



HAL
open science

**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**

P. J. Hayden, T. Sirait, Linda Koster, John A. Snowden, Ibrahim
Yakoub-Agha

► **To cite this version:**

P. J. Hayden, T. Sirait, Linda Koster, John A. Snowden, Ibrahim Yakoub-Agha. 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. *Current Research in Translational Medicine*, 2019, *Current Research in Translational Medicine*, 67, pp.79-88. 10.1016/j.retram.2019.05.002 . hal-04517445

HAL Id: hal-04517445

<https://hal.univ-lille.fr/hal-04517445>

Submitted on 22 Mar 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en



Original article

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

P.J. Hayden^{a,*}, T. Sirait^b, L. Koster^b, J.A. Snowden^c, I. Yakoub-Agha^d

^a Dept. of Haematology, Trinity College Dublin, St. James's Hospital, Dublin 8, Ireland

^b EBMT Data Office, 2300 Leiden, the Netherlands

^c Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

^d CHU de Lille, LIRIC, INSERM U995, Université de Lille, 59000, Lille, France

ARTICLE INFO

Article history:

Received 7 May 2019

Accepted 21 May 2019

Available online 8 June 2019

Keywords:

CAR T

CAR T-cells

Patient selection

Patient eligibility

Long-term follow-up

ABSTRACT

Purpose of the study: Two chimeric antigen receptor (CAR) T-cell therapies - Tisagenlecleucel (Kymriah[™]) and Axicabtagene ciloleucel (Yescarta[™]) - have been approved for commercial use. In order to inform forthcoming EBMT guidelines on the management of adults and children undergoing autologous CAR T-cell therapy, we undertook a survey of experienced clinicians.

Methods: An online survey with a dual focus on (1) 'real world' patient eligibility criteria and (2) models of care for patient follow-up was sent to experienced physicians.

Results: There were 41 respondents (10 countries) and 93% worked in FACT-JACIE-accredited transplant centres. Most felt that a history of malignancy (57%), prior allo-HCT for B-NHL (78%–81%) and prior treatment with anti-CD19/CD3 BiTE antibodies (76%–86%) do not constitute contra-indications to CAR T therapy. Clinicians were divided as to whether CNS involvement represented an exclusion criterion. There was agreement that patients with viral infections (HIV, Hepatitis B or Hepatitis C) are not eligible. There is no common model of care for long-term follow-up. Most respondents believed that patients should attend the hospital two (43%) to three (33%) times weekly during the first month following discharge. A majority (69%) of respondents work in centres where there is an MDT meeting with a specific focus on follow-up following CAR T Therapy. Follow-up care is currently delivered either in HCT or haematology-oncology outpatient clinics.

Conclusion: The responses reveal wide variation in perceived patient eligibility criteria and highlight the need for consensus guidelines. The findings also illustrate the embryonic nature of current follow-up arrangements.

© 2019 The Authors. Published by Elsevier Masson SAS. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

After decades in pre-clinical evaluation and clinical development, two chimeric antigen receptor (CAR) T-cell therapies - Tisagenlecleucel (Kymriah[™]) and Axicabtagene ciloleucel (Yescarta[™]) - were approved for commercial use by the FDA and EMA over the last two years. Autologous CAR T-cells represent a novel form of personalised cellular immunotherapy in that autologous T-lymphocytes are collected, transfected with an engineered fusion construct containing an antigen-binding domain, and reinfused into the patient, hence the use of the term 'living drug' [1–3].

Tisagenlecleucel (Kymriah[™], previously CTL019, Novartis, Basel, Switzerland) is an immunocellular therapy comprised of autologous T cells genetically modified *ex vivo* using a lentiviral vector encoding an anti-CD19 CAR. It is indicated for the treatment of children and young adult patients up to the age of 25 years with relapsed/refractory B cell acute lymphoblastic leukemia (B-ALL) and was approved by the US Food and Drug Administration (FDA) in August 2017 [4,5]. It was subsequently FDA-approved for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) that is relapsed or refractory after two or more lines of systemic therapy in May 2018 [6]. The EMA approved both indications in August 2018.

Axicabtagene ciloleucel (Yescarta[™], previously KTE-C19, Gilead, USA) is a CD19-directed genetically modified (retroviral transduction) autologous T-cell immunotherapy and is indicated for the treatment of adult patients with relapsed or refractory DLBCL and

* Corresponding author.

E-mail address: phayden@stjames.ie (P.J. Hayden).

primary mediastinal large B-cell lymphoma (PMBCL) after two or more lines of systemic therapy [7,8]. It was FDA-approved in October 2017 and EMA-approved in August 2018.

Some of the inclusion and exclusion criteria used in three of the licensing trials are shown in Table 1. These are similar across the studies. In general, all patients needed to have adequate renal and hepatic function and lymphoma patients had to meet blood count criteria reflecting adequate bone marrow reserve. In addition, cardiac and pulmonary function had to exceed pre-determined thresholds. Exclusion criteria included clinically significant active infection, hepatitis B and C, and CNS disease involvement. Patients could not have received prior anti-CD19/anti-CD3 therapy and the lymphoma patients could not have undergone allogeneic HCT (allo-HCT). In real world clinical practice, however, many patients who would have been ineligible for enrolment onto the clinical trials based on these criteria are now being referred to CAR T centres for treatment.

To date, most centres have limited experience and there has, as yet, been no guidance as to the optimal models of care for CAR T cell recipients, either in the short or long term. However, current FACT-JACIE standards now cover immune effector cells (IECs), with a view to providing quality standards for the facilities, infrastructure and

training and to ensure competency across clinical, pharmacy and scientific staff in the administration of CAR T cells and the management of complications. In addition, centres require adequate data management infrastructure to meet the regulatory requirement for mandatory reporting of follow-up for 15 years.

