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Monitoring the neurological complications of chimeric antigen receptor (CAR) T-cell therapy in patients with sensory and physical impairments and non-native-speaking backgrounds using modified immune effector cell-associated encephalopathy (ICE) scores: a case series

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ABSTRACT

Background Immune effector cell-associated neurotoxicity syndrome (ICANS) is a common complication of chimeric antigen receptor (CAR) T-cell therapy. Current practice guidelines recommend the immune effector cell-associated encephalopathy (ICE) score for the assessment and monitoring of ICANS.

Objective To demonstrate modifications to ICE score to patients with vision and hearing impairments or who are who are from non-native-speaking backgrounds.

Methods We discuss five cases and the modifications made to adapt the ICE score to meet patients' needs.

Results Modifications to ICE score was feasible and it assisted with CAR T cell therapy outcome monitoring.

Discussion These cases highlight the need for flexible and patient-tailored strategies and the importance of collaboration between multidisciplinary teams and patients' families/caregivers when monitoring patients for ICANS after CAR T-cell therapy.

INTRODUCTION

Chimeric antigen receptor (CAR) T-cell therapy has emerged as a novel and promising treatment for haematological malignancies. Its rapidly growing use in standard-of-care and clinical trial settings has been driven by its efficacy and has led to significant improvements in disease remission and patient survival.[1] More recently, CAR T-cell therapy has also been considered for a variety of autoimmune, systemic and neurological conditions.[2] As the

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Chimeric antigen receptor (CAR) T-cell therapy has revolutionised treatment of haematological cancers and usage for other conditions is expanding. A common side effect of CAR T-cell therapy is the development of neurotoxicity. The immune effector cell-associated encephalopathy (ICE) score is used to detect neurotoxicity after CAR T-cell therapy.

WHAT THIS STUDY ADDS

⇒ This case series demonstrates that it is feasible to modify the items of the ICE score to accommodate a patient's motor, sensory and language needs. Modification is preferable over the omission of items to maximise sensitivity to neurotoxicity.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Clinicians and nursing staff can adapt neurotoxicity assessments when the standard assessment is inappropriate.

indications for CAR T-cell therapy increase, so does our need for standardised approaches to monitor its unique complications and side effects. One common complication of CAR T-cell therapy is immune effector cell-associated neurotoxicity syndrome (ICANS). The incidence of ICANS ranges from 37% to 75% in those who have received CAR T-cell therapy for haematological malignancies,

with differences seen across cohorts depending on the ICANS grading system used, CAR-T product and disease indication.[3] ICANS has diverse clinical manifestations including cognitive dysfunction and tremor, which in severe cases can progress to seizures, cerebral oedema and coma.[4] Early identification and treatment of ICANS is essential to prevent severe and possibly irreversible neurotoxicity. Standard management includes supportive care; the use of corticosteroids, anakinra and where indicated, the use of antiseizure medications and medical/surgical management of cerebral oedema.[5 6] Patients with a high risk of ICANS may also be considered for more frequent monitoring and the institution of prophylactic measures in an attempt to abrogate or delay its onset or worsening.[5 6] Hence, ICANS monitoring is crucial for timely diagnosis and management.

In 2019, the American Society for Transplantation and Cellular Therapy published its consensus grading scheme for ICANS and a standardised assessment tool, immune effector cell-associated encephalopathy (ICE) score.[4] The ICE score is composed of five items: (1) orientation to year, month, city and hospital, (2) naming of three objects, (3) the ability to follow a simple command, (4) sentence writing and (5) serial 10s (subtraction of 10 from 100 serially).[2] This results in a score out of 10. A patient with a score less than 10 is classified as having ICANS.

