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Long-term neurocognitive effects of chimeric antigen receptor T-cell therapy: Integrating assessments into nursing practice

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ABSTRACT
Chimeric antigen receptor t-cell (CAR-T) therapy is a newly evolving therapy with well-known acute neurotoxic effects. While the long-term neurotoxic effects of this therapy are under-researched, they exist in subsets of the post-treatment population. Nurses can focus on assessments before and after CAR-T therapy to determine the degree to which these neurotoxic effects progress. These assessments include subjective and objective tools, as well as an understanding of risk factors associated with a higher degree of adverse cognitive events. By utilizing current research, hematological nurses can advocate for this unmet need to be monitored and intervened upon to improve patient outcomes.

Keywords: chimeric antigen receptor therapy, nursing assessments, neurotoxic effects

Chimeric antigen receptor t-cell (CAR-T) therapy is becoming more prevalent within healthcare with more than 1,000 CAR-T clinical trials registered as of October 2023 – of which 25 are open to recruitment in Canada (National Library of Medicine, 2023). This novel therapy has given people with hematological malignancies and limited treatment options an opportunity for elongation of life and even remission (Grigor et al., 2019). The short-term toxicities of CAR-T therapy are well known, but the literature on longitudinal effects is lacking (Clout et al., 2023; Ruark et al., 2020). Patients with hematological malignancies who undergo CAR-T therapy have been shown to develop negative neurocognitive effects, such as anxiety, depression, and cognitive difficulties that last longer than three months, and the assessment of these negative outcomes should be incorporated into standard nursing practice (Hoogland et al., 2021; Ruark et al., 2020; Whisenant et al., 2021). This article will review the acute and chronic neurotoxicities associated with CAR-T therapy, and explore patient-reported and objective assessments of long-term neurocognitive changes in this population that can be incorporated into nursing practice.

BACKGROUND
Chimeric antigen receptor therapy entails the genetic modification of t-cells which, when infused into the patient, allow for their immune system to recognize better and destroy the cancer. There are several known acute toxicities associated with this therapy including tumour lysis syndrome, cytokine release syndrome, increased risk of infection, neutropenia, anemia, and thrombocytopenia. As patients enter long-term follow-up, other adverse events have been documented such as hypogammaglobulinemia, secondary malignancies, cytopenias, and late infections (Anglin et al., 2021; Scott et al., 2022). These side effects are expected given the mechanism of action and the heavily pre-treated population. However, there are neurocognitive changes associated with CAR-T therapy that are sequelae of the neurotoxic effects of the infusion and unique in nature to this treatment.

NEUROTOXICITY
Neurotoxic side effects refer to changes in neurocognitive abilities, specifically due to exposure to toxic substances. These symptoms include memory loss, vision problems, headache, limb weakness or numbness, and cognitive or behavioural problems (National Institute of Neurological Disorders and Stroke, 2023). Many studies do not clearly define the terms of neurotoxicity, but refer to changes in neurocognition, such as difficulty concentrating, depression, or memory changes, and some group all neurotoxic effects into the category of neurocognitive changes (Hoogland et al., 2021; Whisenant et al., 2021; Tan et al., 2021; Sidana et al., 2022). One of the first neurocognitive changes observed in the days to weeks following infusion is immune effector cell-associated neurotoxicity syndrome (ICANS). Testing for ICANS allows staff to assess a combination of cognitive domains and includes assessment of recall, level of consciousness, memory, and dysgraphia. Hoogland et al. (2021) describe other acute neurotoxic events within the first 90 days, such as problems with concentration, fatigue, and depression. The authors note that these symptoms were mostly resolved in three months. However, some unspecified symptoms were still ongoing. As evidenced from the literature described above, there is a breadth of knowledge of the acute neurotoxic effects of CAR-T therapy. Unfortunately, the discourse on long-term neurocognitive changes and impact on patient outcomes is not well described.

