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IMMUNO-ONCOLOGY AND TECHNOLOGY

REVIEW

Solid tumour cellular therapy — principles of toxicity management

M. Julve[1†], Y. N. S. Wong[2†], K. H. J. Lim[3,4] & A. J. S. Furness[1*]

[1]Department of Medical Oncology, The Royal Marsden NHS Foundation Trust, London, UK; [2]Division of Medical Oncology, National Cancer Centre Singapore, Singapore, Singapore; [3]Division of Cancer Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester; [4]Advanced Immunotherapy and Cell Therapy Team, Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK

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Following the Food and Drug Administration (FDA) approval of lifileucel and afami-cel for patients with advanced melanoma and synovial sarcoma, respectively, there is a need for improved understanding and guidance regarding the management of toxicity associated with adoptive cellular therapies (ACTs) for solid tumours. Further approvals are expected in coming years, with toxicity management representing a significant consideration for centres looking to implement such advanced therapy medicinal products. Importantly, first-generation tumour-infiltrating lymphocyte therapies are associated with unique toxicities compared with gene-modified T-cell therapies such as chimeric antigen receptor T-cell therapy (CAR T) and T-cell receptor-modified therapy (TCR T), presenting novel challenges for treating healthcare professionals. Extrapolating from experience with CAR T in the field of haemato-oncology, coupled with the historical use of high-dose interleukin-2 in solid tumour therapeutic regimens and more recently lifileucel and afami-cel, has led to the development of core principles for managing toxicity, which is discussed here. Looking to the future, a rapidly developing field with next-generation ACT products, a basic knowledge of such core principles will be an important foundation for healthcare professionals working in this space.
Key words: tumour-infiltrating lymphocyte therapy, T-cell receptor-modified T-cell therapy, chimeric antigen receptor T-cell therapy, immune-related adverse events, cytokine release syndrome

INTRODUCTION

Immunotherapy has transformed outcomes for patients with metastatic solid cancers in the past decade. In particular, immune-checkpoint inhibitors targeting the programmed cell death protein 1 (PD-1) receptor and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) have provided the opportunity for durable disease control among patients with metastatic melanoma.[1] Nevertheless, there remains heterogeneity in response between patients, with lower efficacy rates observed across other cancer subtypes. Furthermore, a major limitation of immune-checkpoint inhibition is the dependence on the intrinsic quantity and repertoire of, mostly exhausted, T cells *in vivo*.[2] A potential solution is adoptive cellular therapy (ACT), whereby autologous immune cells are expanded *ex vivo* before subsequent reconstitution in patients, for example, tumour-infiltrating lymphocyte (TIL) therapy or engineered T cells, which have shown promising results in a range of solid tumours including the potential for durable clinical benefit.[3-6]

In the first phase III randomised controlled trial of TIL therapy in solid tumours, the median progression-free survival was 7.2 months following the administration of unselected polyclonal TILs, compared with 3.1 months with ipilimumab (hazard ratio 0.50, 95% confidence interval 0.35-0.72, $P < 0.001$).[7] Notably, 20% (17/84) of patients had a complete response to TIL therapy. In parallel, similar clinical benefit was observed with lifileucel, Iovance's proprietary autologous TIL product, which had subsequently been granted accelerated approval for the treatment of unresectable or metastatic melanoma by the US Food and Drug Administration (FDA) in February 2024.[5] This marked the first FDA-approved cell therapy for solid tumours.

In addition, the FDA recently granted accelerated approval to afamitresgene autoleucel (afami-cel), an autologous, affinity-enhanced MAGE-A4-directed T-cell receptor-modified T-cell therapy (TCR T), for patients with pretreated, advanced synovial sarcoma. Efficacy was evaluated from the phase II SPEARHEAD-1 study, where an overall response rate of 43.2% (95% confidence interval 28.4% to 59%) was achieved. This approval represents the

*Correspondence to: Dr Andrew Furness, Department of Medical Oncology, The Royal Marsden NHS Foundation Trust, Fulham Road, London SW3 6JJ, UK. Tel: +44-(0)20-7808-2103
E-mail: andrew.furness@rmh.nhs.uk (A. J. S. Furness).

†These authors contributed equally to this work.

first genetically modified solid tumour cellular therapy product to reach this milestone.[8]

Adverse effects associated with ACT are best described within the acute phase, often either related to the administration of the cell product or other parts of the treatment regimen. This includes lymphodepleting chemotherapy and high-dose interleukin-2 (IL-2), which are necessary to improve efficacy and maintain the survival of infused TIL. Long-term follow-up data for these therapies remain limited. Consequently, as ACT has become more widely used, there is a need to consolidate the literature in the management of the toxicities pertaining to ACT. The historical guidance on the management of high-dose IL-2 requires re-evaluation in the context of TIL cell therapy protocols, where IL-2 is utilised to optimise T-cell function rather than as a monotherapy. Recently, an expert consensus guideline on the management and best practice for TIL therapy has been published.[9] Moreover, while the management of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) from chimeric antigen receptor T-cell therapy (CAR T) in solid cancers may be extrapolated from established haematology guidelines, to date we are not aware of a specific ACT toxicity review that encompasses all ACT.

Here, we provide a scoping review summarising the major immediate or acute and chronic adverse events associated with T-cell therapy in solid tumours from reported studies.

MODALITIES OF ACT

Within the spectrum of ACT for solid tumours, there are currently three principal modalities: TIL therapy, CAR T and TCR T. Broadly, the patient pathway is composed of procurement (tissue and/or blood), manufacture, non-myeloablative lymphodepletion (NMA-LD) and cellular infusion.[4,10]

Tumour-infiltrating lymphocyte therapy

TIL therapy represents a technology that has been in development since the 1980s, with pioneering work led by Steven Rosenberg and colleagues[11] displaying the anticancer efficacy of autologous T lymphocytes isolated from tumour tissue. The cellular product represents a bespoke but endogenous, unselected, polyclonal population (Figure 1). Constituent cells are predominantly made up of antitumourigenic CD8+ and CD4+ T-cell populations; however, the presence of protumourigenic (T regulatory) lymphocyte populations has also been documented and may negatively correlate with response.[12,13] In addition, antigenic targets are typically unknown with significant differences in product specifications between patients.[14] When compared with CAR T and TCR T therapies, TIL requires surgical tumour removal for TIL extraction and expansion, as well as postinfusion IL-2, resulting in a unique toxicity profile.[9]

Gene-modified T-cell therapies (TCR T/CAR T)

For CAR T and TCR T therapies, peripheral blood lymphocytes are harvested via apheresis, before undergoing genetic modification to express receptors that confer specificity to a desired tumour antigen.

TCR T therapy involves genetic modification of autologous T cells to induce the expression of endogenous TCR with bespoke specificity.[6] TCRs are heterodimeric glycoproteins consisting of TCR-α and β chains associated with a CD3 complex (Figure 1). TCR T cells can recognise antigens derived from both membrane and intracellular proteins presented by major histocompatibility complex (MHC) and are therefore advantageous in view of a broad targetable antigen repertoire. Conversely, the requirement of MHC for antigen presentation has been suggested as a limitation, with MHC downregulation thought to represent a mechanism of immune evasion/treatment resistance.[6] Furthermore, the use of MHC/human leukocyte antigen machinery restricts the use of TCR-engineered products to patients with compatible genetic haplotypes.[17]

CAR T cells are genetically engineered T cells with synthetic receptors consisting of an antibody-derived antigen-binding moiety fused to an intracellular signalling region, typically consisting of the CD3ζ chain and costimulatory domains (CD28 or 4-1BB; Figure 1).[18] One advantage of CARs over their ACT counterparts is their ability to target tumour antigens in an MHC-independent fashion. Furthermore, CARs have the ability to bind to a range of cell surface proteins such as glycosylation variants rather than being limited to protein antigens, which may widen the potential for tumour-specific antigenic targets.[19] Although CAR-T cells are able to target antigens in an MHC-unrestricted manner, they are limited to targeting cell surface epitopes only.

