CADTH Health Technology Review

Anticytokine Therapy and Corticosteroids for Cytokine Release Syndrome and for Neurotoxicity Following T-Cell Engager or CAR T-Cell Therapy

Rapid Review

Key Messages

What Is the Issue?

- Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) are the most common toxicities secondary to T-cell engager or chimeric antigen receptor (CAR) T-cell therapy.
- The US FDA and Health Canada approved tocilizumab, an anti-interleukin-6 receptor antagonist, for the management of severe or life-threatening cases of CRS.
- Corticosteroids also play an important role in CRS management and are the mainstay of ICANS management.
- Decision-makers are interested in understanding the use of anticytokine drugs (i.e., tocilizumab, anakinra, siltuximab) and/or corticosteroids in the management of CRS and ICANS following T-cell engager or CAR T-cell therapy.

What Did We Do?

- We identified and summarized the literature comparing the clinical effectiveness and safety of anticytokine therapy and/or corticosteroids with alternative care or treatment as usual for treating and preventing of CRS and ICANS. We also searched for evidence-based recommendations for the use of anticytokine therapy and/or corticosteroids to treat and prevent CRS and ICANS.
- A research information specialist conducted a literature search of peer-reviewed and grey literature sources published between January 1, 2019 and February 26, 2024 for CRS; and between January 1, 2019 and March 4, 2024 for ICANS. One reviewer screened citations for inclusion based on predefined criteria, critically appraised the included studies, and narratively summarized the findings.

What Did We Find?

- This report presents evidence-based findings on 3 retrospective chart review studies, 2 prospective cohort studies, and 4 consensus guidelines.
- Limited and low-quality clinical evidence from studies with a high risk of bias suggested that early use of tocilizumab or corticosteroids, or prophylactic use of tocilizumab or anakinra may reduce the risk of a high-grade CRS without a negative impact on neurotoxicity or immunotherapy treatment outcomes.

Key Messages

- The included guidelines recommend the use of tocilizumab for treatment of higher-grade CRS, or for treatment of grade 1 CRS if symptoms persist for 3 days or more. Corticosteroids could be added in conjunction if there is no improvement or persistent symptoms after tocilizumab therapy.

- For the management of ICANS in the absence of concurrent CRS, supportive care is the preferred treatment option for grade 1 ICANS, while corticosteroids are recommended for the management of grade 2 to 4 ICANS. In the presence of concurrent CRS, guidelines recommend tocilizumab therapy as per management of CRS, and corticosteroids should be continued until improvement to grade 1.

- We did not identify any clinical evidence regarding the clinical efficacy and safety of anticytokine therapy and/or corticosteroids for treatment of CRS and ICANS compared with alternative treatment or treatment as usual.

- We also did not identify any guidelines for the use of prophylactic anticytokine therapy, corticosteroids, or both for the prevention of CRS and ICANS.

What Does This Mean?

- Despite limited and low-quality evidence, the findings suggest some potential benefits of prophylactic or early use of anticytokine therapy and corticosteroids for the management of immunotherapy-related toxicities. Guidelines offer guidance on the management of CRS, ICANS and other less common toxicities related to immunotherapy based on the available low-quality evidence.

- When using the clinical evidence and recommendations summarized in this report to inform decisions, decision-makers should consider that the evidence is limited and of low quality.

- To improve the certainty of findings, there is a need for more robust prospective clinical trials with larger sample sizes, and lower risk of bias.

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Abbreviations

AE	adverse event
ASCO	American Society of Clinical Oncology
ASTCT	American Society for Transplantation and Cellular Therapy
CAR T	chimeric antigen receptor-T
CRR	complete response rate
CRS	cytokine release syndrome
EBMT	European Society for Blood and Marrow Transplantation
ICANS	immune effector cell-associated neurotoxicity syndrome
ICU	intensive care unit
IL	interleukin
JACIE	Joint Accreditation Committee of the International Society for Cell Therapy and EBMT
NCCN	National Comprehensive Cancer Network
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
SITC	Society for Immunotherapy of Cancer

Context and Policy Issues

What Is CAR T–Cell Therapy and T–Cell Engager Therapy?

CAR T-cell therapy is a new form of immunotherapy in which T-cells, obtained from the same individuals (autologous) or different donors (allogenic), are genetically engineered to express a specific receptor called a CAR, allowing it to recognize and kill cancer cells.[1] Currently, there are 6 CAR T products approved for use in the US and Canada.[2] Three products (tisagenlecleucel, axicabtagene ciloleucel, lisocabtagene maraleucel) are for B-cell leukemia and lymphoma, 1 product (brexucabtagene autoleucel) for mantle cell lymphoma, and 2 products (idecabtagene vicleucel, ciltacabtagene autoleucel) for multiple myeloma.[2]

T-cell engager therapy involves bispecific antibodies that are engineered to redirect the immune system' T-cells to recognize and kill cancer cells.[3] Blinatumomab was the first bispecific T-cell engager approved by Health Canada for treatment of adult patients as well as pediatric patients (Notice of Compliance with Conditions) with relapsed or refractory B-cell precursor acute lymphoblastic leukemia.[4] Health Canada recently approved teclistamab for adult patients with relapsed or refractory multiple myeloma after at least 3 lines of therapy, including a proteasome inhibitor, an immunomodulatory drug and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.[5]

What Are the Common T–Cell Engager– or CAR T–related Toxicities?

Introduction of CAR T-cells or T-cell engagers will trigger a systemic immune response leading to the production of inflammatory cytokines and chemokines such as interleukins (IL), tumour necrosis factors and interferons that attack cancer cells; however, they can also attack healthy cells.[3,6] The 2 most common adverse events (AEs) associated with CAR T-cell therapy and T-cell engager therapy are CRS and ICANS.[3,6] The American Society for Transplantation and Cellular Therapy (ASTCT) guidelines established a consensus grading system (grade 1 to 4) for both CRS and ICANS.[7]

CRS usually appears within 1 to 2 weeks after infusion.[6,8] The signs and symptoms of CRS can range from mild flu-like symptoms (e.g., fever, myalgia, headache, and fatigue) to life-threatening conditions (e.g., vasodilatory shock, capillary leak, hypoxia, and end-organ dysfunction).[8] According to the ASTCT grading system, CRS severity is graded based on 3 clinical parameters, which are fever, hypotension, and hypoxia.[7]

ASTCT consensus grading for CRS:

- Grade 1: Fever (≥ 38°C).
- Grade 2: Fever with hypotension not requiring vasopressors and/or hypoxia requiring low-flow nasal cannula or blow-by.
- Grade 3: Fever with hypotension requiring a vasopressor with or without vasopressin and/or hypoxia requiring high-flow cannula, face mask, nonrebreather mask, or Venturi mask.
- Grade 4: Fever with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (e.g., CPAP, BiPAP, intubation, mechanical ventilation).

ICANS usually starts after the onset of CRS, and higher grades of ICANS can occur concurrently with higher grade of CRS.[8] Symptoms of ICANS can range from encephalopathy to seizures, obtundation, and death.[9] Atypical manifestations include transient aphasia, facial paresis, myoclonus, and hemifacial spasms.[9] In the ASTCT grading system,[7] the final ICANS grade is determined by the most severe events among 5 different domains: ICE (immune effector cell-associated encephalopathy) score, depressed level of consciousness, seizure, motor findings, and elevated ICP (intracranial pressure)/cerebral edema.[7]

ASTCT consensus grading for ICANS:

- Grade 1: ICE score: 7 to 9 with no depressed level of consciousness.
- Grade 2: ICE score: 3 to 6; and/or mild somnolence awaking to voice.
- Grade 3: ICE score: 0 to 2; and/or depressed level of consciousness awakening only to tactile stimulus; and/or any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on electroencephalogram (EEG) that resolve with intervention; and/or focal or local edema on neuroimaging.
- Grade 4: ICE score: 0 (patient is unarousable and unable to perform ICE); and/or stupor or coma; and/or life-threatening prolonged seizure (> 5 minutes) or repetitive clinical or electrical seizures without return to baseline in between; and/or diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing or papilledema, sixth cranial nerve palsy, or papilledema; or Cushing triad.

What Is the Current Practice?

For most patients with lower grades of CRS or ICANS, management of toxicities relies mainly upon supportive care. In 2017, the US FDA approved tocilizumab, an IL-6 receptor antagonist, for treatment of severe or life-threatening CAR T-cell-induced CRS in adults and in pediatric patients 2 years of age and older.[10,11] Subsequently, the drug was also approved by Health Canada for severe or life-threatening CRS in patient populations specified for authorized CAR T-cell products.[12] However, prescribing information for individual CAR T products advises using tocilizumab at lower grades of CRS.[13-17] Depending on the persistent symptoms and severity of CRS, tocilizumab with or without systemic corticosteroids is generally administered in many centres.[18] In the case of refractory CRS, several third-line drugs have been proposed, including siltuximab (an antiIL-6 antibody), anakinra (an IL-1 receptor antagonist), etanercept (anti−tumour necrosis factor), and infliximab (anti−tumour necrosis factor).[8,9]

For ICANS, the therapeutic strategy is based on the grade of neurotoxicity.[7] Corticosteroids form the mainstay of ICANS management in addition to supportive care.[8] Grade 1 ICANS is mainly treated with supportive care. Dexamethasone is used for grade 2 and 3, and high-dose of methylprednisolone is recommended for treatment of grade 4.[8] Anti-IL-6 therapy, such as tocilizumab, is used only in patients with concurrent CRS due to the possibility that tocilizumab may exacerbate ICANS.[8]

Why Is It Important to Do This Review?

There remains limited guidance or standardized treatment approach for the optimal management of CRS and ICANS, especially those of higher grades that are refractory to tocilizumab and steroids.[19]

Objective

To support decision-making about the role of anticytokine drugs (i.e., tocilizumab, anakinra, siltuximab) and corticosteroids for the treatment and prevention of CRS and ICANS, we prepared this Rapid Review to summarize and critically appraise the available studies on the clinical efficacy and safety of those drugs following T-cell engager or CAR T-cell therapy.

Research Questions

1. What is the clinical effectiveness and safety of anticytokine drugs, corticosteroids, or both for the treatment of cytokine release syndrome and for the treatment of neurotoxicity following T-cell engager therapy or CAR T-cell therapy?

2. What is the clinical effectiveness and safety of prophylactic or early use of anticytokine therapy, corticosteroids, or both for the prevention of cytokine release syndrome and neurotoxicity following T-cell engager therapy or CAR T-cell therapy?

3. What are the evidence-based guidelines for the use of anticytokine agents, corticosteroids, or both in the treatment of cytokine release syndrome and neurotoxicity following T-cell engager therapy or CAR T-cell therapy?

4. What are the evidence-based guidelines for the use of prophylactic or early of anticytokine therapy, corticosteroids, or both for the prevention of cytokine release syndrome and neurotoxicity following T-cell engager therapy or CAR T-cell therapy?

Methods

Literature Search Methods

An information specialist conducted a literature search on key resources, including MEDLINE, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of those in Canada and major international health technology agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concepts were CRS, ICANS, CAR T or T-cell therapies, and anticytokine drugs. The search was completed on February 26, 2024 for CRS, on March 4, 2024 for ICANS, and limited to English-language documents published since January 1, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Criteria	Description
Population	Patients (adults and/or pediatrics) with or at risk of CRS and neurotoxicity following T-cell engager therapy or CAR T-cell therapy
Intervention	Q1 and Q3: Anticytokine drugs (tocilizumab, anakinra, siltuximab), corticosteroids, or both for the treatment of CRS and neurotoxicity
	Q2 and Q4: Prophylactic anticytokine therapy (tocilizumab, anakinra, siltuximab), corticosteroids, or both for the prevention of CRS and neurotoxicity
Comparator	Q1 and Q2: Alternative treatment or treatment as usual for CRS and neurotoxicity (e.g., antiseizure medication, IV fluids, anti-inflammatory medication, oxygen, mechanical ventilation, blood transfusion, dialysis, electrolyte management, alternative medication)
	Q3 and Q4: Not applicable
Outcomes	Q1 and Q2: Clinical effectiveness and safety (e.g., response rates, CRS or neurotoxicity improvement, CRS or neurotoxicity prevention, ICU use, hospital length of stay, mortality, serious toxicity, stroke, severe neurologic impairment, adverse events)
	Q3: Recommendations regarding the use of anticytokine drugs, corticosteroids, or both for the treatment of CRS and neurotoxicity following T-cell engager or CAR T-cell therapy (e.g., dose, length of treatment, appropriate patient populations, appropriate drug administration)
	Q4: Recommendations regarding the use of prophylactic anticytokine therapy, corticosteroids, or both for the prevention of CRS and neurotoxicity following T-cell engager or CAR T-cell therapy (e.g., dose, length of treatment, appropriate patient populations, appropriate drug administration)
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, nonrandomized studies, evidence-based guidelines

CAR T = chimeric antigen receptor T-cell; CRS = cytokine release syndrome; ICU = intensive care unit.

Exclusion Criteria

We excluded articles that did not meet the selection criteria outlined in Table 1, or articles published before 2019. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

One reviewer critically appraised the included publications using the following tools as a guide: The Downs and Black checklist[20] for nonrandomized studies, and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument[21] for guidelines. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

We identified a total of 318 citations from the literature search. Following screening of titles and abstracts, we excluded 290 citations and retrieved 28 potentially relevant reports from the electronic search for full-text review. We also retrieved 6 potentially relevant publications from the grey literature search. Of these potentially relevant articles, we excluded 25 publications for various reasons, and included 9 publications

that met the inclusion criteria. These comprised 5 nonrandomized studies and 4 evidence-based guidelines. Appendix 1 presents the PRISMA[22] flow chart of the study selection.

