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doi.org/10.58931/cht.2026.5291

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Post CAR T-Cell Therapy Care: Monitoring and Toxicity Management

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Chimeric antigen receptor (CAR) T-cell therapy is an immunotherapy that has transformed the treatment of several hematologic malignancies. Unlike conventional cancer therapies, CAR T cells can cause unique immune-mediated toxicities, some of which can be severe and potentially life-threatening. As the use of CAR T-cell therapy expands, early recognition and standardized management of toxicities are increasingly important. With appropriate monitoring and management, these toxicities can be reduced. This review provides an overview of the management of patients after CAR T-cell therapy, as summarized in ***Figure 1****.*

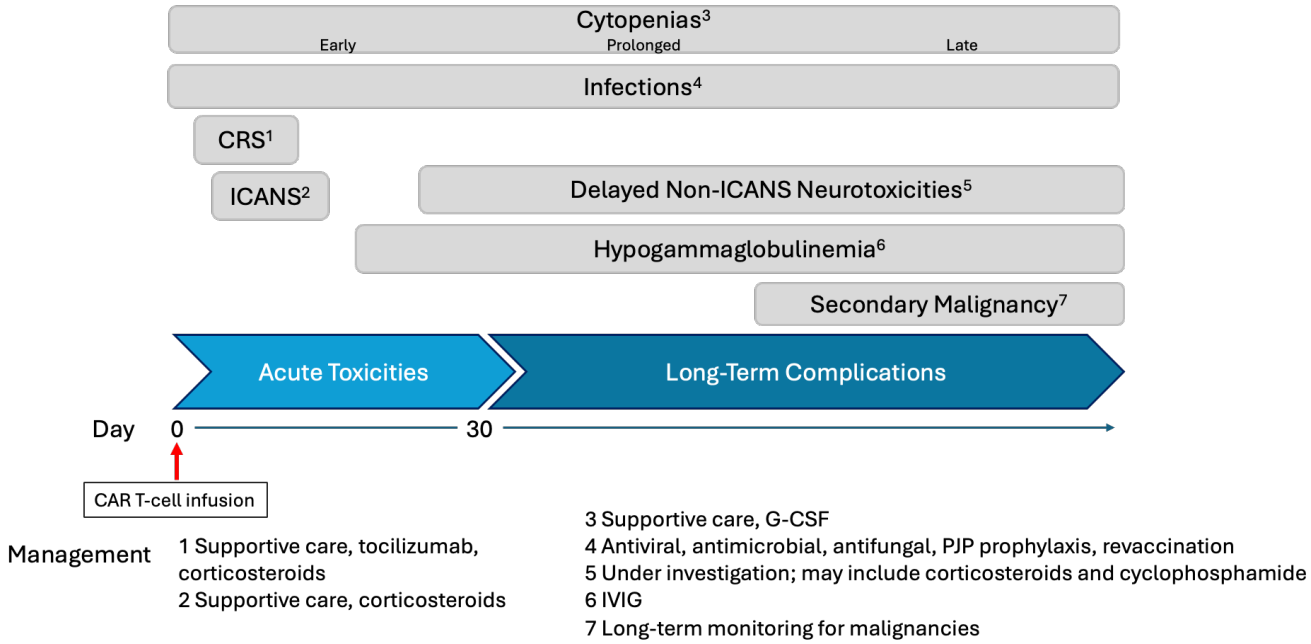

Figure 1. Timeline of toxicities, complications and management of patients following CAR T-cell infusion. Superscript numbers link toxicities to corresponding management strategies; *courtesy of Justine Lai, PhD, Peng Wang, MD, PhD, FRCPC, and Michael P. Chu, MD, FRCPC.*

Abbreviations: CAR: chimeric antigen receptor; **CRS:** cytokine release syndrome; **G-CSF:** granulocyte colony-stimulating factor; **ICANS:** immune effector cell-associated neurotoxicity syndrome; **IVIG:** intravenous immunoglobulin; **PJP:** Pneumocystis jirovecii pneumonia.