While the ICE score is a valuable tool for monitoring ICANS, its validity depends on several factors including the patient's ability to engage with verbal or visual questioning. This includes adequate motor, auditory and visual sensory function and a degree of proficiency in the language in which the test is administered. Hence, cognitive assessment of people with hearing or visual impairments as well as people from non-native-speaking backgrounds poses a challenge for clinical staff. This is a particularly relevant clinical issue due to our population demographics; first, many patients eligible for CAR T-cell therapy are older in age and, therefore, there is a higher likelihood of sensory or physical impairments, and second, as Australia is a linguistically and culturally diverse country, there is a proportion of the population who are non-English speaking. Finally, individuals may also have pre-existing neurological conditions that may affect their baseline assessments and so subsequent post-CAR T-cell therapy monitoring needs modification to account for the pre-existing disability.

Below we describe how the ICE score was modified for five patients who received CAR T-cell therapy at our institution, The Alfred in Melbourne, Australia. These modifications were made after extensive discussion within our multidisciplinary team comprising of haematology, neuroimmunology and neuropsychology. At our institution, the ICE score is completed at baseline preinfusion and at least daily postinfusion until day+28 postinfusion. The frequency of assessment is increased up to hourly as clinically indicated. In addition to ICE testing, standard of care in our institution includes daily neurology and neuropsychology review.

Cases 1 and 2: language other than English background

A patient in their 40s from a Mandarin-speaking background and very little English proficiency received BCMA-directed CAR T-cell therapy for multiple myeloma. Interpreter services were used when possible. However, given the frequency of ICE testing, a modified ICE score was needed for situations when a quick assessment was required and an interpreter was unavailable.

The ICE score was modified so that orientation questions, simple commands and instructions for serial 10s and handwriting were provided in a written format in simplified Chinese on flashcards (figure 1). At baseline, the patient was able to state the year, city and hospital and perform serial 10s in English. For orientation to month, a flashcard with the months written in simplified Chinese was provided and the patient was asked to point to their answer. For visual confrontation naming, flashcards with multiple-choice options written in simplified Chinese were provided. The patient was shown the flashcards and then asked to point to the name of the pictured image from the choices. All flashcards were administered to the patient at baseline. Readers should note that any flashcards that the patient answers incorrectly at baseline should not be used, as an incorrect response given postinfusion may be confused for ICANS rather than a lack of vocabulary knowledge. For sentence writing, the patient was asked to write a sentence in simplified Chinese. Clinical staff reviewed the patient's sentence writing by comparing it to their baseline sentence. During their admission, the patient consistently scored 10 out of 10 in our modified ICE score. They did not develop ICANS.

A patient in their 70s from a Mandarin-speaking background received axicabtagene ciloleucel for diffuse large B-cell lymphoma (DLBCL). The modified ICE score described above was used to monitor this patient. Nursing staff fluent in Mandarin also occasionally aided with the administration of serial 10s. The patient developed grade 1 ICANS day+4 postinfusion. Their ICE score initially dropped to 9 losing points for handwriting, and so monitoring and the frequency of the ICE score was increased. Examples of their sentence writing are depicted in figure 2; this demonstrates that sentence writing in the patient's native language can also be informative. The patient's subsequent ICE scores fluctuated between a score of 8–10, with points occasionally lost for handwriting and serial 10s. The patient was commenced on dexamethasone day+6 postinfusion.

Case 3: congenital retinal blindness

A patient in their 70s with congenital retinal blindness received axicabtagene ciloleucel for DLBCL. Due to their blindness, two items from the ICE score were deemed inappropriate to administer: visual confrontation naming and sentence writing. The literature has previously suggested the use of naming from verbal descriptions as an alternative to visual confrontation naming.[7 8] Hence, the ICE naming items were substituted with items from the Auditory Naming Task.[9] While the Auditory Naming

Figure 1 Example of ICE score items, multiple-choice visual naming items and commands written in patient's native language (Simplified Chinese). The first column depicts the flashcards of the orientation questions and the instruction to write a sentence. The middle column depicts flashcard examples for visual naming with multiple-choice options. The last column depicts flashcards with command instructions. ICE, immune effector cell-associated encephalopathy.

