

Severe cytopenia after CD19 CAR T-cell therapy: a retrospective study from the EBMT Transplant Complications Working Party

Olaf Penack ^{1,2}, Christophe Peczynski,^{2,3} Christian Koenecke,^{2,4} Emmanuelle Polge,^{2,3} Andrea Kuhl,⁵ Nathalie Fegueur,⁶ Michael Daskalakis,⁷ Nicolaus Kröger,⁸ Peter Dreger,^{9,10} Caroline Besley,¹¹ Urs Schanz,¹² Adrian Bloor,¹³ Arnold Ganser,¹⁴ Edouard Forcade,¹⁵ Lucia López Corral,¹⁶ Jakob R Passweg,¹⁷ Urban Novak,¹⁸ Ivan Moiseev,^{2,19} Hélène Schoemans,^{2,20} Grzegorz W Basak,^{2,10} Christian Chabannon ^{21,22} Anna Sureda,²³ Dina Averbuch,^{24,25} Bertram Glass,^{26,27} Rafael de la Camara ^{24,28} Zinaida Peric^{2,29}

To cite: Penack O, Peczynski C, Koenecke C, *et al*. Severe cytopenia after CD19 CAR T-cell therapy: a retrospective study from the EBMT Transplant Complications Working Party. *Journal for ImmunoTherapy of Cancer* 2023;**11**:e006406. doi:10.1136/jitc-2022-006406

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/jitc-2022-006406>).

Accepted 23 March 2023



© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr Olaf Penack;
olaf.penack@charite.de

ABSTRACT

We investigated the incidence and outcome of anti-CD19 chimeric antigen receptor (CAR) T-cells-associated Common Terminology Criteria for Adverse Events (CTCAE) \geq grade 3 cytopenia. In the EBMT CAR-T registry, we identified 398 adult patients with large B-cell lymphoma who had been treated with CAR-T-cells with axicel (62%) or tisacel (38%) before August 2021 and had cytopenia status documented for the first 100 days. Most patients had received two or three previous lines of therapy, however, 22.3% had received four or more. Disease status was progressive in 80.4%, stable in 5.0% and partial/complete remission in 14.6%. 25.9% of the patients had received a transplantation before. Median age was 61.4 years (min–max; IQR=18.7–81; (52.9–69.5)). The cumulative incidence of \geq grade 3 cytopenia was 9.0% at 30 days (95% CI (6.5 to 12.1)) and 12.1% at 100 days after CAR T-cell infusion (95% CI (9.1 to 15.5)). The median time from CAR-T infusion to cytopenia onset was 16.5 days (min–max; IQR=1–90; (4–29.8)). Grade 3 and grade 4 CTCAE cytopenia occurred in 15.2% and 84.8%, respectively. In 47.6% there was no resolution. Severe cytopenia had no significant impact on overall survival (OS) (HR 1.13 (95% CI 0.74 to 1.73), $p=0.57$). However, patients with severe cytopenia had a poorer progression-free survival (PFS) (HR 1.54 (95% CI 1.07 to 2.22), $p=0.02$) and a higher relapse incidence (HR 1.52 (95% CI 1.04 to 2.23), $p=0.03$). In those patients who developed severe cytopenia during the first 100 days ($n=47$), OS, PFS, relapse incidence and non-relapse mortality at 12 months after diagnosis of severe cytopenia were 53.6% (95% CI (40.3 to 71.2)), 20% (95% CI (10.4 to 38.6)), 73.5% (95% CI (55.2 to 85.2)) and 6.5% (95% CI (1.7 to 16.2)), respectively. In multivariate analysis of severe cytopenia risk factors, only year of CAR-T infusion (HR=0.61, 95% CI (0.39 to 0.95), $p=0.028$) and total number of treatment lines before CAR-T infusion (one or two lines vs three or more, HR=0.41, 95% CI (0.21 to 0.83), $p=0.013$) had a significant positive association with the incidence of

cytopenia. Other factors, such as previous transplantation, disease status at time of CAR-T, patient age and patient sex, had no significant association. Our data provide insight on frequency and clinical relevance of severe cytopenia after CAR T-cell therapy in the European real-world setting.

