prevents the "off" signal from being sent, allowing the T cells to kill cancer cells.

Drug acts against a checkpoint protein called CTLA-4. Other immune checkpoint inhibitors act against a checkpoint protein called PD-1 or its partner protein PD-L1. Some tumours turn down the T cell response by producing more of PD-L1.

Checkpoint inhibitors also known as checkpoint proteins they block, such as CTLA-4 inhibitors, and PD-L1 inhibitors.

Some examples of checkpoint inhibitors include:

- Anti-CTLA-4 therapies: Ipilimumab (Yervoy) and tremelimumab
- Anti-PD-1 therapies: Cemiplimab, dostarlimab, nivolumab (OPDIVO), pembrolizumab (Keytruda), retifanlimab-dlwr, and tislelizumab
- Anti-PD-L1 therapies: Atezolizumab (Tecentriq), avelumab, and durvalumab
- Anti-LAG-3 therapy: Relatlimab

THE LIST OF ICIS WITH THE CANCER TYPE INDICATION:

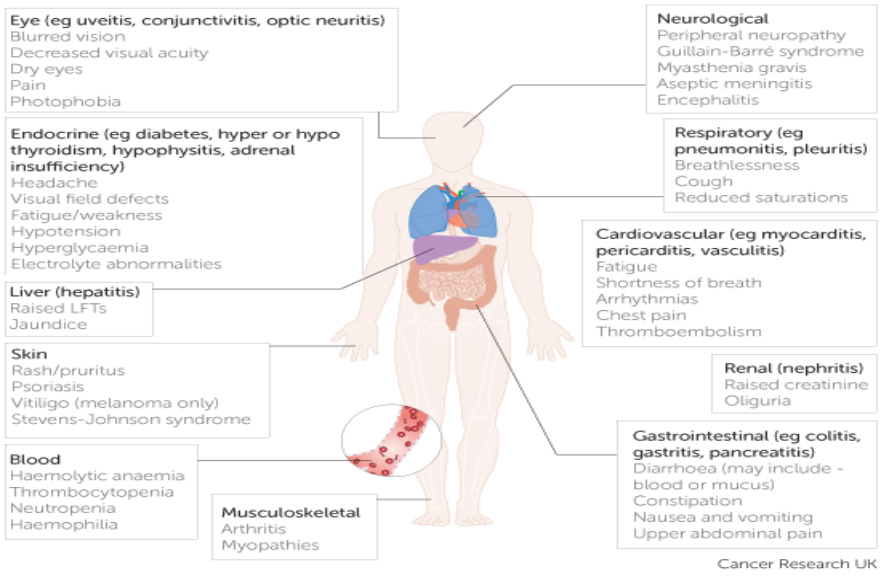
Drug	Target	Approval	FDA-Approved Indications
Nivolumab	PD-1	March 2015	MSI-H or dMMR CRC, HNSCC, HCC, melanoma, cHL, NSCLC, RCC, urothelial cancer, SCLC
Pembrolizumab	PD-1	October 2016	Cervical cancer, gastric cancer, HNSCC, HCC, cHL, melanoma, MCC, MSI-H/dMMR cancers, NSCLC, primary mediastinal DLBCL, urothelial cancer
Atezolizumab	PD-L1	October 2016	NSCLC, urothelial cancer
Cemiplimab	PD-1	September 2018	Cutaneous SCC
Ipilimumab	CTLA-4	August 2010	Melanoma, MSI-H/dMMR CRC, intermediator poor-risk RCC (in combination with nivolumab)
Avelumab	PD-L1	March 2017	MCC, urothelial cancer
Durvalumab	PD-L1	February 2016	NSCLC, urothelial carcinoma

cHL = classic Hodgkin lymphoma; CTLA-4 = cytotoxic T lymphocyte associated antigen 4; CRC = colorectal cancer; DLBCL = diffuse large B-cell lymphoma; dMMR = deficient mismatch repair; FDA = US Food and Drug Administration; HCC = hepatocellular carcinoma; HNSCC = head and neck squamous cell carcinoma; MCC = Merkel cell carcinoma; MSI-H = microsatellite instability-high; NSCLC = non-small cell lung cancer; PD-1 = programmed cell death protein 1;
PD-L1 = programmed cell death ligand 1; RCC = renal cell carcinoma; SCC = squamous cell carcinoma; SCLC = small cell lung cancer.

