Original Article

DOI: 10.14235/bas.galenos.2024.58815
Bezmialem Science 2024;12(4):470-8

# Evaluation of Toxicity Associated with CAR-T Cell Therapy and Nursing Interventions

## CAR-T Hücre Tedavisi ile İlişkili Toksisite Değerlendirme ve Yönetiminde Hemşirelik Girişimleri

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## ABSTRACT

**Objective:** Chimeric antigen receptor (CAR)-T cell therapy is a new immunotherapy approach that has started to been used in recent years and is developing rapidly. CAR-T cells, which are used as an immunotherapy treatment, destroy the tumor cell both directly and by increasing the release of cytokines. Our aim in this study is to evaluate inpatient CAR-T cell therapy patients in our clinic in line with cytokine release syndrome (CRS) and CAR-T related encephalopathy syndrome (CRES) management and to guide clinical practices by sharing the nursing interventions we apply in the management of CAR-T cell post-treatment toxicities.

**Methods:** Thirteen patients who received CAR-T cell therapy between 2020 and 2023 were included in this descriptive study. Following CAR-T cell infusion, the following nine-day period was retrospectively examined from the patients' files. CRS toxicity findings that might occur after CAR-T cell infusion, CRES toxicity findings, cognitive findings recorded in the CARTOX-10 neurological evaluation form, as well as treatment methods and nursing interventions applied, were evaluated and recorded.

**Results:** When we evaluated the CAR-T cell infusion toxicity findings, 38.46% of the patients had CRS stage 1, 30.79% had CRES stage 2, 15.38% had dysgraphia, 23.07% had cognitive impairment, 7.69% had somnolence and contraction in the arm and shoulder muscles were detected in 7.69%. It was determined that two patients were transferred to the intensive care unit due to both CRS and CRES toxicity findings.

**Conclusion:** The role of nurses is important in monitoring and managing toxicity after CAR-T cell infusion, which is a new

## ÖZ

**Amaç:** Kimerik antijen reseptörü (CAR)-T hücre tedavisi son yıllarda kullanılmaya başlanan ve hızlı gelişim gösteren yeni bir immünoterapi yaklaşımıdır. Bir immünoterapi tedavisi olarak kullanılan CAR-T hücreleri ise tümör hücresini hem direkt olarak hem de sitokin salınımını artırma yoluyla yok etmektedirler. Bu çalışmada amacımız, sitokin salınım sendromu (CRS) ve CAR-T ilişkili ensefelopati sendromu (CRES) yönetimi doğrultusunda, kliniğimizde yatarak CAR-T hücre tedavisi yapılan hastaları değerlendirmek ve ortaya çıkan CAR-T hücre tedavi sonrası toksisitelerinin yönetiminde uyguladığımız hemşirelik girişimlerini paylaşarak klinik uygulamalara rehberlik edebilmektir.

**Yöntemler:** Tanımlayıcı nitelikte olan bu çalışmaya 2020-2023 yılları arasında CAR-T hücre tedavisi yapılan 13 hasta dahil edildi. CAR-T hücre infüzyonunu takip eden dokuz günlük takip süreci hastaların dosyasından retrospektif olarak incelendi. CAR-T hücre infüzyonu sonrası ortaya çıkabilen CRS toksisite bulguları, CRES toksisite bulguları ve CARTOX-10 nörolojik değerlendirme formuna kayıt edilen bilişsel bulgular ile uygulanan tedavi yöntemleri değerlendirilerek kayıt edildi.

**Bulgular:** CAR-T hücre infüzyonu toksisite bulgularını değerlendirdiğimizde hastaların %38,46'sında CRS evre 1, %30,79'unda CRES evre 2, %15,38'inde disgrafi, %23,07'sinde bilişsel durumda bozulma, %7,69'unda somnolans, %7,69'unda kol ve omuz kaslarında kasılma geliştiği saptandı. İki hastanın ise hem CRS hem de CRES toksisite bulguları nedeniyle yoğun bakım ünitesine transfer edildiği belirlendi.

