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Case Report

Management of neurotoxicity syndrome complicated by autologous hematopoietic stem cell transplantation bridge to chimeric antigen receptor T-Cell therapy: A case report

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ABSTRACT

Effectively addressing the challenges posed by relapsed and refractory diffuse large B-cell lymphoma, particularly when employing autologous hematopoietic stem cell transplantation and CAR-T therapy, requires a comprehensive approach to treatment and nursing. This case report emphasizes a nursing strategy focused on managing neurotoxicity post-CAR-T therapy. Nursing interventions include the identification of neurotoxicity symptoms, neuropsychiatric management, careful support during lumbar puncture and intrathecal administration, psychological assistance, and adaptive nutritional guidance. The diligent application of treatment and nursing care resulted in a remarkable recovery for the patient, as evidenced by the alleviation of central facial paralysis, improvement in swallowing function (from Grade 4 to Grade 2), and enhanced vocalization. Consistent and specialized nursing care is paramount for effectively managing complications, especially neurotoxicity, in patients undergoing CAR-T therapy. A thorough monitoring of symptoms and personalized care contribute to optimizing treatment outcomes and ensuring patient safety.

Introduction

Autologous stem cell transplantation (ASCT) boasts notable clinical advantages such as rapid hematopoietic reconstruction, swift immune function recovery, and low transplantation-related complications. It has become a standard treatment choice for patients with highly aggressive, relapsed/refractory lymphomas.[1] Chimeric antigen receptor T-cell (CAR-T) therapy has the characteristics of strong targeting and obvious effect, making it one of the most promising immunotherapy methods for hematological malignancies that have emerged in recent years.[2] As researchers delve deeper into treatments for relapsed/refractory lymphomas, the treatment plan of ASCT bridging to CAR-T has become a hotspot in the field. This approach is hypothesized to provide a window of minimal residual disease or disease stability, wherein the patient's own T cells can be genetically modified to target cancer cells more effectively. The bridging with ASCT is expected to enhance the efficacy of subsequent CAR-T therapy by reducing tumor burden and potentially improving the patient's immune response to the modified T cells. Some studies have shown that while this approach can enhance patient survival rates, the incidence of neutropenic infections is significantly higher than that for those undergoing ASCT alone. Additionally, the potential long-term complications after treatment discharge may also increase.[3] A significant adverse reaction during CAR-T therapy is the development of immune effector cell–associated neurotoxicity syndrome (ICANS), which can be life-threatening in severe cases.[4] This report examines the observation and nursing care of a patient with relapsed and refractory diffuse large B-cell lymphoma (DLBCL) who experienced delayed ICANS following ASCT bridging to CAR-T therapy. The aim is to enhance understanding of adverse reactions associated with this treatment approach and share nursing experience.

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Case presentation

The patient is a 54-year-old male. Due to an injury, a positron emission tomography computed tomography scan revealed thickening of both adrenal glands accompanied by a marked increase in glucose metabolism in November 2021. Later, a laparoscopic examination and lesion biopsy confirmed malignant B-cell lymphoma (diffuse large B-cell type, activated subtype). Starting on December 31, 2021, he underwent six rounds of chemotherapy, a regimen including Ottuzumab, Cyclophosphamide, Vindesine, Doxorubicin, and Dexamethasone (G-CHOP). An evaluation by positron emission tomography computed tomography in April 2022 showed a complete remission. On June 1, a brain magnetic resonance imaging (MRI) scan + enhanced magnetic resonance spectroscopy revealed multiple abnormal signals in areas such as the right parietal lobe and the semiovale center. Given the patient's medical history, central nervous system involvement was suspected. A lumbar puncture was performed, and the cerebrospinal fluid showed no immature cells or abnormal cells. Starting from June 20, the patient underwent chemotherapy with zebutinib and high-dose methotrexate (Z-HD-MTX) chemotherapy, and T cells were harvested on July 25 to prepare CAR-T cells. A follow-up brain MRI and lymphoma examination on July 26 showed a marked reduction in lesion size.

