

Management of complications of chimeric antigen receptor T-cell therapy: a report by the European Society of Blood and Marrow Transplantation

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Abstract

Chimeric antigen receptor (CAR) T cells are in standard clinical use to treat relapsed or refractory hematologic malignancies, such as non-Hodgkin lymphoma, multiple myeloma and acute lymphoblastic leukemia. Owing to the rapidly progressing field of CAR T-cell therapy and the lack of generally accepted treatment guidelines, we hypothesized significant differences between European centers in prevention, diagnosis and management of short- and long-term complications. To capture the current CAR T-cell management among European Society for Blood and Marrow Transplantation (EBMT) centers and to determine the medical need and specific areas for future clinical research the EBMT Transplant Complications Working Party performed a survey among 227 EBMT CAR T-cell centers. We received complete survey answers from 106 centers (47%) addressing questions in the areas of product selection, CAR T-cell logistics, management of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome as well as management in later phases including prolonged cytopenias. We identified common patterns in complication management, but also significant variety in clinical management of the centers in important aspects. Our results demonstrate a high medical need for treatment harmonization and future clinical research in the following areas: treatment of steroid-refractory and very severe cytokine release syndrome/neurotoxicity, treatment of cytopenia, early discharge and outpatient management, as well as immunoglobulin substitution.

Introduction

Chimeric antigen receptor (CAR)-positive T cells entered clinical routine in Europe. CAR T cells targeting CD19 (lymphomas, leukemias) or B-cell maturation antigen (multiple myeloma) have already become standard treatment for relapsed or refractory hematologic malignancies.^{1-7,8,9} Table 1 shows the products currently approved in Europe and their respective indications. We expect that CAR T cells with different antigen specificities will be used more widely in the near future, as demonstrated by the numerous clinical studies that are underway in various tumor entities.

CAR T cells can be effective even in advanced lines of treatment. However, short- and long-term side effects can

be substantial. Therefore, management of patients undergoing CAR T-cell therapy requires specialized supportive care, which is currently administered in dedicated CAR T-cell centers. Clinical management is applied mainly based on expert knowledge and small clinical trials. We therefore hypothesized that the results would show significant differences in prevention, diagnosis, and management of patients undergoing CAR T-cell therapy. In order to determine the medical need and specific areas for future clinical research, we wanted to describe the current management of short- and long term complications associated with CAR T-cell therapy in Europe.

Our main objectives were to describe: i) in which clinical setting patients are treated, ii) how severe- and ste-

roid-refractory cases of cytokine release syndrome (CRS) are managed, iii) which diagnostic procedures and which drugs are used in severe immune effector cell-related neurotoxicity syndrome (ICANS), iv) how cytopenias after CAR T-cell therapy are managed and what role autologous hematopoietic stem cell transplantation plays as well as v) where and how long-term care of patients after CAR T-cell therapy is applied. These main objectives were based on areas where we assumed a high medical need because of their high likelihood of influencing outcome.

Methods

The European Society for Blood and Marrow Transplantation (EBMT) is a professional association of transplant centers that are required to report regular follow-up on all consecutive stem cell transplantations. Recently, the EBMT registry started to collect reports on CAR T-cell patients, through the design and implementation of a Cellular Therapy Form (CTF). In the CAR T-cell registry of the EBMT a significant fraction of commercial CAR T-cell therapies in Europe are registered and data on outcome are periodically updated at predefined intervals of time, up to 15 years after treatment. Audits are routinely performed to determine the accuracy of the data. The study was planned and approved by the Transplant Complications Working Party of the EBMT and by the EBMT board. We designed questions as well as answer choices and discussed/edited them together with the co-authors. The questions and the respective choices of answers are provided in the tables of this manuscript. Most questions were close-ended. However, a couple of questions offered the opportunity to provide free text as a response, either to provide reasoning or to provide an unlisted, alternative answer. The EBMT Transplant Complications Working Party then designed an online survey and distributed it among the PI from European CAR T-cell centers. The survey was launched on February 23, 2023 and was closed on April 27, 2023. All responses were submitted within this 2-month time period. All of the data used in this manuscript was collected through the questionnaire prepared in the online survey tool. We didn't use any data from the Cellular Therapy Form in the EBMT Registry. Responses were analyzed using descriptive statistics. Continuous variables were summarized using median, interquartile range (IQR) and range (minimum and maximum). Categorical variables were presented using counts and percentages.

