
Article:
Hayden, P.J., Roddie, C., Bader, P. et al. (33 more authors) (2022) Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA). Annals of Oncology, 33 (3). pp. 259-275. ISSN 0923-7534

https://doi.org/10.1016/j.annonc.2021.12.003

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA)

P. J. Hayden[1†], C. Roddie[2,3*†], P. Bader[4], G. W. Basak[5], H. Bonig[6], C. Bonini[7], C. Chabannon[8], F. Ciceri[9], S. Corbacioglu[10], R. Ellard[11], F. Sanchez-Guijo[12], U. Jäger[13], M. Hildebrandt[14], M. Hudecek[15], M. J. Kersten[16], U. Köhl[17,18], J. Kuball[19], S. Mielke[20], M. Mohty[21], J. Murray[22], A. Nagler[23], J. Rees[3,24], C. Rioufol[25], R. Saccardi[26], J. A. Snowden[27], J. Styczynski[28], M. Subklewe[29], C. Thieblemont[30], M. Topp[15], Á. U. Ispizua[31], D. Chen[3,32], R. Vrhovac[33], J. G. Gribben[32], N. Kröger[34], H. Einsele[15] & I. Yakoub-Agha[35]

[1]Department of Haematology, Trinity College Dublin, St. James's Hospital, Dublin, Ireland; [2]UCL Cancer Institute, London; [3]University College London Hospital NHS Foundation Trust, London, UK; [4]Clinic for Children and Adolescents, University Children's Hospital, Frankfurt, Germany; [5]Medical University of Warsaw, Department of Hematology, Transplantation and Internal Medicine, Warsaw, Poland; [6]Institute for Transfusion Medicine and Immunohematology of Goethe University and German Red Cross Blood Service, Frankfurt, Germany; [7]Ospedale San Raffaele and Università Vita-Salute San Raffaele, Milan, Italy; [8]Aix-Marseille université, Inserm CBT-1409, Institut Paoli-Calmettes, centre de thérapie cellulaire, unité de transplantation et de thérapie cellulaire, département de biologie du cancer, Marseille, France; [9]Università Vita-Salute San Raffaele, IRCCS Ospedale San Raffaele, Milan, Italy; [10]Department of Pediatric Hematology, Oncology and Stem Cell Transplantation, University Franz-Josef-Strauss-Allee 11, University Hospital of Regensburg, Regensburg, Germany; [11]Royal Marsden Hospital, Fulham Rd, London, UK; [12]IBSAL-Hospital Universitario de Salamanca, CIC, Universidad de Salamanca, Salamanca, Spain; [13]Clinical Department for Hematology and Hemostaseology, Medical University of Vienna, Vienna, Austria; [14]Department of Transfusion Medicine, Cell Therapeutics and Haemostaseology, LMU University Hospital Grosshadern, Munich; [15]Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg, Würzburg, Germany; [16]Department of Hematology, Amsterdam UMC, University of Amsterdam, Cancer Center Amsterdam and LYMMCARE, Amsterdam, The Netherlands; [17]Fraunhofer Institute for Cell Therapy and Immunology (IZI) and Institute of Clinical Immunology, University of Leipzig, Leipzig; [18]Institute of Cellular Therapeutics, Hannover Medical School, Hannover, Germany; [19]Department of Hematology and Centre for Translational Immunology, University Medical Center Utrecht, Utrecht, The Netherlands; [20]Karolinska Institutet and University Hospital, Department of Laboratory Medicine/Department of Cell Therapy and Allogeneic Stem Cell Transplantation (CAST), Stockholm, Sweden; [21]Hôpital Saint-Antoine, APHP, Sorbonne Université, INSERM UMRs 938, Paris, France; [22]Christie Hospital NHS Trust, Manchester, UK; [23]The Chaim Sheba Medical Center, Tel-Hashomer, affiliated with the Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel; [24]UCL Institute of Neurology, University College of London Hospitals NHS Foundation Trust, London, UK; [25]Hospices Civils de Lyon, UCBL1, EMR 3738 CICLY, Lyon, France; [26]Cell Therapy and Transfusion Medicine Department, Careggi University Hospital, Florence, Italy; [27]Department of Haematology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK; [28]Department of Pediatric Hematology and Oncology, Collegium Medicum, Nicolaus Copernicus University Torun, Bydgoszcz, Poland; [29]German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany; [30]AP-HP, Saint-Louis Hospital, Hemato-oncology, University of Paris, Paris, France; [31]Department of Hematology, ICMHO, Hospital Clínic de Barcelona, Barcelona, Spain; [32]Centre for Haemato-Oncology, Barts Cancer Institute, Queen Mary University of London, London, UK; [33]Department of Haematology, University Hospital Centre Zagreb, Zagreb, Croatia; [34]Department of Stem Cell Transplantation, University Medical Center Hamburg, Germany; [35]CHU de Lille, Univ Lille, INSERM U1286, Infinite, Lille, France

Available online 16 December 2021

Background: Several commercial and academic autologous chimeric antigen receptor T-cell (CAR-T) products targeting CD19 have been approved in Europe for relapsed/refractory B-cell acute lymphoblastic leukemia, high-grade B-cell lymphoma and mantle cell lymphoma. Products for other diseases such as multiple myeloma and follicular lymphoma are likely to be approved by the European Medicines Agency in the near future.

Design: The European Society for Blood and Marrow Transplantation (EBMT)-Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association collaborated to draft best practice recommendations based on the current literature to support health care professionals in delivering consistent, high-quality care in this rapidly moving field.

Results: Thirty-six CAR-T experts (medical, nursing, pharmacy/laboratory) assembled to draft recommendations to cover all aspects of CAR-T patient care and supply chain management, from patient selection to long-term follow-up, post-authorisation safety surveillance and regulatory issues.

*Correspondence to: Dr Claire Roddie, UCL Cancer Institute, 72 Huntley Street, London, WC1E 6DD, UK. Tel: +44-(0)20-7679-6500
E-mail: c.roddie@ucl.ac.uk (C. Roddie).

†These authors contributed equally to this work and should both be considered as first authors.

Conclusions: We provide practical, clinically relevant recommendations on the use of these high-cost, logistically complex therapies for haematologists/oncologists, nurses and other stakeholders including pharmacists and health sector administrators involved in the delivery of CAR-T in the clinic.

Key words: CAR T-cells, B-cell acute lymphoblastic leukemia (B ALL), large B-cell lymphoma (LBCL), multiple myeloma (MM), cytokine release syndrome (CRS), immune effector cell associated neurotoxicity syndrome (ICANS)

INTRODUCTION

CD19 chimeric antigen receptor T-cell (CAR-T) therapeutics are widely used for relapsed/refractory (r/r) B-cell malignancies including acute lymphoblastic leukemia (B-ALL), large B-cell lymphoma (LBCL) and mantle cell lymphoma (MCL).[1-3] CAR-T are also under evaluation in multiple myeloma, acute myeloid leukemia and solid tumours.[4,5]

Three CAR-T products are licensed: Tisagenlecleucel (Kymriah®, Novartis [Novartis International AG, Basel, Switzerland]) for r/r paediatric B-ALL and adult LBCL; axicabtagene ciloleucel (Yescarta®, Gilead [Gilead Sciences, Foster City, CA]) for r/r adult LBCL and Tecartus (brexucabtagene autoleucel) for r/r adult MCL. In the United States, lisocabtagene maraleucel (Liso-Cel, BMS [Bristol Myers Squibb, New York, NY]) is approved for r/r LBCL and idecabtagene vicleucel (ide-cel, Abecma)[6] and JNJ-4528[7] have been approved for r/r multiple myeloma.[4] In Spain, regulators have approved academic CD19 CAR-T (ARI-0001) for r/r B-ALL.[8]

CAR-T confers a risk of potentially life-threatening immunological toxicities and comprehensive training of personnel involved in CAR-T delivery, including intensive care unit (ICU) and neurology specialists, is key.[9]

Post-marketing pharmacovigilance over 15 years post-infusion is mandated by the European Medicines Agency (EMA) to ensure ongoing evaluation of the efficacy and safety of licensed CAR-T in the real-world setting via the European Society for Blood and Marrow Transplantation (EBMT) registry. The Center for International Blood and Marrow Transplant Research (CIBMTR) fulfils a similar role. Further, the post-authorization safety studies (PASS) initiative makes an assessment of the value of CAR-T in relation to standard-of-care treatments.

METHODOLOGY

In 2021, EBMT and European Haematology Association (EHA) proposed an expanded revision of the 2019 EBMT-Joint Accreditation Committee of ISCT and EBMT (JACIE) CAR-T guidelines.[10,11] Thirty-six CAR-T experts (medical, nursing, pharmacy/laboratory) assembled to draft recommendations based on the current literature, to reflect current best practice in this rapidly moving field and to support health care professionals in delivering consistent, high-quality care. Given the absence of randomised trial evidence, a decision was made not to grade these recommendations. They therefore represent the consensus view of the authors.

The recommendations principally apply to licensed CAR-T therapies. For CAR-T clinical trials, health care teams should follow relevant trial protocols.

PATIENT ELIGIBILITY

Patient eligibility should be assessed by a CAR-T centre multi-disciplinary team including cellular therapy and haematology/oncology disease specialists. Medical history, performance status and CAR-T product should be considered with respect to tolerability (Table 1).

SCREENING LABORATORY TESTS AND IMAGING

To ensure patient eligibility and fitness, the screening tests in Table 2 should be considered. This list is not exhaustive, and, in the trial setting, trial protocols should be followed.

WORK-UP FOR LEUKAPHERESIS

Leukapheresis procurement in the European Union (EU) must comply with the Tissue and Cell Directives (2004/23/EC; 2006/17/EC; 2006/86/EC). Shipment across borders requires current viral serology and compliance with regulations in both the countries of origin and destination.[12,13]

A pre-leukapheresis checklist and suggested washout periods for pre-leukapheresis therapeutics are listed in Tables 3 and 4, respectively.

CARRYING OUT LEUKAPHERESIS

To be a CAR-T delivery site, accreditation with Foundation for the Accreditation of Cellular Therapy (FACT)-JACIE is recommended. Pharmaceutical providers and health service commissioners may have additional requirements.

CAR-T product prescription/order and non-mobilised leukapheresis[14,15] scheduling/shipping are coordinated with the CAR-T manufacturing facility (often via proprietary web-based platforms).

Most manufacturers stipulate storage of fresh leukapheresis at 2-8°C before shipping. Novartis additionally accepts locally cryopreserved starting material (within 30 months).

Accredited, validated leukapheresis testing methods should be compatible with manufacturer's requirements and authorizations. An absolute lymphocyte count (ALC) threshold of $0.2 \times 10^9/l$[15,16] is generally recommended,[17,18] but emerging evidence supports CAR-T leukapheresis in paediatric and adult patients with low ALC.[19,20]

Infectious disease markers must be tested on peripheral blood within 30 days of leukapheresis (with results available on the day of shipment). Microbial contamination is rare and the presence of leukemic blasts is acceptable to manufacturers.

