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Supplementary information

Current understanding and management of CAR T cell-associated toxicities

In the format provided by the authors and unedited

Supplementary Table 1 | ASTCT consensus grading for CRS

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[a]	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
WITH				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
AND/OR[b]				
Hypoxia	None	Requiring low-flow[c] nasal cannula or blow-by	Requiring high-flow[c] nasal cannula, facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (for example, CPAP, BiPAP, intubation and mechanical ventilation)

ASTCT, American Society of Transplantation and Cellular Therapy; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CRS, cytokine-release syndrome. [a]Fever: defined as temperature ≥38°C not attributable to any other cause. Fever is no longer required to grade subsequent CRS severity in patients who have CRS and then receive antipyretic or anticytokine therapy; in these patients, CRS grading is determined by hypotension and/or hypoxia. [b]CRS grading is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. [c]Low-flow nasal cannula is defined as oxygen delivery at ≤6 l/min; low flow also includes blow-by oxygen delivery. High-flow nasal cannula is defined as oxygen delivery >6 l/min. Adapted with permission from ref.[1], Elsevier.

Supplementary Table 2 | Prospectively evaluated preventative strategies for CAR T cell toxicity management

Preventative strategy	Patient population	CAR Product(s)	Sample size	Detailed intervention approach	CRS and ICANS outcomes	Anticancer response outcomes
Risk-adapted cell dosing and administration						
Higher disease burden patients receive lower CAR T cell doses[2]	Adult B cell ALL	19-28z (MSKCC investigational product)	*n* = 53 patients in trial. *n* = 33 patients with risk-adapted dosing.	High disease burden patients: ≥5% bone marrow ALL involvement or extramedullary malignancy. High disease burden patients: 1×10^6 CAR^+ T cells/kg. Low disease burden patients: 3×10^6 CAR^+ T cells/kg.	Higher disease burden patients associated with greater incidence of severe CRS[a] and neurotoxicity, despite subset of patients receiving risk-adapted cell dosing. Grade ≥3 CRS in high burden patients: 41%. Grade ≥3 CRS in low burden patients: 5%. Any neurotoxicity[b] in high burden patients: 59%. Any neurotoxicity in low burden patients: 14%.	No impact of cell dose on CR rate. All patients on trial: 83% CR rate.
High cell doses administered in fractionated doses[3]	Adult B cell ALL	Tisa-cel	*n* = 35 across all 3 cohorts *n* = 20 in high dose fractionated cohort	High cell dose: 5×10^8 CAR T cells. Low cell dose: 5×10^7 CAR T cells. High CAR T cell doses were given either as a single infusion or fractionated over 3 days (day 1: 10%; day 2: 30%; day 3: 60%), with potential to hold days 2–3 doses depending on CRS or neurological toxicity.	Fractionated cell dosing resulted in lower rates of severe CRS[c]. Grade 4–5 CRS in high cell dose single-infusion cohort: 50%. Grade 4–5 CRS in high cell dose fractionated-dosing cohort: 5%.	High cell dose, single-infusion cohort: 50% CR rate. High cell dose, fractionated-dosing cohort: 90% CR rate. Median EFS highest in fractionated high cell dose cohort (19.4 months versus ≤2.1 months in other cohorts).
Preventative use of immunosuppressive therapies						
Prophylactic tocilizumab for prevention of CRS (ZUMA-1, cohort 3)[4,5]	Adult LBCL	Axi-cel	*n* = 34	Tocilizumab 8 mg/kg on day +2. Levetiracetam seizure prophylaxis starting on day 0.	Low rates of grade ≥3 CRS[d], but possibly higher rates of grade ≥3 neurotoxicity[b] in historical comparison with ZUMA-1 cohorts 1–2. Grade ≥3 CRS: 3%, compared with 13% in ZUMA-1 cohorts 1–2. Grade ≥3 neurological toxicity: 41% (1 death from cerebral oedema), compared with 28% in ZUMA-1 cohorts 1–2.	NR
Prophylactic tocilizumab for prevention of CRS[6]	Adult B cell non-Hodgkin lymphoma	Locally manufactured investigational anti-CD19 product with 4-1BB co-stimulatory domain or tisa-cel	*n* = 20	Tocilizumab 8 mg/kg completed 1 h prior to CAR T cell infusion for all patients	Low rates of severe CRS[d] without clear increase in expected neurotoxicity. Any CRS in 50% with prophylactic tocilizumab, versus 75% in historical comparison.	ORR: 85% CR rate: 75%