1. Overview of CAR T-Cell Treatment

Currently approved CAR T-cell therapy uses autologous T cells, which are genetically engineered to express receptors that bind to antigens on cancer cells, although allogeneic and in vivo CAR T approaches are currently being investigated in clinical trials. By combining the CAR with T-cell cytotoxicity, these cells can specifically target and kill tumour cells independent of traditional antigen presentation. CAR T cells can persist in the body for years, allowing for prolonged tumour cell killing.[1]

The standard process of manufacturing CAR T-cells is a complex, multi-step procedure.[2] It begins with leukapheresis, followed by isolation of CD3+ T cells, typically using magnetic beads. T cells are activated using anti-CD3 and anti-CD28 antibodies in combination with cytokine cocktails, then transduced with the CAR gene, commonly via viral vectors. These transduced cells are expanded *ex vivo* and subsequently reinfused into the patient. Prior to infusion, patients typically receive lymphodepleting chemotherapy to enhance CAR T-cell survival and durability of the response.[3]

The CAR structure influences activation kinetics, cytokine release magnitude, and the rate of T-cell expansion, thereby affecting both efficacy and toxicity.[4] CARs contain an extracellular domain responsible for target antigen recognition and an intracellular domain that activates the T cell. The extracellular domain most commonly consists of a single-chain variable fragment (scFv), hinge or spacer region, and transmembrane domain. The scFv provides antigen specificity and affinity, with higher affinity generally producing stronger, more sustained CAR activation and increased cytokine release. However, this may have the inverse effect in some cases, such as in solid tumours, due to T-cell exhaustion or activation-induced cell death.[5] The intracellular domain contains CD3ζ, the primary signalling component, and one or more co-stimulatory domains, most commonly CD28 or 4-1BB. CD28 is associated with rapid T-cell expansion and higher peak cytokine levels, leading to earlier and more severe toxicities. In contrast,

Grade	Fever	Hypotension	Hypoxia
Grade 1	≥38°C	None	None
Grade 2	≥38°C	Not requiring vasopressors; responds to fluid	Requiring minimal oxygen supplementation
Grade 3	≥38°C	Requiring one vasopressor	Requiring high-flow oxygen delivery
Grade 4	≥38°C	Requiring multiple vasopressors	Requiring positive-pressure ventilation

Table 1. CRS grading based on ASTCT consensus criteria; *courtesy of Justine Lai, PhD, Peng Wang, MD, PhD, FRCPC, and Michael P. Chu, MD, FRCPC.*

To meet the criteria for grade 2–4 CRS, fever, hypotension and/or hypoxia are required.

Abbreviations: ASTCT: American Society for Transplantation and Cellular Therapy; **CRS:** cytokine release syndrome.

4-1BB promotes slower CAR T expansion, greater persistence, lower cytokine levels, and reduced toxicities.

Five generations of CAR have been developed. Currently, the clinically approved CAR T-cell therapies are generally second-generation CARs, including an scFv, hinge and transmembrane domain, CD3ζ signalling domain, and one costimulatory domain.

There are currently five CAR T-cell therapies that are authorized by Health Canada for the treatment of hematologic malignancies. There are four anti-CD19 CAR T-cell products used primarily for relapsed/refractory B-cell lymphomas and leukemias: axicabtagene ciloleucel, tisagenlecleucel, lisocabtagene maraleucel, and brexucabtagene autoleucel.[6-9] Ciltacabtagene autoleucel targets B-cell maturation antigen (BCMA) for the treatment of relapsed/refractory multiple myeloma.[10]

2. Immediate Post-Infusion Monitoring

Immediate post-infusion monitoring requires hospitalization or close outpatient monitoring, with patients remaining near a healthcare facility for at least 10–14 days to monitor for toxicities.[11] During this period, history and physical examination, complete blood counts, complete metabolic profile (glucose, electrolytes, liver enzymes, bilirubin, and creatinine), and markers of inflammation (C-reactive protein [CRP] and ferritin) should be assessed daily. Vital signs should be monitored every four hours for those treated in the inpatient and daily for those treated in the outpatient setting. Coagulation profiles should be monitored at least twice a week. Patients should be daily assessed for cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).