In order to inform forthcoming EBMT recommendations on the management of adults and children undergoing autologous CAR T-cell therapy, we undertook a survey of experienced clinicians to assess their opinions on patient eligibility criteria and post-treatment care.

Methodology

The Practice Harmonisation and Guidelines subcommittee of the Chronic Malignancies Working Party (CMWP) of the European Society for Blood and Marrow Transplantation (EBMT) proposed in December 2018 that an EBMT-wide group be formed to produce practical clinical recommendations on the management of adults and children undergoing autologous CAR T-cell therapy. This initiative was adopted by the EBMT board after which experts in the field were invited to participate.

Table 1
Inclusion and exclusion criteria used in three of the CAR T clinical trials.

Criteria	Tisagenlecleucel Children and Young Adults with B-ALL ELIANA, Maude SL et al, 2018(4)	Tisagenlecleucel Adult relapsed or refractory DLBCL JULIET, Schuster SJ et al, 2019(6)	Axicabtagene Ciloleucel Refractory Large B-cell Lymphoma ZUMA-1, Neelapu et al, 2017(7)
Inclusion			
Confirmation of disease	For relapsed patients, CD19 tumor expression demonstrated in bone marrow or peripheral blood by flow cytometry within 3 months of study entry; Bone marrow with $\geq 5\%$ lymphoblasts by morphologic assessment at screening	Sufficient FFPE tumour samples must be available for histological and molecular subtype testing	Histologically confirmed aggressive B cell NHL, Chemotherapy-refractory disease
Haematology		Adequate bone marrow reserve defined as ANC > 1000/mm ³ , ALC > 300/mm ³ , Platelets > 50,000/mm ³ , Hb > 8 g/dl	ANC > 1000/mm ³ , Platelets > 50,000/mm ³
Renal function	Adequate renal function based on age- and gender-specific serum creatinine thresholds	Serum creatinine of < 1.5 x ULN; eGFR > 60 ml/min/1.73m ²	Serum creatinine ≤ 1.5 mg/dL
Hepatic function	ALT ≤ 5 times the ULN for age; Bilirubin < 2.0 mg/dl (< 34 μ mol/l)	ALT ≤ 5 times the ULN for age; Bilirubin < 2.0 mg/dl (< 34 μ mol/l) with exception of patients with Gilbert's syndrome	Serum ALT/AST ≤ 2.5 ULN; Total bilirubin ≤ 1.5 mg/dl (< 26 μ mol/l), except in subjects with Gilbert's syndrome
Pulmonary	Must have a minimum level of pulmonary reserve defined as \leq Grade 1 dyspnea and pulse oxygenation > 91% on room air	Must have a minimum level of pulmonary reserve defined as \leq Grade 1 dyspnea and pulse oxygenation > 91% on room air	
Cardiac	LVSF $\geq 28\%$ confirmed by echocardiogram, or LVEF $\geq 45\%$ confirmed by echocardiogram or MUGA within 7 days of screening	Haemodynamically stable and LVEF > 45% confirmed by echocardiogram or MUGA	Cardiac ejection fraction $\geq 50\%$ and no evidence of pericardial effusion as determined by an ECHO
Imaging		Measurable disease at time of enrolment	MRI of the brain showing no evidence of CNS lymphoma; at least one measurable lesion according to the revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007)
Exclusion			
Virology	Active or latent hepatitis B or active hepatitis C (test within 8 weeks of screening)	Uncontrolled active or latent hepatitis B or active hepatitis C	Known history of infection with hepatitis B (HBsAg positive) or hepatitis C virus (anti-HCV positive)
HIV	Human Immunodeficiency Virus (HIV) positive test within eight weeks of screening	HIV positive patients	Known history of infection with HIV
CNS	Active CNS involvement by malignancy, defined as CNS-3 per NCCN guidelines. Patients with history of CNS disease that has been effectively treated will be eligible	Active CNS involvement by malignancy	Subjects with detectable cerebrospinal fluid malignant cells, or brain metastases, or with a history of cerebrospinal fluid malignant cells or brain metastases
Infection	Any uncontrolled infection at screening	Uncontrolled acute life-threatening bacterial, viral or fungal infection (e.g. blood culture positive < 72 h prior to infusion)	Clinically significant active infection (e.g. Simple UTI, bacterial pharyngitis allowed) or currently receiving IV antibiotics or have received IV antibiotics within 7 days prior to enrolment (Prophylaxis antibiotics, antivirals and antifungals are permitted)
Fertility	Women of child-bearing potential (defined as all women physiologically capable of becoming pregnant) and all male participants, unless they are using highly effective methods of contraception for a period of one year after the CTL019 infusion	Women of child-bearing potential and all male participants must agree to use highly effective methods of contraception for one year following CD19 CART therapy	Females of childbearing potential must have a negative serum or urine pregnancy test

In order to inform these guidelines, a survey was devised and sent to physicians with experience in administering CAR T-cell therapies to solicit feedback on current approaches to the topics covered in these guidelines. The survey was broadly composed of two sections reflecting clinical management prior to and after the administration of CAR T therapies.

The first section addressed patient eligibility criteria including age, medical history and co-morbidities; next, eligibility criteria for leukapheresis, first in general, and then specifically for the two commercially approved products, tisagenlecleucel ((Kymriah™) and axicabtagene ciloleucel (Yescarta™), and, finally, eligibility criteria for the administration of lymphodepleting conditioning chemotherapy.

The second section assessed patient follow-up from discharge to Day+100; the role of the multi-disciplinary team and written unit policies; the organisation and model of care of the long-term follow-up service including the role of medical and nursing staff in providing this care; shared care management and transitional care for both adults and children; and, finally, health promotion information and measures taken for regulatory compliance.