Test assesses a different neural system to the Visual Naming Test,[10] previous studies suggest that the tests are complementary.[9 11] For our patient, items from the Auditory Naming Task were randomised into groups of three (see table 1) to replace the three naming items on the standard ICE items (see table 1). These groups were created as alternate options for the purposes of serial testing to reduce practice effects. Object naming through tactile stimuli was also used by neurologists during their daily examination.

Regarding sentence writing, writing in braille was considered. However, after extensive discussion, it was felt that this alternative would not be equivalent to handwriting. In patients with intact vision, poor sentence writing due to mild ICANS typically reflects tremor, rather than true dysgraphia. Assessment of tremor and language (ie, through confrontation naming and spontaneous speech) by the neurology and neuropsychology teams would be a suitable substitute for sentence writing.

Therefore, the sentence writing item of the ICE score was omitted, resulting in a modified 9-point ICE score.

During the patient's admission, there were a few instances of ICE score dropping to 8/9 with points lost for naming. This first occurred on day+1 postinfusion. On daily neurology review, there were also some mild fluctuations in their delayed recall and attention. On day+7 postinfusion, the neuropsychology review demonstrated reduced working memory, higher-order attention, processing speed and acquisition/learning of new verbal information; however, the ICE score at the time was 9/9. While there were subtle neurocognitive deficits compared with their baseline, the modified ICE score provided reassurance that possible ICANS were mild and so treatment of ICANS was not unduly escalated.

Case 4: hearing impairment

A patient in their 60s received axicabtagene ciloleucel for chronic lymphocytic leukaemia. The patient had

Figure 2 Case 2's handwriting in simplified Chinese comparing baseline with tremulous handwriting. Baseline handwriting on day+0 (17 June 2024) and day+1 (18 June 2024) is depicted in the first three rows. Change in handwriting due to tremor during ICANS on day+4 (21 June 2024) and day+5 (22 June 2024) is depicted in the last three rows. ICANS, immune effector cell-associated neurotoxicity syndrome.

pre-existing right-sided hearing loss secondary to cholesteatoma single-stage operation. A few days before their infusion, the patient presented with sudden-onset left-sided hearing loss. They were provided with an auditory listening device, which aided them during ICE tests. The use of gestures and non-verbal language was also beneficial. Written instructions were also considered if the aforementioned strategies were ineffective. Using written instructions to accommodate for hearing impairment has been successful in other cognitive tests, such as the Montreal Cognitive Assessment.[12] During the patient's admission, their ICE scores were consistently 10/10 and they did not develop ICANS.

Case 5: multiple sclerosis with pre-existing tremor and dysmetria

A patient in their 50s received axicabtagene ciloleucel for DLBCL. The patient had a pre-existing mild postural and kinetic tremor and dysmetria in the context of multiple sclerosis. They completed the ICE score at baseline scoring 10/10 and were able to write a sentence despite their tremor. The ICE score was unmodified, and nursing and medical staff were advised to refer back to their baseline when assessing their sentence writing so that their pre-existing tremor was not misattributed to possible ICANS. The patient developed ICANS grade 4 on day+4

postinfusion. The patient's initial symptoms were mild word-finding difficulties in spontaneous conversation, dysnomia on visual confrontation naming (Sydney Language Battery naming subtest[13]) and reduced attention and processing speed on a computerised cognitive task on neuropsychology review. An hour later, their ICE score dropped to 6/10 with points lost for orientation to year and month, serial 10s and sentence writing (figure 3). They were subsequently admitted to the intensive care unit and were treated with dexamethasone, anakinra and levetiracetam. The patient's ICE score returned to 10/10 consistently approximately 24 hours later (day+5).

