

# Nursing management for ICANS of CAR T-cell therapy in B cell acute lymphoblastic leukemia<sup>†</sup>



Review

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**Abstract:** **Objective:** Immune effector cell-associated neurotoxic syndrome (ICANS) is one of the most concerning complications because of its life-threatening trait during chimeric antigen receptor (CAR) T-cell therapy and requires specialized management. We summarized the nursing procedures of CAR T-cell therapy for ICANS to provide some references for the standardized nursing care of ICANS.

**Methods:** Based on previous experience and literature research, the professional team developed nursing procedures for ICANS for patients receiving CAR T-cell therapy.

**Results:** The professional team developed step-by-step, sophisticated care procedures before, during, and after ICANS, including active communication and collaboration, knowledge updates, personalized nursing plans, advanced assessments, close monitoring of vital signs and laboratory tests, medication plans, timely and correct drug administration, dietary nursing interventions, safety care, nursing of other complications, follow-up of toxicities, and keeping an eye on the potential side effects.

**Conclusions:** ICANS is unique, with varying clinical symptoms and rapid progression. Timely and accurate treatment and care of patients is an effective way to manage ICANS. Professional and detailed procedures are required to guide nurses to manage patients' ICANS, so as to improve the safety of patients and the promotion of CAR T-cell therapy

**Keywords:** *chimeric antigen receptor-T cell therapy • immune effector cell associated neurotoxicity syndrome • management • nursing roles • symptom management*

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## 1. Introduction

The use of immune cells to eradicate tumors, or immunotherapy, has become more popular than the more conventional cancer treatments like radiation, chemotherapy, and surgery. One of the most widely used immunotherapies available today, chimeric antigen receptor (CAR) T-cell therapy, has revolutionized the treatment of hematological malignancies. According to reports, 60%–90% of patients with recurrent or resistant acute B lymphoblastic leukemia (B-ALL) experience full remission following CAR T-cell treatment.<sup>1–5</sup>

Although the quality and efficiency of treatment are surprising, its peculiar adverse effects also pose a problem. Immune effector cell-associated neurotoxic syndrome (ICANS) and cytokine release syndrome (CRS) are the 2 most unusual side effects. ICANS symptoms include headaches, trouble identifying words, dysgraphia, altered mental state, dyskinesia, and potential seizures.<sup>6–8</sup> While the majority of symptoms resolve on their own, others can quickly worsen to the point of becoming life-threatening. ICANS is a major factor in patient mortality,<sup>9</sup> and it also prevents CAR T-cell treatment from being used more widely in the clinical settings.<sup>10</sup> Studies and varied illness subtypes have different incidence rates and symptoms. According to a meta-analysis, the incidence rate of ICANS is around 21.7%,<sup>11</sup> whereas 32.8% of patients experience transitory neurotoxicity and 1.7% experience slightly severe neurotoxicity.<sup>12</sup> The incidence rate was higher in past research. However, the majority of patients' critical problems can be promptly assessed and efficiently managed,<sup>13</sup> with the nurse playing a crucial role.

There are now suggested procedures for ICANS management.<sup>14</sup> However, because nursing is essential for treating side effects, the nursing profession during CAR T-cell therapy requires thorough summation and direction.<sup>15</sup> This article summarizes the nursing management of ICANS patients during CAR T-cell therapy, aiming to provide a reference for standardized care of ICANS.

### 1.1. Theory background

Symptom management theory (SMT) is a theoretical framework created by members of the University of California, San Francisco School of Nursing.<sup>16</sup> It aims to describe the core concepts of symptom experience, symptom management strategies, and management effects and their interrelationships. The theory holds that symptom management is a multidimensional process affected by many factors. Effective symptom management includes 3 basic components: symptom

experience, symptom management strategy, and management effect. On the basis of evidence and SMT, this study constructs a scientific, systematic, and comprehensive nursing process, which provides a reference for the whole process management of CAR T cell therapy patients.

## 2. Material and methods

A team of doctors and nurses with rich experience in the management and nursing of CAR T-cell therapy was established. Based on 109 patients' previous management experience and document retrieval, the nursing procedure of ICANS after CAR T-cell therapy was determined through multiple rounds of discussion. Throughout the nursing process, we used symptom recognition and symptom severity assessment to describe the patient's symptom experience, and evaluated the improvement of symptoms after nursing intervention to evaluate the management effect.

*Inclusion criteria:* Patients who were diagnosed with B-ALL and received CAR T cell therapy; patients gave informed consent and volunteered to participate in this study.

*Exclusion criteria:* Unclear consciousness, unable to communicate normally; patients who did not cooperate.