In order to ensure that the responses reflected a broad range of opinions, we contacted fifty physicians with experience in the use of CAR T cell therapies, both with the commercially available products and with agents under evaluation in clinical trials. Participants were given a short deadline of 14 days to complete the survey and the pooled results were analysed on 4th April 2019. A total of 41 of the 50 physicians responded within the required timeframe. All responses have been aggregated.

Please note that from Tables 3 to Table 12, inclusive, the term 'Total Answers' refers to the number of valid answers received, followed, in brackets, by the percentage that this number represents of the 41 participants. The subsequent breakdown of responses are then given as absolute numbers followed, in brackets, by the percentage of the total number of valid answers that these represent.

To ease interpretation of the Tables, the most frequently chosen response is often shown in bold type.

The responding participants and their affiliations are listed at the end of the manuscript.

Countries and centre characteristics

Cities and countries are shown in Table 2. A total of 16 (39%) of the centres were in the United States where the two commercially available CAR T therapies were first approved. China is relatively under-represented in this survey, given the number of trials taking place there.

Centre characteristics are shown in Table 3. The overwhelming majority (90%) of the clinicians were treating patients with the commercially approved products. As regards disease types, most experience, as expected, was with ALL (76%) and high-grade B-cell Non-Hodgkin Lymphoma (56%). There is, as yet, no licensed product for the treatment of myeloma; these six centres must therefore have been participating in clinical trials. In addition, almost all (93%) were FACT-JACIE accredited for allo-HCT, reflecting the preferential roll-out of this new technology in established transplant centres which is in line with the recommendations of the Francophone Society of Bone Marrow Transplantation and Cellular Therapy (SFGM-TC) [9].

Age eligibility criteria

Age eligibility criteria are shown in Table 4.

There is no upper age limit specified in the summaries of product characteristics (SPC) for the use of either product in the treatment of high-grade B-cell lymphoma. The majority of respondents (67%) felt that there should be no upper age limit although nine (23%) specified upper age limits ranging from 65 to

Table 2
Cities and countries.

Country	City	N (%)	N (Country)
USA	Seattle	3 (7)	16
	Tampa	3 (7)	
	Portland	2 (5)	
	Chicago	1 (2)	
	Jacksonville	1 (2)	
	Not disclosed	1 (2)	
	Nashville	1 (2)	
	New York	1 (2)	
	Philadelphia	1 (2)	
	Rochester	1 (2)	
	Saint Louis	1 (2)	
France	Paris	3 (7)	6
	Lille	2 (5)	
	Lyon	1 (2)	
Spain	Madrid	2 (5)	5
	Badalona	1 (2)	
	Barcelona	1 (2)	
	Salamanca	1 (2)	
Germany	Cologne	1 (2)	3
	Hamburg	1 (2)	
	Würzburg	1 (2)	
UK	Bristol	1 (2)	3
	London	1 (2)	
	Manchester	1 (2)	
Saudi Arabia	Riyadh	2 (5)	2
Italy	Milano	1 (2)	2
	Rome	1 (2)	
Netherlands	Amsterdam	1 (2)	2
	Utrecht	1 (2)	
China	Hangzhou	1 (2)	1
Israel	Tel Hashomer	1 (2)	1
Total			41 (100)

Table 3
Centre characteristics.

Centre characteristics	N (%)
Centre involved in delivering commercial CAR T-cell therapies	Yes 37 (90)
	No 4 (10)
Diseases treated with CAR T in the centre	ALL 31 (76)
	NHL 23 (56)
	Low-grade Lymphoma 12 (30)
	Multiple Myeloma 6 (15)
Centre is FACT-JACIE accredited	Yes, fully FACT-JACIE accredited for allo-HCT 38 (93)
	No, working towards FACT-JACIE accreditation 2 (5)
	No, not accredited 1 (2)

Abbreviations: ALL: acute lymphoblastic leukemia; NHL: (High Grade) non-Hodgkin lymphoma; FACT: Foundation for the Accreditation of Cellular Therapy; JACIE: Joint Accreditation Committee ISCT-Europe & EBMT; Allo-HCT: hematopoietic cell transplantation.

75 years. In clinical practice, performance status, somewhat correlated with age, is more likely than chronological age to determine physician choice.

Tisagenlecleucel (Kymriah™) has been approved for the treatment of children and young adults up to the age of 25 years. There is no lower age limit, a policy supported by 45% of respondents. In the survey, five (13%) participants supported lower age limits ranging from two to three years of age. Equally, a relatively large percentage of clinicians (42%) did not feel able to provide a lower age limit, once again highlighting the difficulty of providing absolute age thresholds for any therapy.

Table 4
Age eligibility criteria.

Eligibility criteria: Age	N (%)	
Upper age limit for CAR T-cell therapy in adults	Total answers	39 (95)
	> 65 years	1 (3)
	> 70 years	4 (10)
	> 75 years	4 (10)
	No limit	26 (67)
Lower age limit for CAR T-cell therapy in children	Don't know	4 (10)
	Total answers	38 (93)
	< 2 years	1 (3)
	< 3 years	4 (10)
	No limit	17 (45)
	Don't know	16 (42)

Medical history

Eligibility criteria based on medical history are shown in [Table 5](#).

A number of clear distinctions emerge when clinical trial inclusion and exclusion criteria are assessed against current clinical practice. Most (57%) did not agree that a history of malignancy by itself constitutes an exclusion criterion though the majority (70%) felt that, if there was a history of malignancy, the patient should be disease-free and off therapy for three years.