Since their initial approval for the treatment of advanced melanoma, their use has expanded to the treatment of several other advanced cancer.

Unfortunately, immune checkpoint inhibitors have also been associated with the emergence of a new subset of autoimmune-like toxicities, known as immune-related adverse events. These toxicities differ depending on the agent, malignancy, and individual susceptibilities.

Although the skin and colon are most involved, any organ may be affected, including the liver, lungs, kidneys, and heart. Most of these toxicities are diagnosed by excluding other secondary infectious or inflammatory causes.



Examples of immune-related Adverse Events and some possible symptom

IMMUNE RELATED ADVERSE EVENTS (IRAES) AS PER ASCO GUIDELINES

irAE	Grade 1	Grade 2	Grade 3	Grade 4
Dermatitis	Macules/papules covering <10% BSA +/− associated symptoms (e.g., pruritis, burning, tightness)	Macules/papules covering 10–30% BSA +/− associated symptoms (e.g., pruritis, burning, tightness) AND limiting ADLs	Macules/papules covering >30% BSA +/− associated symptoms (e.g., pruritis, burning, tightness) AND limiting self-care ADLs AND local superinfection	Life-threatening; SJS or widespread mucosal ulcerations (complicated rash with full-thickness dermal ulceration or necrosis)
Hypothyroidism	Asymptomatic; fT4 normal AND TSH >10 mUI/L	Moderate sx (e.g., fatigue, constipation, weight gain, loss of appetite, dry skin, eyelid edema, puffy face, hair loss); Low fT4 +/− TSH >10 mUI/L	Severe sx (e.g., bradycardia, hypotension, pericardial effusion, depression, hypoventilation, stupor, lethargy); very low fT4 and very high TSH	Life-threatening; extremely low fT4 and extremely high TSH (myxedema coma)
Hyperthyroidism	Asymptomatic; fT4 normal AND TSH suppressed (<0.3 mUI/L)	Moderate sx (e.g., weight loss, increased appetite, anxiety and irritability, muscle weakness, menstrual irregularities, fatigue, tachycardia); fT4 high AND TSH suppressed (<0.1 mUI/L)	Severe sx (e.g., arrhythmia, tremor, sweating, insomnia, diarrhea); fT4 normal AND TSH suppressed (<0.1 mUI/L)	Life-threatening; fT4 high AND TSH suppressed (<0.1 mUI/L)
Hypophysitis	Asymptomatic or mild sx (e.g., fatigue, weakness); clinical or diagnostic observations only	Moderate sx (e.g., headache, hypotension); limits IALDs	Severe or medically significant sx but not life-threatening; limiting self-care ADLs	Life-threatening consequences or any visual disturbances; urgent intervention indicated
Adrenal Insufficiency	Asymptomatic or mild sx (e.g., fatigue); clinical or diagnostic observations only	Moderate sx requiring medical intervention	Severe sx requiring hospitalization	Life-threatening adrenal crisis requiring urgent intervention (e.g., severe hypotension or hypovolemic shock, acute abdominal pain, vomiting, fever)

DERMATOLOGICAL TOXICITIES :

Dermatological toxicities are the most common reactions seen with ICIs and usually occur within the first 2 to 3 weeks after initiation of therapy been reported. The most common form of rash is a spongiotic dermatitis-like eczema described as maculopapular, faintly erythematous, and pruritic.

ENDOCRINE TOXICITIES:

Endocrine irAEs often include thyroid dysfunction, hypophysis, and, less often, primary adrenal insufficiency and type 1 diabetes mellitus. Hypothyroidism is more common than hyperthyroidism, The most serious endocrine irAEs is primary adrenal insufficiency.

