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)

Ibrahim Yakoub-Agha,1 Christian Chabannon,2 Peter Bader,3 Grzegorz W. Basak,4 Halvard Bonig,5 Fabio Ciceri,6 Selim Corbacioglu,7 Rafael F. Duarte,8 Hermann Einsele,9 Michael Hudecek,9 Marie José Kersten,10 Ulrike Köhl,11 Jürgen Kuball,12 Stephan Mielke,13 Mohamad Mohty,14 John Murray,15 Arnon Nagler,16 Stephen Robinson,17 Riccardo Saccardi,18 Fermín Sanchez-Guijo,19 John A. Snowden,20 Micha Srour,21 Jan Styczynski,22 Alvaro Urbano-Ispizua,23 Patrick J. Hayden24 and Nicolas Kröger25

1CHU de Lille, LIRIC, INSERM U995, Université de Lille, Lille, France; 2Institut Paoli-Calmettes & Module Biothérapies, INSERM CST-1409, Centre d’Investigations Cliniques de Marseille, Marseille, France; 3Clinic for Children and Adolescents, University Children’s Hospital, Frankfurt, Germany; 4Department of Hematology, Oncology and Internal Medicine, Medical University of Warsaw, Warsaw, Poland; 5Institute for Transfusion Medicine and Immunohematology of Goethe University and German Red Cross Blood Service, Frankfurt, Germany; 6Università Vita-Salute San Raffaele, IRCCS Ospedale San Raffaele, Milan, Italy; 7Department of Pediatric Hematology, Oncology and Stem Cell Transplantation, University Hospital of Regensburg, Regensburg, Germany; 8Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain; 9Medizinische Klinikum Poliklinik II, Universitätsklinikum Würzburg, Würzburg, Germany; 10Department of Hematology, Amsterdam UMC, University of Amsterdam, Cancer Center Amsterdam and LYMCCARE, Amsterdam, the Netherlands; 11Fraunhofer Institute for Cellular Therapeutics and Immunology (IZI) and Institute of Clinical Immunology, University of Leipzig, Leipzig as well as Institute for Cellular Therapeutics, Hannover Medical School, Hannover, Germany; 12Department of Hematology and Laboratory of Translational Immunology, University Medical Center Utrecht, Utrecht, the Netherlands; 13Department of Laboratory Medicine/Department of Cell Therapy and Alogeneic Stem Cell Transplantation (CAST), Karolinska Institutet and University Hospital, Stockholm, Sweden; 14Hôpital Saint-Antoine, AP-HP, Sorbonne Université, INSERM UMR 938, Paris, France; 15Christie Hospital NHS Trust, Manchester, UK; 16The Chaim Sheba Medical Center, Tel-Hashomer, Affiliated with the Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel; 17University Hospitals Bristol NHS Foundation Trust, Bristol, UK; 18Hematology Department, Careggi University Hospital, Florence, Italy; 19IBBASal Hospital Universitario de Salamanca, OIC, Universidad de Salamanca, Salamanca, Spain; 20Department of Haematology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK; 21Service des Maladies du Sang, CHU de Lille, Lille, France; 22Department of Pediatric Hematology and Oncology, Collegium Medicum, Nicolaus Copernicus University Torun, Bydgoszcz, Poland; 23Department of Hematology, ICMHO, Hospital Clínico de Barcelona, Barcelona, Spain; 24Department of Hematology, Trinity College Dublin, St. James’s Hospital, Dublin, Ireland and 25Department of Stem Cell Transplantation, University Medical Center Hamburg, Hamburg, Germany

Correspondence:
PATRICK J. HAYDEN
pohayden@stjames.ie

Received: June 16, 2019.
Accepted: November 19, 2019.
Pre-published: November 21, 2019.

doi:10.3324/haematol.2019.229781

Check the online version for the most updated information on this article, online supplements, and information on authorship & disclosures: www.haematologica.org/content/105/2/297

©2020 Ferrata Storti Foundation

Material published in Haematologica is covered by copyright. All rights are reserved to the Ferrata Storti Foundation. Use of published material is allowed under the following terms and conditions:
https://creativecommons.org/licenses/by-nc/4.0/legalcode.
Copies of published material are allowed for personal or internal use. Sharing published material for non-commercial purposes is subject to the following conditions:
https://creativecommons.org/licenses/by-nc/4.0/legalcode, sect. 3. Reproducing and sharing published material for commercial purposes is not allowed without permission in writing from the publisher.
care and supply chain management under the following headings: patient eligibility, screening laboratory tests and imaging and work-up prior to leukapheresis, how to perform leukapheresis, bridging therapy, lymphodepleting conditioning, product receipt and thawing, infusion of CAR T cells, short-term complications including cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, antibiotic prophylaxis, medium-term complications including cytopenias and B-cell aplasia, nursing and psychological support for patients, long-term follow-up, post-authorization safety surveillance, and regulatory issues. These recommendations are not prescriptive and are intended as guidance in the use of this novel therapeutic class.

Introduction

The first experimental attempts to engineer T cells to express chimeric antigen receptors (CAR) were performed 30 years ago. The ultimate goal was to produce functional, high-affinity, CAR T cells in which the T-cell receptor is re-directed towards a tumor antigen of choice. Following refinements in the signaling properties of a CAR within the context of a T cell, development progressed rapidly from the laboratory to clinical trials and CAR T cells targeting CD19 now represent a novel and promising therapy for patients with refractory/relapsed B-cell malignancies including acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL). CAR T cells are also being assessed as treatment for other hematologic diseases such as multiple myeloma and acute myeloid leukemia as well as for solid tumors.

Tisagenlecleucel (Kymriah™, previously CTL019, Novartis, Basel, Switzerland) consists of autologous CAR T cells genetically modified ex vivo using a lentiviral vector encoding an anti-CD19 CAR that includes a domain of the 4-1BB co-stimulatory molecule. It is indicated for the treatment of children and young adults up to the age of 25 years with relapsed/refractory B-ALL and was approved by the Food and Drug Administration (FDA) on 30th August, 2017. It was subsequently FDA-approved on May 1st, 2018 for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, high-grade B-cell lymphoma and DLBCL arising from follicular lymphoma. The European Medicines Agency (EMA) approved similar indications on August 22nd, 2018.

Axicabtagene ciloleucel, (Yescarta™, previously KTE-C19, Gilead, USA) is an autologous CAR T-cell product which has been genetically modified ex vivo using a retroviral vector encoding an antibody fragment targeting CD19 and an intracellular domain including the CD28 co-stimulatory molecule. It was FDA-approved on October 18th, 2017 for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. The EMA approved its use in relapsed or refractory DLBCL and primary mediastinal large B-cell lymphoma after two or more lines of systemic therapy, on August 29th, 2018.

While CAR T cells are rationally designed, targeted therapies, they nevertheless frequently induce life-threatening toxicities that can be mitigated by planning and proper hospital organization. Comprehensive training should be provided to all categories of personnel including scientists, nurses and physicians, and close collaboration with a range of other specialists, especially intensive care unit staff and the neurology/neuroradiology services, is required. As CAR T cells represent a novel class of therapy and as both of the currently available products have only been evaluated in phase II studies to date, close post-marketing surveillance is mandatory. The EMA has endorsed the use of the European Blood and Marrow Transplantation (EBMT) registry for the collection of 15-year follow-up data on treated patients in order to ensure that evaluation of the efficacy and safety of commercially available CAR T cells continues on an ongoing basis. The Center for International Blood and Marrow Transplant Research (CIBMTR) fulfills a similar function in the United States of America (USA). The newly updated EBMT Registry Cellular Therapy form is designed to capture the efficacy and side-effects of modern cellular therapies and to provide the required post-marketing surveillance through Post-Authorization Safety Surveillance (PASS) and other studies. The main objective for professionals in the field is to evaluate how these innovative treatments compare with the alternative therapeutic options and current standards-of-care. Phase III studies are underway.

The clinical use of CAR T cells is early in its evolution and it is, as yet, unclear whether CAR T-cell therapy constitutes a definitive treatment or whether disease cure will require further immunologically based consolidation such as allogeneic stem cell transplantation, especially for ALL. In trials on the use of CAR T-cell therapy in DLBCL, long-term disease control is observed in up to 50% of patients. As some of these patients may be cured, allogeneic transplantation as consolidation may not be necessary. This issue can only be resolved with longer follow-up.

Research areas include dual antigen targeting to counter one of the most common resistance mechanisms, which is loss of the targeted antigen, the inclusion of safety switches such as suicide genes in order to mitigate side-effects when they occur, ‘off the shelf’ allogeneic CAR T products, the refinement of co-stimulatory domains to enhance persistence and avoid immune escape, and the use of non-viral vectors and semi-automated on-site production to simplify the manufacturing process.

Although this field will inevitably change over the coming years, these first EBMT guidelines on CAR T cells are intended to provide practical, clinically relevant recommendations for hematologists and other cancer specialists and their teams involved in the administration of CAR T-cell therapies, especially the commercially available products. These guidelines may also be a useful resource for other stakeholders such as pharmacists or health service administrators involved in the planning and delivery of
CAR T-cell therapies, given the complexity of their production and administration and their high cost.

Methodology

The Practice Harmonization and Guidelines subcommittee of the Chronic Malignancies Working Party of the EBM T proposed the project in December 2018. The EBM T Board accepted the proposal and worked with experts in the field to produce practical clinical recommendations on the management of adults and children undergoing autologous CAR T-cell therapy. A survey was sent to centers active in this field to solicit feedback on current approaches to the topics covered in these guidelines. Their responses (41 of 50 centers) along with a literature review and assessment of both the licensing study protocols and the summaries of product characteristics (SPC) of the commercially available CAR T-cell products inform these recommendations. Finally, three teleconferences were held in preparation for a 2-day workshop that took place in Lille on 4th-5th April, 2019.