					Grade ≥3 CRS with prophylactic tocilizumab: 0% Fatal CRS in historical control group: 12.5% Any ICANS[b] with prophylactic tocilizumab: 25% Grade ≥3 ICANS with prophylactic tocilizumab: 5%	
Prophylactic corticosteroids and early intervention with tocilizumab and corticosteroids for CRS and neurological toxicity (ZUMA-1 cohort 6)[5,7]	Adult LBCL	Axi-cel	*n* = 40	Dexamethasone 10 mg daily from day 0 prior to cell infusion through day +2. Levetiracetam seizure prophylaxis starting on day 0. Tocilizumab 8 mg/kg for grade ≥2 CRS, grade 1 CRS lasting >24 h, and for CRS occurring with grade ≥2 neurological toxicity. Corticosteroids for grade ≥1 neurological toxicity, grade ≥2 CRS, and grade 1 CRS lasting >3 days. Per-protocol doses ranging from dexamethasone 10 mg once to methylprednisolone 1,000 mg/day for 3 days, depending on toxicity grade.	Low incidence of grade ≥3 neurological toxicity[b] and no grade ≥3 CRS[d], and lower cumulative corticosteroid doses, with response rates comparable to ZUMA-1 cohorts 1–2. Grade 1–2 CRS: 80%. Grade ≥3 CRS: 0%, compared with 13% in ZUMA-1 cohorts 1–2. Any neurological toxicity: 58% Grade ≥3 neurological toxicity: 13%, compared with 28% in ZUMA-1 cohorts 1–2. Propensity score matching analysis: grade ≥3 CRS still numerically lower than in ZUMA-1 cohorts 1–2, when controlled for tumour burden and other patient factors; however, grade ≥3 neurological toxicity similar to cohorts 1–2.	ORR: 95% CR rate: 80% In propensity score matching analysis, the ORR was 94% for both ZUMA-1 cohorts 1–2 and cohort 6. Median peak blood CAR T cell levels were 65 cells/µl (cohort 6) and 43 cells/µl (cohorts 1–2).
Prophylactic anakinra for prevention of grade ≥3 ICANS[8]	Adult LBCL or MCL	Axi-cel, brexu-cel or tisa-cel	*n* = 31	Subcutaneous anakinra 100 mg q12h on days +2–10 (or longer depending on toxicity). Initiate anakinra prior to day +2 for 2 temperatures ≥38.5°C. Anakinra dose frequency could be increased to q6h for persistent grade 1–2 CRS.	Low incidence of severe ICANS[e]. All-grade ICANS: 19% Grade ≥3 ICANS: 9.7% All-grade CRS: 74% Grade ≥3 CRS: 6.5%	ORR: 77% CR rate: 65%
Preventative use of small molecules						
Ibrutinib initiated prior to and continued after CAR T cell infusion[9]	Adults with CLL	Locally manufactured investigational anti-CD19 CAR T cell product (University of Washington)	*n* = 19 in concurrent ibrutinib cohort *n* = 19 in historical non-ibrutinib cohort	Concurrent ibrutinib cohort: ibrutinib 420 mg daily starting ≥2 weeks prior to leukapheresis and continuing until ≥3 months after CAR T cell infusion	Decrease in severity of CRS in ibrutinib cohort; one grade 5 event possible due to ibrutinib and CAR T cell combination (due to arrythmia). One grade 5 event due to CRS and neurological toxicity in historical non-ibrutinib cohort.	CR/PR rate 83% in concurrent ibrutinib cohort versus 56% in non-ibrutinib historical cohort

					Grade ≥3 CRS[d] in 0% of concurrent ibrutinib cohort versus 11% of historical cohort. Grade ≥3 neurological toxicity[b] in 26% of concurrent ibrutinib cohort versus 37% of historical cohort.	
Itacitinib for prevention of CRS[10]	Adults with LBCL	Axi-cel	*n* = 23 in itacitinib arm *n* = 24 in placebo arm	Randomized study of itacitinib 200 mg twice daily starting 3 days prior to cell infusion through day +26, versus placebo	Lower rate of grade ≥2 CRS[e] and ICANS[e] in the itacitinib arm: 17.4% and 8.6%, respectively, versus 56.5% and 21.7% in the placebo arm	Itacitinib arm: ORR 78.3% and CR rate 60.9% Placebo arm: ORR 73.9% and CR rate 47.8%

ALL, acute lymphocytic leukaemia; ASTCT, American Society for Transplantation and Cellular Therapy; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukaemia; CR, complete remission; CRS, cytokine-release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; EFS, event-free survival; h, hours; ICANS, immune effector cell-associated neurotoxicity syndrome; LBCL, large B cell lymphoma; MCL, Mantle cell lymphoma; MSKCC, Memorial Sloan Kettering Cancer Center; NR, not reported; ORR, overall response rate; PR, partial remission; q6h, every 6 hours; q12h, every 12 hours. [a]CRS graded per MSKCC grading scale. [b]Neurotoxicity graded by the CTCAE grading system. [c]CRS graded per University of Pennsylvania Scale. [d]CRS per 2014 Lee criteria. [e]CRS and ICANS graded by ASTCT criteria.

