Cell Therapy, Nursing Implications and Care

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Abstract

Over recent years cellular therapy has seen substantial progress across Europe, particularly cell-based immunotherapy/ immune effector cells (IECs), with the approval of autologous CD19 CAR-T products for patients with relapsed/refractory B-cell malignancies-diffuse large B cell lymphoma, acute lymphoblastic leukaemia (paediatric, teenage and young adult) and mantle cell lymphoma). Whilst this development has delivered benefit to patients with poor risk disease, there is potential for associated toxicities which require careful patient selection, assessment, monitoring, treatment and follow-up care. Nurses play a crucial role in supporting patients throughout this pathway. This chapter focuses on autologous cell-based immunotherapies (CAR-T) process, infusion, toxicities, management and the patient pathway, whilst also exploring non-cell-based immunotherapies, cell therapy in solid tumours and the role of clinical trials.

Keywords

Chimeric antigen receptor therapy (CAR-T) · Tumour infiltrating lymphocytes (TILS) · T cell receptor (TCR) · Immunotherapy · Immune effector cells (IECs) · Cytokine release syndrome (CRS) · Immune effector cell associated encephalopathy syndrome (ICANS) · Nursing management

7.1 What Is Cellular Therapy

The term cellular therapy is a label that can be applied to treatments that aim to introduce new, healthy cells into the recipient's body to replace diseased or missing one. The cells may be stem cells, progenitors, or mature cells, such as T lymphocytes; and these T lymphocytes may be unmanipulated, such as donor lymphocyte infusion (DLI) or sorted and/or cultured and/ or genetically manipulated, such as CAR-T cells.

Cell-based immunotherapies add to the broader field of immunotherapies, now populated with monoclonal antibodies including immune checkpoint inhibitors, immune-conjugates, and

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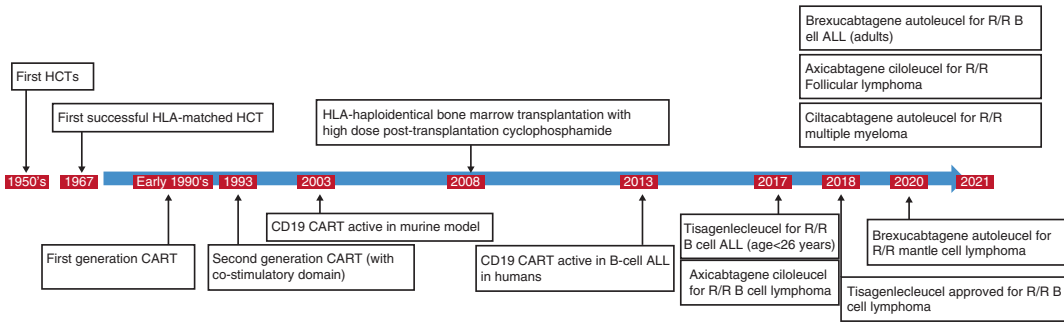

Fig. 7.1 Advances in HCT and IEC (from Jain et al. 2021)

bi- and tri-specific antibodies (Kröger et al. 2022), which are briefly described below.

Chimeric antigen receptor T cell therapy (CAR-T) represents a new class of medicinal products that are genetically engineered from T cells. This is a rapidly evolving field, as outlined in the timeline in Fig. 7.1 against the backdrop of HSCT. It is expected that many other forms of immune effector cells-based therapies will follow.

Basic Principles

The immune system has a natural ability to detect and destroy abnormal cells and in doing so prevents the development of many cancers.

However, cancer cells are sometimes able to avoid detection and destruction by the immune system by using a variety of strategies.

Cancer Cells May

- Reduce the expression of tumour antigens on their surface, making it harder for the immune system to see them
- Express proteins on their surface that inactivate or neutralise immune cells
- Encourage cells in the surrounding environment to release substances that suppress immune responses and help to promote tumour cell growth and survival

Non-cell-Based Immunotherapy

This is a type of cancer treatment that is designed to harness the body's natural defences to fight the cancer by involving or using components of the immune system.

Some cancer immunotherapies consist of antibodies that bind to, and inhibit the function of, proteins expressed by cancer cells. Other cancer immunotherapies include vaccines and T cell infusions.

Several approaches are described briefly below.

Monoclonal Antibodies

Monoclonal antibodies, also known as mAbs, are substances developed in a laboratory that seek out and bind to specifically selected proteins wherever they may be in the body. The mAbs are structured by the binding of two heavy and two light polypeptide chains by a disulphide bond.

There are four different types of monoclonal antibodies outlined (see Table 7.1) (from Bayer 2019).

Several mechanisms of action exist including impeding tumour cell survival cascades, inhibiting tumour growth by interfering with tumour angiogenesis, eluding programmed cell death, and evading immune checkpoints (Bayer 2019).

Adverse reactions to mAbs are most often experienced by treatment-naïve patients. While anaphylactic reactions are rare with mAbs, infusion reactions are relatively common and while usually mild, they manifest as chills, urticaria, dyspnoea, nausea, headache or abdominal pain (Guan et al. 2015)

Table 7.1 4 Different types of monoclonal antibody (from Bayer 2019)

Type	Key concepts	Example
Murine	Uses harvested B lymphocytes from mice that are fused with an immortal myeloma cell line lacking the hypoxanthine-guanine-phosphoribosyl transferase gene Allergic reactions are common in humans, with potential limited benefit because of a short half-life	Blinatumomab
Chimeric	Approximately 65% human derived, 35% murine derived, uses murine antigen-specific variable region, and heavy and light chains of human sp Demonstrate extended half-life in humans with reduced immunogenicity; still able to induce anti-drug antibodies	Rituximab
Humanised	Murine hypervariable regions of the light and heavy chains are fused onto a human Ab framework approximately 95% human Has decreased production of anti-drug antibodies; limitations because the process to create is difficult	Alemtuzumab
Human	Fully human monoclonal antibodies Less antigenic and better tolerated; appear to have the longest half-life in humans	Daratumumab

Immune Checkpoint Inhibitors

Immune checkpoints are pathways embedded into the immune system that keep immune responses in check. They help to limit the strength and duration of immune responses and prevent strong responses that might damage normal as well as abnormal cells. Tumours appear to hijack certain immune checkpoint pathways and their proteins and use them to suppress normal immune responses.

This therapy targets the immune checkpoint pathways so that when the immune checkpoint proteins are blocked, the 'brakes' on the immune system are released and it behaves normally once again and destroys the cancer cells.

Immune checkpoint inhibitors with antibodies that target cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and the programmed cell death protein 1 pathway (PD-1/PD-L1) have shown promising results in a variety of malignancies. Examples include Nivolumab - CTLA-4 and Pembrolizumab – PD-1, both active in Hodgkin Lymphoma.

Therapeutic Antibodies

Therapeutic antibodies are 'drug'-based antibodies produced to destroy cancer cells.

One group of therapeutic antibodies is called antibody–drug conjugate (ADC). An antibody is connected to a toxic ingredient such as a drug, toxin, or radioactive substance. When the antibody–drug conjugate (ADC) binds to the cancer cell, it is absorbed, and the toxic substance is released killing the cell.

Not all therapeutic antibodies are connected to toxic substances. Some antibodies cause cancer cells to commit suicide (apoptosis), and others can make the cancer cells more recognisable to certain immune cells (complement) and help to facilitate cell death. Examples include Inotuzumab (anti-CD22 ADC) and Gemtuzumab (anti-CD33 ADC).

Therapeutic Cancer Vaccines

Another approach to immunotherapy is the use of cancer vaccines. These vaccines are usually made from a patient's own cancer cells or from substances produced by cancer cells. It is intended that when a vaccine containing cancer-specific antigens is injected into a patient, these antigens will stimulate the immune system to attack cancer cells without causing harm to normal cells.