These recommendations are intended to reflect current best practice in this novel and rapidly moving field and to support clinicians and other healthcare professionals in delivering consistent, high-quality care. They principally apply to the CAR T-cell therapies that are currently commercially available for the treatment of hematologic malignancies. Given the absence of randomized trial evidence in this field, a decision was made not to grade these recommendations. They therefore represent the consensus view of the authors.

When patients are receiving CAR T-cell therapies in clinical trials, physicians should follow the relevant trial protocols. The management of disease relapse following CAR T-cell therapy is outside the scope of these recommendations.

Patient eligibility for chimeric antigen receptor T-cell therapy

The decision to treat a patient with CAR T cells therapy should be made collectively at a multidisciplinary team meeting in a designated center for CAR T-cell therapy. The patients’ medical history and physical condition are important factors in determining their suitability for treatment.

Trial eligibility criteria and EBM T recommendations are shown in Table 1.

Screening laboratory tests and imaging

Table 2 summarizes a recommended minimum set of tests that should be performed at screening in order to assess organ function and patient eligibility.

Work-up prior to apheresis

The current set of rules that apply to human tissue and cell procurement in the European Union derives from the Tissue and Cell Directives published in 2004 (2004/23/EC) and 2006 (2006/17/EC; 2006/66/EC). The European Union Commission recently convened a stakeholder meeting to examine whether revision of the Tissue and Cell Directives was required. Although a number of arguments, including manufacturing of Advanced Therapy Medicinal Products, were brought forward in favor of revising the directives, no formal decision has yet been made.

The current rules are solely based on the donor-recipient relationship, whether autologous or allogeneic, and do not address the intended use of the collected material. As a consequence, the same requirements apply both to the collection of mononuclear cells for stem cell transplantation and when procuring the starting material for the manufacture of Advanced Therapy Medicinal Products, unless the Marketing Authorization Holder stipulates specific additional requirements.

Cross-border shipment of the collected cell product requires compliance with national regulations both in the country of origin and in the country of destination. Obtaining authorization to export human autologous-derived elements will require knowledge of the patient’s viral serology.

Table 3 presents a checklist that should be verified before starting the leukapheresis procedure.

How to perform leukapheresis

Scheduling of leukapheresis must be coordinated with the pharmaceutical company as lack of manufacturing capacity is currently one of the bottlenecks in the availability of CAR T-cell therapies. Confirmation of an agreed manufacturing slot is therefore mandatory prior to deciding on a date for apheresis. With technical advances and more patients likely to become candidates for these treatments in the coming years, limitations in the capacity of collection centers are likely to become a challenge.

Any of the commercially available leukapheresis devices are, in principle, suitable for apheresis. While companies may suggest preferences for devices or systems, local experience, local permits and the regulatory approval status of individual devices and systems should guide the selection of technology. Technically, unmobilized leukapheresis is most similar to apheresis for off-line 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. Proof of proper validation and maintenance of equipment and established training processes for personnel operating or supervising the use of cell processors are key elements required by the Marketing Authorization Holders in order to qualify and onboard sites that are authorized to collect cells for CAR T-cell manufacturing. Prior accreditation in compliance with the 7th edition of the Foundation for the Accreditation of Cellular Therapy (FACT) - Joint Accreditation Committee of the International Society for Cell Therapy and EBM T (JACIE) Standards for Hematopoietic Cellular Therapies or the FACT Standards for Immune Effector Cells confirms the presence of a pre-existing Quality Management System, although additional requirements are often identified, including those from pharmaceutical providers and health service commissioners.

Further information on the technical aspects of apheresis is provided in the Online Supplement.
**Table 1. Eligibility criteria for the selection of patients for clinical trials.**

| Characteristics | ELIANA (ALL Kymriah™) | JULIET (DLBCL Kymriah™) | ZUMA-1 (High-grade B-cell NHL Yescarta™) | EBMT recommendations | Comment |
|-----------------|------------------------|--------------------------|------------------------------------------|----------------------|---------|
| Age limit (NHL) | N/A                    | ≥18 years                | N/A                                      | No upper age limit   | Decision should be based on physical condition rather than age |
|                  |                        |                          | SPC - No data are available on children < 18 years of age |                      |         |
| Age limit (ALL) | ‘Age 3 years at the time of screening to age 21 years at the time of initial diagnosis’ | N/A | N/A | Follow SPC | Ability to collect sufficient cells by apheresis can be a limiting factor in infants and small children |
| ECOG PS          | Karnofsky (age ≥16 years) or Lansky (age <16 years) PS ≥50 at screening | ECOG PS of either 0 or 1 at screening | ECOG PS of 0 or 1 | >2 not recommended Note, however, that real-world data with Yescarta™ included patients with ECOG PS ≥2 | Prognosis may be less poor if the decline in PS is due to active disease |
| Performance Status |                        |                          |                                          |                      |         |
| History of malignancy | No prior malignancy, except carcinoma in situ of the skin or cervix treated with curative intent and with no evidence of active disease | No previous or concurrent malignancy except adequately treated BCC or SCC, in situ cancer of the breast or cervix treated and without recurrence for 3 years, primary malignancy resected and in remission for more than 5 years | No history of malignancy other than nonmelanoma skin cancer or carcinoma in situ (e.g. cervix, bladder, breast) or follicular lymphoma unless disease free for at least 3 years | Absence of history of malignancy other than carcinoma in situ (e.g. cervix, bladder, breast) unless disease-free and off therapy for at least 3 years |         |
| Prior allo-HCT   | Not excluded; however, excluded if grade II-IV acute or extensive chronic GvHD | Excluded | Excluded | Not a contraindication | Active GvHD is listed as a reason to delay treatment in the Kymriah™ and Yescarta™ SPC |
| Prior anti-CD19/anti-CD3 BITE antibodies or any other CD19 therapy | Excluded | Not a contraindication as per SPC | Excluded if prior CD19 targeted therapy | Not a contraindication | Further CART-cell therapy outside of clinical trials is to be avoided |
| Previous CART-cell therapy | Not applicable in trials Not in SPC | Not applicable in trials Not in SPC | Excluded | Not a contraindication | Individualized risk-benefit assessment required |
| History of autoimmune disease | Not an exclusion criterion | Not an exclusion criterion | Not an exclusion criterion | Not recommended in active autoimmune disease resulting in end-organ injury or requiring systemic immunosuppression or systemic disease-modifying agents within the last 2 years |         |
| Current systemic immunosuppressive treatment | Any GvHD therapy must be stopped more than 4 weeks prior to enrollment to confirm that GvHD recurrence is not observed | Any immunosuppressive medication must be stopped more than 4 weeks prior to enrollment | Any immunosuppressive medication must be stopped more than 4 weeks prior to enrollment | Contraindication | Intermittent topical, inhaled or intranasal corticosteroids are allowed |
| Existing or suspected fungal, bacterial, viral, or other infection | Active or latent HBV or HCV (test within 8 weeks of screening) or any uncontrolled infection at screening | Uncontrolled active or latent HBV or active HCV; Uncontrolled acute life-threatening bacterial, viral or fungal infection (e.g. blood cultures positive <72 h prior to screening) | Known history of HIV, HBV (HepBs Ag positive) or HCV (anti-HCV); Clinically significant active infection, or currently receiving IV antibiotics or within 7 days of enrollment | Relative contra-indication; individualized risk-benefit assessment required | Active infection should be controlled and on treatment prior to leukapheresis |

*continued on the next page*
Management of patients undergoing CAR T-cell therapy

Table 2. The minimum required tests.

| Test methods          | Trials and/or SPC | EBMT recommendations | Comment                                           |
|-----------------------|-------------------|----------------------|---------------------------------------------------|
| Disease confirmation  | Histology only for NHL Immunophenotyping for ALL          |                      |                                                   |
| Hematology            | ANC > 1.0x10^9/L in NHL trials | ANC > 1.0x10^9/L     | Evidence of adequate bone marrow reserve          |
| Chemistry             | Bilirubin < 26-34 µmol/L        | < 34 µmol/L; higher limit acceptable (< 43 µmol/L) with Gilbert syndrome |
|                       | AST/ALT < 5xULN | < 5xULN               | Attempt to identify causes e.g. active infections |
|                      | Creatinine clearance | > 30 mL/min       | Caution is required in patients with CrCl of < 60 mL/min |
| Virology              | Hepatitis B*      | Mandatory in some countries. To be done within 30 days of leukapheresis and results must be available at the time of collection and shipment | As per national guidelines Serology/molecular testing |
|                       | Hepatitis C*      | Mandatory in some countries. To be done within 30 days of leukapheresis and results must be available at the time of collection and shipment | As per national guidelines Serology/molecular testing |
|                      | HIV*              | Mandatory in some countries. To be done within 30 days of leukapheresis and results must be available at the time of collection and shipment | Kymriah™ is using a lentiviral vector whereas Yescarta™ uses a retroviral vector |
| Other work-up         | Cardiac function  | LVEF > 40%; assess for pericardial effusion by echocardiography; ECG | Work-up of effusions required to identify causes |
|                      | CNS imaging       | MRI not required except in those with a history of CNS disease or current neurological symptoms of concern | A baseline MRI can be helpful, should severe neurological toxicities arise |
|                      | Lumbar puncture   | Lumbar puncture not required except in those with a history of CNS disease or current neurological symptoms of concern |                                                   |
|                      | Fertility         | Females of childbearing potential must have a negative serum or urine pregnancy test within 48 h of infusion (ELIANA) | Test must be repeated and confirmed negative within 8 days of the CAR T-cell infusion |

SPC: summary of product characteristics; EBMT: European Society for Blood and Marrow Transplantation; NHL: non-Hodgkin lymphoma; ALL: acute lymphoblastic leukemia; ANC: absolute neutrophil count; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ULN: upper limit of normal; CrCl: creatinine clearance; HIV: human immunodeficiency virus; CAR: chimeric antigen receptor; LVEF: left ventricular ejection fraction; MUGA: multiple-gated acquisition; MRI: magnetic resonance imaging; CNS: central nervous system. *Leukapheresis material for Kymriah™ manufacturing will not be accepted from patients with a positive test for active hepatitis B virus, hepatitis C virus or HIV (SPC)
Only one of the commercial CAR T-cell manufacturers – Novartis – currently requires cryopreservation of the mononuclear cells on site. It is stipulated that the white blood cell count should be adjusted to 1.0 (0.5-2.0) x10^9/mL, that an approved (approved by the company and local regulators) cryoprotectant be added slowly and that the cells be frozen in controlled-rate freezers prior to storage in vapor phase liquid nitrogen. To produce Kymriah™, Novartis will accept cells that have been harvested within the preceding 18 months and cryopreserved with appropriate quality management surveillance. Whether autologous blood mononuclear cells intended for CAR T-cell manufacturing should be prospectively collected and cryopreserved in selected patients at high risk of relapse is already under debate. The other commercial manufacturers will collect fresh apheresis product packed in their own specified shipping containers. Until shipping, these apheresis products are stored refrigerated (2-8°C).