## 3. Results

Due to the potentially life-threatening nature of ICANS caused by CAR T-cell therapy, which is one of the main reasons for the failure of CAR T-cell therapy, we pay special attention to the nursing management of ICANS. Pre-ICANS care, during-ICANS care, and post-ICANS care are the 3 sections that make up the nursing management program (Table 1).

### 3.1. Pre-ICANS care

#### 3.1.1. Knowledge updates

Nurses must have a thorough understanding of ICANS in order to recognize and treat encephalopathy associated with CAR T-cell treatment. First and foremost, nurses must update their expertise, paying particular attention to ICANS recommendations and the most recent clinical studies. Furthermore, hiring a skilled nursing staff that is proficient in all facets of ICANS management requires employee training. The nursing team should also be well-versed in ICANS emergency protocols and treatments, including cerebral edema management; comprehend the various levels of ICANS treatment in detail; and ensure that every first aid device is ready for use and in a state of readiness. A list or even study manuals provide the exact material

| Variety   | Items   |
|---|---|
| <b>Pre-ICANS care</b>   |   |
| Nurse preparation   | <input type="checkbox"/> Know the latest research progress and guidelines<br><input type="checkbox"/> Understand the patient's condition as deeply as possible<br><input type="checkbox"/> Rescue equipment in standby state<br><input type="checkbox"/> CAR T-cell therapy-related training                                |
| Communication with patients   | <input type="checkbox"/> Introduce the presentation, identification, and management of ICANS to patients<br><input type="checkbox"/> To communicate with the patients and their families as much as possible  |
| Relevant evaluation and baseline data collection                      | <input type="checkbox"/> Do the ICE score for patients as basic data<br><input type="checkbox"/> ICANS risk factor observation table<br><input type="checkbox"/> Evaluate the psychological status<br><input type="checkbox"/> Administration of antiepileptic drugs<br><input type="checkbox"/> Personalized nursing plans |
| <b>During-ICANS care</b>  |   |
| Symptomatic treatment of ICANS  | <input type="checkbox"/> ICE score<br><input type="checkbox"/> Correct and timely administration<br><input type="checkbox"/> Report the condition timely to the doctor<br><input type="checkbox"/> Keep records<br><input type="checkbox"/> Dietary nursing interventions   |
| Management of other complications                                     | <input type="checkbox"/> Activity care<br><input type="checkbox"/> Round-the-clock monitoring<br><input type="checkbox"/> Safety care<br><input type="checkbox"/> Nursing of other complications  |
| <b>Post-ICANS care</b>  |   |
| Continue to pay attention to the follow-up of the patient             | <input type="checkbox"/> Follow-up of toxicities  |
| Reflect on the areas that still need improvement in the whole process | <input type="checkbox"/> Keep an eye on the potential side effects<br><input type="checkbox"/> Distribute symptoms and contact cards  |

Note: ICANS, immune effector cell-associated neurotoxic syndrome; ICE, Immune Effector Cell-Associated Encephalopathy.

**Table 1.** Nursing procedures for ICANS.

- The latest ICANS management guideline
- The latest clinical reports and important articles
- ICANS gradings
- Symptoms of ICANS
- Drugs to treat ICANS, including usage and dosage
- Assessment tools for ICANS
- The use of instruments and equipment for ICANS management
- Emergency plan for ICANS complications
- Nursing of other complications

Note: ICANS, immune effector cell-associated neurotoxic syndrome.

**Table 2.** Knowledge reserve checklist for nurses before nursing ICANS.

that nurses must acquire, comprehend, and get ready for; nonetheless, they ought to be updated on a regular basis (Table 2).

### 3.1.2. Active communication and collaboration

Close cooperation and open communication are key to the rigorous and proper administration of CAR T-cell

therapy. The management of ICANS requires the collaboration of multidisciplinary teams, including oncologists, neurologists, nurses, psychologists, and social workers. Nurses play a crucial role in facilitating and carrying out bedside patient care. They must communicate effectively with other medical professionals, such as doctors, dietitians, pharmacists, ICU teams, and anesthesiologists. When a patient chooses to sign up for CAR T-cell treatment, there is an initial communication period during which the patient is informed about the entire procedure, how to participate during the therapy, the potential side effects, and preventative measures. Subsequently, regular contact is maintained and the patient's comprehensive nursing plan is modified in accordance with each phase of treatment. However, education and patient condition notification are the 2 primary components of communication with patients and their families, which is also very important.<sup>17</sup> To ensure that family members and patients are well-informed and not unduly anxious when ICANS occurs, it is necessary to educate them on the clinical features, manifestations, occurrence time, and solutions of ICANS. Additionally,

talking with patients' caregivers can help patients comply with their therapy and make it easier for clinical staff to get first-hand patient data.