Summary of Study Characteristics

Appendix 2 provides details regarding the characteristics of 5 included primary studies[23-27] and 4 evidence-based guidelines.[28-30]

Included Studies for Question 1: What is the clinical effectiveness and safety of anticytokine drugs, corticosteroids, or both for the treatment of cytokine release syndrome (CRS) and for the treatment of neurotoxicity following T-cell engager therapy or CAR T-cell therapy?

We did not identify any studies comparing the clinical effectiveness and safety of anticytokine drugs, corticosteroids, or both with alternative treatment or treatment as usual for treatment of CRS and ICANS.

Included Studies for Question 2: What is the clinical effectiveness and safety of prophylactic or early use of anticytokine therapy, corticosteroids, or both for the prevention of CRS and neurotoxicity following T-cell engager therapy or CAR T-cell therapy?

Study Design

We identified 3 retrospective chart review studies[23,24,27] and 2 prospective cohort studies.[25,26] All included studies were conducted at a single institution, and were published in 2024,[23] 2023,[24-26] and 2021.[27]

Of the included studies, the study by Scott et al. (2023)[25] involved prophylactic tocilizumab to prevent CRS, and the study by Strati et al. (2023)[26] used prophylactic anakinra to mitigate ICANS. The remaining 3 studies[23,24,27] evaluated the consequences of early management approach of tocilizumab or corticosteroids on the incidence and severity of CRS and ICANS, and CAR T-cell treatment efficacy.

Country of Origin

Four included studies[23,25-27] were conducted by authors from the US, and 1 study[24] was conducted by authors from Switzerland.

Patient Population

The retrospective chart review studies by Gaffney et al. (2024)[23] and by Lakomy et al. (2023)[24] included patients with various hematologic malignancies who underwent CAR T-cell therapy. The prospective cohort study by Scott et al. (2023)[25] and the retrospective chart review study by Banerjee et al. (2021)[27] included patients with relapsed/refractory multiple myeloma, who underwent bispecific T-cell engager therapy or CAR T-cell therapy, respectively. The prospective cohort study by Strati et al. (2023)[26] included patients with relapsed/refractory large B-cell lymphoma who underwent CAR T-cell therapy. Patients in all included studies were adults.

Interventions and Comparators

The retrospective chart review study by Gaffney et al. (2024)[23] compared early and standard management protocols. The early management protocol administered tocilizumab (8 mg/kg IV [IV], maximum of 800 mg/

dose) when grade 1 CRS persisted for 24 hours. The standard management protocol administered the first dose of tocilizumab at 72 hours of persistent symptoms.

The retrospective chart review study by Lakomy et al. (2023)[24] compared early corticosteroids plus standard tocilizumab schedule with the standard tocilizumab schedule. In the early corticosteroids group, 10 mg dexamethasone was administered before each dose of tocilizumab in case of low-grade CRS.

In the prospective cohort study by Scott et al. (2023),[25] the cohort of 53 patients received CAR T (teclistamab) therapy at the step-up dosing at least 48 hours apart (0.06 mg/kg, 0.3 mg/kg, and 1.5 mg/kg). The authors evaluated the first 15 patients and found that the median time to CRS from the administration of the first-prime dose was 48 hours. This group of patients was considered as no prophylactic tocilizumab group. The remaining 38 patients were administered with tocilizumab (8 mg/kg IV, maximum of 800 mg/dose) over 1 hour prophylactically at 44 hours (i.e., 4 hours before the second step-up dose level of teclistamab), and this group was considered as prophylactic tocilizumab group. The outcomes were compared between the prophylactic tocilizumab group and the no prophylactic tocilizumab group, as well as between the prophylactic tocilizumab group and the cohort of the MajesTEC-1 study,[31] a phase I/II that treated patients with relapsed/refractory multiple myeloma with teclistamab.

In the prospective cohort study by Strati et al. (2023),[26] anakinra was administered 6 hours before CAR T-cell infusion on day 0 at a dose of 100 mg daily (n = 10) or 100 mg every 12 hours (n = 10) for 7 days. Results in this study cohort were compared with those of a contemporaneous matched cohort treated without anakinra.

The retrospective chart review study by Banerjee et al. (2021)[27] divided 50 patients into 3 groups based on time-to-tocilizumab intervals. Patients in the early tocilizumab group (n = 19) received tocilizumab at most 12 hours after CRS onset, while those in the late tocilizumab group (n = 19) received tocilizumab at least 12 hours after CRS onset and the remaining 12 patients were grouped in the no tocilizumab group. Toxicity outcomes were compared between early and late tocilizumab groups, while efficacy outcomes of CAR T therapy were compared among 3 groups.

Outcomes

The outcomes reported in the included studies were:

- incidence of CRS[23-27]
- incidence of ICANS[23-27]
- level of care (e.g., hospital length of stay, intensive care unit [ICU] transfer)[23-25]
- other AEs and mortality[23,25,27]
- efficacy outcomes of immunotherapy.[23-25,27]

Included Studies for Question 3: What are the evidence-based guidelines for the use of anticytokine drugs, corticosteroids, or both in the treatment of CRS and neurotoxicity following T-cell engager therapy or CAR T-cell therapy?

We identified 4 guidelines. These are the National Comprehensive Cancer Network (NCCN) guideline by Thompson et al. (2022),[28] the American Society of Clinical Oncology (ASCO) guideline by Santomasso et al. (2021),[29] the European Society for Blood and Marrow Transplantation (EBMT) and Joint Accreditation Committee of the International Society for Cell Therapy and EBMT (JACIE) guideline by Yakoub-Agha et al. (2020),[30] and the Society for Immunotherapy of Cancer (SITC) guideline by Maus et al. (2020).[32]

Study Design

All 4 identified guidelines[28-30,32] were consensus-based whose recommendations were made from critical evaluation of evidence derived from literature review, integrated with the clinical expertise and consensus of a multidisciplinary panel of cancer specialists, clinical experts, and researchers. Due to the low level of evidence, the recommendations were usually not graded, and they represented the consensus views of the authors.

Country of Origin

The authors of the NCCN,[28] ASCO,[29] and SITC[32] guidelines were from US, while those of the EBMT and JACIE guideline[30] were from various countries in Europe.

Patient Population

The target population in the NCCN,[28] EBMT and JACIE,[30] and SITC[32] guidelines was adults and children, while that in the ASCO guideline[29] was restricted to adult patients only. The intended users of the guidelines[28-30,32] were health care practitioners who provide care to patients with cancer, as well as patients receiving CAR T-cell therapy, and their caregivers.

Intervention and Practice Considered

The included guidelines[28-30,32] considered various management strategies of immune-related AE associated with CAR T-cell therapy.

Outcomes

The included guidelines[28-30,32] considered all efficacy and safety outcomes of CAR T-cell therapy.

Included Studies for Question 4: What are the evidence-based guidelines for the use of prophylactic or early use of anticytokine therapy, corticosteroids, or both for the prevention of CRS and neurotoxicity following T-cell engager therapy or CAR T-cell therapy?

We did not identify any guidelines on the use of prophylactic anticytokine therapy, corticosteroids, or both for the prevention of CRS and ICANS following T-cell engager therapy or CAR T-cell therapy.

Summary of Critical Appraisal

Appendix 3 provides details regarding the strengths and limitations of included primary studies[23-27] and guidelines[28-30,32] (Table 5).

Primary Studies

The included primary studies comprised 3 retrospective chart review studies[23,24,27] and 2 prospective cohort studies.[25,26] The latter were reported as a correspondence (i.e., letter to editor).

All included studies[23-27] were explicit in term of reporting, but had several limitations related to the external and internal validity that may reduce the certainty and generalizability of the findings.

For reporting, the authors of the included studies[23-27] clearly described the objective of the study, the main outcomes to be measured, the characteristics of the patients included in the study, the interventions of interest, and the main findings. Actual P values were reported for the main outcomes in 3 retrospective chart review studies[23,24,27] but not in 2 prospective cohort studies.[25,26]

For external validity, the treatment settings (i.e., hospitals) in all 5 studies[23-27] appeared to be representative of the treatment received by most of the patients with cancer undergoing immunotherapy. However, the patients may not be representative of the entire population from which they were selected, as the authors of each of the included studies[23-27] conducted the research from a single hospital with a small sample size.

For internal validity related to bias, all 5 studies[23-27] had several limitations, including risks of selection bias and missing data. Three studies[23,24,27] were of retrospective design and 2 prospective studies[25,26] indirectly compared the outcomes of its cohort with those of another cohort that underwent similar treatment. The authors of the retrospective chart review studies,[23,24,27] but not those of the prospective cohort studies,[25,26] used statistical tests appropriately for comparison of variables. All included studies[23-27] assessed the main outcome measures using accurate and reliable method. For instance, CRS and ICANS, the 2 main safety outcomes following immunotherapy, were graded according to the ASTCT criteria.[7] Clinical responses were categorized using the International Myeloma Working Group criteria.[33]

For internal validity related to confounding, the baseline characteristics of the treatment groups in all included studies[23-27] appeared to be balanced, thus reducing the risk of confounding bias. However, due to the nature of the nonrandomized studies,[23-27] residual confounding factors may exist, and failure to identify and adjust for those factors in the analyses may have an impact on the findings. The authors in all studies[23,24,27] did not report whether sample size calculations were performed, and it is unclear whether the nonsignificant differences in certain outcomes were because the studies were underpowered for those outcomes.

Guidelines

The included guidelines[28-30,32] had several strengths related to reporting. They were explicit in terms of scope and purpose (i.e., objectives, health questions and population), and had clear presentation of recommendations (i.e., specific, unambiguous, and easy to find key recommendations, with options for managing the different conditions or health issues). In terms of stakeholder involvement, the authors of all included guidelines[28-30,32] clearly defined target users and the development groups but did not report whether the views and preferences of the patients were sought. As most recommendations were based on the consensus of the authors, there were no explicit links between recommendations and the supporting evidence.[28-30,32] The methods of formulating the recommendations in all guidelines were described, but not in

great details.[28-30,32] Also, the authors of all guidelines[28-30,32] considered health benefits and risks of side effects in formulating the recommendations.

However, there were also some limitations related to guideline methodology, implementation, and review. The authors of the guidelines[28-30,32] did not clearly report methods for evidence collection, criteria for selection, and methods for evidence synthesis. The authors did not report the procedures for updating the guidelines.[28-30,32] The applicability (i.e., facilitators and barriers to application, advice and/or tools on how the recommendations can be put into practice, and monitoring or auditing criteria) was unclear in the included guidelines.[28-30,32] For editorial independence, the authors of all guidelines[28-30,32] reported that all guideline development group members had no competing interest. The authors of 2 guidelines[28,30] did not report if the views of the funding body had any influence on the content of the guidelines.

Summary of Findings

Appendix 4 presents the main study findings, which are the incidence of CRS (Table 6), the incidence of ICANS (Table 7), the level of care (Table 8), other AEs and mortality (Table 9), and clinical outcomes of immunotherapies (Table 10).

Clinical effectiveness and safety of prophylactic or early use of anticytokine therapy, corticosteroids, or both for the prevention of CRS and neurotoxicity following T-cell engager therapy or CAR T-cell therapy

Two studies involved the prophylactic approach of tocilizumab[25] or anakinra,[26] 2 studies[23,27] used early treatment with tocilizumab, and 1 study[24] involved early use of corticosteroids.

Incidence of CRS

Prophylaxis

The study by Scott et al. (2023)[25] compared prophylactic tocilizumab (administered 4 hours before the second step-up dose level of CAR T-cell therapy) with no prophylactic tocilizumab and found that CRS all grades occurred in 21.1% of patients in the prophylactic group compared with 73.3% of patients in the no prophylactic group. Most of the CRS events was of grade 1 in both groups (i.e., 21.1% of patients in the prophylactic group versus 67.7% of patients in the no prophylactic group). The difference was not statistically compared. Two patients (2.6%) in the prophylactic group versus no patients (0%) in the no prophylactic group had CRS grade 2 and 3.

The study by Strati et al. (2023)[26] compared prophylactic anakinra (administered 6 hour before CAR T-cell infusion on day 0 at a dose of 100 mg daily (n = 10) or 100 mg every 12 hour (n = 10) for 7 days) with no prophylactic anakinra (from a contemporaneous cohort), and found that patients in both cohorts experienced similar CRS incidence for all grades, grade 2 to 4, or grade 3 and 4. Median duration of CRS after the onset was 5 days (range, 2 to 9 days) and 3 days (range, 2 to 9 days), respectively. Statistical comparison between groups was not performed.

Early Management

In the study by Gaffney et al. (2024)[23] where early management protocol (tocilizumab given if grade 1 CRS persists for 24 hour) was compared with standard management protocol (first dose of tocilizumab given at 72 hour of persistent symptoms), there were no statistically significant difference in the incidence of CRS all grades (P = 0.73) and CRS grade 3 and 4 (P = 1.0) of CRS between treatment groups.

The study by Banerjee et al. (2021)[27] compared early tocilizumab (administered at ≤ 12 hour after CRS onset) with late tocilizumab (administered at > 12 hour after CRS onset) groups, or with no tocilizumab group. The study found that both early and late tocilizumab groups had similar incidence of CRS grade 1 (95% versus 95%, P = 1.00) and 2 (5% versus 5%, P = 1.00). However, the median CRS duration of the early tocilizumab group was numerically lower than that in the late tocilizumab group (18.6 hours [range, 5.1 to 106.7] versus 84.7 hours [range, 20.0 to 188.0 hours]). For 7 patients (58%) in the no tocilizumab group who developed CRS (grade was not reported), the median CRS duration was 42.1 hour (range, 1.7 to 141.1 hour).