Although patients who had undergone prior allo-HCT were excluded from the lymphoma trials, most (81% (Tisagenlecleucel) and 78% (Axicabtagene ciloleucel)) would not apply this exclusion criterion in routine clinical practice. In addition, a history of treatment with anti-CD19/CD3 BiTE antibodies was not felt to be a contra-indication to CART therapy, reflecting the widespread use of blinatumomab in the treatment of relapsed ALL. Equally, only one third (38%) considered prior CART therapy to be a contra-indication to treatment although reimbursement is unlikely to be available for the use of the commercially available products in this setting.

There was no consensus regarding autoimmune disease. Although 19 (51%) agreed that it should continue to be a contra-indication, 16 (43%) did not. The lack of any consensus may reflect the lack of specificity in this question in that autoimmune disease ranges from relatively mild organ-specific disorders such as hypothyroidism to more disabling systemic autoimmune diseases such as scleroderma and knowledge of the severity of the given disorder would allow for a more informed physician choice.

Table 5
Exclusion and inclusion criteria.

Eligibility criteria: Medical history	N (%)			
	Agree	Don't agree	Don't know	Total answers
Absence of history of malignancy other than non-melanoma skin cancer or CIS	16 (43)	21 (57)	0 (0)	37 (90)
Absence of history of malignancy unless disease-free and off therapy for at least three years	26 (70)	9 (24)	2 (6)	37 (90)
Absence of prior allogeneic stem cell transplantation (Yescarta™)	7 (19)	28 (78)	1 (3)	36 (88)
Absence of prior allogeneic stem cell transplantation (Kymriah™ - NHL)	6 (17)	29 (81)	1 (2)	36 (88)
Absence of prior allogeneic stem cell transplantation (Kymriah™ - ALL)	2 (6)	34 (92)	1 (2)	37(90)
Absence of prior anti-CD19/CD3 BiTE antibodies treatment (Kymriah™ - NHL)	7 (19)	28 (76)	2 (5)	37 (90)
Absence of prior anti-CD19/CD3 BiTE antibodies treatment (Kymriah™ - ALL)	2 (6)	32 (86)	3 (8)	37 (90)
Absence of prior CAR T-cell therapy or other genetically modified T-cell therapy	14 (38)	20 (54)	3 (8)	37 (90)
Absence of history of autoimmune disease	19 (51)	16 (43)	2 (6)	37 (90)
Absence of ongoing treatment with chronic immunosuppressants	30 (79)	8 (21)	0 (0)	38 (93)
Toxicities due to prior therapy must be stable and recovered to ≤ Grade 1	24 (63)	13 (34)	1 (3)	38 (93)
Absence of history of Grade ≥2 hemorrhage within 30 days	14 (38)	21 (57)	2 (5)	37 (90)
Absence of any indwelling line or drain	12 (32)	25 (66)	1 (2)	38 (93)
Absence of existing or suspected fungal, bacterial, viral, or other infection	32 (84)	6 (16)	0 (0)	38 (90)
In the physician's judgment, the patient has to be able to complete all required visits or procedures	35 (92)	3 (8)	0 (0)	38 (90)
Females of childbearing potential must have a negative serum or urine pregnancy test	36 (95)	2 (5)	0 (0)	38 (90)
No evidence of pericardial effusion as determined by an echocardiogram (ECHO)	18 (47)	20 (53)	0 (0)	38 (90)
No clinically significant electrocardiogram (ECG) findings	23 (61)	15 (39)	0 (0)	38 (90)

Equally, however, there is legitimate concern at the risk of autoimmune disease following CAR T therapy.

Most (79%) felt that ongoing immunosuppression was an exclusion criterion and a large majority (84%) agreed that existing or suspected fungal, bacterial, viral, or other infection represented a contra-indication to treatment.

Comorbidities

Eligibility criteria based on comorbidities are shown in [Table 6](#) and [Fig. 1](#).

When asked about organ function and the results of laboratory work-up, two-thirds (71%) of respondents agreed that significant hypoxaemia is a contra-indication.

The responses regarding CNS disease indicate that clinicians are divided as to whether active CNS disease is an exclusion criterion even though it was one in the licensing clinical trials. As CNS involvement is not uncommon in relapsed ALL, it is understandable that some respondents were reluctant to be unable to treat patients with 'a history of cerebrospinal fluid (CSF) malignant cells', especially if they subsequently achieved a remission.

There was broad agreement that patients with viral infections such as HIV or hepatitis B or C (HBV or HCV) are not eligible for treatment. This almost certainly reflects concern at the effect of immunosuppression on any active viral infection. Patients with HIV infection were excluded from clinical trials. It is written in the EMA SPC for Tisagenlecleucel (Kymriah™) that "there is no experience with manufacturing Kymriah for patients with a positive test for active HBV, HCV or HIV. Therefore, leukapheresis material from these patients will not be accepted for Kymriah™ manufacturing."

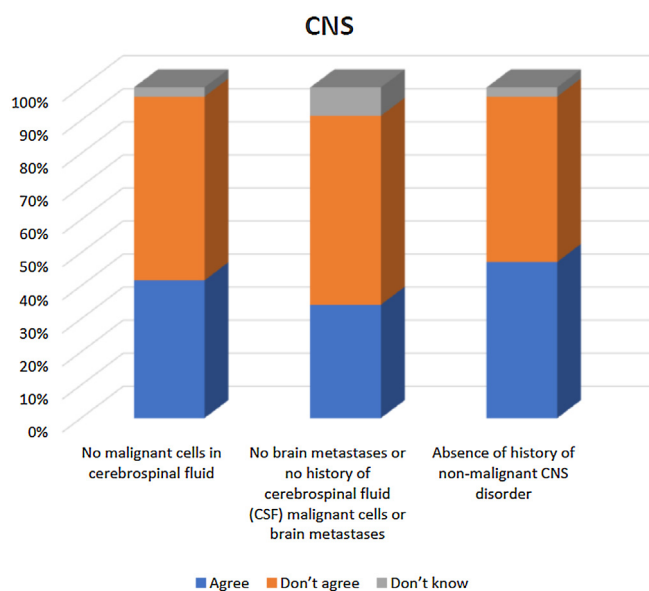
Leukapheresis

Eligibility criteria for leukapheresis are shown in [Tables 7 and 8](#).