3. Cytokine Release Syndrome

CRS is the most common toxicity observed following CAR T-cell infusion. It results from the hypersecretion of cytokines, including interleukin (IL)-6, IL-1, tumour necrosis factor (TNF)-α, and interferon (IFN)-γ, triggered by activation of CAR T-cells, and subsequently, innate immune cells, such as monocytes, dendritic cells, and macrophages. The clinical manifestations of CRS are broad, ranging from mild symptoms, including fever, fatigue, and rash, to severe symptoms, including tachycardia, hypoxia, hypotension, coagulopathy, and multiorgan dysfunction.[12] The onset of CRS is typically within 2–7 days following CAR T-cell infusion, although it may present as late as three weeks post-infusion.

Grading of CRS is standardized by the American Society for Transplantation and Cellular Therapy (ASTCT).[13] The ASTCT grading criteria are based on the presence of fever, which is required for all CRS grades, and the presence and severity of hypotension and hypoxia. CRS is graded on a scale from 1 to 4, as summarized in **Table 1**.

The incidence of CRS post-CAR T-cell therapy has ranged from 42–93% in clinical trials.[14] Several factors have been found to predict CRS incidence and severity, including high tumour burden, intensive lymphodepleting regimens, and pre-existing comorbidities.[12,15] Additionally, a low platelet count prior to lymphodepletion, and elevated lactate dehydrogenase (LDH), creatinine, CRP, and ferritin levels have been associated with

Grade	ICE Score	Level of Consciousness	Seizures	Elevated Intracranial Pressure/Cerebral Edema	Motor Weakness
Grade 1	7–9	Awakens spontaneously	None	None	None
Grade 2	3–6	Awakens to voice	None	None	None
Grade 3	0–2	Awakens to tactile stimulus	Any seizure that rapidly resolves	Focal/local edema on imaging	None
Grade 4	0	Unarousable or only responsive to vigorous or repeated stimulation	Repetitive or life-threatening prolonged seizure	Diffuse cerebral edema on imaging or clinical signs of elevated intracranial pressure	Deep focal weakness or paralysis

Table 2. ASTCT consensus grading of ICANS: *courtesy of Justine Lai, PhD, Peng Wang, MD, PhD, FRCPC, and Michael P. Chu, MD, FRCPC.*

The ICE score is a 10-point scale assessing orientation, naming, following commands, writing, and attention.

Abbreviations: ASTCT: American Society for Transplantation and Cellular Therapy; **ICANS: i**mmune effector cell-associated neurotoxicity syndrome; **ICE:** immune effector cell-associated encephalopathy.

an increased risk of CRS.[16,17] Treatment-related factors also contribute, with higher CAR T-cell doses having increased toxicity. Structural features of the CAR construct may also play a role, with CARs containing CD28 (e.g., axicabtagene ciloleucel) generally having higher rates of CRS than those with 4-1BB (e.g., tisagenlecleucel).[18]

Treatment of CRS depends on its grade. Based on ASTCT guidelines, treatment for grade 1 CRS is supportive care. For CRS grade ≥2, first-line therapy is tocilizumab, a Health Canada–authorized IL-6 receptor antagonist, which should be initiated promptly upon observation of CRS symptoms to reduce the likelihood of progression to a higher grade. Institutional practices vary, with some centres using tocilizumab as an early-intervention strategy for grade 1 CRS. Corticosteroids, including dexamethasone or methylprednisolone, are added for persistent or worsening symptoms of severe CRS (i.e., grades 3 or 4). In refractory CRS, alternative anti-cytokine therapies may be used, including siltuximab, an IL-6 antagonist, or anakinra, an IL-1 receptor antagonist.[19] Other targets to treat CRS currently under investigation include IFN-γ (emapalumab) and granulocyte-macrophage colony-stimulating factor (GM-CSF; lenzilumab).[12]

To mitigate the risk of CRS, several strategies are being used. Prophylactic tocilizumab and anakinra have both been shown in trials to decrease the incidence and severity of CRS.[20-22] Other strategies include prophylactic corticosteroids and fractionated dosing of CAR T cells over several days.[23]

4. Immune effector cell-associated neurotoxicity syndrome

ICANS is the second most common toxicity of CAR-T cell treatment after CRS, with an overall incidence of approximately 30% reported from clinical trials.[24] ICANS typically presents with a spectrum of neurological symptoms, including headache, confusion, aphasia, dysgraphia, dysarthria, tremor, seizures, and rarely, cerebral edema.[25] The median time to onset of ICANS is between 4 and 10 days post-infusion.[26] It is typically self-limited, with symptoms resolving after 5–17 days.[27] ICANS and CRS can co-occur, with ICANS generally presenting after the onset of CRS.[26]