In the study by Lakomy et al. (2023),[24] early use of corticosteroids (10 mg dexamethasone administered before each dose of tocilizumab) was associated with statistically significant lower incidence of high-grade CRS (3 and 4) (0%) compared with standard tocilizumab schedule (10%); P = 0.0497. However, early use of corticosteroids resulted in higher incidence of CRS grade 1 (67% versus 33%; P = 0.0021).

Incidence of ICANS

Prophylaxis

The study by Scott et al. (2023)[25] compared prophylactic tocilizumab (administered 4 hours before the second step-up dose level of CAR T-cell therapy) with no prophylactic tocilizumab and found that the incidence of concurrent ICANS with CRS was 5.3% compared with 20%. Statistical comparison between groups was not performed.

The study by Strati et al. (2023)[26] compared prophylactic anakinra (administered 6 hour before CAR T-cell infusion on day 0 at a dose of 100 mg daily (n = 10) or 100 mg every 12 hour (n = 10) for 7 days) with no prophylactic anakinra (from a contemporaneous cohort), and found that patients treated with anakinra had lower incidence of ICANS of any grade (35% versus 60%), with overlapped 95% confidence intervals. The median onsets of ICANS were 7 days (range, 3 to 9 days) versus 5 days (1 to 14 days), and the median durations of ICANS were 2 days (range, 2 to 17 days) versus 3 days (1 to 24 days). Statistical comparisons for those outcomes were not performed.

Early Management

In the study by Gaffney et al. (2024)[23] where early management protocol (tocilizumab given if grade 1 CRS persists for 24 hour) was compared with standard management protocol (first dose of tocilizumab given at 72 hour of persistent symptoms), there were no statistically significant difference in the incidence of ICANS all grades (P = 1.0) and ICANS grade 3 and 4 (P = 1.0) between treatment groups.

The study by Banerjee et al. (2021)[27] compared early tocilizumab (administered at ≤ 12 hour after CRS onset) with late tocilizumab (administered at > 12 hour after CRS onset) or with no tocilizumab group. The study

found that both early and late tocilizumab groups had similar incidence of ICANS all grades (21% versus 37%, P = 0.48). The incidence of ICANS in the no tocilizumab group was not reported.

The study by Lakomy et al. (2023)[24] found no statistically significant differences in any grades of ICANS (from grade 1 to 4) between early use of corticosteroids (10 mg dexamethasone administered before each dose of tocilizumab) and standard tocilizumab schedule groups.

Level of Care

Prophylaxis

The study by Scott et al. (2023)[25] found no patients in the prophylactic tocilizumab group readmitted to the hospital within 14 days of discharge. Results on hospital readmission in the no prophylactic tocilizumab group were not reported.

In the study by Gaffney et al. (2024),[23] there were no statistically significant differences between early management protocol and standard management protocol in terms of outpatient administration (P = 0.43), length of hospital stay (P = 0.78), and ICU transfer (P = 0.24).

In the study by Lakomy et al. (2023),[24] there were no statistically significant differences between early corticosteroids plus standard tocilizumab schedule and standard tocilizumab schedule in terms of length of hospital stay (P = 0.76), and ICU transfer (P = 0.37).

Other AEs and Mortality

Prophylaxis

The study by Scott et al. (2023)[25] made an indirect comparison between prophylactic tocilizumab cohort in their study with the cohort in the MajesTEC-1 study,[31] which underwent standard treatment for AEs, and found that prophylactic tocilizumab did not increase the incidence of grade 3 or 4 neutropenia (42.2% versus 64.2%).

Early Management

Other AEs reported in the study by Gaffney et al. (2024),[23] included infection and cytopenia. There were no statistically significant differences between groups in terms of 90-day incidence of infection (P = 0.20) and cytopenia, including neutropenia (all grades [P = 1.0], or grade 3, 4 [P = 0.6]), anemia (all grades [P = 0.38], or grade 3, 4 [P = 0.40]), and thrombocytopenia (all grades [P = 0.68], or grade 3, 4 [P = 0.52]). The study also found no statistically significant difference between groups in treatment-related mortality (P = 0.32).

Efficacy Outcomes of CAR T−Cell Therapy

In all included studies,[23-25,27] early use or prophylaxis of tocilizumab or corticosteroids did not have negative impact on the efficacy of CAR T-cell therapy.

Prophylaxis

The study by Scott et al. (2023)[25] reported that the use of prophylactic tocilizumab resulted in ORR of 70%, which was comparable to that of the MajesTEC-1 study (63%).[31]

Early Management

In the study by Gaffney et al. (2024),[23] patients who received early management for CRS with tocilizumab had a statistically significantly higher overall response rate (ORR) (77% versus 56%; P = 0.0003) and complete response rate (CRR) (64% versus 33%; P = 0.01) at 30 days compared to those who were managed by standard protocol. However, there was no statistically significant difference in ORR (P = 0.14) and CRR (P = 0.29) at 90 days.

The study Banerjee et al. (2021)[27] found that early tocilizumab management of CRS did not have negative impact on CAR T-cell therapy efficacy regarding response rates and survival compared with late tocilizumab and no tocilizumab. In fact, the 30-day ORR of the 3 groups were 74%, 79%, and 33%, respectively. The overall difference between groups were statistically significant (P = 0.03). Likewise, the 30-day CRR were 89%, 53%, and 50%, respectively (P = 0.02). The median progression-free survival (PFS) was 35.7 months in the early tocilizumab group, 13.2 months in the late tocilizumab group, and 7.8 months in the no tocilizumab group. The median overall survival (OS) was not reached in the early tocilizumab group, 25.0 months in the late tocilizumab group, and 26.4 months in the no tocilizumab group.

In the study by Lakomy et al. (2023),[24] both cohorts (i.e., early corticosteroids in combination with standard tocilizumab versus standard tocilizumab) had no statistically significant difference in ORR (P = 0.79), CRR (P = 0.66), PFS (P = 0.63), and OS (P = 0.12).

Guidelines Regarding the Use of anticytokine drugs, corticosteroids, or both in the treatment of CRS and neurotoxicity following T-cell engager therapy or CAR T-cell therapy

The recommendations in all included guidelines[28-30,32] were not systematically graded due to low-quality evidence. The NCCN guideline[28] classified all of its recommendations by consensus as category 2A (based on lower level of evidence). The ASCO guideline[29] assigned the strength of its recommendations as moderate (benefits outweigh harms). The EBMT and JACIE guideline[30] and the SITC guideline[32] did not grade their recommendations.

Three guidelines (NCCN,[28] ASCO,[29] and EBMT and JACIE[30]) provided an algorithm outlining the management of CRS or ICANS according to the level of its severity (grade 1 to 4), which was graded based on the ASTCT criteria.[7] The SITC guideline[32] provided a set of recommendations similar to those in the other 3 guidelines,[28-30] but with less details. The following statements summarize the recommendations on the use of anticytokine drugs or corticosteroids of the included guidelines[28-30,32] for the management of CRS and ICANS. Information on additional supportive care is presented in Table 11 for CRS and Table 12 for ICANS.

Management of CRS

- Grade 1 CRS:
  - All included guidelines[28-30,32] recommend 1 dose of tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg) for patients with prolonged CRS (> 3 days), significant symptoms, comorbidities and/or they are older adults.

- The NCCN guideline[28] recommends dexamethasone 10 mg IV every 24 hours for early-onset CRS (< 72 hours after infusion) for patients undergoing idecabtagene and lisocabtagene CAR T therapy.
- The EBMT and JACIE guideline,[30] noted that corticosteroids are contraindicated in the absence of life-threatening complications.

- Grade 2 CRS:
  - All included guidelines[28-30,32] recommend tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg).
  - If there is no improvement or persistent symptoms, the included guidelines[28-30,32] recommend repeating tocilizumab; with no more than 3 doses in 24 hours, with a maximum of 4 doses total. Alternatively, the EBMT and JACIE guideline,[30] recommends that treatment could be switched to siltuximab IV 11 mg/kg, 1 dose per day.
  - If CRS does not improve after 1 to 2 doses of tocilizumab, 3 guidelines[28-30] recommend dexamethasone 10 mg IV every 6 to 24 hours depending on the product. The SITC guideline[32] recommends alternative treatment with third line drugs, including anakinra, siltuximab, and high-dose methylprednisolone if CRS does not improve after 2 doses of tocilizumab (and steroids).

- Grade 3 CRS:
  - All guidelines[28-30,32] recommend tocilizumab therapy as per grade 2 if maximum dose not reached within 24-hour period. The EBMT and JACIE guideline,[30] recommends that treatment could be switched to siltuximab IV 11 mg/kg, 1 dose per day.
  - The included guidelines[28-30,32] recommend dexamethasone 10 to 20 mg IV given every 6 hours for 1 to 3 days. If refractory occurs, patients should be managed as per grade 4 CRS.

- Grade 4 CRS:
  - All guidelines[28-30,32] recommend tocilizumab therapy as per grade 2 if maximum dose not reached within 24-hour period.
  - The guidelines[28-30] recommend dexamethasone 10 to 20 mg IV given every 6 hours for 3 days, with progressive tapering within 3 to 7 days.
  - If refractory occurs, 3 guidelines[28-30] recommend high-dose methylprednisolone IV 1,000 mg per day or per every 12 hours for 3 days with progressive tapering. The NCCN guidelines[28] noted that other drugs such as anakinra, siltuximab, ruxolitinib, cyclophosphamide, IV immunoglobulin, antithymocyte globulin, or extracorporeal cytokine adsorption with continuous renal replacement therapy might be considered.

Management of ICANS
- Grade 1:
  - Without concurrent CRS: All included guidelines[28-30,32] recommend supportive care only for ICANS grade 1. The NCCN guideline[28] recommends dexamethasone 10 mg IV every 12 to 24 hours for

2 doses if ICANS develops within 72 hours after infusion of either lisocabtagene maraleucel or idecabtagene vicleucel for CAR T-cell therapy.

- With concurrent CRS: Three included guidelines[28-30] recommend tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose). The SITC guideline[32] noted that evidence on the efficacy and safety of tocilizumab for treatment of ICANS was still limited, and that tocilizumab may worsen neurotoxicity; and, therefore, it did not include tocilizumab or other antiinterleukin-6 drugs in its recommendations.

- Grade 2:

  - Without concurrent CRS: All included guidelines[28-30,32] recommend supportive care and a dose of dexamethasone 10 mg IV, followed by reassessment of ICANS. If there is no improvement, 3 guidelines[28-30] recommend a repeat of dexamethasone every 6 to 12 hours.

  - With concurrent CRS: Three guidelines[28-30] recommend tocilizumab therapy as per management of CRS. Patients should be transfer to ICU if neurotoxicity is developed concurrently with CRS of Grade 2 or more.[28-30] The ASCO guideline[29] recommends that dexamethasone (10 mg IV every 6 to 12 hours) or methylprednisolone equivalent (1 mg/kg IV every 12 hours) should be initiated if refractory to tocilizumab past the first dose occurs. Corticosteroids should be continued until improvement to grade 1, and then rapidly taper as clinically appropriate.[29]

- Grade 3:

  - Without concurrent CRS: All guidelines[28-30,32] recommend ICU care and dexamethasone or methylprednisolone therapy as per ICANS grade 2 management. The EBMT and JACIE guideline[30] recommends a dexamethasone dose increase to 20 mg.

  - With concurrent CRS: Three guidelines[28-30] recommend tocilizumab therapy as per management of CRS. The ASCO guideline[29] recommends that dexamethasone (10 mg IV every 6 to 12 hours) or methylprednisolone equivalent (1 mg/kg IV every 12 hours) should be initiated if refractory to tocilizumab past the first dose occurs, and corticosteroids should be continued until improvement to grade 1, and then rapidly taper as clinically appropriate.

- Grade 4:

  - Without concurrent CRS: Three guidelines[28-30] recommend high-dose corticosteroids (i.e., methylprednisolone IV 1,000 mg 1 to 2 times per day for 3 days. If not improving, consider 1,000 mg of methylprednisolone 2 to 3 times per day or alternate therapy. Continue corticosteroids until improvement to grade 1, and then taper as clinically appropriate.)

  - With concurrent CRS: Three guidelines[28-30] recommend tocilizumab therapy as per management of CRS in addition to methylprednisolone therapy. Continue corticosteroids until improvement to grade 1, followed by rapid tapering.

Limitations

Evidence Gaps

No evidence was found for the following 2 research questions:

- The clinical effectiveness and safety of anticytokine therapy, corticosteroids, or both for the treatment of CRS and neurotoxicity following T-cell engager therapy or CAR T-cell therapy compared with alternative treatment or usual care.
- Recommendations from evidence-based guidelines on the use of prophylactic anticytokine therapy, corticosteroids, or both for the prevention of CRS and neurotoxicity following T-cell engager therapy or CAR T-cell therapy.

Generalizability

The included clinical studies were conducted by authors in the US[23,25-27] and Switzerland.[24] The included guidelines were developed in US[28,29,32] and Europe.[30] Thus, the clinical findings of the included studies and the recommendations from the included guidelines may be generalizable to the health care context in Canada. However, as patients in all-included studies were adults, it is unclear if the treatment applies to the pediatric population. Although the target population of 3 guidelines[28,30,32] was adults and children, there were no specific recommendations for children.