With a central nervous system relapse of DLBCL, under the condition of second complete remission, the patient was preconditioned with azacytidine combined with the thiotepa, busulfan, and cyclophosphamide regimen on August 19. All autologous peripheral stem cells were infused back on September 1. During the preconditioning and postinfusion phases, the patient exhibited symptoms of gastrointestinal mucositis, such as diarrhea, oral mucositis, perianal skin breaks, and hematemesis. After active symptomatic treatment, the condition improved. From September 5 to 7, the patient was infused with autologous CAR-T cells targeting CD19+ and CD22+, accounting for 10%, 30%, and 60% of the total reinfusion volume. On September 7, the patient began to experience recurrent fever accompanied by decreased pulse oximetry and blood pressure. Considering grade III cytokine release syndrome (CRS), intermittent use of low-dose steroids and upgraded antibiotics were administered. On day +11 post-ASCT, the patient achieved granulocyte reconstruction, and on day +17 post-ASCT, platelets returned without transfusion. On September 18, the patient was discharged to recuperate at home. On November 21, he suddenly experienced headaches, vomiting, facial drooping, and aphonia. Head computed tomography and MRI scans indicated possible central involvement by lymphoma. He was readmitted to the hospital. On November 28, a comprehensive lumbar puncture was performed, suspecting central nervous system relapse and potential delayed ICANS. On November 29, the patient received an intrathecal administration of cytarabine 40 mg, methotrexate 15 mg, and dexamethasone 5 mg. Systemic treatments included anti-inflammatory steroids, anti-infectives, dehydration to reduce intracranial pressure, anti-epileptics, gastric protection, and nutritional support. On December 5, cytomegalovirus (CMV)-DNA tested positive. The patient was then treated with a combination of ganciclovir, anticytomegalovirus immunoglobulin, and sodium phosphomycin for CMV infection. On December 6, the patient exhibited more severe symptoms, with a shallower left forehead wrinkle, a less pronounced nasolabial fold, and a rightward deviation of the mouth corner, suggestive of CMV encephalitis. Consequently, we continued with the antiviral treatment, including administering anti-CMV immunoglobulin (5 g *qod* intravenously) to enhance his immune function. Following this treatment, the patient's CMV-DNA test returned negative. During the period of bone marrow suppression, we initiated measures to support his hematopoiesis, such as administering granulocyte colony-stimulating factor to stimulate white blood cell production, thrombopoietin to support platelet production, and sucrokinase to promote overall hematopoiesis. On December 7, a follow-up MRI showed multiple abnormal signals, with a slight reduction in the size of the lesion on the left parietal lobe. By December 14, the patient's condition, such as drooping eyelids and diminished forehead lines, had improved, and he was discharged.

Nursing considerations

Nursing of delayed ICANS.

Identification of neurological symptoms

ICANS refers to the pathological processes and functional dysfunctions in the central nervous system after immunotherapy or as a result of the activation or response of infused T cells or endogenous immune-effector cells.[5] It is the second most common adverse effect in CAR-T therapy, and the main clinical manifestations include headaches, delirium, cognitive impairments, tremors, ataxia, speech impairments, neuroparalysis, sensory disturbances, drowsiness, and intermittent epileptic episodes.[6] Earlier, researchers believed that neurotoxicity was included within CRS. However, due to its distinct temporality and its response to interventions, neurotoxicity is now recognized as independent. Neurological symptoms might appear during the course of CRS symptoms or more often after CRS (though rarely before CRS). These manifestations vary among different patients. Unlike CRS, the pathophysiology of these neurological symptoms remains unclear.[7] In this case, the patient experienced a Grade III CRS reaction after bridging ASCT to CAR-T treatment and showed ICANS-related symptoms 74 days after treatment, highlighting the characteristics of delayed-onset ICANS. However, this patient had a history of central nervous system involvement and recurrence and displayed post-transplant immune deficiencies. Therefore, meticulous observation of the patient's neurological symptom changes, identification of ICANS-specific symptoms, and prompt correct differential diagnosis and disease control are crucial.

For this purpose, we adopted both general and specific neurological observation and assessment methods. Based on the standard neurological evaluation, an individualized list of initial symptoms was compiled according to the patient's presentation. Concurrently, every shift involved item-by-item assessments. The content covered the following: (1) the degree and frequency of headache, dizziness, eye tremors, confusion, language impairments, hallucinations, drowsiness, and convulsions; (2) using the CAR-T therapy–related neurotoxicity assessment tool (CARTOX score) developed by the MD Anderson Cancer Center in the United States[8] for specific assessment of neurological symptoms, such as correctly answering the year, month, hospital name, city name, and the name of the national leader (5 points); correctly naming three objects (3 points); speaking a complete sentence (1 point); counting backward from 100 by tens to 10 (1 point), with a total score of 10 indicating normal cognitive function. The daily neurological score of the patient was recorded regularly, handed over every shift, and shared with the doctor. The physician adjusted the medical intervention timely, based on the neurological scoring changes provided by us.