Based on the observation that T cells suffer qualitative damage from chemotherapy, feasibility of pre-emptive

Table 1. Patient eligibility criteria for CAR-T

Eligibility criteria	EBMT/EHA recommendations	Comments
Age limit	No age limit	Decision should be based on physical condition rather than age, although ability to collect sufficient cells by apheresis can be a limiting factor in infants and small children. Real-world CAR-T data suggest that 5.9% of treated patients with B-ALL were <3 years old and 53.5% of treated patients with NHL were >65 years old and that CR rates were comparable in both groups to the rest of the population.
Performance status	ECOG <2, Karnofsky >60% or Lansky >60%	Although patients with ECOG >1 were treated outside clinical trials, it was associated with significantly decreased OS and PFS.
Life expectancy	>6-8 weeks	Requires careful consideration in terms of risk—benefit ratio.
High tumour burden	Risk—benefit assessment required	High tumour burden in B-ALL and LBCL is a risk factor for treatment failure and greater toxicity and careful consideration of the individual risk—benefit ratio is required.
History of malignancy	Absence of active malignancy requiring treatment other than non-melanoma skin cancer or carcinoma *in situ* (e.g. cervix, bladder, breast).	Requires careful consideration of the risk—benefit ratio.
Prior allo-HCT	Not a contraindication	Not a contraindication when off immunosuppression but in ALL may increase risk of CAR-T-associated toxicity
Prior treatments directed toward antigenic target of CAR-T, e.g. bispecific antibodies/prior CAR-T	Not a contraindication, but antigen-negative escape should be excluded at relapse post-targeted therapy and before CAR-T especially in B-cell ALL	Reduced CD19 expression may not decrease the efficacy of anti-CD19 CAR-T in B-ALL; however, prior treatment with blinatumomab may impair efficacy.[73] A second infusion of anti-CD19 CAR T cells may be feasible and can induce remission in a subset of patients.[74] In MM, re-treatment with anti-BCMA CAR-T is possible[75]
Immunosuppressive treatment	Relative contraindication	Any systemic immunosuppressive treatment may impair the efficacy of CAR-T. Intermittent topical, inhaled, or intranasal corticosteroids are permitted
Bacterial or fungal infections	Active infection is a contraindication	Infection should be treated and well controlled such that the patient should be stable before leukapheresis. In most cases, active infection requires only a temporary deferral
Viral infection	Viremia is a contraindication. Treatment should be delayed in cases of positive COVID-19 PCR.[69]	Active viral infection should prompt deferral of initiation of CAR-T therapy until the infection is controlled. Some latent infections e.g. HIV, are a contraindication to manufacturing for several (but not all) commercial and trial CAR-T products. When proceeding to CAR-T in cases of latent HBV, HCV or HIV infections, prophylactic anti-viral treatment is required. Asymptomatic patients testing positive for COVID-19 by qPCR may proceed to CAR-T manufacture, but this is done at risk and at the physician's discretion. Before proceeding, feasibility should be checked with the CAR-T manufacturer well in advance of leukapheresis
History of central nervous system (CNS) involvement	Relative contraindication	Requires careful consideration of the risk—benefit ratio. LBCL: for ZUMA-1[78] and Juliet 4, CNS involvement was an exclusion criterion, but in Transcend-world,[76] controlled SCNSL was permitted on study. MCL: on ZUMA-2,[79] CNS involvement was an exclusion. B-ALL: on ELIANA,[1] active CNS involvement was an exclusion. Real-world evidence (RWE) on CAR-T for CNS involvement in DLBCL is emerging: suggesting that it is well tolerated and has potential efficacy.[76,80-82] MM: CNS involvement was an exclusion in KarMMa study[77]

B-ALL, B-cell acute lymphoblastic leukemia; CAR-T, chimeric antigen receptor T cell; COVID-19, coronavirus disease 2019; CR, complete response; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCT, hematopoietic cell transplantation; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LBCL, large B-cell lymphoma; MM, multiple myeloma; OS, overall survival; PFS, progression-free survival; qPCR, quantitative PCR; SCNSL, secondary central nervous system lymphoma.

leukapheresis in high-risk patients is currently being explored, but with significant regulatory, infrastructural and cost implications.

BRIDGING THERAPY

'Bridging' therapy, administered in the 4-6 weeks between leukapheresis and CAR-T administration, aims to reduce disease burden and, in doing so, increase CAR-T efficacy improve intention-to-treat and reduce immunotoxicity.[21-23]

Patient-specific bridging recommendations should be made by a multi-disciplinary team following review of response to prior therapy, overall tumour burden and anatomical sites of disease. Bridging can be omitted if the CAR-T 'vein-to-vein' time is short and the disease burden is low. Otherwise, bridging is broadly split into: (i) high-dose chemotherapy, (ii) low-dose chemotherapy, (iii) radiotherapy and (iv) novel agents/approaches. Radiation therapy can be an effective bridge, but the impact on circulating lymphocytes should be considered if radiation is commenced before leukapheresis. Further studies are warranted to optimise bridging approaches.[24]

Bridging can be delivered at the CAR-T centre or at the referring centre, provided there is clear communication regarding the selected bridging strategy, management of complications and scheduling of bridging in relation to CAR-T admission, fastidiously observing recommended washout periods (Table 5).

HOSPITALISATION

Outpatient CAR-T administration can be done safely, provided clear policies, appropriate infrastructure, well-trained staff and capacity for 24/7 hospitalisation in the event of

Table 2. Screening tests before CAR-T therapy

Screening tests	EBMT/EHA recommendations	Comments
Disease confirmation	Diagnosis should be confirmed using appropriate tests	E.g. histology for NHL; immunophenotyping for ALL
Haematology	Evidence of adequate bone marrow reserve	Bone marrow reserve is difficult to evaluate in high burden r/r ALL and MM
Bilirubin	<34 µmol/l in trials; higher limit acceptable (<43 µmol/l) with Gilbert's syndrome	No trial data regarding patients outside of these parameters
AST/ALT	<4× ULN a contraindication in some trials	Attempt to identify cause of liver derangement, e.g. infection, drug toxicity including antifungals, VoD, GvHD
Creatinine clearance	>30 ml/min	Physicians should consider appropriate dose reductions in cyclophosphamide and fludarabine when creatinine clearance is <60 ml/min and potentially an increased interval between LD and CAR-T return to permit clearance of fludarabine metabolites
Hepatitis B	As per national guidelines	Serology/molecular testing
Hepatitis C	As per national guidelines	Serology/molecular testing
HIV	Leukapheresis for Kymriah™ manufacturing will not be accepted from patients with a positive test for active HBV, HCV or HIV (SPC). This is not the case for Yescarta™	Kymriah™ employs lentiviral vectors for CAR gene transfer whereas Yescarta™ uses retroviral vectors. There is a theoretical concern regarding lentiviral recombination events
COVID-19	Nasopharyngeal PCR before leukapheresis should be negative	Asymptomatic patients testing positive for COVID-19 by qPCR may proceed to CAR-T manufacture, but this is done at risk and at the physician's discretion. Before proceeding, feasibility should be checked with the CAR-T manufacturer well in advance of leukapheresis
COVID-19 vaccination	Recommended	Though data are limited, patients should be vaccinated against COVID-19, where possible, before admission for CAR-T
Cardiac function	TTE to assess cardiac function and exclude significant pericardial effusions and structural abnormalities—LVEF <40% (via 4DEF or Simpson's biplane method) is a relative contraindication ECG to exclude significant arrhythmias Cardiac biomarkers (troponin and NT-proBNP) at baseline CMR to assess extent of disease in PMBCL with cardiac involvement	Consider cardio-oncology review for further assessment of treatment suitability and scope for cardiac optimisation
CNS imaging	MRI not required except in those with a history of CNS disease or current neurological symptoms	
Lumbar puncture	Lumbar puncture not required except in those with a history of CNS disease or current neurological symptoms	
Fertility	Females of childbearing potential must have a negative serum or urine pregnancy test	Test must be repeated and confirmed negative within 8 days of the CAR-T-cell infusion

ALL, acute lymphoblastic leukemia; CAR-T, chimeric antigen receptor T cell; CMR, cardiac magnetic resonance; CNS, central nervous system; EBMT, European Society for Blood and Marrow Transplantation; ECG, electrocardiogram; EHA, European Haematology Association; GvHD, graft-versus-host disease; LD, lymphodepletion; LVEF, left ventricular ejection fraction; MM, multiple myeloma; MRI, magnetic resonance imaging; NHL, non Hodgkin lymphoma; NT-proBNP, N-terminal-pro-Brain-Natriuretic-Peptide; PMBCL, primary mediastinal B-cell lymphoma; qPCR, quantitative PCR; TTE, transthoracic echocardiogram; ULN, upper limit of normal; VoD, veno-occlusive disease.

complications are in place.[13] As such facilities are not available in most European centres, we recommend that patients remain hospitalised for at least 14 days following infusion (Table 6).

LYMPHODEPLETING CONDITIONING

Lymphodepleting conditioning (LD) acts to enhance CAR-T proliferation by modulating cytokine and immune pathways. Fludarabine and cyclophosphamide (FC) is widely used.[25] Fludarabine dosing is consistent between products and indications (25-30 mg/m^2/day × 3 days) whilst cyclophosphamide schedules differ.[26] Bendamustine (± fludarabine) has been tested in CD30 CAR-T for Hodgkin lymphoma as an alternative to FC.[27]

LD is administered following CAR-T product release, the week before CAR-T infusion with a minimum of 2 rest days. Where CAR-T infusion is delayed by ≥4 weeks, repeat LD is recommended, with consideration given to patient fitness, blood counts and prior fludarabine exposure.[10]

Potential complications from LD include pancytopenia, immunosuppression, infection, neurotoxicity, haemorrhagic cystitis, pericarditis and secondary malignancy. Renal or hepatic impairment should prompt appropriate dose modification. Considerations before LD are outlined in Table 7.

PRODUCT RECEIPT

Oversight and responsibility for this process varies internationally nationally. Country-specific guidance is beyond the scope of this document. Centres should have regulatory approval for storage of genetically modified organisms (GMOs).

Transport tracking on the manufacturer's website enables the date and time of product shipment to be known in advance. At receipt, checks should include: (i) inspection of the dry shipper seal for breaches; (ii) review of the temperature log throughout transportation; (iii) inspection of product integrity; (iv) CAR-T identity label checks, before completion of receipt forms. In the event of a non-conformance, cells are quarantined, and the hospital delegate and manufacturer should be immediately informed. Back-up bags are sometimes available as a replacement for defective products.

Out-of-specification (OOS) CAR-T may still be used (exceptions include microbial/noxious contamination), provided the release certificate lists the OOS details, written

Table 3. Checklist before leukapheresis

Before Apheresis	EBMT/EHA recommendations	Comments
Performance status	ECOG <2, Karnofsky >60%	At discretion of leukapheresis practitioner
Interval following exposure to chemotherapy	Allow sufficient time for recovery from cytotoxic chemotherapy/immunosuppression/ steroids (see Table 4 for washout periods)	Adequate marrow recovery from prior chemotherapy required
Interval following exposure to steroids	A minimum of 3 days before leukapheresis Optimally, 7 days to minimise impact on leukapheresis	Physiological replacement doses of hydrocortisone permitted, topical and inhalational steroids also permitted
Blood oxygen saturation	≥92% on room air	
Hepatitis B, hepatitis C, HIV, syphilis and HTLV	To be done within 30 days of leukapheresis. Results must be available at the time of collection and shipment. Mandatory in some countries	In some countries, only serological testing is required; nucleic acid testing (NAT) is not necessary if all serological testing is negative
COVID-19 PCR	Not a contraindication in asymptomatic patients. Contraindication in symptomatic patients	Apheresis physician and manufacturing facility should be informed if positive PCR
COVID-19 vaccination	Recommended	Though data are limited, patients should be vaccinated against COVID-19, where possible, before admission for CAR-T
Standard electrolytes and renal function	Required	Leukapheresis can be complicated by electrolyte imbalance and fluid shifts during the procedure
Haemoglobin	Haemoglobin >80 g/l recommended Hematocrit >0.24 recommended	To help establish a good interface during leukapheresis
Absolute lymphocyte count (ALC)	$\geq 0.2 \times 10^9$/l recommended	Low counts indicate insufficient haematological recovery and may predict for production failure. Higher count required in small children Of note, 0.2×10^9/l $CD3^+$ count is the minimum recommended threshold
Platelet count	$>30 \times 10^9$/l recommended	Transfuse as required, particularly for insertion of central line before leukapheresis
Full blood count (FBC)	To be repeated at the end of apheresis procedure	Apheresis can remove >30% of circulating platelets

CAR-T, chimeric antigen receptor T cell; COVID-19, coronavirus disease 2019; EBMT, European Society for Blood and Marrow Transplantation; ECOG, Eastern Cooperative Oncology Group; EHA, European Haematology Association; HIV, human immunodeficiency virus; HTLV, human T-lymphotropic virus.

agreement is provided from the manufacturer (with acceptance of responsibility by both manufacturer and physician) and the patient has given written consent.[28-30]

THAWING AND INFUSION

Before thawing and infusion, patients are medically assessed to ensure they are fit to proceed (Table 8); identity and consent is confirmed, the prescription reviewed and vital signs and intravenous (i.v.) access (central venous catheter or a newly inserted and pre-tested peripheral cannula) checked at the bedside. Pre-medication with paracetamol and antihistamine (NOT corticosteroids) is recommended. No concurrent medication should be administered during CAR-T infusion.