Whether based on ECOG or Karnofsky scores, most respondents agreed that poor performance (ECOG > 2, Karnofsky <70%) status constitutes an exclusion criterion. Although only 54% of survey respondents agreed that patients with either atrial or ventricular lymphoma involvement were ineligible, a vast majority (88%) believed that significant cardiac disease is a contra-indication. Most (68%) considered that a history of DVT/PE within six months does not represent an exclusion criterion.

Table 6
Eligibility criteria based on comorbidities.

Eligibility criteria: Comorbidities	N (%)			Total answers
	Agree	Don't agree	Don't know	
Lung function				
No clinically significant pleural effusion	18 (47)	19 (50)	1 (3)	38 (93)
Baseline oxygen saturation > 92% on room air	27 (71)	9 (24)	2 (5)	38 (93)
Patients without detectable malignant cells in their cerebrospinal fluid	17 (45)	20 (53)	1 (2)	38 (93)
Patients without known brain metastases or with a history of cerebrospinal fluid (CSF) malignant cells	13 (35)	21 (57)	3 (8)	37 (90)
Absence of history of non-malignant CNS disorder or any autoimmune disease with CNS involvement	18 (47)	19 (50)	1 (3)	38 (93)
Absence of lymphoma that is known to involve the full thickness of the gastric wall	7 (19)	24 (65)	6 (16)	37 (90)
Absence of history of human immunodeficiency virus (HIV) (Yescarta™)	25 (66)	11 (29)	2 (5)	38 (93)
Absence of history of human immunodeficiency virus (HIV) (Kymriah™)	29 (76)	7 (18)	2 (6)	38 (93)
Absence of infection or acute or chronic active hepatitis C infection	25 (66)	12 (32)	1 (2)	38 (93)
Absence of infection or acute or chronic active hepatitis B infection	24 (64)	13 (34)	1 (2)	38 (93)
Patients with history of Hepatitis B or Hepatitis C infection must have cleared their infection	32 (86)	4 (11)	1 (3)	37 (90)
Absence of treatment with a live, attenuated vaccine within six weeks of the planned start of the conditioning regimen or anticipation of the need for such a vaccine during the course of the study	25 (66)	7 (18)	6 (16)	38 (93)

**Fig. 1.** Responses regarding CNS disease involvement.

Although 88% agreed that a history of class III or IV congestive heart failure (CHF) or severe non-ischemic cardiomyopathy, unstable or poorly controlled angina, myocardial infarction, or ventricular arrhythmia within the previous six months constituted a contra-indication to proceeding with lymphodepletion conditioning, there was less agreement as to the threshold ejection fraction (EF) required. A total of 15% favoured a normal EF value (50–60%) as opposed to a further 65% who were satisfied with an EF equal to or greater than 40%.

When the survey participants were asked about product-specific eligibility criteria for leukapheresis (Table 8), the choices were broadly similar in the two cohorts. Between one fifth and

one third of clinicians felt that it was reasonable to proceed with the collection as long as the absolute lymphocyte count exceeded $0.1 \times 10^9/L$. There was no consensus regarding threshold levels of either renal or hepatic function in this setting. Of note, a majority of respondents were in favour of a level of International ratio (INR) or partial thromboplastin time (PTT) < 1.5 ULN before leukapheresis.

Lymphodepletion conditioning

The responses regarding the eligibility criteria before lymphodepletion conditioning are shown in Table 9(a) and (b).

As when asked the same question in relation to leukapheresis, most respondents agreed that poor performance (ECOG > 2, Karnofsky < 70%) status constituted an exclusion criterion. Once again, a significant cardiac history continued to be recognised as an issue and there was a range of opinions as to what represented a sufficient cardiac ejection fraction.

A total of 73% would proceed with lymphodepleting conditioning regardless of the absolute lymphocyte count. It should be noted that some investigators have suggested that lymphodepletion may not be necessary for patients with low lymphocyte counts ($ALC > 0.1 \times 10^9/L$) as these patients are already “lymphodepleted”.

Models of care and follow-up

There was no consensus regarding threshold levels of either renal or hepatic function in this setting.

There is no common model of care for the long-term follow-up (LTFU) of recipients of these new therapeutic agents at this early stage. Although the issue of relapse is of prime importance in the early and medium term, the needs of long-term survivors will also have to be addressed [10]. At present, it is understandable that there is relatively little experience in LTFU outside the specific requirements of clinical trials as most centres have not yet had sufficient numbers of patients to justify the development of dedicated arrangements.

Table 7
Eligibility criteria for leukapheresis.

Eligibility criteria: before leukapheresis		N (%)	
Grade of Eastern Cooperative Oncology Group (ECOG) performance status considered as a contraindication for leukapheresis	Total answers	35 (85)	
	> 0	0 (0)	
	> 1	4 (11)	
	> 2	20 (57)	
	> 3	6 (17)	
	None	4 (11)	
Grade of Karnofsky Performance Scale Index considered as a contraindication for leukapheresis	Don't know	1 (4)	
	Total answers	35 (85)	
	< 90	1 (4)	
	< 80	4 (11)	
	< 70	9 (26)	
	< 60	11 (31)	
Patients without cardiac atrial or cardiac ventricular lymphoma involvement	< 50	5 (14)	
	None	5 (14)	
	Total answers	34 (83)	
	Agree	19 (54)	
	Don't agree	9 (26)	
	Don't know	6 (18)	
Absence of history of class III or IV congestive heart failure (CHF) or severe non- ischemic cardiomyopathy, unstable or poorly controlled angina, myocardial infarction, or ventricular arrhythmia within the previous six months prior to leukapheresis.	Total answers	34 (83)	
	Agree	30 (88)	
	Don't agree	4 (12)	
	Don't know	0 (0)	
	Absence of history of deep vein thrombosis (DVT) or pulmonary embolism within six months of enrolment	Total answers	34 (83)
		Agree	9 (26)
Don't agree		23 (68)	
Don't know		2 (6)	
Level of cardiac ejection fraction is required before leukapheresis	Total answers	35 (85)	
	≥ 60% (normal)	2 (6)	
	≥ 50%	3 (9)	
	≥ 45%	11 (31)	
	≥ 40%	12 (34)	
	≥ 30%	6 (17)	
	Don't know	1 (3)	