Effective management of neuropsychiatric symptoms

Upon admission, the patient displayed central facial palsy symptoms such as drooping mouth corners, drooling, eyelid ptosis, and disappearance of forehead lines. Consequently, daily assessments of the condition's progress were made, proactive communication with the rehabilitation doctors was established, and related literature was consulted. With the patient's agreement and cooperation, a facial muscle rehabilitation exercise regimen was developed, targeting five areas: the head and neck, lips, lower jaw/cheeks, and facial expressions, comprising 10 actions.[9] The specific methods included the followiong: (1) daily application of a hot towel (50–60 °C) to the affected side of the face for 15 min; (2) assisting the patient in a spiral massage of the face using the heel of the hand, moving upward from the affected corner of the mouth; (3) facial muscle rehabilitation exercises, where each action is not necessarily perfect, but the patient should attempt to move the facial muscles as

much as possible. The patient progressed from initially completing 30% of an action to completing more than 50% of three actions. Through regular exercises, the patient's self-awareness improved, his cooperation increased, his forehead lines gradually returned, and the asymmetry of the mouth corners was relieved.

Delirium was the initial psychiatric symptom manifested by the patient. After admission, the absence of family visits and the restrictive hospital environment exacerbated this condition. To manage this, we used the Intensive Care Delirium Screening Checklist (ICDSC) for the identification and grading of the patient's consciousness disorder. Strategies such as maintaining natural daylight exposure and lighting variations were implemented to assist the patient in distinguishing day from night. Antianxiety medications and sleep aids were timely administered to mitigate emotional distress. Furthermore, we prioritized enhanced communication with both the patient and their family, taking into account the patient's unique characteristics and provided focused emotional support and health education.

Dysphagia was the most troubling neurological symptom for the patient. Upon admission, the patient was drooling profusely, was unable to speak, and had communication difficulties. Based on the water-swallow test,[10] his swallowing function was rated at level 4. To control the progression of the condition swiftly, drug treatments such as bromadiolone were administered. To ensure that the patient took medications on time and in the right dosage, a nasogastric (NG) tube of suitable thickness was inserted. Simultaneously, we selected soft foods with uniform density and appropriate stickiness, which were nondeformable and easy to pass through the mouth and pharynx, and without residues, to assist the patient in practicing swallowing. Using illustrations, we explained the structure of the tongue and pharyngeal muscles and the key points of movement during swallowing, guiding the patient in reflex training, pronunciation exercises, breathing exercises, dry swallowing exercises, and functional training for the oropharyngeal, cheek, and tongue muscles to enhance the strength and coordination of the swallowing muscles.[11]

With effective cooperation and intervention, the patient's symptoms, such as eyelid ptosis and the disappearance of forehead lines, improved. His swallowing function improved to level 2, vocal conditions were better than before, and the symptoms were promptly controlled.

Nursing care for lumbar puncture and intrathecal injection

The patient's MRI indicated central involvement. After admission, several lumbar puncture tests and intrathecal drug injections were completed. The patient instinctively developed a fear of the lumbar examination after admission, with several puncture wound marks visible at the lumbar puncture site. In order to diagnose earlier, after thoroughly understanding the patient's previous puncture experiences, we comforted him and explained the purpose of the operation and the precautions in detail once again. We assisted the patient in preparing his posture and accompanied him throughout the procedure. An expert physician performed the puncture to increase the success rate, and to alleviate pain, local anesthesia was administered prior to the puncture. During the procedure, we paid attention to observe the patient's facial expression and engaged in friendly conversation to divert his attention and relieve the discomfort caused by the puncture.

After the procedure, we instructed the patient to lie flat without a pillow for 4–6 h to prevent low intracranial pressure headaches. Two hours after operation, we helped the patient turn once, transitioning from a flat supine position to a lateral position. A low pillow was placed under his head, maintaining the head's elevation at the body's sagittal-line level. The limbs were positioned for comfort or function, depending on the patient's condition. After 1 or 2 h, based on the patient's tolerance, the lying posture was adjusted to supine or left/right lateral positions, which significantly enhanced the patient's comfort and prevented occurrences of low intracranial pressure and localized pressure injuries.[12] At the same time, we assisted the patient with meals, drinking, and attending to his daily needs such as toileting.

The lumbar puncture and intrathecal injection site were covered with sterile dressings. We monitored the condition of the dressing at the puncture site during each shift to prevent infections.

Implementation of personalized psychological interventions

The patient has experienced a significant psychological toll from the onset of his illness to relapse, then transitioning to CAR-T bridging therapy, and now was manifesting with neurological symptoms. Before admission, the patient had once given up on treatment, felt mentally deflated, and was additionally burdened with financial worries. This made the patient highly sensitive and unstable mentally. After admission, due to the closed environment and lack of family presence, he exhibited severe delirium. The interplay of pathological and physiological complexities posed another significant challenge in nursing care for this patient.