BACKGROUND

Commercial CD19 targeting chimeric antigen receptor (CAR)-T cell products are currently in clinical use in patients with relapsed or refractory large B-cell lymphoma (LBCL). Since this new class of antitumor therapy may have unknown side effects, a major clinical task is to discover and understand the complete risk profile. Recent real-world data suggest that severe cytopenia may be an underestimated adverse effect of CD19+CAR T-cells.^{1–4}

Health agencies such as the Food and Drug Administration and European Medicines Agency issued an obligation to Marketing Authorization Holders that they document toxicities in patients receiving commercial CAR T-cell products. In Europe, patients are registered and their follow-up reported in the continental database of the EBMT, with secondary use of data for post-authorization safety studies (PASS). A PASS is a study that is carried out after a medicinal product has been authorized. The aim of PASS is to obtain further information on a medicine's safety, or to measure the effectiveness of risk-management measures. In the current study, we have used the EBMT database⁵ to assess the real-world safety of CD19 CAR T-cell medicinal products. For the present manuscript, we

have investigated the incidence of severe cytopenia and its clinical impact after therapy with commercial CD19 CAR T-cell products in patients with LBCL in the EBMT database.

METHODS

Study design and data collection

This is a retrospective multicenter analysis using the data set of the EBMT registry. The EBMT is a professional association of more than 600 transplant centers that are required to report regular follow-up on all consecutive stem cell transplantations. Recently the EBMT registry added the capacity to collect reports on CAR T-cell patients, through the design and implementation of a cellular therapy form. 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 is 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. All patients provide their written informed consent to collect, transfer and use their personal information for research purposes at time of treatment. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Eligibility criteria for this analysis included patients 18 years of age or older undergoing CD19+CAR-T-cell therapy for LBCL before the end of July 2021. We only included patients with an available status on severe cytopenia during the first 100 days after CAR-T. Further exclusion criteria were lack of information on survival status after CAR-T.

Data on severe cytopenia was collected via a form designed for the post-authorization studies on CAR T-cell therapy. In this form, occurrence, time of onset and grading of severe cytopenia were reported. Grading was performed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, online supplemental table 1).⁶ Severe cytopenia was defined as grade 3 (hemoglobin (Hb) <80 g/L; neutrophils <1×10⁹/L; platelets <50×10⁹/L) or grade 4 (Hb <6.5 g/dL; neutrophils <0.5×10⁹/L; platelets <10×10⁹/L) for the purposes of this study. To fulfill the definition of severe cytopenia, respective changes in one cell line (either neutrophils, or platelets of Hb) was sufficient.

CAR T-cell products

Patients were treated with the commercial products axicabtagene ciloleucel (axicel) or tisagenlecleucel (tisacel). Both products are autologous anti-CD19 T-cell products containing a second-generation CAR. Axicel is generated with a retroviral vector and contains a CD28 co-stimulatory domain. Tisacel is produced with a

lentiviral vector and contains a CD137 (4-1BB) costimulatory domain.

Statistical analysis

The primary study endpoint was incidence of severe cytopenia (CTCAE grade 3 or 4) in the first 100 days after CAR T-cell infusion. Secondary study endpoints were overall survival (OS), progression-free survival (PFS) non-relapse mortality (NRM) and relapse incidence (RI). Start time was the date of CAR T-cell infusion for all endpoints. NRM was defined as death without relapse/progression, PFS was defined as survival without relapse or progression. Probabilities of OS and PFS were calculated using the Kaplan-Meier method. For the estimation of the cumulative incidence of severe cytopenia, death was considered a competing event. Cumulative incidence functions were used to estimate NRM and RI in a competing risk setting, death, and relapse competing with each other.⁷

Multivariate analysis of the risk factors for developing severe cytopenia in the first 100 days was performed using the Cox proportional-hazards model with the following variables: year of CAR-T cell infusion, patient age, patient sex, previous transplantation, disease status at CAR-T and total number of treatment lines before CAR-T infusion. These risk factors were chosen clinically as potentially relevant covariates, removing the ones with too much missing data.

To assess the impact of onset of severe cytopenia on survival outcomes, multivariate models were implemented using the Cox proportional hazards model for OS, PFS and RI, putting occurrence of severe cytopenia as a time-dependent variable. The number of events was too low for a reliable multivariate analysis of NRM.

The same risk factors as previously reported were put in the models.

Finally, we estimated OS, PFS, NRM and RI in the subgroup of patients who developed severe cytopenia in the first 100 days, starting from the date of onset of severe cytopenia.

All tests were two-sided. Statistical analyses were performed with R V.4.1.2 software (R Development Core Team, Vienna, Austria) packages.

RESULTS

Cell product, disease and patient characteristics

We identified 398 adult patients with LBCL who had undergone CD19+CAR-T-cell therapy with available data on severe cytopenia during the first 100 days. Patient and disease characteristics of the whole population are shown in [table 1](#). The median follow-up was 13.1 months. Patients were treated with axicel (61.6%) or tisacel (38.4%).