**3.1.3. Personalized nursing plans**

Every patient has a different ICANS period and set of symptoms, so each patient's care strategy needs to be unique, particularly for those with risk factors. Some studies suggest that neurological problems, younger age, large tumor load, and extramedullary or central nervous system-related disorders in the past are risk factors for ICANS. A patient's response to treatment may also be influenced by other variables, such as early fever, elevated inflammatory cytokine levels 3 days after CAR T cell infusion, peak amplification of CAR T cells, high-grade CRS, and other CAR T-self traits like CAR structure.<sup>10,18-27</sup> As a result, the nursing plan needs to include a list of the patient's previously indicated risk factors, be developed in great detail, and be rigorously followed. During each shift, it is essential to keep an eye out for patients who pose a risk and make sure to report them accurately.

**3.1.4. Advanced assessments**

Preventing ICANS is more important than treating it, thus the medical team must assess the patient's condition as soon as possible and look for any toxicity associated with CAR T-cell therapy.<sup>21,22</sup> It is advised to utilize the Immune Effector Cell-Associated Encephalopathy (ICE) score (Table 3), which has been modified by CAR-T-cell-therapy-associated Toxicity (CARTOX)-10, since it is simple to obtain, simple to use, and reusable.<sup>6</sup> Once a day prior to infusion and twice a day following CAR T-cell infusion until discharge, nurses evaluate patients using the ICE score. Examining

individuals more frequently is recommended when they exhibit symptoms and are thought to have ICANS. Early on in ICANS, alterations in the patient's handwriting were noted in this center. Moreover, stuttering has been documented as the initial symptom of ICANS,<sup>27</sup> and delirium is an early predictor of the condition in patients.<sup>11</sup> However, in our center, 4 patients were observed as silent and sluggish at the beginning of ICANS. Then it gradually manifested as lisp, apathy, disorientation, handwriting changes, unrelated reactions, delirium, irritability, aphasia, and even seizure. Sometimes, progress is rapid and astonishing. As a result, even at this point, it is necessary to increase the frequency of patient observation every half hour or less, and pay more attention to the patient's minor changes, particularly in their demeanor and feelings. The 4 ICANS patients at our facility all showed indifferent attitudes, sluggish reflexes, avoidance of eye contact, and increased silence throughout the early phases of the illness. In order to better understand patients, it is crucial to get in touch with them as soon as possible. This will enable to ascertain the patient's health and track the healing of any lingering effects. The ICE score is usually evaluated by a nurse, and if the score is <10, another nurse or doctor should evaluate the ICE score.

**3.1.5. Psychological assessments**

In clinical practice, it is also observed that patients at this period experience higher levels of psychological stress. Timely understanding of the patient's psychological condition and explaining the relevant procedures to them can help alleviate the relevant stress. Building patient confidence in this difficult treatment is beneficial. Patients should be encouraged to use the relevant scales for evaluation, such as anxiety assessment scales.

| Variety            | Items  | Point | Maximum points |
|--------------------|--|-------|----------------|
| Orientation        | Year   |       | 1              |
|                    | Month  |       | 1              |
|                    | City   |       | 1              |
|                    | Hospital   |       | 1              |
| Naming             | Object 1 (e.g. clock)  |       | 1              |
|                    | Object 2 (e.g. pen)  |       | 1              |
|                    | Object 3 (e.g. button)   |       | 1              |
| Following Commands | Ability to follow a simple command (e.g. "Show me 2 fingers" or "Close your eyes and stick out your tongue") |       | 1              |
| Writing            | Ability to write a standard sentence (e.g. "Our national bird is the bald eagle")                            |       | 1              |
| Attention          | Ability to count backward from 100 by 10   |       | 1              |

**Table 3.** ICE score.

### **3.1.6. Close monitoring of vital signs and laboratory tests**

Prior to the onset of neurological symptoms, studies have demonstrated higher levels of C-reactive protein (CRP), ferritin, and cytokines.<sup>28</sup> Furthermore, another research has demonstrated that patients with an early fever are more likely to have ICANS,<sup>7</sup> and that ICANS is typically accompanied by severe CRS.<sup>29,30</sup> Therefore, these indicators of patients should also be the key concerns of nurses. When these indicators have changed, the nurses should pay closer attention to the patients, including increasing the frequency of assessment of the ICE score.