Manufacturers’ requirements for quality control are currently very limited and may be exceeded by local requirements. There may also be differences between FDA and EMA requirements. Accredited and validated testing methods must be used. In addition to testing for infectious disease markers in peripheral blood samples on the day of collection, reasonable quality control should include sterility testing as well as some hemocytometric parameters (white blood cell count, hematocrit, CD3+, and viable CD4+ counts). Sampling of the collected cell product must follow the manufacturer’s requirements so as not to compromise downstream processing steps, while also complying with local manufacturing authorizations. Depending on the disease burden, it may be possible to arrange for leukapheresis before starting salvage chemotherapy to treat disease relapse. There is evidence that cumulative chemotherapy exposure adversely affects the quality of circulating T cells. Although apheresis can be performed in patients with absolute lymphocyte counts as low as 0.1x10^9/L, the likelihood of reaching the target number of autologous lymphocytes and successfully manufacturing the drug product is higher in individuals with absolute lymphocyte counts exceeding 0.5x10^9/L. In addition, the choice of salvage therapy (chemotherapy, hydrocortisone permitted, prednisolone 5 mg equivalent).

Table 3. Checklist prior to apheresis.

| Prior to apheresis | Trials/SPC | EBMAT recommendations | Comment |
|--------------------|------------|------------------------|---------|
| ECOG PS score      | Not specified | ECOG PS score ≥2       | At discretion of apheresis practitioner |
| Days after last chemotherapy | Allow for recovery from cytotoxic chemotherapy | Need for marrow recovery from prior chemotherapy |
| Days off corticosteroids | Three (Kymriah™) to 7 (Yescarta™) days off or on no more than prednisolone 5 mg equivalent | Ideally, 7 days to minimize effect on lymphocyte collection | A shorter period of as few as 3 days was considered acceptable by Kansagra et al. Physiological replacement doses of hydrocortisone permitted |

**Mandatory blood tests**

| Hepatitis B, hepatitis C, HIV, syphilis, and HTLV | Mandatory for all trials | Mandatory in some countries. To be done within 30 days of leukapheresis and results must be available at the time of collection and shipment | Only serological testing is required; nucleic acid testing is not necessary if all serological testing is negative |

**Blood tests to ascertain suitability for apheresis**

| C-reactive protein | Recommended to assess for ongoing infection | In patients with active infection, eligibility for apheresis will need to be decided on a case-by-case basis |
|--------------------|----------------------------------------------|--------------------------------------------------|
| Standard electrolytes and renal function | Required | Apheresis may predispose to electrolyte imbalance and limited fluid tolerance |

**Blood values required for optimal apheresis performance**

| Hemoglobin | Hemoglobin > 80 g/L | To establish a good interface during collection |
|------------|---------------------|-----------------------------------------------|
| Absolute neutrophil count | > 1.0x10^9/L | Consistent with recovery from prior chemotherapy |
| Absolute lymphocyte count | > 0.2x10^9/L* | Higher count required in small children. Of note, 0.2x10^9/L CD3+ count is the minimum threshold |
| Platelet count | > 30x10^9/L | Transfuse as required |
| Full blood count | To be repeated at the end of apheresis procedure | Apheresis can remove more than 30% of circulating platelets |

*: This threshold specifically applies to count recovery following corticosteroid therapy where an absolute lymphocyte count >0.2 is a surrogate marker of corticosteroid washout.
serotherapy and radiotherapy) may adversely affect subsequent attempts at leukapheresis and washout periods need to be considered.

Table 4 provides recommendations on washout periods following various salvage treatments before starting leukapheresis. In addition, it should be noted that prior use of blinatumomab is not a contraindication to anti-CD19 CAR T-cell therapy.20

**Bridging therapy**

Bridging therapy refers to the administration of anti-cancer drugs including chemotherapy to maintain disease control during the period between lymphocyte collection and the final administration of the CAR T-cell product.6 This time window may be longer than anticipated for logistical reasons, sometimes but not always related to manufacturing, and will be specifically monitored through EBMT Registry collection of ‘real world’ data.

The goal of bridging therapy is to prevent clinically significant disease progression leading to impaired organ function or any other complications that might prevent the patient proceeding with lymphodepletion and receiving the CAR T cells. It is also hoped that treatment of rapidly proliferating disease will establish a balanced in vivo target-effector ratio to allow for effective CAR T-cell adoptive immunotherapy. In brief, the aim is not so much to achieve disease remission as to establish adequate disease control prior to the CAR T-cell infusion.

The optimal bridging therapy for any individual will depend on disease- and patient-specific factors. However, clinicians should bear in mind that patients receiving chemotherapeutic agents, either alone or in combination, will subsequently receive lymphodepleting therapy and will be at risk of specific CAR T-cell-related complications such as cytokine release syndrome (CRS), encephalopathy and tumor lysis syndrome. Bridging therapy should therefore ideally not induce major complications, such as infections, bleeding or any organ dysfunction that might interfere with the planned lymphodepleting therapy and CAR T-cell infusion. Bridging therapy can be omitted in the presence of stable, low burden disease if the turn-around time for the CAR T cells is expected to be short. Importantly, certain agents, especially immunotherapeutic drugs with a longer half-life, may interfere with the expansion or persistence of the infused CAR T cells and should be avoided. Examples include alemtuzumab, daratumumab, checkpoint inhibitors and brentuximab vedotin.

When choosing bridging therapy for lymphoma patients, factors to be considered include the prior response to chemotherapy and chemo-immunotherapy, the overall tumor burden and the distribution and sites of tumor involvement. Options include parenteral agents such as rituximab, gemcitabine, oxaliplatin, bendamustine or pixantrone; oral chemotherapy regimens e.g. variants of prednisolone, etoposide, procarbazine, and cyclophosphamide (PEP-C), or oral cyclophosphamide 100 mg once daily; novel targeted therapies such as lenalidomide or ibrutinib; high-dose corticosteroids e.g. dexamethasone 40 mg for 4 days or high-dose methylprednisolone, repeated as needed; or radiotherapy to symptomatic or large masses.21,22

In ALL, the risk of CRS has been found to correlate with the leukemic blast burden at the time of the CAR T-cell infusion. Bridging chemotherapy is therefore especially important in ALL and the chosen agents are typically drawn from known B-ALL chemotherapy regimens although doses are often reduced to lower the risk of infectious complications and organ dysfunction.5,26 Novel and targeted agents, for example, tyrosine kinase inhibitors and monoclonal antibodies, may also be used although it is important to consider whether the agent is capable of inducing a rapid response and whether the therapy might interact with subsequent lymphodepleting and CAR T-cell therapy. Whatever treatment is chosen, bridging therapy should only be given after leukapheresis so that the quality of the CAR T-cell product is not affected.

The patient can be monitored after leukapheresis and during and following bridging chemotherapy either at the treating center or at the referring center provided that there are clear lines of communication between the centers regarding the choice of any treatments and the management of any complications. Frequent monitoring, including laboratory testing and imaging, is mandatory in

**Table 4. Wash-out period before leukapheresis (adapted from Kansagra et al.23).**

| Type of therapy | SPC | EBMT recommendations | Comments |
|----------------|-----|----------------------|----------|
| Allo-HCT       | No guidance | Patients should be off immunosuppression and GvHD-free | A minimum of 1 month is recommended |
| Donor lymphocyte infusion | No guidance | 4 weeks | 6 to 8 weeks may be safer to rule out any GvHD |
| High-dose chemotherapy | No guidance | 3-4 weeks depending on the intensity of the chemotherapy | Recovery from cytopenias is required |
| CNS-directed therapy | No guidance | 1 week | |
| Short-acting cytotoxic/anti-proliferative drugs | No guidance | 3 days | Recovery from cytopenias is required |
| Systemic corticosteroids | No guidance | Ideally, 7 days to minimise any effect on lymphocyte collection | A shorter period of as few as 3 days was considered acceptable by Kansagra et al.12 Regardless of timing, an ALC>0.2 x10^9/L is preferable given the likely effect of recent corticosteroids on lymphocyte quality |

SPC: summary of product characteristics; EBMT: European Society for Blood and Marrow Transplantation; Allo-HCT: allogeneic hematopoietic cell transplantation; GvHD: graft-versus-host disease; CNS: central nervous system; ALC: absolute lymphocyte count.
order to prevent or rapidly treat complications that might arise while awaiting the arrival of the CAR-T-cell product.

Lymphodepleting conditioning

The use of lymphodepleting (LD) conditioning prior to the CAR-T-cell infusion creates a ‘favorable’ environment for CAR-T-cell expansion and survival in vivo, probably by eliminating regulatory T cells. In addition, it can lead to the upregulation of tumor immunogenicity and improve disease control. Furthermore, there are data demonstrating that LD conditioning works to promote homeostatic proliferation of adoptively transferred T cells via increases in the pro-survival/proliferation cytokines, interleukin (IL)-7 and IL-15, and in conjunction with a lack of competition with wildtype T cells.