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**Received:** 23.02.2024
**Accepted:** 29.08.2024

**Cite this article as:** Erdal S, Küni A, Selçuk S, Can G. Evaluation of Toxicity Associated with CAR-T Cell Therapy and Nursing Interventions. Bezmialem Science. 2024;12(4):470-8

**ABSTRACT**

treatment option, in determining the patient's clinical status changes, in the care of the patient, and in expanding the knowledge base on this subject.

**Keywords:** CAR-T cell therapy, hematology, immunotherapy, nursing

**ÖZ**

**Sonuç:** Yeni bir tedavi seçeneği olan CAR-T hücre infüzyonu sonrası toksisite takibi ve yönetiminde, hastanın klinik durum değişikliklerini belirlemede, hastanın bakımında ve bu konuda bilgi tabanını genişletmede hemşirelerin rolü önemlidir.

**Anahtar Kelimeler:** CAR-T hücre tedavisi, hematoloji, immünoterapi, hemşirelik

## Introduction

Chimeric antigen receptors (CAR) are receptor proteins designed to give T-cells a new ability to target a specific antigen. CAR-T cell therapy is a new immunotherapy approach that has started to been used in recent years and is developing rapidly (1). While immunotherapies boost the immune system, some immunotherapies directly target cancer cells (2). CAR-T cells used as immunotherapy destroy the tumor cell both directly and through an increased release of cytokines (3).

In CAR-T cell therapy, the patient's T-cells are equipped with the ability to seek out and destroy cancer cells by combining the specificity of a monoclonal antibody with the cytotoxic and memory capabilities of T-cells (4). T lymphocytes are genetically engineered to express these artificial receptors to fight cancer cells; it may be called immunotherapy, gene therapy or cancer treatment (5). Immunotherapy is also known as biotherapy because the immune system can naturally recognize pathogens and cancer cells (6).

CAR-T cell therapy is used to reduce tumor burden by lymphodepletion, reduce the number of regulatory T-cells that may negatively affect CAR-T cell functions, and make the cytokine profile suitable for immunotherapy (7). The treatment is carried out by modifying T-cells with CAR under laboratory conditions, targeting them to any surface-expressed antigen and infusing the cells back into the patient after their numbers have been increased (8). The number of T-cells infused into the patient varies depending on the patient's condition, but the average number of CAR-T cells to be infused is between 1-5x$10^6$ and these cells can remain in the bloodstream for 30 to 300 days (9,10).

Today, CAR-T cell therapy is approved in trials targeting CD19 in hematologic and non-hematologic cancers and is used as a promising treatment for cancer patients whose cancer is resistant and recurrent or whose cancer does not respond to other treatments (11). CD19 is a surface glycoprotein that is expressed from the earliest stages of B-cell development until terminal differentiation of plasma cells, where its expression is lost (12). However, the efficacy of CAR-T cell therapy in non-hematologic malignancies that do not exhibit CD19 positivity has not yet been fully established (13,14). In hematologic cancers, their efficacy has been demonstrated in diseases such as acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia, multiple myeloma and non-Hodking's lymphoma (NHL) (15). In particular, the use of CAR-T cell therapy in children and young adult patients for the treatment of relapsed/refractory CD19-positive B-cell ALL and B-cell NHL is now widespread (16).

Many factors play a role in the success of CAR-T cell therapy. The success of the treatment is determined by the treatment plan, management of cytopenia, antibiotic treatment, infusion management of T-cells, toxicity management of cytokine release syndrome (CRS), toxicity management of immune effector cell-related encephalopathy syndrome (CRES), and management of other potential short-term complications that may arise, as well as appropriate nursing interventions that impact patient psychological support and long-term follow-up (17-19).

Despite the successes of CAR-T cell therapy, the toxicities associated with CRS and CRES, which can be fatal during treatment, are serious conditions that must be managed during the treatment process. The chimeric antigen receptor toxicity assessment form (CARTOX-10) and neurological assessment are crucial for early intervention in monitoring CRS symptoms and especially for early diagnosis of CRES-related toxicity (20). Therefore, a multidisciplinary approach and specific nursing education and intervention are required to successfully implement CAR-T cell therapy.

Our aim in this study is to evaluate inpatient CAR-T cell therapy patients in our clinic in line with CRS and CRES management and to guide clinical practices by sharing the nursing interventions we apply in the management of CAR-T cell post-treatment toxicities.