NON-MYELOABLATIVE LYMPHODEPLETION

A common requirement across the diverse field of solid tumour ACT remains the need for NMA-LD. This optimises the tumour microenvironment by reducing competition for essential cytokines as well as eliminating immunosuppressive cellular populations, such as T-regulatory and myeloid-derived suppressor cells.[9] Toxicity profiles of the two frequently used chemotherapy agents, cyclophosphamide and fludarabine, are now well documented.[20] Dosage and schedule of delivery can vary across trials and modalities, with TIL therapy generally using a higher dosing range (cyclophosphamide 60-120 mg/kg, fludarabine 75-125 mg/m^2) in comparison to established CAR T protocols (cyclophosphamide 35 mg/kg, fludarabine 75 mg/m^2).[9,21] These agents are primarily administered to in-patients through an intravenous (IV) cannula over 3-5 days,[20] with cyclophosphamide requiring adequate prehydration to preserve renal function.[22] Furthermore, mesna is concurrently administered to mitigate the known risk of haemorrhagic cystitis associated with cyclophosphamide. It is important to note that the use of fludarabine renders the need for lifelong irradiated blood products after lymphodepletion. Specifically for TIL therapy, lymphodepletion-associated hydration

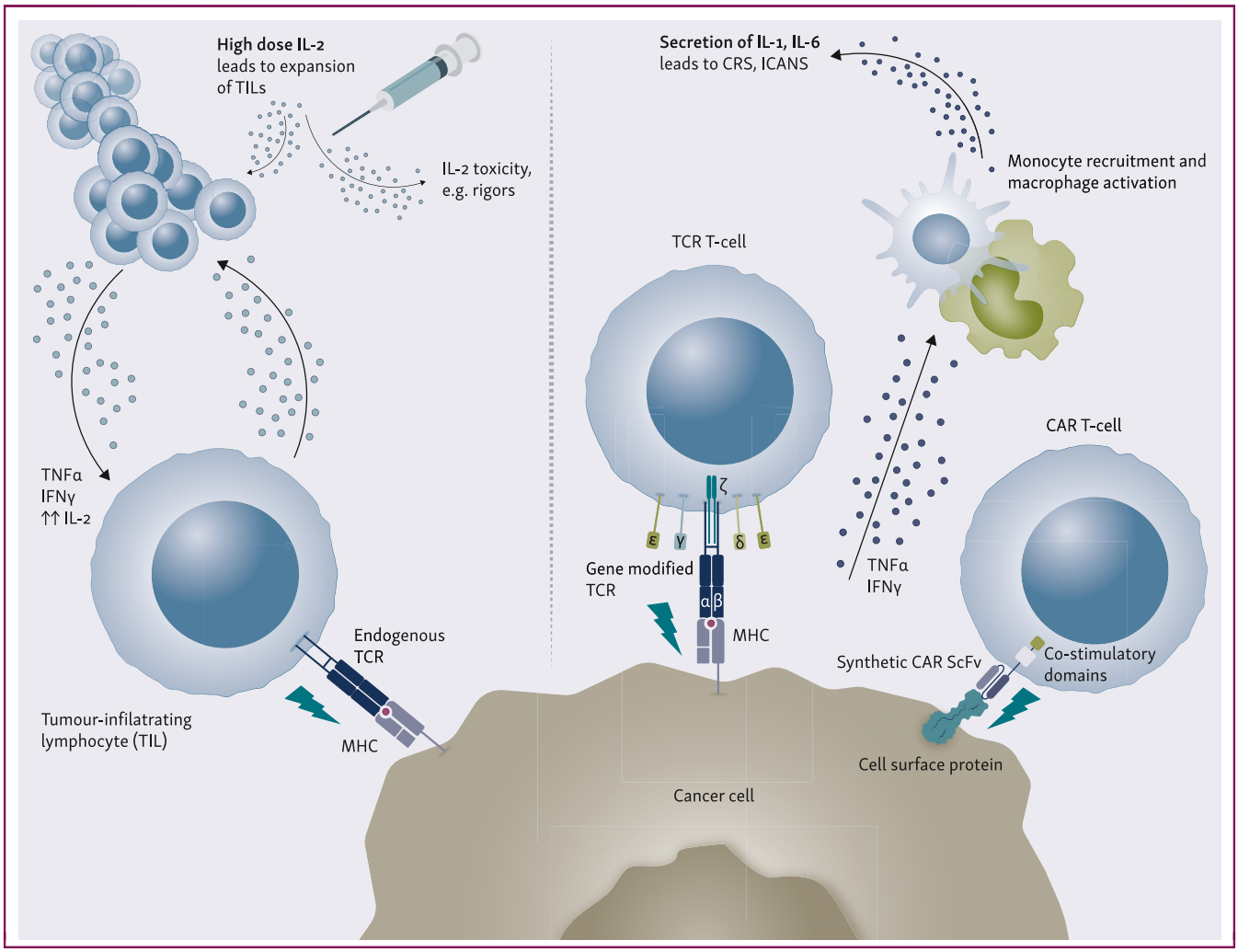

Figure 1. Modalities of adoptive cellular therapy (ACT) and interaction with tumour. High-dose IL-2 leads to the expansion of TIL, the interaction of endogenous TCR with cancer cell MHC and the subsequent T-cell activation and IL-2 toxicity. Secretion of proinflammatory cytokines TNF-α, IFN-γ and IL-2 further propagates T-cell activation.[15] TCR-modified T cells interact via gene-modified TCRs with cancer cell MHC machinery. CAR T cells interact via synthetic CAR SvFc with cell surface proteins. TCR T and CAR T cell therapies induce monocyte/macrophage activation and secretion of IL-1 and IL-6, leading to the development of CRS and ICANS.[16] CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; IFN-γ, interferon-gamma; IL, interleukin; MHC, major histocompatibility complex; TCR, T-cell receptor; TIL, tumour-infiltrating lymphocyte; TNF-α, tumour necrosis factor alpha.

requires careful fluid balance assessment with the goal of ensuring euvolaemia and baseline weight before cellular infusion.[9]

As with other high-dose chemotherapy regimens, the predominant acute toxicities associated with NMA-LD are pancytopenia, nausea, vomiting, mucositis and alopecia.[20] These are now well documented with standardised management approaches,[9,23] and hence not the focus of this review.