Product thawing is carried out 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). CAR-T is stable at room temperature for 30-90 min after thawing.[31]

CAR-T should be administered rapidly after thawing during working hours by competent medical or nursing personnel.[12,13] Vital signs should be assessed and recorded before, during and following infusion. Using aseptic non-touch technique, cells in vials are drawn up into a syringe to be administered as a slow bolus. CAR-T infusion bags are infused through a non-filtered giving set. Fluid infusion sets with sub-micrometre bacterial filters and blood transfusion sets with leukocyte depletion filters should NOT be used for CAR-T infusion.

Infusion reactions are rare but should be treated symptomatically. Corticosteroids should be avoided unless the patient becomes critically unwell.

Table 4. Washout period before leukapheresis

Type of therapy	EBMT/EHA recommendations	Comments
Allo-HCT	Patients should be off immunosuppression and GvHD free	A minimum of 1 month is recommended with the requirement to be GvHD free and off immunosuppression
DLI	At least 4 weeks	6-8 weeks may be safer to rule out any GvHD
High-dose chemotherapy	3-4 weeks	Recovery from cytopenias is required
Intrathecal therapy	1 week	
Short-acting cytotoxic/anti-proliferative drugs	3 days	Recovery from cytopenias is required
Systemic corticosteroids	Minimum of 3 days but ideally 7 days	ALC $\geq 0.2 \times 10^9$/l is recommended

Adapted from Kansagra et al.[70]
ALC, absolute lymphocyte count; allo-SCT, allogeneic stem cell transplantation; DLI, donor lymphocyte infusion; EBMT, European Society for Blood and Marrow Transplantation; EHA, European Haematology Association; GvHD, graft-versus-host disease.

Table 5. Washout period between the bridging therapy and the onset of LD conditioning (expert opinion)

Type of therapy	EBMT/EHA recommendations	Comments
High-dose chemotherapy	3-4 weeks	To avoid additional toxicity and prolonged cytopenias
Intrathecal therapy	1 week	To avoid additional toxicity
Short-acting cytotoxic/ anti-proliferative drugs	3 days	To avoid additional toxicity
Radiotherapy	1 week (2 weeks for lung)	To avoid additional toxicity
TKI	3 days	To avoid additional toxicity

EBMT, European Society for Blood and Marrow Transplantation; EHA, European Haematology Association; LD, lymphodepletion; TKI, tyrosine kinase inhibitor.

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.

SHORT-TERM COMPLICATIONS: ADMISSION TO DAY +28

Tumour lysis syndrome

Tumour lysis syndrome (TLS) can occur following LD/CAR-T, and should be prevented and managed with standard local protocols.

Infection

Active infection should be controlled before initiation of LD. Following LD, all patients will be neutropenic. A fever should prompt empiric antimicrobial therapy (based on institutional protocols) and investigation with blood and urine cultures; chest X-ray and/or high-resolution computed tomography (CT) of the chest, when indicated; respiratory viral screening including coronavirus disease 2019 (COVID-19) or more comprehensive respiratory viral screening panels; cytomegalovirus (CMV) and Epstein—Barr virus (EBV) nucleic acid testing; and lumbar puncture (LP) and brain magnetic resonance imaging (MRI) in selected cases. The specific risk profile of the patient (duration of neutropenia, prior allohematopoietic cell transplantation (HCT), previous infections and local antibiotic resistance profiles) should guide diagnostic work-up and selection of antimicrobial agents.

Cytokine release syndrome (CRS)

CRS affects 30%-100% of all patients, with grade ≥3 CRS reported in 10%-30%.[32] The incidence depends on the CAR-T product, disease characteristics and CRS grading system used. Typical onset is between 1 and 14 days post-CAR-T infusion and duration is commonly between 1 and 10 days. Rare delayed cases are reported.[9]

CRS is characterised by fever ≥38°C, haemodynamic instability and hypoxemia. Severity is graded according to the American Society for Transplantation and Cellular Therapy consensus criteria (Figure 1)[33] and the differential diagnosis includes neutropenic sepsis. Empiric, broad-spectrum i.v. antibiotics should be commenced.

CAR-T activation leads to effector cytokine release [interferon-γ (IFN-γ), tumour necrosis factor-α, interleukin (IL)-2] which can trigger pro-inflammatory cytokine release [IL-1, IL-6, IFN-γ, IL-10 and monocyte chemoattractant protein-1 (MCP1)], with increased C-reactive protein (CRP) and hyperferritinemia.[22] Risk factors for high-grade CRS include tumour burden, concurrent infection, CAR-T dose and product and LD conditioning intensity.[34]

CRS management combines symptomatic measures (antipyretics, fluids) with tocilizumab (IL-6 receptor antagonist) ± corticosteroids.[10] When two doses of tocilizumab (8 mg/kg) fail to control CRS, dexamethasone should be administered. Tocilizumab should be used earlier in older, comorbid patients. Early/prophylactic tocilizumab has been studied in CRS but there are insufficient data to date to support a formal recommendation of this approach.[83]

Clinicians should be vigilant for occult sepsis emerging post-tocilizumab. Gastrointestinal perforation has also been reported.[35] Corticosteroids should be subject to rapid taper once CRS is controlled.

If CRS does not respond to tocilizumab/corticosteroids, alternative therapeutic options include siltuximab and anakinra, but limited clinical data are available.[36] There should additionally be a high index of suspicion for underlying/concurrent infection or macrophage activation syndrome (MAS). A suggested CRS management algorithm is shown in Figure 1.

Macrophage activation syndrome

Persistent fever despite tocilizumab with organomegaly, cytopenias (± hemophagocytosis in the bone marrow), hyperferritinemia (>10 000 ng/ml), liver dysfunction, coagulopathy (hypofibrinogenemia requiring cryoprecipitate/ fibrinogen concentrate) and hypertriglyceridemia favours a CRS/MAS overlap syndrome rather than CRS.[37]

Patients should be monitored with twice-daily blood tests (full blood count, liver function, ferritin, CRP) and treated

Table 6. Recommendations on hospitalisation in the first 28 days after CAR-T infusion

Period	EBMT/EHA recommendations	Comments
Day 0 to day +14 post-infusion	Ideally 14 days' hospitalisation Consider 10 days in patients with no post-infusion complications	Outpatient follow-up is possible in centres that can provide 24/7 contact with immediate availability of specialist inpatient care. For this arrangement, patients should be located within 30-60 min of the CAR-T centre
From hospital discharge to day +28 post-infusion	Patients should be located within 60 min of the centre and the continuous presence of a caregiver who is educated to recognise the signs and symptoms of CRS and ICANS is required	Delayed CRS and ICANS can emerge following discharge from hospital

CAR-T, chimeric antigen receptor T cell; CRS, cytokine release syndrome; EBMT, European Society for Blood and Marrow Transplantation; EHA, European Haematology Association; ICANS, immune effector cell-associated neurotoxicity syndrome.

Table 7. Checklist before starting LD conditioning

Criterion	EBMT/EHA recommendations	Comments
CAR T-cell product	LD should be administered following receipt of CAR-T product on site	Exceptional situations may necessitate the administration of LD following confirmation of successful CAR-T manufacture, but before receipt
Clinical conditions	Active infections should be ruled out before starting LD	Patient should be medically fit to proceed to LD
Blood oxygen saturation	≥92% on air	
WBC	Administer LD to all patients irrespective of WBC or ALC	The SPC for Kymriah™ state that patients with low WBC ($< 1 \times 10^9$/l) 1 week before CAR-T infusion may not require LD. Some investigators use LD with caution when unexplained neutropenia pre-dates CAR-T admission. However, LD is important to CAR-T activity and proceeding with CAR-T without LD is not generally recommended
C-reactive protein, ferritin, lactate dehydrogenase, metabolic profiling, fibrinogen level	Required to rule out ongoing infection	Baseline assessments of risk for CRS and ICANS
Bilirubin	<34 μmol/l; higher limit acceptable (>43 μmol/l) with Gilbert's syndrome Trial criteria	No trial data regarding patients outside of these parameters
AST/ALT	≤4 × ULN or trial-specific criteria should be met	Attempt to identify cause of liver derangement, e.g. infection, drug toxicity including antifungals, VoD, GvHD, disease
Creatinine clearance	>30 ml/min	Physicians should consider appropriate dose reductions in cyclophosphamide and fludarabine when creatinine clearance is <60 ml/min and potentially an increased interval between LD and CAR-T return to permit clearance of fludarabine metabolites
Cardiac function	Repeat cardiac investigations only if clinically indicated, e.g. clinical signs and symptoms of heart failure, cardiotoxic bridging chemotherapy	Repeat TTE, ECG and cardiac biomarkers (troponin and NT-proBNP); cardio-oncology assessment is required
Assessment of disease burden	Baseline assessment	PET—CT/other imaging; bone marrow; LP as indicated

ALC, absolute lymphocyte count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAR-T, chimeric antigen receptor T cell; CRS, cytokine release syndrome; EBMT, European Society for Blood and Marrow Transplantation; ECG: electrocardiogram; EHA, European Haematology Association; GvHD, graft-versus-host disease; ICANS, Immune effector cell-associated neurotoxicity syndrome; LD, lymphodepleting conditioning; LP, lumbar puncture; NT-proBNP, N-terminal-pro-brain-natriuretic-peptide; PET—CT, positron emission tomography—computed tomography; TTE, transthoracic echocardiography; ULN, upper limit of normal; VoD, veno-occlusive disease; WBC, white blood cell count.

with anakinra, a recombinant humanised IL-1 receptor antagonist, in combination with corticosteroids[38] (Figure 2). In refractory CRS/MAS, chemotherapy can be used, although there is a lack of data and a high risk of ablating the CAR-T. Where there is neurological involvement, intrathecal chemotherapy can be considered.[39,40]

Immune effector cell-associated neurotoxicity syndrome (ICANS)

ICANS affects 20%-60% of CD19 CAR-T patients (grade ≥3, 12%-30%). Onset is typically 3-5 days after CAR-T but can occur concurrently with/shortly after CRS, and 10% of patients develop 'delayed ICANS' >3 weeks after the infusion.[41,42] Classical ICANS is also reported, to a lesser extent, with CD22- and B cell maturation antigen (BCMA)-targeting CAR-T.[4] In the phase 1b/2 CARTITUDE-1 study (NCT03548207) study of LCAR-B38M, a series of movement/neurocognitive disorders/nerve palsies/peripheral motor neuropathies have been observed (12% of cases), not temporally associated with CRS, that are of later onset (median day 27) and take longer to resolve (median 75 days).[43] These will require ongoing evaluation in clinical trials. ICANS is rarely reported in solid tumour CAR-T studies.