The responses regarding follow-up from discharge to Day +100 are shown in [Table 10](#). Most respondents felt that patients should attend the hospital two (43%) to three (33%) times weekly during the first month following discharge. The frequency then reduced to once weekly (39%) to every two weeks (39%) during the second month and, finally, fortnightly to monthly during the third month post-discharge. The range of these responses likely reflects the widely varying levels of experience in centres at this time.

The answers regarding the role of multidisciplinary teams and standard operating procedures (SOPs) in long-term follow-up after Day +100 are shown in [Table 11](#). A majority (69%) of respondents work in centres where there is a MDT meeting with a specific focus on follow-up following CAR T Therapy. A slightly smaller percentage (64%) had a process for reviewing patients with late complications. Fewer again (53%) had a robust document-controlled policy on long-term monitoring and management of late complications and they vary in the extent to which these policies cover the various areas listed in the survey: remission status, late complications and CAR T persistence.

Most centres have not yet put in place dedicated follow-up clinics. As our survey reports, LTFU care is currently delivered either in HCT or haematology-oncology outpatient clinics. The responses are shown in [Table 12](#). Although 58% of respondents worked in centres with an outreach service to the primary referral base, relatively few had formal policies defining the responsibilities and relationships with the referral base such as regarding the transfer of patients in case of late complications.

Table 8
Product-specific eligibility criteria for leukapheresis.

Criteria	Kymriah™ N (%)	Yescarta™ N (%)	
Level of absolute neutrophil count (ANC) required before leukapheresis	Total answers	34 (83)	34 (83)
	≥ 0.5x10 ⁹ /L	7 (21)	5 (15)
	≥ 0.8x10 ⁹ /L	1 (3)	1 (3)
	≥ 1.0x10 ⁹ /L	11 (32)	14 (41)
	≥ 1.5x10 ⁹ /L	1 (3)	0 (0)
	Don't know	1 (3)	1 (3)
	Any number	13 (38)	13 (38)
Level of platelet count required before leukapheresis (in the absence of transfusion support within seven days)	Total answers	33 (80)	34 (83)
	≥ 20x10 ⁹ /L	6 (18)	5 (15)
	≥ 30x10 ⁹ /L	5 (15)	6 (18)
	≥ 50x10 ⁹ /L	12 (37)	11 (32)
	≥ 75x10 ⁹ /L	4 (12)	6 (18)
	Don't know	1 (3)	2 (6)
	Any number	5 (15)	4 (12)
Level of absolute lymphocyte count (ALC) required before leukapheresis	Total answers	33 (80)	34 (83)
	≥ 0.1x10 ⁹ /L	8 (24)	13 (38)
	≥ 0.2x10 ⁹ /L	3 (9)	3 (9)
	≥ 0.3 x10 ⁹ /L	11 (33)	5 (15)
	≥ 0.4x10 ⁹ /L	4 (12)	6 (18)
	Don't know	2 (6)	4 (12)
	Any number	5 (15)	3 (9)
Level of International ratio (INR) or partial thromboplastin time (PTT) required before leukapheresis	Total answers	33 (80)	35 (85)
	< 1.5 ULN	18 (54)	21 (60)
	Don't know	5 (15)	5 (14)
	Any number	10 (30)	9 (26)
Level of creatinine clearance (as estimated by Cockcroft Gault) required before leukapheresis	Total answers	33 (80)	34 (83)
	≥ 60 mL/min	8 (24)	8 (24)
	≥ 50 mL/min	1 (3)	2 (6)
	≥ 40 mL/min	10 (30)	10 (29)
	≥ 30 mL/min	11 (33)	11 (32)
	Don't know	3 (9)	3 (9)
	Any number	33 (80)	34 (83)
Level of Serum ALT/AST required before leukapheresis	Total answers	33 (80)	34 (83)
	≤ 2.5 ULN	11 (33)	12 (35)
	≤ 3 ULN	6 (18)	9 (26)
	≤ 3.5 ULN	2 (6)	1 (3)
	≤ 4 ULN	1 (3)	0 (0)
	≤ 5 ULN	8 (24)	7 (21)
	Don't know	5 (15)	5 (15)
Level of Total bilirubin, except in subjects with Gilbert's syndrome, required before leukapheresis	Total answers	33 (80)	33 (80)
	≤ 1.5 ULN	6 (18)	6 (18)
	≤ 2 ULN	6 (18)	6 (18)
	≤ 2.5 ULN	6 (18)	5 (15)
	≤ 3 ULN	4 (12)	5 (15)
	≤ 4 ULN	3 (9)	3 (9)
	Don't know	8 (24)	8 (24)

Abbreviations: ULN: upper limit of normal.