Most patients had received two or three previous lines of therapy before, however, at least 22.3% had received four or more. They were mainly men (61.1%) and had a median age of 61.4 years (min–max; IQR=18.7–81; (52.9–69.5)). Karnofsky performance score was 90% or higher in 62.3% of patients (information missing for

Table 1 Baseline characteristics

Variable	Level	Overall population (n=398)	Patients who developed severe cytopenia (n=48)
Year of CAR-T therapy	Median (min–max) (IQR)	2020 (2018–2021) (2019–2020)	2019 (2018–2021) (2019–2020)
Previous transplantation	No previous transplant	295 (74.1%)	36 (75%)
	Previous transplant	10 (25.9%)	12 (25%)
*Disease status at time of CAR-T therapy	CR/PR	58 (14.6%)	7 (14.6%)
	No CR/PR	339 (85.4%)	41 (86%)
	Missing	1	0
Patient age (years)	Median (min–max) (IQR)	61.4 (18.7–81) (52.9–69.5)	64.3 (25.2–80.2) (52.6–70.4)
Patient sex	Male	243 (61.1%)	32 (66.7%)
	Female	155 (38.9%)	16 (33.3%)
Karnofsky score	≥90	197 (62.3%)	23 (63.9%)
	<90	119 (37.7%)	13 (36.1%)
	Missing	82	12
CAR T-cell product	Axicel	245 (61.6%)	36 (75%)
	Tisacel	153 (38.4%)	12 (25%)
Total number of treatment lines before CAR-T infusion	1	39 (10.5%)	4 (8.5%)
	2	108 (29%)	8 (17%)
	≥2 (not specified)	1 (0.3%)	0 (0%)
	3	131 (35.2%)	22 (46.8%)
	≥3 (not specified)	10 (2.7%)	0 (0%)
	4	41 (11%)	6 (12.8%)
	5	24 (6.5%)	5 (10.6%)
	6	11 (3%)	1 (2.1%)
	7	5 (1.3%)	1 (2.1%)
	8	2 (0.5%)	0 (0%)
	Missing	26	1
Type of lymphodepletion	Fludarabine–cyclophosphamide	393 (99%)	48 (100%)
	†Other	4 (1%)	0 (0%)
	Missing	1	0
Time between diagnosis and CAR-T	≤1 year	137 (34.4%)	22 (45.8%)
	>1 year	261 (65.6%)	26 (54.2%)

*The disease status given is directly at CAR-T therapy meaning after bridging therapy or after watch and wait during the CAR-T production period.
†Other (4) = 1 cyclophosphamide, 1 bendamustine, 1 fludarabine, 1 fludarabine+bendamustine.
CAR, chimeric antigen receptor; CR, complete remission; PR, partial remission.

82 patients). Overall, 26% of the patients had a prior transplantation (22.4% autologous stem-cell transplant (autoSCT) only, 2.1% allogeneic SCT (alloSCT) only and 1.5% both autoSCT and alloSCT). Disease status before CAR T-cell therapy was mainly refractory (in 85% of the patients).

Incidence, onset, grading and resolution of severe cytopenia

The cumulative incidence of severe cytopenia was 9.0% at 30 days (95% CI (6.5 to 12.1)) and 12.1% at 100 days after CAR T-cell infusion (95% CI (9.1 to 15.5)) (table 2). The median time from CAR T-cell infusion to onset of severe cytopenia was 16.5 days (min–max; (IQR)=1–90; (4–29.8)). Grades 3 and 4 CTCAE cytopenia occurred in

15.2% and 84.8% of patients, respectively (missing data for 15 patients). Of note, 47.6% suffered from prolonged severe cytopenia without resolution before day+100 after CAR-T cell infusion (data missing for six patients).

Major survival outcomes in the global population

OS was 84.1% (95% CI 80.6 to 87.8) at 3 months and 55.8% (95% CI 50.9 to 61.3) at 12 months after CAR T-cell infusion. Mortality was mainly due to relapse/progression of LBCL accounting for 167 of 195 deaths (85.6%). PFS was 66.7% (95% CI 62.2 to 71.6) at 3 months and 33.1% (95% CI 28.6 to 38.5) at 12 months. RI was 29.2% (95% CI 24.7 to 33.8) at 3 months and 60.9% (95% CI 55.7 to 65.8) at 12 months. NRM was 2.6% (95% CI 1.4 to 4.6) at

Table 2 Incidence, grading, type and resolution of severe cytopenia

Variable		n=48
Incidence of severe cytopenia	At 30 days	9.0% (95% CI 6.5 to 12.1)
	At 100 days	12.1% (95% CI 9.1 to 15.5)
Time from CAR-T to severe cytopenia (days)	median (min–max) (IQR)	16.5 (1–90) (4–29.8)
Severe cytopenia grade	3	5 (15.2%)
	4	28 (84.8%)
	Missing	15
Type of cytopenia	Neutropenia	12 (46.2%)
	Neutropenia+anemia+thrombocytopenia	12 (46.2%)
	Anaemia+thrombocytopenia	1 (3.8%)
	Neutropenia+thrombocytopenia	1 (3.8%)
	Missing	22
Severe cytopenia resolved until day+100	No	20 (47.6%)
	Yes	22 (52.4%)
	Missing	6

CAR, chimeric antigen receptor.