Table 8. Potential complications to be ruled out before product thawing and CAR-T infusion

Complications	EBMT/EHA recommendations	Comments
Active infection	Contraindication	CAR T-cell infusion should be delayed until the infection is controlled
Clinical evidence of fluid overload or congestive cardiac failure	Contraindication	Specific individualised risk—benefit; cardio-oncology assessment is required
Cardiac arrhythmia not controlled with medical management	Contraindication	Specific individualised risk—benefit; cardio-oncology assessment is required
Hypotension requiring vasopressor support	Contraindication: work-up is required to identify cause	CAR T-cell infusion should be delayed until the hypotension is controlled
New-onset or worsening of another non-hematologic organ dysfunction grade ≥3	Work-up is needed to identify the cause	Specific individualised risk—benefit assessment required
Significant worsening of clinical condition since the start of LD	Work-up is needed to identify the cause	Specific individualised risk—benefit assessment required
Neurological evaluation including ICE score (adult) or CAPD score (children)	To be routinely carried out	Serving as a baseline

CAPD, central auditory processing disorder; CAR-T, chimeric antigen receptor T cell; EBMT, European Society for Blood and Marrow Transplantation; EHA, European Haematology Association; ICE, Immune Effector Cell Encephalopathy; LD, lymphodepleting conditioning.

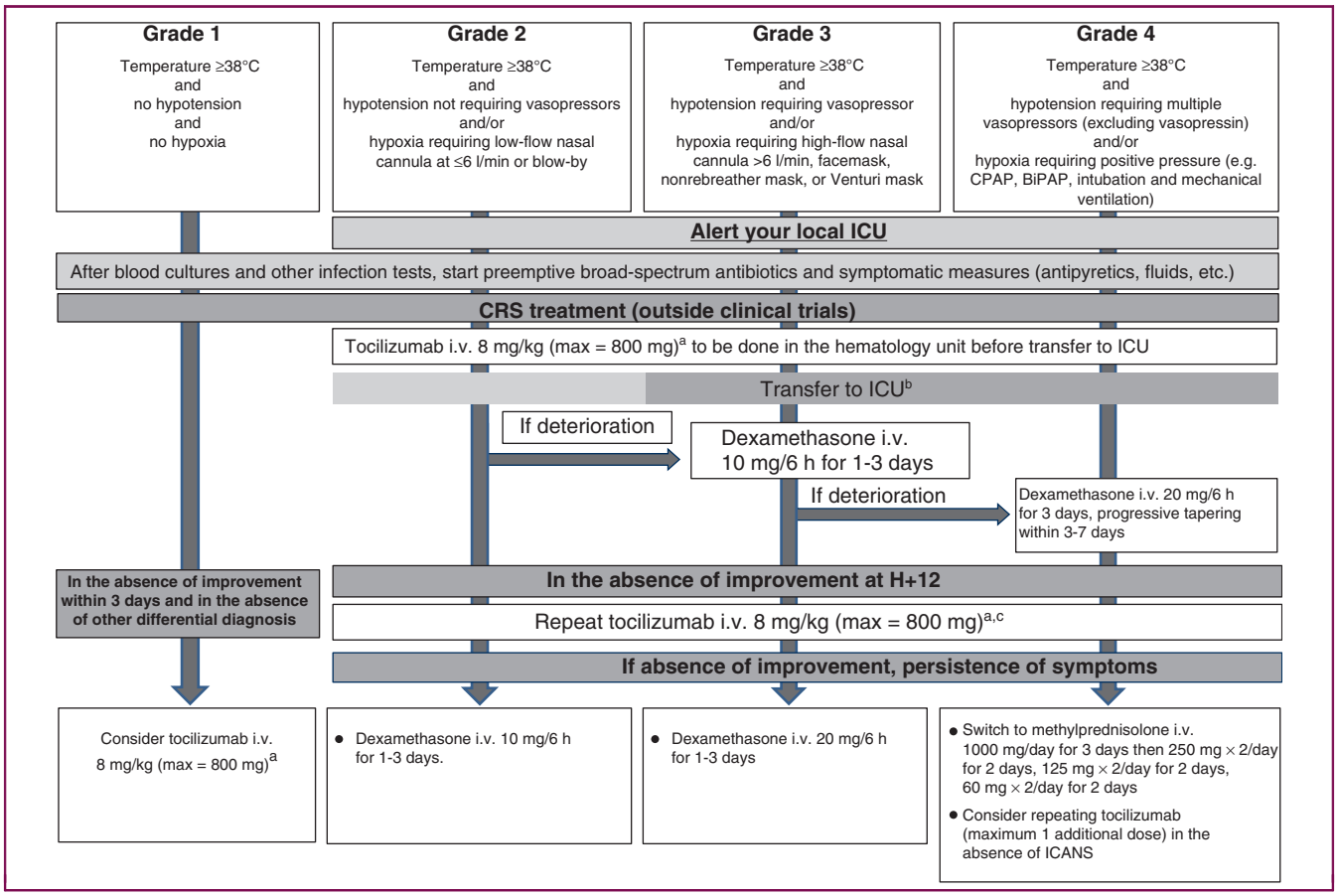

Figure 1. Algorithm outlining the grading and management of cytokine release syndrome (CRS).
BiPAP, bi-level positive airway pressure; CPAP, continuous positive airway pressure; i.v., intravenous; ICANS, immune effector cell-associated neurotoxicity syndrome; ICU, intensive care unit.
[a]In children <30 kg, tocilizumab is given at the dose of 12 mg/kg.
[b]In centres with little experience, it is recommended to transfer the patients from grade 2.
[c]In grade 2 CRS, dexamethasone can be concurrently administered with the second dose of tocilizumab if needed.

The pathophysiology of ICANS is likely to be due to a combination of inflammatory cytokines increasing vascular permeability; endothelial activation leading to blood—brain barrier breakdown; increased cerebrospinal fluid (CSF) cytokines and in some cases leads to cerebral edema.[38] Pharmacokinetics indicate that greater, earlier CAR-T expansion *in vivo* correlates with higher ICANS risk.[44] Risk factors for grade ≥3 ICANS include CD28-CAR-T products, higher CAR-T doses, high disease burden, pre-existing neurological conditions, low platelet count and early, severe CRS.[45] High fever (≥38.9°C) and haemodynamic instability within 36 h of CAR-T infusion predicts for severe ICANS with high sensitivity.[44]

Symptoms include tremor, confusion, agitation and seizures. Dysphasia, hesitant speech and deterioration in handwriting are prominent and can progress to expressive and receptive aphasia.[33] Routine anti-convulsant prophylaxis is not recommended except in high-risk cases. Fatal cerebral oedema has been described.[33] Late psychiatric presentations have also been reported.[46]

ICANS is a clinical diagnosis, but MRI of the brain and CSF examination can exclude alternative diagnoses.[10] Electroencephalogram (EEG) can be normal but can also demonstrate slowing and non-convulsive status epilepticus. Diagnostic work-up should include CT of the head, clotting screen/fibrinogen and EEG, MRI and LP in severe ICANS, or steroid-refractory cases.

Duration and frequency of ICANS monitoring should be conducted as per product label/trial protocol. The 10-point Immune Effector Cell Encephalopathy (ICE) score in adults (Table 9) and the Cornell Assessment of Paediatric Delirium (CAPD) assessment in children (Table 10) are usually carried out twice daily. ICANS grading integrates the ICE/CAPD scores into an overall assessment of neurological function (Figure 3).

Management is supportive for grade 1 ICANS. Corticosteroid therapy with a rapid taper is indicated for grade ≥2 ICANS and ICU transfer should be considered (Figure 3). Evidence suggests that steroids do not impact CAR-T efficacy, although longer courses can be associated with shorter progression-free survival.[47] Seizures are treated with levetiracetam and status epilepticus with benzodiazepines. There is no clear therapeutic role for tocilizumab in ICANS and it has been suggested that it may contribute to ICANS through increased circulating IL-6.[44] In the specific setting of grade 1 CRS with concurrent grade ≥2 ICANS, it is

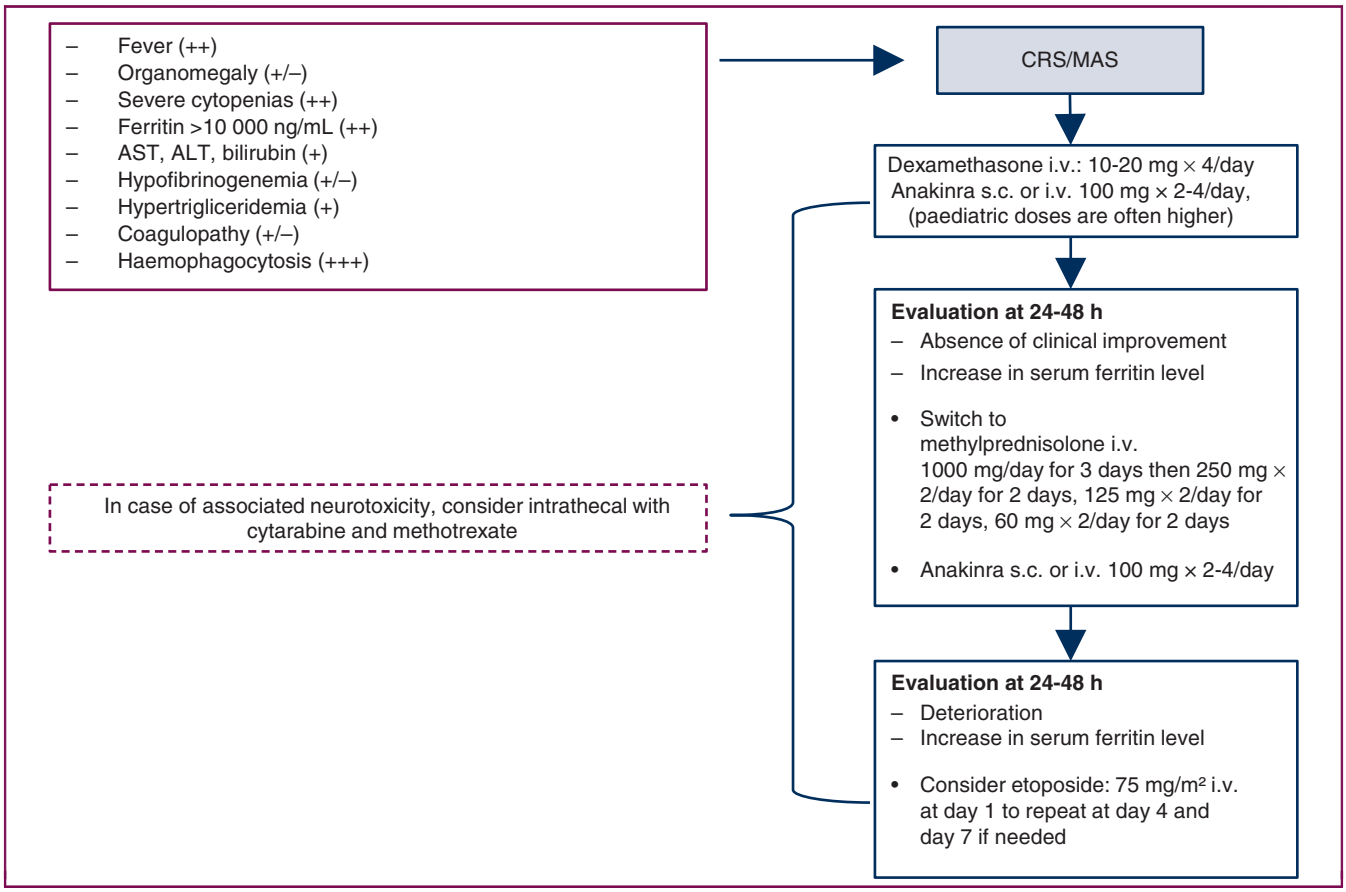

Figure 2. Management of cytokine release syndrome (CRS)/macrophage activation syndrome (MAS) (expert opinion based on literature review).[36-40]
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

appropriate that steroids (and not tocilizumab) be administered, but this does not apply in higher-grade CRS. Alternative agents include siltuximab and anakinra, but clinical data on their utility in ICANS are limited. A management algorithm for ICANS is shown in Figure 3.