Many drugs have been used for LD conditioning including cyclophosphamide, fludarabine, pentostatin and benzamustine as well as total body irradiation. In a clinical trial involving 50 patients with B-ALL at the Fred Hutchinson Cancer Research Center, fludarabine and cyclophosphamide was associated with superior CAR-T-cell persistence and better disease-free survival when compared to single-agent cyclophosphamide or cyclophosphamide in combination with etoposide.

LD conditioning is usually administered on a 3-to-5 day schedule prior to the infusion of the CAR T cells. If the center 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.

Items to consider before starting LD conditioning are shown in Table 5A.

Laboratory tests to review before starting LD conditioning are shown in Table 5B. If there is a long delay (in general, more than 3 weeks) between completing LD conditioning and the subsequent CAR-T-cell infusion, and the white blood cell count is >1.0×10^9/L, then consideration should be given to re-treating the patient with LD chemotherapy prior to administration of the CAR T cells.

Product receipt and thawing

The currently licensed CAR-T-cell products are delivered frozen and must be maintained at very low temperatures during shipping, receipt and temporary storage until they are thawed immediately prior to use. Hospitals have adopted different approaches to product receipt, taking into account local organizational and regulatory issues. 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.

As the manufacturing companies use differently sized cryostorage cassettes, custom-made cryo racks, at least one for each company, must be obtained. A storage site with secured access and an adequate number of trained staff licensed to work with biohazards and liquid nitrogen are required, both at the hospital pharmacy and at the cell processing facility.

The designated receiving laboratory will receive advance notice from the manufacturer and the product will be delivered in a sealed liquid nitrogen dewar (vacuum flask). Upon receipt, the seals of the dewar are inspected for breaches; seals are broken, if applicable; the temperature log is read out; and the product is inspected for bag integrity and identity according to the label; the bag in its cassette is subsequently transferred to a liquid nitrogen storage container until it is brought to the bedside. The company-specific product receipt documentation must be completed; personnel authorized to handle products are provided with specific and detailed training from the relevant manufacturer. When the ward is ready to receive the product, the cassette is transferred to a laboratory dewar and this is transported to the ward.

In some countries, the use of water baths, carefully calibrated to 35-37°C, remains acceptable; use of an automated thawing device is preferable. Representative examples of such devices are the Sahara (Sarstedt) and Plasmatherm (Barkey) devices. While the thawing of CAR T cells is, in principle, the same as for cryopreserved hematopoietic progenitor cells collected by apheresis, the much smaller volumes of CAR-T-cell products only require very short thawing times. We recommend that thawing times be established locally with similarly-sized mock products, ideally with mononuclear cell suspensions in protein-saline-dimethylsulfoxide freezing buffer and testing of post-thaw viability, but at a minimum, with protein-saline-dimethylsulfoxide buffer without cells and observation of the time until the buffer assumes the slushy consistency of a ready-to-spike cryo product. 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. The spike ports of the thawed product are uncapped, disinfected and aseptically spiked with the transfusion set, the air trap is filled completely with the cell suspension (no falling drops, as this shears cells) and air is evacuated from the infusion line. The individual responsible for the thawing and preparation of the infusion varies between countries and health care systems. We propose that the decision as to who is responsible should be primarily based on competence, meaning that those individuals who normally thaw autologous transplants are likely best qualified. On this basis, pharmacy, processing facility and clinical transplant staff are all acceptable candidates and bedside thawing is preferable.

Infusion of chimeric antigen receptor T cells

Before starting to thaw the CAR-T-cell product, the patient should be assessed. Some factors to consider are shown in Table 6. A transfusion set is required for the administration of the cells. In general, a typical transfusion filter set with 50-200 μm pore size is used; this is, in fact, mandatory in some countries. Importantly, fluid infusion sets are not suitable because of the sub-micrometer bacterial filters. Transfusion sets with leukocyte-depletion filters are also unacceptable. It should be noted that the manufacturers recommend the use of non-filtered tubing sets although our recommendations, and some local regulatory requirements, deviate from this approach.

Pre-medication to prevent adverse reactions is reasonable with the important exception of corticosteroids
which may damage the CAR T-cell product; typically, paracetamol derivatives and antihistamines, such as chlorpheniramine or diphenhydramine, are used. Individual guidelines are provided by the manufacturers.

The product is aseptically connected to the port of a central venous catheter. The line to be used for the CAR T-cell infusion must be clearly designated; as with blood and stem cell products, no concurrent medication may be given during the CAR T-cell infusion. Infusion should begin as rapidly after spiking as possible, but no later than 30 min thereafter. The small volumes and cell numbers allow for rapid (less than 30 min) drip infusion of the cell suspension. The infusion bag and set should be disposed of as a biohazard and genetically modified organism waste in compliance with institutional policies and country-specific regulations. Transfusion of the low-volume CAR T-cell product is typically uneventful.

**Short-term complications and management: infusion to day +28**

The rapid *in vivo* proliferation of CAR T cells may be associated with potentially life-threatening toxicities such as CRS and neurotoxicity, which generally occur within 14 and 28 days of the CAR T-cell infusion, respectively.11,36-38 LD conditioning may also contribute to the cytopenias.

**Hospitalization**

Some centers have established policies and infrastructure that allow for the safe administration of CAR T cells on an outpatient, ambulatory care basis. However, for ambulatory care to work, clear protocols, staffing and training need to be in place so that patients are able to access a coordinator on a 24/7 basis. Centers must also be able to provide both immediate review and the emergency admission of patients under the care of experienced staff. As such arrangements are not currently available in most European centers, we recommend that patients are admitted to hospital during the early post-infusion period unless high-level ambulatory care and rapid re-admission pathways are already well established, as in centers already providing ambulatory hematopoietic cell transplantation (HCT).

Table 7 summarizes our recommendations relating to the first 28 days following the CAR T-cell infusion. These are in line with a number of clinical trial protocols and the recommendations of scientific societies.33,39

---

*Table 5A. Checklist before starting the conditioning.*

| SPCs | EBMT recommendations | Comments |
|------|----------------------|----------|
| CAR T-cell product | The availability of the CAR T-cell product must be confirmed prior to starting LD conditioning | LD conditioning should only be administered following receipt of product on site | Exceptional situations may necessitate the administration of LD conditioning following confirmation of successful production but prior to arrival |
| Clinical conditions | LD conditioning should be administered before the Kymriah™ infusion unless the WBC count within 1 week of the infusion is ≤1.0x10⁹/L | Active infections must be excluded or under control before starting LD conditioning | Patient has to be able to tolerate LD conditioning |
| WBC | LD conditioning should be administered before the Kymriah™ infusion unless the WBC count within 1 week of the infusion is ≤1.0x10⁹/L | Administer LD conditioning to all patients regardless of WBC or ALC | Some investigators have suggested that patients with low ALC (<0.1x10⁹/L) may not require LD as these patients are already “lymphodepleted” |

*Table 5B. Checklist of laboratory tests prior to conditioning.*

| Test methods | Trials and SPC | EBMT recommendations | Comment |
|--------------|---------------|----------------------|---------|
| C-reactive protein and/or fibrinogen level | Required to rule out ongoing infection | LD is contraindicated in patients with active infection. Active infection must be excluded or under control before starting LD | |
| Bilirubin | <26.34 μmol/L | <34 μmol/L; higher limit acceptable (>43 μmol/L) with Gilbert syndrome | No trial data regarding patients outside of these parameters |
| AST/ALT | <5xULN | <5xULN | Attempt to identify causes e.g. active infections |
| Creatinine clearance | > 30 mL/min | Modify drugs doses according to creatinine clearance |

*Other work-up*

- Repeat cardiac investigations only if clinically indicated (e.g. cardiotoxic bridging chemotherapy) | LVEF >40%; assess for pericardial effusion by echocardiogram; ECG |

**Chemistry**

- Required to rule out ongoing infection | LD is contraindicated in patients with active infection. Active infection must be excluded or under control before starting LD |

*SPC: summary of product characteristics; EBMT: European Society for Blood and Marrow Transplantation; CAR: chimeric antigen receptor; LD: lymphodepletion; WBC: white blood cell count; ALC: absolute lymphocyte count.*
Tumor lysis syndrome

CAR T-cell therapy can result in the rapid destruction of tumor cells and therapy-associated adverse events including tumor lysis syndrome.40-42 Standard hospital protocols should apply. Tumor lysis in certain locations (gut, biliary tree, lungs, genitourinary tract) may lead to perforation and the release of commensal organisms resulting in peritonitis.43

Infections

Active infections should be fully treated and under control prior to the administration of LD conditioning and the

Table 6. Checklist and pre-medication before chimeric antigen receptor T-cell infusion.

|                         | SPC | EBMT recommendations | Comment |
|-------------------------|-----|----------------------|---------|
| Active infection        |     | Contraindication     |         |
|                         |     | CAR T-cell infusion should be delayed until the infection has been successfully treated or controlled |
| Cardiac arrhythmia not controlled with medical management | Reasons to delay treatment: unresolved SAR (esp. pulmonary reactions, cardiac reactions or hypotension) from preceding chemotherapies (Kymriah™ and Yescarta™) | Cardiologist opinion is required | Specific individualized risk-benefit assessment required |
| Hypotension requiring vasopressor support | See above | Contraindication | CAR T-cell infusion should be delayed until the hypotension has been fully treated |
| New-onset or worsening of another non-hematologic organ dysfunction ≥ grade 3 | | Work-up is needed to identify the cause | Specific individualized risk-benefit assessment required |
| Significant worsening of the clinical condition since start of LD | Reasons to delay treatment: significant clinical worsening of leukemia burden or lymphoma following LD chemotherapy (Kymriah™) | Work-up is needed to identify the cause | Specific individualized risk-benefit assessment required |
| Pre-medication | “It is recommended that patients be pre-medicated with paracetamol and diphenhydramine or another H1 antihistamine within approximately 30 to 60 minutes prior to Kymriah™ infusion” “Paracetamol given orally and diphenhydramine or chlorpheniramine intravenous or oral (or equivalent) approximately 1 hour before Yescarta™ infusion is recommended” | As per SPC |
| Concomitant medication | Corticosteroids should NOT be used prior to or around the time of the infusion except in case of a life-threatening emergency | As per SPC |

SPC: summary of product characteristics; EBMT: European Society for Blood and Marrow Transplantation; CAR: chimeric antigen receptor; SAR: severe adverse reaction; LD: lymphodepletion.