GASTROINTESTINAL TOXICITIES :

Diarrhoea is defined as increased stool frequency and colitis as the presence of symptoms (e.g., abdominal pain, nausea, vomiting, fever, bloody stools These toxicities usually occur 6 to 7 weeks after therapy initiation. Initial work-up for patients with diarrhoea includes the exclusion of infectious aetiologies, such as Clostridium difficile, Salmonella, and other bacterial, parasitic, or viral causes, including cytomegalovirus.

Hepatitis tends to occur Hepatitis tends to occur within 8 to 12 weeks after initiation of therapy and usually consists of asymptomatic elevation of aspartate aminotransferase alanine aminotransferase, and bilirubin (less common) levels and fever (rarely).

PULMONARY TOXICITIES :

Pneumonitis is a potentially fatal irAEs Pulmonary and extrapulmonary sarcoidosis-like syndrome has also been described as part of the pulmonary spectrum.

RHEUMATOLOGIC TOXICITIES:

Arthralgias have been reported in patients taking ICIs. Inflammatory arthritis has been reported. Arthritis usually develops with other irAEs, occurs after 5 months of therapy, and can affect large, medium, or small joints. It may be destructive and persist after discontinuation of immunotherapy. Other rheumatoid-like toxicities include inflammatory myositis, rhabdomyolysis, giant cell arteritis, and polymyalgia-like syndrome.

NEUROLOGIC TOXICITIES:

Headache, peripheral and central nervous system symptoms may also involve. Motor or sensory peripheral neuropathies, Other peripheral toxicities include a myasthenia gravies like

syndrome, which may cause diaphragmatic involvement, and fatal Guillain-Barré-like syndrome toxicity. Central toxicities include aseptic meningitis, autoimmune encephalitis, posterior reversible encephalopathy syndrome, and transverse myelitis.

RENAL TOXICITIES:

The most common forms of nephrotoxicity include acute interstitial nephritis, lupus-like nephritis, granulomatous nephritis, diffuse interstitial nephritis, or minimal change disease toxicity include acute interstitial nephritis, Presentation varies from asymptomatic to oliguria, haematuria, and peripheral oedema

OCULAR TOXICITIES:

Ocular toxicities include conjunctivitis, episcleritis, keratitis, blepharitis, and uveitis. Uveitis may cause photophobia, blurry vision, pain, and eye dryness.

HEMATOLOGIC TOXICITIES:

Anaemia, Neutropenia, immune thrombocytopenic purpura, pure red cell aplasia, disseminated intravascular coagulopathy, and acquired haemophilia

CARDIAC TOXICITIES:

Cardiac toxicities from ICIs include myocarditis, pericarditis, arrhythmias and heart block, and new-onset heart failure[2]

irAE	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea/colitis	<4 stools/day above pt baseline	4–6 stools/day above pt baseline AND associated abdominal pain, mucus, or blood in the stool	≥7 stools/day above pt baseline AND incontinence or need for hospitalization for IV fluids ≥24 h	Life-threatening; grade 3 sx plus fever or peritoneal signs consistent with perforation or ileus
Hepatitis (these ranges may differ if the patient is receiving ICI for HCC)	AST/ALT up to 3× ULN or t-bili up to 1.5× ULN (or <2× baseline)	AST/ALT >3× ULN or t-bili >1.5–3× ULN (or >2× baseline)	AST/ALT >5–20× ULN or t-bili >3–10× ULN	AST/ALT >20× ULN or t-bili >10× ULN
Pneumonitis	Asymptomatic, diagnosis is radiographic	Sx, medical intervention is indicated as it limits IADLs	Severe sx that limit self-care ADLs; supplemental O2 is indicated	Life-threatening respiratory compromise; urgent intervention indicated
Nephritis	Serum Cr > ULN AND >1.5–2× pt baseline; 1+ proteinuria (<1 g/24 h)	Serum >2–3× pt baseline; 2+ proteinuria (<1.0–3.4 g/24 h)	Serum Cr >3× pt baseline; proteinuria >3.5 g/24 h	Life-threatening; serum Cr >6× ULN; dialysis indicated
Neurotoxicity	Asymptomatic or mildly sx	New onset moderate sx limiting IALDs	New onset severe sx (e.g., vision changes, weakness, sensory deficits); affecting self-care ADLs; not life-threatening	Life-threatening; urgent intervention indicated
Cardiotoxicity	Abnormal cardiac biomarkers or ECG	Abnormal screening tests with mild sx	Moderately abnormal testing or sx with mild activity	Life-threatening; moderate to severe decompensation, intervention required