## Methods

This descriptive study included 13 patients who received CAR-T cell therapy at a private hospital in İstanbul between 2021 and 2023. Ethics committee approval for the study was given by the Ethics Committee of Acıbadem University (decision number: 15/20, date: 12.08.2021). The period of nine days after CAR-T cell infusion was retrospectively examined in the patient records. Personal characteristics of the patients (age, gender, marital status), clinical characteristics (disease diagnosis, stage, presence of concomitant diseases, central nervous system involvement, hematopoietic stem cell transplantation), vital signs (body temperature, pulse, blood pressure, oxygen saturation), the number of CAR-T cells administered, CRS toxicity findings that may occur after CAR-T cell infusion, CRES toxicity findings, cognitive findings recorded in the CARTOX-10 neurological assessment form, and the treatment methods and care measures used were evaluated and recorded.

During the follow-up of the patients, the body temperature was measured via the armpit using an electronic thermometer (with digital display). When the patients' body temperature was evaluated, 38 °C and above was considered a high fever (21). A digital vital signs monitor was used to measure heart rate. When evaluating patients' heart rate, a heart rate of 100/min or more was considered tachycardia (22). A digital vital signs monitor was used to assess the patients' blood pressure. It was assessed as systolic blood pressure >140 mm/Hg hypertension and diastolic blood pressure <90 mm/Hg hypotension (23). When assessing patients' oxygen saturation, an $O_2$ value of <80% in arterial blood was considered hypoxemia (24). In assessing the presence of nausea and vomiting in the patients, the Baxter Retching Faces scale was used to determine nausea, and the scores obtained were 1-4: mild, 4-7: moderate, and 7-10: severe (25). The Visual analog scale (VAS) was used to assess the presence of headache and muscle pain in the patients. The scores obtained were rated as follows: 1-4: mild, 4-7: moderate, 7-10: severe (26). The CARTOX-10 score sheet was used to determine the cognitive status of the subjects (orientation, attention span, concentration, naming, following commands, writing). In the CARTOX-10 score sheet, which contains a total of 10 points, 1 point was awarded for each question and the total score achieved by the patient was calculated and recorded. For example, a full score of 10 means that the patient is not affected by toxicity findings, while a score of 9 means that they are negatively affected by toxicity findings (27). The CRES form was used to recognize neurological toxicity findings of the cases, and the CRS form was used to recognize toxicity findings of CRS. The CRES form was used to assess and record the symptoms of cases that may develop with the toxic encephalopathic state, such as confusion, delirium symptoms, seizures, sleep disturbances, incontinence, and cerebral edema. The CRS form was used to record possible symptoms such as high fever, hypotension, tachycardia and hypoxia.

### Statistical Analysis

The IBM SPSS Statistics 18 program was used for the statistical analysis of the study data. The distribution of results was reported using descriptive statistics such as percentage, mean, median and standard deviation. Chi-square test, t-test, Mann-Whitney U test, ANOVA and Kruskal-Wallis test were used to compare the values of the numerical data. Spearman correlation analysis was performed to determine the relationship between the values of the numerical data. In the statistical analyzes, the significance level was accepted as $p<0.05$.

## Results

Most of the patients included in the study were male (76.9%) and married (53.8%). Most patients were treated with a diagnosis of NHL (61.5%), 100% had resistant disease and 92.3% had no central nervous system (CNS) involvement. Most patients had previously received hematopoietic stem cells (69.3%) and 46.2% had a Karnofsky Performance score of 80 (good) (Table 1).

Evaluation of toxicity findings after CAR T-cell infusion revealed that the cognitive impairment developed in 23.01% of patients, CRS stage 2 in 23.1%, CRES stage 2 in 15.4%, somnolence in 7.7%, dysgraphia in 15.4%, high fever in 38.5%, tachycardia in 53.8%, hypotension in 30.8%, headache in 15.4%, and myalgia in 15.4%. Only 15.4% of patients were transferred to the intensive care unit (ICU) due to both CRS and CRES toxicity findings (Table 2).