The survey focused on the use of commercially available CAR T-cell products in Europe. These were in short:

- i) Tisagenlecleucel (Tisa-Cel, Novartis, CD19) for treatment of acute lymphoblastic leukemia, diffuse-large-cell B-cell (diffuse LBL) lymphoma and follicular lymphoma.
- ii) Axicabtagene ciloleucel (Axi-Cel, Kite/Gilead, CD19) for treatment of diffuse LBCL, high grade B-cell lymphoma, primary mediastinal LBCL and follicular lymphoma.

iii) Lisocabtagene maraleucel (Liso-Cel, BMS, CD19) for treatment of diffuse LBCL, primary mediastinal large B-cell lymphoma and follicular lymphoma.

iv) Brexucabtagene autoleucel (Brexu-Cel, Kite/Gilead, CD19) for treatment of acute lymphoblastic leukemia, diffuse LBCL and mantle cell lymphoma.

v) Idecabtagene vicleucel (Ide-Cel, BMS, BCMA) for treatment of multiple myeloma.

vi) Ciltacabtagene autoleucel (Cilta-Cel, Janssen, BCMA) for treatment of multiple myeloma.

Results

One hundred and six EBMT CAR T centers completed the online survey. We present the results in the following categories: product selection (Figure 1), CAR T-cell logistics (Figure 2), management of CRS (Figure 3), management of ICANS (Figure 4) and management in later phases including prolonged cytopenias (Table 1).

Product selection (Figure 1)

Most centers (86%) were certified for use of more than one CAR T-cell product. A consort diagram is given in Figure 1. The proportion of responding centers certified for each licensed CAR T-cell product are shown. For use of CD19 targeting CAR T-cell products, the following percentages of centers were certified: Kymriah (Tisa-Cel) 90%, Yescarta (Axi-Cel) 84%, Tecartus (Brexu-Cel) 71% and Breyanzi (Liso-Cel) 24%. The overall percentage of centers certified for use of the BCMA targeting products used in multiple myeloma was lower with 24% for Abecma (Ide-Cel) and 18% for Carvykti (Cilta-Cel).

Currently, three products are approved for treatment of LBCL (Kymriah, Yescarta and Breyanzi). We were interested how centers decide which of these products they use and asked for preferences. The majority of centers (54%) answered that they are using more often Yescarta compared to Kymriah or Breyanzi; 17% of centers only use Yescarta and also 17% use the three products in roughly equal proportions. The share of centers using only Kymriah (3%), using Kymriah more often than the other products (5%) and using Breyanzi more often than the other products (2%) was relatively low. The primary factor driving the product selection in LBCL is higher effectiveness (81%). Other relevant factors for product selection were named to be the production slot availability (41%), a better tolerability (35%) and the possibility of cryopreservation (28%). The leukapheresis product that is used for production of Kymriah can be cryopreserved as opposed to the other products, which are mandate for fresh leukapheresis products. Cryopreservation therefore can enable earlier apheresis, which is an advantage in patients in need for immediate lymphoma therapy.

In multiple myeloma, currently two B-cell maturation antigen (BCMA) targeting products are approved in Europe

(Abecma and Carvykti) and some of the centers are certified for use of both products. Similar to the situation in LBCL, we asked how these centers decide which of these projects they use: 47% of centers answered that they are using exclusively Abecma and 19% use only Carvykti; 13% use more often Abecma but sometimes Carvykti and 6% the other way around, preferentially using Carvykti but sometimes Abecma. Finally, 9% answered that they use

both products in roughly equal proportions. Different from the situation in LBCL, the primary factor driving CAR T-cell product selection decisions in multiple myeloma is the availability of production slots (56%). The 'effectiveness of the product' was only rated by 33% of centers as the primary reason for product selection, probably reflecting the recent/current difficulties with production slots for BCMA targeting commercial products.