Cardiovascular toxicity

Typically, 10%-20% of CAR-T patients experience cardiovascular complications.[48] Whilst hypotension requiring vasopressor support was the main cardiac complication observed in early paediatric CAR-T studies, arrhythmias, myocardial impairment, left ventricular systolic dysfunction (LVSD), decompensated cardiac failure and cardiovascular death are also reported.[49]

Table 9. ICE score for neurological toxicity assessment

Test	Points
Orientation: orientation to year, month, city, hospital	4
Naming: ability to name three objects (e.g. table, television, pillow)	3
Following commands: ability to follow simple commands (e.g. 'smile' or 'open your mouth')	1
Writing: ability to write a standard sentence (e.g. 'Happy to have my family around')	1
Attention: ability to count backwards from 100 to 0 by 10s	1

Adapted from Lee et al.[33]
ICE, Immune Effector Cell Encephalopathy.

Risk factors for CAR-T cardiotoxicity include grade ≥2 CRS,[50] high disease burden and pre-existing cardiac dysfunction following prior exposure to cardiotoxins including anthracyclines, radiation and tyrosine kinase inhibitors.

Thorough pre-CAR-T cardiovascular assessment with appropriate surveillance and risk reduction strategies may reduce CAR-T cardiovascular complications. Elevated baseline serum cardiac biomarkers (troponin, N-terminal-pro-brain-natriuretic-peptide), may signal a greater risk of CAR-T cardiotoxicity. Electrocardiograph (ECG) will exclude underlying arrhythmias and prolonged QT interval (as a surrogate for cardiac repolarisation abnormalities) and transthoracic echocardiography (TTE) defines baseline left ventricular ejection fraction (LVEF) and diastolic function to identify pre-existing LVSD (using four-dimensional volumetric, two-dimensional Simpson's biplane and global longitudinal strain assessment tools). Cardiac magnetic resonance (CMR) can be considered in the setting of poor image quality, including patients with pericardial/myocardial involvement on positron emission tomography, to assess lymphomatous infiltration.

On admission, baseline 'dry weight' and daily weights should be recorded, where weight increase as a surrogate

Table 10. CAPD for encephalopathy assessment in children <12 years

Test	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	5	4	3	2	40

Adapted from Traube et al.[71]
CAPD, Cornell Assessment of Pediatric Delirium.

for fluid overload should prompt repeat cardiac assessment with serum biomarkers, ECG, TTE and cardiologist review.

Tocilizumab is also associated with rapid improvement in cardiovascular complications.[51] One retrospective analysis showed a 1.7-fold increased risk of CAR-T cardiotoxicity with each 12-h delay in tocilizumab administration from CRS onset.[50] Current experience suggests that CAR-T cardiotoxicity is an early, largely reversible phenomenon, with rare LVSD beyond 6 months and no late cardiovascular effects at 1 year.[46]

Laboratory testing

CRP, fibrinogen, liver function tests and ferritin are checked daily. Cytokine testing is not routinely carried out in most centres. Atypical lymphocytes that resemble leukemic blasts are not uncommon at peak CAR-T expansion. Repeat microbiological testing and imaging to exclude infection is recommended in febrile patients.

MEDIUM-TERM COMPLICATIONS: DAY +28 TO DAY +100

Delayed TLS/CRS/ICANS

Although rare, delayed events can occur and should be managed according to standard protocols (Figures 1-3). Table 11 outlines recommended testing during this period to monitor for complications.

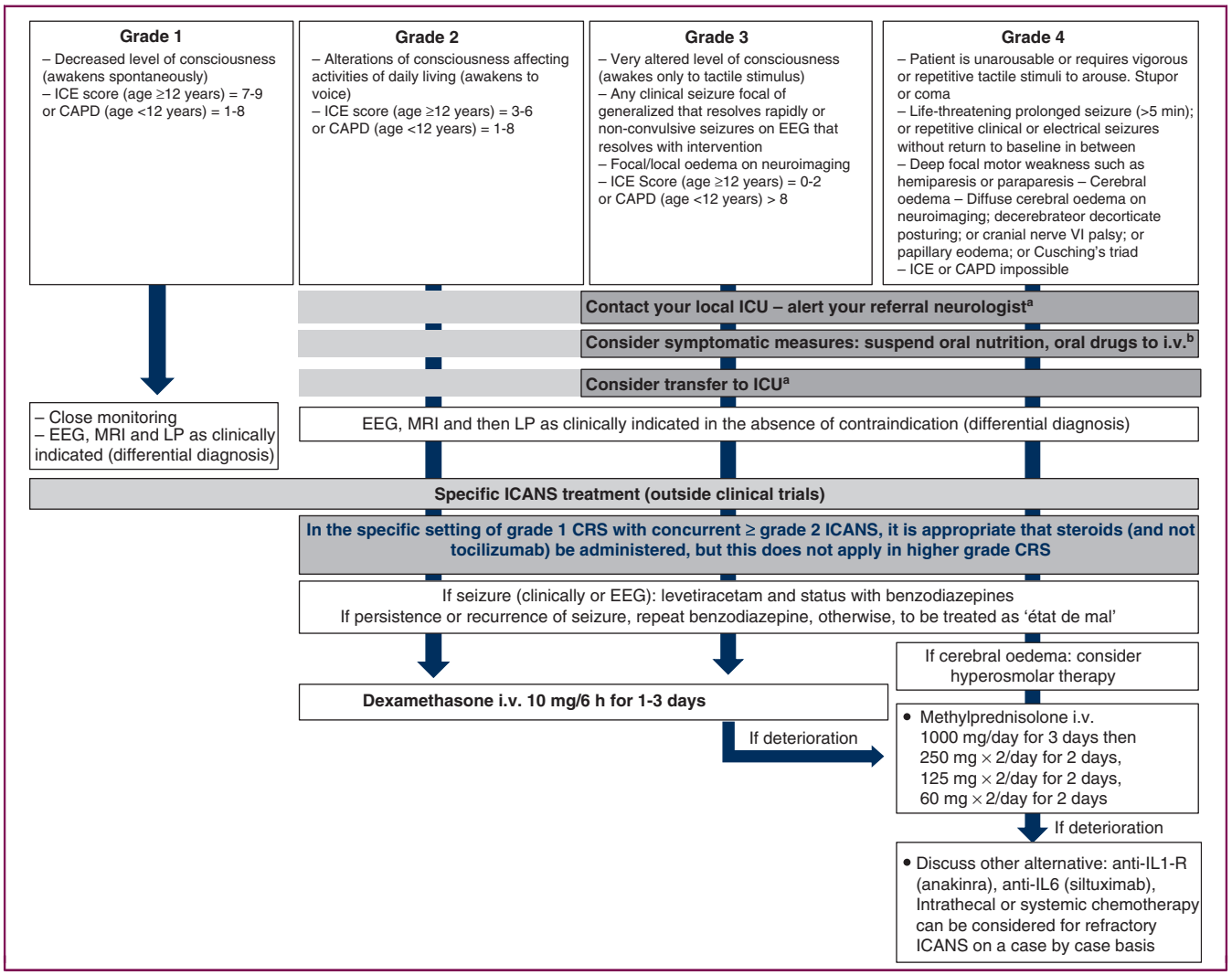

Figure 3. Grading and management of immune effector cell-associated neurotoxicity syndrome (ICANS).
CAPD, Cornell Assessment of Pediatric Delirium; EEG, electroencephalogram; ICE, Immune Effector Cell Encephalopathy; MRI, magnetic resonance imaging; LP, lumbar puncture.
[a]In centres with little experience, it is recommended to alert neurologist and transfer the patients from grade 2.
[b]In patients with rapidly resolutive grade 2 ICANS, there is no need for suspending nutrition and switching to i.v.

Table 11. Patient monitoring during medium-term follow-up

Tests	EBMT/EHA recommendations		Comments
	Purpose	Frequency	
FBC, biochemistry panel, AST, ALT, bilirubin, LDH, fibrinogen, CRP	Standard follow-up	At every visit and as clinically indicated	
CMV, EBV, adenovirus, COVID-19	Viral reactivation/infection (post-allo-HCT)	As clinically indicated	
Quantitative immunoglobulins or serum protein electrophoresis	Immune reconstitution	1-3 monthly	Consider i.v. (or s.c.) immunoglobulin replacement
Peripheral blood immunophenotyping—CD3/4/8/16+56/19+	Immune recovery	Once monthly for first 3 months, three monthly thereafter in first year	Guide to anti-infective prophylaxis and vaccination schedule
CAR-T monitoring	CAR-T persistence	Peripheral blood flow cytometry or transgene by molecular methods as clinically indicated	This is not feasible in most centres. For B-ALL, B-cell aplasia may be used as a surrogate for persistence

ALT, alanine aminotransferase; AST, aspartate aminotransferase; B-ALL, B-cell acute lymphoblastic leukemia; CAR-T, chimeric antigen receptor T cell; CMV, cytomegalovirus; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; EBMT, European Society for Blood and Marrow Transplantation; EBV, Epstein—Barr virus; EHA, European Haematology Association; FBC, full blood count; HCT, hematopoietic cell transplantation; i.v., intravenous; LDH, lactate dehydrogenase; s.c., subcutaneous.
Additional tests and imaging can be carried out as clinically indicated.

Infections and antimicrobial prophylaxis

Opportunistic infections are common and prophylaxis is warranted until immune reconstitution (Table 12).[41] Risks include prior autologous/allo-HCT, bridging therapy and steroids/tocilizumab for CRS/ICANS. Prolonged neutropenia, CD4 T-cell lymphopenia and B-cell aplasia/hypogammaglobulinemia (affecting up to 46% of patients at day +90) also contribute. Neutropenia beyond day +30 and beyond day +90 affects 30% and 10%-20% of patients, respectively. Prolonged CD4 T-cell lymphopenia resolves to >200/μl by 1 and 2 years in 65% and 86% of patients, respectively.[52]

Most early infections (first 30 days) are bacterial, or respiratory viral infections. Invasive fungal infections are rare. Risk factors include B-ALL with prior allo-HCT, prior fungal infection and prior long-term/high-dose steroid exposure.[53]

Beyond day +30, viral infections predominate. Herpes simplex virus and varicella-zoster virus reactivation is uncommon in patients on valaciclovir prophylaxis. CMV, EBV, adenovirus, human herpesvirus 6, BK polyoma virus and John Cunningham virus reactivation is rare and routine monitoring is not advised, except in high-risk patients (allo-HCT; high-dose/long-term corticosteroids).[54] COVID-19 is a formidable challenge in CAR-T patients and consortium guidance on how to maintain CAR-T delivery through the pandemic is available.