3 months and 4.5% (95% CI 2.5 to 7) at 12 months after CAR T-cell infusion.

Risk factors for severe cytopenia

In multivariate analysis of severe cytopenia risk factors, only year of CAR-T cells infusion (as a continuous variable, HR=0.61, 95% CI (0.4 to 0.95), $p=0.03$) and total number of treatment lines before CAR-T infusion (one or two lines vs three or more, HR=0.41, 95% CI (0.21 to 0.83), $p=0.013$) had a significant positive impact on the incidence of cytopenia. Other factors had no significant impact: previous transplantation versus no previous transplantation (HR=1.47, 95% CI (0.72 to 3), $p=0.29$), disease status at time of CAR-T no complete remission/partial remission (CR/PR) versus CR/PR (HR=0.74, 95% CI (0.32 to 1.71), $p=0.49$), patient age as a continuous variable with 5 years increment (HR=1.05, 95% CI (0.93 to 1.19), $p=0.44$) and patient sex female versus male (HR=0.75, 95% CI (0.41 to 1.38), $p=0.36$).

Impact of severe cytopenia on survival outcomes

As a time-dependent variable, severe cytopenia had no significant impact on OS (HR 1.13 (95% CI 0.74 to 1.73),

$p=0.57$) but was significantly associated with reduced PFS (HR 1.54 (95% CI 1.07 to 2.22), $p=0.02$) and increased RI (HR 1.52 (95% CI 1.04 to 2.23), $p=0.03$) (table 3).

NRM occurred in only 3 out of 47 patients with severe cytopenia after CAR T-cell therapy for LBCL. Because of this low absolute number, we did not measure the impact of severe cytopenia on NRM. Causes of death are described in online supplemental table 2. NRM by non-infectious toxicities or by infectious-complications played a minor role. However, because infections are a major clinical concern in patients with severe cytopenia, we described them in more detail. Online supplemental table 3 summarizes sites and timing of infections that were reported. With 46 cases, bacteremia was the most frequently reported infectious complication. Coagulase-negative staphylococci followed by *Escherichia coli* were the predominant pathogens found in blood cultures. Other organ infections were pneumonia, upper respiratory tract infection, enteritis and cystitis. Most reported pathogens in these organ infections were bacteria (as opposed to virus or fungi). Of note, 15 cases of cytomegalovirus (CMV) reactivation occurred in the whole population,

Table 3 Outcomes in patients with severe cytopenia within 100 days after CAR T-cell therapy

Outcome	Time after diagnosis of severe cytopenia	Patients with severe cytopenia, n=48
Non-relapse mortality	At 3 months (95% CI)	6.5% (1.7 to 16.2)
	At 12 months (95% CI)	6.5% (1.7 to 16.2)
Overall survival	At 3 months (95% CI)	80.9% (70.3 to 92.9)
	At 12 months (95% CI)	53.6% (40.3 to 71.2)
Progression-free survival	At 3 months (95% CI)	49.7% (37.1 to 66.5)
	At 12 months (95% CI)	20% (10.4 to 38.6)
Relapse incidence	At 3 months (95% CI)	43.8% (29 to 57.7)
	At 12 months (95% CI)	73.5% (55.2 to 85.2)

suggesting a clinical relevance after CAR T-cell therapy for LBCL.

Clinical outcomes and infections in patients with severe cytopenia

In the subgroup of patients who developed severe cytopenia within 100 days (characteristics of the subgroup in [table 1](#)), we evaluated outcomes with the date of severe cytopenia diagnosis as starting point ([table 3](#) and [figure 1](#)). OS was 80.9% (95% CI 70.3 to 92.9) at 3 months and 53.6% (95% CI 40.3 to 71.2) at 12 months after onset of severe cytopenia. Similar to the whole population, mortality was mainly due to relapse/progression of the lymphoid malignancy accounting for 22 of 25 total deaths (online supplemental table 2). PFS was 49.7% (95% CI 37.1 to 66.5) at 3 months and 20% (95% CI 10.4 to 38.6) at 12 months. RI was 43.8% (95% CI 29 to 57.7) at 3 months and 73.5% (95% CI 55.2 to 85.2) at 12 months after onset of severe cytopenia. Finally, NRM was 6.5% (95% CI 1.7 to 16.2) at 3 months and at 12 months.