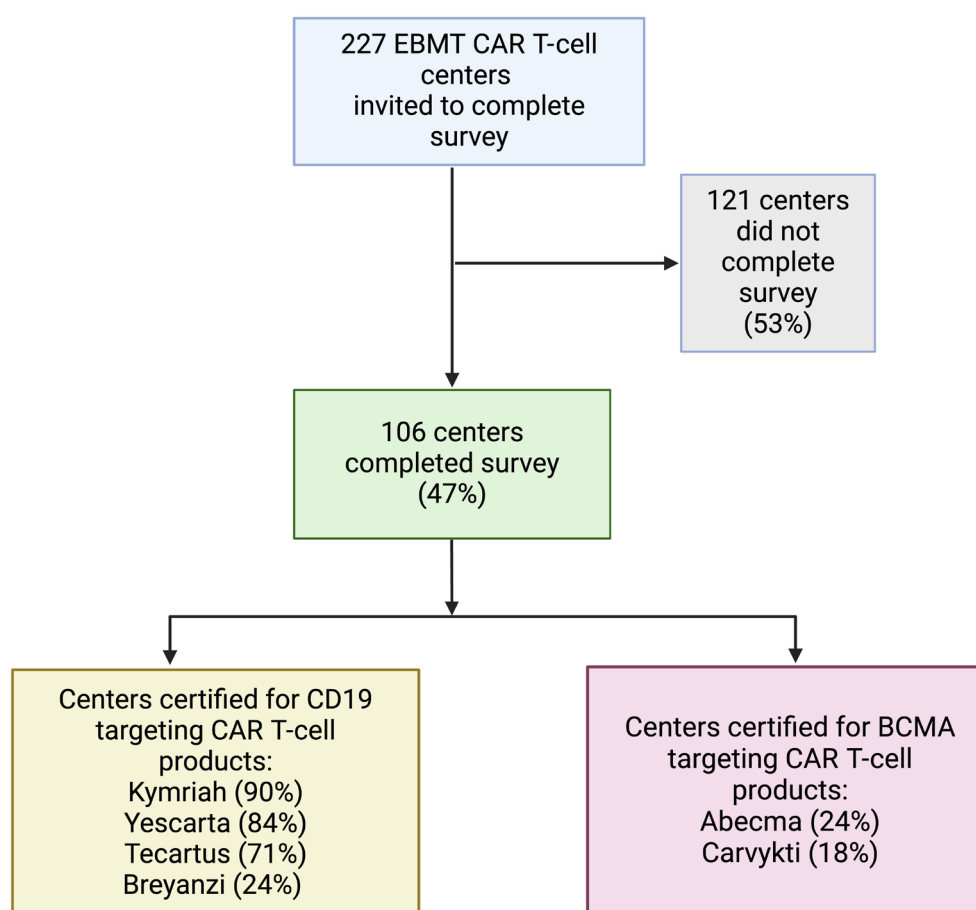


Figure 1. Consort diagram of a survey of European Society for Blood and Marrow Transplantation CAR T-cell centers on the management of complications of therapy. The proportion of responding centers certified for each licensed chimeric antigen receptor (CAR) T-cell product are shown. Created with BioRender.com. EBMT: European Society for Blood and Marrow Transplantation.