### **3.1.7. Medication plans**

Antiepileptic medication use is still debatable. As a prophylactic measure, 0.75 g of the antiepileptic medication levetiracetam was given every 12 h from the day before the CAR T cell infusion until 30 days after infusion. The patient is informed about the value of taking their prescription to increase compliance. Typically, additional drugs are required for patients to treat various issues. Therefore, it is necessary to help them develop medication plans to avoid missing or mistakenly taking them.

## **3.2. During-ICANS care**

### **3.2.1. Timely and correct drug administration**

ICANS can appear in varying degrees and can happen with or without CRS. It typically happens 4–12 days following the infusion of CAR T cells. While the majority of patients heal promptly and without complications, some cases advance swiftly.<sup>6,18</sup> If there is a combination of CRS, tocilizumab is infused intravenously along with medicines to control the occurrence of ICANS. ICANS can last anywhere from <2 h for a single patient to 11 days at our facility. Some patients, however, were more subtle in their symptoms (they just don't respond or don't want to communicate). Furthermore, a few individuals required more intensive treatment due to their severity (e.g., potential for sudden agitation or seizure), which included sedation, epilepsy prevention, intracranial pressure reduction, and coagulation factor replenishment. It is also important to build 2 or more sets of venous pathways. The amount and frequency of medication will also change in response to variations in the severity of ICANS. Based on the patient's condition, medication must be administered accurately and promptly in accordance with the doctor's orders; arrange medication in a reasonable order; be mindful of the various requirements and effects of drugs; promptly provide the doctor with updates on the patient's condition; and

meticulously maintain records. Sometimes, when the situation is very urgent, emergency treatment measures need to be done in a short time.

### **3.2.2. Dietary nursing interventions**

According to a study, there is a correlation between the gut microbiome and the toxicity and effectiveness of CAR T-cell therapy.<sup>31</sup> Therefore, it is important to maintain the normal microbiome of patients. After undergoing lymphodepletion treatment, fever, and CAR T-cells infusion, patients often experience a decreased appetite. Some studies have shown that all patients develop diarrhea due to nutrient deficiency.<sup>11</sup> Therefore, patients need to eat a light, digestible, and hygienic diet. In most cases, oral feeding is encouraged; when the patient is unable to eat, the nutritionist will give advice based on the patient's nutritional status. Meanwhile, the diet of patients is exactly the part that they tend to forget to give feedback to doctors, while the levels of albumin and total cholesterol after CAR T-cell infusion are negatively correlated with the grading of CRS, and may be negatively correlated with ICANS.<sup>15,17</sup> Due to the crucial importance of a healthy diet for the normal functioning of the immune system, nurses should actively monitor the nutritional status of patients and provide timely feedback to doctors.

### **3.2.3. Safety care**

As directed by the physician, sedative and antiepileptic medications should be administered promptly to a patient who is agitated and epileptic. To stop the patient from hurting themselves, a tongue spatula should be inserted into their mouth. If needed, restraint tapes are used. The risk of patients falling down and falling out of bed is assessed, and based on the findings, preventative measures are implemented. To ensure the patient's safety, it is advised that a family member accompany the patient.

### **3.2.4. Nursing of other complications**

In addition to ICANS, there are other complications that need to be managed at the same time. The duty of nursing is complicated and detailed, including high fever nursing, blood coagulation abnormality nursing, ventilation obstacle nursing, hypotension or hypertension management, bleeding management, and so on. A study has shown that hematologic toxicity is the most common complication in patients within a month after infusion,<sup>32,33</sup> and the prevention of hemorrhage and infection is also the key focus of nursing work at this stage. Excellent nursing staff can always handle this complex situation

in an organized manner, allowing patients to gradually recover. Comprehensive understanding of the disease is a crucial step. This is why learning relevant knowledge from the beginning of nursing is emphasized.

### 3.3. Post-ICANS care

#### 3.3.1. Follow-up of toxicities

Studies have shown that some patients also suffered from depression and anxiety,<sup>34,35</sup> while other studies state that patients did not complain of any discomfort. This may be due to negligence or patients' lack of insight about their cognitive impairment. Thus, we summarize the following part for nursing patients after ICANS. Nurses are encouraged to actively understand patients' real ideas, evaluate their psychological state via psychometric questionnaire tests in a timely manner, and contact the psychological counseling team if necessary. Objective neurocognitive tests, including formal neuropsychiatric tests or computer-assisted applications, should be applied at this stage. Some studies have shown delayed ICANS. When the patient is discharged, a list of ICANS symptoms should be provided to them, including some symptoms of ICANS and the doctor's contact information. They need to be informed to contact their doctor when they experience these symptoms.