When we examined the distribution of toxicity findings after CAR T-cell infusion among the patients, it was found that the CARTOX-10 score could not be determined in case 1 due to the development of somnolence on the seventh day of treatment, it was scored as CRES stage 1, and CRS did not develop in this case. It was determined that case 2 was assessed as CRS stage 2 due to the occurrence of high fever, tachycardia, hypotension, and muscle pain with a VAS score of 6 on the fifth day of treatment. It was noted that case 5 was assessed as CRS stage 2 due to the occurrence of high fever and tachycardia on the fourth day of treatment. It was noted that case 7 was assessed as CRS stage 2 due to the development of hypotension on the first day of treatment, high fever and tachycardia on the third day and CRES stage 2 due to the development of impaired handwriting in addition to CRS on the seventh day. For case 8, it was determined that the high fever and tachycardia that occurred on the second day of treatment were not considered signs of toxicity because they were due to a viral infection. It was noted that case 9 was assessed as CRS stage 2 due to the occurrence of

**Table 1.** Personal and clinical characteristics of patients receiving CAR-T cell infusion (n=13)

| | | n | % |
|---|---|---|---|
| **Gender** | Male | 10 | 76.9 |
| | Female | 3 | 23.1 |
| **Marital status** | Single | 6 | 46.2 |
| | Married | 7 | 53.8 |
| **Diagnosis** | NHL | 8 | 61.5 |
| | ALL | 5 | 38.5 |
| **Disease stage** | Relaps | 13 | 100.0 |
| **Chronic disease** | No | 10 | 76.9 |
| | Yes | 3 | 23.1 |
| **CNS involvement** | No | 12 | 92.3 |
| | Yes | 1 | 7.7 |
| **HSCT** | No | 4 | 30.8 |
| | Allogeneik | 5 | 38.5 |
| | Autologous | 4 | 30.8 |
| **Karnofsky score** | 50 | 1 | 7.7 |
| | 60 | 2 | 15.4 |
| | 70 | 3 | 23.1 |
| | 80 | 6 | 46.2 |
| | 90 | 1 | 7.7 |

NHL: Non-Hodking lymphoma, ALL: Akut Lymphoblastic lymphoma, CNS: Central nervous system, HSCT: Hematopoietic stem cell transplantation, CAR: Chimeric antigen receptors

high fever, tachycardia and headache with a severity score of VAS 4 on the second day of treatment, and on the eighth day he was assessed as CRES stage 2 due to the development of impaired handwriting in addition to CRS. Case 13 was assessed as CRS stage 1 because oxygen saturation fell below 80% on the fifth day of treatment, and the patient who developed contractions in the shoulders and arms in addition to CRS on the ninth day of treatment was assessed as CRES stage 2. It was determined that the patient whose hypoxemia progressed on the ninth day of treatment was transferred to the general ICU to receive biphasic positive airway pressure support (Table 3).

**Table 2.** Number of patients with toxicity findings occurring after CAR-T cell infusion (n=13)

| | n | % |
|---|---|---|
| Impairment in cognitive status | 3 | 23.1 |
| CRS stage 1 | 2 | 15.4 |
| CRS stage 2 | 3 | 23.1 |
| CRES stage 1 | 2 | 15.4 |
| CRES stage 2 | 2 | 15.4 |
| Somnolence | 1 | 7.7 |
| Dysgraphia | 2 | 15.4 |
| Muscle contraction | 1 | 7.7 |
| ICU transfer | 2 | 15.4 |
| High fever | 5 | 38.5 |
| Tachycardia | 7 | 53.8 |
| Hypotension | 4 | 30.8 |
| Hypoxia | 1 | 7.7 |
| Nausea | 1 | 7.7 |
| Vomiting | 1 | 7.7 |
| Headache | 2 | 15.4 |
| Muscle pain | 2 | 15.4 |

CRS: Cytokine release syndrome, CRES: CAR-T related encephalopathy syndrome, ICU: Intensive care unit, CAR: Chimeric antigen receptors

When we evaluated the treatment response status of the cases after CAR-T cell infusion, there was a partial response in ten cases (76.9%) and a complete response in two cases (15.4%). If we look at the overall survival time, the average survival time was 210 days and the cases relapsed after an average of 86 days. The CAR-T cells were administered to the cases on two different days on average, and the average number of CAR-T cells infused was $3.60x10^6$ (Table 4).