Evidence suggests that CAR-T manufacturing is feasible in hepatitis B virus (HBV), hepatitis C virus and human immunodeficiency virus infection and treatment is safe provided the virus is undetectable before apheresis and before starting LD. In hepatitis B infection (especially if HBV surface antigen positive and HBV DNA positive), long-term entecavir/tenofovir/equivalent prophylaxis is recommended.

B-cell aplasia and hypogammaglobulinemia

Following CAR-T, B-cell aplasia is associated with sinopulmonary infections and should be measured regularly.[10] Eighty-three percent of paediatric B-ALL patients on the ELIANA study (NCT02435849)[1] had ongoing B-cell aplasia at 6 months. In ZUMA-1 (NCT02348216)[78] responders, 25% had ongoing B-cell aplasia at 12 months.

Due to immunological immaturity, immunoglobulin replacement is routine in paediatric CAR-T. In adults, long-lived plasma cells following CD19 CAR-T may confer an immune-protective effect, but a common approach is immunoglobulin replacement for hypogammaglobulinemia (<4 g/l) with serious or recurrent/chronic infections. Data on efficacy of immunoglobulin replacement in CAR-T are limited and current recommendations are mainly extrapolated from primary immunodeficiencies (e.g. Bruton's agammaglobulinemia). One study showed that increased serum immunoglobulin G led to significantly less sinopulmonary infection post-CAR-T.[55]

Immunoglobulin replacement aims to maintain serum levels >4 g/l in adults and within age-adapted normal ranges for children, titrated to the incidence of breakthrough infection.

Intravenous immunoglobulins (0.4 g/kg) and subcutaneous immunoglobulins (0.1-0.15 g/kg) are administered 3-6 weekly and weekly, respectively. After reaching a steady state, levels should be measured 3 monthly.

Cessation of immunoglobulin replacement should be guided by recovery of functional B cells. B cell aplasia also provides a surrogate for functional CAR-T persistence and may be useful in clinical decision making, particularly in B-ALL.

Vaccinations

General guidance is outlined in Table 13, applicable to adults and children. Incomplete immune reconstitution or ongoing immunosuppression confers a high likelihood of lower vaccine responses (including COVID-19), but consensus view is that vaccination may reduce infection rates and improve clinical outcome. Recommendations and adherence to national schedules require individualised assessment based on infection history and laboratory

Table 12. Infection prophylaxis post-CAR-T

	EBMT/EHA recommendation	Comments
Neutropenia	G-CSF to shorten duration of neutropenia from day +14 or after resolution of CRS or ICANS Can consider starting earlier, e.g. day 5,[a] if patient is at high risk of infection, e.g. ALL, post-allo-HCT, high-dose steroids. For persistent neutropenia ($<0.5 \times 10^9$/l) following day +28, consider G-CSF	Avoid if patient has CRS or ICANS
Antibacterial prophylaxis	Not routinely recommended[b]	Can be considered in case of prolonged neutropenia and should be based on local guidelines, e.g. with levofloxacin or ciprofloxacin
Anti-viral	Valaciclovir 500 mg bid or aciclovir 800 mg bid	Start from LD conditioning until 1-year post-CAR T-cell infusion AND until $CD4^+$ count $>0.2 \times 10^9$/l
Anti-pneumocystis	Co-trimoxazole 480 mg once daily or 960 mg three times each week To start from LD conditioning until 1-year post-CAR-T cell infusion AND until $CD4^+$count $>0.2 \times 10^9$/l Where there is prolonged myelosuppression, postpone start after ANC $>0.5 \times 10^9$/l	Can be started later depending on centre guidelines In case of co-trimoxazole allergy (or cytopenias precluding use of co-trimoxazole), pentamidine inhalation (300 mg once every month), dapsone 100 mg daily or atovaquone 1500 mg once daily can be considered
Systemic anti-fungal prophylaxis	Not recommended routinely; consider posaconazole (300 mg/day) or fluconazole (200 mg/day) or micafungin (50 mg i.v./day) in patients with severe (ANC $<0.5 \times 10^9$/l) or prolonged (>14 days) neutropenia and/or in patients on long-term or high-dose (>72 h) corticosteroids or in patients post-allo-HCT	In patients with prior allo-HCT, prior invasive aspergillosis and those receiving corticosteroids, posaconazole prophylaxis should be considered
i.v. Immunoglobulin	Routine in children. Consider in adults with serious/ recurrent infections with encapsulated organisms and hypogammaglobulinemia (<4 g/l)	Clinical evidence does not support routine use in adults following allo-HCT

Allo-HCT, allogeneic hematopoietic cell transplantation; ANC, absolute neutrophil count; CAR-T, chimeric antigen receptor T cell; CRS, cytokine release syndrome; EBMT, European Society for Blood and Marrow Transplantation; EHA, European Haematology Association; G-CSF, granulocyte colony-stimulating factor; ICANS, immune effector cell-associated neurotoxicity syndrome; LD, lymphodepleting conditioning; NCCN, The National Comprehensive Cancer Network.

[a] A negative impact of G-CSF applied earlier after CAR-T has not been clearly demonstrated; a recent report starting G-CSF on day 5 after CAR-T infusion showed no increase in CRS or ICANS, indicating that earlier application may be safe and may reduce duration of neutropenia. Further data to support this observation are required.[63]

[b] In patients with neutropenic fever, empiric treatment with broad-spectrum antibiotics is strongly recommended.

assessments of cellular/humoral immunity, where available. Specific antibody responses to vaccination should be assessed where possible. A recent analysis in adults following CD19- and BCMA-CAR-T indicated that despite hypogammaglobulinemia, CD19-CAR-T patients developed seroprotection comparable with the general population (with the exception of specific pathogens, e.g. pneumococcus), but that in BCMA-CAR-T patients, fewer pathogen-specific antibodies were detected.[56] This highlights the need for vaccine and immunoglobulin replacement studies in this at-risk population. Further analysis of T-cell vaccine responses is also warranted in this group.

Graft-versus-host disease

CAR-T post-allo-HCT is generally considered safe without increased risk of high-grade graft-versus-host disease (GvHD). However, a recent publication describes histologically confirmed GvHD in four paediatric patients post-Kymriah™.[57] GvHD post-CAR-T should be diagnosed and managed using standard protocols, balancing the benefits of systemic immunosuppression against the adverse impact on CAR-T viability.

Delayed cytopenias

Haematological toxicity has a cumulative 1-year incidence of 58% post-CD19-CAR-T, is often prolonged and can follow a biphasic temporal course, with initial neutrophil recovery followed by a 'second dip'.[58]

Duration and severity vary between products and indications, but there is a high incidence of persistent grade ≥3 neutropenia (30%-38%), thrombocytopenia (21%-29%) and anaemia (5%-17%) after day +28.[59-62] Risk factors include baseline cytopenias, pre-treatment bone marrow disease burden, an inflammatory state, prior allo-HCT within 1 year and severe CRS/ICANS.[58,59] Protracted cytopenias are less pronounced in BCMA- and solid tumour-targeting CAR-T.[61]

The pathophysiology remains poorly understood and there may be product-intrinsic and/or disease-specific factors. Investigations should consider hematinic deficiency, myelosuppressive medications (co-trimoxazole) and viral infections (human herpesvirus 6, parvovirus B19). Bone marrow biopsy may be useful beyond day 28 to exclude recurrent disease, hemophagocytosis and rarely, myelodysplasia.

Granulocyte colony-stimulating factor (G-CSF) can be used for severe neutropenia ($<0.5 \times 10^9$/l) from day +14 onwards, following resolution of CRS/ICANS. Recent data on earlier prophylactic G-CSF found no effect on immunotoxicity, CAR-T expansion or prognosis.[63]

G-CSF-refractory neutropenia (absolute neutrophil count <100/μl) lasting ≥30 days affects 5%-10% of patients, and confers a risk of fungal infection.[64] Autologous stem cell rescue is an option, where cells are available[65] and donor-derived, unconditioned CD34+-selected 'top-up' can be considered in post-allo-HCT patients.[66] Anti-inflammatory therapies such as dexamethasone and erythropoietin/thrombopoietin agonists may have a role. Allo-HCT is the last resort in patients with refractory cytopenias.

Table 13. Eligibility criteria for vaccination in patients receiving CD19-targeted CAR T-cell therapy

Agent	EBMT/EHA recommendations		Comments
	Pre-CAR-T	Post-CAR-T	
Influenza vaccine	Preferably vaccinate 2 weeks before LD In B-cell aplasia low likelihood of serological response	>3 months after CAR-T patients should be vaccinated irrespective of immunological reconstitution	Where there is incomplete immune reconstitution[a] or ongoing immunosuppression, there is a high likelihood of lower vaccine responses. Consensus view is that vaccination may still be beneficial to reduce rates of infection and improve clinical course. Consider boost upon B-cell recovery
SARS-CoV-19	Preferably vaccinate before CAR-T therapy In B-cell aplasia low likelihood of serological response	>3 months after CAR T-cell infusion	Limited data is available on vaccine response after CAR-T, and early reports suggest impaired serological responses.[84] However, SARS-CoV-19 vaccine-induced protection relies heavily on T-cell-mediated immunity, therefore B-cell aplasia does not seem to be a contraindication; no T-cell threshold has been defined. Post-vaccination response monitoring is desirable. Guidance on re-vaccination post-CAR-T and frequency/dosing of booster vaccines will vary between countries. National guidelines should be followed in this area of rapidly evolving clinical practice
Killed/inactivated vaccines		>6 months after CAR-T and >2 months after immunoglobulin replacement	Contraindications include concurrent immunosuppressive or cytotoxic therapy
Live and non-live adjuvant vaccines		1 year after CAR-T and fully immune reconstituted[a]	Contraindications include <2 years post-allo-HCT, <8 months after completion of immunoglobulin replacement

Adapted from Hill and Seo.[72]
CAR-T, chimeric antigen receptor T cell; EBMT, European Society for Blood and Marrow Transplantation; EHA, European Haematology Association; HCT, hematopoietic cell transplantation LD, lymphodepleting conditioning; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a] Absolute CD4 T cells >0.2 × 10^9/l, CD19 or CD20 positive B cells >0.2 × 10^9/l, no concomitant immunosuppressive or cytotoxic therapy.

LONG-TERM FOLLOW-UP (LTFU): FROM DAY +100

LTFU should be conducted by a multi-disciplinary team (CAR-T physicians, disease-specific specialists, LTFU nursing staff, data managers, clinical trial staff) to capture disease status and late effects.[13]

Prolonged cytopenias, hypogammaglobulinemia and infections are common. Neurological complications and pulmonary toxicity confer an increased mortality risk. Secondary malignancy is rare: a single report of relapse following transduction of a leukemic B cell during the manufacturing process is described[67] and a case of myelodysplastic syndrome was reported in the ZUMA-1 trial. A recent publication described CAR-T-derived malignancies following genome-edited CD19-CAR-T due to insertional mutagenesis.[68] This area requires ongoing surveillance.

Table 14. Recommended minimum frequency of attendance at CAR-T centre for patients in remission for late effects monitoring

Period	EBMT/EHA recommendations	
	Visit frequency	Outcomes to be monitored
Day +100 to 1 year 1-2 years 2-15 years	Monthly Six-monthly Annually	• Disease—remission, minimal residual disease (MRD) status, relapse, death • Subsequent treatments including allo-HCT and other IEC therapy/ATMP • Immunological status—immune cell markers, immunoglobulins, CAR-T persistence • New cancers/secondary myeloid diseases • Autoimmunity and new autoimmune diseases • Endocrine, reproductive and bone health including growth and development • Neurological status (recovery from ICANS) • Psychological status and quality of life • Cardiovascular disease, including risk factors such as metabolic syndrome • Respiratory function • Gastrointestinal and liver health • Vaccination guidance (see Section 3.4) • Patients who proceed to subsequent allo-HCT, cytotoxic therapy and/or immune effector cell therapy should be followed as per Majhail et al. 2012131[85]

ATMP, advanced therapy medicinal products; CAR-T, chimeric antigen receptor T cell; EBMT, European Society for Blood and Marrow Transplantation; EHA, European Haematology Association; HCT, hematopoietic cell transplantation; ICANS, immune effector cell-associated neurotoxicity syndrome; IEC, immune effector cells.