Cell-Based Immunotherapy or Immune Effector Cell Therapy

Cell-based immunotherapies use the cells of our immune system to eliminate cancer. Some approaches use our own selected immune cells

Table 7.2 Different types of cell-based immunotherapy (adapted from Waldman et al. 2020, Cancer Research Institute accessed Feb 2021 https://www.cancerresearch.org/en-us/immunotherapy/treatment-types/adoptive-cell-therapy)

Therapy	Description
Tumour-Infiltrating lymphocytes (TILs)	Uses naturally occurring T cells that have already infiltrated a tumour. These are isolated from biopsy, activated and expanded
Engineered T Cell receptors (TCRs)	Uses T cells from the patient and equips them with a new T cell receptor so they can target specific cancer antigens
Chimeric antigen receptor T (CAR-T) cells	Uses T cells from the patient and genetically modifies them to express a synthetic receptor known as a CAR. Here CARs bypass MHC restriction and can bind to cancer cells even if their antigens are not presented on the surface by using a target molecule e.g., CD19 on the surface of the malignant cell
Natural killer (NK) cells	Uses NK cells rather than T cells. Potential to equip NK cells with CARs is under investigation

and expand their numbers, while others involve engineering our immune cells via gene therapy to enhance their capability to fight cancer.

There are several different types of cell-based immunotherapies (see Table 7.2) (adapted from Waldman et al. 2020, Cancer Research Institute accessed Feb 2021 https://www.cancerresearch.org/en-us/immunotherapy/treatment-types/adoptive-cell-therapy).

The main focus of the chapter is primarily on CAR-T cell therapy.

7.2 Indications for Use

This is an evolving field with new indications, products and accompanying experience continuing to grow. This section offers an outline of developments to date.

In 2018 Europe saw the approval of two CD19 CAR-T products for patients with B Cell malignancies:

- Tisagenlecleucel (Kymriah®, Novartis) for relapsed/refractory paediatric B-ALL and adult large B cell lymphoma;
- Axicabtagene ciloleucel (Yescarta®, Gilead), for r/r adult large B cell lymphoma, or primary mediastinal lymphoma

European Approvals in 2021

Brexucabtagene autoleucel (Tecartus, Gilead), for r/r adult mantle cell lymphoma (Hayden et al. 2022).

- Idecabtagene Vicleucel (Abecma, BMS) for r/r multiple myeloma. It is used in adults who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and whose disease has worsened since the last treatment (European Medicines Agency 2021)

European Approvals in 2022

- Lisocabtagene Maraleucel (Breyanzi, BMS) for diffuse large B cell lymphoma (DLBCL); primary mediastinal large B cell lymphoma (PMBCL); follicular lymphoma grade 3B (European Medicines Agency 2022a)
- Ciltacabtagene Autoleucel (Carvykti, Janssen-Cilag, R/R Multiple Myeloma. It is used in adults who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and whose disease has worsened since the last treatment (European Medicines Agency 2022b)

The target for the B cell malignancies (DLBCL, mantle cell lymphoma and ALL) is CD19. Whereas for the multiple myeloma the target is the protein called B cell maturation antigen (BCMA).

CAR-T and other cell therapies are also being investigated in clinical trials for other haematological malignancies such as multiple myeloma, chronic lymphocytic leukaemia and also solid

tumours. It is expected that other forms of immune effector cells-based therapies will soon reach the market (Kröger et al. 2022).

7.3 The Role of Cellular Therapy in Solid Tumours: TCR/TILS

In the setting of solid tumour cancers immune effector cell products known as TCRs (engineered T cell receptors) and TILs (tumour infiltrating lymphocytes) are more commonly used (Li et al. 2019).

Engineered T Cell Receptors Similar to CAR-T cell therapy, TCRs are genetically engineered with a viral vector to produce an extracellular receptor which recognises molecules on the surface of cancerous cells. To do this TCR therapy utilises the cell's human leukocyte antigen (HLA), as cancers in the solid tumour setting do not have cell surface 'CDs', as seen in haematological cancers. Engineered T cell receptors will be manufactured to recognise a specific combination of cell surface HLA and neoantigens, specific to the tumour they are targeting (Zhao and Cao 2019). T cells are collected for this product in the same way as that for CAR-Ts, through the process of apheresis. Currently TCR therapy has been used in the clinical trial setting in lung, melanoma and synovial sarcomas (Clinical Trials 2022a).

Tumour Infiltrating Lymphocyte (TIL) TIL therapy utilises naturally occurring lymphocytes already found in the tumour itself and are expanded in the manufacturing laboratory to develop a product specific to that tumour and patient. As TILs come directly from the patient's tumour they are already equipped to recognise many of its surface targets (Boldt 2021).

TILs are manufactured quite differently to the products previously discussed. Initially samples of tumour tissue will be extracted and sent to the manufacturing lab. In the lab the tumour will be cut into many pieces and broken down to release the lymphocytes. These lymphocytes are then grown and expanded over time, in a medium called interleukin-2 (IL-2), with the result being an infusible product (Boldt 2021). Currently TILs have been used in the clinical trial setting in melanoma, lung and breast cancers (Clinical Trials 2022b).

Both the above products will be returned to the treatment site frozen, and after thawing are infused back to patients in the same way as CAR-T or a stem cell infusion. The toxicity profile, inclusive of cytokine release syndrome and immune cell associated neurotoxicity syndrome, is expected to be similar, and in some cases milder, to that of CAR-T cell therapy.

Currently, CAR-T cells are not used in the setting of solid tumour cancers, other than in clinical trials, due to various factors negating their success. These have been seen to include the inability to successfully navigate the complex tumour microenvironment, increased evidence of 'on target off tumour' toxicities and also, trafficking and infiltration into tumour tissue. Although many clinical trials are working to overcome these obstacles, through the blocking of cytokines and immunosuppressive cells, they are still in the early stages (Zhao and Cao 2019).

7.4 The Role of Clinical Trials/ Academic Products

The commissioning of commercial CAR-T cell products would not have been possible without the promising clinical data demonstrated in early phase trials. Many of the treatments given daily in haematology and cell therapy transplant all have a rooting in clinical trials.

Clinical trials are important for a variety of reasons. Initially their main aim is to establish if a treatment works in the way it is intended to, and what side effects it may cause. This is done

through progressing phases, starting from animal model trials to Phase 1, 2 and 3 in human clinical trials. Following this, some treatments will also be tested in a randomised control trial to establish if they work better than currently available treatments.

Aside from this, trials also play an important role in establishing the logistics of a new treatment, for example, if medicines are administered to patients in a new way, how feasible is this for both the patient and the treating team (HealthTalk.org 2019).

Currently there are over 2000 clinical trials running worldwide for the three most common products in the field of IECs (1051 for CAR-Ts, 606 for TILs and 652 for TCRs), and this isn't counting various other products under investigation, such as CAR-NK cells (Clinical Trials 2022b). TILs have the longest running history of trial activity, with their clinical significance being established as early as 1994 (Rohaan et al. 2019).

The current and future aim of IEC clinical trials is to continue to develop a solely personalised cell therapy product for a wide application of malignancies, whilst negating the known toxicity profile and obstacles of the individual products efficacy. The current landscape of clinical trials shows a range of development opportunities, which can be seen in the genetic engineering of TIL therapy to improve its functionality, the continued development of 4th Generation CARs to improve their in vivo durability, and also randomised control trials, used to establish if IECs products are more effective than currently available treatments (Rohaan et al. 2019). Additionally, research is also focused on access to "off-the-shelf" allogeneic CAR-T products, simplifying the manufacturing process and mitigating side effects, among other aims (Kröger et al. 2022).

Clinical trials have supplied a vast amount of important data, both scientifically and holistically, on the improving efficacy of IEC products. However, this data has also been able to highlight the areas in which significant progression is still required.