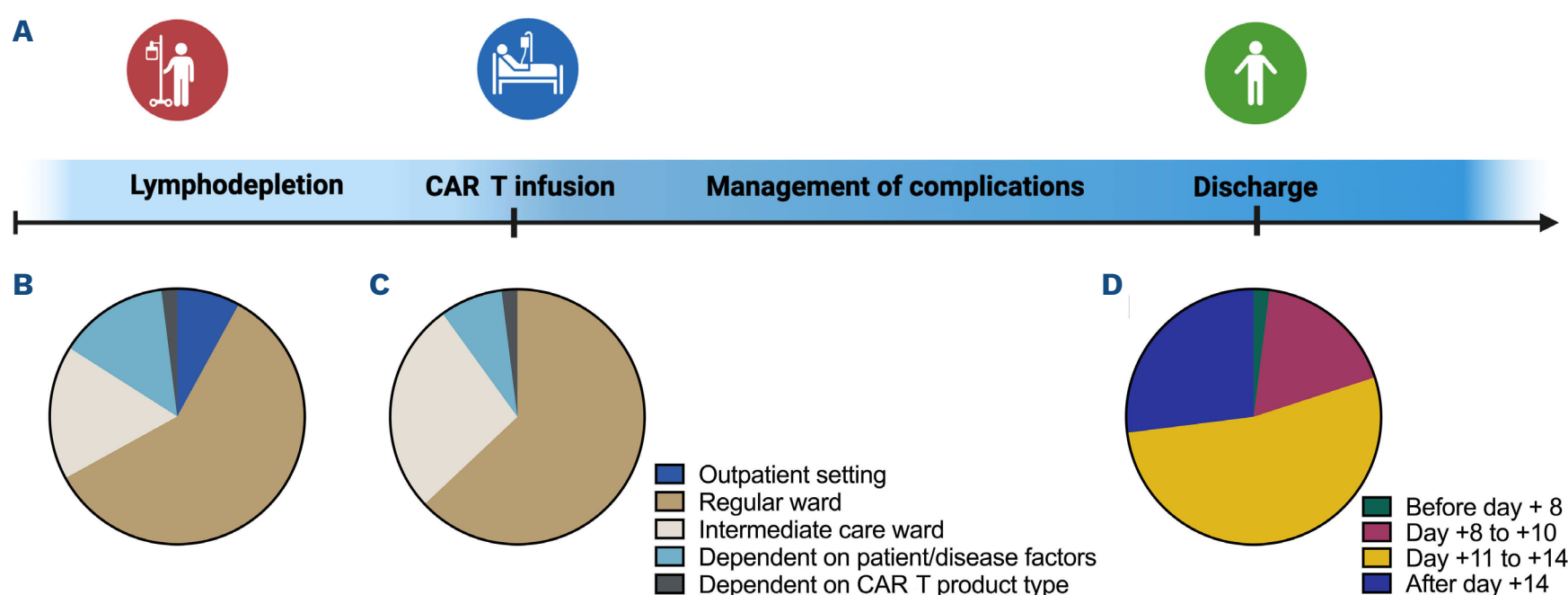


Figure 2. Clinical setting for CAR T-cell delivery at European Society for Blood and Marrow Transplantation centers. (A) Schematic diagram of chimeric antigen receptor (CAR) T-cell patient journey. (B) Clinical setting for lymphodepletion chemotherapy. (C) Clinical setting for CAR T-cell infusion, (D) Usual timing of discharge from hospital in days post CAR T-cell infusion in patients without serious complications. Created with BioRender.com.

CAR T-cell logistics (Figure 2)

We were specifically interested where patient care takes place, before, during and after CAR T-cell administration. Roughly 60% of CAR T-cell centers administer the lymphodepletion, as well as the infusion of CAR T cells, on regular wards (as opposed to intermediate care wards). Interestingly, 8% of centers answered that lymphodepletion is performed in the outpatient setting; 27% of centers answered that CAR T-cell infusion is usually done on an intermediate care ward and 8% answered that it is a decision based on patient-related factors to treat on intermediate care versus normal ward. Of note, the type of product played no relevant role in the decision where to infuse CAR T cells in the great majority of centers.

The majority of centers (53%) discharge patients without severe complications from hospital between day +11 and day +14 post CAR T infusion; 27% discharge patients even later after day +14 post CAR T administration. As expected,

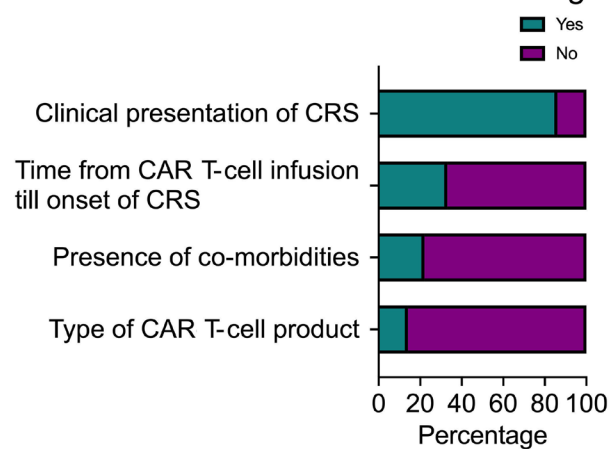
few centers perform very early discharge before day +8 (2%). However, a significant share of centers (18%) discharge patients relatively early between day +8 and day +10 after CAR T infusion.

Cytokine release syndrome management (Figure 3)

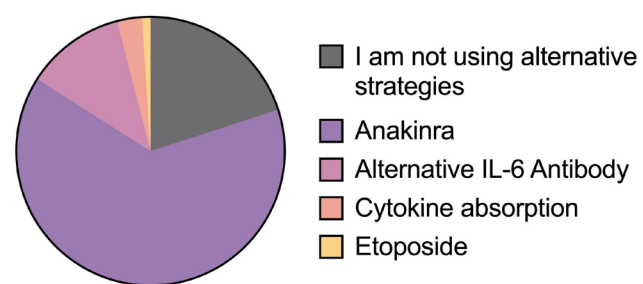
We were mainly interested in pharmacologic management of CRS because we identified this as an area of broad variability of clinical care. The clinical presentation of CRS is by far the most important factor for the decision to start first-line treatment with tocilizumab, as well as the second-line treatment with steroids. However, the presence of comorbidities, the time from CAR T infusion to onset of CRS and the type of product administered were additionally named as relevant factors contributing to the decision to start first- and second-line therapy for CRS.