Table 15. Recommended tests to be carried out at LTFU clinic

Test	Purpose	EBMT/EHA recommendations	Comments
		Frequency	
Full blood count, biochemistry panel	Standard follow-up	At every visit	
Viral infection (PB PCR, NPA)	Viral reactivation/infection	As clinically indicated	
Quantitative immunoglobulins ± serum protein electrophoresis	Immune reconstitution	At every visit	
Peripheral blood immunophenotyping—CD3/4/8/16+56/19[a]	Immune reconstitution	Every second visit	No longer required following normalisation
CAR-T monitoring where commercial kits are available for routine monitoring of anti-CD19 CAR-T[a]	CAR-T persistence	Every visit	No longer required when absent for two consecutive tests
Endocrine function and other standard late effects testing appropriate to age	Standard follow-up	Yearly or as clinically indicated	

CAR-T, chimeric antigen receptor T cell; EBMT, European Society for Blood and Marrow Transplantation; EHA, European Haematology Association; LTFU, long-term follow-up; NPA, nasopharyngeal aspiration; PB, peripheral blood.
[a] Equivalent test methods for other immune effector cells as they become available.

CAR-T centres should liaise with referral centres, providing protocols and policies for LTFU, to sustain shared care arrangements.

A recommended LTFU schedule of attendance and testing schedule are outlined in Tables 14 and 15, respectively.

POST-AUTHORISATION SAFETY SURVEILLANCE/REGISTRY

CAR-T qualify as GMOs and competent authorities (United States Food and Drug Administration; EMA) mandate LTFU for 15 years.

PASS collect data on adverse events via pre-existing or dedicated registries. The EBMT Registry has created a Cellular Therapy Form to register and monitor European CAR-T recipients.

Working with the North American CIBMTR Cellular Immunotherapy Data Resource, EBMT is uniquely positioned to provide a global overview of this new therapy class. Further, EBMT and EHA established the GoCART consortium to harmonise standards, guidelines and regulatory requirements relating to advanced therapy medicinal products delivery across the EU (https://www.ebmt.org/ebmt/gocart-coalition).

JACIE AND REGULATORY ISSUES

FACT-JACIE standards guide accreditation of HCT program activity across the United States and the EU with the aim of improving outcomes. Version 6.1 included a section on immune effector cells (IECs). The currently active seventh and eighth editions of the standards subsequently integrated IEC standards covering CAR-T therapy throughout the clinical, collection and processing sections. Documentation is available at http://www.jacie.org.

EBMT and JACIE recommend that CAR-T is best delivered from within an accredited HCT program. JACIE facilitate inspections and ensure that programs comply with data submission to the EBMT Registry, with a view to benchmarking purposes.

ACKNOWLEDGEMENTS

The authors thank all respondents to the international survey on the management of patients receiving CAR-T therapy and all administrative staff from EHA and EBMT who supported this initiative including Sophie Terwel.

FUNDING

None declared.

DISCLOSURE

PJH—Janssen, Takeda, Amgen, Celgene, Alnylam. CR—Novartis, Gilead, BMS. PB—Neovii, Riemser, Medac, Novartis, Gilead, Celgene BMS, Miltenyi, Jazz, Riemser, Amgen, Servier. GWB—Kite/Gilead, Novartis, Celgene/BMS and FamicordTx. HB—Novartis and Celgene. CB—Intellia Therapeutics, TxCell, Novartis, GSK, Molmed, Kite/Gilead, Miltenyi, Kiadis, QuellTx, Janssen, Allogene. CC—Sanofi SA, Miltenyi Biotech, Fresenius Kabi, Gilead, Novartis, Celgene, Terumo BCT, Bellicum Pharmaceuticals, Janssen. RE—Kite Gilead, BMS Celgene, Janssen. FSG—Novartis, Kite/Gilead, Celgene/BMS, Pfizer, Incyte, Amgen, Takeda, and Roche. UJ—Novartis, Janssen, Gilead, BMS, Miltenyi. MH—T-CURX GmbH. MJK—BMS/Celgene, Kite/Gilead, Miltenyi Biotec, Novartis, Roche. UK—AstraZeneca, Affimed, Glycostem, GammaDelta, Zelluna. JK—Novartis, Miltenyi Biotech, Gadeta, Gilead/BMS. SM—Celgene/BMS, Novartis, DNA Prime SA, Gilead/KITE, Miltenyi, Immunicum. MM—Sanofi, Jazz, Amgen, Takeda, Novartis, Janssen, Celgene, Adaptive Biotechnologies, Astellas, Pfizer, Stemline, GSK, outside the submitted work. JM—Kite/Gilead, Jazz, Janssen, and Mallinckrodt. CR—Kite/Gilead, Novartis, Celgene/BMS, Janssen. RS—Novartis, Gilead, Janssen. JAS—Gilead, Jazz, Janssen, Mallinckrodt, Medac. JS—MSD, Gilead, Pfizer, Kite, Novartis, TEVA. MS—Amgen, Gilead, Miltenyi Biotec, Morphosys, Roche, Seattle Genetics, BMS, Celgene, Pfizer, Novartis, Roche, Janssen, Novartis. CT—BMS/Celgene, Abbvie, Takeda, Roche, Novartis, Gilead/Kyte, Incyte, Novartis, Cellectis, Amgen, Sanofi, Janssen, AstraZeneca, ADC Therapeutics. MT—Gilead/KITE, Regeneron, Roche, Novartis,

Janssen, Celgene/BMS. JGG—Abbvie, Amgen, Astra Zeneca, BMS, Janssen, Kite/Gilead, Morphosys, Novartis, Takeda. NK—AOP Phama, Novartis, Amgen, Sanofi, Neovii, JAZZ, Gilead/Kite, Celgene, Riemser. HE—Janssen, BMS/Celgene, Amgen, Sanofi, GSK, Novartis, Takeda. IY-A—Kite/Gilead, Novartis, Celgene/BMS and Janssen. All other authors have declared no conflicts of interest.

REFERENCES

1. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med*. 2018;378:439-448.
2. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med*. 2019;380:45-56.
3. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *N Engl J Med*. 2020;382:1331-1342.
4. Beauvais D, Danhof S, Hayden PJ, et al. Clinical data, limitations and perspectives on chimeric antigen receptor T-cell therapy in multiple myeloma. *Curr Opin Oncol*. 2020;32:418-426.
5. Gauthier J, Yakoub-Agha I. Chimeric antigen-receptor T-cell therapy for hematological malignancies and solid tumors: clinical data to date, current limitations and perspectives. *Curr Res Transl Med*. 2017;65:93-102.
6. Raje N, Berdeja J, Lin Y, et al. Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma. *N Engl J Med*. 2019;380:1726-1737.
7. Zhao WH, Liu J, Wang BY, et al. A phase 1, open-label study of LCAR-B38M, a chimeric antigen receptor T cell therapy directed against B cell maturation antigen, in patients with relapsed or refractory multiple myeloma. *J Hematol Oncol*. 2018;11:141.
8. Ortiz-Maldonado V, Rives S, Castella M, et al. CART19-BE-01: a multicenter trial of ARI-0001 cell therapy in patients with CD19(+) relapsed/refractory malignancies. *Mol Ther*. 2021;29:636-644.
9. Gauthier J, Turtle CJ. Insights into cytokine release syndrome and neurotoxicity after CD19-specific CAR-T cell therapy. *Curr Res Transl Med*. 2018;66:50-52.
10. Yakoub-Agha I, Chabannon C, Bader P, et al. Management of adults and children undergoing chimeric antigen receptor T-cell therapy: best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE). *Haematologica*. 2020;105:297-316.
11. Hayden PJ, Sirait T, Koster L, et al. An international survey on the management of patients receiving CAR T-cell therapy for haematological malignancies on behalf of the Chronic Malignancies Working Party of EBMT. *Curr Res Transl Med*. 2019;67:79-88.
12. Chabannon C, Larghero J. Considerations pertaining to cell collection and administration of industry-manufactured autologous CAR-T cells, in relation to French healthcare organization and regulations. *Curr Res Transl Med*. 2018;66:59-61.
13. Yakoub-Agha I. Clinical units to set up chimeric antigen receptor T-cell therapy (CAR T-cells): based on the recommendations of the Francophone Society of Bone Marrow Transplantation and Cellular Therapy (SFGM-TC). *Curr Res Transl Med*. 2018;66:57-58.
14. Jarisch A, Rettinger E, Sorensen J, et al. Unstimulated apheresis for chimeric antigen receptor manufacturing in pediatric/adolescent acute lymphoblastic leukemia patients. *J Clin Apher*. 2020;35:398-405.
15. Korell F, Laier S, Sauer S, et al. Current challenges in providing good leukapheresis products for manufacturing of CAR-T cells for patients with relapsed/refractory NHL or ALL. *Cells*. 2020;9(5):1225.
16. Allen ES, Stroncek DF, Ren J, et al. Autologous lymphapheresis for the production of chimeric antigen receptor T cells. *Transfusion*. 2017;57:1133-1141.
17. Hutt D, Bielorai B, Baturov B, et al. Feasibility of leukapheresis for CAR T-cell production in heavily pre-treated pediatric patients. *Transfus Apher Sci*. 2020;59:102769.
18. Pasquini MC, Hu ZH, Curran K, et al. Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma. *Blood Adv*. 2020;4:5414-5424.
19. Maitta RW, Vasovic LV, Mohandas K, et al. A safe therapeutic apheresis protocol in paediatric patients weighing 11 to 25 kg. *Vox Sang*. 2014;107:375-380.
20. Bojanic I, Mazic S, Rajic L, et al. Large volume leukapheresis is efficient and safe even in small children up to 15 kg body weight. *Blood Transfus*. 2017;15:85-92.
21. Maude SL, Teachey DT, Porter DL, Grupp SA. CD19-targeted chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. *Blood*. 2015;125:4017-4023.
22. Hay KA, Hanafi LA, Li D, et al. Kinetics and biomarkers of severe cytokine release syndrome after CD19 chimeric antigen receptor-modified T-cell therapy. *Blood*. 2017;130:2295-2306.
23. Gauthier J, Bezerra ED, Hirayama AV, et al. Factors associated with outcomes after a second CD19-targeted CAR T-cell infusion for refractory B-cell malignancies. *Blood*. 2021;137:323-335.
24. Sim AJ, Jain MD, Figura NB, et al. Radiation therapy as a bridging strategy for CAR T cell therapy with axicabtagene ciloleucel in diffuse large B-cell lymphoma. *Int J Radiat Oncol Biol Phys*. 2019;105:1012-1021.
25. Turtle CJ, Hanafi LA, Berger C, et al. Immunotherapy of non-Hodgkin's lymphoma with a defined ratio of CD8+ and CD4+ CD19-specific chimeric antigen receptor-modified T cells. *Sci Transl Med*. 2016;8:355ra116.
26. Hirayama AV, Gauthier J, Hay KA, et al. The response to lymphodepletion impacts PFS in patients with aggressive non-Hodgkin lymphoma treated with CD19 CAR T cells. *Blood*. 2019;133:1876-1887.
27. Ramos CA, Grover NS, Beaven AW, et al. Anti-CD30 CAR-T cell therapy in relapsed and refractory Hodgkin lymphoma. *J Clin Oncol*. 2020;38:3794-3804.
28. Regulation (EC) N° 1394/2007 of the European Parliament and of the Council of 13 November 2007 on Advanced Therapy Medicinal Products and amending Directive 2001/83/EC and Regulation (EC) n°726/2004 (text with EEA relevance). 2007.
29. Consolidated text: Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (Text with EEA relevance) Text with EEA relevance 2007;2021.
30. Commission Directive 2009/120/EC of 14 September 2009 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products (Text with EEA relevance). 2009.
31. Li R, Johnson R, Yu G, et al. Preservation of cell-based immunotherapies for clinical trials. *Cytotherapy*. 2019;21:943-957.
32. Frey N, Porter D. Cytokine release syndrome with chimeric antigen receptor T cell therapy. *Biol Blood Marrow Transplant*. 2019;25(4):e123-e127.
33. Lee DW, Santomasso BD, Locke FL, et al. ASBMT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.
34. Hay KA. Cytokine release syndrome and neurotoxicity after CD19 chimeric antigen receptor-modified (CAR-) T cell therapy. *Br J Haematol*. 2018;183:364-374.
35. Caimi PF, Pacheco Sanchez G, Sharma A, et al. Prophylactic tocilizumab prior to anti-CD19 CAR-T cell therapy for non-hodgkin lymphoma. *Front Immunol*. 2021;12:745320.
36. Beauvais D, Karleskind O, Loridant S, et al. Potential role of tocilizumab in severe gastrointestinal barrier damage after CAR T-cell therapy. *J Microbiol Immunol Infect*. 2021;54:327-330.
37. Maus MV, Alexander S, Bishop MR, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune effector cell-related adverse events. *J Immunother Cancer*. 2020;8(2):e001511.
38. Halyabar O, Chang MH, Schoettler ML, et al. Calm in the midst of cytokine storm: a collaborative approach to the diagnosis and treatment of hemophagocytic lymphohistiocytosis and macrophage activation syndrome. *Pediatr Rheumatol Online J*. 2019;17:7.