Supplementary Table 3 | ASTCT consensus grading for ICANS

Neurotoxicity domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7–9	3–6	0–2[a]	0 (patient is unarousable and unable to perform ICE)[a]
Depressed level of consciousness[b]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma.
Seizure	NA	NA	Any clinical seizure, focal or generalized, that resolves rapidly, or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 minutes); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings[c]	NA	NA	NA	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP and/or cerebral oedema	NA	NA	Focal/local oedema on neuroimaging[d]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilloedema; or Cushing's triad

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, or raised ICP and/or cerebral oedema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as having grade 3 ICANS. ASTCT, American Society of Transplantation and Cellular Therapy; CRS, cytokine-release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; EEG, electroencephalogram; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune effector cell encephalopathy; ICP, intracranial pressure; NA, not applicable. [a]A patient with an ICE score of 0 can be classified as having grade 3 ICANS if awake with global aphasia or as having grade 4 ICANS if unarousable. [b]Depressed level of consciousness should be attributable to no other cause (for example, no sedating medication). [c]Tremors and myoclonus associated with immune effector cell therapies can be graded according to CTCAE version 5.0, but they do not influence ICANS grading. [d]Intracranial haemorrhage with or without associated oedema is not considered a neurotoxicity feature and is excluded from ICANS grading, but can be graded according to CTCAE version 5.0. Adapted with permission from ref.[1], Elsevier.

Supplementary references

1 Lee, D. W. *et al.* ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biology of Blood and Marrow Transplantation* **25**, 625-638, doi:10.1016/j.bbmt.2018.12.758 (2019).

2 Park, J. H. *et al.* Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia. *N Engl J Med* **378**, 449-459, doi:10.1056/NEJMoa1709919 (2018).

3 Frey, N. V. *et al.* Optimizing Chimeric Antigen Receptor T-Cell Therapy for Adults With Acute Lymphoblastic Leukemia. *J Clin Oncol* **38**, 415-422, doi:10.1200/JCO.19.01892 (2020).

4 Locke, F. L. *et al.* Preliminary Results of Prophylactic Tocilizumab after Axicabtageneciloleucel (axi-cel; KTE-C19) Treatment for Patients with Refractory,Aggressive Non-Hodgkin Lymphoma (NHL). *Blood* **130**, 1547, doi:https://doi.org/10.1182/blood.V130.Suppl_1.1547.1547 (2017).

5 Oluwole, O. O. *et al.* Prophylactic corticosteroid use in patients receiving axicabtagene ciloleucel for large B-cell lymphoma. *Br J Haematol* **194**, 690-700, doi:10.1111/bjh.17527 (2021).

6 Caimi, P. F. *et al.* Prophylactic Tocilizumab Prior to Anti-CD19 CAR-T Cell Therapy for Non-Hodgkin Lymphoma. *Front Immunol* **12**, 745320, doi:10.3389/fimmu.2021.745320 (2021).

7 Oluwole, O. O. *et al.* Prophylactic Corticosteroid Use with Axicabtagene Ciloleucel (Axi-Cel) in Patients (Pts) with Relapsed/Refractory Large B-Cell Lymphoma (R/R LBCL): One-Year Follow-up of ZUMA-1 Cohort 6 (C6). *Blood* **138**, 2832, doi:https://doi.org/10.1182/blood-2021-147403 (2021).

8 Park, J. H. *et al.* CD19 CAR T-cell therapy and prophylactic anakinra in relapsed or refractory lymphoma: phase 2 trial interim results. *Nat Med* **29**, 1710-1717, doi:10.1038/s41591-023-02404-6 (2023).

9 Gauthier, J. *et al.* Feasibility and efficacy of CD19-targeted CAR T cells with concurrent ibrutinib for CLL after ibrutinib failure. *Blood* **135**, 1650-1660, doi:10.1182/blood.2019002936 (2020).

10 Frigault, M. J. *et al.* Itacitinib for the Prevention of Immune Effector Cell Therapy-Associated Cytokine Release Syndrome: Results from the Phase 2 Incb 39110-211 Placebo-Controlled Randomized Cohort. *Blood* **142**, 356, doi:https://doi.org/10.1182/blood-2023-180205 (2023).