OBJECTIVES:

Immune checkpoint inhibitors (ICIs) have significantly improved treatment for advanced malignancies, targeting checkpoints such as PD-1, PD-L1, and CTLA-4. These therapies have been approved by the FDA in various types of cancers, with response rates ranging from 15 to 30% in most solid tumours to 45-60% in melanoma and MSI-H tumours. However, a significant proportion of patients do not respond to these therapies, necessitating the identification of biomarkers to predict the most benefit from treatment. Predictive biomarker research has primarily focused on tumour signatures, but clinical biomarkers, including early-on-treatment pharmacodynamic markers, have been less studied. Immune-related adverse event (IRAE) onset may be a clinical biomarker for ICI response.

Patients experiencing IRAEs while on therapy with anti-PD-1 and anti-PD-L1 antibodies have been documented to experience improved outcomes, but this association has been less uniform in patients treated with anti-CTLA-4 antibodies. The relationship between IRAE site, severity, timing of onset, and management influences ICI effectiveness. This review will discuss seminal studies that have addressed these questions and shaped the narrative about the predictive value of IRAE onset for patients on ICIs, focusing on FDA-approved indications for ICI therapy and those involving ICIs alone.

Fatigue is a common adverse reaction (irAEs) associated with the use of Immune Checkpoint Inhibitor (ICIs), with incidence rates ranging from 16% to 71% when combined with other anticancer therapies. Fatigue is usually mild and does not interfere with daily activities. ICIs often cause dermatological toxicities within the first 2-3 weeks of therapy. Rash or pruritus is common in 50% of patients treated with anti-CTLA-4 antibodies, 40% with anti-PD-1 or anti-PD-L1 therapy, and 60% with combination therapy. Pneumonitis is a potentially fatal irAEs with an incidence of 5% in patients receiving ICIs, particularly with combination therapy and in patients with lung cancer. It occurs more often with anti–PD-1 than anti–CTLA-4 therapy, with a median time to presentation of almost 3 months.[3]

Studies have shown an association between IRAE onset and the efficacy of anti-PD-1 and anti-PD-L1 antibodies in NSCLC patients. In a retrospective study, 89.3% of patients received anti-PD-1, while 10.7% received anti-PD-L1 antibodies. Patients with IRAEs had superior progression-free survival (PFS) and overall survival (OS) compared to those without IRAEs. In a large retrospective analysis, 43.6% of patients developed IRAEs, with the most common sites being endocrine, dermatologic, and gastrointestinal toxicities. Other studies have also demonstrated similar correlations between IRAE onset and ICI efficacy. A retrospective study found that 42.2% of metastatic RCC patients treated with ICIs experienced IRAEs, with common sites being dermatologic, gastrointestinal, and endocrine. IRAEs were associated with improved overall survival and treatment. A retrospective analysis of 389 pre-treated metastatic RCC patients with nivolumab showed that 20% experienced IRAEs, with prolonged survival and a 1-year OS of 75.4 and 59.8%, respectively[4]

Common adverse events (irAEs) in cancer treatment vary based on the type of ICI treatment. Patients receiving ICI targeting CTLA-4 (53.8%) had higher incidences of irAEs than those targeting PD-1 (26.5%) or PD-L1 (17.1%). Grade 3/4 irAEs were more common with ICIs targeting CTLA-4 (31%). PD-1/PD-L1 blockade therapies, such as durvalumab, atezolizumab, and pembrolizumab, were associated with higher rates of colitis. Concurrent, dual blockade of CTLA-4 and PD-1/PD-L1 system components has increased rates of irAEs, potentially leading to treatment discontinuation. Combination therapies have shown synergistic antitumor responses and are recommended for cancer treatment.[5]