Overall, 14 infectious complications were reported in the 48 patients with severe cytopenia after CAR T-cell therapy (online supplemental table 3). Notably, no viral reactivations were reported in this group (eg, CMV, Epstein-Barr-Virus, Human Herpesvirus Type 6, adenovirus). Taken together, we found infectious complications after CAR T-cell therapy in the whole population as well as in patients with severe cytopenia without a strong signal pointing towards a massively increased incidence in the severe cytopenia group.

DISCUSSION

In this EBMT analysis in patients with LBCL, we found 12.1% cumulative incidence of severe cytopenia at 100 days. There was a significant relation of CAR T-cell therapy-related severe cytopenia with PFS and with incidence of relapse, while NRM was relatively low in the whole population and in patients with severe cytopenia.

Incidence of severe cytopenia

In previous publications, the incidences of severe cytopenia after CD19+CAR-T-cell therapy were variable. Of note, patient populations and CAR-T products studied were inconsistent in between the different studies. On top of this, the definitions of severe cytopenia or prolonged cytopenia used are heterogeneous, making comparisons difficult. One manuscript described that after axicel infusion for LBCL or acute lymphoblastic leukemia in 31 patients, grades 3–4 neutropenia, anemia and thrombocytopenia occurred in 29%, 16% and 42%, respectively.⁸ After lisocel infusion in 269 patients with LBCL prolonged cytopenia was reported in 37% of patients.⁷ In a study by the Memorial Sloan-Kettering Cancer Center including 83 patients with different diagnoses and CAR T-cell products, the overall incidence of severe cytopenia was >50%.⁹ Overall, our results and previous publications demonstrate a clinically significant number of severe cytopenias

after CD19+CAR-T infusion. However, limitations of our study are: (1) the overall limited absolute number of patients with severe cytopenia after CAR-T cell therapy (n=48); (2) the lacking data on incidence of cytopenias in previous treatment cycles; (3) lack of follow-up data beyond day+100; and (4) missing data on type of cytopenia in 22 patients. Due to the last point, we were not able to analyze the differential impact of certain subtypes of cytopenia on outcome.

In addition, we are unable to quantify the number of patients receiving bridging therapy versus no bridging therapy because it is not included in the database. We found that 14.6% of patients had PR/CR suggesting that at least some of the patients received treatment after their disease was deemed relapsed or refractory. Previous publications,^{1–3} own experience as well as discussion with colleagues suggest that a large portion of patients in Europe receive bridging therapy (eg, in contrast to a recent axicel trial).¹⁰ For the near future, we aim at collecting more information on bridging therapy in the EBMT database.

Relation of severe cytopenia with relapse and PFS

Very few previous studies attempted to correlate the incidence of severe cytopenia after CAR T-cell infusion with clinical outcome. This was mainly due to the smaller size of the patient population studied and/or the heterogeneity of the patient populations. However, our finding, showing that patients with severe cytopenia after CAR T-cell therapy (who did not have aplasia before CAR T-cell infusion) had a lower PFS, is in line with a previous publication in a multi-center study of a large patient population. Rejeski *et al* investigated 258 patients receiving axicel or tisacel for relapsed/refractory LBCL and developed the CAR-HEMATOTOX model, which predicts hematotoxicity.² A high CAR-HEMATOTOX score ≥ 3 resulted in significantly worse PFS. The overall response rate of the LBCL at 3 months was 66.6% in patients with a low CAR-HEMATOTOX score compared with 36% in patients with a high score. Our data and the results from the previous publication suggest that patients with severe cytopenia after CD19 CAR T-cell therapy for LBCL have reduced PFS. In absence of experimental studies, which are warranted to determine the underlying mechanisms, we can only speculate on the possible reasons for the reduced PFS in patients after CAR-T infusion with severe cytopenia. One possible reason could be that the cellular and humoral immune system including mediators, such as cytokines and chemokines, are relevant for tumor growth as well as for the immunobiology of CAR-T cells. Reduction or absence of these factors may increase tumor growth and could impair the antitumor activity of CAR-T cells. Of note, tumor burden correlated with severity of cytopenia as well as with relapse rates in previous CAR-T studies.^{9,11} However, we did not find this correlation in our collective.