A word of caution against the omission of sentence writing from the ICE score

We examined the ICE scores of patients who did not require modifications at our institution. 64 patients received CAR T-cell therapy between September 2022 and April 2024, and 59 patients were monitored with the unmodified ICE score. Of these 59 patients, 24 patients demonstrated at least one imperfect ICE score during their admission. 10 patients were felt not to have ICANS; their ICE scores of 9 were one-time occurrences and were thought to be minor attentional lapses. The remaining 14 patients were classified as having ICANS (see table 2). In most cases (nine patients), the first imperfect ICE score

Table 1 Examples of the Auditory Naming Task items randomised into groups of three for serial ICE testing

Item	Answer
Option 1	
An instrument you beat with sticks	DRUM
The room of a house where people cook	KITCHEN
What an old man uses to walk with	CANE/WALKING STICK
Option 2	
The organ that pumps blood	HEART
The part of the shirt that covers the arms	SLEEVES
The thing that unlocks a door	KEY
Option 3	
A device used for taking pictures	CAMERA
What a car engine runs on	PETROL
Where you go to borrow or deposit money	BANK
Option 4	
An insect that produces honey	BEE
The eating utensil used for slicing	KNIFE
The hard outside edges of bread	CRUST
Option 5	
A kind of boat that travels underwater	SUBMARINE
A black and blue mark on the skin	BRUISE
The kind of book containing word definitions	DICTIONARY

ICE, immune effector cell-associated encephalopathy.

was 9 with the point lost for sentence writing. Tremor, or worsening of pre-existing tremor, was often the cause of poor handwriting. Tremor was also reported as a common early sign of neurotoxicity at another Australian CAR T-cell therapy centre.[14] If the sentence writing item was omitted from the ICE score in these 14 patients, ICANS detection would have been delayed in 6 patients and missed in 3 patients (see table 2 for further details). This highlights that the omission of the sentence writing item can reduce the sensitivity of the ICE score to detect mild ICANS.

DISCUSSION

The ICE score is vital for the early detection of ICANS and its related neurocognitive changes. It is a tool that is easily administered by nursing and medical staff with a high degree of reproducibility, and its brevity enables it to be repeated several times per day as clinically indicated. Like other observations such as blood pressure, temperature and oxygenation, the ICE score in the CAR-T cell therapy population provides insight into the patient's clinical state and can monitor change over time. However, the ICE score has yet to be validated for patients with sensory or physical impairments or from non-English-speaking backgrounds. This retrospective review demonstrates the need for modification and optimisation of ICE score for these patients and provides practical examples of such modifications. This study also cautions clinicians to avoid the omission of items from the ICE score (particularly sentence writing) as this may reduce the sensitivity of the ICE score.

64 patients received CAR T-cell therapy at The Alfred between September 2022 and April 2024. The average age of these patients was 63.97±13.03 years. This is consistent with the median age of diagnoses for many haematological cancers, multiple myeloma (72.4 years), leukaemia (70.0 years) and lymphoma (68.7 years).[15] Given the older age of many patients planned for CAR T-cell therapy, sensory impairments are highly likely. Indeed, of Australians aged 65 and over, 1.7% have partial or complete blindness and 33.5% have partial or complete deafness.[16] In case 3 (patient with congenital retinal blindness), we modified the ICE score to replace visual confrontation naming with an auditory naming task. For day-to-day communication, the use of Braille also assisted with their management. In case 4 (patient with hearing impairment), the patient was provided with an auditory assistance device, and visual aids and written information were also used. Overall, these strategies were helpful to ensure both patients were monitored for signs of neurotoxicity regularly and in a systematic manner.

The utility of the ICE score for those with non-native speaking backgrounds has yet to be demonstrated in the literature. According to the 2021 Australian census data, 21% of Australians spoke a language other than English at home, and 3.4% of Australians reported that they 'speak English not well or not at all'.[17] There are over 300 languages spoken in Australian homes, and the most common other than English are Mandarin, Arabic, Vietnamese and Cantonese.[17] In many regions of the country, especially the Northern Territory, Indigenous languages were commonly spoken.[18] This exemplifies the need to adjust clinical assessment tools to tailor to the patient's native language or their preferred language of use. In two of the above cases (cases 1 and 2), the ICE score was modified with the use of flashcards with the items written in simplified Chinese. Sentence writing was also done in simplified Chinese. Although not all clinicians could read or understand the sentence, its variation to the baseline sentence written by the same patients provided sufficient clues when a change occurred in the sentence. It was easily demonstrable as per case 2 that as the person developed ICANS their sentence appeared 'different' to their baseline (pre-CAR T-cell infusion) sentence, and hence