Heterogeneity

There was substantial heterogeneity among the included clinical studies[23-27] in terms of protocols of anticytokine therapy and corticosteroid treatment), as well as patient population (i.e., having different underlying diagnoses and receiving different CAR T products). Therefore, it was difficult to provide a strong conclusion based on the findings of the included studies.

Certainty of Evidence

The quality of the evidence from the included studies or from the guidelines was generally low as the evidence was derived mainly from nonrandomized cohort studies or follow-up studies. All 5 included clinical studies[23-27] had a small number of patients and were from a single centre. Three studies were of retrospective design[23,24,27] and 2 studies[25,26] were of prospective cohort design that indirectly compared the results of their cohorts with those of a similar study without using any statistical methods. The findings in the included studies[23-27] should be interpreted with cautions due to methodological problems. All the recommendations in the included guidelines[28-30,32] are expert consensus that were based on low-quality evidence (i.e., without randomized evidence).

Conclusions and Implications for Decision- or Policy-Making

This review included 5 clinical studies (3 retrospective chart review studies[23,24,27] used early treatment approach and 2 prospective cohort studies[25,26] used prophylactic approach) and 4 consensus-based guidelines.[28-30,32]

The prophylactic or early use of tocilizumab resulted in either lower incidence of CRS, mostly grade 1,[25] or no major differences in the incidence or severity of CRS between treatment groups[23,25,27] following CAR T-cell therapy. Despite no difference in the incidence of CRS between groups, it was found that the median CRS duration of the early tocilizumab group was numerically lower than those in the late tocilizumab group or in the no tocilizumab group.[27] Early use of corticosteroids was associated with overall higher CRS incidence, mostly grade 1, with no high-grade (3 and 4) CRS.[24] There was no apparent difference in the incidence, grade, and duration of CRS between prophylactic and no prophylactic anakinra groups.[26]

With regard to ICANS, there was no difference in the incidence of all grades when comparing with prophylactic or early use of tocilizumab,[23,25,27] corticosteroids,[24] or anakinra[26] treatments with no prophylactic or no early treatments.

Early use of tocilizumab[23] or corticosteroids[24] following CAR T-cell therapy did not affect the length of hospital stay and incidence of ICU transfer. The incidence and severity of other AEs and/or treatment-related mortality were also not affected by early treatment[23,27] or prophylaxis with tocilizumab.[25]

Early use of tocilizumab[23,27] or corticosteroids[24] did not appear to have a negative impact on treatment outcomes of CAR T-cell therapy, including response rates and survival. Similar findings were observed with prophylactic tocilizumab.[25]

For the management of CRS, the included guidelines[28-30,32] recommend that tocilizumab can be considered for grade 1 if symptoms persist for 3 days or more. For grade 2 to 4 CRS, all guidelines[28-30,32] recommend the use of tocilizumab, while corticosteroids such as dexamethasone or methylprednisolone can be added in conjunction if there is no improvement or persistent symptoms after tocilizumab therapy. Proposed alternatives to tocilizumab are siltuximab and anakinra.

For the management of ICANS, treatment recommendations of the guidelines[28-30] were based on the absence or presence of concurrent CRS. In the absence of concurrent CRS, supportive care is the preferred treatment option for grade 1 ICANS. Corticosteroids such as dexamethasone or high-dose methylprednisolone are recommended for the management of grade 2 to 4 ICANS until improvement to grade 1, and then taper as clinically appropriate. In the presence of concurrent CRS, the guidelines[28-30] recommend tocilizumab therapy as per management of CRS. Corticosteroids should be continued until improvement to grade 1, followed by rapid tapering.

Considerations for Future Research

Prospective, randomized, and multicentre trials with large patient population are needed to validate the findings. Clinical trials should also involve the pediatric population. Future research is also needed to better understand the underlying mechanism of the disease and to develop novel therapeutic strategies for more

effective prevention and management of CRS and ICANS. Future guidelines should consider the following points: recommendations should be made based on higher-quality evidence; evidence and recommendations should be graded using validated tools; recommendations should be made specific for pediatric population if children are included in the target population; methods should be reported clearer; and there must be an explicit link between evidence and recommendations.

Implications for Clinical Practice

Although the findings of this report are not conclusive, they suggest that early use of tocilizumab or corticosteroids, or prophylactic use of tocilizumab or anakinra may reduce the risk of the development of high-grade CRS without negative impact on neurotoxicity or immunotherapy treatment outcomes. However, no identified guidelines recommend prophylactic use of anticytokine therapy and/or corticosteroids for the prevention and management of CAR T-associated CRS or ICANS; therefore, no recommendations can be given. When using the clinical evidence and guidelines summarized in this report to inform decisions, decision-makers should consider that the evidence is limited and of low quality.
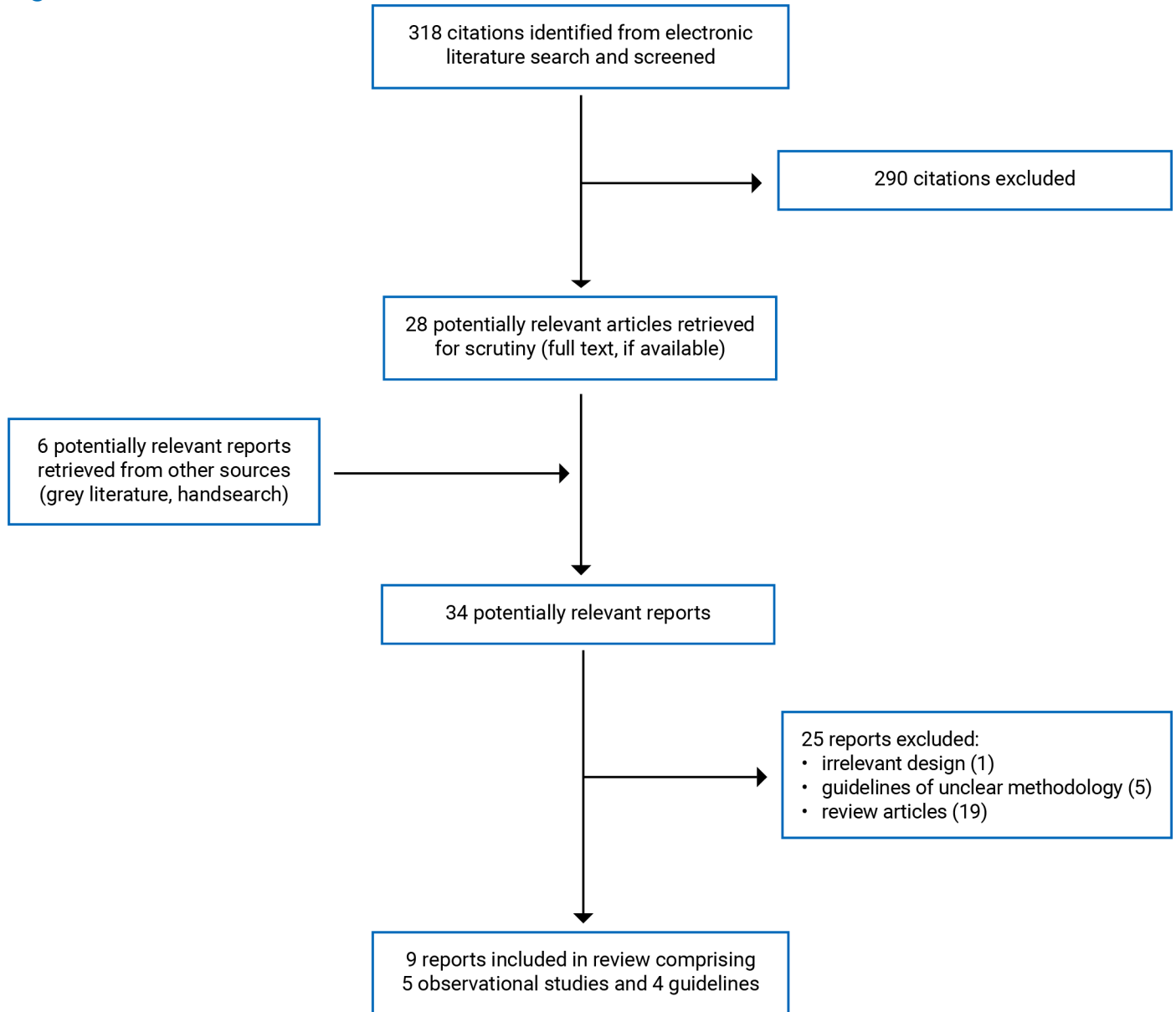
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Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies

318 citations identified from electronic literature search and screened

290 citations excluded

28 potentially relevant articles retrieved for scrutiny (full text, if available)

6 potentially relevant reports retrieved from other sources (grey literature, handsearch)

34 potentially relevant reports

25 reports excluded:
- irrelevant design (1)
- guidelines of unclear methodology (5)
- review articles (19)

9 reports included in review comprising 5 observational studies and 4 guidelines

Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Gaffney et al. (2024)[23] US **Funding source:** The authors reported no financial support received for the research.	Retrospective chart review	Patients with various hematologic malignancies (nonhodgkin lymphoma, acute lymphoblastic leukemia, multiple myeloma) treated with CAR T-cell therapy. Age: NR 23 of 40 patients (57%) aged 65 years and over. Gender, n/N (%) • Male: 21/40 (53) • Female: 19/40 (47)	**Intervention:** Early management (n = 22) – recommends tocilizumab (8 mg/kg IV, maximum of 800 mg/dose) if grade 1 CRS persists for 24 hour. **Comparator:** Standard management (n = 18) – recommends the first dose of tocilizumab at 72 hour of persistent symptoms.	Outcomes: • Incidence of CRS • Incidence of ICANS • Outpatient administration • Length of hospital stay • ICU transfer • Infection within 90 days • Cytopenia • ORR • CRR • Treatment-related mortality Follow-up: NR (Retrospective chart review of patients treated with CAR T over a 3-year period)
Lakomy et al. (2023)[24] Switzerland **Funding source:** The authors reported that the research received no external funding.	Retrospective chart review	Patients with hematological malignancies treated with CAR T-cell therapy. Median age (IQR), years: • Early corticosteroids + standard tocilizumab schedule: 64 (18 to 82) • Standard tocilizumab schedule alone: 68 (25 to 79) Gender, male/female: • Early corticosteroids + standard tocilizumab schedule:19/24	**Intervention:** Early corticosteroids + standard tocilizumab schedule (n = 43) – 10 mg of dexamethasone was administered before each dose of tocilizumab for low-grade CRS. **Comparator:** Standard tocilizumab schedule alone (n = 40) – Tocilizumab was initiated at grade 1 CRS if there was no improvement after 3 days.	Outcomes: • Incidence of CRS • Incidence of ICANS • Length of hospital stay • ICU transfer • ORR • CRR • PFS • OS Follow-up: up to 12 months

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		• Standard tocilizumab schedule alone: 19/21		
Scott et al. (2023)[25] US **Funding source:** NR	Prospective cohort study (reporting as a correspondence)	Patients with RRMM who underwent bispecific T-cell engager therapy (teclistamab step-up dosing – 0.06, 0.3, and 1.5 mg/kg; administered at least 48 hour apart) Median age (IQR), years: • Prophylactic: 69 (43 to 83) • No prophylactic: 58 (47 to 73)	**Intervention:** Prophylactic tocilizumab (n = 38) – administered tocilizumab (8 mg/kg IV, maximum of 800 mg/dose) over 1 hour prophylactically at 44 hour (4 hour before the second step-up dose level of teclistamab) **Comparator:** No prophylactic tocilizumab (n = 15) and the MajesTEC-1 study.[31]	Outcomes: • Incidence of CRS • Duration of CRS • Incidence of ICANS • Hospital readmission • ORR • Incidence of grade 3 or 4 neutropenia Follow-up: Median 113 days (IQR, 3 to 254 days)
Strati et al. (2023)[26] US **Funding source:** NR	Prospective cohort study (reporting as a correspondence)	Patients with hematological malignancies who were treated with CAR T-cell therapy. Median age (IQR), years: • Prophylactic (anakinra): 58 (26 to 81) • No prophylactic: 56 (21 to 79) Gender: Male: • Prophylactic (anakinra): 16/20 (80%) • No prophylactic: 14/20 (70%) Female: • Prophylactic (anakinra): 4/20 (20%) • No prophylactic: 6/20 (30%)	**Intervention:** Prophylactic anakinra (n = 20) – Starting 6 hour before CAT-T-cell infusion on day 0, anakinra was administered at a dose of 100 mg daily (n = 10) or 100 mg every 12 hour (n = 10) for 10 days. **Comparator:** No prophylactic anakinra (n = 20) – a contemporaneous matched cohort underwent similar CAR T-cell therapy without anakinra.	Outcomes: • Incidence of CRS • Duration of CRS • Incidence of ICANS • Duration of ICANS Follow-up: Median 12 months (95% CI, 7 to 17 months)
Banerjee et al. (2021)[27] US **Funding source:** The authors	Retrospective chart review	Patients with RRMM who received BCMA-directed CAR T therapy. Age: • < 65 years: 30/50 (65%)	**Intervention:** Early tocilizumab (n = 19) – tocilizumab was administered ≤ 12 hours after CRS onset	Outcomes: • Incidence of CRS • Incidence of ICANS

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
reported that they have nothing to disclose.		• ≥ 65 years: 20/50 (40%) Gender: • Male: 27/50 (54%) • Female: 23/50 (46%)	**Comparator:** • Late tocilizumab (n = 19) – tocilizumab was administered > 12 hours after CRS onset • No tocilizumab (n = 12).	• Severe infections • Hospital length of stay • CRS duration • ORR • CRR • PFS • OS Follow-up: Median 15.3 months (IQR, 1.8 to 37.8 months)

BCMA = B-cell maturation antigen; CAR T = chimeric antigen receptor T-cell; CI = confidence interval; CRR = complete response rate; CRS = cytokine release syndrome; h = hour; ICANS = immune effector cell-associated neurotoxicity syndrome; IQR = interquartile range; NR = not reported; ORR = objective (or overall) response rate; OS = overall survival; PFS = progression-free survival; RRMM = relapse/refractory multiple myeloma.