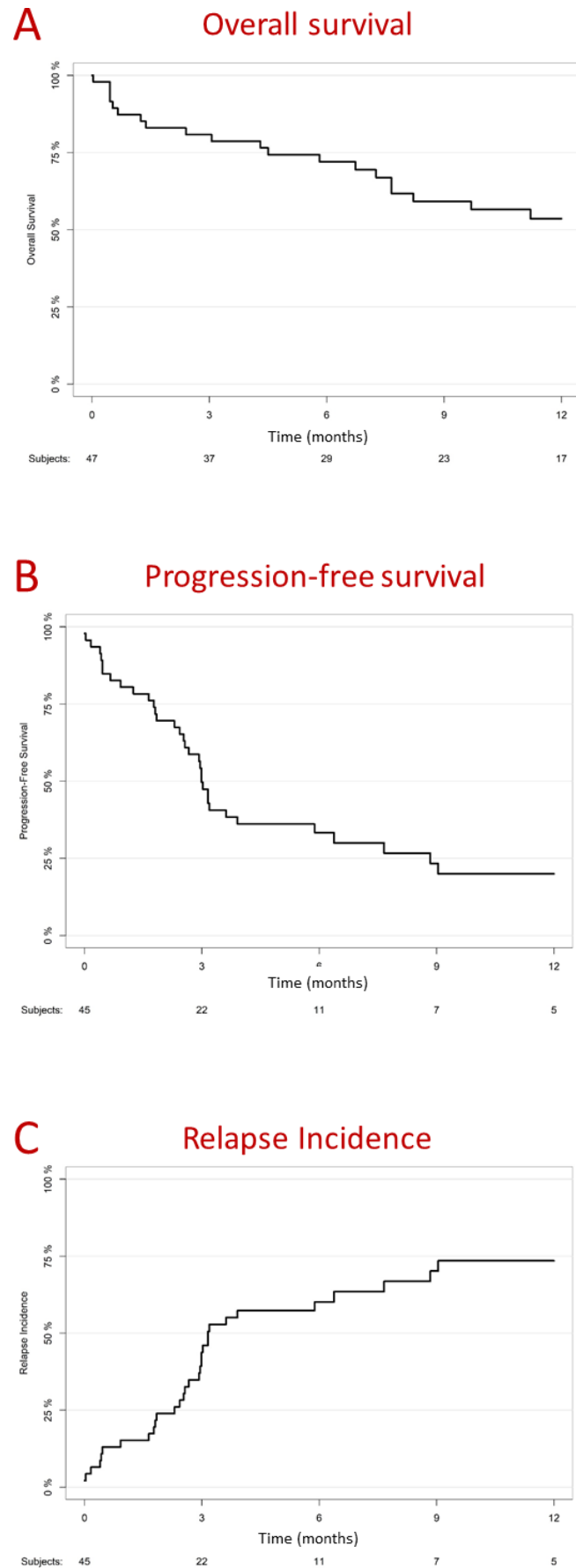


Figure 1 Overall survival (A), progression-free survival (B) and relapse incidence (C) in patients with severe cytopenia after CAR T-cell therapy for LBCL. CAR, chimeric antigen receptor; LBCL, large B-cell lymphoma.

Relation of severe cytopenia with infections and NRM

Two key results of our study were that (1) NRM was relatively low in patients with or without severe cytopenia; and (2) the mortality after the occurrence of infections was not high. This may be an effect of improved management of infections during cytopenia. These results are in line with the previously discussed international study by Rejeski *et al*, who also found a stronger association of severe cytopenia with relapse and no pronounced association with NRM.² In contrast, a recent German real-world analysis found a relatively high 10% NRM at 24 months after CAR T-cell infusion in patients with LBCL.¹ In this analysis, infections were the leading cause of NRM and roughly two-third of NRM cases occurred beyond day+28. A significantly larger proportion of patients with late NRM had persistent grade 4 neutropenia at day+100 or last follow-up (27% vs 5%, $p=0.011$). Taken together, the available data suggest that severe cytopenia can be a significant risk factor for NRM depending on the patient population studied. Of note, the administration of autologous peripheral blood stem cells to patients with severe cytopenia after CAR T-cell therapy is increasingly used and has the potential to reduce fatal infections as well as NRM.^{3,4} This may in part explain the relatively low NRM in patients with severe cytopenia in our study. However, our registry analysis has limitations since no detailed information on treatment of cytopenias (eg, autoSCT boost, Granulocyte-Colony Stimulating Factor, thrombopoietin agonists, transfusions and supportive care) are available. To start addressing the question of how severe cytopenia after CAR T-cell therapy is managed, the EBMT is currently performing a survey in European CAR-T centers.

A limitation that our present study has in common with other clinical CAR-T publications is that we are not shedding light on the biologic mechanisms that link CAR-T cell-associated severe cytopenia with response and relapse rates in patients with LBCL. There are several factors that can be involved in CAR-T cell-associated cytopenia including higher age, poor bone-marrow reserve, tumor burden, severity of hyperinflammation (cytokine release syndrome, neurotoxicity) and prevalence of clonal hematopoiesis of indeterminate potential.¹² However, it is likely that preclinical studies in adequate animal models are necessary to discover the major mechanisms involved.