The severity of ICANS in adults is graded from 1 to 4 according to the ASTCT consensus (**Table 2**).[26,28] Screening for ICANS using the immune effector cell-associated encephalopathy (ICE) score, a 10-point bedside assessment of cognitive function, should be performed daily during the high-risk period (day 0–14 post-infusion).[27] If a patient develops symptoms of ICANS, the grade should be assessed at least every 8 hours. Patients younger than 12 years of age or those with developmental delay should be assessed using the Cornell Assessment of Pediatric Delirium Score.

Monitoring for ICANS is important to allow early recognition and treatment, preventing morbidity and mortality, though it often presents later than CRS and can have a bimodal presentation. If ICANS is present, the

mainstay of treatment is supportive care and corticosteroids.[13] Management of grade 1 ICANS is mainly supportive, although dexamethasone may be considered. Grade 2–3 ICANS is managed with supportive care and dexamethasone, while grade 4 ICANS is treated with methylprednisolone. Anakinra can be administered to patients with grade 2–4 ICANS who are refractory to corticosteroids (i.e., no improvement after six hours of corticosteroids). Tocilizumab can be added for concurrent CRS for all grades of ICANS; however, it is not effective for isolated ICANS as it does not cross the blood-brain barrier and may increase circulating IL-6 levels, potentially worsening neurotoxicity if used alone.

Multiple clinical and biological factors have been correlated with the presence and severity of ICANS. The occurrence of CRS is one of the strongest predictors of ICANS, with ~90% of patients with ICANS previously experiencing CRS, and the risk increases with high-grade CRS.[29] A high pre-treatment tumour burden is also associated with an elevated risk of ICANS, likely due to greater tumour cell killing and stronger immune response.[25] Similar to CRS, a high dose of CAR T-cells and the use of a CD28 rather than a 4-1BB costimulatory domain have been linked to an increased risk of developing ICANS.[24,25] Elevated levels of inflammatory biomarkers, including CRP, serum ferritin, IL-6, IL-10, and IL-15, have also been correlated with ICANS.[29]

5. Non-ICANS Neurotoxicities

Neurotoxicities beyond ICANS have been reported following CAR T-cell infusion and are currently less well characterized. Among these, movement and neurocognitive toxicity (MNT) is a neurological complication associated with some anti-BCMA CAR T-cell therapies. In contrast to ICANS, MNT has a delayed onset, presenting weeks to months after infusion.[30] This toxicity is relatively uncommon, occurring in 2-10% of patients in clinical trials and real-world studies.[31] Risk factors for MNT include high tumour burden, older age, development of ICANS, and elevated peak absolute lymphocyte count (≥3 × 10^9/L) after infusion, indicating increased CAR-T cell expansion. The clinical features of MNT resemble those of Parkinson's disease and include bradykinesia, rigidity, tremor, postural instability, hypophonia, personality change, and cognitive impairment. Management of MNT remains under investigation; however, reported strategies include the use of corticosteroids and cyclophosphamide.

Other non-ICANS neurological complications after CAR T-cell therapy include cranial nerve palsies, most commonly involving the facial nerve, peripheral neuropathies, and myelopathies.[30] These complications are not well characterized, and further investigation is needed to better inform management strategies.

6. Long-Term Monitoring

Patients may experience persistent immune dysregulation following CAR T-cell infusion, necessitating long-term surveillance. Cytopenias are common immediately after infusion and typically resolve within the first 30 days. However, in some patients, cytopenias can be prolonged, lasting up to 90 days after infusion, or late, persisting more than 90 days after infusion.[32] Alternative etiologies for cytopenias include infection, lymphoma with bone marrow involvement, or therapy-related myelodysplastic syndrome or acute myeloid leukemia. Patients with cytopenias, including anemia, thrombocytopenia, and neutropenia, can present with fatigue, shortness of breath, easy bruising and bleeding, and frequent infections. The workup for cytopenias includes a CBC with differential, a peripheral blood smear, and a reticulocyte count.[27] First-line management includes supportive care and, for more severe cases, granulocyte colony-stimulating factor (G-CSF) to support neutrophil recovery.