The model of care in the long-term follow-up service is shown in [Table 13](#). A total of 61% agreed that transplant physicians who are part of the team that delivered the CAR T therapy should also lead long-term monitoring of these patients. However, 42% felt that other specialist consultants who are part of the team would be appropriate in this role, a situation analogous to that of dedicated late effects physicians in some allo-HCT centres at present. Only 17% felt that senior nursing staff with expertise in haemato-oncology and/or HCT would be suitable. This perception may evolve as centres become more

Table 9
Eligibility criteria before lymphodepletion conditioning.

(a)		
Eligibility criteria: before lymphodepletion conditioning		N (%)
Grade of Eastern Cooperative Oncology Group (ECOG) performance status considered as a contraindication for lymphodepletion conditioning	Total answers	33 (80)
	> 0	0 (0)
	> 1	3 (9)
	> 2	22 (67)
	> 3	4 (12)
	None	2 (6)
Grade of Karnofsky Performance Scale Index as a contraindication for lymphodepletion conditioning	Total answers	33 (80)
	< 90	0 (0)
	< 80	6 (18)
	< 70	9 (27)
	< 60	9 (27)
	< 50	6 (18)
Patients without cardiac atrial or cardiac ventricular lymphoma involvement	Total answers	32 (78)
	Agree	18 (56)
	Don't agree	9 (28)
	Don't know	5 (16)
Absence of history of class III or IV congestive heart failure (CHF) or severe non-ischemic cardiomyopathy, unstable or poorly controlled angina, myocardial infarction, or ventricular arrhythmia within the previous six months prior to lymphodepletion conditioning	Total answers	33 (80)
	Agree	29 (88)
	Don't agree	3 (9)
	Don't know	1 (3)
Absence of history of deep vein thrombosis (DVT) or pulmonary embolism within six months of enrolment	Total answers	33 (80)
	Agree	11 (33)
	Don't agree	18 (55)
	Don't know	4 (12)
Level of cardiac ejection fraction required before lymphodepletion conditioning	Total answers	33 (80)
	≥ 60% (normal)	2 (6)
	≥ 50%	7 (21)
	≥ 45%	9 (27)
	≥ 40%	9 (27)
	≥ 30%	4 (12)
	Don't know	2 (6)

(b)		
Eligibility criteria: before lymphodepletion conditioning		N (%)
Level of absolute neutrophil required count (ANC) before lymphodepletion conditioning	Total answers	33 (80)
	≥ 0.5x10 ⁹ /L	7 (21)
	≥ 0.8x10 ⁹ /L	1 (3)
	≥ 1.0x10 ⁹ /L	6 (18)
	≥ 1.5x10 ⁹ /L	0 (0)
	Don't know	1 (3)
	Any number	18 (55)
Level of platelet count required before lymphodepletion conditioning (in the absence of transfusion support within seven days)	Total answers	33 (80)
	≥ 20x10 ⁹ /L	4 (12)
	≥ 30x10 ⁹ /L	3 (9)
	≥ 50x10 ⁹ /L	4 (12)
	≥ 75x10 ⁹ /L	2 (6)
	Don't know	1 (3)
	Any number	19 (58)
Level of absolute lymphocyte count (ALC) required before lymphodepletion conditioning	Total answers	33 (80)
	≥ 0.1x10 ⁹ /L	1 (3)
	≥ 0.2x10 ⁹ /L	2 (6)
	≥ 0.3x10 ⁹ /L	2 (6)
	≥ 0.4x10 ⁹ /L	2 (6)
	Don't know	2 (6)
	Any number	24 (73)
Level of creatinine clearance (as estimated by Cockcroft Gault) required before lymphodepletion conditioning	Total answers	33 (80)
	≥ 60 mL/min	7 (21)
	≥ 50 mL/min	6 (18)
	≥ 40 mL/min	9 (27)
	≥ 30 mL/min	9 (27)
	Don't know	2 (6)
Level of Serum ALT/AST required before lymphodepletion conditioning	Total answers	33 (80)
	≤ 2.5 ULN	14 (42)
	≤ 3 ULN	11 (33)
	≤ 3.5 ULN	0 (0)
	≤ 4 ULN	0 (0)
	≤ 5 ULN	5 (15)
	Don't know	3 (9)

Table 9 (Continued)

(b)		
Eligibility criteria: before lymphodepletion conditioning		N (%)
Level of Total bilirubin, except in subjects with Gilbert's syndrome, required before lymphodepletion conditioning	Total answers	33 (80)
	≤ 1.5 ULN	9 (27)
	≤ 2 ULN	5 (15)
	≤ 2.5 ULN	6 (18)
	≤ 3 ULN	6 (18)
	≤ 4 ULN	3 (9)
Don't know	4 (12)	

Abbreviations: ULN: upper limit of normal.

experienced and if a cohort of dedicated nurse practitioners take an interest in this area.

As regards shared care management, particularly transitional care, there is little common vision. The responses are shown in Table 14. There is no clear pattern as to the frequency of visits to the treating centre for those patients referred from elsewhere.

The experience of LTFU units or 'Late Effects' clinics as a standard within the HCT community provides a model of care by which patients who receive treatment with CAR T-cells can be followed. Such LTFU models of care accommodate not only the inevitable transition of patients from paediatric to adult services, where the original paediatric teams need to be involved, but also involve the referring clinician closer to the patient's home, where necessary, via shared care arrangements [11]. There is much commonality particularly as all patients will have been exposed to previous cytotoxic therapies, including many to HCT, and will therefore require LTFU either in the administering and/or referring centres. However, there are also likely to be some very specific requirements in patients following CAR T therapy that need the oversight of the administering centre, ranging from monitoring of CAR T-cell persistence to specific complications such as chronic immunoglobulin deficiency and neurological follow-up of immune effector cell-associated neurotoxicity syndrome (ICANS) [12,13]. Moreover, there is a need for the mandatory reporting of data to the EBMT Registry, an EMA requirement that will reside with the administering centre for 15 years.