We also asked about the management of very severe CRS cases. The majority of centers (68%) answered that they

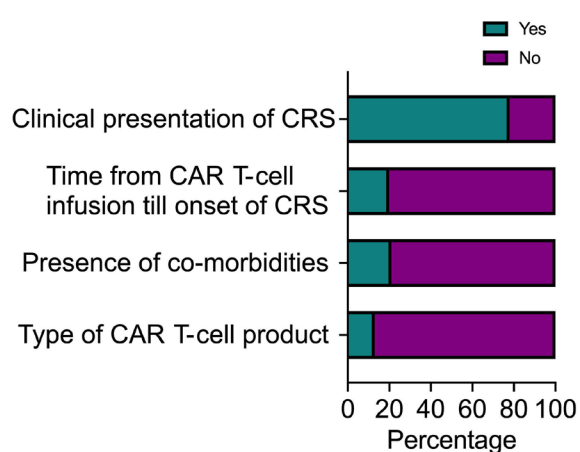
What factors have a decisive influence on your decision to use tocilizumab for CRS management?



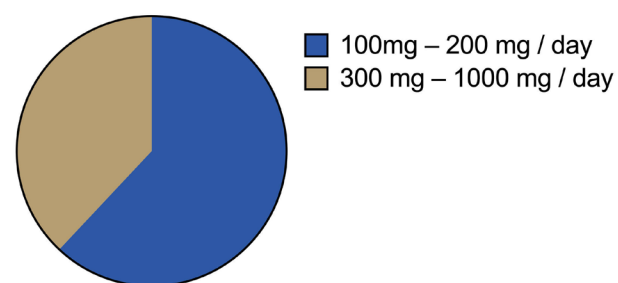
Which substance/strategy is the primary standard in your center for the treatment of severe CRS where there is no improvement after tocilizumab or steroids?



What factors have a decisive influence on your decision to use steroids for CRS management?



What is the standard daily dose of anakinra in your center for the treatment of severe CRS?



Which statements are correct regarding your CRS management with other substances (beyond tocilizumab and steroids)?

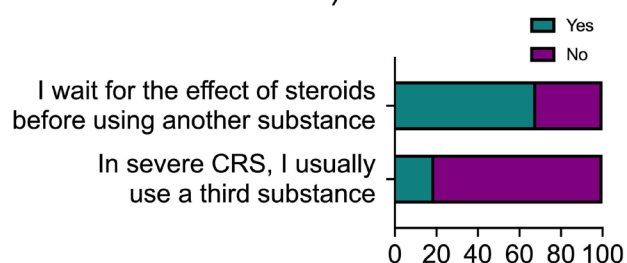


Figure 3. Survey results regarding the management of cytokine release syndrome. CRS: cytokine release syndrome; IL-6: interleukin 6; CAR: chimeric antigen receptor.

are always waiting for response to steroids before administering a third agent (on top of tocilizumab and steroids). Only 19% of centers primarily use a third substance together with steroids, in very severe CRS cases.

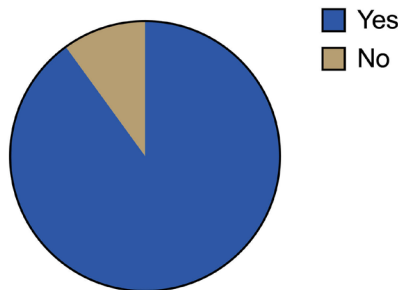
Anakinra is the third-line CRS therapy of choice in the majority of centers (64%). However, the dosages used are variable: 62% of centers use 100-200 mg/day, which is the approved dose for rheumatoid arthritis; 38% of centers use 300-1,000 mg anakinra/day, which is also recommended for more acute and severe inflammatory diseases, such as Cryopyrin-associated periodic syndrome (CAPS).¹⁰ Other third-line therapies that are preferred by the centers are an alternative interleukin 6 (IL-6) antibody (12%) and cytokine absorption (3%). Of note, 20% of centers answered that they are not using any alternative strategies in addition to tocilizumab and steroids.

Immune effector cell-related neurotoxicity syndrome management (Figure 4)

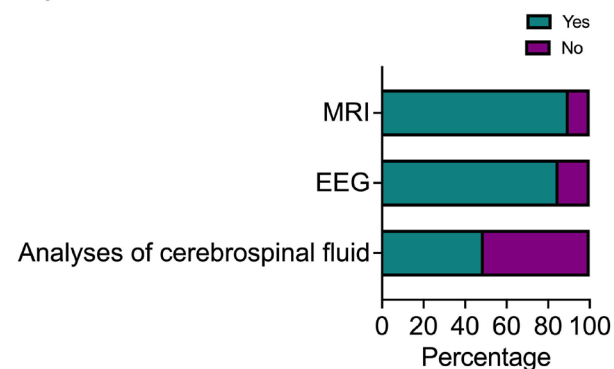
We first asked for the diagnostic work-up in case ICANS is suspected or diagnosed clinically: 90% of centers perform magnetic resonance imaging (MRI), 85% request an electroencephalography and approximately 50% do a cerebrospinal fluid puncture to determine routine parameters. Similar to the management of CRS, the clinical presentation of ICANS is the most important factor determining if steroids are used or not. Additional relevant factors for steroid treatment decisions are the presence of comorbidities, time from CAR T-cell infusion until ICANS onset and the type of CAR-T product administered.