Further considerations for NMA-LD

Adequate IV access is essential before the initiation of NMA-LD and cell transfer. Because of the complication of pancytopenia and potential interventional procedures, it is recommended that definitive IV access is achieved before NMA-LD. Peripherally inserted central catheter (PICC) line or central venous catheterisation (CVC) is recommended to ensure reliable IV access throughout ACT pathways.[9,24]

Owing to the long-term immune dysfunction associated with NMA-LD, oral opportunistic infection prophylaxis is recommended for all patients, typically with aciclovir 400 mg three times a day (tds) and co-trimoxazole 480 mg twice a day (bd) 3×/week from the initiation of NMA-LD, as well as fluconazole 400 mg from the day of TIL infusion until absolute neutrophil count $>1000/mm^3$. The length of prophylaxis required is not clearly defined; however, recent guidance suggests a continuation of opportunistic infection prophylaxis for 6 months or until CD4 count recovers to >200 cells/mm^3.[9,24]

Cyclophosphamide, an alkylating agent, has been shown to be associated with acute cardiac toxicity with an incidence of 7%-33% in the haemato-oncology setting.[25] Its mechanism is postulated to consist of toxic metabolite production and oxidative endothelial damage, with subsequent microthrombi, interstitial oedema/haemorrhage and pericardial/myocardial effusion.[25] The onset typically occurs within the first 48 h but can be observed up to 10 days after

administration.[25] Although the impact of this toxicity is yet to be fully understood in the solid tumour ACT setting, in a pooled analysis of 103 patients with metastatic melanoma who received standard dose NMA-LD, there were 3 cases of early deaths attributed to cyclophosphamide-induced cardiotoxicity before TIL infusion.[20] Baseline cardiovascular function is therefore essential to consider and assess, especially in the context of patients with heavily pretreated malignancy or multiple comorbidities.[26]

The use of NMA-LD in patients with brain metastases remains controversial owing to the risk of thrombocytopenia and intracranial haemorrhage.[27] Consequently, patients with intracranial disease have historically been omitted from solid tumour ACT clinical trials. A study of 18 patients with intracranial metastatic melanoma undergoing TIL therapy[27] documented intracranial haemorrhage in 2/18, with 1 patient requiring craniotomy for clot evacuation. In an effort to assess whether low-dose NMA-LD regimens may be appropriate for this patient population, a clinical study[28] is currently enrolling, with results expected in late 2025. Currently, patients with untreated intracranial metastases are not recommended for NMA-LD; however, investigations are ongoing regarding the use of NMA-LD for primary central nervous system (CNS) tumour ACT.[9,29–31]

ACT TOXICITY

Owing to the biological nuances across the three major modalities of solid tumour ACT, there remain important differences in associated toxicities (Figure 1). High doses of IL-2 lead to the expansion of TILs, as well as IL-2-related toxicities. The cognate interaction of endogenous TCR with MHC leads to T-cell activation and further expansion of TILs, which leads to secretion of proinflammatory cytokines TNF-α, interferon-gamma (IFN-γ) and IL-2 propagating T-cell expansion.[15] TCR-modified T cells interact via gene-modified TCRs with cancer cell MHC machinery, while CAR T cells interact via synthetic CAR SvFc with cell surface proteins. TCR T and CAR T cell therapies induce monocyte/macrophage activation, leading to the secretion of IL-1 and IL-6 and the potential development of CRS and ICANS.[16] Clinical understanding of what to expect and how to manage such events is essential to the set up and delivery of a solid tumour cellular therapy service.

TUMOUR-INFILTRATING LYMPHOCYTE THERAPY

Following the recent FDA approval of lifileucel for pretreated, advanced melanoma, there has been much interest in the management of TIL-associated toxicities and optimal management strategies.[5] Although considered a novel therapy, multiple clinical trials since the 1980s have documented the adverse event profile of TIL therapy (Table 1), from which some general principles can be extrapolated.

Following TIL infusion, the immediate risk of hypersensitivity reactions has been reported in <4% of patients.[9] Prophylactic interventions such as chlorphenamine and paracetamol are effective and such toxicities are not expected to induce significant physiological dysfunction when adequately managed as per local institutional guidelines. Transient TIL-related dyspnoea (due to TIL passing through pulmonary circulation), chills and fever are occasionally seen but are usually self-limiting (Figure 2).[44] The prophylactic use of systemic corticosteroids is not recommended due to its potential impact on TIL efficacy, and should only be considered in emergency situations.[9]

Although nearly all patients experience toxicity from TIL therapy, this is almost entirely due to the acute effects of high-dose IL-2 or NMA-LD chemotherapy.[13] In the seminal phase III study,[7] treatment-related adverse events of grade 3 or higher occurred in all patients in the TIL group ($n = 80$), with NMA-LD-associated neutropenia (100%), thrombocytopenia (89%) and febrile neutropenia (86%) being the most common; 15% of patients in the TIL cohort experienced toxicity that was considered serious, with adult respiratory distress syndrome ($n = 3$ patients) documented as the most common. Others that affected more than one patient were increased cardiac troponin ($n = 2$), myocarditis ($n = 2$) and venous thromboembolism ($n = 2$); 10% of patients required organ support in intensive care and one patient died due to an arterial thromboembolism, which was not considered to be related to treatment.

CRS and ICAN are rarely seen with unmodified, first-generation TIL products.[5,7] This is likely to be a consequence of TIL representing a naturally occurring cellular product which has undergone immune selection for self-tolerance.[9] In addition, TIL reactivity is thought to be directed towards tumour-specific neoantigens, reducing the impact of on-target, off-tumour (OTOT) toxicities that have been associated with genetically modified products.[13] Subsequently, the use of the anti-IL-6 agent tocilizumab is not typically used in the routine management of TIL-associated toxicity (Figure 1).[9]

Interleukin-2

IL-2 represents a pleiotropic, immunogenic cytokine, known to be endogenously secreted by CD4+ T cells following activation.[45] Following its development as an anticancer therapy for metastatic renal cell carcinoma in the 1990s, its toxicity profile has been well documented.[46] Management of IL-2 toxicity within TIL therapy differs, however, due to the physiological changes induced by NMA-LD (namely cytopenia) and the abbreviated course used in TIL regimes. Because of the biological necessity of IL-2 for successful TIL transfer, it is known to be accountable for a significant proportion of TIL toxicity. Early studies in patients receiving IL-2 alone or with lymphocyte-activated killer cells indicated that the addition of lymphocyte-activated killer cells did not significantly contribute to the overall toxicity profile.[47] This suggests that although the physiological dysfunction seen with IL-2 is related to lymphocyte activation, TIL infusate is not the causative driver. A wide range of toxicities have been observed following the administration of IL-2 and a broad understanding of these is important in the management of patients undergoing TIL therapy.