B-cell aplasia is an on-target, off-tumour effect associated with anti-CD19 CAR T-cell therapy, and killing of B cells can persist for years.[1] Prolonged aplasia may lead to hypogammaglobulinemia, increasing the risk of infections. Patients often require intravenous immunoglobulin (IVIG) therapy, even when serum IgG levels do not fall below the traditional threshold of 0.4 mg/L, to prevent serious or recurrent infections.[33]

The immunosuppressed state following CAR T-cell therapy increases susceptibility to infections, which can occur for several months after infusion. To reduce this risk, antiviral prophylaxis is recommended for 6–12 months post-infusion.[32] Antibacterial prophylaxis can be initiated if neutropenia is detected and continued until it resolves. *Pneumocystis jiroveci pneumonia* (PJP) prophylaxis can be started 30 days after infusion and continued for at least six months,

or until CD4+ T cell counts exceed a threshold of 200 cells/mm^3.[34] Antifungal prophylaxis is not universally agreed upon but is considered important in patients with prolonged neutropenia or in those who require high-dose corticosteroids for more than 72 hours.[35]

Vaccination after CAR T-cell therapy is recommended to mitigate immune dysfunction. Influenza and coronavirus disease 2019 (COVID-19) vaccines can be given three months post-infusion, and other routine inactivated vaccines, such as the Tdap vaccine, and vaccines for Hepatitis B and pneumococcal disease can be initiated at six months.[34] Live-attenuated vaccines are generally contraindicated for at least 12 months after therapy.

7. Secondary Malignancy Monitoring

An important safety consideration for patients treated with CAR T-cell therapy is the development of secondary malignancies. The increased risk is multifactorial and may reflect factors independent of CAR T-cell therapy, including prior therapy exposure and underlying disease biology. There is a theoretical risk of secondary malignancies due to insertional mutagenesis associated with the viral vectors used in CAR T-cell production; however, documented cases are exceedingly rare.[36] Studies have shown that secondary malignancies have occurred in 4–16% of patients within five years after CAR T-cell infusion.[1] Given these findings, long-term monitoring is essential to detect and manage secondary malignancies.

8. Cell Therapies Beyond Second-Generation CAR T-Cell Therapies

Beyond traditional CAR T-cell therapy, other cell therapies and advancements to CAR T-cells, including T-cell-receptor (TCR)-engineered T cells, tumour-infiltrating lymphocytes (TILs), and next-generation CARs, are being investigated. These therapies have different efficacy, indications, and toxicity profiles compared with conventional CAR T-cell therapy, with some approaches potentially offering improved safety profiles. Unlike traditional CAR T-cells, TCR-engineered T cells recognize intracellular tumour antigens presented on major histocompatibility complex (MHC) molecules, expanding their potential to target solid tumours.[37] TCR-engineered T cells are associated with capillary leak syndrome, but with lower rates of CRS and ICANS. TIL therapy involves expansion and reinfusion of tumour-derived T cells without genetic modification, retaining native TCRs that may bind to unknown tumour antigens. This therapy is used in solid tumours, particularly melanoma. Compared with CAR T-cells, TILs have a more favourable safety profile, as they do not typically cause severe CRS or ICANS. However, capillary leak syndrome occurs in approximately a third of patients.[38] Additionally, fourth-generation (armoured) CAR T-cells are designed to overcome the immunosuppressive tumour microenvironment through expression of additional components, including cytokines and anti-programmed cell death protein 1 (PD)-1 antibodies.[39] These CARs have a toxicity profile similar to earlier generations of CARs, including CRS and ICANS, but with improved efficacy.[39,40]

Summary

CAR T-cell therapy has been highly effective in treating hematologic malignancies that have historically been challenging to manage; however, it is associated with unique and potentially life-threatening toxicities that require specialized care. Advancements in toxicity grading, clinical protocols, and early intervention strategies have reduced the severity of adverse events. As CAR T-cell therapy moves into earlier lines of treatment, the development of reliable predictive biomarkers and algorithm-driven strategies for toxicity prevention will be critical, particularly to support the safe expansion of outpatient CAR T-cell delivery.