When examining the factors that influenced toxicity findings after CAR T-cell infusion, gender, response rate, age, number of CAR T-cells administered and $SpO_2$ had no effect on toxicity findings after CAR T-cell infusion ($p>0.05$). Disease diagnosis, Karnofsky score and elevated body temperature during treatment were found to be important variables.

The CRES findings were more frequent in patients with low Karnofsky performance score (Spearman r=-0.64 p=0.02). Karnofsky score was found to have no effect on CRS toxicity findings (Spearman r=-0.09 p=0.77). Body temperature was found to increase with increasing CRS toxicity findings (Spearman r=0.73 p=0.05), but there was no increase in CRES toxicity findings (Spearman r=0.16 p=0.61). The relationship between CRS and CRES scores was found to be statistically borderline (Spearman r=-0.54 p=0.055).

**Table 3.** Toxicity findings after CAR-T cell infusion and distribution by cases (μ)

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 | Case 8 | Case 9 | Case 10 | Case 11 | Case 12 | Case 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cartox 10 score | 0 | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 9 | 10 | 10 | 10 | 8 |
| CRS | 0 | 2 | 0 | 0 | 2 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 1 |
| CRES | 1 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 2 |
| Fever °C | 37.2 | 40.5 | 37.5 | 36.9 | 38.8 | 37.5 | 40 | 38.7 | 39.04 | 36.3 | 36 | 36.6 | 36.9 |
| Pulse /mn | 102 | 126 | 96 | 88 | 117 | 110 | 140 | 120 | 106 | 68 | 86 | 76 | 96 |
| Blood pressure/ mmHg | 114/86 | 95/56 | 120/70 | 135/78 | 120/70 | 130/70 | 90/50 | 98/58 | 90/44 | 115/70 | 95/60 | 115/60 | 120/70 |
| $SpO_2$ | 91.5 | 98.7 | 96.7 | 97 | 97.1 | 95.3 | 98.4 | 96.8 | 96.3 | 99.4 | 96.6 | 98.8 | <90 |
| Nausea (BARF) | 0 | 0 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 0 | 0 | 0 |
| Vomiting (BARF) | 0 | 0 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 0 | 0 | 0 |
| Headache (VAS) | 0 | 0 | 0 | 0 | 0 | 0 | 8 | 0 | 4 | 0 | 0 | 0 | 0 |
| Stomachache (VAS) | 0 | 6 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 0 | 0 | 0 |
| Somnolans | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Dysgraphia | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 |
| Muscle contraction | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |

CRS: Cytokyn release syndrome, CRES: CAR-T related encephalopathy, BARF: Baxter retching faces scale, VAS: Visual analog scale, CAR: Chimeric antigen receptors

**Table 4.** Treatment response status of cases after CAR-T cell infusion (n=13)

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 | Case 8 | Case 9 | Case 10 | Case 11 | Case 12 | Case 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment response | PR | PR | NR | PR | PR | PR | PR | PR | PR | CR | PR | CR | PR |
| General survival days | 254 | 437 | 377 | 449 | 219 | 45 | 209 | 131 | 90 | 310 | 90 | 82 | 40 |
| Day of relaps | 63 | 365 | 15 | 59 | 171 | 45 | 209 | 115 | 45 | 0 | 30 | 0 | 1 |
| Infused CAR-T cell number x10$^6$ | 5 | 6.4 | 4.5 | 4.8 | 4 | 7.3 | 2.48 | 4.75 | 2.2 | 1.3 | 2 | 1 | 1.18 |
| Days with CAR T cells infusion | 1-3 | 1-3 | 1-3. | 1-3-6 | 1-3 | 1-3-7 | 1-3 | 1-3-7 | 1-3 | 1-3 | 1-3-7 | 1-3 | 1-3 |

PR: Partial remission, NR: No response, CR: Complete Remission, CAR: Chimeric antigen receptors

## Discussion

Cytokine release syndrome and CRES toxicity symptoms observed in patients during CAR-T cell therapy are quite common (19). As a result of appropriate supportive treatment of toxicity symptoms, patients' symptoms may resolve within weeks, but evidence-based standard approaches for the management of CAR T-cell toxicity are still unclear. Therefore, monitoring, management and treatment of toxicity symptoms in patients receiving CAR-T cell therapy are crucial (28,29).