7.5 Patient Selection and Referral:

Patients who are considered eligible for CAR-T therapy should be assessed and discussed at local multi-disciplinary team meetings and a referral made to the CAR-T treatment centre. A National screening board may also sit to determine if the patient is suitable, review images and histology and approve that the patient is able to enter the program. Health insurance considerations may need to be satisfied in some countries. Criteria to go ahead are outlined by EBMT/EHA/JACIE (Hayden et al. 2022) and include the physical condition which should be an ECOG<2, Karnofsky or Lansky >60%. Have a life expectancy of more than 6–8 weeks, the absence of an active malignancy and not be on immunosuppressive treatment. Be free from infection, particularly viral infections.

Once accepted onto the program this triggers referral to the apheresis team with manufacturing slots booked, laboratory informed and the provisional booking of an infusion date.

7.6 Apheresis/Manufacturing/Laboratory/Chain of Identity

7.6.1 Apheresis

The production of autologous CAR-T cells requires collection of non-mobilized mature lymphocytes through apheresis of mononuclear cells (MNCs) (Tuazon et al. 2019; Mahadeo et al. 2019). Absolute lymphocyte count (ALC) thresholds to proceed with leukapheresis can vary between different CAR-T products (Mahadeo et al. 2019). The leukapheresis is similar to apheresis for extracorporeal photopheresis or for the collection of allogeneic mononuclear cells intended for post-transplant immunotherapy (donor lymphocyte infusions); no specific apheresis protocols have so far been proposed by cell processor manufacturers or by the CAR-T cell manufacturers (Yakoub-Agha et al. 2018).The apheresis procedure might be technically chal-

lenging, as patients are heavily pre-treated with multiple lines of previous therapy and often have low leukocyte and lymphocyte counts (Ceppi et al. 2018). The targeted cell dose for leukapheresis can vary depending on the specific product and manufacturing process (Mahadeo et al. 2019).

Timing for apheresis is critical in most patients and should be closely coordinated with the primary physicians and CAR-T cell team, as it should be when patients recover but prior to the need for additional chemotherapy and after an appropriate washout period. This is especially challenging for patients with relapsed disease and a high blast count. The apheresis must be coordinated with the pharmaceutical company to ensure the availability of the production slot. Some products are sent fresh to the production facility where others are sent frozen.

Paediatric apheresis procedures are considered safe but challenging as it has potentially more side effects than in adults due to the small body mass and unique physiology of children. The main problems are the extracorporeal volume of the cell separator device, poor venous access and metabolic complications due to citrate toxicity (Del Fantea et al. 2018).

- The extracorporeal volume of the cell separator device is static. In low weight children (weighing less than 20–25 kg) there is a need for blood priming of the cell separator according to institutional policy.
- Good venous access is essential for the success of the apheresis procedure. The slow inlet rates may lead to delays in establishing and maintaining a stable interface, increasing both total volumes processed and procedure time. Apheresis centres have various policies regarding the required venous access. Paediatric patients may need a leukapheresis catheter for cell collection (Mahadeo et al. 2019).
- Citrate toxicity- In children, symptoms related to citrate-induced hypocalcemia must be promptly recognized and treated immediately. Aside from the classic symptoms of hypocalcaemia in low body weight children abdominal pain and restlessness may be the first signs. Children need Ca supplement IV or PO throughout the procedure.

Pre-apheresis Consultation

- Age-appropriate preparation for the procedure
- Verification of consent/assent prior to apheresis
- Coordination of the best timing for apheresis
- Assessment by apheresis nurses of patient adequacy of peripheral veins
- In low weight children assessment of the need for blood priming- according to centre policy
- CD3 enumeration for potential assessment of duration and timing of apheresis.

7.6.2 Manufacturing/Laboratory/Pharmacy/Chain of Identity

The Memorial Sloan Kettering Cancer centre in New York describes how to build a CAR-T cell program, having eight essential tasks to success: Patient intake; CAR-T cell consultation service; collection, ordering, shipping and receiving; Bridging strategy; Cell infusion; Post infusion care day 0–30; Post infusion care day 30 onwards; Financing, regulatory and reporting requirements (Perica et al. 2018). This process may differ across countries and continents, but broadly speaking following this outline would result in a positive outcome for the patient and the institution.

Defined procedures aid the tracking and verification of the product identity from the point of harvest via any manipulation on site and storage prior to shipping for production. Once the T cells have been delivered to the commercial facility the product is manipulated, expanded, cryopreserved and delivered back to the host institution for infusion into the patient. Manufacturers work very closely with each centre to ensure that a chain of identity is maintained and accurate; this requires an extensive quality program and engagement from multiple MDT members (Perica et al. 2018).

CAR-T cell manufacture occurs following leukapheresis. The T cells once isolated are transduced with the CAR gene. The cells are treated, expanded in culture over approx. 1 month and sent back to the transplant centre for re-infusion. During the processing stages the cells are monitored for viability and are screened for bacterial contamination. The process may sometimes fail to produce enough product and the apheresis may need to be performed again. Once CAR-T cells are manufactured and genetically modified they become an advanced therapy medicinal product (ATMP), and the responsibility of the hospital pharmacy. Under current European Union regulations, CAR-T cell therapies fall under the advanced therapy medicinal products (ATMPs) framework. ATMPs represent a category of medicinal products defined in EU Regulation 1394/2007 (Kröger et al. 2022). Therefore, the process has tightly regulated coordination between the medical and nursing team, cellular therapy laboratory, manufacturing site and pharmacy.

7.7 Patient Preparation and Consent

All eligible patients should be counselled in clinic and provided with written and verbal information regarding the procedure. Opportunities for questions are important and the input from the specialist nursing team is vital. Prior to apheresis patients require a series of tests and assessments, the 'Work-up'. These will include a thorough examination of treatment history, physical assessment, imaging, bone marrow examination and routine blood tests, including virology. A COVID-19 screen which will need to be valid within 30 days of harvest. An absolute lymphocyte count of $>0.2 \times 10^9$/L is recommended to ensure an adequate collection. Nursing staff will perform a vein assessment and potentially the patient may require the insertion of a central venous catheter if peripheral access is poor. Once all pre-assessment tests have been satisfied the patient will be passed as eligible and suitable for treatment and then consented in clinic.

7.8 Bridging Therapy

From apheresis to infusion of CAR-T is approx. 4–6 weeks. This has obvious problems for patients, especially those with rapidly progressive and aggressive disease. In order that patients can receive CAR-T therapy they may require bridging therapy following apheresis and prior to the lymphodepleting conditioning treatment. Ideally bridging therapy should be commenced within 3 days of apheresis. The choice of therapy is determined by the MDT and considers the overall tumour burden and anatomical site of disease. The aim is for disease and symptom control rather than remission induction. Bridging therapy can be split into four categories; high dose chemotherapy; low dose chemotherapy; radiotherapy; novel agents. There should be a focus on minimal organ toxicity and infection (Hayden et al. 2022). These therapies may all be employed and each institution will have a preference, please refer to your own SOP. Examples of bridging therapy; in high grade lymphoma frequently used bridging therapies include radiotherapy to bulky disease and Polatuzumab with Rituximab and Bendamustine; in mantle cell lymphoma frequently used bridging therapies including a BTK inhibitor with radiotherapy to bulk; in acute leukaemia frequently used bridging therapies include Inotuzumab or a Tyrosine Kinase Inhibitors. CD19 targeted bridging therapy should, however, be avoided.

7.9 Product Receipt

Once the CAR-T products are genetically modified there will be coordination between the manufacturing facility and cellular therapy centre. The unit receiving the CAR-T cell products will need to have suitable storage containers and facilities for genetically manipulated material; depending on national legislation, a storage site may need regulatory approval as gene therapy medicinal products are also genetically modified organisms (Yakoub-Agha et al. 2018). On receipt of the cells from the manufacturing facility the laboratory will need to ensure the following: (1)

inspection of the dry shipper seal for breaches; (2) review of the temperature log throughout transportation; (3) inspection of product integrity; (4) CAR-T identity label checks, prior to completion of receipt forms (Hayden et al. 2022).