Author affiliations

¹Medical Clinic, Department for Haematology, Oncology and Tumorimmunology, Charité Universitätsmedizin Berlin, Berlin, Germany

²EBMT Transplant Complications Working Party, Paris, France

³EBMT Paris study office; Department of Haematology, Saint Antoine Hospital; INSERM UMR-S 938, Sorbonne University, Paris, France

⁴Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany

⁵Departement of Haematological Medicine, Kings College Hospital, London, UK

⁶Département d'Hématologie Clinique, CHU Lapeyronie, Montpellier, Languedoc-Roussillon, France

⁷Department of Hematology and Central Hematology Laboratory, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

⁸University Hospital Eppendorf, Bone Marrow Transplantation Centre, Hamburg, Germany

⁹University of Heidelberg, Medizinische Klinik u. Poliklinik V, Heidelberg, Germany

¹⁰Department of Hematology, Oncology and Internal Medicine, the Medical University of Warsaw, Marseille, Poland

¹¹Departement of Paediatric Oncology/BMT, Bristol Royal Hospital for Children, Bristol, UK

¹²University Hospital, Clinic of Hematology, Zurich, Switzerland

¹³Christie NHS Trust Hospital, Adult Leukaemia and Bone Marrow Transplant Unit, Manchester, UK

¹⁴Department of Haematology, Hemostasis, Oncology, Hannover Medical School, Hannover, Germany

¹⁵CHU Bordeaux, Hôpital Haut-leveque, Bordeaux, France

¹⁶Hospital Clínico, Servicio de Hematología, Salamanca, Spain

¹⁷University Hospital, Hematology, Basel, Switzerland

¹⁸Department of Medical Oncology, Bern University Hospital, University of Bern, Bern, Switzerland

¹⁹First Pavlov State Medical University of St Petersburg, St Petersburg, Russia

²⁰Department of Hematology, University Hospitals Leuven and KU Leuven, Leuven, Belgium

²¹EBMT Cellular Therapy and Immunobiology Working Party, Leiden, The Netherlands

²²Institut Paoli-Calmettes Comprehensive Cancer Centre, Inserm CBT-1409, Aix-Marseille Université, Marseille, France

²³Clinical Hematology Department, Institut Català d'Oncologia-Hospitalet, Institut de Ciències Biomèdiques de Bellvitge (IDIBELL), Universitat de Barcelona, Barcelona 08908, Spain

²⁴Faculty of Medicine, Department of Pediatric Infectious Diseases, Hadassah Medical Center, Hebrew University of Jerusalem, Jerusalem, Israel

²⁵EBMT Infectious Diseases Working Party

²⁶Department of Hematology, Oncology, and Tumor Immunology, Helios Klinikum Berlin-Buch, Berlin, Germany

²⁷EBMT Lymphoma Working Party

²⁸Department of Haematology, Hospital Universitario de la Princesa, Madrid, Spain

²⁹University Hospital Centre Zagreb and School of Medicine, University of Zagreb, Zagreb, Croatia

Twitter Christian Chabannon @CChabannon

Acknowledgements OP acknowledges the support of José Carreras Leukämie-Stiftung (3R/2019, 23R/2021), Deutsche Krebshilfe (70113519), Deutsche Forschungsgemeinschaft (PE 1450/7–1, PE 1450/9–1) and Stiftung Charité BIH (BIH_PRO_549, Focus Group Vascular Biomedicine).

Contributors OP, CP and ZP analyzed data and wrote the manuscript. The remaining authors provided data, reviewed and approved the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests OP has received honoraria or travel support from Gilead, Jazz, MSD, Novartis, Pfizer and Therakos. He has received research support from Incyte and Priothera. He is member of advisory boards to Equillium Bio, Jazz, Gilead, Novartis, MSD, Omeros, Priothera, Sanofi, Shionogi and Sobi. CC: Bellicum Pharmaceuticals: Membership on an entity's Board of Directors or advisory committees, BMS/Celgene: Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; EBMT: Membership on an entity's Board of Directors or advisory committees; Fresenius Kabi: Research Funding; Gilead: Membership on an entity's Board of Directors or advisory committees, Speakers Bureau, Honoraria; Janssen Pharmaceuticals: Membership on an entity's Board of Directors or advisory committees; Miltenyi Biotec: Research Funding; Novartis: Speakers Bureau, Sanofi SA: Honoraria, Research Funding, Speakers Bureau, Terumo BCT: Speakers Bureau. The remaining authors declare no conflict of interests.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by EBMT review board and Review Boards of all EBMT centers. Nr. EA1/083/18. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.