LONG-TERM NEUROCognitive TOXiCITy
The literature varies when describing what timeframe constitutes long-term; some have looked at a year and beyond, while others have described chronic effects beginning at three months after infusion. For the purposes of this review, long-term is described as lasting greater than three months (Cordeiro et al., 2020; Hoogland et al., 2021). Ongoing
subjective changes such as cognitive difficulties, headaches, problems with concentration and memory issues are reported (Scott et al., 2022; Wang et al., 2021; Whisenant et al., 2021). Along with cognitive and neural changes reported by patients, objective changes in cognitive abilities have been reported, such as impaired memory and processing speed (Tan et al., 2021). One study \((n = 86)\) found that 10% of patients had new neurological findings at one year after therapy requiring intervention (Cordeiro et al., 2020). Furthermore, neuropsychiatric changes, mainly anxiety and depression, have also been described, which continue to be reported as distressing long-term adverse events (Sidana et al., 2022; Stenson et al., 2023). Overall, these studies demonstrate a trend toward lasting neurocognitive issues. However, the sample sizes are small and homogenous, and they did not make comparisons to the subject’s cognitive status prior to CAR-T therapy (Scott et al., 2022; Sidana et al., 2022; Stenson et al., 2023; Tan et al., 2021; Whisenant et al., 2021). To be eligible to receive CAR-T therapy, patients are required to have completed at least two prior lines of treatment, which may include a hematopoietic stem cell transplant (HSCT) or even a third line to bridge them to infusion (Anglin et al., 2021). Therefore, the data on how these treatments have affected neurocognition needs to be examined to determine how the emerging literature fits into the clinical picture.

**EFFECTS OF TREATMENT BEFORE CAR-T INFUSION**

Treatment for hematological malignancies include chemotherapy, radiation, and immunotherapies (Anglin et al., 2021). These can cause impairments related to memory, attention, concentration, executive function, anxiety, and depression (Koll et al., 2020; Libert et al., 2016; Williams et al., 2016). When comparing cognition prior to HSCT to after HSCT, it was found that 50% of patients displayed cognitive impairments prior to transplant (Nakamura et al., 2020). The presence of these impairments is indicative of slower recovery and persistent decline after HSCT (Harrison et al., 2021; Koll et al., 2020). Given that patients receiving CAR-T therapy are heavily pre-treated, this data supports that this population may develop neurocognitive issues prior to receiving CAR-T therapy.

The literature described previously does not provide compelling evidence that the changes observed are due to CAR-T therapy itself, or are ongoing from previous therapy. However, an article published by Ruark et al. (2020) compared neurotoxic effects prior to CAR-T therapy and one year after infusion, and found that 50% of patients reported anxiety, depression, or other cognitive difficulties prior to CAR-T therapy. One year after CAR-T treatment, they found that a subset of patients had worse psychiatric and cognitive impairment compared to before CAR-T therapy, illustrating the need for intervention and follow-up (Ruark et al., 2020). These findings are further supported by Cordeiro et al. (2020), who found that up to one year after therapy, 10% of patients presented with new neurological findings. Clearly, there is limited data comparing neurotoxic symptoms before and after CAR-T therapy. However, the neurotoxic effects of multiple lines of therapy for those with hematological malignancies is well established in the literature. Therefore, these patients are more likely to be experiencing neurocognitive symptoms after infusion, whether a result of CAR-T therapy or not. Consequently, nurses should continue to assess these symptoms and provide intervention after CAR-T therapy to allow for better patient outcomes.

**NURSING ASSESSMENTS**

As this therapy evolves to treat different diseases with multiple CAR-T products, transplant programs are liable to ensure nurses have ongoing education regarding appropriate assessment skills (Taylor et al., 2019). This includes outpatient clinic nurses not directly involved in the program. Education should include relevant assessment and professional skills, and ongoing communication about most up-to-date evidence-based practices (He et al., 2024; Steinbach et al., 2023). Part of this education should also include identifying risk factors and assessment tools for monitoring long-term neurotoxic effects.