7.10 Lymphodepleting Chemotherapy (LD), Product Thawing and Infusion

7.10.1 Lymphodepleting Chemotherapy (LD)

The patient will be admitted to either an ambulatory care or ward setting in a qualified cellular therapy unit. If the centre does not have established policies and infrastructure to allow for safe outpatient-based administration, hospitalization is recommended during this period to ensure close monitoring and optimal hydration (Yakoub-Agha et al. 2018).

The patient will receive lymphodepleting chemotherapy (also known as conditioning chemotherapy) which is used prior to product infusion. The purpose of LD is to help create space in the immune system for the infused CAR-T cells to expand and proliferate. Patients in most protocols will receive lymphodepleting chemotherapy, which creates a favourable immune environment for adoptively transferred CAR-T cells, improving their in vivo expansion, subsequent persistence, and clinical activity (Hay and Turtle 2017).

The choice of LD is dependent on the CAR-T product or clinical trial protocol. Fludarabine and cyclophosphamide are the two main chemotherapy drugs used in combination. Fludarabine dosing is consistent between products and indications (25–30 mg/m^2/day ×3 days) whilst cyclophosphamide schedules differ. Other chemotherapy agents can be used depending on the product or trial, these include drugs such as Bendamustine, or Cytarabine & Etoposide. LD conditioning is usually administered on a 3-to-5 days schedule prior to the infusion of the CAR-T cells (Yakoub-Agha et al. 2018), allowing two rest days prior to product infusion.

The medical and nursing team should ensure the patient has received all appropriate investigations that are required on admission before commencing LD. Considerations prior to commencing LD are set out in the Management of Adults and Children receiving CAR-T cell therapy EBMT guidelines (Hayden et al. 2022) these cover blood parameters, disease status, cardiac function, clinical condition and receipt of CAR-T product.

7.10.2 Product Thawing and Infusion

The patient will receive a medical review and need to be deemed fit to proceed. Complications following LD can develop; The EBMT guidelines (Hayden et al. 2022) outline complications which should be ruled out prior to infusion.

There will be coordination between the laboratory, pharmacy and the clinical area, agreeing a time for infusion. Patients will have been informed and consented prior to admission. However further preparation of the patient and reconfirmation of information prior to product infusion is considered good practice. The patient will have appropriate intravenous access (a central line or peripheral cannula), written, verbal information and confirmation of consent and an explanation of the procedure ensuring any questions are answered.

Product infusion has some differences to stem cell infusion; these should be outlined in the local standard operating procedure. Centres will have a thawing device and an agreed process on where thawing takes place, and which staff are responsible and competent for this. Product thawing is performed in a pharmacy clean room, cell therapy unit or patient bedside, double wrapped in a watertight plastic bag, using thawing devices according to manufacturer's instructions and local regulations (automated thawing device, 37 ± 2 °C water bath, or dry-thaw method) (Hayden et al. 2022). The current licensed products are in bags; however clinical trials may differ with the use of vials requiring syringing. The trial protocol needs to be followed ensuring that thawing and infusion meet the requirements of the trial.

Table 7.3 Process of product infusion

Confirmation of infusion time, ideally in daytime hours
Premedication with paracetamol and antihistamines (avoiding corticosteroids)
Attach appropriate giving set to central line or cannula (standard blood transfusion 170–200 microns sets are acceptable). There should not be a leucocyte depletion filter, and fluid infusion sets are not suitable
Check if patient identifiers match with the prescription and product documentation
Remove the product and verify if it matches the patient, prescription and documentation
The product should be inspected prior to thawing to ensure bag integrity and placed in sterile outer bag
If thawing is conducted in a water bath, the spike ports that protrude out of the water must be carefully massaged to ensure that they thaw in synchrony with the rest of the product. Additionally the much smaller volumes of CAR-T cell products only require very short thawing times. (Yakoub-Agha et al. 2018)
Once the product is thawed the bag should be carefully be connected to the giving, using aseptic non-touch technique ANTT
The patient should have observations recorded before, during and after the infusion, with care taken to the recognition of reactions. Documentation of timings are recorded, this includes removal of product from the shipper, thawing start and end time, infusion start and end time
Following infusion, the vial/bag and giving set should be disposed of as a GMO biohazard in compliance with institutional policies and country-specific regulations (Hayden et al. 2022)
Confirmation of infusion time, ideally in daytime hours

Product Infusion

The process of product infusion is outlined, see Table 7.3.

7.11 Potential Complications and Nursing Implications

Patients are at risk post CAR-T infusion of complications; there are short term (up to 30 days) and long term (post 30 days). The nurse requires knowledge and understanding of when these may occur, what monitoring is required, appropriate interventions and escalation, playing an essential role in patient education and management.

Short-Term Effects

During the immediate phase following infusion there are clear documented toxicities that nurses need to be aware of. These include tumour lysis syndrome, infection, neutropenia, anaemia, thrombocytopenia, cytokine release syndrome (CRS), immune effector cell associated neurological syndrome (ICANS) and haemophagocytic lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS). It is recommended that patients are admitted to hospital during the early post-infusion period unless high-level ambulatory care and rapid readmission pathways are already well established, as in centres already providing ambulatory haematopoietic cell transplantation (Yakoub-Agha et al. 2018).

7.11.1 Tumour Lysis Syndrome (TLS)

There were some cases of TLS reported in the pivotal CAR-T trials (Maude et al. 2018; Neelapu et al. 2017; Schuster et al. 2019). For patients with significant disease burden, especially ALL with extensive marrow infiltration or Non-Hodgkin's Lymphoma with bulky adenopathy, many groups start allopurinol for TLS prophylaxis prior to chemotherapy or cell infusion (Brudno and Kochenderfer 2016). There should be careful monitoring of the patient for TLS following CAR-T infusion utilising standard protocols.

7.11.2 Infection Risk, Neutropenia, Anaemia and Thrombocytopenia

Most patients who present for CD19 CAR-T cell immunotherapy have poor immune function due to both the effects of their malignancy and prior cytotoxic treatments (Hill et al. 2017).

Patients will have received lymphodepleting chemotherapy and therefore develop neutropenia, anaemia and thrombocytopenia. Their risk

factors should be assessed and appropriate management and supportive treatment commenced during this phase. During the period of neutropenia the patient is at most risk of bacterial infections, or respiratory viral infection. Invasive fungal infections are rare; however there are increased risk factors for B-ALL with prior allo-HCT; prior fungal infection and prior long-term/high-dose steroid exposure (Gudiol et al. 2021). Prophylaxis medication will be commenced on admission as per the cellular therapy centres local policy and should include Antiviral (Aciclovir), anti-pneumocystis (Co-trimoxazole or Pentamidine). Systemic anti-fungal prophylaxis if the patient has risk factors for developing a fungal infection. Recommendations for prophylaxis and timings are set further detailed in the EBMT best practice guidelines (Hayden et al. 2022).

The nurse needs to respond promptly to the development of a fever or other signs of infection, ensuring that appropriate intravenous antibiotics are commenced. This is particularly important given the overlap in some of the cellular therapy related toxicities.

7.11.3 Cytokine Release Syndrome (CRS)

The nurse has a fundamental role in understanding, recognising and the management of CRS. CRS is the most common acute adverse event associated with CAR-T cell therapy. It's a systemic inflammatory response triggered by the release of cytokines by CAR-T cells following their activation upon tumour recognition in vivo (Lee et al. 2018). The cytokines implicated in CRS may be directly produced by the infused CAR-T cells, or other immune cells such as macrophages that might produce cytokines in response to cytokines produced by the infused CAR-T cells (Brudno and Kochenderfer 2016). There are many cytokines which can be released in CRS; one of the notable ones is interleukin 6, which has been shown to correlate to severe CRS. Other cytokines and chemokines such as IL-8, IL-10, IL-15, IFN-g, and MCP-1 have also been shown to associate with severe CRS (Neelapu 2019), additionally CRS can lead to increased C-reactive protein (CRP) and hyperferritinemia are useful laboratory markers. CRS can progress to life-threatening vasodilatory shock, capillary leak, hypoxia and end-organ dysfunction (Frey and Porter 2019).