The majority of centers (70%) answered that they are always waiting for response to steroids before administering

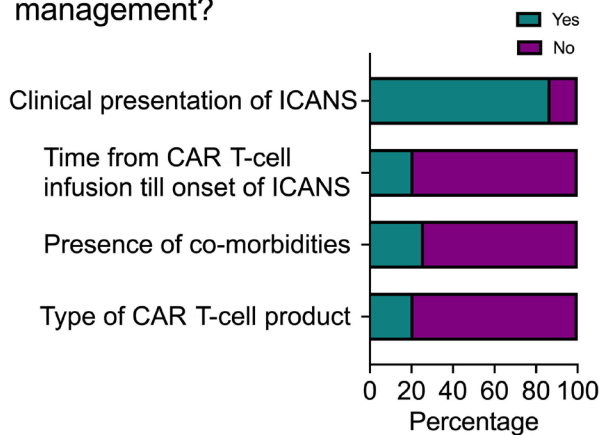
After a clinical diagnosis of ICANS, do you initiate any further diagnostics (MRI, EEG, cerebrospinal fluid) in the case of typical manifestations?



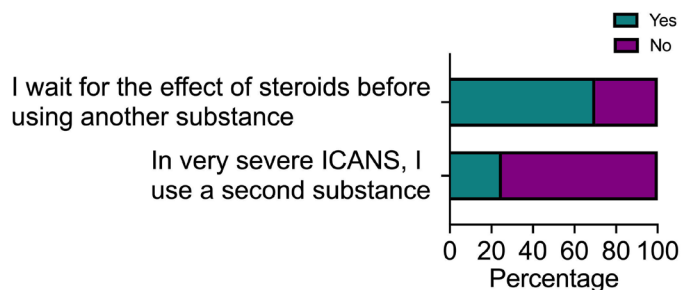
Which diagnostic procedure are you performing initially in ICANS?



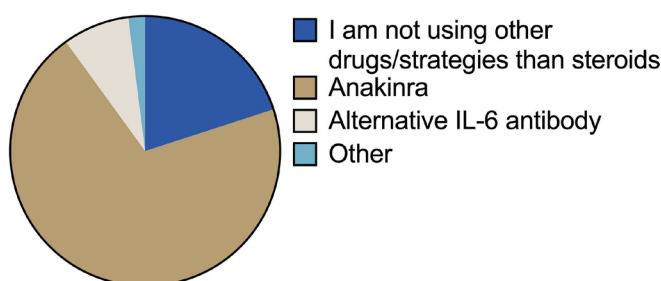
Which factors have a decisive influence on your decision to use steroids for ICANS management?



Which statements are correct regarding your ICANS management with other substances (beyond steroids)?



Which substance/strategy is the primary standard in your center for the treatment of severe ICANS when there is no improvement after steroids?



What is the standard daily dose of anakinra in your center for the treatment of severe ICANS?

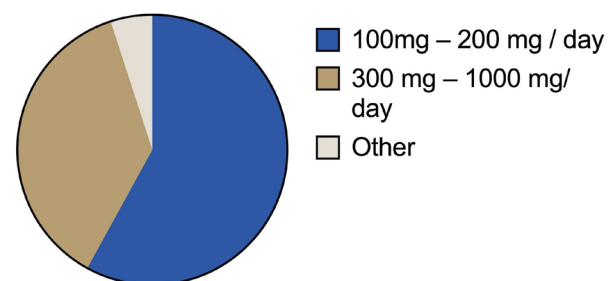


Figure 4. Survey results regarding management of immune effector cell-associated neurotoxicity syndrome. ICANS: immune effector cell-associated neurotoxicity syndrome; MRI: magnetic resonance imaging; EEG: electroencephalography; IL-6: interleukin 6.

a third agent (on top of tocilizumab and steroids). Only 25% of centers primarily use a third substance together with steroids, in very severe ICANS cases. Anakinra is the drug of choice in patients who are refractory to steroids in most centers (70%). Similar to the CRS management with anakinra, the dosages used are variable. An alternative option for treatment of steroid-refractory ICANS are alternative IL-6 antibodies. Interestingly, 20% of centers answered that they are not using other drugs/strategies on top of steroids in very severe ICANS.