Table 7. Recommendations regarding the first month after chimeric antigen receptor T-cell infusion.

| Period | SPC and protocols | EBMT recommendations | Comments |
|--------|-------------------|----------------------|----------|
| Day 0 to day +14 post-infusion | Some protocols require 5-14 days hospitalization after the infusion | Ideally, 14 days hospitalization | Shorter hospitalization periods as well as outpatient follow-up are possible in centers that can provide 24/7 contact with immediate availability of specialist inpatient care. Patients must be located within 30 min of the center |
| From hospital discharge to day +28 post-infusion | Some protocols require that patients be located within 30 to 60 min of the center | Patients must be located within 60 min of the treating unit or a well-equipped center* The continuous presence of a caregiver who is educated to recognize the signs and symptoms of CRS and ICANS is required | CRS and, in particular, ICANS can occur after the patient has left the hospital. In addition, life-threatening complications may occur during this period e.g. septic shock in neutropenic patients |

SPC: summary of product characteristics; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome. * Centers competent to manage such complications.
infusion of CAR T-cell products, especially given the likely cytokine-driven exacerbation of inflammatory processes. The presence of fever should prompt blood and urine cultures, a chest radiograph, and, depending on symptoms, respiratory viral screening, cytomegalovirus and Epstein-Barr virus nucleic acid testing, computed tomography imaging, lumbar puncture, and/or brain magnetic resonance imaging. Empiric antimicrobial therapy based on symptoms and institutional protocols should not be delayed based on the presumption of CRS and clinicians should consider the prior duration of neutropenia.\(^{49}\)

To reduce the time from recognition of suspected sepsis to treatment with antimicrobial medications, institutions may consider the use of patient group directives or conditional orders. These orders allow nursing staff to respond rapidly to signs and symptoms of infection, an example being the automatic administration of specific intravenous antibiotics following the detection of a fever.

**Cytokine release syndrome**

CRS is a form of systemic inflammatory response following the infusion of CAR T cells. However, CRS has also been described following the administration of various monoclonal antibodies including bi-specific antibodies and anti-lymphocyte globulin and as a complication of haploidentical transplantation.\(^{44,46}\) CRS is the most common complication after CAR T-cell therapy. Depending on the type of CAR T-cell therapy, 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%.\(^{49}\)

The activation of CAR T cells is the triggering event of CRS. This leads to the release of effector cytokines such as interferon-\(\gamma\), tumor necrosis factor-\(\alpha\) and IL-2. These molecules act inter alia and do not generally trigger specific interventions. The spectrum of symptoms and signs is nonspecific, ranging from confusion, headaches, tremors, hallucinations and abnormal movements to seizures, papilloedema and coma. Any neurological symptom occurring after the CAR T-cell infusion must therefore be considered as CAR T-related until proven otherwise. However, the ASTCT consensus panel recommended excluding non-specific symptoms such as headache, tremor, myoclonus, asterixis, and hallucinations as they are usually managed symptomatically and do not generally trigger specific interventions.

Severe cases have been reported, occasionally leading to death, due to multifocal hemorrhage, cerebral edema and laminar cortical necrosis. The severity is correlated with the increase in specific biomarkers such as C-reactive protein, ferritin and IL-6.\(^{36,40}\) Close monitoring of patients using validated nursing tools is necessary to identify early manifestations of neurotoxicity. This requires serial cognitive testing.

Rapid access to neurological expertise is needed. Cross-sectional imaging (computed tomography, magnetic resonance imaging), electroencephalography, and cerebrospinal fluid examination may all be required in the management of these complex patients. Anti-epileptic prophylaxis with agents such as levetiracetam is not routinely recommended except in patients with a history of seizures or central nervous system disease.

Pre-existing neurological comorbidities may be a risk factor for the development of ICANS. Disease-associated factors include ALL, tumor burden, history of meningeal involvement and prior central nervous system-directed therapies.\(^{11,58-60}\) The intensity of ICANS has been correlated with the depth of lymphopenia and the homeostatic expansion of CAR T cells. Moreover, the severity of ICANS has also been found to be associated with 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.

The CARTOX scoring system was updated by the

---

**Neurological toxicity**

The neurological toxicity seen in CAR T-cell recipients, previously called CAR-related encephalopathy syndrome (CRES), has recently been termed immune effector cell-associated neurotoxicity syndrome (ICANS).\(^{12,52,56}\) This is the second most common adverse event following CAR T-cell infusion and its incidence has been reported at rates varying from 12% to 55%. In a recent study of 100 patients, the median time-to-onset of the first neurological symptoms was 6 days (range, 1-34 days) after the CAR T-cell infusion.\(^{57}\) The duration of symptoms is generally between 2 and 9 days although late complications may occur.\(^{12,56,58}\) In general, it develops either at the same time as or following resolution of CRS. Deterioration in handwriting has been shown to be an early predictor of central neurotoxicity. Therefore, daily writing tests over the first months following the CAR T-cell infusion can be used as a simple tool to detect incipient ICANS.

The spectrum of symptoms and signs is non-specific, ranging from confusion, headaches, tremors, hallucinations and abnormal movements to seizures, papilloedema and coma. Any neurological symptom occurring after the CAR T-cell infusion must therefore be considered as CAR T-related until proven otherwise. However, the ASTCT consensus panel recommended excluding non-specific symptoms such as headache, tremor, myoclonus, asterixis, and hallucinations as they are usually managed symptomatically and do not generally trigger specific interventions.

Severe cases have been reported, occasionally leading to death, due to multifocal hemorrhage, cerebral edema and laminar cortical necrosis. The severity is correlated with the increase in specific biomarkers such as C-reactive protein, ferritin and IL-6.\(^{36,40}\) Close monitoring of patients using validated nursing tools is necessary to identify early manifestations of neurotoxicity. This requires serial cognitive testing.

Rapid access to neurological expertise is needed. Cross-sectional imaging (computed tomography, magnetic resonance imaging), electroencephalography, and cerebrospinal fluid examination may all be required in the management of these complex patients. Anti-epileptic prophylaxis with agents such as levetiracetam is not routinely recommended except in patients with a history of seizures or central nervous system disease.

Pre-existing neurological comorbidities may be a risk factor for the development of ICANS. Disease-associated factors include ALL, tumor burden, history of meningeal involvement and prior central nervous system-directed therapies.\(^{11,58-60}\) The intensity of ICANS has been correlated with the depth of lymphopenia and the homeostatic expansion of CAR T cells. Moreover, the severity of ICANS has also been found to be associated with 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.

The CARTOX scoring system was updated by the
ASTCT consensus panel and has been replaced by the Immune Effector Cell-Associated Encephalopathy (ICE) score shown in Table 8. A different assessment tool for screening delirium in children, adapted from Traube et al., is shown in Table 9.

**Laboratory monitoring of cytokine release syndrome and neurotoxicity**

In addition to routine daily hematology and chemistry laboratory tests, C-reactive protein and ferritin levels are of use in the monitoring of patients developing CRS and neurotoxicity. Although assaying IL-6 or other cytokine levels is theoretically interesting, cytokine testing is not routinely performed in most centers at present.

Atypical lymphocytes that can mimic blasts are not uncommon at the peak of CAR T-cell expansion and can be found in the peripheral blood, bone marrow, and even the cerebrospinal fluid of patients treated with these therapies. Flow cytometry can be used to exclude relapse. Repeating microbiological testing and imaging to rule out infection is recommended in febrile patients.

**Antibiotic prophylaxis**

The combined effect of prior treatments (immunochemotherapy and/or autologous or allogeneic HCT, bridging chemotherapy administered after leukapheresis and LD conditioning) all increase the risk of opportunistic infections in patients receiving CAR T-cell therapy. Approximately one-third of patients have prolonged neutropenia (beyond day +30) and up to 20% of patients have neutropenia lasting more than 90 days. B-cell depletion and hypogammaglobulinemia are additional risk factors for infections.

After CRS and ICANS, infections are one of the most common side effects of CAR T-cell therapy. Most infections are seen within the first 30 days and are bacterial, and to a lesser extent, respiratory viral infections. Invasive fungal infections are rare and are mostly observed in ALL patients who have undergone prior allogeneic stem cell transplantation.

CAR T-cell recipients, like patients undergoing allogeneic HCT, are at increased risk of a range of infections at the...
different stages of their treatment course and appropriate antimicrobial prophylaxis is required. In general, centers performing allogeneic HCT will be familiar with the care of such patients and there is, as yet, no evidence that there are infectious issues specific to CAR T-cell therapy. Table 10 summarizes recommendations for prophylaxis against the most common infections.