39. Mehta P, Cron RQ, Hartwell J, et al. Silencing the cytokine storm: the use of intravenous anakinra in haemophagocytic lymphohistiocytosis or macrophage activation syndrome. *Lancet Rheumatol*. 2020;2:e358-e367.
40. Aqel A, Fakhreddine O, Atoui A, et al. The use of intrathecal chemotherapy and dexamethasone for secondary prevention of blinatumomab-related neurotoxicity. *Curr Res Transl Med*. 2021;69:103285.
41. Shah NN, Johnson BD, Fenske TS, et al. Intrathecal chemotherapy for management of steroid-refractory CAR T-cell-associated neurotoxicity syndrome. *Blood Adv*. 2020;4:2119-2122.
42. Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nat Rev Clin Oncol*. 2018;15:47-62.
43. Yassine F, Iqbal M, Murthy H, et al. Real world experience of approved chimeric antigen receptor T-cell therapies outside of clinical trials. *Curr Res Transl Med*. 2020;68:159-170.
44. Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. *Lancet*. 2021;398:314-324.
45. Gust J, Hay KA, Hanafi LA, et al. Endothelial activation and blood-brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T cells. *Cancer Discov*. 2017;7:1404-1419.
46. Rubin DB, Danish HH, Ali AB, et al. Neurological toxicities associated with chimeric antigen receptor T-cell therapy. *Brain*. 2019;142:1334-1348.
47. Cordeiro A, Bezerra ED, Hirayama AV, et al. Late events after treatment with CD19-targeted chimeric antigen receptor modified T cells. *Biol Blood Marrow Transplant*. 2020;26:26-33.
48. Karschnia P, Jordan JT, Forst DA, et al. Clinical presentation, management, and biomarkers of neurotoxicity after adoptive immunotherapy with CAR T cells. *Blood*. 2019;133:2212-2221.
49. Ganatra S, Redd R, Hayek SS, et al. Chimeric antigen receptor T-cell therapy-associated cardiomyopathy in patients with refractory or relapsed non-Hodgkin lymphoma. *Circulation*. 2020;142:1687-1690.
50. Guha A, Addison D, Jain P, et al. Cardiovascular events associated with chimeric antigen receptor T cell therapy: cross-sectional FDA adverse events reporting system analysis. *Biol Blood Marrow Transplant*. 2020;26:2211-2216.
51. Alvi RM, Frigault MJ, Fradley MG, et al. Cardiovascular events among adults treated with chimeric antigen receptor T-cells (CAR-T). *J Am Coll Cardiol*. 2019;74:3099-3108.
52. Burstein DS, Maude S, Grupp S, et al. Cardiac profile of chimeric antigen receptor T cell therapy in children: a single-institution experience. *Biol Blood Marrow Transplant*. 2018;24:1590-1595.
53. Strati P, Varma A, Adkins S, et al. Hematopoietic recovery and immune reconstitution after axicabtagene ciloleucel in patients with large B-cell lymphoma. *Haematologica*. 2020;106:2667-2672.
54. Gudiol C, Lewis RE, Strati P, Kontoyiannis DP. Chimeric antigen receptor T-cell therapy for the treatment of lymphoid malignancies: is there an excess risk for infection? *Lancet Haematol*. 2021;8:e216-e228.
55. Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. *Blood*. 2016;127(26):3321-3330.
56. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med*. 2017;377:2531-2544.
57. Arnold DE, Maude SL, Callahan CA, et al. Subcutaneous immunoglobulin replacement following CD19-specific chimeric antigen receptor T-cell therapy for B-cell acute lymphoblastic leukemia in pediatric patients. *Pediatr Blood Cancer*. 2019;67:e28092.
58. Walti CS, Krantz EM, Maalouf J, et al. Antibodies against vaccine-preventable infections after CAR-T cell therapy for B cell malignancies. *JCI Insight*. 2021;6(11):e146743.
59. Gabelli M, Marks DI, Sharplin K, et al. Graft-versus-host disease induced by tisagenlecleucel in patients after allogeneic stem cell transplantation. *Br J Haematol*. 2021;195(5):805-811.
60. Jain T, Knezevic A, Pennisi M, et al. Hematopoietic recovery in patients receiving chimeric antigen receptor T-cell therapy for hematologic malignancies. *Blood Adv*. 2020;4:3776-3787.
61. Fried S, Avigdor A, Bielorai B, et al. Early and late hematologic toxicity following CD19 CAR-T cells. *Bone Marrow Transplant*. 2019;54(10):1643-1650.
62. Logue JM, Zucchetti E, Bachmeier CA, et al. Immune reconstitution and associated infections following axicabtagene ciloleucel in relapsed or refractory large B-cell lymphoma. *Haematologica*. 2021;106:978-986.
63. Nahas GR, Komanduri KV, Pereira D, et al. Incidence and risk factors associated with a syndrome of persistent cytopenias after CAR-T cell therapy (PCTT). *Leuk Lymphoma*. 2020;61(4):940-943.
64. Sesques P, Ferrant E, Safar V, et al. Commercial anti-CD19 CAR T cell therapy for patients with relapsed/refractory aggressive B cell lymphoma in a European center. *Am J Hematol*. 2020;95:1324-1333.
65. Galli E, Allain V, Di Blasi R, et al. G-CSF does not worsen toxicities and efficacy of CAR-T cells in refractory/relapsed B-cell lymphoma. *Bone Marrow Transplant*. 2020;55:2347-2349.
66. Haidar G, Dorritie K, Farah R, et al. Invasive mold infections after chimeric antigen receptor-modified T-cell therapy: a case series, review of the literature, and implications for prophylaxis. *Clin Infect Dis*. 2020;71:672-676.
67. Godel P, Sieg N, Heger JM, et al. Hematologic rescue of CAR T-cell-mediated prolonged pancytopenia using autologous peripheral blood hematopoietic stem cells in a lymphoma patient. *Hemasphere*. 2021;5:e545.
68. Mainardi C, Ebinger M, Enkel S, et al. CD34(+) selected stem cell boosts can improve poor graft function after paediatric allogeneic stem cell transplantation. *Br J Haematol*. 2018;180:90-99.
69. Ruella M, Xu J, Barrett DM, et al. Induction of resistance to chimeric antigen receptor T cell therapy by transduction of a single leukemic B cell. *Nat Med*. 2018;24:1499-1503.
70. Bishop DC, Clancy LE, Simms R, et al. Development of CAR T-cell lymphoma in two of ten patients effectively treated with piggyBac modified CD19 CAR T-cells. *Blood*. 2021;139:1504-1509.
71. Pillai V, Muralidharan K, Meng W, et al. CAR T-cell therapy is effective for CD19-dim B-lymphoblastic leukemia but is impacted by prior blinatumomab therapy. *Blood Adv*. 2019;3:3539-3549.
72. Gauthier J, Bezerra ED, Hirayama AV, et al. Factors associated with outcomes after a second CD19-targeted CAR T-cell infusion for refractory B-cell malignancies. *Blood*. 2021;137:323-335.
73. Gazeau N, Beauvais D, Yakoub-Agha I, et al. Effective anti-BCMA retreatment in multiple myeloma. *Blood Adv*. 2021;5:3016-3020.
74. Hu Y, Tan Su Yin E, Yang Y, et al. CAR T-cell treatment during the COVID-19 pandemic: management strategies and challenges. *Curr Res Transl Med*. 2020;68(3):111-118.
75. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet*. 2020;396:839-852.
76. Wang M, Jain P, Chi TL, et al. Management of a patient with mantle cell lymphoma who developed severe neurotoxicity after chimeric antigen receptor T-cell therapy in ZUMA-2. *J Immunother Cancer*. 2020;8.
77. Abramson JS, Palomba ML, Gordon LI, et al. Pivotal safety and efficacy results from transcend NHL 001, a multicenter phase 1 study of lisocabtagene maraleucel (liso-cel) in relapsed/refractory (R/R) large B cell lymphomas. *Blood*. 2019;134:241.
78. Frigault MJ, Dietrich J, Martinez-Lage M, et al. Tisagenlecleucel CAR T-cell therapy in secondary CNS lymphoma. *Blood*. 2019;134:860-866.
79. Ghafouri S, Timmerman J, Larson S, Mead MD. Axicabtagene ciloleucel CAR T-cell therapy for relapsed/refractory secondary CNS non-Hodgkin lymphoma: comparable outcomes and toxicities, but shorter remissions may warrant alternative consolidative strategies? *Bone Marrow Transplant*. 2021;56:974-977.
80. Munshi NC, Anderson LD Jr, Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. *N Engl J Med*. 2021;384:705-716.
81. Kansagra AJ, Frey NV, Bar M, et al. Clinical utilization of chimeric antigen receptor T cells in B cell acute lymphoblastic leukemia: an expert opinion from the European Society for Blood and Marrow Transplantation and the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2019;25:e76-e85.

82. Traube C, Silver G, Kearney J, et al. Cornell assessment of pediatric delirium: a valid, rapid, observational tool for screening delirium in the PICU*. *Crit Care Med*. 2014;42:656-663.
83. Abid MA, Abid MB. SARS-CoV-2 vaccine response in CAR T-cell therapy recipients: A systematic review and preliminary observations. *Hematol Oncol*. 2021.
84. Hill JA, Seo SK. How I prevent infections in patients receiving CD19-targeted chimeric antigen receptor T cells for B-cell malignancies. *Blood*. 2020;136:925-935.
85. Majhail NS, Rizzo JD, Lee SJ, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2012;18(3):348-371.