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Financial Disclosures

J.L.: None declared.
P.W.: None declared.
M.P.C.: None declared.

References

1. Cappell KM, Kochenderfer JN. Long-term outcomes following CAR T cell therapy: what we know so far. Nat Rev Clin Oncol. 2023;20(6):359–71. doi:10.1038/s41571-023-00754-1
2. Ayala Ceja M, Khericha M, Harris CM, Puig-Saus C, Chen YY. CAR-T cell manufacturing: Major process parameters and next-generation strategies. J Exp Med. 2024;221(2):e20230903. doi:10.1084/jem.20230903
3. Amini L, Silbert SK, Maude SL, Nastoupil LJ, Ramos CA, Brentjens RJ, et al. Preparing for CAR T cell therapy: patient selection, bridging therapies and lymphodepletion. Nat Rev Clin Oncol. 2022;19(5):342–55. doi:10.1038/s41571-022-00607-3
4. Jayaraman J, Mellody MP, Hou AJ, Desai RP, Fung AW, Pham AHT, et al. CAR-T design: Elements and their synergistic function. EBioMedicine. 2020;58:102931. doi:10.1016/j.ebiom.2020.102931
5. Shabaneh TB, Stevens AR, Stull SM, Shimp KR, Seaton BW, Gad EA, et al. Systemically administered low-affinity HER2 CAR T cells mediate antitumor efficacy without toxicity. J Immunother Cancer. 2024;12(2):e008566. doi:10.1136/jitc-2023-008566
6. Gilead Sciences Canada Inc. Yescarta (axicabtagene ciloleucel): product monograph. Mississauga (ON): Gilead Sciences Canada Inc.; 2025 Jun 24.
7. Novartis Pharmaceuticals Canada Inc. Kymriah (tisagenlecleucel): product monograph. Montreal (QC): Novartis Pharmaceuticals Canada Inc.; 2024 Oct 29.
8. Bristol-Myers Squibb Canada. Breyanzi (lisocabtagene maraleucel): product monograph. Saint-Laurent (QC): Bristol-Myers Squibb Canada; 2025 Oct 3.6.
9. Gilead Sciences Canada Inc. Tecartus (brexucabtagene autoleucel): product monograph. Mississauga (ON): Gilead Sciences Canada Inc.; 2025 Jun 26.
10. Janssen Inc. Carvykti (ciltacabtagene autoleucel): product monograph. Toronto (ON): Janssen Inc.; 2026 May 13.
11. The University of Texas MD Anderson Cancer Center. IEC therapy toxicity assessment and management (CARTOX) – adult. Version 5. 2023.
12. Gabriel K, Heinzerling L, von Baumgarten L, Subklewe M, Kobold S. The role of cytokines in cytokine release syndrome (CRS) after CAR T cell therapy. Biochim Biophys Acta Mol Cell Res. 2026;1873(3):120115. doi:10.1016/j.bbamcr.2026.120115
13. Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. 2019;25(4):625–38. doi:10.1016/j.bbmt.2018.12.758
14. Yamshon S, Gribbin C, Alhomoud M, Chokr N, Chen Z, Demetres M, et al. Safety and toxicity profiles of CAR T cell therapy in non-Hodgkin lymphoma: A systematic review and meta-analysis. Clin Lymphoma Myeloma Leuk. 2024;24(6):e235-e256.e2. doi:10.1016/j.clml.2024.02.007
15. Tedesco VE, Mohan C. Biomarkers for predicting cytokine release syndrome following CD19-targeted CAR T cell therapy. J Immunol. 2021;206(7):1561–8. doi:10.4049/jimmunol.2001249
16. Greenbaum U, Strati P, Saliba RM, Torres J, Rondon G, Nieto Y, et al. CRP and ferritin in addition to the EASIX score predict CAR-T-related toxicity. Blood Adv. 2021;5(14):2799–806. doi:10.1182/bloodadvances.2021004575
17. Zandaki D, Selukar S, Bi Y, Li Y, Zinsky M, Bonifant CL, et al. EASIX and m-EASIX predict CRS and ICANS in pediatric and AYA patients after CD19-CAR T-cell therapy. Blood Adv. 2025;9(2):270–9. doi:10.1182/bloodadvances.2024014027
18. Ying Z, Song Y, Zhu J. Effectiveness and safety of anti-CD19 chimeric antigen receptor-T cell immunotherapy in patients with relapsed/refractory large B-Cell lymphoma: A systematic review and meta-analysis. Front Pharmacol. 2022;13:834113. doi:10.3389/fphar.2022.834113
19. Canadian Agency for Drugs and Technologies in Health. Anticytokine therapy and corticosteroids for cytokine release syndrome and for neurotoxicity following T-cell engager or CAR T-cell therapy: rapid review [Internet]. 2024 [cited 2026 Mar 22]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK604827/
20. Scott SA, Marin EM, Maples KT, Joseph NS, Hofmeister CC, Gupta VA, et al. Prophylactic tocilizumab to prevent cytokine release syndrome (CRS) with teclistamab: A single-center experience. Blood Cancer J. 2023;13(1):191. doi:10.1038/s41408-023-00963-y
21. Korst CLBM, Groen K, Bosman PWC, van der Valk F, Verkleij CPM, Kruyswijk S, et al. Prophylactic tocilizumab reduces the incidence of cytokine release syndrome in relapsed/refractory myeloma patients treated with teclistamab: Implications for outpatient step-up dosing. HemaSphere. 2024;8(7):e132. doi:10.1002/hem3.132
22. Nair R, Peddi A, Gourisetti S, Menon P, Hickman L, Adroja S, et al. Real-world use of prophylactic anakinra to mitigate CRS and ICANS in CAR-T therapy. Transplant Cell Ther. 2026;32(2):S186. doi:10.1016/j.jtct.2025.12.256
23. Banerjee R, Fakhri B, Shah N. Toci or not toci: innovations in the diagnosis, prevention, and early management of cytokine release syndrome. Leuk Lymphoma. 2021;62(11):2600–11. doi:10.1080/10428194.2021.1924370