Table 1. Notable TIL trials with reported TIL/IL-2-associated toxicities

Paper	ACT	Tumour type	Phase	Patients, *n*	Acute toxicity (grade 3-4 unless otherwise stated) related to TIL/IL-2
Rohaan et al.[7]	TIL	Melanoma	3	84	Hypophosphatemia (60%), fever (45%), dyspnoea (19%), hypertension (14%), rash (11%), CK rise (11%), ALT/AST rise (11%), hypotension (8%), chills (8%), CLS (1%) Other key AEs (any grades): CLS (30%), vitiligo (11%), uveitis (8%), hearing loss (4%)
Sarnaik et al., JCO 2021[32]	TIL	Melanoma	2	66	Hypophosphatemia (30%), pyrexia (17%), hypoxia (15%), hypotension (11%), rash (9%), chills (6%), dyspnoea (5%), raised liver enzymes (3%), fatigue (2%) 1 death
Chandran et al.[33]	TIL	Uveal melanoma	2	21	Raised creatinine (29%), infection (24%), raised liver enzymes (14%), dyspnoea (10%), hypophosphataemia (10%), cardiac arrhythmia (5%), renal failure (5%), thrombosis (5%), hypoxia (5%), neuropathy (5%) Other key AEs (any grades): uveitis (5%), rash (5%), oedema (5%), vitiligo (5%), hypotension (10%) 1 toxic death (infection)
Dudley et al., JCO 2013[34]	TIL	Melanoma	2	69	Febrile neutropenia (41%), sepsis (20%), other infection (5%), dyspnoea (4%), intubated for somnolence (3%)
Rosenberg et al.[35]	TIL (partial LD)	Melanoma	1	86	Nausea (43%), chills (28%), diarrhoea (23%), disorientation (15%), fatigue (9%), respiratory distress (8%), pruritus (4%), infection (3%), oedema (1%) Other key AEs (any grades): hypotension (46%), arrythmias (6%), coma (3%), somnolence (3%), Toxic death (1%)
Rosenberg et al.[36]	TIL (no LD)	Melanoma	1	20	All grades: Hypotension (65%), nausea (55%), chills (50%), diarrhoea (45%), disorientation/coma/somnolence (30%), respiratory distress (10%)
Rosenberg et al.[37]	TIL +/− TBI	Melanoma	2	93	1 toxic death (1.1%) (other data not specified)
Besser et al.[38]	TIL	Melanoma	2	20	All grades: Pulmonary congestion (35%), renal failure (25%), diarrhoea (20%), prolonged hypotension (15%), confusional state (5%),
Dudley et al.[39]	TIL	Melanoma	2	93	All grades: Infection (22%), intubated for somnolence (10%), uveitis (2%) 1 death (bowel perforation sepsis)
Goff et al.[40]	TIL +/− TBI	Melanoma	2	101	CRS (6.1%), cardiac arrhythmia (5%), haemofiltration/ haemodialysis (3%), intubation (2%) 1 toxic death (1%)
Creelan et al.[41]	TIL + Nivo	Lung	1/2	13	All grades: Nausea (86%), hypophosphataemia (75%), raised liver enzymes (55%), skin rash (55%), diarrhoea (55%), CRS (45%); total severe toxicity: 12.5%
Stevanović et al.[42]	TIL	HPV	2	29	Metabolic disorders (41.4%), nausea (20.7%), hypoxia (27.6%), dyspnoea (13.8%), ICANS (3.4%)
Kverneland et al.[43]	Ipi, TILs, Nivo	Pan-tumour	2	25	Fever (16%), PS drop (12%), dyspnoea (8%), transaminase elevation (4%)

ACT, adoptive cellular therapy; AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; CK, creatinine kinase; CLS, capillary leak syndrome; CRS, cytokine release syndrome; HPV, human papillomavirus; ICANS, immune effector cell-associated neurotoxicity syndrome; IL-2, interleukin-2; Ipi, ipilimumab; LD, lymphodepletion; Nivo, nivolumab; PS, performance status; TBI, total body irradiation; TIL, tumour-infiltrating lymphocyte.

IL-2 is typically delivered as an IV bolus at a dose of 600 000 IU/kg every 8-12 h from day 1 (starting 3-24 h after TIL infusion) to day 4 with a maximum of six doses.[9] Before the initiation of IL-2, it is essential to ensure that patients have had antihypertensive medications discontinued (>24 h before IL-2), are haemodynamically stable and euvolaemic.[9] Owing to the short half-life and dose-limiting effects of IL-2, the key to optimal administration is regular clinical assessment and the delay/omission of subsequent dosing until physiological parameters have normalised.[46] Importantly, data from previous studies have suggested that the number of IL-2 doses administered is not associated with response, and therefore early discontinuation due to toxicity should always be considered.[48] Suggested toxicity management by organ system is listed in Table 2, with further discussion in the following sections.

Fever and rigors

Following IL-2 administration, fever and rigors are often the first toxicities encountered. Premedication is recommended with paracetamol and nonsteroidal anti-inflammatory drugs; however, significant chills with associated rigors are often experienced 1-2 h after administration.[46] The use of IV pethidine at a dose of 25 mg at 15-min intervals is usually adequate to terminate rigors and maintain patient stability. About 4 h after IL-2 administration, fevers commonly develop following episodes of chills/rigors. Careful clinical

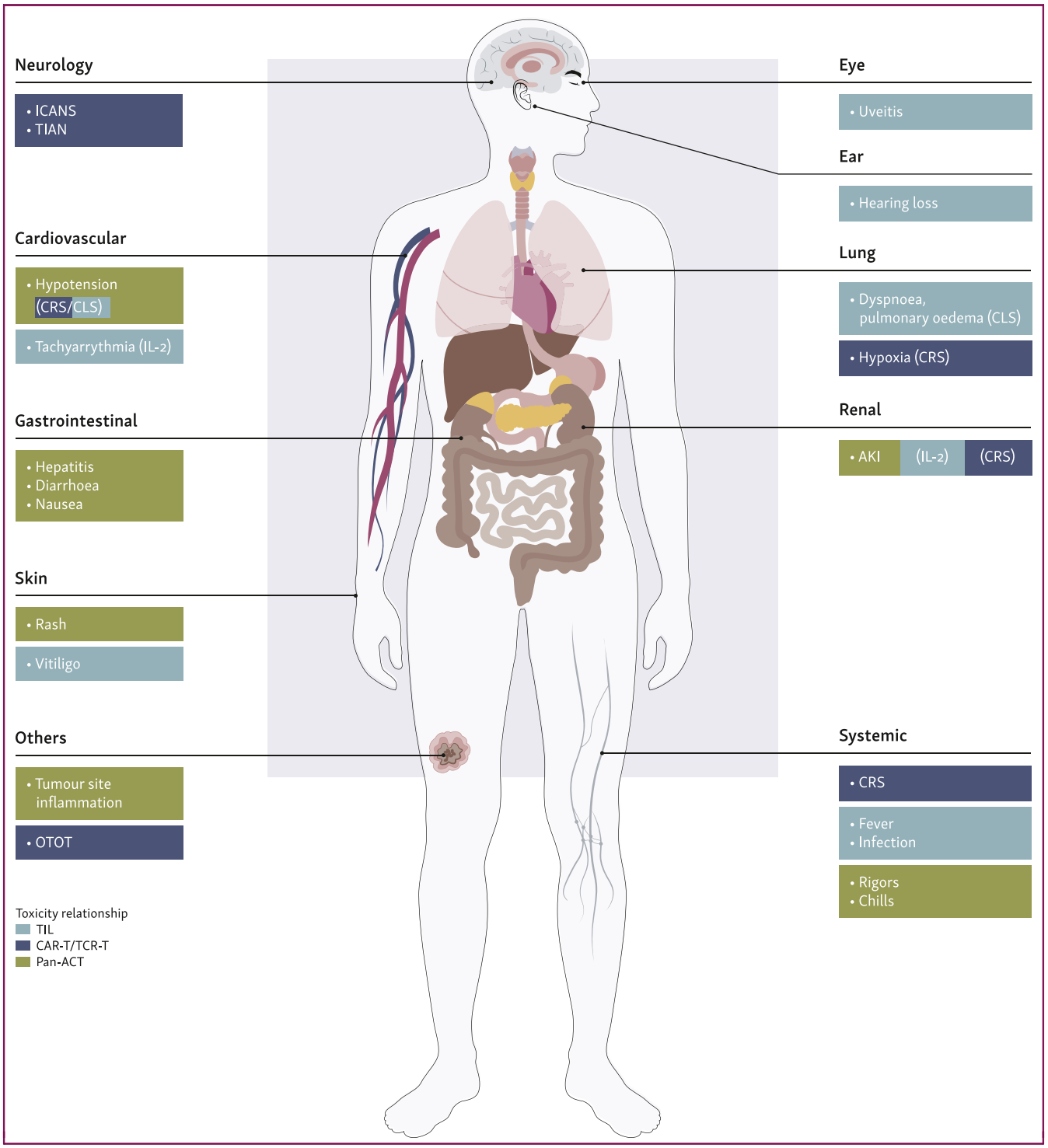

Figure 2. Adoptive cellular therapy (ACT) modalities and associated toxicities.
AKI, acute kidney injury; CLS, capillary leak syndrome; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; IL, interleukin; OTOT, on-target, off-tumour; TCR, T-cell receptor; TIAN, tumour inflammation-associated neurotoxicity; TIL, tumour-infiltrating lymphocyte.