The cases of CRS varies dependent on the product, the disease characteristics and the grading system which has been used, the reported incidence has ranged from 30–100% and for CRS grade 3 or 4 from 10–30% (Frey and Porter 2019). These variations will continue due to more clinical trials and potential future licensed products.

There have been varying grading systems used to recognise and grade CRS. The ASTCT consensus grading (2018) modified other grading systems and is widely used across cellular therapy centres; however other grading systems may be used in clinical trials for example. The ASTCT guidelines for the diagnosis of CRS are applicable to adults and children alike; however, high vigilance for diagnosis might be especially important among children and AYAs (Ragoonanan et al. 2021).

The Common Terminology Criteria for Adverse Events CTCAE. Nurses caring for cellular therapy patients will need to know how to use the grading system, and necessary interventions and escalation.

CRS is characterised by fever ≥38 °C, haemodynamic instability and hypoxemia. Severity is graded according to the ASTCT consensus criteria (below) and the differential diagnosis includes neutropenic sepsis. Empiric, broad-spectrum IV antibiotics should be commenced (Hayden et al. 2022). Local standard operating procedures will outline the management, intervention and appropriate escalation. The common symptoms of CRS are not unique to CRS. Practitioners must be cautious and exclude other causes of fever, hypotension, hemodynamic instability, and/or respiratory distress, such as an overwhelming infection (Lee et al. 2018).

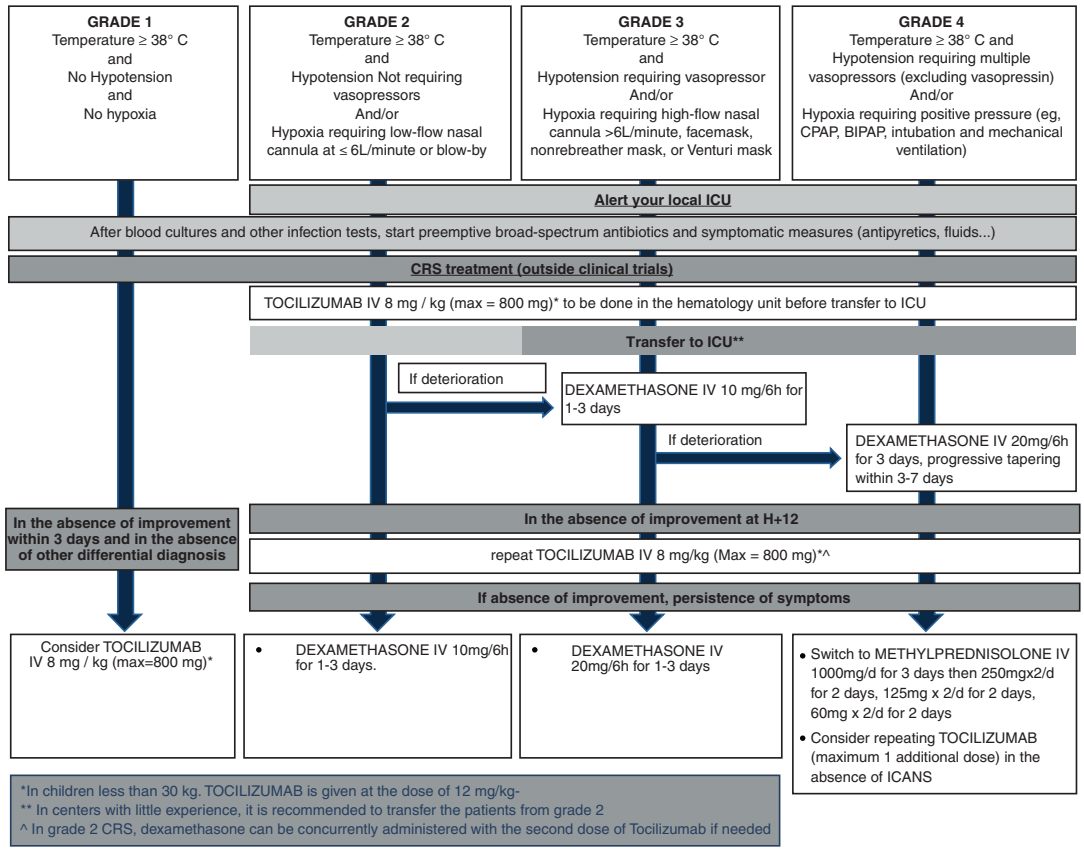

Fig. 7.2 Algorithm outlining the grading and management of cytokine release syndrome (CRS) (adapted from Hayden et al. 2022)

CRS can either be self-limited (requiring only supportive care with antipyretics and intravenous fluids) or it may require intervention with anticytokine-directed therapy such as corticosteroids or tocilizumab (Frey and Porter 2019).

Tocilizumab is licensed for first line use and is a monoclonal antibody treatment against IL6 receptor. It has been shown to be effective for most patients; those who do not respond to an initial dose often clinically improve with a second administration and/or the addition of corticosteroids. In addition to being an effective tool to manage CRS, tocilizumab is attractive because blocking the IL-6 receptor may provide toxicity management without impacting the antitumor effect of the CAR-Ts (Frey and Porter 2019).

Cellular therapy centres should have doses of Tocilizumab readily available for patients at risk of developing CRS. Corticosteroids are used for second line treatment. In early CAR-T studies, they reported reduced expansion and lacking persistence of CAR-T cells in patients who received corticosteroids (Davila et al. 2014). However, in subsequent studies early steroid use has not been associated with detrimental effects on clinical remission rates or CAR-T cell persistence (Topp et al. 2019; Liu et al. 2020). Figure 7.2 is an algorithm outlining the grading and management of cytokine release syndrome (CRS) (EBMT/EHA/JACIE best practice guidelines; Hayden et al. 2022)

Grade 1 The patient will have a temperature >38 °C, and no hypotension or hypoxia.

Nursing management will consist of blood cultures and infection management starting broad spectrum antibiotics, regular recording of vital signs, CRS grading, fluid balance monitoring.

Patient will have their bloods monitored for full blood count, urea and electrolytes, and liver function, C-reactive protein, ferritin and coagulation.

Grade 2 The patient will have a temperature >38 °C, and hypotension (not requiring vasopressors) and/or hypoxia requiring low flow nasal cannula at <6 l/min or blow by.

Nursing management will be the same as grade 1, with rationale for increasing the frequency of vital signs and fluid monitoring. Hypotension can be supported with careful fluid replacement which should be monitored cautiously given the risk of vasodilatation, capillary leak and consequent oedema in patients with progressive CRS (Schuster et al. 2019). In children hypotension should be accounting to age and the patient's individual baseline. Indications for Tocilizumab are met at grade 2. The patient can be managed on the CAR-T unit; however, there should be discussions with critical care colleagues and careful monitoring to assess for deterioration. When two doses of tocilizumab (8 mg/kg) fail to control CRS, dexamethasone should be administered (Hayden et al. 2022).

Grade 3 The patient will have a temperature >38 °C, and hypotension requiring vasopressors and/or hypoxia requiring high flow nasal cannula at >6 l/min, facemask, non-rebreather mask or venturi mask. The patient should be managed in a critical care unit, where there is support to deliver vasopressors and or high flow oxygen.

Grade 4 The patient will have a temperature >38 °C, and hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (e.g. CPAP, BiPAP intubation and mechanical ventilation). The patient will be on critical care for further intervention, due to capillary leak leading to pulmonary oedema and impairment of ventilation in addition to oxygenation. These patients tend to respond to positive pressure ventilation, which may be accomplished in several ways, up to and including intubation and mechanical ventilation (Lee et al. 2018).