Table 3: Characteristics of Included Guidelines

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
NCCN, Thompson et al. (2022)[28]						
Intended users: Physicians, nurses, pharmacists, payers, patients and their families, and many others. **Target population**: Adults and children with cancer undergoing CAR T-cell therapy.	Management strategies of immune-related AEs related to CAR T-cell therapy	CAR T-cell therapy related major AEs (e.g., CRS)	Literature review was performed by electronic search of PubMed database.	NCCN categories for recommendations are based on both the level of clinical evidence available and the degree of consensus within the NCCN Guidelines Panel.[a] All recommendations are category 2A.	Panel of experts reviewed the literature and discussed the new evidence. Recommendations were made from critical evaluation of evidence, integrated with the clinical expertise and consensus of a multidisciplinary panel of cancer specialists, clinical experts, and researchers.	Internally reviewed the draft guideline, posted the preliminary version for international feedback, reviewed and revised the guideline, and posted the final version in the NCCN. org.
ASCO, Santomasso et al. (2021)[29]						
Intended Users: Health care practitioners who provide care to patients with cancer, as well as patients receiving CAR T-cell therapy, and their caregivers. **Target Population**: Adult patients with cancer receiving	Management strategies of immune-related AEs associated with CAR T-cell therapy	CAR T-cell therapy related major AEs (e.g., CRS)	Literature search was performed using PubMed database. Systematic review of evidence was conducted based on prespecified criteria of PICO.	Due to the paucity of high-quality evidence, recommendations are based on expert consensus. All recommendations were expert consensus-based; benefits outweighed harms; strength of recommendation: moderate.	A multidisciplinary panel of experts including patient advocacy groups was convened to develop the clinical practice guideline. Members of the expert panel reviewed the literature, developed the guideline, provided critical reviewed, and finalized the guideline recommendations.	The guideline was circulated for external reviewed, revised, and submitted to a peer-reviewed journal for publication.

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
treatment with CAR T-cell therapy.						
EBMT and JACIE, Yakoub-Agha et al. (2020)[30]						
Intended users: Hematologists and other cancer specialists and their team involved in the administration of CAR T-cell therapy, pharmacists, or health service administrators. **Target population**: Adults and children undergoing CAR T-cell therapy.	Management strategies of AEs in adults and children undergoing CAR T therapy	Efficacy and safety outcomes of CAR T therapy.	Evidence was collected from literature review and responses from survey sent to centres active in the field of CAR T therapy.	Due to absence of randomized evidence, the recommendations were not graded. They therefore represented the consensus views of the authors.	A Guidelines subcommittee proposed the project. EBMT board accepted the proposal and worked with experts in the field to produce practical clinical recommendations on the management of adults and children undergoing CAR T-cell therapy.	The guideline was published in a peer-reviewed journal.
SITC, Maus et al. (2020)[32]						
Intended users: Medical professionals involved in the treatment of patients undergoing CAR T-cell therapy. **Target population**: Adults and children	Management strategies of AEs in adults and children undergoing CAR T-cell therapy	Efficacy and safety outcomes of CAR T-cell therapy	Details on literature review, evidence collection, selection and synthesis were not reported.	Evidence was graded based on the Oxford Levels of Evidence 2.[b]	Evidence- and consensus-based recommendations were developed using the Institute of Medicine's Standards for Developing trustworthy Clinical Practice Guidelines. Panel of expert drafted the recommendations based on evidence from the published literature,	The guideline was published in a peer-reviewed journal.

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
undergoing immune effector cell therapies including CAR T-cell therapy.					discussed during in-person consensus meeting, and graded the evidence supporting panel recommendations.	

AE = adverse event; ASCO = American Society of Clinical Oncology; CAR T = chimeric antigen receptor T-cell; CRS = cytokine release syndrome; EBMT = European Society for Blood and Marrow Transplantation; IL = interleukin; JACI = Joint Accreditation Committee of the International Society for Cell Therapy and EBMT; NCCN = National Comprehensive Cancer Network; NR = not reported; PICO = population, intervention, comparator, and outcomes; SITC = Society for Immunotherapy of Cancer.

[a]Categories of evidence and consensus:

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate;

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate;

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate;

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

[b]Summary of The Oxford Levels of Evidence 2:

Level 1: Systematic review or meta-analysis

Level 2: Randomized trial or observational study with dramatic effect

Level 3: Nonrandomized controlled cohort or follow-up study

Level 4: Case series, case-control, or historically controlled study

Level 5: Mechanism-based reasoning

Note that this appendix has not been copy-edited.

Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

Table 4: Strengths and Limitations of Clinical Studies Using the Downs and Black Checklist[20]

Strengths	Limitations
Gaffney et al. (2024)[23]	
Reporting: • The objective of the study, the main outcomes to be measured, the characteristics of the patients included in the study, the interventions of interest, and the main findings were clearly described. • Actual P values were reported for the main outcomes. • Efficacy and safety outcomes of the intervention were reported. **External validity:** • The study was conducted in a hospital setting. The staff, places, and facilities where the patients were treated, were representative of the treatment most of the patients receive. **Internal validity – bias:** • Statistical tests were appropriately used to compare differences between groups, and the main outcome measures were accurate and reliable. **Internal validity – confounding:** • The baseline characteristics of the treatment groups appeared to be balanced, thus reducing the risk of confounding bias.	**External validity:** • The retrospective cohort study with small sample size was conducted from a single hospital. The patients may not be representative of the entire population from which they were treated. **Internal validity – bias:** • Risk of selection bias is a main limitation of a retrospective cohort study. **Internal validity – confounding:** • Residual confounding factors may exist, and failure to identify and adjust for those factors in the analyses may have an impact on the findings. • The study did not report whether sample size was calculated.
Lakomy et al. (2023)[24]	
Reporting: • The objective of the study, the main outcomes to be measured, the characteristics of the patients included in the study, the interventions of interest, and the main findings were clearly described. • Actual P values were reported for the main outcomes. • Efficacy and safety outcomes of the intervention were reported. **External validity:** • The study was conducted in a hospital setting. The staff, places, and facilities where the patients were treated, were representative of the treatment the majority of the patients receive. **Internal validity – bias:** • Statistical tests were appropriately used to compare differences between groups, and the main outcome measures were accurate and reliable. **Internal validity – confounding:** The baseline characteristics of the treatment groups appeared to be balanced, thus reducing the risk of confounding bias.	**External validity:** • The retrospective cohort study with small sample size was conducted from a single hospital. The patients may not be representative of the entire population from which they were treated. **Internal validity – bias:** • Risk of selection bias is a main limitation of a retrospective cohort study. **Internal validity – confounding:** • Residual confounding factors may exist, and failure to identify and adjust for those factors in the analyses may have an impact on the findings. • The study did not report whether sample size was calculated.

Strengths	Limitations
Scott et al. (2023)[25]	
Reporting: • The objective of the study, the main outcomes to be measured, the characteristics of the patients included in the study, the interventions of interest, and the main findings were clearly described. • Efficacy and safety outcomes of the intervention were reported. **External validity:** • The study was conducted in a hospital setting. The staff, places, and facilities where the patients were treated, were representative of the treatment most of the patients receive. **Internal validity – bias:** • The main outcome measures appeared to be accurate and reliable. **Internal validity – confounding:** • The baseline characteristics of the treatment groups appeared to be balanced, thus reducing the risk of confounding bias.	**Reporting:** • Actual P values were not reported for the main outcomes. **External validity:** • The retrospective cohort study with small sample size was conducted from a single hospital. The patients may not be representative of the entire population from which they were treated. **Internal validity – bias:** • Risk of selection bias is a main limitation of this cohort study, as the outcome measures were indirectly compared with the those of another cohort study with similar treatment. • Statistical tests were not used to compare differences between groups. **Internal validity – confounding:** • Residual confounding factors may exist, and failure to identify and adjust for those factors in the analyses may have an impact on the findings. • The study did not report whether sample size was calculated.
Strati et al. (2023)[26]	
Reporting: • The objective of the study, the main outcomes to be measured, the characteristics of the patients included in the study, the interventions of interest, and the main findings were clearly described. • Efficacy and safety outcomes of the intervention were reported. **External validity:** • The study was conducted in a hospital setting. The staff, places, and facilities where the patients were treated, were representative of the treatment most of the patients receive. **Internal validity – bias:** • The main outcome measures appeared to be accurate and reliable. **Internal validity – confounding:** • The baseline characteristics of the treatment groups appeared to be balanced, thus reducing the risk of confounding bias.	**Reporting:** • Actual P values were not reported for the main outcomes. **External validity:** • The retrospective cohort study with small sample size was conducted from a single hospital. The patients may not be representative of the entire population from which they were treated. **Internal validity – bias:** • Risk of selection bias is a main limitation of this cohort study, as the outcome measures were indirectly compared with the those of another cohort study with similar treatment. • Statistical tests were not used to compare differences between groups. **Internal validity – confounding:** • Residual confounding factors may exist, and failure to identify and adjust for those factors in the analyses may have an impact on the findings. • The study did not report whether sample size was calculated.
Banerjee et al. (2021)[27]	
Reporting: • The objective of the study, the main outcomes to be measured, the characteristics of the patients included in the study, the interventions of interest, and the main findings were clearly	**External validity:** • The retrospective cohort study with small sample size was conducted from a single hospital. The patients may not be representative of the entire population from which they were

Strengths	Limitations
described. • Actual P values were reported for the main outcomes. • Safety outcomes including adverse events of the intervention were reported. **External validity:** • The study was conducted in a hospital setting. The staff, places, and facilities where the patients were treated, were representative of the treatment the majority of the patients receive. **Internal validity – bias:** • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. **Internal validity – confounding:** • The baseline characteristics of the treatment groups appeared to be balanced, thus reducing the risk of confounding bias.	treated. **Internal validity – bias:** • Risk of selection bias is a main limitation of a retrospective cohort study. **Internal validity – confounding:** • Residual confounding factors may exist, and failure to identify and adjust for those factors in the analyses may have an impact on the findings. • The study did not report whether sample size was calculated.

Table 5: Strengths and Limitations of Guidelines Using AGREE II[21]

Item	NCCN, Thompson et al. (2022)[28]	ASCO, Santomasso et al. (2021)[29]	EBMT and JACIE, Yakoub-Agha et al. (2020)[30]	SITC, Maus et al. (2020)[32]
Domain 1: Scope and purpose				
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes	Yes	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes	Yes	Yes
Domain 2: Stakeholder involvement				
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Yes	Yes	Yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Yes	Yes	Yes	Yes
6. The target users of the guideline are clearly defined.	Yes	Yes	Yes	Yes
Domain 3: Rigour of development				
7. Systematic methods were used to search for evidence.	No	No	No	No
8. The criteria for selecting the evidence are clearly described.	No	No	No	No
9. The strengths and limitations of the body of evidence are clearly described.	No	No	No	No
10. The methods for formulating the recommendations are clearly described.	Partially yes	Partially yes	Partially yes	Partially yes

Item	NCCN, Thompson et al. (2022)[28]	ASCO, Santomasso et al. (2021)[29]	EBMT and JACIE, Yakoub-Agha et al. (2020)[30]	SITC, Maus et al. (2020)[32]
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes	Yes	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	No	No	No	No
13. The guideline has been externally reviewed by experts before its publication.	Yes	Yes	Yes	Yes
14. A procedure for updating the guideline is provided.	Unclear	Unclear	Unclear	Unclear
Domain 4: Clarity of presentation				
15. The recommendations are specific and unambiguous.	Yes	Yes	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes	Yes	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes	Yes	Yes
Domain 5: Applicability				
18. The guideline describes facilitators and barriers to its application.	Unclear	Unclear	Unclear	Unclear
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Unclear	Unclear	Unclear	Unclear
20. The potential resource implications of applying the recommendations have been considered.	Unclear	Unclear	Unclear	Unclear
21. The guideline presents monitoring and/or auditing criteria.	Unclear	Unclear	Unclear	Unclear
Domain 6: Editorial independence				
22. The views of the funding body have not influenced the content of the guideline.	NR	No	NR	No
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	Yes	Yes	Yes

AGREE II = Appraisal of Guidelines for Research and Evaluation II; ASCO = American Society of Clinical Oncology; EBMT = European Society for Blood and Marrow Transplantation; JACIE = Joint Accreditation Committee of the International Society for Cell Therapy and EBMT; NCCN = National Comprehensive Cancer Network; NR = not reported.

Appendix 4: Main Study Findings

Note that this appendix has not been copy-edited.