consideration is required to ensure that infective causes are not overlooked and a full workup is advised including appropriate antibiotic therapy.[9,46]

Capillary leak syndrome

The triad of hypotension, generalised oedema (including pulmonary) and elevated haematocrit secondary to IL-2 is referred to clinically as capillary leak syndrome (CLS). At a cellular level, it is a result of increased capillary permeability to proteins, with subsequent loss of plasma from venous circulation into peripheral tissues.[49] Although it can represent a morbid toxicity, it is usually low grade and able to be managed without escalation to intensive care. For example, in the seminal phase III study, 30% of patients receiving TIL developed CLS; however, only one case was classified as

Table 2. IL-2-associated toxicities, clinical features and management principles (adapted from[9,46])

Toxicity	Typical clinical features	Management principles	Criteria for IL-2 cessation
Fevers/rigors	• Rigors 1-2 h after IL-2 • Fevers 2-4 h after IL-2	• Regular paracetamol (1 g qds) and NSAIDs (renal caution) • Pethidine 25 mg IV bolus. Can be repeated PRN to max dose 50 mg q4h • Fevers/rigors alone is not an indication to hold the next IL-2 dose	• Fevers/rigors alone is not an indication to discontinue
Hypotension	• Hypotension nadir at 4-6 h after IL-2 • Diminished recovery after each dose	• 250-ml IV fluid boluses • Increase maintenance IV fluid rate • Titrate to individual patient targets based on baseline readings • Low threshold for transfer to ICU for inotropes • Hold the next IL-2 dose if haemodynamically unstable	• Hypotension refractory to fluid replacement
Acute kidney injury	• Oliguria • Rising creatinine	• Monitor creatinine two times daily • Increase maintenance fluid rate • Hold the next IL-2 dose if there is ongoing deterioration	• Urine output $<$4 ml/kg over 8 h • sCR $>$ 265 µmol/l • sCR 2$\times$ baseline • Persistent acidosis
Respiratory	• Tachypnoea/dyspnoea • Pulmonary oedema	• Baseline CXR and repeat with development of symptoms • Aim saturations $>$92% • Diuresis if evidence of pulmonary oedema	• New supplemental O_2 requirement at the time of the next IL-2 dose • Chest drain/tap indicated • Crepitations audible $\geq$halfway up the chest
Cardiovascular	• Tachycardia • Arrhythmia • Peaks 2-4 h after IL-2	• Assess fluid status and administer 250-ml fluid bolus if hypovolaemic • Monitor electrolytes and replace deficiencies • Cardiology review for sustained tachyarrhythmias	• Persistent despite correction of reversible factors • Significant cardiac event/arrhythmia
Gastrointestinal	• Diarrhoea • Nausea/vomiting • Cholestasis	• Diarrhoea: stool MC&S, PRN loperamide once infective cause is ruled out • Nausea/vomiting: PRN antiemetics • Cholestasis is usually transient, resolving after IL-2 cessation	• Diarrhoea $>$1000 ml/12 h $\times$2 • Grade $\geq$3 CTCAE hepatic dysfunction
Neurological	• Delusions • Hallucinations • Usually temporary	• IL-2 therapy is to be withheld until the cause/trajectory established	• Persistent neurological dysfunction
Skin	• Rash/pruritus/erythema • Dry desquamation	• Regular emollient • Antihistamine for pruritus • Consider dermatology review if topical steroids required	Nil defined
Endocrine	• Hypothyroidism • Usually slow onset after completion of IL-2	• Replacement levothyroxine if persistent	Nil defined
Peripheral oedema/CLS	• 5%-10% weight gain common • Extremity tightness	• Peripheral oedema is to be treated symptomatically • Baseline weight and repeated daily • Initiate diuretics after completion of IL-2 if persistent	• Extremity paraesthesias
Haematologic	• Thrombocytopenia • Lymphocytosis • Eosinophilia	• Transfuse platelets if $<20 \times 10^9$/l • Investigate if significant anaemia develops	• Frank bleeding (haemoptysis/haematemesis/haematochezia)

CLS, capillary leak syndrome; CTCAE, common terminology criteria for adverse events; CXR, chest X-ray; ICU, intensive care unit; IL-2, interleukin-2; IV, intravenous; MC&S, microscopy, culture and sensitivity; NSAID, nonsteroidal anti-inflammatory drug; O_2, oxygen; PRN, per required needs; qds, four times a day; sCR, serum creatinine.

severe (grade $\geq$3).[7] While hypotension is a clinical feature of CLS, its development as an independent event during TIL therapy is possible due to shifts in peripheral vascular resistance.[46] It is recommended that target blood pressures be based on baseline readings and reassessed before each dose.[9] Management strategies must be customised for individual patients based on baseline cardiac function and other comorbidities. The recommended interventions are IV fluid, furosemide and a low threshold for transfer to the ICU for ionotropic support and/or diuresis (Table 2).[46]

Melanoma antigen-specific toxicities

Rare but notable autoimmune-like toxicities, including uveitis (8%), vitiligo (11%) and hearing loss (4%), have been reported in TIL therapy trials.[7,13] These are specific to the melanoma treatment setting and therefore are likely to relate to the recognition of overlapping melanoma/normal tissue antigens. It has been postulated that the development of these toxicities in unison may closely resemble the Vogt—Koyanagi—Harada syndrome.[50] Workup for uveitis should include ophthalmology consultation and typically

responds well to topical corticosteroids.[51] Of note, the incidence of melanoma antigen-specific autoimmunity is less significant than that seen in TCR T therapy targeting MART-1 and GP100 melanoma antigens and may be an important reflection regarding the polyclonality of TIL compared with TCR T therapies.[52]

CAR T AND TCR T THERAPY

Following the success of CAR T cell therapy in the field of haematology, there have been ongoing efforts to optimise gene-modified ACT for use in the solid tumour setting (Table 3). Small patient numbers and the early-phase nature of many of these trials are noteworthy, with a paucity of subsequent safety data.

Engagement of CAR T cells with the tumour microenvironment is known to release proinflammatory cytokines such as IL-6, IFN-γ, IL-1 and IL-2, along with the downstream activation of myeloid cells. This process leads to the characteristic inflammatory features known as CRS and ICANS (Figures 1-3).[24] CRS remains the most commonly reported toxicity of CAR T cell therapy in the solid tumour setting (Table 3), while ICANS is less common. A challenging toxicity related to CAR T and TCR T therapies is OTOT toxicities, as candidate target antigens are often coexpressed on nonmalignant tissues, creating a substantial risk of adverse events. Varying severity of OTOT has been reported in clinical studies using genetically modified T-cell targeting antigens shared by malignant and nonmalignant tissues.[70,71] One notable example of OTOT in solid cancer was documented by Morgan and colleagues[72]: a 39-year-old patient with human epidermal growth factor receptor 2 (HER-2)-positive metastatic colon cancer received a single infusion of high-dose anti-HER2 CAR T and subsequently developed acute respiratory distress, followed by death 5 days after the infusion. It was subsequently found that a considerable number of highly active anti-HER-2-directed T cells localised in the lung immediately following the infusion, triggering a cytokine storm upon recognising low levels of HER-2 on normal lung epithelial cells. Tables 3 and 4 document the toxicities observed in key early phase I/II clinical trials of CAR T and TCR T therapy in solid cancers, respectively.