If CRS does not respond to tocilizumab/corticosteroids, alternative therapeutic options include siltuximab and anakinra, but limited clinical data is available (Maus et al. 2020). Corticosteroids should be subject to rapid taper once CRS is controlled (Hayden et al. 2022).

The ASTCT consensus states that the resolution of CRS has less clarity than the onset this is because temperature often normalizes within a few hours after tocilizumab administration, whereas the other components of CRS take longer to resolve. Once such therapies are used, the patient is considered to still have CRS, even in the absence of fever, until all signs and symptoms leading to the diagnosis of CRS have resolved (Lee et al. 2018). Most patient have had resolution of CRS within 14 days.

7.11.4 Haemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome (HLH/MAS)

HLH/MAS is a life-threatening hyperinflammatory syndrome that can occur in patients with severe infections, malignancy or autoimmune diseases. It is also a rare complication of haematopoietic stem cell transplantation (HSCT), with high mortality and has additional been observed in CAR-T therapy (Sandler et al. 2020).

Patients may have symptoms which overlap meaning there is a differential diagnosis. HLH/MAS are a syndrome which can overlap with CRS. HLH is also an inflammatory syndrome which occurs from pathological T cell and macrophage activation. Hence, the CAR-T cell CRS picture overlaps the commonly known clinical scenario of HLH including elevated ferritin levels (peak ferritin levels of >10,000 ng/ml), coagulopathy, liver dysfunction, and other end organ involvement (Shalabi et al. 2021). It may occur at

the same time as CRS or after it has resolved. Patients should be monitored closely with an increase in blood test including full blood count, liver function, ferritin, CRP and coagulation. HLH/MAS can be seen in severe CRS and the patient and likely to be in intensive care if organ support is required.

A survey in EBMT centres reported an absence of standard protocols (Sandler et al. 2020). Neelapu et al. (2019) also reported there are no formal guidelines for the management of CAR-T-associated HLH/MAS which currently exist. Throughout the literature the general recommendations are for anakinra) a recombinant humanised IL-1 receptor antagonist) and corticosteroids. The EBMT best practice guidelines outline a table from expert opinion based on a literature review with timings and dosage detailed. The nurse's role is fundamental for vigilance in monitoring and prompt escalation to the medical team.

7.11.5 Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS):

Neurological toxicity is the second most reported toxicity following CAR-T treatment (Neelapu et al. 2017). The incidences vary depending on the clinical trial reporting and ranges from 20–60% of CD19 CAR-T patients (grade ≥3, 12–30%). Onset is typically 3 to 5 days after CAR-T but can occur concurrently with/shortly after CRS, and 10% of patients develop 'delayed ICANS' more than 3 weeks after infusion (Hayden et al. 2022). Patients that have early and severe CRS are at risk for ICANS, showing that the severity and early onset of CRS as measured by the extent of fever within 36 h of the infusion, hemodynamic instability, tachypnea and hypoalbuminemia reflecting loss of vascular integrity and capillary leakage (Yakoub-Agha et al. 2018). Therefore careful monitoring and vigilance of patients is essential in nursing care.

Initially neurological toxicity was named CAR-T cell-related encephalopathy syndrome (CRES); however, the ASTCT consensus grading 2018 renamed the syndrome immune effector cell-associated neurotoxicity syndrome (ICANS). This was more inclusive of other symptoms, as well as to acknowledge other cellular immunotherapies and therapeutics, such as bispecific antibodies, that may have similar neurologic side effects (Lee et al. 2018).

ICANS is less well understood and the pathophysiology is likely to be due to the combination of inflammatory cytokines increasing vascular permeability; endothelial activation leading to blood-brain barrier breakdown (Hayden et al. 2022).

ICANS can present with a subtle onset. The utilisation of the ASTCT immune effector cell encephalopathy (ICE) score is an essential tool for nurses to effectively grade ICANS. Similar to CRS grading, it consists of a grade 1–4. This grading consists of a series of nine questions and a written sentence, with 1 point for every question the patient answers correctly. The patient will be asked these usually twice a day, or more frequent if they deteriorate. An example of assessment is below (Table 7.4):

The grade will be calculated based on the patients score. The first signs for example could be difficulty in word finding in changes in their writing. The nurse has a fundamental role in ensuring clear documentation and effective communication between each shift and to the medical team.

Grade 1: This constitutes an ICE score of 7–9, meaning the patient has at between 1–3 questions wrong. The patient requires close monitoring, and investigations such as MRI, EEG and LP as clinically indicated.

Grade 2: The ICE score is 3–6. Investigations will be as grade 1. Medications should be reviewed in case there are any difficulties in swallowing or increased confusion. Corticosteroid therapy with a rapid taper is indicated for grade ≥2 ICANS (Hayden et al. 2022). There will need

Table 7.4 ICANS assessment table

ICE	Question
1	Year
2	Month
3	City
4	Hospital
5	Follow commands e.g., close your eyes
6-8	Name 3 objects (one point for each)
9	Write a standard sentence (patient can choose but use the same one each time)
10	Count backwards from 100 in 10's
Grade	Score
0	10
1	7–9
2	3–6
3	0–2 (see also other signs below)
4	Patient critical/obtunded
Grade 1	
ICE score 7–9	
Level of consciousness–AVPU A	
Grade 2	
ICE score 3–6	
Level of consciousness–AVPU V	
Grade 3	
ICE score 0–2	
Level of consciousness–AVPU P	
Seizure–any clinical seizure focal or generalized that resolves rapidly or non-convulsive seizures on EEG that resolve with intervention	
Elevated ICP/Cerebal oedema—focal/local oedema on neuroimaging	
Grade 4	
ICE score 0 (unable to perform)	

to be discussion with a neurologist and also intensive care.

Grade 3: The ICE score is 0–2. The patient should be managed in intensive care, due to altered level of consciousness and potential seizures. Patients with grade 3 ICANS have severe global aphasia and do not speak or follow commands even when wide awake and thus may be unable to answer any of the ICE questions (Lee et al. 2018). Imaging may show local/focal oedema. Steroids are indicated at grade 2 and the patient should be commenced on levetiracetam if seizures clinically or on EEG and status epilepticus with benzodiazepines (Hayden et al. 2022).

Grade 4: The ICE score is 0 on the ICE assessment due to being unarousable and unable to perform the ICE assessment. This depressed level of consciousness should be attributable to no other causes, for example, no sedating medication (Lee et al. 2018). Seizures are described as life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between. The may be deep focal motor weakness such as hemiparesis or paraparesis. There is also potential for elevated ICP/Diffuse cerebral oedema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad (Lee et al. 2018). The patient should be managed in intensive care and may require mechanical ventilation for airway management and seizures.

Whilst Tocilizumab is effective for CRS, there is limited efficacy for ICANS due to not crossing the blood brain barrier (Schubert et al. 2020) and should only be administered if the patient has concurrent CRS. Corticosteroids are the main recommended treatment, with agents such as Siltuximab and Anakinra but clinical data on their utility in ICANS is limited (Hayden et al. 2022).

ICANS is a complex and challenging toxicity and patients can deteriorate rapidly. Most patients, however, do respond to treatment and it is considered a reversible toxicity. Due to the possibility of late ICANS, patients should be advised not to drive for up to 8 weeks post product infusion, this is recommended by all the current licensed products.

The EBMT best practice guidelines (Hayden et al. 2022) illustrated in Fig. 7.3 outlines management of the patient with ICANS.