While high fever, tachycardia and hypotension, which are CRS symptoms, were frequently observed in our data, muscle pain, headache and hypoxemia occurred less frequently. Among the CRES toxicity symptoms, impaired handwriting, somnolence and stiffness in the arms and shoulders were less frequently observed. The fact that CRS findings were more frequent and CRES findings less frequent was similar to the studies on recent developments in CAR-T cell toxicity and another study on CRS and CRES neurotoxicity findings after CAR-T cell therapy (30,31).

When we examined the toxicity classification after CAR-T cell infusion, patients who developed high fever, hypotension, tachycardia, and hypoxemia as CRS toxicity symptoms were classified as CRS stage 1, whereas patients with organ toxicity findings such as muscle pain, headache, nausea, and vomiting in addition to CRS stage 1 symptoms were classified as CRS stage 2. Our CRS and CRES grading criteria are similar to the studies on grading toxicity after CAR-T cell infusion (8,9,17,19,32).

While the normal score on the CARTOX-10 cognitive assessment, which contributes to the early detection of CRES, should be 10, patients who develop impaired handwriting (dysgraphia) have a score of 9, a mild CRES stage 1, and patients who additionally develop muscle pain, headache, vomiting and nausea have a score of 9 and have been assessed as having CRES stage 2. The patient who developed drowsiness was categorized as CRES stage 1 with only one finding. In a study that comprehensively reviewed the staging models for CRS and CRES toxicity findings emerging in the literature, it was emphasized that despite the use of the CRS, CRES and CARTOX-10 staging models, the staging models should be updated in the future due to the emergence of unique toxicity profiles of CAR-T products (33).

When we examine the correlation analysis of the data, although there is no direct study in the literature showing that CRES toxicity findings are more common in patients with low Karnofski scores, the patients' ability to perform daily living activities and their low dependency status may explain the higher incidence of neurological findings. For this reason, in studies on CAR-T cell therapy, patients with a Karnofski score of 60% and above are generally included in the treatment, supporting our findings. The increase in body temperature in patients who develop CRS can be explained by the fact that high fever is the most common toxicity symptom among CRS toxicity findings (34).

When we evaluate all of our data, as in the CAR-T cell therapy toxicity management studies in the literature, the recommendations and practices, management of findings, and interventions for the CRS and CRES toxicity symptoms experienced by our patients parallel the practices in the literature and include supportive care. However, the literature emphasizes that the evidence-based standard approaches for toxicity management are still not clear and that the monitoring, management and care of toxicity symptoms in patients receiving CAR-T cell therapy are crucial (28,29).

Toxicity profiles for our group of patients with previously treated/refractory disease who received an average of 5.38x10$^6$ CAR-T cells were acceptable and similar to those reported in the literature (8,9).

### Nursing Intervention Algorithm

In accordance with CRS and CRES management, we have created an algorithm that includes nursing measures for the assessment of CAR-T cell therapy patients in our clinic and that we use in the management of toxicities following CAR-T cell therapy. We used this algorithm as a guide for patient follow-up and toxicity management and intended it to guide our colleagues (Table 5, 6).

In nursing practice, patients and their families were initially informed about CRS and CRES toxicity findings that developed after CAR-T cell infusion, their awareness was raised, and collaboration was achieved.

In nursing practice, the vital signs of patients classified as CRS stage 1 were monitored every 30 minutes and the vital signs of patients classified as CRS stage 2 were monitored every 15 minutes. Oxygen supplementation was initiated in patients who developed hypoxemia, and fall prevention measures were