To address this, we intensified our collaboration with the patient's family, understanding his character traits. Based on his interests and regular life habits, we tailored treatment and daily-care schedules. A personalized psychological care plan was drafted, which included increasing the daily bedside companionship time and engaging in topics of interest to the patient. A diverse range of health education methods were used during treatment to repeatedly emphasize the treatment process and the importance of maintaining a positive mental state. We encouraged the patient to express his discomfort in various ways and ensured they felt understood and respected, allowing him to undergo treatment in the best psychological state.[13] Before every medical procedure, we thoroughly explained the precautions and objectives. We discussed the etiology, clinical manifestations, and prognosis of delayed facial nerve palsy, explaining potential adverse reactions during treatment and proactive measures, thereby bolstering his confidence to overcome the disease.

Upon admission, the patient was in a nonverbal state. To alleviate the anxiety and tension caused by communication barriers, we used a writing board to communicate. Essentials were placed within the patient's reach, and we strived to meet his reasonable needs without upsetting him. Given the patient's difficulty in swallowing and speech, combined with facial asymmetry and slurred speech, we provided patient and meticulous guidance. We reinforced communication using nods, smiles, and thumbs-up gestures, continuously guiding him toward a positive treatment mindset. Simultaneously, we regarded the patient and his family as a unit. Daily communication was held with the family members, monitoring his visiting emotions, and helping stabilize his feelings to prevent him from conveying anxiety to the patient. Family members communicated with the patient daily via video walls and phones, ensuring emotional support. We also encouraged the patient to watch his favorite TV shows, listen to music, and relax his mind to positively cooperate with the treatment.

Dynamic implementation of nutrition support program, providing effective nutritional support

Nutritional supplementation is crucial for ensuring disease treatment and functional recovery. The patient had a compromised nutritional status due to disease catabolism and prolonged treatment. Based on the Nutritional Risk Screening 2002 (NRS2002) assessment scale, his nutritional risk score was 6 points. After admission, a combination of enteral and parenteral nutrition was used. Nutritional fluids were administered via a NG tube based on the patient's energy requirements. During NG feeds, the patient's gastric retention was evaluated, abdominal bowel sounds were auscultated, and the patient was monitored for symptoms

such as bloating, diarrhea, nausea, and vomiting, adjusting the feeding speed as necessary. To actively promote the patient's swallowing and facial muscle function recovery, dietary care was provided alongside NG feeds, with targeted management of each aspect of the patient's food intake.[14] The risk of aspiration and reflux was minimized; NG feeds were paused during eating training, the head of the bed was raised to an angle of 30°–45°, and feeding was resumed 30 min after the training, gradually increasing the dosage from slow to fast. After eating, the patient was assisted with mouth rinsing to clear residual food. The patient initially had poor tolerance to enteral nutrition, so parenteral nutritional support was provided alongside NG feeds. As the patient's neurological and mental symptoms gradually improved and his swallowing function recovered, the NG tube was removed, and they were put on a diet of liquids and semiliquids, such as rice porridge, juice, and soft noodles, in small frequent meals.[15] Sequential shifts between enteral and parenteral nutrition, coupled with swallowing function training, ensured the patient's nutritional needs were met during treatment, providing substantial support for accelerating the recovery from ICANS symptoms.

Conclusions

ASCT bridging CAR-T treatment for relapsed/refractory DLBCL is an avant-garde therapeutic approach. The effectiveness, potential complications, and response strategies require continuous research and experience accumulation. In this case, the patient underwent ASCT-bridging CAR-T treatment during secondary remission after relapse to improve the quality of life. After treatment, he exhibited central nervous system symptoms, making him a high-risk individual for delayed-onset ICANS, central nervous system infiltration, and viral encephalitis due to immunodeficiency. Hence, accurate assessment of early central nervous system symptoms, management of neuropsychiatric symptoms, and effective management of psychological and nutritional aspects are of paramount importance for controlling disease progression, enhancing survival rates, and improving quality of life. This case provides a valuable nursing experience for administering ASCT-bridging CAR-T treatment to patients with refractory lymphoma, serving as a guide for professionals in this field in the future.

Ethics statement

The patient has given his written informed consent for this case report to be published. The patient understands that his name and initial will not be published and due efforts will be made to conceal his identity.

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Declaration of competing interest

The authors declare no conflict of interest. The 7th author, Dr. Lu Lin, is a member of the editorial board of the Asia-Pacific Journal of Oncology Nursing. The article underwent the journal's standard review procedures, with peer review conducted independently of Dr. Lin and their research groups.

Declaration of Generative AI and AI-assisted technologies in the writing process

No AI tools/services were used during the preparation of this work.

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