There is no evidence to suggest that cytomegalovirus, 

Table 8. Immune Effector Cell-Associated Encephalopathy (ICE) score to neurological toxicity assess. Adapted from Lee et al.24

| 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 by 10 | 1      |

Table 9. Cornell Assessment of Pediatric Delirium (CAPD) to assess encephalopathy in children <12 years. Adapted from Traube et al.21

| 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             | 4      | 3     | 2         | 1      | 0     |

Table 10. Anti-infective prophylaxis after chimeric antigen receptor T-cell therapy.

| Trials                                      | EBMT recommendation | Comment |
|---------------------------------------------|---------------------|---------|
| Neutropenia                                 | G-CSF should be used according to published guidelines | Avoid if patient has CRS or ICANS There are theoretical concerns regarding macrophage activation |
| Antibacterial prophylaxis                   | Not recommended     | Not recommended* Can be considered in case of prolonged neutropenia and should be based on local guidelines e.g. with levofloxacin or ciprofloxacin |
| Anti-viral prophylaxis                       | Subjects should receive prophylaxis for infection with herpes virus, according to NCCN guidelines or standard institutional practice | Valaciclovir 500 mg bid or aciclovir 800 mg bd Start from LD conditioning until 1 year post-CAR T-cell infusion and/or until CD4+ count >0.2x10^9/L |
| Anti-pneumocystis prophylaxis               | Subjects should receive prophylaxis for infection with Pneumocystis pneumonia, according to NCCN guidelines or standard institutional practice | 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/or until CD4+ count >0.2x10^9/L Can be started later depending on center guidelines In case of co-trimoxazole allergy, pentamidine inhalation (300 mg once every month), dapsone 100 mg daily or atovaquone 1500 mg once daily are other agents to consider |
| Systemic anti-fungal prophylaxis            | Subjects should receive prophylaxis for fungal infections according to NCCN guidelines or standard institutional practice | Not recommended routinely; however, consider in patients with prolonged neutropenia and corticosteroids In patients with prior allo-HCT, prior invasive aspergillosis and those receiving corticosteroids, posaconazole prophylaxis should be considered |
| IV immunoglobulins                          | Gammaglobulin will be administered for hypogammaglobulinaemia according to institutional guidelines. At a minimum, trough IgG levels should be kept above 400 mg/4L, especially in the setting of infection | Routine in children, consider in adults who have had infections with encapsulated organisms Clinical evidence does not support routine use in adults following allo-HCT |

EBMT European Society for Blood and Marrow Transplantation; G-CSF: granulocyte colony stimulating factor; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; NCCN: National Comprehensive Cancer Network; LD: lymphodepleting conditioning; IV: intravenous; IgG: immunoglobulin G; allo-HCT: allogeneic hematopoietic cell transplantation. *In patients with neutropenic fever empiric treatment with broad spectrum antibiotics is strongly recommended.
Epstein-Barr virus or adenoviruses are significant clinical problems after CAR T-cell therapy. Little is known regarding the risk of hepatitis B and C virus reactivation as patients with these infections were specifically excluded from the trials. It is not possible to provide recommendations regarding the use of CAR T-cell therapy in patients with human immunodeficiency virus infection as seropositive individuals were also excluded. The pharmaceutical companies may, however, manufacture a drug product for a patient positive for hepatitis B, hepatitis C or human immunodeficiency virus if the viral load is below the level of detection following treatment. For patients with a history of hepatitis B infection, prophylaxis with tenofovir is recommended.46

Medium-term complications and management: day +28 to day +100

Potential toxicities during this period include delayed tumor lysis syndrome, delayed hemophagocytic lymphohistiocytosis/macrophage activation syndrome and CRS, B-cell aplasia, hypogammaglobulinemia, graft-versus-host disease (GvHD), and infections. Neutropenia, thrombocytopenia and anemia are common but generally resolve slowly over several months. Growth factor support may be indicated in the early stages.

Table 11 summarizes tests to be performed during this period and their recommended frequency.

Delayed macrophage activation syndrome and cytokine release syndrome

In the experience of CAR T-cell therapy for ALL, CRS typically occurred between 1 and 14 days after the CAR T-cell infusion, whereas in patients with chronic lymphocytic leukemia, CRS usually occurred later, between 14 and 21 days after the infusion.42 Regardless of the timing, delayed macrophage activation syndrome and CRS are managed using standard approaches.

B-cell aplasia and hypogammaglobulinemia

B-cell aplasia is an almost universal on-target, off-tumor toxicity and results in hypogammaglobulinemia. It occurs in all responding patients and can persist for several years. This absence of CD19-positive cells correlated with functional persistence of CTL019 cells below the limits of detection of flow cytometry, whereas CTL019 remained detectable by means of quantitative polymerase chain reaction analysis.42 B-cell aplasia can therefore serve as a marker for monitoring CD19-specific CAR T-cell activity over time.42,67

Persistent B-cell lymphopenia is associated with sino-pulmonary infections, notably with encapsulated bacteria; consideration can be given to vaccination although there is no evidence and immunoglobulin levels should be monitored.68 It has therefore been standard practice in pediatric centers to administer empiric immunoglobulin replacement following the administration of CAR T cells. Children with B-cell aplasia should receive immunoglobulin replacement to maintain IgG levels according to institutional guidelines for IgG substitution (i.e. ≥500mg/dL).61 In some cases, this may be a long-term requirement.

There is no consensus regarding systematic supplementation in adults who have been shown to have long-lived CD19-negative plasma cells that continue to confer humoral immunity in patients who were successfully treated with CAR T cells targeting CD19. Nevertheless, intravenous immunoglobulin replacement is recommended in patients with hypogammaglobulinemia and recurrent infections with encapsulated bacteria. Patients may transition to home-administered subcutaneous immunoglobulins after 6 months.

Graft-versus-host disease

Donor-derived CAR T cells may rarely trigger GvHD if harvested from, and then returned to, patients who have undergone allogeneic HCT. Current evidence suggests that the risk of inducing GvHD with the use of donor-derived CAR T cells is low.68-70 However, vigilance is required as this complication is potentially severe and life-threatening. If suspected, GvHD should be diagnosed and managed using standard protocols, balancing the potential benefit of introducing systemic immunosuppression against its effect on anti-tumor CAR T-cell function.

Infections

Beyond 30 days, viral infections predominate including respiratory viral infections, cytomegalovirus viremia and pneumonia. Later infections may reflect prolonged immunoglobulin deficiency (up to 46% at day 90) as well as lymphopenia.47 Severe co-infections with CRS include respiratory virus infections (some nosocomial),

| Test | Purpose | Frequency | Comment |
|------|---------|-----------|---------|
| FBC, biochemistry panel, LDH, fibrinogen, CRP | Standard follow-up | At every visit and as clinically indicated | |
| CMV, EBV, adenovirus | Viral reactivation | As clinically indicated | |
| Quantitative immunoglobulins or serum protein electrophoresis | Immune reconstitution | Monthly | Consider IV immunoglobulins |
| Peripheral blood immunophenotyping – CD3/4/8/16/19 | Immune recovery | Once monthly for first 3 months, three monthly thereafter in first year | Guide to anti-infective prophylaxis |
| CAR T-cell monitoring where kits are available for routine monitoring of anti-CD19 CAR T cells | CAR T-cell persistence | Peripheral blood flow cytometry or transgene by molecular methods as clinically indicated | Not recommended by CAR T-cell manufacturers |

---

FBG: full blood count; LDH: lactate dehydrogenase; CRP: C-reactive protein; CMV: cytomegalovirus; EBV: Epstein-Barr virus; IV: intravenous; CAR: chimeric antigen receptor.
cytomegalovirus, human herpes virus-6 or Epstein-Barr virusemia, *Clostridium difficile* colitis, cholangitis, and viral encephalitis.⁶⁷,⁷²-⁷⁴

**Nursing and psychological support of patients**

CAR T cells are generally being administered in a small number of regional specialist centers to which patients are referred from general hospitals. Patients who are treated with CAR T cells may therefore experience high levels of anxiety due to their new environment as well as their prognosis. Many will be socially isolated and at a significant distance from their established support networks. The role of the clinical nurse specialist is vital to the success of the procedure as well as providing essential bedside support. Referral to local counselling/psychology services should be offered to these patients when appropriate.

Patients who are being treated on an outpatient basis and their caregivers should receive comprehensive education on the symptoms of CRS and neurotoxicity and patients should attend the treating hospital without delay in the event that they begin to feel unwell. On discharge, they should be instructed to remain within 1 hour’s travel of the treating hospital for at least 4 weeks following the infusion, during which time a caregiver should always be present. If the patient lives further away, then alternative accommodation, such as a local hotel or apartment, will be required. Independently of whether the patient is living at home or lodging in a local apartment, ambulatory care arrangements for rapid re-admission should be well established.

All patients must be informed of the potential risks and the precautions that they need to take, as described in the relevant product patient information leaflet. They may also receive further written information, according to local practice, in the form of a patient information booklet or leaflet. This should include information and education on the symptoms of CRS and serious neurological adverse reactions, the need to report any symptoms immediately to their treating physician and the need to remain in close proximity to the center in which the CAR T cells were administered for at least 4 weeks following the infusion.

Patients must be advised to keep their Patient Advice Card with them at all times and to show it to any healthcare professional they encounter, especially if they are admitted to another hospital. Patients are advised not to drive for 8 weeks after the infusion and only after resolution of any neurological symptoms. This is due to the risk of delayed neurological toxicity. It is also preferable to have a responsible adult such as a parent, spouse or other caregiver available during the first 3 months following the infusion. A reliable, consistent and well-informed caregiver is essential.

**Long-term follow-up from day +100 onwards – ‘late effects’**

Little is known about the long-term effects of CAR T-cell therapy. Only a small cohort of patients has been followed for more than 2 years. The main identified complications are prolonged cytopenias and hypogammaglobulinemia.