Cytokine release syndrome

The classical signs and symptoms of CRS include fevers, chills, hypotension, sinus tachycardia, dyspnoea and hypoxia. The median time to onset of CRS is 2-7 days and typically occurs within 14 days of CAR T cell infusion,[74] although high-grade CRS has been observed just hours after CAR T cell infusion (Figure 3).[23] The onset of CRS is often marked primarily by fever, which is the most frequent presenting sign.[23] CRS can be difficult to differentiate, or can overlap, with other toxicities. For example, mild confusion observed during high-grade fevers in CRS can be mistaken for early ICANS or even secondary haemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS). The incidence of CRS ranges from 5% to 70% (grades 1-2) and 4% to 25% (grades 3-4) in patients treated with CAR T or TCR T therapy for solid tumours.[24]

There are several guidelines recognised globally in the management of CRS, specifically, the American Society of Clinical Oncology (ASCO),[75] the International Society for Cell and Gene Therapy (ISCT), European Society for Blood and Marrow Transplantation (EBMT), European Hematology Association (EHA),[76] the Society for the Immunotherapy of Cancer (SITC)[23] and the National Comprehensive Cancer Network (NCCN). Subtle differences exist between these guidelines, but the general principles and thresholds of CRS management are similar. The SITC guidelines[23] were first published in 2020 and are the most generic and open-ended, while the NCCN guidelines are the most recent (December 2023) and most specific, incorporating product-specific management recommendations. While these guidelines are all specific to CAR T cells in haematological malignancies, they serve as a valuable resource in assisting the CRS management in solid cancers.

The first-line therapy for treating CRS is the IL-6 receptor antagonist tocilizumab, with a typical IV dose of 8 mg/kg[23] for grade $\geq$2 CRS and persistent grade 1 CRS ($>$3 days). Repeat tocilizumab is recommended after 8-12 h if there is no improvement.[76] Glucocorticoids are recommended for tocilizumab-refractory CRS, with dexamethasone or methylprednisolone at escalating doses with immediate cessation or tapering, if necessary, once toxicity control has been achieved (Table 4). Nevertheless, the optimal dosing and timing of glucocorticoids is yet to be established and differs between the published guidelines. Moreover, there have been conflicting suggestions regarding the dose and duration of glucocorticoid therapy which may be critical in determining the efficacy of CAR T.[24]

Immune effector cell-associated neurotoxicity syndrome

A major concern with the use of CAR T cell therapy remains the risk of neurological toxicity. The varied array of potential neurological symptoms associated with ICANS includes encephalopathy, varying degrees of reduced alertness, dysphasia, dysgraphia, apraxia, and in severe cases, cerebral oedema.[23] Less common neurological toxicities may manifest with localised or generalised muscle weakness, myoclonus and seizures.[73] Notably, the frequency of ICANS is rare in reported clinical trials for the treatment of solid tumours (Table 5). The effectiveness of CAR T cell therapy in treating solid cancers has been somewhat limited, and there is a potential for an increase in the occurrence of ICANS as more effective therapies are developed. Two studies have reported potential ICANS: one patient (33%) treated with a CARv3-TEAM-E CAR T cell for glioblastoma,[56] and three patients (33%) treated with MAGE-A3 TCR T therapy, which resulted in two deaths.[68] Notably, two of these patients experienced a partial response.

The immune effector cell-associated encephalopathy score incorporates the domains of orientation, naming, following commands, writing and attention which is universally used to assess for ICANS.[73] The consensus ICANS

Table 3. CAR and TCR T cell therapy toxicities

Target	Tumour Type	Phase	Patients, n	Toxicities		
				Type	Grade 1/2, *n* (%)	Grade 3/4, *n* (%)
CD70 allogeneic CAR T[53]	RCC	1	16	CRS	8 (50)	Nil
				Infections	3 (19)	3 (19)
				GvHD	Nil	Nil
GD2 CAR T[54]	Neuroblastoma	1/2	27	CRS	19 (70)	1 (4)
				Elevated LFTs	13 (48)	7 (26)
				ICH	Nil	1 (4)
Anti-HER CAR T[55]	HER-2-positive sarcoma	1/2	19	CRS	1 (5)	Nil
				Back pain	Nil	3 (16)
				Muscle weakness	Nil	1 (5)
				Seizure	2 (11)	Nil
				Elevated LFTs	6 (32)	Nil
CARv3-TEAM-E T cells[56]	Glioblastoma	1	3	CRS	3 (100)	Nil
				ICANS	Nil	1 (33)
				Fatigue	Nil	1 (33)
CD133 CAR T[57]	HCC	1/2	21	CRS	Nil	Nil
				Raised bilirubin	Nil	4 (19)
CAIX CAR T[58]	RCC	1/2	12	Liver toxicity	8 (66)	4 (33)
Claudin18.2 CAR T[59]	GI cancers	1	98	CRS	95 (95.6)	Nil
				GI disorders	91 (93)	19 (19)
				Raised bilirubin	62 (63)	22 (22)
CLDN6 CAR T[60]	Solid cancers	1	22	CRS	10 (46)	5 (23)
				ICANS	1 (5)	Nil
				Elevated LFTs	1 (5)	4 (18)
TCR HPV16 E6[61] [HLA-A*02:01]	HPV epithelial cancers	1/2	12	CRS	Not reported	Nil
				Infection		4 (31)
				Diarrhoea		1 (8)
				Rash		1 (8)
				Syncope		1 (8)
				Pulmonary haemorrhage		1 (8)
TCR MAGE-A4[62] [HLA-A*02]	Synovial sarcoma, myxoid round cell liposarcoma	2	52	CRS	36 (69)	1 (2)
				Fever	10 (19)	2 (4)
				Dyspnoea	1 (2)	1 (2)
				Thromboembolic events	Nil	3 (6)
				Hepatic cytolysis	Nil	1 (2)
TCR MART-1 (DMF5)[52] [HLA-A*02]	Melanoma	2	20	Skin toxicity	14 (70)	Nil
				Uveitis	11 (55)	Nil
				Hearing loss	Nil	8 (40)
TCR gp100 [HLA-A*02]			16	Skin toxicity	15 (94)	Nil
				Uveitis	4 (25)	Nil
				Hearing loss	4 (25)	1 (6)
TCR MART-1[63] [HLA-A*02:01]	Melanoma	2	13	ARDS (likely CRS-related)	Not reported	2 (15)
TCR MART-1[64] [HLA-A*02:01]	Melanoma (including 5 uveal)	1/2	12	CRS	3 (25)	2 (17)
				Fever	6 (50)	4 (33)
				Dermatitis	4 (33)	6 (50)
				AST increased	6 (50)	2 (17)
				Uveitis	2 (17)	Nil
				Hearing loss	Nil	2 (17)
				Death: 1 patient		
TCR NY-ESO-1[65] [HLA-A*02:01]	Melanoma	2	6	None		
	Synovial cell sarcoma		11			
TCR NY-ESO-1[66] [HLA-A*02]	Synovial sarcoma	1/2	12	CRS	3 (25)	2 (17)
TCR NY-ESO-1[67] [HLA-A*02]	Synovial sarcoma	1/2	30	Not reported		
TCR MAGE-A3[a,68] [HLA-A*02]	Melanoma, synovial sarcoma, oesophageal cancer	1/2	9	ICANS	Nil	3 (33)
				CLS	Nil	2 (22)
				Death: 2 patients		
TCR Mesothelin[69] [*HLA unrestricted]	Mesothelioma, NSCLC, ovarian, cholangiocarcinoma	1/2	32	CRS	17 (53)	8 (25)
				Pneumonitis	Nil	5 (16)
				Pleuritis	Nil	2 (6)
				Pericarditis	Nil	1 (3)
				Pulmonary haemorrhage	Nil	1 (3)

ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; CAR, chimeric antigen receptor; CLS, capillary leak syndrome; CRS, cytokine release syndrome; GI, gastrointestinal; GvHD, graft versus host disease; HCC, hepatocellular carcinoma; HER-2, human epidermal growth factor receptor 2; HLA, human leukocyte antigen; HPV, human papillomavirus; ICANS, immune effector cell-associated neurotoxicity syndrome; ICH, intracranial haemorrhage; LFT, liver function test; NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma; TCR, T-cell receptor.

[a]High dose IL-2 (720 000 IU/kg) was given every 8 h to tolerance.

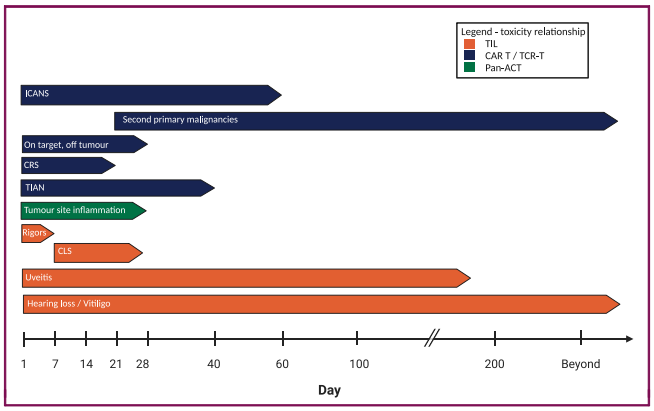

Figure 3. Timeline of predominant adoptive cellular therapy (ACT)-related adverse events.
ACT adoptive cellular therapy; CAR T, chimeric antigen receptor T cell therapy; CLS, capillary leak syndrome; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity; TCR T, T cell receptor-modified T-cell therapy; TIAN, tumour inflammation-associated neurotoxicity; TIL, tumour-infiltrating lymphocyte.

grading scale also includes the patient's level of alertness and any seizure, motor defect or raised intracranial pressure/cerebral oedema (Table 5). Glucocorticoids remain the primary first-line treatment for ICANS, although the optimal timing for starting glucocorticoid therapy remains uncertain. Initially, guidelines recommended reserving glucocorticoids for CTCAE grade $\geq$3 neurological toxicity due to worries regarding the potential impact on CAR T cell proliferation and persistence.[24] However, similar to CRS management, there has been a shift to administer dexamethasone in early grade 1 and 2 ICANS, and to taper the dose quickly with improvement.[23]

Anakinra, an IL-1 receptor antagonist, has now become a standard treatment for glucocorticoid-resistant ICANS.[77] Despite its widespread use, whether anakinra can effectively reduce the need for steroids remains uncertain, and data from one case series indicate that it does not facilitate quicker steroid tapering.[78] Anakinra has shown efficacy in preventing CAR T cell-induced neurotoxicity in *in vivo* models.[79] More recently, a phase II study suggested that anakinra could be effective in preventing ICANS,[80] and anakinra has increasingly been used in the prophylactic setting.

Additional toxicities associated with genetically modified T-cell therapy

Further serious but rare complications from CAR T-cell therapy have been reported in the field of haematology, including HLH/MAS.[24] This is a life-threatening hyperinflammatory syndrome involving macrophage activation, characterised by cytopenia, coagulopathy, elevated serum ferritin levels, hypertriglyceridemia, pulmonary compromise

Table 4. Management of CRS (adapted from[24])

AE grade[a]	Management	Assessment and investigations
Grade 1: • Fever $\geq$ 38°C • No hypotension or hypoxia	• Monitor • Regular paracetamol IV • Intravenous fluids • Tocilizumab 8 mg/kg if fever lasting >3 days	• Baseline laboratory tests: CRP, ferritin, magnesium, phosphate, FBC, clotting screen • ECG; formal cardiology evaluation for patients with a history of CVD • Rule out infectious causes of fever: blood cultures, nasal swabs for SARS-CoV-2 and other respiratory viruses, urine cultures and sputum cultures. • Treat any infections if identified • Administer empiric antibiotics for neutropenic fever
Grade 2: • Fever $\geq$38°C • Hypotension responding to fluids; not requiring vasopressors • Hypoxia requiring low-flow nasal cannula	• As above • Administer a second dose of tocilizumab with glucocorticoids if no improvement in CRS • Dexamethasone 10 mg IV bd • Consider vasopressors for hypotension refractory to fluid boluses and tocilizumab	• As above • Obtain central venous access • Assess ECG, troponin and BNP levels, and TTE
Grade 3: • Fever $\geq$ 38°C • Hypotension requiring a vasopressor with or without vasopressin • Hypoxia requiring high-flow nasal cannula, facemask, non-rebreather mask, venturi mask	• As above • Tocilizumab 8 mg/kg (maximum 3 doses/day; total 4 doses) • Dexamethasone 10 mg IV bd • If refractory, dexamethasone 10 mg IV qds	• As above • For CRS refractory to two doses of tocilizumab and glucocorticoids, consider anakinra, siltuximab and high-dose methylprednisolone
Grade 4: • Fever $\geq$38°C • Hypotension requiring multiple vasopressors (excluding vasopressin) • Hypoxia requiring positive pressure (e.g. CPAP, BiPAP, intubation and mechanical ventilation)	• As above • Dexamethasone 10 mg IV qds • If refractory, three doses of IV methylprednisolone 1—2 g per day; for continued refractory CRS, consider dosing every 12 h	• Consider ruxolitinib, emapalumab, antithymocyte globulin and/or cyclophosphamide

AE, adverse event; ASTCT, American Society of Transplantation and Cellular Therapy; BiPAP, bi-level positive airway pressure; BNP, B-type natriuretic peptide; CPAP, continuous positive airway pressure; CRP, C-reactive protein; CRS, cytokine release syndrome; CVD, cardiovascular disease; ECG, electrocardiogram; FBC, full blood count; IV, intravenous; qds, four times a day; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TTE, transthoracic echocardiogram.
[a]Using the ASTCT ICANS Consensus Grading for Adults.[73]

Table 5. Management of ICANS (adapted from[24])