**Risk Factors**

There are three risk factors described in the literature that are associated with poorer neurocognitive outcomes for hematological patients. The first risk factor is age, as the older population is at higher risk for those symptoms thought of as typical neurocognitive decline, e.g. processing, memory, and recall (Libert et al., 2016; Kotb et al., 2019). On the other hand, the younger population is noted to experience more severe symptoms of anxiety and depression (Harrison et al., 2021; Williams et al., 2016). Consequently, when considering age, nurses should be aware of differences in neurocognitive impairments between populations. This is particularly important as CAR-T therapy moves toward becoming first-line therapy, and younger populations are treated more frequently.

Comorbidities are another risk factor identified in the literature, as certain comorbidities place a person at higher risk of neurotoxic effects. Hypertension, diabetes, and viral hepatic conditions were found to be associated with worse cognitive functioning after non-transplant therapies, and those with multiple health conditions also trended toward negative cognitive outcomes (Kotb et al., 2019). Furthermore, substance use was identified as a risk factor that negatively impacts cognitive toxicities prior to HSCT (Nakamura et al., 2020). Therefore, nurses should assess patient comorbidities prior to CAR-T therapy to determine the risk of cognitive decline after.

Finally, the type of malignancy and treatment has shown to impact neurocognitive changes. Certain hematological cancers have shown an inclination toward greater cognitive impairment at baseline; for example, patients with leukemia and myelodysplastic syndrome were found to display worse cognition at baseline, as compared to other blood cancers (Williams et al., 2016). Additionally, many therapies have been found to negatively influence cognition, such as whole-brain radiation (Williams et al., 2016). The nuanced difference between various hematological cancers and their treatments will impact cognitive impairments in the CAR-T population. The complexity of risk factors makes it difficult to discern who will
experience cognitive decline and to what degree. This complexity is further exacerbated by CAR-T therapy in which the long-term neurotoxic effects are not as clear; therefore, it is important that nurses be aware of the most prevalent risk factors and the impact that these can have on patient outcomes.

### Table 1

<table>
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<tr>
<th>Risk Factors Impacting Neurological Outcomes</th>
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<tr>
<td><strong>Age</strong></td>
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<td>Older – typical neurocognitive changes</td>
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<tr>
<td>Younger – anxiety and depressive symptoms</td>
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<td><strong>Comorbidities</strong></td>
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<td>Hypertension</td>
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<td>Substance use</td>
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<td><strong>Type of Malignancy and Treatment</strong></td>
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<tr>
<td>Leukemias and myelodysplastic syndrome</td>
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<td>Whole brain radiation</td>
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### Patient Reported Outcome Tools

Along with assessing risk factors, nurses are required to have specialized knowledge and skills when caring for hematological oncology patients, including routine screening using validated assessment tools (Puts et al., 2021). Many clinics are integrating validated Patient Reported Outcome Tools (PROs) to capture symptoms. These have been shown to improve patient-physician communication, to effectively address patient symptoms, and to improve quality of life in cancer care (Basch et al., 2018; Valsangkar et al., 2020). Three tools have been commonly reported in the literature of the assessment of neurocognitive symptoms in hematological malignancies: The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; the 36-Item Short Form Survey; and the Patient Reported Outcome Measures Information System (Chakraborty et al., 2019; Koll et al., 2020; Williams et al., 2015). Each has strengths and limitations, such as length of questionnaire, clinician bias when interpreting answers and different scales to measure cognition (Chakraborty et al., 2019; Kuenstner et al., 2022; Shaw et al., 2018). However, integration of these tools is not always feasible into clinical practice, especially as clinics work within larger systems that require the same tools be used by multiple groups. Studies demonstrated that patients with solid tumours also have chemotherapy induced cognitive changes, proving the need for the use of PROs in nursing practice to identify better and evaluate these symptoms (Kim et al., 2020; Schagen et al., 2022). Furthermore, use of PROs aide in the identification of early impairment and facilitation of early intervention (Schagen et al., 2022). This type of research supports the integration of PROs across oncological specialities, which can assist hematology nurses with their advocacy for the use of these particular PROs in health systems and the incorporation into routine healthcare.