Table 6: Summary of Findings by Outcome — Incidence of CRS

Study citation and study design	Intervention vs. Comparator	Results	Notes
Gaffney et al. (2024)[23] Retrospective chart review	Early management protocol (n = 22) vs. Standard management protocol (n = 18)	CRS: • All grades: 17/22 (77%) vs. 13/18 (72%); P = 0.73 • Grade 3 and 4: 1/22 (5%) vs. 0/18 (0%); P = 1.0 There were no major differences in the incidence or severity of CRS between treatment groups.	The main difference between early management and standard management protocols is the approach toward grade 1 CRS. Early management protocol recommends tocilizumab (8 mg/kg, maximum 800 mg/dose) if grade 1 CRS persists for 24 hour. Standard management protocol recommends the first dose of tocilizumab at 72 hour of persistent symptoms.
Lakomy et al. (2023)[24] Retrospective chart review	Early corticosteroids + standard tocilizumab schedule vs. standard tocilizumab schedule	CRS: • All grades: 39/43 (91%) vs. 28/40 (70%); P = 0.0249 • High-grade (3 and 4): 0 (0%) vs. 4/40 (10%); P = 0.0497 • Grade 1: 26/43 (67%) vs. 13/40 (33%); P = 0.0021 • Grade 2: 10/43 (23%) vs. 11/40 (28%); P = 0.8013 • Grade 3: 0 (0%) vs. 3/40 (8%); P = 0.1075 • Grade 4: 0 (0%) vs. 1/40 (3%); P = 0.4819	In the early corticosteroids group, 10 mg dexamethasone IV was administered before each dose of tocilizumab in case of low-grade CRS.
Scott et al. (2023)[25] Prospective cohort study (reporting as a correspondence)	Prophylactic tocilizumab (n = 38) vs. No prophylactic tocilizumab (n = 15)	CRS: • All grades of entire cohort (N = 53): 21/53 (39.6%) • All grades: 10/38 (26.3%) vs. 11/15 (73.3%) • Grade 1: 8/38 (21.1%) vs. 10/15 (66.7%) • Grade 2: 1/38 (2.6%) vs. 0/15 (0%) • Grade 3: 1/38 (2.6%) vs. 0/15 (0%)	CAR T (teclistamab) therapy was administered at the step-up dosing at least 48 hour apart (0.06, 0.3, and 1.5 mg/kg). Dexamethasone 16 mg, diphenhydramine 25 to 50 mg, and acetaminophen 650 mg were administered 30 minute before each dose. No prophylactic tocilizumab, 15 patients were first evaluated, and the median time to CRS from the administration of the first-priming dose was 48 hour. For prophylactic tocilizumab, tocilizumab 8 mg/kg IV (maximum dose of 800 mg) was administered at 44 hour (4 hour before the second step-up dose level).

Study citation and study design	Intervention vs. Comparator	Results	Notes
Strati et al. (2023)[26] Prospective cohort study (reporting as a correspondence)	Prophylactic anakinra (n = 20) vs. No prophylactic anakinra (n = 20) of a contemporaneous matched cohort	CRS: • All grade: 19/20 (95% [95% CI, 75.1 to 99.9]) vs. 19/20 (95% [95% CI, 75.1 to 99.9]) • Grade 2 to 4: 8/20 (40% [95% CI, 19.1 to 63.9]) vs. 10/20 (50% [95% CI, 27.2 to 72.8]) • Grade 3 to 4: 1/20 (5% [95% CI, 0.1 to 24.9]) vs. 1/20 (5% [95% CI, 0.1 to 24.9]) • Median duration, days (range): 5 (2 to 9) vs. 3 (2 to 9); P = NR	In the study cohort, anakinra was administered 6 hours before CAR T-cell infusion on day 0 at a dose of 100 mg daily (n = 10) or 100 mg every 12 hours (n = 10) for 7 days. Results in the study cohort were compared with those of a contemporaneous matched cohort treated without anakinra.
Banerjee et al. (2021)[27] Retrospective chart review	Early Toci (n = 19) vs. Late Toci (n = 19) no Toci (n = 12)	CRS: • Grade 1: 18/19 (95%) vs. 18/19 (95%); P = 1.00 • Grade 2: 1/19 (5%) vs. 1/19 (5%); P = 1.0 Median duration, h (range): 18.6 (5.1 to 106.7) vs. 84.7 hour (20.0 to 188.0). 7 patients in the no Toci group developed CRS. Median CRS duration was 42.1 hour (range, 1.7 to 141.1 hour)	Early Toci: Tocilizumab was administered at ≤ 12 hour after CRS onset. Late Toci: Tocilizumab was administered at > 12 hour after CRS onset. Median time-to-Toci intervals were 7.2 hour (range, 0.8 to 11.7 hour) for the Early Toci group and 22.2 hour (range, 12.6 to 185.7 hour) for the Late Toci group.

CAR T = chimeric antigen receptor T-cell; CRS = cytokine release syndrome; h = hour; vs. = versus.

Table 7: Summary of Findings by Outcome — Incidence of ICANS

Study citation and study design	Intervention vs. comparator	Results	Notes
Gaffney et al. (2024)[23] Retrospective chart review	Early management protocol (n = 22) vs. Standard management protocol (n = 18)	ICANS: • All grades: 7/22 (32%) vs. 6/18 (33%); P = 1.0 • Grade 3 and 4: 2/22 (19%) vs. 2/18 (11%); P = 1.0	The main difference between early management and standard management protocols is the approach toward grade 1 CRS. Early management protocol recommends tocilizumab (8 mg/kg, maximum 800 mg/dose) if grade 1 CRS persists for 24 hour. Standard management protocol recommends the first dose of tocilizumab at 72 hour of persistent symptoms.
Lakomy et al. (2023)[24] Retrospective chart review	Early corticosteroids + standard tocilizumab schedule (n = 43) vs. standard tocilizumab schedule (n = 40)	ICANS: • All grades: 14/43 (91%) vs. 12/40 (70%); P = 0.8177 • High-grade (3 and 4): 6/43 (14%) vs. 8/40 (20%); P = 0.5624 • Grade 1: 4/43 (9%) vs. 3/40 (8%); P > 0.9999 • Grade 2: 5/43 (12%) vs. 1/40 (3%); P = 0.2033 • Grade 3: 5/43 (12%) vs. 6/40 (15%);	In the early corticosteroids group, 10 mg dexamethasone IV was administered before each dose of tocilizumab in case of low-grade CRS.

Study citation and study design	Intervention vs. comparator	Results	Notes
		P = 0.7515 • Grade 4: 1/43 (2%) vs. 2/40 (5%); P > 0.9999	
Scott et al. (2023)[25] Prospective cohort study (reporting as a correspondence)	Prophylactic tocilizumab (n = 38) vs. No prophylactic tocilizumab (n = 15)	Concurrent ICANS: • 5.3% vs. 20%; P = NR	CAR T (teclistamab) therapy was administered at the step-up dosing at least 48 hour apart (0.06, 0.3, and 1.5 mg/kg). Dexamethasone 16 mg, diphenhydramine 25 to 50 mg, and acetaminophen 650 mg were administered 30 minute before each dose. No prophylactic tocilizumab, 15 patients were first evaluated, and the median time to CRS from the administration of the first-priming dose was 48 hour. For prophylactic tocilizumab, tocilizumab 8 mg/kg IV (maximum dose of 800 mg) was administered at 44 hour (4 hour before the second step-up dose level).
Strati et al. (2023)[26] Prospective cohort study (reporting as a correspondence)	Prophylactic anakinra (n = 20) vs. Treatment without anakinra (n = 20)	ICANS: • All grades: 7/20 (35% [95% CI, 15.4 to 59.2]) vs. 12/20 (60% [95% CI, 36.1, 80.9]) • Grade 3 and 4: 4/20 (20% [95% CI, 5.7 to 43.7]) vs. 6/20 (30% [95% CI, 11.9 to 54.3]) • Median onset, days (range): 7 (3 to 9) vs. 5 (1 to 14); P = NR • Median duration, days (range): 2 (2 to 17) vs. 3 (1 to 24); P = NR	In the study cohort, anakinra was administered 6 hour before CAR T-cell infusion on day 0 at a dose of 100 mg daily (n = 10) or 100 mg every 12 hour (n = 10) for 7 days. Results in the study cohort were compared with those of a contemporaneous matched cohort treated without anakinra.
Banerjee et al. (2021)[27] Retrospective chart review	Early Toci (n = 19) vs. Late Toci (n = 19) no Toci (n = 12)	ICANS: • All grades: 4/19 (21%) vs. 7/19 (37%): P = 0.48	Early Toci: Tocilizumab was administered at ≤ 12 hour after CRS onset. Late Toci: Tocilizumab was administered at > 12 hour after CRS onset. Median time-to-Toci intervals were 7.2 hour (range, 0.8 to 11.7 hour) for the Early Toci group and 22.2 hour (range, 12.6 to 185.7 hour) for the Late Toci group.

CAR T = chimeric antigen receptor T-cell; CI = confidence interval; CRS = cytokine release syndrome; h = hour; ICANS = immune effector cell-associated neurotoxicity syndrome; NR = not reported; vs. = versus.

Table 8: Summary of Findings by Outcome — Level of Care

Study citation and study design	Intervention vs. comparator	Results	Notes
Gaffney et al. (2024)[23] Retrospective cohort study	Early management protocol vs. Standard management protocol	Outpatient administration: 19/22 (86%) vs. 13/18 (72%); P = 0.43 Median length of hospital stay, days (range): 14 (0 to 52) vs. 14 (8 to 28); P = 0.78 ICU transfer: 3/22 (14%) vs. 0/18 (0%); P = 0.24	The main difference between early management and standard management protocols is the approach toward grade 1 CRS. Early management protocol recommends tocilizumab (8 mg/kg, maximum 800 mg/dose) if grade 1 CRS persists for 24 hour. Standard management protocol recommends the first dose of tocilizumab at 72 hour of persistent symptoms.
Lakomy et al. (2023)[24] Retrospective chart review	Early corticosteroids + standard tocilizumab schedule vs. standard tocilizumab schedule	Median length of hospital stay, days (range): 21 (16 to 46) vs. 22 (14 to 52); P = 0.7611 ICU transfer: 5/43 (12%) vs. 8/40 (20%); P = 0.3709	In the early corticosteroids group, 10 mg dexamethasone IV was administered before each dose of tocilizumab in case of low-grade CRS.
Scott et al. (2023)[25] Prospective cohort study (reporting as a correspondence)	Prophylactic tocilizumab vs. No prophylactic tocilizumab	Hospital readmission within 14 days of discharge: 0/38 (0%) vs. NR	CAR T (teclistamab) therapy was administered at the step-up dosing at least 48 hour apart (0.06, 0.3, and 1.5 mg/kg). Dexamethasone 16 mg, diphenhydramine 25 to 50 mg, and acetaminophen 650 mg were administered 30 minute before each dose. For no prophylactic tocilizumab, 15 patients were first evaluated, and the median time to CRS from the administration of the first-priming dose was 48 hour. For prophylactic tocilizumab, tocilizumab 8 mg/kg IV (maximum dose of 800 mg) was administered at 44 hour (4 hour before the second step-up dose level).

CAR T = chimeric antigen receptor T-cell; CRS = cytokine release syndrome; h = hour; ICU = intensive care unit; NR = not reported; vs. = versus.

Table 9: Summary of Findings by Outcome — Other Adverse Events and Mortality

Study citation and study design	Intervention vs. comparator	Results	Notes
Gaffney et al. (2024)[23]	Early management protocol vs. Standard	Infection within 90 days: 8/17 (47%) vs. 1/9 (11%); P = 0.20 Cytopenia at Day 90:	The main difference between early management and standard management protocols is the

Study citation and study design	Intervention vs. comparator	Results	Notes

Retrospective cohort study	management protocol	• Neutropenia:
		  ○ All grades: 10/17 (59%) vs. 5/9 (85%); P = 1.0
		  ○ Grade 3 to 4: 5/17 (29%) vs. 1/9 (11%); P = 0.6
		• Anemia:
		  ○ All grades: 12/17 (71%) vs. 8/9 (89%); P = 0.38
		  ○ Grade 3 to 4: 0/17 (0%) vs. 1/9 (11%); P = 0.40
		• Thrombocytopenia:
		  ○ All grades: 7/17 (41%) vs. 5/9 (85%); P = 0.68
		  ○ Grade 3 to 4: 1/17 (6%) vs. 2/9 (22%); P = 0.52
		Treatment-related mortality: 1/22 (5%) vs. 0/18 (0%); P = 0.32
			approach toward grade 1 CRS. Early management protocol recommends tocilizumab (8 mg/kg, maximum 800 mg/dose) if grade 1 CRS persists for 24 hour. Standard management protocol recommends the first dose of tocilizumab at 72 hour of persistent symptoms.

Scott et al. (2023)[25] Prospective cohort study (reporting as a correspondence)	Prophylactic tocilizumab vs. No prophylactic tocilizumab (in the MajesTEC-1 study[31])	Neutropenia: • Grade 3 or 4: 42.1% vs. 64.2%	CAR T (teclistamab) therapy was administered at the step-up dosing at least 48 hours apart (0.06, 0.3, and 1.5 mg/kg). Dexamethasone 16 mg, diphenhydramine 25 to 50 mg, and acetaminophen 650 mg were administered 30 minute before each dose. For no prophylactic tocilizumab, 15 patients were first evaluated, and the median time to CRS from the administration of the first-priming dose was 48 hours. For prophylactic tocilizumab, tocilizumab 8 mg/kg IV (maximum dose of 800 mg) was administered at 44 hours (4 hours before the second step-up dose level).
Banerjee et al. (2021)[27] Retrospective chart review	Early Toci (n = 19) vs. Late Toci (n = 19) no Toci (n = 19)	Severe infections: • Yes: 1/19 (5%) vs. 1/19 (5%); P = 1.0 • No: 18/19 (95%) vs. 18/19 (95%); P = 1.0	Early Toci: Tocilizumab was administered at ≤ 12 hour after CRS onset. Late Toci: Tocilizumab was administered at > 12 hour after CRS onset. Median time-to-Toci intervals were 7.2 hours (range, 0.8 to 11.7 hours) for the Early Toci group and 22.2 hours (range, 12.6 to 185.7 hours).