The use of ICE in children may be limited to those age ≥12 years with sufficient cognitive ability to perform it. In children age <12 years,

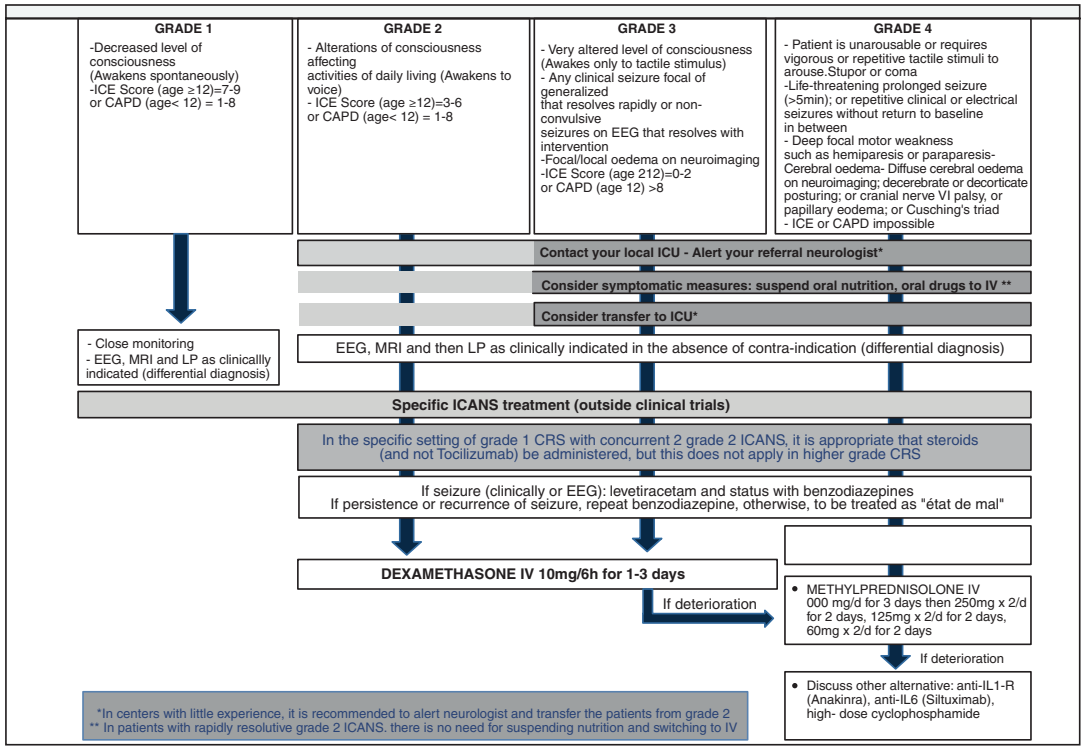

Fig. 7.3 The EBMT best practice guidelines (adapted from Hayden et al. 2022)

	always	often	sometimes	rarely	never
Eye contact with caregiver	0	1	2	3	4
Purposeful actions	0	1	2	3	4
Aware of their surroundings	0	1	2	3	4
Being restless	4	3	2	1	0
Being inconsolable	4	3	2	1	0
Being underactive	4	3	2	1	0
Slow response to interactions	4	3	2	1	0
Communicating needs and wants	4	3	2	1	0

Fig. 7.4 Cornell assessment of pediatric delirium (CAPD) to assess encephalopathy in children <12 years. Adapted from Lee et al. (2018)

the Cornell Assessment of Pediatric Delirium (CAPD) is recommended to aid in the overall grading of ICANS (Lee et al. 2018) (see Fig. 7.4).

7.12 Discharge

Discharging the patient can be arranged when they are deemed medically fit and has recovered from any toxicities. The patient and family should be appropriately prepared and supported with information to go home with.

- On discharge, they should be instructed to remain within 1 h travel of the treating hospital for at least 4 weeks following the infusion, during which time a caregiver should always be present (Yakoub-Agha et al. 2018).
- They should receive all their going home medication with written and verbal instructions on what the medications are, what they are for, when and how to take them.
- They must be advised not to drive for 8 weeks following the infusion of cellular product.

- They should be reviewed in either an ambulatory care, or day unit facility to assess their bloods and any potential toxicities, for example, ICANS. This should be within a few days of discharge. Additionally outpatient clinic appointment should be arranged. Centres should have a follow-up local policy to support this pathway.
- They should have contact numbers of the clinical team (e.g. nurse specialist) and also contact for out of hours.
- Patients must be advised to keep their Patient Advice Card with them at all times and to show it to any health care professional they encounter, especially if they are admitted to another hospital (Yakoub-Agha et al. 2018).

7.13 Follow Up Process

Follow up for CAR-T recipients can be considered in three phases

Short term	Admission to D+28
Medium term	D+28 to D+100
Long term	From D+100

The process for admission to D+28 is described in previous sections.

7.13.1 Medium-Term Follow-Up

Information provided to the patient and carers at discharge should include complications, signs to report and to who and advice on delayed TLS/CRS and ICANS. While rare, these can occur at this stage and should be managed according to standard unit protocols.

Testing can vary according to disease, product and unit, however the table, patient monitoring during medium-term follow-up (Hayden et al. 2022) offers a standardised approach in line with EBMT/EHA recommendations.

7.13.2 Infectious Complications

Prior treatment with HCT, bridging and CRS/ICANS therapy contribute to infection risks. Prolonged neutropenia beyond D+30 affects approximately a third of patients while lymphopenia can take as long as 2 years to resolve (Burstein et al. 2018) and even then, only in 86% of patients.

Most infections in the first 30 days are bacterial and respiratory viruses with viral infections predominating beyond D+30 (Strati et al. 2021).

Anti-viral and anti-pneumocystis prophylaxis are routinely recommended while anti-bacterial is only considered in cases of prolonged neutropenia.

Prolonged Cytopenias: Patients receiving cellular therapy treatments may have issues with prolonged cytopenias. Haematological recovery after lymphodepletion and CAR-T cell infusion varies across CAR-T cell products; however, haematological recovery for CD19-directed CAR-T cell therapies may be more delayed (Maus et al. 2020). Early cytopenias can be attributed to LD chemotherapy; however, the pathophysiology remains poorly understood and there may be product-intrinsic and/or disease-specific factors. Bone marrow biopsy may be useful beyond day 28 to exclude recurrent disease, hemophagocytosis and, rarely, myelodysplasia (Hayden et al. 2022)

Reports of cytopenias lasting more than 30 days have been reported in both patients receiving both axicabtagene ciloleucel and tisagenlecleucel (Neelapu et al. 2017; Schuster et al. 2019). Therefore providing ongoing potential challenges for both the patient and clinical teams. Prophylactic antimicrobials against bacterial and/or fungal infections should be considered in patients with prolonged grade 4 neutropenia. In addition, if the conditioning therapy included fludarabine, prophylaxis against herpes zoster and *Pneumocystis jiroveci* pneumonia is recommended for at least 1 year (Neelapu 2019). Cellular therapy centres will a have local policy to support post CAR-T prophylactic medications.

Patient will continue to be supported in the outpatient setting requiring regular blood tests and assessment for toxicities. GCSF can be used in prolonged cytopenias, G-CSF can be used for severe neutropenia ($<0.5 \times 10^9$/L) from day +14 onwards, following as long as CRS/ICANS has resolved (Hayden et al. 2022). Local policy

should be followed for support with anaemia and or thrombocytopenia. These cytopenias usually resolve in most patients, and they do not seem to place patients at a major risk of late-onset complications (Locke et al. 2019).

The patient should have regular follow -up support and information on risk factors of cytopenias such as infective complications. There may be shared care between the referring centre and cellular therapy centre, therefore clear lines of communication between both and the patient are required.

7.13.3 B Cell Aplasia and Hypogammaglobulinemia

B cell aplasia is ongoing in about a quarter of responders at 12 months (Frigault et al. 2019) and hypogammaglobulinemia can result in serious or recurrent/chronic infections necessitating replacement therapy. Both B cell aplasia and hypogammaglobulinemia can be seen in patient post cellular therapy and is well documented in CAR-T therapy when CD-19 is the target. The on-target off-tumour effect of CD19-directed CAR-T cells on normal B cells, B cell aplasia and hypogammaglobulinemia are expected toxicities after CD19-directed CAR-T cell treatment (Schubert et al. 2020). This means the CAR-T cells are targeting normal B cells as well as malignant ones. It occurs in all responding patients and can persist for several years (Yakoub-Agha et al. 2018).