The three PROs described above have been validated for hematological malignancies and, despite minor differences, have been shown to effectively assess for cognitive changes in the CAR-T treated population (Chakraborty et al., 2019). The biggest limitation of these tools is that they are subjective, which relies on patient insight and interpretation by the clinician (Kamal et al., 2021). Therefore, incorporating an objective assessment tool may be beneficial to determining an accurate representation of a patient’s cognitive deterioration.

### OBJECTIVE ASSESSMENT TOOLS

The two assessments described in the literature are the Montreal Cognitive Assessment (MoCA) and the Mini-Cog assessment. The MoCA has a high sensitivity and specificity for mild impairments, especially in those individuals who have completed higher education, and has been validated for use in hematological patients (Chakraborty et al., 2019; Tuch et al., 2021). The Mini-Cog assessment is shorter and has been validated across ethnically diverse groups with lower literacy and education levels (Tuch et al., 2021). Depending on the population being served, one tool may be preferred over another. Regardless, given the high subjectivity of PRO assessments, integrating a process to further assess neurocognitive changes objectively can further improve patient outcomes.

Some studies suggest different tools delivered at different time points may be most beneficial to symptom management (Chakraborty et al., 2019; Kamal et al., 2020). However, the utility of this should be contemplated; clinicians should examine the threshold for intervention and logistical complications that arise of regular assessments being completed in the short time frame of a clinic visit. As the use of PROs become common practice in clinical settings, incorporation of objective assessments should accompany changes in subjective cognition. Nurses can advocate for objective assessments to be completed before and after each treatment regimen to understand better the neurotoxic effects of each line. It is vital that CAR-T programs support nurses in the use of these tools through education and resource support (Steinbach et al., 2023). Providing nurses with the tools to manage their patients effectively can provide insight into recognizing early cognitive changes and improve patient outcomes.

### FUTURE RESEARCH

There are neurocognitive changes occurring in patients undergoing CAR-T therapy. The extent of this is still not well understood, and future research needs to focus on cognitive assessments before and after CAR-T therapy to explore the extent of these changes relative to baseline. Furthermore, the impact of integrating these tools into nursing practice should be evaluated and, in turn, interventions established for patients with new or worsening neurocognitive impairments. In addition, current research does not address racial differences accurately as most patient samples were homogenous and represented a small portion of the population (Ruark et
al, 2020; Sidana et al., 2022; Tan et al., 2021; Whisenant et al., 2021). In most provinces, CAR-T therapy is only approved to treat lymphoma, which is more prevalent in the Caucasian population (Kirtane & Lee, 2017). However, as more hematological malignancies, such as multiple myeloma, are treated with CAR-T therapy, racial differences need to be considered as some of these malignancies are more common in other racial groups. These demographic differences have been shown to impact cognitive impairment negatively (Kirtane & Lee, 2017; Nakumara et al., 2020). Research of the impact of sociodemographic variables on neurocognitive outcomes after CAR-T therapy will provide nurses with a better understanding of these complex risk factors.

**IMPLICATIONS FOR PRACTICE**

CAR-T therapy can worsen pre-existing cognitive deficits in a subset of the population treated. As CAR-T therapy gains traction and becomes a first or second line of therapy for hematological patients, its impact on neurocognition will become more apparent. Therefore, nurses should examine how these changes in cognition are assessed in their current practice and how they can advocate for incorporation of these assessments into that daily practice. While nurses can support the implementation of CAR-T therapy and the management of its side effects through neurocognitive assessments to identify early changes, managing CAR-T therapy is not the responsibility of a single discipline, but requires a multidisciplinary approach to manage these changes.

**CONCLUSION**

CAR-T therapy is a new advancement in cancer care that is evolving quickly to include, not just hematological malignancies but, solid tumors as well. Nurses need to understand the long-term cognitive impairments this heavily pre-treated population can exhibit, identify risk factors, and implement interventions to improve patient outcomes. Nurses can advocate for time and tools that allow for the assessment of these complex patients and their cognitive needs. Ensuring that assessments are done at multiple time points upon the patient’s disease trajectory can help track the burden of neurotoxicity development. As CAR-T research continues to evolve, nurses education and practice should use emerging literature to support integration of assessments for the neurotoxic effects of CAR-T therapy.

**REFERENCES**