Management in later phases including management of prolonged cytopenias (Table 1)

Deficiency of immunoglobulin G (IgG) frequently occur in patients treated with CD19- or BCMA-targeting CAR T cells. We were interested in the center strategies to substitute IgG and if these strategies are following European Medicines Agency (EMA) guidelines.¹¹ We found a high variability with a significant proportion performing substitution already in asymptomatic patients (57% [<4 g/L in 46% of centers and <3 g/L in 11% of centers]). A significant proportion of

centers (40%) answered that they only substitute IgG if severe infections are observed in combination with IgG deficiency following the EMA guidelines. Only 3% of centers would not routinely substitute IgG in patients after CAR T-cell therapy. In patients without available stem cell back-up (previously collected CD34⁺ autologous stem cells), only 11% of centers consider collecting a back-up in patients at high risk for prolonged cytopenia; 55% of centers infuse stem cell back-ups in patients with severe CAR T-cell associated prolonged cytopenia. However, there is no consensus on the ideal time point of stem cell administration in this situation. A majority regard the best time point after day +45 but some investigators also consider earlier time points between day +16 to day +45 after CAR T-cell infusion. Eighty percent of centers are routinely using granulocyte colony-stimulating factor (G-CSF) in patients with neutropenia after CAR T-cell therapy, but again there is no consensus regarding severity of neutropenia as a trigger for G-CSF. Fifty percent of centers answered that they are using a cutoff at $<50 \times 10^9$ neutrophils/L and the remaining centers use different cutoffs such as $<20 \times 10^9$ /L or $<100 \times 10^9$ /L.

Table 1. Survey results regarding management in later phases including prolonged cytopenias.

Questions and answer choices	Percentage of answers selected
Which statements are correct regarding your management of IgG deficiency? I substitute IgG in asymptomatic patients at levels <4 g/L I substitute IgG in asymptomatic patients at levels <3 g/L I substitute IgG exclusively when there is a combination of IgG deficiency and severe infections I never substitute IgG after CAR T	46 11 40 3
Do you collect autologous stem cells as a backup prior to CAR T-cell therapy (when there are no backups from a previous or planned autoSCT)? Never Always Yes, if cytopenia risk is increased	88 1 11
Which statements are correct regarding the administration of autoSCT in patients with severe hematotoxicity after CAR T in your center? I do not administer autologous stem cell transplants in severe hematotoxicity First, waiting for a spontaneous improvement and then, if necessary, the administration of autoSCT transplants after d+45 is a good strategy Giving autoSCT grafts between d+16 and d+45 after CAR T infusion is a good strategy Early delivery of autoSCT grafts before d+15 after CAR T infusion is a good strategy	46 42 12 1
Which statements are correct regarding the administration of GCSF when patients have severe neutropenia after CAR T? I do not administer GCSF in this situation I administer GCSF to patients with neutrophils $<20 \times 10^9$ /L I administer GCSF to patients with neutrophils $<50 \times 10^9$ /L I administer GCSF to patients with neutrophils $<100 \times 10^9$ /L	19 16 50 14
Which methods are you using to measure CAR T-cell persistence in patients peripheral blood? I do not measure CAR T-cell persistence Flow cytometry PCR Indirectly by B-cell aplasia	23 59 11 7

IgG: immunoglobulin G; CAR: chimeric antigen receptor; autoSCT: autologous stem cell transplant; d: day; GCSF: granulocyte colony-stimulating factor; PCR: polymerase chain reaction.

Next, we asked if and how centers measure CAR T-cell persistence in peripheral blood. About two thirds of centers perform CAR T-cell measurement. Flow cytometry based methods are most frequently used, followed by polymerase chain reaction-based methods.

Finally, we were interested if there were any apparent differences in management of complications according to the country in which the institution is based. We therefore re-analyzed our data according to different countries but focused on the three most contributing countries Germany, Italy and France to be able to detect patterns. In none of the areas (product selection, logistics, CRS, ICANS and later phase) did we find any apparent differences in management according to the country of origin.

Discussion

In this survey performed among European CAR T-cell centers, we found a considerable variety in practice patterns of complication management. This reflects the absence of generally accepted treatment guidelines as well as the lack of extensive clinical data from the relatively small clinical trials leading to approval of the CAR T-cell products. With more than 100 centers responding to the survey, we had a higher response rate than we had assumed. However, on the other hand less than 50% of invited centers answered raising the question if our results are representative for the European real-world setting. In this regard, we can't be sure and we have no opportunity of proving this. We can only state that the list of countries in our survey answers is representative in that the top countries (Germany, France, Italy) are the countries in which most CAR T-cell therapies are performed in Europe.¹² A further limitation is that we have not gathered data if the described management was performed in the framework of institutional clinical standards or was based on individual decisions.