### Table 12. Recommended minimum frequency of attendance at centers for monitoring for late effects after chimeric antigen receptor T-cell therapy.

| Post CAR-T                  | Stable patients | Complications                  | Disease monitoring                              | Comment |
|-----------------------------|-----------------|--------------------------------|-------------------------------------------------|---------|
| Day +100 to 1 year          | Three-monthly   | As clinically indicated        | Frequency of visits required is disease-specific and monitoring could be performed by CAR T-cell center or referring clinician | Patients who proceed to subsequent allo-HCT, cytotoxic therapy and/or immune effector cell therapy should be followed as per Majhail et al. 2012²⁵ |
| One year to 15 years        | Annually        |                                |                                                 |         |

CAR: chimeric antigen receptor; allo-HCT: allogeneic hematopoietic cell transplantation

### Table 13. Recommended tests to be performed at long-term follow-up clinics.

| Test                                      | Purpose                                   | Frequency          | Comment                                      |
|-------------------------------------------|-------------------------------------------|--------------------|----------------------------------------------|
| Full blood count, biochemistry panel      | Standard follow-up                        | At every visit     |                                              |
| Viral infection (PB PCR, NPA)             | Viral reactivation                        | As clinically indicated |                                              |
| Quantitative immunoglobulins ± serum protein electrophoresis | Immune reconstitution | At every visit |                                              |
| Peripheral blood immunophenotyping – CD3/4/8/16 +56/19* | Immune reconstitution | Every second visit | No longer required following normalization |                                                |
| CAR T-cell monitoring where kits are available for routine monitoring of anti-CD19 CAR T* | CAR T-cell persistence | Every visit. However, no longer required when absent for two consecutive tests | Testing for CAR T-cell persistence is not standard. Checking for B-cell depletion as a surrogate marker is an option |                              |
| Endocrine function and other standard late effects testing appropriate to age | Standard follow-up | As clinically indicated |                                              |

PB: peripheral blood; PCR: polymerase chain reaction; NPA: nasopharyngeal aspirate; CAR: chimeric antigen receptor. *Equivalent test methods for other immune effector cells as they become available
linemia. There are also more theoretical concerns about the risk of secondary malignancies and both neurological and autoimmune diseases.

It should be recognized that all patients will have been treated previously with multiple anti-cancer therapies, some having also undergone allogeneic HCT. Some patients may receive CAR T-cell treatment at overseas centers and may then return to a CAR T-cell therapy or HCT center. There is a duty-of-care on all CAR T-cell-administering centers to arrange for appropriate local follow-up. In cases of geographical transition, formal communication, including discharge correspondence and other clinical material such as imaging files, should be provided to new health care providers.

Protocols and policies (standard operating procedures) for long-term follow-up will need to be put in place. These should cover shared care and out-reach arrangements and should be based on service level agreements between CAR T-cell centers and referring centers.

Multidisciplinary teams dealing with CAR T-cell therapies should arrange for long-term follow-up of treated patients in order to capture disease status and the late effects of CAR T-cell and prior treatments. The multidisciplinary team should include a physician with responsibility for CAR T-cell administration, disease-specific specialists, long-term follow-up nursing staff, data managers and clinical trial staff.

Long-term follow-up clinics may be incorporated into local arrangements for generic allogeneic HCT ‘late effects’ clinics with other allogeneic HCT patients, although dedicated clinics for the late effects of CAR T-cell therapy can be developed if a critical mass of survivors is reached.

The clinic should systematically monitor for the following outcomes: (i) disease status – remission, minimal residual disease, relapse, management of relapse, death, (ii) further treatments administered after CAR T-cell therapy, including allogeneic HCT and other immune effector cell therapy/Advanced Therapy Medicinal Products; (iii) late effects – for stable patients in ongoing remission, 3-monthly monitoring for the first year, annually thereafter or as clinically appropriate; (iv) infections, (v) immunological status – cell markers, immunoglobulins, including CAR T-cell persistence; (vi) new cancers, including secondary myeloid diseases; (vii) new autoimmunity and autoimmune diseases; (viii) endocrine, reproductive and bone health (including growth and development in children and young adult patients); (ix) neurological status (including recovery from ICANS); (x) psychological status.
and quality of life; (xi) cardiovascular status, including echocardiographic assessments and risk factors for cardiovascular disease, such as ‘metabolic syndrome’; (xii) respiratory status; and (xiii) gastrointestinal and hepatic status.

The role of vaccination following CAR T-cell therapy remains unclear. Until further evidence is available, no specific recommendation can be made. This is, in particular, a problem with small children who might not yet have completed their basic immunization schedule and who therefore need close follow-up.

In view of long-term B-cell depletion, the advisability of vaccination and adherence to the standard recommended national schedules needs to be evaluated for each individual based on the history of infections and laboratory assessments of cellular and humoral immunity. If vaccines are given, specific antibody responses should be assessed.

**Post-authorization safety surveillance**

As tisagenlecleucel (Kymriah™) and axicabtagene ciloleucel (Yescarta™) are the first agents in a novel class of therapies based on the genetic modification of autologous T cells using viral vectors, the EMA and the FDA have made marketing approval conditional on 15-year post-authorization safety surveillance (PASS). At an EMA-sponsored stakeholder workshop on how to best capture the long-term side effects of different CAR T-cell products over the next 15 years, it was felt that the reporting of CAR T-cell safety and efficacy in one European registry would avoid the creation of data silos and would allow for the risks and benefits of the different agents to be transparently compared on a common platform. Such a registry would also set an excellent example as to how public registries can not only improve patient care but also help to support affordable health care. In March 2019, the EBMT received a qualification opinion from the EMA which found the cellular therapy module of the EBMT registry to be fit-for-purpose for the regulatory overseeing of pharmaco-epidemiological studies concerning CAR T-cell therapy.

A modified version of the MED-A cell therapy form will be used for CAR T cells and other academic- or industry-manufactured cell therapies. The data submission time points are day 0, day +100, 6 months, and annually thereafter. This module has already proven to be effective in capturing basic data sets on academic and commercial CAR T-cell infusions, although the EMA has requested additional safeguards during data capture for regulatory purposes. However, the current minimal data set requested by the EMA for commercial products does not require detailed product information such as CD4 and CD8 ratios or transduction efficiencies, as companies consider these to be sensitive proprietary information. Agreed access to a more detailed data set regarding products being evaluated in clinical trials might benefit all those working in the CAR T-cell research field.

In the USA, the FDA has implemented product-specific Risk Evaluation and Mitigation Strategy (REMS) programs. In parallel, the National Cancer Institute-funded Moonshot Initiative program called Cellular Immunotherapy Data Resource, awarded to the CIBMTR in October 2018, will allow for the collection of real-world data. In recent years, the EBMT has worked with the CIBMTR to develop common data collection policies so the prospect of robust global datasets on the efficacy and safety of CAR T-cell therapies is on the horizon.

It is expected that patients receiving CAR T-cell therapies in both investigator-led and pharma-sponsored trials might also have their follow-up data collected in the EBMT registry. In order to address concerns that pharmaceutical companies may have about the confidentiality of commercially sensitive clinical data, trial data reported to the EBMT registry can be embargoed until investigating centers decide to make such data accessible to the public. Early data collection might also create a virtuous circle whereby knowledge of increased activity might help those lobbying for an improved infrastructure for CAR T-cell therapies across Europe in terms of funding opportunities, regulatory frameworks, and, ultimately, commercial drug approval. EMA approval for the use of the EBMT registry also places certain responsibilities on the EBMT. As a formal data controller, the EBMT will need to guarantee a fair and transparent mode of data sharing in order to improve the assessment of the many different agents and ultimately to improve our knowledge on how best to use CAR T-cell therapies.

**JACIE and regulatory issues**

FACT-JACIE standards were initially developed for the accreditation of HCT programs. The current 7th edition of the standards also covers immune effector cells (IEC) to accommodate the rapidly evolving field of cellular therapy, mainly, although not exclusively, genetically modified cells, such as CAR T cells. FACT-JACIE standards do not cover the manufacturing of CAR T cells but do include the supply chain and handover of responsibilities when the product is provided by a third party. Specific clauses in the standards detail the following requirements, among others: the need for the appropriate recognition of side effects related to the infusion of IEC, a policy for the rapid escalation of care in critically ill patients, the availability of specific drugs for CRS and other complications and a labeling system to guarantee both the identification and traceability of the product from the collection to the manufacturer and back to the clinical unit. In all involved areas, there is the need for evidence of adequate staffing and training, satisfactory levels of competency, validated procedures and efficient communication. Documentation is available at www.jacie.org.

During the introductory phase of developing CAR T cells, some centers received ‘focused’ site visits for IEC. However, now that the 7th edition of the standards is well established, inspection of IEC standards should be routinely incorporated within standard JACIE site visits, particularly as there is much dependency on the wider accreditation requirements of the HCT program i.e., clinical, apheresis, pharmacy and processing laboratory service, along with quality management system requirements. In fact, in the current 7th edition, only 2% and 6% of items are specifically related to either IEC or HCT, respectively, and 92% of the items are common to all forms of cellular therapy.

In addition to JACIE, the complexity of the clinical management of patients receiving CAR T-cell therapy has led to competent authorities and other regulatory bodies in some European countries requiring the administration of CAR T cells and other IEC within the context of an
accredited allogeneic HCT program, where established facilities, staffing and expertise can support most aspects of the CAR T-cell pathway. Regardless, the logistical impact of IEC administration within a HCT program has to be carefully planned; an implementation plan aimed at meeting all accreditation and other regulatory requirements, while engaging all professionals, services and infrastructure, is essential. Before starting, an assessment of the number of eligible patients and likely resource requirements will usually have to be reviewed by the competent authorities and other regulators, as well as by funding bodies. As mandated by the EMA, the pharmaceutical manufacturers also have their own requirements and routinely inspect facilities before a CAR T-cell program is commenced.

The EBMT and JACIE expect that most CAR T-cell activity in Europe will be delivered by experienced allogeneic HCT centers and, ultimately, as the accreditation cycles of centers roll through to the 7th edition of the standards, the IEC standards will be covered at routine accreditation inspections. For the minority of centers that undertake CAR T-cell therapy outside of an accredited allogeneic HCT program, there are a number of options. Given that CAR T-cell therapy is predominantly in B-cell non-Hodgkin lymphoma, there is the possibility of achieving the IEC standards as part of the accreditation covering autologous HCT, granted that referral for autologous HCT is common in lymphoma practice. The same considerations could also apply to myeloma specialists working outside of allogeneic HCT programs, as IEC accreditation standards could be aligned to autologous HCT activity or referral routes routinely established in every myeloma service.