**Table 5.** Nursing algorithm for CRS toxicity findings that may occur after CAR-T cell infusion

| CRS nursing intervention algorithm | | | |
|---|---|---|---|
| **General symptoms** | **CRS stage 1** | **CRS stage 2** | **CRS stage 3 or 4** |
| **Fever**<br>**Fatigue**<br>**Loss of appetite**<br>**Nausea/vomiting**<br>**diarrhea**<br>**Head/body pains**<br>**Rashes on the skin** | Patient/relative education<br>Vital signs follow-up every 30 minutes<br>Assistance with activities of daily living<br>Antipyretic according to physician order,<br>Administration of analgesics | Patient/relative education<br>Vital sign monitoring every 15 minutes<br>Evaluation with Glasgow coma scale<br>Supportive care<br>Elevating the head of the bed if there is aspiration risk<br>Oral medications switch to intra venous<br>Administration of antipyretic, analgesic | Transfer to intensive care unit |
| **If cardiac symptoms are added to the general symptoms, the following nursing interventions should be applied in addition to the general nursing interventions in the CRS stages** | | | |
| **Heart and blood vessels** | | | |
| **Tachycardia**<br>**Arrhythmia**<br>**Hypotension**<br>**Edema** | Cardiac monitoring<br>Liquid support | IL-6 inhibitor Tocilizumab (Aktembra), IL-1 inhibitor Kineret (Anakinra), inotrope and corticosteroid administration<br>Cardiac monitoring | |
| **If neurogical symptoms are added to the general symptoms, the following nursing interventions should be applied in addition to the general nursing interventions in the CRS stages** | | | |
| **Brain and nervous system** | | | |
| **Confusion**<br>**Dizziness**<br>**Coordination and movement problems**<br>**Difficulty swallowing**<br>**Epileptic seizures**<br>**Hallucinations** | Fall precautions<br>CARTOX-10 rating 24$^{st}$ one<br>Switch treatments to Intra Venous | Fall precautions<br>CARTOX-10 rating 12$^{st}$ one<br>Switch treatments to Intra Venous | |
| **If pulmonary symptoms are added to the general symptoms, the following nursing interventions should be applied in addition to the general nursing interventions in the CRS stages** | | | |
| **Pulmonary system** | | | |
| **Cough**<br>**Decrease in lung function**<br>**Shortness of breath**<br>**Difficulty breathing** | $O_2$ support<br>Highly concentrated $O_2$ support<br>Position (semi fowler) | $O_2$ support<br>Highly concentrated $O_2$ support<br>Position (semi fowler) | |

CRS: Cytokyn release syndrome, CAR: Chimeric antigen receptors, IL: Interleukin

taken in patients who developed hypotension to avoid the risk of falling. In addition, patients who developed CRS symptoms were treated with analgesics, antipyretics, antibiotics, fluid therapy, interleukin (IL) 6 and IL-1 inhibitors as directed by the physician. Patients who developed CRS symptoms were monitored closely until symptoms improved. After the symptoms had completely disappeared, the patients were closely monitored for a further 4 hours. After vital signs were monitored at 2 hour intervals for the next 24 hours, standard treatment was started.

The cognitive status evaluation form, which was evaluated every twenty-four hours in patients with CRES stage 1 and CRES stage 2, was now performed every twelve hours. Neurological assessment was performed every 4 hours using the Glasgow Coma scale.

The patient who developed drowsiness slept for more than twenty hours and the drowsiness disappeared spontaneously without medical intervention. The patient's CRES neurological assessment, previously performed every twenty-four hours, was

**Table 6.** Nursing algorithm for CRES toxicity findings that may occur after CAR-T cell infusion

| CRES nursing intervention algorithm | | | |
|---|---|---|---|
| **General symptoms** | **CRES stage 1** | **CRES stage 2** | **CRES stage 3 or 4** |
| **Headache**<br>**Seizures**<br>**Delirium**<br>**Anxiety**<br>**Tremor**<br>**Disgraphia**<br>**Aphasia**<br>**Decreased consciousness**<br>**Coma with cerebral edema** | Fall precautions<br>Cartox 10 rating 24st one<br>Switch treatments to IV | Fall precautions<br>Cartox 10 rating 12st one<br>Switch treatments to IV[1]<br>Evaluate with Glasgow coma scale<br>Supportive care<br>Raise the head of the bed if there is aspiration risk<br>Oral medications switch to IV<br>Administration of antipyretic, analgesic<br>(IL-6 inhibitor Tocilizumab (Aktembra), IL-1 inhibitor Kineret (Anakinra), inotrope and corticosteroid administration<br>Cardiac monitoring | Transfer to intensive care unit |

CRES: CAR-T related encephalopathy syndrome, CAR: Chimeric antigen receptors, IV: Intravenous, IL: Interleukins

now performed every twelve hours and supportive treatment was scheduled. Oral treatments and nutrition were administered intravenously. To minimize the risk of aspiration, the head of the bed was kept elevated by 30 degrees. The patient was repositioned every two hours to prevent the development of pressure ulcers. Care was taken not to use drugs that could cause CNS depression. While the patient slept, he/she was monitored with a cardiac monitor to avoid missing any signs of his health condition. As the patient's basal $SpO_2$ was low at 91% due to the presence of the cervical mass, the $SpO_2$ was maintained at 96% by oxygenation.