Of note, we focused on the setting of approved therapies. In addition a considerable portion of patients undergoing CAR T-cell therapy in Europe are currently managed in clinical trial investigations with either novel products or approved products in new indications. With our collected data we can't comment on this commercial trial setting where the management may differ.

We found distinct drivers for product selection in CD19⁺ CAR T products used for LBCL *versus* BCMA targeting products used for multiple myeloma. Interestingly, we found that in LBCL the primary driving factor for product decisions is efficacy. This creates a medical need for efforts to collect high quality real-world data, because data from the clinical trials leading to approval of the three products (Kymriah, Yescarta and Breyanzi) does not allow to compare efficacy. First efforts to use real-world data to compare the outcome in LBCL patients treated with the different products have been undertaken and the evidence basis

is currently improving.^{2,3,13,14} During the period where the survey was done (February to April 2023) and before, the production slot availability for BCMA targeting products was extremely restricted, which explains that in multiple myeloma the primary driver for product decision making was the production slot availability.

As expected, the survey documents that outpatient treatment during CAR T-cell infusion and in the early phase after CAR T administration plays no role in the European health care setting yet. This is probably due to the strict requirements on patient care in many countries. In the future, it will be important to lay the structural and regulatory basis for early discharge and for outpatient CAR T treatment, which has been successfully used in the US and other countries.¹⁵

Standard primary management of CRS and ICANS is already homogeneous.¹⁶ One important area of medical need is to homogenize the management of steroid-refractory cases and very severe forms of CRS/ICANS. In this regard our survey shows that Anakinra, an IL-1 receptor antagonist, is widely used in this situation and should be recommended in future guidelines. However, more preclinical and clinical data are needed to determine the optimal dosing schedule of anakinra in this setting as we found that roughly two thirds of centers use relatively low doses (100-200 mg/day) according to approved treatment for rheumatoid arthritis.¹⁰ In contrast, approximately one third of centers use higher anakinra doses, probably as a reaction to reports that higher doses are needed for effective treatment of severe CRS/ICANS.¹⁷

There is no generally accepted definition for diagnosis and grading of CAR T-cell therapy-related cytopenia preventing the establishment of evidence-based standardized treatment algorithms.¹⁸⁻²⁰ We recently found in the EBMT CAR T database that the cumulative incidence of \geq grade 3 cytopenia was 12.1% at 100 days after CD19⁺ CAR T-cell infusion.²¹ In ~50% of cases there was no resolution of cytopenia until day +100, demonstrating the clinical relevance of the problem. An attractive opportunity to treat post CAR T-cell cytopenia is the administration of stem cell boosts (autologous peripheral blood stem cell transplants).^{22,23} In the current survey, more than 50% of centers answered that they consider stem cell boosts in this situation. Our results show that the optimal timing of stem cell boosts remains to be determined, as demonstrated by a high variety in clinical practice. Of note, we found that only a small minority of centers are collecting hematopoietic stem cell boosts prior to CAR T-cell therapy, probably reflecting logistic challenges including reimbursement and storage capacity issues.

Patients after CD19 targeting and BCMA targeting CAR T-cell therapies are at high risk for hypo-gammaglobulinaemia and increased risk of infections.^{24,25} However, there is no generally accepted standard for substitution of IgG fitting to our result of a high heterogeneity in clinical management. In summary, our survey documents the variety in management of CAR T-cell-related complications in Europe. A

validation of our results can be attempted by similar surveys in other health care settings, e.g., in North America or Asia. Our results highlight the need for collection of more clinical evidence. A good way to address this need is to integrate concepts for complication management in clinical CAR T-cell trials. Another good option to collect evidence and improve clinical standards is to augment the quality of collected real world data and to increase collaborative efforts of harmonization. One such example is the GoCART coalition, founded by the EBMT and by the European Hematology Association (EHA). GoCART is a multi-stakeholder coalition of patient representatives, health care professionals, pharmaceutical companies, regulators, Health Technology Assessment bodies and reimbursement agencies, and medical organizations, collaborating to maximize the potential of cellular therapies. Specific tasks for EBMT and for GoCART include i) the more extensive and exact assessment of CAR T-cell-related complications in the post-authorization safety studies (PASS) and in the EBMT cellular therapy data forms, ii) conduct formal workshops by harmonization committees²⁶ and iii) lobby and stand for a more adequate compensation of documentation efforts by CAR T-cell centers.

Disclosures

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Contributions

OP designed research, analyzed data and wrote the manuscript. WB, CP, CK and ZP designed research, analyzed data and edited the manuscript. The remaining authors designed research and edited the manuscript.

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Data-sharing statement

The data that support the findings of this study are available on request from the corresponding author.

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