In the event of CAR T-cell or related therapies becoming more broadly applicable to non-hematologic cancers and therefore potentially outside mainstream transplant practice, there are a number of possible routes. First, there may be referral to an accredited HCT program, where shared care arrangements can be easily accommodated within the quality management systems and service level agreements. This is a model that already applies to occasional HCT in solid tumors, such as germ cell tumors, where patients are referred back at a mutually agreed, often early, stage after transplantation for ongoing care by the referring medical or clinical oncologists.

An alternative strategy would be to undertake independent IEC accreditation specifically for CAR T-cell and other IEC therapies. This would have to be an individual decision, based on the number of patients undergoing therapy in a given center, as to whether the establishment of a functional quality system and other generic measures were justified just for CAR T-cell or other IEC therapy. The EBMT and JACIE are currently evaluating the demand and feasibility of this approach, which has been adopted by FACT.

Currently, the general recommendation from the EBMT and JACIE is that CAR T cells and other IEC are best delivered within the framework of an accredited HCT program, whether allogeneic or autologous, with shared care policies and service level agreements incorporated into the quality systems of the HCT program. Importantly, JACIE also provides a robust method to ensure that programs meet the quality and other requirements for mandatory long-term data submission to the EBMT registry, as well as potential benchmarking of survival outcomes.

Acknowledgments
The authors would like to thank all respondents to the international survey on the management of patients receiving CAR T-cell therapy.

References
1. Kuwana Y, Asakura Y, Utsunomiya N, et al. Expression of chimeric receptor composed of immunoglobulin-derived V regions and T-cell receptor-derived C regions. Biochem Biophys Res Commun. 1987;149(3):960-966.
2. Gross G, Waks T, Esthar Z. Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity. Proc Natl Acad Sci U S A. 1989;86(24):10024-10028.
3. Queensel B. CAR T-cells: a John von Neumann legacy. Curr Res Transl Med. 2018;66(2):55-56.
4. Sadelan M, Brentjens R, Riviere I. The basic principles of chimeric antigen receptor design. Cancer Discov. 2013;3(4):388-398.
5. Gauthier J, Yakoub-Agha I. Chimeric antigen receptor T-cell therapy for haematologic malignancies and solid tumors: clinical data to date, current limitations and perspectives. Curr Res Transl Med. 2017;65(3):99-102.
6. Ghobadi A. Chimeric antigen receptor T-cell therapy for non-Hodgkin lymphoma. Curr Res Transl Med. 2018;66(2):43-49.
7. Grupp S. Beginning the CAR T cell therapy revolution in the US and EU. Curr Res Transl Med. 2018;66(2):62-64.
8. Feldmann A, Arndt C, Bergmann R, et al. Retargeting of T lymphocytes to FSCA- or PSMA positive prostate cancer cells using the novel modular chimeric antigen receptor platform technology “UniCAR”. Oncotarget. 2017;8(19):31568-31585.
9. Atanackovic D, Radhakrishnan SV, Bhaward J, Luetkens T. Chimeric antigen receptor (CAR) therapy for multiple myeloma. Br J Haematol. 2016;172(5):685-696.
10. Radhakrishnan SV, Bhaward J, Luetkens T, Atanackovic D. Novel anti-myeloma immunotherapies targeting the SLAM family of receptors. Oncoimmunology. 2017;6(5):e1306618.
11. Gauthier J, Turtle CJ. Insights into cytokine release syndrome and neurotoxicity after CD19-specific CAR-T cell therapy. Curr Res Transl Med. 2018;66(2):50-52.
12. 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(3):e76-e85.
13. Chabannon C, Kuball J, Bondanza A, et al. Hematopoietic stem cell transplantation in its 60s: a platform for cellular therapies. Sci Transl Med. 2018;10(406).
14. Kochenderfer JN, Somerville RFT, Lu T, et al. Long-duration complete remissions of diffuse large B-cell lymphoma after anti-CD19 chimeric antigen receptor T cell therapy. Mol Ther. 2017;25(10):2245-2253.
15. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol. 2019;20(1):31-42.
16. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019;380(1):45-56.
17. Hayden PJ, Sairat T, Koster L, Snowden JA, Yakoub-Agha I. 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(3):79-88.
18. Theiblement C, Legoul S, Di Blasi R, et al. Real-world results on CD19 CAR T-cell for 60 French patients with relapsed/refractory diffuse large B-cell lymphoma included in a temporary authorization for use (ATU) program. EHA Library. 2019:S1600.
19. Frigault MJ, Dieich PJ, Martinez-Lage M, et al. Tisagenleucel CAR-T cell therapy in secondary CNS lymphoma. Blood.
Thierry C, L-A, et al. Durable molecular remissions in chronic lymphocytic leukemia treated with CD19-specific chimeric antigen receptor-modified T cells after failure of ibrutinib. J Clin Oncol. 2017;35(15):1652-1668.

Yakoub-Agha I, Cabestan C, et al. Poor survival and anti-IL-6 therapy is safe and well tolerated. Biol Blood Marrow Transplant. 2019;25(4):625-638.

Yakoub-Agha I. Clinical units to set up chimeric antigen receptor T-cell therapy (CAR-T): Considerations and recommendations of the Francophone Society of Bone Marrow Transplantation and Cellular Therapy (SGCM-TC). Bull Cancer. 2017;104(125):548-558.

Kohl U, Arsenieva S, Holzinger A, Abken H. CAR T cells in trials: recent achievements and challenges that remain in the production of modified T cells for clinical applications. Hum Gene Ther. 2018;29(5):559-568.

Park HJ, Riviere I, Genen M, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. N Engl J Med. 2018;378(5):449-459.

Mounier N, El Gnaoui T, Tilly H, et al. Retuximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II lymphoma study of the Society for Clinical Oncology. 2019;98(11):1726-1731.

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 Jun 5. [Epub ahead of print].

Maude SL. Tsiganekeliseul in pediatric patients with acute lymphoblastic leukemia. Clin Adv Hematol Oncol. 2018;16(10):664-666.

Suryadevara CM, Desai R, Farber SH, et al. Preventing Lck activation in CAR T cells confers treg resistance but requires 4-1BB signaling for them to persist and treat solid tumors in nonlymphodepleted hosts. Clin Cancer Res. 2018;24(1):558-566.

Hirayama AV, Gauthier J, Hay KA, et al. The response to lymphodepletion impacts PFS in patients with aggressive non-Hodgkin lymphoma treated with CD19 CD20 T cells. Blood. 2019;133(15):1876-1877.

Gattinoni L, Finkelstein SE, Klebanoff CA, et al. Removal of homeostatic cytokine sinks by lymphodepletion enhances the efficacy of persistently transfected antileukemic tumor-specific CD4+ T cells. J Exp Med. 2005;202(7):907-912.

Thiant S, Yakoub-Agha I, Magro L, et al. Plasma levels of IL-7 and IL-15 in the first month after myeloablative BMT are predictive biomarkers of both acute GVHD and relapse. Bone Marrow Transplant. 2010;45(10):1546-1552.

Thiant S, Labalette M, Traet J, et al. Plasma levels of IL-7 and IL-15 in the first month after myeloablative conditioned allo-SCT and relationship to acute GVHD. Bone Marrow Transplant. 2011;46(10):1574-1581.

Shank BR, Do B, Sevin A, et al. Chimeric antigen receptor T cells in hematologic malignancies. Pharmacotherapy. 2017;37(3):353-364.

Turtle CJ, Hanafi I-AA, Berger C, et al. Immunotherapy of non-Hodgkin’s B lymphoma with a defined ratio of CD8+ and CD4+ CD19-specific chimeric antigen receptor-modified T cells. Sci Transl Med. 2016;8(355):355ra116.

Hay KA, Gauthier J, Hirayama AV, et al. Factors associated with durable EFS in adult B-cell ALL patients achieving MRD-negative CR after CD19 CAR T-cell therapy. Blood. 2019;133(11):860-866.

67. 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(5):439-448.
68. Dai H, Zhang W, Li X, et al. Tolerance and efficacy of autologous or donor-derived T cells expressing CD19 chimeric antigen receptors in adult B-ALL with extramedullary leukemia. Oncoimmunology. 2015;4(11):e1027469.
69. Kebrtase F, Singh H, Huls MH, et al. Phase I trials using Sleeping Beauty to generate CD19-specific CAR T cells. J Clin Invest. 2016;126(9):3363-3376.
70. Anwer F, Shaukat AA, Zahid U, et al. Donor origin CAR T cells: graft versus malignancy effect without GVHD, a systematic review. Immunotherapy. 2017;9(2):123-130.
71. Hill JA, Li D, Hay KA, et al. Infectious complications of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy. Blood. 2018;131(1):121-130.
72. Kochenderfer JN, Dudley ME, Feldman SA, et al. B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor-transduced T cells. Blood. 2012;119(12):2709-2720.
73. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124(2):188-195.
74. Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. Blood. 2016;127(26):3321-3330.
75. 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(5):S48-S71.
76. European Medicines Agency. CAR T cell therapy registries workshop. 2019 [cited; Available from: https://www.ema.europa.eu/en/documents/report/report-car-t-cell-therapy-registries-workshop_en.pdf
77. European Medicines Agency. Qualification opinion on cellular therapy module of the European Society for Blood & Marrow Transplantation (EBMT) Registry. 2019 February 28, 2019 [cited; Available from: https://www.ebm.org/ebmt/news/ebmt-receives-regulatory-qualification-european-medicine-agency-ema-use-its-patient
78. Snowden JA, McGrath E, Duarte RF, et al. JACIE accreditation for blood and marrow transplantation: past, present and future directions of an international model for healthcare quality improvement. Bone Marrow Transplant. 2017;52(10):1567-1571.
79. Saccardi R, McGrath E, Snowden AJ. JACIE accreditation of HSCT programs. The EBMT Handbook. 2019:35-40.