The study analysed 318 reported G ≥ 2 irAEs in 318 patients, with 229 experiencing at least one toxicity. The most common irAEs were endocrine disorders, skin toxicity, gastrointestinal toxicities, pulmonary, and hepatitis. 140 toxicities led to treatment discontinuation or temporary interruption, with 44 in LC and 96 in Mel patients. The most frequently associated regimen was the anti-CTLA4-anti-PD(L)1 combination. Gastrointestinal irAEs and hepatitis were more frequent in the Mel group, while pneumonitis and rheumatological irAEs were more frequent in LC. Thirty-six patients were challenged with a second ICI line after developing a G ≥ 2 toxicity.[6]

A study involving 517 patients with ir-fatigue data from June 2014 to April 2019 found that 74.7% of them were eligible for clinical outcomes analysis. The majority were NSCLC, melanoma, renal cell carcinoma, and other malignancies. The median age was 68 years, with 44.0% being elderly. The majority experienced grade ir-AEs, with 19.9% experiencing early ir-fatigue and 38.9% experiencing delayed ir-fatigue. 61 patients experienced both early and delayed ir-fatigue[7]

The study evaluated the incidence of colitis and diarrhea in patients with PD using single-agent ipilimumab, anti-PD-1 or anti-PD-L1, or combination therapy with ipilimumab and nivolumab. All-grade colitis occurred in 9.1% of patients with ipilimumab alone, while grade 3-4 colitis occurred in 6.8% and grade 3-4 diarrhea in 7.9%. Single-agent anti-PD-1 had lower incidences at 1.4%, 0.9%, and 1.3% for all-grade colitis, grade 3-4 colitis, and grade 3-4 diarrhea, respectively. Combination therapy with ipilimumab and nivolumab showed a higher incidence of all-grade colitis, grade 3-4 colitis, and grade 3-4 diarrhea.[8]

The incidence of cutaneous inflammatory reactions (irAEs) in patients treated with immunosuppressive drugs (ICIs) varies depending on the ICI used. Anti-CTLA-4 monotherapy has a higher incidence (44-59%) than anti-PD-1 and anti-PD-L1 monotherapy, while combination therapy with anti-PD-1 and anti-CTLA-4 agents has the highest incidence (59-72%). In severe cases, cutaneous irAEs are observed in approximately 25% of patients treated with anti-CTLA-4 agents, with 2.4% being grade 3 and 4. The prevalence of cutaneous irAEs depends on the type of cancer treated with ICIs, with MM being more likely to experience irAEs than NSCLC and RCC. Histology may affect the TME, immune infiltrate, adaptive immune response, and neoantigen formation, causing different skin toxicities.[9]

The incidence of irAEs did not significantly influence the overall survival (OS) and progression-free survival (PFS) in the entire cohort. The risk of irAEs was significantly higher with dual-agent therapy (ipilimumab/nivolumab combination) and high disease burden. The only haematological

parameter significantly different between the groups was the mean PLR, which was lower in the irAEs group. None of the thresholds for baseline haematological factors could predict the incidence of irAEs. The number of doses of ICI people who had irAEs was low compared to the non-irAEs group. Other factors such as type of primary malignancy, lung cancer, stage of the diseases at the time of ICI therapy, stage IV disease, and higher ALC seem to have a considerable association with irAEs, though the association is not statistically significant. Multivariate logistic regression showed PLT/ALC ratio as the most associated predictor in the presence of other clinical factors.[10]

CONCLUSION:

Cancer immunotherapy the Immune checkpoint inhibitors have transformed the treatment scope in various malignancies over the past two decades. Clinicians should be aware of unique toxicities Profiles. Immune checkpoint point inhibitors allow the body's innate immune system to target cancer cells by inhibiting the inhibitory signals that cancer cells transmit to T cells. Adverse effects unique to ICIs, termed as irAEs, results in immunostimulatory effect in multiple organs. While irAEs are mild, severe cases do occur can be rapidly fatal. Immunosuppressive agents initiated for the primary treatment. This extensive use had widened treatment-related and survival considerations behind creating an anti-tumour immune response to include long lasting consequences on quality of life.

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