24. Han MW, Jeong SY, Suh CH, Park H, Guenette JP, Huang RY, et al. Incidence of immune effector cell-associated neurotoxicity among patients treated with CAR T-cell therapy for hematologic malignancies: systematic review and meta-analysis. Front Neurol. 2024;15:1392831. doi:10.3389/fneur.2024.1392831
25. Kennedy LB, Salama AKS. A review of cancer immunotherapy toxicity. CA Cancer J Clin. 2020;70(2):86–104. doi:10.3322/caac.21596
26. Chou CK, Turtle CJ. Assessment and management of cytokine release syndrome and neurotoxicity following CD19 CAR-T cell therapy. Expert Opin Biol Ther. 2020;20(6):653–64. doi:10.1080/14712598.2020.1729735.
27. Santomasso BD, Nastoupil LJ, Adkins S, Lacchetti C, Schneider BJ, Anadkat M, et al. Management of immune-related adverse events in patients treated with chimeric antigen receptor T-cell therapy: ASCO Guideline. J Clin Oncol. 2021;39(35):3978–92. doi:10.1200/JCO.21.01992
28. Pennisi M, Jain T, Santomasso BD, Mead E, Wudhikarn K, Silverberg ML, et al. Comparing CAR T-cell toxicity grading systems: application of the ASTCT grading system and implications for management. Blood Adv. 2020;4(4):676–86. doi:10.1182/bloodadvances.2019000952
29. Grant SJ, Grimshaw AA, Silberstein J, Murdaugh D, Wildes TM, Rosko AE, et al. Clinical presentation, risk factors, and outcomes of immune effector cell-associated neurotoxicity syndrome following chimeric antigen receptor T cell therapy: A systematic review. Transplant Cell Ther. 2022;28(6):294–302. doi:10.1016/j.jtct.2022.03.006
30. Graham CE, Velasco R, Alarcon Tomas A, Stewart OP, Dachy G, Del Bufalo F, et al. Non-ICANS neurological complications after CAR T-cell therapies: recommendations from the EBMT Practice Harmonisation and Guidelines Committee. Lancet Oncol. 2025;26(4):e203–13. doi:10.1016/S1470-2045(24)00715-0
31. Lim KJC, Tan M, Parrondo R, Chhabra S, Dooley K, De Menezes Silva Corraes A, et al. Clinical course, risk factors and mitigating strategies for Immune effector cell-associated late onset neurotoxicities after ciltacabtagene autoleucel CAR-T in multiple myeloma. Blood Cancer J. 2025;16(1):18. doi:10.1038/s41408-025-01441-3
32. Jain T, Olson TS, Locke FL. How I treat cytopenias after CAR T-cell therapy. Blood. 2023;141(20):2460–9. doi:10.1182/blood.2022017415
33. Doan A, Pulsipher MA. Hypogammaglobulinemia due to CAR T-cell therapy. Pediatr Blood Cancer. 2018;65(4). doi:10.1002/pbc.26914
34. Shahid Z, Jain T, Dioverti V, Pennisi M, Mikkilineni L, Thiruvengadam SK, et al. Best practice considerations by the American Society of Transplant and Cellular Therapy: Infection prevention and management after chimeric antigen receptor T cell therapy for hematological malignancies. Transplant Cell Ther. 2024;30(10):955–69. doi:10.1016/j.jtct.2024.07.018
35. Hayden PJ, Roddie C, Bader P, Basak GW, Bonig H, Bonini C, et al. Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA). Ann Oncol. 2022;33(3):259–75. doi:10.1016/j.annonc.2021.12.003
36. Ghilardi G, Fraietta JA, Gerson JN, Van Deerlin VM, Morrissette JJD, Caponetti GC, et al. T cell lymphoma and secondary primary malignancy risk after commercial CAR T cell therapy. Nat Med. 2024;30(4):984–9. doi:10.1038/s41591-024-02826-w
37. Brudno JN, Maus MV, Hinrichs CS. CAR T cells and T-cell therapies for cancer: A translational science review. JAMA. 2024;332(22):1924–35. doi:10.1001/jama.2024.19462
38. Betof Warner A, Hamid O, Komanduri K, Amaria R, Butler MO, Haanen J, et al. Expert consensus guidelines on management and best practices for tumor-infiltrating lymphocyte cell therapy. J Immunother Cancer. 2024;12(2):e008735. doi:10.1136/jitc-2023-008735
39. Wang JY, Wang L. CAR-T cell therapy: Where are we now, and where are we heading? Blood Sci. 2023;5(4):237–48. doi:10.1097/BS9.0000000000000173
40. Tomasik J, Jasiński M, Basak GW. Next generations of CAR-T cells - new therapeutic opportunities in hematology? Front Immunol. 2022;13:1034707. doi:10.3389/fimmu.2022.1034707