7.13.4 Vaccinations

Vaccination guidance follows similar principles to that used following HSCT starting from 3 months after infusion with influenza and SARS-COV-19, inactivated vaccines later from 6 months and live vaccines from 1 year or later depending on status of immune reconstitution or if allo-HSCT history or immunoglobulin replacement. Vaccine responses are likely to be lower in this group; however, the consensus view is that vaccination may reduce infection rates and improve clinical outcomes (Hayden et al. 2022).

7.14 Psychological Care

Patient-reported outcomes from 40 patients 1–5 years after CAR-T therapy revealed depression, anxiety and cognitive difficulty in 19/40 with 7/19 reporting difficulty in two areas and 2/19 patient reporting difficulty in all three areas (Ruark et al. 2020). In this study, having more post-CAR-T cognitive difficulties appeared to be associated with worse global mental health and global physical health. Furthermore, that almost 50% of the patients in this cohort reported at least 1 clinically meaningful neuropsychiatric outcome, strongly indicates that a significant number of patients would likely benefit from some form of psychological support or mental health service following CAR-T therapy.

A multi-disciplinary team approach that takes a comprehensive clinical and holistic view of these patients is essential. This should include CAR-T physicians, disease-specific physicians, specialist nurses, data managers and clinical trial staff as well as psychosocial health professionals to capture the range of needs that may be experienced by these patients in the long-term follow-up period.

Complementary and essential to this is the ongoing relationship and liaising with the referring centres which is just as critical to patient care as at the initial time of referral. Distributing protocols and policies and providing continued opportunities for referral staff education can help to sustain shared care arrangements which are especially important for those patients referred from a greater distance.

7.15 Post 30–100 Days: Relapse/Non-response/Disease Progression/Therapy

Post day 28 patients should be reviewed regularly. In contrast to post autologous and allogeneic transplant patients, little is known about the long-term effects of CAR-T cell therapy beyond 1–2 years. Only a small cohort of patients has been followed for more than 2 years. The identified complications include prolonged cytopenias, hypogammaglobulinaemia and delayed B and T cell immune reconstitution with consequent atypical infection. Other longer term toxicities may

emerge with longer term follow-up of larger cohorts of patients. Exact timing of discharge will be based on the clinical condition of the patient, availability of carers, pre-existing co-morbidities, distance from home to hospital and suitability for ambulatory discharge care.

Routine blood tests will be taken at each follow-up clinic within the first 100 days and should include, FBC, biochemistry, liver profile, fibrinogen, CRP and viral pcr of CMV and EBV, and immunoglobulin levels. Assessing immune recovery with Immunophenotyping monthly for 3 months followed by 3 monthly for 1 year is recommended alongside flow cytometry for CAR-T persistence (Hayden et al. 2022). Relapse of the original disease is the largest risk, but patients may develop new problems such as a second malignancy, neurological, immune or haematological disorders. Similar to allograft patients, CAR-T recipients also require lifelong irradiated blood products and they should be given patient information and an alert card upon discharge. Patients must be made aware of the potential symptoms of delayed neurological toxicity and advised that they should refrain from driving or operating heavy or potentially dangerous machines until at least 8 weeks post infusion or until resolution of neurologic adverse reactions if longer. Patients experiencing a seizure should inform their countries driving regulators and refrain from driving until authorised to do so.

To prevent opportunistic infections, prophylaxis with anti-viral, anti-biotics and anti-fungal medication common to the HCT patient is employed for at least 12 months or until lymphocyte count is consistently >1 and CD4 >200, whichever is longer. IV immunoglobulins are used routinely in children (for IgG levels <400) and are considered in adults with recurrent infections with encapsulated organisms and hypogammaglobulinaemia <4 g/L (Hayden et al. 2022).

Once clinically stable and having responded to treatment the patient can be referred back to their local teams for follow-up. Requirements for monitoring and follow-up must be shared with the referring team. Patients will also be followed up at the treating centre (in person or via remote consultation) every 6 months (in year 1) and then annually in order to monitor progress and to collect data required for EBMT. Additional follow-up appointments at the treating centre may be required in the event of complications arising from treatment, suspected relapse or as requested by the referring team.

An example of routine monitoring post D+30, this is not exhaustive, and centres will have local SOP and policies to follow, see Table 7.5.

Table 7.5 Routine monitoring post day 30

Day	Disease/complication monitoring	CAR-T monitoring
+30	NHL—PET scan (and marrow or MRD if indicated) ALL—bone marrow, MRD, imaging as indicated Ferritin/CRP/LDH Virology (parvovirus, JC/BK, HHV 6/7/8) if positive at consent visit	Immune monitoring HIV viral load CMV/EBV PCR Immunoglobulins
+60	ALL—marrow, MRD, imaging as indicated Ferritin/CRP/LDH	Immune monitoring HIV viral load CMV/EBV PCR Immunoglobulins
+100	NHL—PET scan (and marrow or MRD if indicated ALL—marrow, MRD, imaging as indicated Vitamin B12, vitamin D, folate	Immune monitoring HIV viral load CMV/EBV PCR Immunoglobulins
Later follow-up	ALL—marrow, MRD, imaging as indicated every 3 months until 24 months post treatment NHL—PET scan at 12 months and thereafter only if concerns about disease progression	Immune monitoring HIV viral load CMV/EBV PCR Immunoglobulins All performed 3 monthly to 24 months post treatment
Further specific investigations may be undertaken as clinically indicated		

NHL Non Hodgkin lymphoma, *ALL* acute lymphoblastic leukaemia

In patients who relapse, of which this occurs in approx. 40–60%, many have undetectable CD19 disease with CAR-T still present in the peripheral blood (Perica et al. 2018). There is no standard of treatment in the post-CAR-T relapsed setting. Patients should be enrolled in clinical trials if they are available. Other options may include salvage chemotherapies or check point inhibitors. A second treatment with CAR-T may be considered if relapse occurs more than 3 months later and tissue biopsy reveals a viable target is still evident.

7.16 Long-Term Follow-Up (LTFU):

Unlike the HSCT setting, the LTFU period starts much earlier at D+100. Hypogammaglobulinemia, infection and prolonged cytopenia are common (Cordeiro et al. 2020). In the same late events paper, reporting patients who survived at least 1 year after treatment, subsequent malignancies occurred in 15% of patients including 5% with MDS.

Screening for second malignancies is recommended through the standard cancer screening programmes (cervical, breast, colorectal) with monitoring of full blood counts for late cytopenia and a low threshold for bone marrow biopsy to exclude secondary MDS/AML (Hayden et al. 2022).

7.17 JACIE

Since the approval of CAR-T in Europe and the expanding role of immune effectors cells, the standards have changed to reflect this. Chapter 1 covers JACIE and Quality Management in HSCT: Implications for Nursing.

7.18 EBMT/EHA/GoCART-Further Education

Immune effector cells have seen progression in recent years. The complexity and rapid changes in the field of cellular therapies demands wide collaboration to maintain up-to-date education on the entire pathway from collection to the manufacturer and back to the clinical unit. GoCART, a multistakeholder coalition launched by EBMT and EHA, offers a platform to provide the required diversified and topic-specific education on CAR-T cell therapies (Kröger et al. 2022). There are many resources available for nurses to learn more about this complex area. EBMT/EHA and GoCART provide excellent European educational opportunities of CAR-T and other immunotherapy treatments.

- www.ebmt.org/education/e-learning
- www.ehacampus.ehaweb.org
- https://thegocartcoalition.com/

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