Data availability statement Data are available upon reasonable request. Data are available upon reasonable request to the communicating author.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Olaf Penack <http://orcid.org/0000-0003-4876-802X>

Christian Chabannon <http://orcid.org/0000-0002-3755-4889>

Rafael de la Camara <http://orcid.org/0000-0002-8189-5779>

REFERENCES

- Bethge WA, Martus P, Schmitt M, *et al*. GLA/DRST real-world outcome analysis of car T-cell therapies for large B-cell lymphoma in Germany. *Blood* 2022;140:349–58.
- Rejeski K, Perez A, Sesques P, *et al*. CAR-HEMATOTOX: a model for CAR T-cell-related hematologic toxicity in relapsed/refractory large B-cell lymphoma. *Blood* 2021;138:2499–513.
- Gagelmann N, Wulf GG, Duell J, *et al*. Hematopoietic stem cell boost for persistent neutropenia after car T-cell therapy: a GLA/DRST study. *Blood Adv* 2023;7:555–9.
- Rejeski K, Burchert A, Iacoboni G, *et al*. Safety and feasibility of stem cell boost as a salvage therapy for severe hematotoxicity after CD19 CAR T-cell therapy. *Blood Adv* 2022;6:4719–25.
- McGrath E, Chabannon C, Terwel S, *et al*. Opportunities and challenges associated with the evaluation of chimeric antigen receptor T cells in real-life. *Curr Opin Oncol* 2020;32:427–33.
- Health, Services H. Common terminology criteria for adverse events (CTCAE) version 5.0. 2017. Available: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
- Abramson JS, Palomba ML, Gordon LI, *et al*. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet* 2020;396:839–52.
- Strati P, Varma A, Adkins S, *et al*. Hematopoietic recovery and immune reconstitution after axicabtagene ciloleucel in patients with large B-cell lymphoma. *Haematologica* 2021;106:2667–72.
- Jain T, Knezevic A, Pennisi M, *et al*. Hematopoietic recovery in patients receiving chimeric antigen receptor T-cell therapy for hematologic malignancies. *Blood Adv* 2020;4:3776–87.
- Locke FL, Miklos DB, Jacobson CA, *et al*. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. *N Engl J Med* 2022;386:640–54.
- Brudno JN, Natrakul D, Lam N, *et al*. Acute and delayed cytopenias following CAR T-cell therapy: an investigation of risk factors and mechanisms. *Leuk Lymphoma* 2022;63:1849–60.
- Sharma N, Reagan PM, Liesveld JL. Cytopenia after CAR-T cell therapy-A brief review of A complex problem. *Cancers (Basel)* 2022;14:1501.

Supplementary Table 1. National Cancer Institute Common Terminology Criteria for Adverse Events.⁶

	Grade 1	Grade 2	Grade 3	Grade 4
Neutrophils	<normal to 1500/ μ L	1000 to 1500/ μ L	500 to 1000/ μ L	<500/ μ L
Platelets	<normal to 75,000/ μ L	50,000 to 75,000/ μ L	25,000 to 50,000/ μ L	<25,000/ μ L
Hemoglobin	<normal to 10 g/dL	8.0 to 10.0 g/dL	<8.0 g/dL	Life-threatening

Supplementary Table 2. Causes of death in the whole population and in patients with severe cytopenia.

Cause of death	Whole population n=170	With Severe cytopenia N=25
Original disease	145 (86.8%)	22 (88%)
Cell therapy related	10 (6.0%)	3 (12%)
Infection	7 (4.2%)	0
Organ toxicity	1 (0.6%)	0
Other	4 (2.4%)	0
missing	3	0

Supplementary Table 3. Infections in the whole population and in patients with severe cytopenia.

Variable	Level	Overall population n=398	With severe cytopenia n=48
Bacteremia	Documented cases	46	5
	Day after CAR-T. Median (min-max)	23.5 (0-80)	43 (28-76)
Pneumonia	Documented cases	21	3
	Day after CAR-T. Median (min-max)	16 (0-85)	22 (3-25)
Upper respiratory tract infection	Documented cases	13	1
	Day after CAR-T. Median (min-max)	25 (4-96)	25 (25-25)
Cystitis	Documented cases	14	2
	Day after CAR-T. Median (min-max)	46 (4-92)	34 (18-50)
Skin infection	Documented cases	7	0
	Day after CAR-T. Median (min-max)	20.5 (17-58)	N/A
Invasive fungal infections	Documented cases	8	1
	Day after CAR-T. Median (min-max)	21 (0-59)	77
Clostridium difficile enteritis	Documented cases	5	2
	Day after CAR-T. Median (min-max)	17 (13-22)	17.5 (14-21)
CMV reactivation	Documented cases	15	0
	Days after CAR-T. Median (min-max)	17 (0-90)	N/A