CAR T = chimeric antigen receptor T-cell; CRS = cytokine release syndrome; h = hour; NR = not reported; vs. = versus.

Table 10: Summary of Findings by Outcome — Efficacy Outcomes of Immunotherapy

Study citation and study design	Intervention vs. comparator	Results	Notes
Gaffney et al. (2024)[23] Retrospective cohort study	Early management protocol vs. Standard management protocol	ORR: • 30 days: 17/22 (77%) vs. 10/18 (56%); P = 0.0003 • 90 days: 16/18 (89%) vs. 7/14 (50%); P = 0.14 CRR: • 30 days: 14/22 (64%) vs. 6/18 (33%); P = 0.01 • 90 days: 11/18 (61%) vs. 6/14 (42%); P = 0.29	The main difference between early management and standard management protocols is the approach toward grade 1 CRS. Early management protocol recommends tocilizumab (8 mg/kg, maximum 800 mg/dose) if grade 1 CRS persists for 24 hours. Standard management protocol recommends the first dose of tocilizumab at 72 hours of persistent symptoms.
Lakomy et al. (2023)[24] Retrospective chart review	Early corticosteroids + standard tocilizumab schedule vs. standard tocilizumab schedule	ORR: • 77% vs. 80%; P = 0.7936 CRR: • 44% vs. 50%; P = 0.6628 Median PFS, months: • 11.4 vs. 17.6; P = 0.6345 Median OS, months: • 10.98 vs. 36.49; P = 0.1215	In the early corticosteroids group, 10 mg dexamethasone IV was administered before each dose of tocilizumab in case of low-grade CRS.
Scott et al. (2023)[25] Prospective cohort study (reporting as a correspondence)	Prophylactic tocilizumab vs. No prophylactic tocilizumab (MajesTEC-1 study[31])	ORR: • 70% vs. 63%	CAR T (teclistamab) therapy was administered at the step-up dosing at least 48 hours apart (0.06, 0.3, and 1.5 mg/kg). Dexamethasone 16 mg, diphenhydramine 25 to 50 mg, and acetaminophen 650 mg were administered 30 minute before each dose. For no prophylactic tocilizumab, 15 patients were first evaluated, and the median time to CRS from the administration of the first-priming dose was 48 hour. For prophylactic tocilizumab, tocilizumab 8 mg/kg IV (maximum dose of 800 mg) was administered at 44 hour (4 hour before the second step-up dose level).
Banerjee et al. (2021)[27] Retrospective chart review	Early Toci (n = 19) vs. Late Toci (n = 19) vs. no Toci (n = 19)	ORR: • 30 days: 14/19 (74%) vs. 15/19 (79%) vs. 6/19 (32%); P = 0.03 when comparing early Toci or late Toci with no Toci; P = 1.00 when comparing between early Toci and late Toci. CRR as best response: • 30 days: 17/19 (89%) vs 10/19 (53%) vs. 9/18 (50%); P = 0.02.	Early Toci: Tocilizumab was administered at ≤ 12 hour after CRS onset. Late Toci: Tocilizumab was administered at > 12 hour after CRS onset. Median time-to-Toci intervals were 7.2 hour (range, 0.8 to 11.7 hour) for

Study citation and study design	Intervention vs. comparator	Results	Notes
		Median PFS, months (95% CI): • Early Toci: 35.7 (11.0 to not reached) • Late Toci: 13.2 (9.5 to not reached) • No Toci: 7.8 (1.9 to not reached) Median OS, months (95% CI): • Early Toci: Not reached (not reached to not reached) • Late Toci: 25.0 (21.4 to not reached) • No Toci: 26.4 (18.7 to not reached)	the Early Toci group and 22.2 hour (range, 12.6 to 185.7 hour) for late Toci group.

CAR T = chimeric antigen receptor T-cell; CI = confidence interval; CRR = complete response rate; CRS = cytokine release syndrome; h = hour; NR = not reported; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; vs. = versus.

Table 11: Summary of Recommendations in Included Guidelines for CSR

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
NCCN, Thompson et al. (2022)[28]	
CRS grade 1[a] • "**Anti-IL-6 Therapy:** *For prolonged CRS (>3 days) in patients or those with significant symptoms, comorbidities and/or are elderly, consider 1 dose of tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg).* • **Corticosteroids:** *For idecabtagene and lisocabtagene, consider dexamethasone 10 mg IV every 24 hours for early-onset CRS (< 72 hours after infusion).* • **Additional Supportive Care:** *Sepsis screen and empiric broad-spectrum antibiotics, consider granulocyte-colony-stimulating factor (G-CSF) if neutropenic. Maintenance IV fluids for hydration. Symptomatic management of organ toxicities."* (p. 391)	Quality of evidence: Low Strength of recommendations: By consensus, Category 2A
CRS grade 2[b] • "**Anti-IL-6 Therapy:** *Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose). Repeat in 8 hours if no improvement; no more than 3 doses in 24 hours, with a maximum of 4 doses total.* • **Corticosteroids:** *For persistent refractory hypotension after 1 to 2 doses of anti-IL-6 therapy: Consider dexamethasone 10 mg IV every 12 to 24 hours depending on product."* (p. 391) • **Additional Supportive Care:** *IV fluid bolus as needed. For persistent refractory hypotension after 2 fluid boluses and anti-IL-6 therapy: Start vasopressors, consider transfer to ICU, consider echocardiogram, and initiate other methods of hemodynamic monitoring. Telemetry, EKG, troponin, and BNP if persistent tachycardia. Manage per grade 3 if no improvement within 24 hours after starting anti-IL-6 therapy. Symptomatic management of organ toxicities."* (p. 391)	Quality of evidence: Low Strength of recommendations: By consensus, Category 2A
CRS grade 3[c] • "**Anti-IL-6 Therapy:** *Anti-IL-6 therapy as per grade 2 if maximum dose not reached within 24-hour period.* • **Corticosteroids:** *Dexamethasone 10 mg IV every 6 hours. If refractory, manage as grade 4.* • **Additional Supportive Care:** *Transfer to ICU, obtain echocardiogram, and perform hemodynamic monitoring. Supplemental oxygen. IV fluid bolus and vasopressors as needed. Symptomatic management of organ toxicities."* (p. 391)	Quality of evidence: Low Strength of recommendations: By consensus, Category 2A

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
CRS grade 4[d] • **"Anti-IL-6 Therapy:** *Anti-IL-6 therapy as per grade 2 if maximum dose not reached within 24-hour period.* • **Corticosteroids:** *Dexamethasone 10 mg IV every 6 hours. If refractory, consider 3 doses of methylprednisolone 1,000 mg/day IV; if refractory, consider dosing every 12 hours.*[e] • **Additional Supportive Care:** *ICU care and hemodynamic monitoring. Mechanical ventilation as needed. IV fluid bolus and vasopressors as needed. Symptomatic management of organ toxicities."* (p.391)	Quality of evidence: Low Strength of recommendations: By consensus, Category 2A
Supporting evidence: • Tocilizumab was approved by the FDA for treatment of severe life-threatening CRS. The approval was based on a retrospective study and prospective trials. • Prescribing information for axicabtagene ciloleucel states that tocilizumab can be considered for grade 1 CRS if CRS symptoms persist for more than 24 hours. This was supported by data from an explanatory safety management cohort of Zuma-1 trial. • Siltuximab, an anti-IL6 antibody, has been proposed as an alternative to tocilizumab. This was supported by prescribing information and data from an animal study, and an in vitro study. • Anakinra, an IL-1Ra, has been considered another potential alternative to tocilizumab. This was supported by 2 preclinical studies in mouse models. Subsequently, there were reports suggesting anakinra may be effective in managing CRS.	
ASCO, Santomasso et al. (2021)[29]	
CRS grade 1[a] • *"Offer supportive care with antipyretics, IV hydration, and symptomatic management of organ toxicities and constitutional symptoms.* • *May consider empiric broad-spectrum antibiotics if neutropenic.* • *May consider G-CSF in accordance with product guidelines. Note: GM-CSF is not recommended.* • *In patients with persistent (> 3 days) or refractory fever, consider managing as per grade 2."* (p. 3982)	Quality of evidence: Low Strength of recommendations: By consensus, Moderate
CRS grade 2[b] • *"Continue supportive care as per grade 1 and include IV fluid bolus and/or supplemental oxygen as needed.* • *Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose). Repeat every 8 hours if no improvement in signs and symptoms of CRS; limit to a maximum of 3 doses in a 24-hour period, with a maximum of 4 doses total.* • *In patients with hypotension that persists after 2 fluid boluses and after one to 2 doses of tocilizumab, may consider dexamethasone 10 mg IV (or equivalent) every 12 hours for one to 2 doses and then reassess.* • *Manage per grade 3 if no improvement within 24 hours of starting tocilizumab."* (p. 3982)	Quality of evidence: Low Strength of recommendations: By consensus, Moderate
CRS grade 3[c] • *"Continue supportive care as per grade 2 and include vasopressors as needed.* • *Admit patient to ICU.* • *If echocardiogram was not already performed, obtain ECHO to assess cardiac function and conduct hemodynamic monitoring.* • *Tocilizumab as per grade 2 if maximum dose is not reached within 24-hour period plus dexamethasone 10 mg IV every 6 hours (or equivalent) and rapidly taper once symptoms improve.* • *If refractory, manage as per grade 4."* (p. 3982)	Quality of evidence: Low Strength of recommendations: By consensus, Moderate

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
CRS grade 4[d] • *"Continue supportive care as per grade 3 plus mechanical ventilation as needed.* • *Administer tocilizumab as per grade 2 if maximum is not reached within 24-hour period.* • *Initiate high-dose methylprednisolone at a dose of 500 mg IV every 12 hours for 3 days, followed by 250 mg IV every 12 hours for 2 days, 125 mg IV every 12 hours for 2 days, and 60 mg IV every 12 hours until CRS improvement to grade 1.* • *If not improving, consider methylprednisolone 1,000 mg IV 2 times a day or alternate therapy."* (p. 3982)	Quality of evidence: Low Strength of recommendations: By consensus, Moderate
Supporting evidence: The authors did not provide any supporting evidence in their discussion for management of CRS.	
EBMT and JACIE, Yakoub-Agha et al. (2020)[30]	
CRS grade 1[a] • *"After blood cultures and other infection tests, start preemptive broad-spectrum antibiotics and symptomatic measures (antipyretics, fluids…).* • *Corticosteroids are contraindicated in the absence of life-threatening complications.* • *In the absence of improvement within 3 days and in the absence of other differential diagnosis, consider tocilizumab IV 8 mg/kg (maximum 800 mg)."* (p. 308)	Quality of evidence: NR Strength of recommendations: Not graded
CRS grade 2[b] • *"Alert local ICU.* • *Tocilizumab IV 8 mg/kg (maximum 800 mg) to be done in the hematology unit before transfer to ICU.* • *If deterioration, consider dexamethasone IV 10 mg/6 hours pendant 1 to 3 days.* • *In the absence of improvement, persistence of symptoms, repeat tocilizumab (maximum 2 additional doses) or switch to siltuximab IV 11 mg/kg x 1/d.* • *Consider dexamethasone IV 10 mg/6 hours for 1 to 3 days."* (p. 308)	Quality of evidence: NR Strength of recommendations: Not graded
CRS grade 3[c] • *"Alert local ICU.* • *Tocilizumab IV 8 mg/kg (maximum 800 mg) to be done in the hematology unit before transfer to ICU.* • *If deterioration, consider dexamethasone IV 10 mg/6 hours pendant 1 to 3 days.* • *In the absence of improvement, persistence of symptoms, repeat tocilizumab (maximum 2 additional doses) or switch to siltuximab IV 11 mg/kg x 1/day.* • *Consider dexamethasone IV 10 mg/6 hours for 1 to 3 days."* (p. 308)	Quality of evidence: NR Strength of recommendations: Not graded
CRS grade 4[d] • *"Alert local ICU.* • *Tocilizumab IV 8 mg/kg (maximum 800 mg) to be done in the hematology unit before transfer to ICU.* • *If deterioration, consider dexamethasone IV 20 mg/6 hours for 3 days, progressive tapering within 3 to 7 days.* • *In the absence of improvement, persistence of symptoms, repeat tocilizumab (maximum 2 additional doses) or switch to siltuximab IV 11 mg/kg x 1/d.* • *Consider methylprednisolone IV 1,000 mg/day for 3 days then 250 mg x 2/day for 6 days, 60 mg x 2/day for 2 days."* (p. 308)	Quality of evidence: NR Strength of recommendations: Not graded