#### 3.3.2. Keep an eye on the potential side effects

The understanding of the pathophysiology of ICANS is still limited. Although there were no sequelae after ICANS in our center, more questionnaires are needed to investigate the sequelae of ICANS in the future. Corticosteroids are used to control ICANS in patients, but when used in large doses, they will also worsen muscle weakness caused by previous chemotherapy.<sup>36</sup> This part of our work needs to be further refined in the future to evaluate the patient's condition as early as possible and provide relevant interventions, so that the patient can recover as soon as possible.

## 4. Discussion

Although CAR T-cell therapy was first proposed in 1989,<sup>37</sup> there has not been much experience with CAR T-cell products, and they have not been used in patients for very long. The efficacy of the product is not the only factor that determines the success of CAR T-cell therapy; nursing plays a critical role in the entire process management of this treatment. In order to provide patients with professional care in the context of the new medical technology period and for the advancement of medical treatment, nurses must constantly study and

discover new things and keep up with the rapid pace of medical treatment, particularly innovative treatments. "More active" and "adventurous" are qualities now needed in nursing staff, rather than retreating or stagnating. Given the current rapid development—more and more CAR T-cell products will be applied to patients—it is necessary to increase the communication and learning of CAR T-cell treatment among nursing staff to promote more in-depth and professional CAR T-cell nursing work. There is urgent need for a nursing team and nursing experts for CAR T-cell therapy, who can provide more professional advice.

Currently, early identification and proactive management are the main goals of ICANS management. However, at this point, nursing staff members must take a more proactive role. The development of a comprehensive ICANS nursing procedure and associated management system is necessary to guarantee the seamless advancement of ICANS therapy and nursing. A thorough and methodical understanding about CAR T-cell treatment is essential. On one hand, it can guarantee the caliber of ICANS nursing and motivate nurses to follow the pertinent procedures. On the other hand, a structured care procedure can enhance the job by encouraging ongoing verification and assessment.

In addition to following the procedure, communication with the patient is crucial during the whole treatment. In the face of this new and risky treatment that is completely different from chemotherapies, patients have a lot of psychological stress. We need to evaluate accurately before taking intervention measures to relieve patients' psychological stress. In clinical practice, it was found that patients were more concerned about the complications of ICANS. Science popularization videos related to CAR T-cell therapy and ICANS can be produced to help patients better understand the relevant processes and knowledge, thereby reducing their anxiety. It is important to communicate with patients as much as possible and understand their personality in order to discover their early symptoms in the future.

Nowadays, the ICE score is used as a tool to evaluate patients' condition. However, there are still some details that need to be improved in the future work. In our center, we have some patients with an ICE score of 10, but their arithmetic ability has decreased. Some patients cannot write. These result in the inability to complete the "write complete sentences" in the ICE score, making it difficult to accurately assess the patient's condition. More sensitive and comprehensive assessment tools need to be developed, and currently there are teams starting to study this issue. For example, a team has developed a 3-step command tool to supplement the ICE score.<sup>21</sup> At the ASH conference in 2022,

another team introduced an assessment tool in the field of neurocognition.

## 5. Conclusions

Faced with the challenge of one of the most promising and revolutionary therapies for hematologic malignancies, nurses, as the closest contacts with patients, stand at the forefront of treatment, and play an indispensable role in managing side effects. The standardized and refined management of ICANS will help improve patient safety and quality of patient care, enabling this new technology to be applied to more diseases. The nursing team developed the nursing process of ICANS and provided a comprehensive nursing management framework, covering the entire treatment process of ICANS patients, from pre-preparation to post-follow-up, showing comprehensive consideration of ICANS patient care. At the same time, the nursing plan emphasizes the importance of formulating personalized nursing strategies according to the specific situation of patients, taking into account the risk factors and symptoms of different patients, which will help to provide more accurate care. We want to emphasize that this nursing procedure is not immutable, and it needs to be further improved in practice.

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## Author contributions

Yang HY and Jin JJ completed the first draft together. Zhang QQ has written and reviewed the article. Liu YX has written and reviewed the article. Ying Wang has reviewed and edited the article. Wang ZX has reviewed and edited the article. Zhang JP has reviewed and edited the article. Xie WJ has reviewed and edited the article.

## Consent to participate

All participants signed an informed consent form in accordance with the Declaration of Helsinki.

## Ethical approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the ethical advisory board of the Institute of Hematology and Blood Disease Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College.

## Conflicts of interest

All contributing authors declare no conflicts of interest.

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