AE grade[a]	Management	Assessment and investigations
Grade 1: • ICE score 7-9 • Awakens spontaneously • No seizure, motor findings or elevated ICP /cerebral oedema	• Dexamethasone 10 mg od/bd • Give at least two doses of dexamethasone and taper quickly once ICANS has improved • Anakinra 100 mg bd	• Consider CT head or MRI brain to evaluate for haemorrhage, increased ICP or cerebral oedema
Grade 2: • ICE score 3-6 • Awakens to voice • No seizure, motor findings or elevated ICP /cerebral oedema	• Dexamethasone 10 mg IV bd/tds/qds • Anakinra 200 mg bd • Levetiracetam 1000 mg bd	• As above • Consider lumbar puncture if coagulopathy is absent or corrected and no evidence of increased ICP
Grade 3: • ICE score 0-2 • Awakens only to tactile stimulus • Any clinical seizure (focal or generalised) that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention • Focal/local oedema on neuroimaging	• Dexamethasone 10 mg IV qds • Anakinra 200 mg bd • Levetiracetam 1500 mg bd	• As above • Assess for papilloedema • Consider repeat neuroimaging with CT or MRI every 2-3 days for persistent grade 3-4 ICANS
Grade 4: • ICE score 0 • Unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma • Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between • Deep focal motor weakness such as hemiparesis or paraparesis • Diffuse cerebral oedema on neuroimaging, decerebrate or decorticate posturing, or cranial nerve VI palsy, or papilledema or Cushing's triad	• As above • Methylprednisolone 1 g IV daily for 3 days • Taper to dexamethasone quickly once ICANS has improved • Consider lacosamide	• As above

AE, adverse event; ASTCT, American Society of Transplantation and Cellular Therapy; bd, twice a day; CT, computed tomography; EEG, electroencephalogram; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune effector cell-associated encephalopathy; ICP, intracranial pressure; IV, intravenous; MRI, magnetic resonance imaging; od, once a day; qds, four times a day; tds, three times a day.
[a]Using the ASTCT ICANS Consensus Grading for Adults.[73]

and dysfunction in the kidneys and/or liver, which may also represent the severe end of CRS in some patients.[24] Thus far, there have not been any reported cases in the literature of HLH/MAS secondary to CAR T cell therapy in solid cancers.

Immune effector cell-associated haematotoxicity

Prolonged cytopenia, now classified as immune effector cell-associated haematotoxicity, has recently been identified as an emerging CAR T toxicity in haematological malignancies.[81] Although the mechanism is poorly understood, it is thought that the process is independent of the target antigen, and therefore potentially applicable to solid tumour ACT. Within the classification, both early and late criteria have been defined, with evidence highlighting the importance of both baseline haematopoietic reserve and the host inflammatory state.[81,82]

Tumour site inflammation

A nuance of solid tumour ACT, in comparison to haematologic malignancies, is the solid nature and varied anatomical location of tumour tissue and the potential for symptoms related to acute tumour site inflammation related to immune effector cell infiltrate. While there is little described in the literature in this regard (8% of all patients in one TCR T study[62]), it can be postulated that this may develop as an additional challenge for patients with tumours at anatomically precarious sites, such as those in close proximity to visceral organs and neurological structures.

A localised neurotoxicity syndrome, distinct from the systemic CRS and ICANS toxicity syndrome, known as tumour inflammation-associated neurotoxicity (TIAN) has emerged in preclinical and clinical experience with cell therapies for CNS tumours.[29,31,83,84] TIAN has varying presentations depending on the location of the tumour within specific neuroanatomical regions.[83] Predictions from preclinical models anticipated the potential impacts of on-tumour and on-target inflammation directly on the tumour and its surrounding sensitive neuroanatomical sites, such as the brainstem or thalamus.[30] The manifestation of TIAN could indicate neuronal dysfunction caused by local inflammation or transient local inflammation-induced oedema, which is distinct from the generalised and diffuse cerebral oedema observed in severe ICANS.[85] This may encompass the concept of 'pseudoprogression', a known treatment effect from immunotherapies associated with intra- and peri-tumoural oedema.[86,87] Interventions such as corticosteroids, cerebrospinal fluid (CSF) diversion and hyperosmolar therapy need to be given in a timely manner to effectively manage obstructive hydrocephalus and reduce peritumoural oedema, preventing neurological damage.[85] Patients with CNS tumours in high-risk locations should be considered for a placement of an Ommaya reservoir (a catheter system placed beneath the scalp to facilitate removal of CSF) or a similar device before

immunotherapy, to monitor intracranial pressure and act as a safety mechanism for promptly draining CSF if required.[85]

LONG-TERM TOXICITY

While long-term toxicity follow-up data in ACT remain limited, CAR T cell therapies in the haematology setting have demonstrated up to 15% of treatment-associated secondary primary malignancies. The US FDA recently issued a warning in November 2023, stating a 'Serious risk of T cell malignancy following BCMA-directed or CD19-directed autologous chimeric antigen receptor (CAR) T cell immunotherapies'.[88] A possible link between CAR transduction and transformation of a secondary malignancy has been hypothesised, due to the mechanism of CAR T transgene insertional mutagenesis, with some cases of secondary T-cell lymphoma found to be 'CAR-positive'. By contrast, secondary myeloid malignancies following these therapies are typically associated with previous chemotherapy treatments or autologous hematopoietic stem cell transplants, rather than directly linked to the CAR T cell product itself.[24] In the solid tumour setting it will be necessary to monitor heavily pretreated patients such as those with advanced sarcoma or germ cell tumours.

Overall, it has been concluded that the benefits of CAR-T cell therapies for haematological malignancies continue to outweigh potential risks.[89] Ongoing follow-up in post-marketing safety/long-term follow-up studies will be required to guide safety management of these cell products for all indications.

FUTURE DIRECTIONS

While ACT for solid tumours represents an exciting therapeutic development, the significant and novel toxicity profile(s) remains a concern for treating centres looking to start using these modalities. One vital aspect to be emphasised is the importance of patient selection, and the understanding/assessment of baseline physiological function, with regular reassessment throughout the ACT pathway. Another important principle is that the majority of adverse events occur during the postinfusion elective admission period while patients are under direct clinical supervision. This allows for rapid assessment, intervention and escalation as indicated.

Understanding the immunological impact of varied ACT modalities is key for the management of associated toxicities; for example, the low incidence of CRS/ICANs arising from TIL when compared with CAR T/TCR T therapies will influence management strategy and requirement for multidisciplinary assessment. In addition, the planning of hospital resources needs to be carefully tailored to patient tumour type, modality of ACT and subsequent toxicity needs.

As a developing field, with limited data in the solid tumour setting, there is a paucity of established guidelines for the management of ACT toxicities. For well-documented toxicities such as CRS and ICANs, extrapolation from the field of haematology is appropriate, and as such treatment strategies according to grade have been developed (as described in the preceding text) and should be adhered to for safe toxicity management. Since the FDA approval of lifileucel for the management of advanced melanoma there has been a need for guidance and an expert consensus has been recently published.[9]

A major challenge in the management of ACT toxicities is the rapidly developing field with new and complex, partially understood, biological mechanisms. CAR T cell therapies armoured with fourth-generation capabilities will likely influence toxicity management, as will the nuances of suicide genes and inducible factors. In the field of TIL therapy while there is minimal cell-related toxicity associated with first-generation products, next-generation genetically modified TIL products that are in development may significantly change this.[5] In addition, the extension of ACT into novel subsets such as NK cell and macrophage populations will require further refinement of toxicity management.

CONCLUDING REMARKS

This review has attempted to collate the current literature and data documenting toxicities arising from ACT in the solid tumour setting. We hope that the use of this paper in conjunction with established guidelines will assist with the education of healthcare professionals seeking to start treating patients with these exciting and novel approaches.

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