Count on CALQUENCE's Experience

5 indications combined across CLL and MCL[1,2]

- **2019:** Previously untreated CLL, as monotherapy or with obinutuzumab
- **2019:** Previously treated CLL, as monotherapy
- **2019:** Previously treated MCL, as monotherapy
- **2025:** Previously untreated CLL, with venetoclax
- **2025:** Previously untreated MCL, with bendamustine + rituximab

5+ years of market availability in Canada (as CLL monotherapy)[3†]

5 Phase 3 trials: AMPLIFY, ELEVATE-TN, ASCEND, ELEVATE-RR, ECHO[1,4]

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CALQUENCE (acalabrutinib tablets) is indicated:

- in combination with obinutuzumab or as monotherapy for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL)
- in combination with venetoclax for the treatment of patients with previously untreated CLL
- as monotherapy for the treatment of patients with CLL who have received at least one prior therapy
- in combination with bendamustine and rituximab for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who are ineligible for autologous stem cell transplant
- as monotherapy for the treatment of patients with MCL who have received at least one prior therapy

Please consult the Product Monograph at calquence-tablet-en.azpm.ca for contraindications, warnings, precautions, adverse reactions, interactions, dosing, and conditions of clinical use. The Product Monograph is also available by calling us at 1-800-668-6000.

† Clinical significance has not been established.

References: 1. CALQUENCE (acalabrutinib tablets) Product Monograph. AstraZeneca Canada Inc. **2.** Data on file – CALQUENCE indication dates. October 20, 2025. **3.** Health Canada Notice of Compliance Database. CALQUENCE (2019-08-23). Accessed at: https://health-products.canada.ca/noc-ac/nocInfo?no=22572. **4.** Byrd JC, *et al*. Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial. *J Clin Oncol*. 2021;39(31):3441-3452.

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