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
Supporting evidence: • Studies using preclinical models (humanized immunodeficiency mice) showed that human monocytes are the main source of IL-1 and IL-6 during CRS. The syndrome can be prevented by blocking the IL-6 receptor with tocilizumab. Anakinra, an anti-IL-1 receptor antagonist appears to prevent CRS and neurotoxicity in animal models. • The authors did not provide any supporting evidence on the use of tocilizumab, and/or corticosteroids for management of CRS.	
SITC, Maus et al. (2020)[32]	
• *"For elderly patients or patients with extensive comorbidities, tocilizumab should be considered earlier in the course of CRS."* (p. 10) Supporting evidence: None; recommendation was made by consensus.	Quality of evidence: None Strength of recommendations: Not graded
• *"For adults who develop ASTCT grade 2 CRS, tocilizumab may be considered."* (p. 10) Supporting evidence: From FDA Approval Summary	• Quality of evidence: Level 3 • Strength of recommendations: Not graded
• *"For pediatric patients, tocilizumab should be administered at ASTCT grade 3 CRS."* (p. 10) Supporting evidence: From case reports of 2 children.	Quality of evidence: Level 3 Strength of recommendations: Not graded
• *"For pediatric patients who develop prolonged ASTCT grade 2 CRS or intolerance to fever, tocilizumab may be administered."* (p.10) Supporting evidence: From case reports of 2 children.	Quality of evidence: Level 4 Strength of recommendations: Not graded
• *"In both adults and children, if CRS does not improve after 1 dose of tocilizumab, then steroids should be administered with a second dose of tocilizumab."* (p. 10) Supporting evidence: From 3 narrative reviews.	Quality of evidence: Level 3 Strength of recommendations: Not graded
• *"If CRS does not improve after 2 doses of tocilizumab (and steroids), third-line drugs, including anakinra, siltuximab, and high-dose methylprednisolone, should be considered."* (p.10) Supporting evidence: From 2 single-arm clinical trials.	Quality of evidence: Level 4 Strength of recommendations: Not graded
• *"If steroids are used in the management of CRS, a rapid taper should be used once symptoms begin to improve."* (p.10) Supporting evidence: None; recommendation was made by consensus.	Quality of evidence: None Strength of recommendations: Not graded

ASCO = American Society of Clinical Oncology; ASTCT = American Society for Transplantation and Cellular Therapy; ATG = antithymocyte globulin; CRS = cytokine release syndrome; EBMT = European Society for Blood and Marrow Transplantation; G-CSF = granulocyte-colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; ICU = intensive care unit; IVIG = IV immunoglobulin; JACI = Joint Accreditation Committee of the International Society for Cell Therapy and EBMT; NCCN = National Comprehensive Cancer Network; NR = not reported.

[a]Grade 1: Fever (≥ 38°C)

[b]Grade 2: Fever with hypotension not requiring vasopressors and/or hypoxia requiring low-flow nasal cannula or blow-by.

[c]Grade 3: Fever with hypotension requiring a vasopressor with or without vasopressin and/or hypoxia requiring high-flow cannula, face mask, nonrebreather mask, or Venturi mask.

[d]Grade 4: Fever with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (e.g., CPAP, BiPAP, intubation, mechanical ventilation).

[e]Other drugs such as anakinra, siltuximab, ruxolitinib, cyclophosphamide, IVIG, ATG, or extracorporeal cytokine adsorption with continuous renal replacement therapy (CRRT) might be considered. Reported experience with these drugs is limited.

Table 12: Summary of Recommendations in Included Guidelines for ICANS

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
NCCN, Thompson et al. (2022)[28]	
ICANS Grade 1[a] • "**No concurrent CRS:** *Consider supportive care. If ICANS develops within 72 hours after infusion of either lisocabtagene maraleucel or idecabtagene vicleucel, consider administering dexamethasone 10 mg intravenously every 12 to 24 hours for 2 doses and reassess.* • **Additional therapy if concurrent CRS:** *Consider tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose). However, it may be preferable to use corticosteroids alone in the patient with grade 1 CRS (fever alone) and concurrent higher-grade neurotoxicity due to the possibility that tocilizumab may exacerbate neurotoxicity."* (p. 393, 398)	Quality of evidence: Low Strength of recommendations: By consensus, Category 2A
ICANS Grade 2[b] • "**No concurrent CRS:** *Consider supportive care and a dose of dexamethasone 10 mg intravenous, followed by reassessment. Dexamethasone may be repeated every 6 to 12 hours, if there is no improvement.* • **Additional therapy if concurrent CRS:** *Consider anti-IL-6 therapy as per Grade 1. Consider transferring patient to ICU if neurotoxicity associated with grade ≥ 2 CRS."* (p. 393, 398, 399)	Quality of evidence: Low Strength of recommendations: By consensus, Category 2A
ICANS Grade 3[c] • "**No concurrent CRS:** *ICU care is recommended. Recommend dexamethasone 10 mg IV every 6 hours or methylprednisolone, 1 mg/kg IV every 12 hours. Consider repeat neuroimaging (CT or MRI) every 2−3 days if patient has persistent grade ≥3 neurotoxicity.* • **Additional therapy if concurrent CRS:** *Consider anti-IL-6 therapy as per Grade 1."* (p. 393, 399)	Quality of evidence: Low Strength of recommendations: By consensus, Category 2A
ICANS Grade 4[d] • "**No concurrent CRS:** *Recommend ICU care and consider mechanical ventilation for airway protection. Recommend high dose of corticosteroids. Consider repeat neuroimaging (CT or MRI) every 2−3 days if patient has persistent grade ≥3 neurotoxicity and treat convulsive status epilepticus per institutional guidelines.* • **Additional therapy if concurrent CRS:** *Consider anti-IL-6 therapy as per Grade 1."* (p. 393, 399)	Quality of evidence: Low Strength of recommendations: By consensus, Category 2A
Supporting evidence: The authors did not provide any supporting evidence in their discussion for management of ICANS.	
ASCO, Santomasso et al. (2021)[29]	
ICANS grade 1[a] • "**No concurrent CRS:** *Offer supportive care with IV hydration and aspiration precautions* • **With concurrent CRS:** *Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose). Repeat every 8 hours as needed. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses. Caution with repeated tocilizumab doses in patients with ICANS. Consider adding corticosteroids to tocilizumab past the first dose."* (p. 3984)	Quality of evidence: Low Strength of recommendations: By consensus, Moderate
ICANS grade 2[b] • "**No concurrent CRS:** *Offer supportive care as per Grade 1. For high-risk products or patients, consider dexamethasone 10 mg IV x 2 doses (or equivalent) and reassess. Repeat every 6 to12 hours if no improvement. Rapidly taper steroids as clinically appropriate once symptoms improve to Grade 1.* • **With concurrent CRS:** *Consider ICU transfer if ICANS associated with ≥ Grade 2 CRS.*	Quality of evidence: Low Strength of recommendations: By consensus, Moderate

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
Administer tocilizumab as per Grage 1. If refractory to tocilizumab past the first dose, initiate dexamethasone (10 mg IV every 6 to 12 hours) or methylprednisolone equivalent (1 mg/kg IV every 12 hours). Continue corticosteroids until improvement to Grade 1, and then rapidly taper as clinically appropriate." (p. 3984)	
ICANS grade 3[c] *« Transfer patient to ICU* • **No concurrent CRS:** *Administer dexamethasone (10 mg IV every 6 to12 hours) or methylprednisolone equivalent (1 mg/kg IV every 12 hours).* • **With concurrent CRS:** *Administer tocilizumab as per Grage 1. If refractory to tocilizumab past the first dose, initiate dexamethasone (10 mg IV every 6 to12 hours) or methylprednisolone equivalent (1 mg/kg IV every 12 hours). Continue corticosteroids until improvement to grade 1, and then rapidly taper as clinically appropriate."* (p. 3984)	Quality of evidence: Low Strength of recommendations: By consensus, Moderate
ICANS grade 4[d] *"Admit patient to ICU if not already receiving ICU care. Consider mechanical ventilation for airway protection.* • **No concurrent CRS:** *Administer high-dose methylprednisolone IV 1,000 mg one to 2 times per day for 3 days. If not improving, consider 1,000 mg of methylprednisolone 2 to 3 times per day or alternate therapy. Continue corticosteroids until improvement to grade 1, and then taper as clinically appropriate. Status epilepticus to be treated as per institutional guidelines.* • **With concurrent CRS:** *Administer tocilizumab as per grade 1 in addition to methylprednisolone 1,000 mg IV one to 2 times per day for 3 days. If not improving, consider 1,000 mg of methylprednisolone IV 2 to 3 times a day or alternate therapy. Continue corticosteroids until improvement to grade 1, and then taper as clinically appropriate."* (p. 3984)	Quality of evidence: Low Strength of recommendations: By consensus, Moderate
Supporting evidence: The authors did not provide any supporting evidence in their discussion for management of ICANS.	
EBMT and JACIE, Yakoub-Agha et al. (2020)[30]	
ICANS Grade 1[a] • *"Consider systemic EEG in the first place. MRI and LP as clinically indicated (differential diagnosis). Close monitoring."* (p. 312)	Quality of evidence: NR Strength of recommendations: Not graded
ICANS Grade 2[b] • *"**No concurrent CRS**: Daily EEG, fundus, MRI and then LP, transfer to ICU. If seizure (clinically or EEG), clonazepam IV 1 mg (0.015 mg/kg up to 1 mg) and introduce levetiracetam 500 mg x 2 (pediatric dose 20 mg/kg x 2, max 3 g daily. If persistent or recurrent of seizure, repeat clonazepam 5 min once, otherwise, to be treated as a "état de mal" If papillary edema, consider acetazolamide IV 1,000 mg, then 250 to 1,000 mg / 12 hours. Consider dexamethasone 10 mg/6 hours for 1 to 3 days.* • **With concurrent CRS:** *Consider tocilizumab IV 8 mg/kg (max = 800 mg) as in the management of CRS."* (p. 312)	Quality of evidence: NR Strength of recommendations: Not graded
ICANS Grade 3[c] • *"**No concurrent CRS**: Management as per Grade 2, except dexamethasone 20 mg/6 hours for 1 to 3 days.* • **With concurrent CRS:** *Consider tocilizumab IV 8 mg/kg (max = 800 mg) as in the management of CRS."* (p. 312)	Quality of evidence: NR Strength of recommendations: Not graded

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
ICANS Grade 4[d] • "**No concurrent CRS:** Initial m*anagement as per grade 2, except methylprednisolone IV 1,000 mg/4 hours for 3 days then 250 mg x 2/day for 2 days, 125 mg x 2/d for 2 days, 60 mg x 2/d for 2 days. Discuss other alternatives: high-dose cyclophosphamide, anti-IL 1R (Anakinra), anti-Il 6 (Siltixumab). If cerebral edema, consider hyperosmolar therapy.* • **With concurrent CRS:** *Consider tocilizumab IV 8 mg/kg (max = 800 mg) as in the management of CRS."* (p. 312)	Quality of evidence: NR Strength of recommendations: Not graded
Supporting evidence: • The authors did not provide any supporting evidence in their discussion for management of ICANS.	
SITC, Maus et al. (2020)[32]	
• *"Because of the possibility that tocilizumab may worsen neurotoxicity, the management of neurotoxicity may take precedence over the management of low-grade CRS. For example, in the case of a patient with concomitant grade 1 CRS (fever) and grade 2 ICANS, steroids should be given."* (p. 13) Supporting evidence: From 1 immunoassay study and 1 single-arm cohort study.	Quality of evidence: None Strength of recommendations: Not graded
• *"If steroids are used in the management of ICANS, at least 2 doses should be given and a fast taper should be used once there is improvement." (p. 13)"* Supporting evidence: From CAR T-cell therapy (axicabtagene ciloleucel and tisagenlecleucel) package inserts.	Quality of evidence: Level 3 Strength of recommendations: Not graded
• *"For patients with grade 2 ICANS after being treated with 4- 1BB CAR T-cell products, such as tisagenlecleucel, steroids may be considered. Steroids are recommended for grade 3 or grade 4 ICANS."* (p. 13) Supporting evidence: From 2 single-arm prospective cohort studies and 1 single-arm retrospective cohort study.	Quality of evidence: Level 3 Strength of recommendations: Not graded
• *"For patients with grade 2 ICANS after being treated with CD28 costimulated CAR T-cell products such as axicabtagene ciloleucel and brexucabtagen autoleucel, steroids should be used to mitigate the duration and severity of ICANS."* (p. 13) Supporting evidence: From 1 single-arm prospective cohort study and follow-up.	Quality of evidence: Level 4 Strength of recommendations: Not graded

ASCO = American Society of Clinical Oncology; ASTCT = American Society for Transplantation and Cellular Therapy; ATG = antithymocyte globulin; CRS = cytokine release syndrome; CT = CT; EBMT = European Society for Blood and Marrow Transplantation; EEG = electroencephalogram; G-CSF = granulocyte-colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = immune effector cell-associated encephalopathy; ICU = intensive care unit; IVIG = IV immunoglobulin; JACI = Joint Accreditation Committee of the International Society for Cell Therapy and EBMT; LP = lumbar puncture; NCCN = National Comprehensive Cancer Network; NR = not reported.

ICANS grading according to ASTCT consensus grading scale:

[a]Grade 1: ICE score: 7 to 9 with no depressed level of consciousness.

[b]Grade 2: ICE score: 3 to 6; and/or mild somnolence awaking to voice.

[c]Grade 3: ICE score: 0 to 2; and/or depressed level of consciousness awakening only to tactile stimulus; and/or any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention; and/or focal or local edema on neuroimaging.

[d]Grade 4: ICE score: 0 (patient is unarousable and unable to perform ICE); and/or stupor or coma; and/or life-threatening prolonged seizure (> 5 minutes) or repetitive clinical or electrical seizures without return to baseline in between; and/or diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing or papilledema, cranial nerve VI palsy, or papilledema; or Cushing triad.