The problem of patients who developed dysgraphia (impaired handwriting) persisted for 15 days. The dysgraphia resolved spontaneously without any special treatment or intervention. During this process, the patients received nursing support based on their needs in daily life.

### Study Limitations

This research had sample limitations because it was applied only to inpatients in a private hospital and CAR-T cell therapy, a new treatment option, was performed in very small numbers. For this reason, the results of the study cannot be generalized to all patients receiving CAR-T therapy.

## Conclusion

In our nursing experience and literature, CAR-T cell therapy presents unique challenges and responsibilities. Nurses play a critical role in the multidisciplinary care team, particularly in monitoring, managing potential complications, and providing information and support to patients and their families. The six key aspects of the nursing perspective in CAR-T cell therapy are; pre-treatment preparation, monitoring and management, toxicity management, patient and family support, ongoing information, collaboration and teamwork. In detail all of the six key aspects are listed below:

### Pre-treatment Preparation

- **Patient education:** Educate patients and their families about the CAR-T cell therapy process, potential side effects, and the importance of reporting symptoms promptly.

- **Protocol familiarity:** Nurses should be well-versed in protocols for managing common side effects, such as CRS and CRES.

### Monitoring and management

- **Vital signs and symptom monitoring:** Regularly monitor the patient's vital signs and be vigilant for early signs of CRS, CRES, and other complications. Use tools like the CARTOX-10 for cognitive assessments.

- **Laboratory testing:** Perform routine lab tests to monitor renal and liver function, blood coagulation factors, electrolytes, and C-reactive protein levels, as well as immunoglobulins and viral tests.

### Toxicity management

- **Medication administration:** Be prepared to administer medications such as tocilizumab, anakinra, and corticosteroids for managing toxicity, under the guidance of the treatment team.

- **Emergency preparedness:** Have emergency equipment and supplies, including an emergency cart, cardiac monitor, and oxygen mask, readily available.

### Patient and family support

- **Communication:** Maintain open lines of communication with the patient and their family, providing updates and reassurance as needed.

- **Emotional support:** Offer emotional and psychological support to help patients and families cope with the stress and uncertainty associated with CAR-T cell therapy.

**Ongoing information**

- **Continual learning:** Stay updated with the latest research and best practices related to CAR-T cell therapy.

- **Knowledge sharing:** Contribute to the collective knowledge by documenting and sharing experiences and outcomes, which can help refine and improve care protocols.

**Collaboration and teamwork**

- **Interdisciplinary collaboration:** Work closely with other healthcare professionals, including physicians, pharmacists, and support staff, to provide comprehensive care.

- **Clinical coordination:** Ensure seamless coordination of care, including scheduling and preparing for follow-up appointments and tests.

In conclusion, nurses are integral to the successful implementation of CAR T-cell therapy, providing essential care, monitoring, and support. Their role in recognizing and responding to complications, informing patients and families, and contributing to clinical research and education is vital for optimizing patient outcomes and advancing the field of CAR-T cell therapy.

**Ethics**

**Ethics Committee Approval:** This study was granted ethical approval by the Ethics Committee of Acıbadem University (decision no: 15/20, date: 12.08.2021).

**Informed Consent:** The patients included in this study were those who granted their consent after being informed about and invited to the study.

**Footnotes**

**Authorship Contributions**

Surgical and Medical Practices: S.E., A.K., S.S., Concept: S.E., Design: S.E., Data Collection or Processing: S.E., A.K., S.S., Analysis or Interpretation: S.E., G.C., Literature Search: S.E., A.K., S.S., Writing: S.E.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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