Date / time	Year	Month	City	Hospital / Place	Follow command	Object 1	Object 2	Object 3	Serial 10s	Handwriting	Score	Grade
1037 13/11/23	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Staff initials MW	Sentence: *I have 3 dogs, 3 cars, 3 motor bikes and a jetski*											
13/11/23 2000	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Staff initials	Sentence: *I have 3 dogs, 3 cars, 3 motorbikes and a jetski*											
14/11/23 0840	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Staff initials TP	Sentence: *I have 3 dogs, 3 cars, 3 motorbike and a jetski*											

Date / time	Year	Month	City	Hospital / Place	Follow command	Object 1	Object 2	Object 3	Serial 10s	Handwriting	Score	Grade
17/11/23 0730	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Staff initials MC	Sentence: *I have 3 dogs, 3 cars, 3 motorbikes and a jetski*											
17/11/23 1250	✗	✓	✓	✓	✓	✓	✓	✓	✗	✗		
Staff initials MC	Sentence: *I have 3 dgers, 3 cars, 3 motorbikes, and a jet eta sketi*											
1400 17/11	✗	✗	✓	✓	✓	✓	✓	✓	✗	✗	6/10	
Staff initials	Sentence: EEG / NA											
	✗	✗	✓	✗	✓	✓	✓	✗	✗	✗	4/10	
Staff initials	Sentence: *iraziuligiy*											

Date / time	Year	Month	City	Hospital / Place	Follow command	Object 1	Object 2	Object 3	Serial 10s	Handwriting	Score	Grade
17/11/23 1644	✗	✗	✓	✗	✗	✓	✓	✓	✗	✗	4/10	2
Staff initials	Sentence: *I hor ghor hg drg ghgdrog igrop al grog rog progrog lopdagrog grog*											
18/11 1830	✗	✗	✗	✗	✗	✓	✓	✗	✗	✗	2/10	3
Staff initials B25 / JT	Sentence											
Staff initials JT	Sentence											

Figure 3 Examples of ICE scores of case 5 at baseline and during onset of ICANS. Baseline handwriting on day+0 (13 November 2023) and day+1 (14 November 2023) is depicted in the first three rows. Change in handwriting during the evolution of ICANS on day+4 (17 November 2023) is depicted. Handwriting is at baseline at 07:30 hours, spelling errors become evident at 12:50 hours and writing is severely dysgraphic at 14:00 hours, 16:21 hours and 18:28 hours. ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune effector cell-associated encephalopathy.

Table 2 Comparing ICE scores with and without sentence writing

ID	First imperfect unmodified ICE score			First imperfect ICE score without sentence writing			Comments regarding unmodified ICE vs ICE without sentence writing	Worst ICANS grade
	Day postinfusion	ICE score	Item(s) with point lost	Day postinfusion	ICE score	Item(s) with point lost		
1	D+15	9/10	Sentence writing	–	–	–	Imperfect ICE scores were only due to points lost in sentence writing. Without sentence writing, ICANS would not have been detected.	1
2	D+2	9/10	Sentence writing	D+3	8/9	Naming	ICE score without sentence writing delayed the detection of ICANS by one day	4
3	D+8	9/10	Sentence writing	–	–	–	Imperfect ICE scores were only due to points lost in sentence writing. Without sentence writing, ICANS would not have been detected.	1
4	D+1	8/10	Year, sentence writing	D+1	8/9	Year	First imperfect ICE score with and without sentence writing was the same ICE administration	1
5	D+1	9/10	Sentence writing	D+2	8/9	Serial 10s	ICE score without sentence writing delayed the detection of ICANS by one day	4
6	D+9	9/10	Sentence writing	D+10	6/9	Month, command, serial 10s	ICE score without sentence writing delayed the detection of ICANS by one day	2
7	D+8	9/10	Sentence writing	D+12	8/9	Serial 10s	ICE score without sentence writing delayed the detection of ICANS by four days	4
8	D+5	9/10	Sentence writing	–	–	–	Imperfect ICE scores were only due to points lost in sentence writing. Without sentence writing, ICANS would not have been detected.	1
9	D+5	7/10	Year, serial 10s, sentence writing	D+5	7/9	Year, serial 10s	First imperfect ICE score with and without sentence writing was the same ICE administration	4
10	D+6	1/10	All items but command	D+6	1/9	All items but command	First imperfect ICE score with and without sentence writing was the same ICE administration	4
11	D+4	8/10	Sentence writing, command	D+4	8/9	Command	First imperfect ICE score with and without sentence writing was the same ICE administration	2
12	D+4	9/10	Sentence writing	D+5	8/9	Year	ICE score without sentence writing delayed the detection of ICANS by one day	1
13	D+4	6/10	Year, month, serial 10s, sentence writing	D+4	6/9	Year, month, serial 10s	First imperfect ICE score with and without sentence writing was the same ICE administration	4
14	D+1	9/10	Sentence writing	D+1	6/9	Place, hospital, naming	ICE score without sentence writing delayed the detection of ICANS by 2.5 hours	4

ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune effector cell-associated encephalopathy.

ICANS was diagnosed. Readers should note that the use of flashcards was appropriate in the discussed cases but is not appropriate in patients who are illiterate. Administration of the ICE score with the aid of the interpreter remains best practice; however, we acknowledge that this can pose a logistical challenge as interpreters are a finite resource and it can be difficult to acquire their services on short notice when prompt ICE assessment is clinically required.

Some patients undergoing CAR T cell therapy may also have pre-existing limb motor or sensory deficits that may hinder or affect their ICE score performance. As demonstrated by case 5 who had a pre-existing neurological disorder (multiple sclerosis) affecting upper limb function, the writing component of the ICE score was abnormal at baseline (pre-CAR T-cell infusion). In these scenarios, change or worsening relative to baseline was monitored. This demonstrates that sentence writing may be particularly sensitive to mild ICANS. In our further analysis of 59 patients with CAR T cell therapy who were monitored with unmodified ICE scores, sentence writing was the most frequent item to become abnormal due to ICANS. Hence, we strongly advise against the omission of sentence writing where possible.

Other considerations to note when administering the ICE score are to ensure that the environment is well-lit and where feasible, to reduce environmental noise and distractors. Patients should be given clear verbal or written instructions where appropriate and for the sentence writing component of the ICE score, a flat solid and even surface to write should be provided. It is also important to consider other factors that may result in a change in ICE score including the presence of delirium, fatigue, poor sleep and lack of motivation/depression. In cases of a one-point ICE score drop, the ICE score should be repeated to exclude transient attentional lapses/the impact of distractors, clinical review by haematology or neurology should be arranged and the frequency of the ICE score should be increased.

While this case series has demonstrated the feasibility of modified ICE assessments, these modifications were made on an ad hoc basis which makes generalisations and recommendations for 'standardised' modifications difficult. This case series is intended to illustrate potential modifications to allow the continuation of ICANS monitoring. Readers seeking to adapt the ICE assessment for their own patients should assess the appropriateness of these modifications before implementing them. Future studies are required to validate modified ICE assessments for different patient populations in larger samples.

CAR T-cell therapy has revolutionised the treatment of various relapsed or refractory B-cell derived malignancies and multiple myeloma, but its side effects and associated neurotoxicity need systematic and rigorous monitoring strategies. Although a useful measure for ICANS monitoring, the ICE score has its limitations and so should always be considered in conjunction with other clinical measures. Importantly, its administration should take the

patient's motor, sensory and language needs into account and where appropriate, should be modified to suit their needs. Future research should focus on the development of assessment tools that can accurately monitor for ICANS while also being inclusive of the person's needs. This is vital to increase safety, improve outcomes and enable a patient-centred approach to monitoring for neurotoxicity.

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