Table 10
Follow-up from discharge to Day+100.

Follow-up from hospital discharge to day +100		N (%)
How frequently should the patient attend ambulatory clinics (in patients without an overt complication and not including hospitalization for transfusion)?		
During the <u>first</u> month following discharge	Total answers	33 (80)
	1 time / week	8 (24)
	2 times / week	14 (43)
	3 times / week	11 (33)
	1 time / month	0 (0)
During the <u>second</u> month following discharge	Total answers	33 (80)
	1 time / week	13 (39)
	2 times / week	3 (9)
	1 time / 2 weeks	13 (39)
	1 time / month	4 (12)
During the <u>third</u> month following discharge	Total answers	33 (80)
	1 time / week	7 (21)
	2 times / week	0 (0)
	1 time / 2 weeks	12 (36)
	1 time / month	13 (39)
Don't know	1 (3)	

Table 11

Long-term follow-up after Day +100: Multidisciplinary team (MDT) and standard operating procedures (SOPs).

Long term follow-up after day 100: Multidisciplinary team and SOPs		N (%)
Is there a formal MDT meeting in your centre, which maintains a list of patients who routinely require long-term monitoring and management of late complications in patients following CAR-T therapy?	Total answers	32 (78)
	Yes	22 (69)
	No	10 (31)
If yes, is there a process for reviewing patients who develop late complications in the MDT, irrespective of where they are being followed up (i.e. in a separate department or referring hospital)?	Total answers	31 (76)
	Not applicable	10 (32)
	Yes	20 (64)
	No	0 (0)
	Don't know	1 (3)
Do you have a fully authorized document-controlled SOP specifically for long-term monitoring and management of late complications in patients following CAR-T therapy?	Total answers	32 (78)
	Yes	17 (53)
	No	14 (44)
	Don't know	1 (3)
If yes, i.e. you have a document-controlled SOP specifically for long-term monitoring and management of late effects in CAR-T treated patients, Is it structured on any of the following?	Remission status and the need for any other treatment after the CAR T-cell infusion	15 (37)
	Late complications e.g. infection and immunity, endocrine/growth/development	16 (39)
	Monitoring of long-term persistence of genetically modified T cells, e.g. analysis of vector integration sites	10 (24)
	Dependent on individual clinician assessment and judgement	5 (12)
	Dependent on internal discussion and/or MDT decision making	3 (7)
	Total answers	24 (58)
	Yes	8 (33)
If there is an SOP, is it external guidance?	No	15 (63)
	Don't know	1 (4)

At this early time-point, 37% of respondents reported that measures to ensure compliance with EMA/FDA and other regulatory requirements have been formally incorporated into a policy for long term follow-up of CAR T-cell recipients and the same percentage stated that they have been formally incorporated into the duties of HCT Data Managers. The answers regarding health promotion information and measures taken for regulatory compliance are shown in Table 15 and Fig. 2.

JACIE (or FACT) accreditation provides the broader quality management system required to support LTFU of patients receiving CAR T therapy. Although the standards pertaining to immune effector cell therapies (i.e. section B7.11 of the 7th edition, <https://www.ebmt.org/jacie-accreditation>) are most directly relevant to the early aspects of CAR T-cell administration, the more general integration of CAR T administration into the broader quality management systems required for accreditation will necessitate document-controlled policies, procedures and

Table 12

Long term follow-up after day 100: Model of long-term follow-up service.

Long term follow-up after day 100: Model of long-term follow-up service	N (%)			
	Yes	No	Don't know	Total answers
In your CAR T-cell programme, which of the following statements describe the organisation and model of the long-term follow-up service?				
A dedicated long-term follow up clinic/service specifically for CAR T-cell-treated patients	8 (20)	24 (59)	0 (0)	41 (100)
Patients are reviewed together with other HCT outpatient activity	17 (53)	15 (47)	0 (0)	32 (78)
Patients are reviewed together with other haematology-oncology outpatient activity (e.g. lymphoma clinic)	18 (58)	13 (42)	0 (0)	31 (76)
Patients are reviewed together with other oncology outpatient activity	5 (16)	26 (84)	0 (0)	31 (76)
Outreach service with primary referral base to lead on either structured shared care or react to problems arising (with ad hoc communication from referral base)	18 (58)	10 (42)	0 (0)	31 (76)
If yes, to the question above, is there a formal SOP agreeing the responsibilities and relationships with the referral base, including transfer of patients in case of late complications?	6 (24)	17 (68)	2 (8)	25 (61)
If yes, to above, does the formal SOP include robust arrangements and responsibilities for data reporting to meet EBMT and EMA/FDA requirements for 15 years following CART infusion?	9 (38)	9 (38)	6 (24)	24 (58)

Table 13

Long term follow-up after day 100: Model of long-term follow-up service.

Long term follow-up after day 100: Model of long-term follow-up service	N (%)
Who should lead long-term monitoring in patients following CAR T-cell therapy?	
Transplant consultants (as per FACT-JACIE definition of consultant transplant physician) who are part of the team that delivered the CAR-T cell therapy	25 (61)
Other specialist consultants who are part of the team that delivered CAR T-cell therapy	17 (42)
Referring consultant (i.e. close to patient's home base)	10 (24)
Other consultant not directly involved with the day-to-day care of the patient but someone who has developed a special interest in late effects of cancer and/or HSCT/cell therapy (e.g. physician/haematologist/oncologist/ endocrinologist)	3 (7)
GPs and/or other primary care	0 (0)
Senior nursing staff with expertise in haemato-oncology. oncology and/or HCT	7 (17)
Another clinician	2 (5)

service level agreements (SLAs) including MDTs for LTFU. Incorporation of transitional and shared care arrangements should provide an effective means of delivering quality assured LTFU in this complex patient group alongside mandatory data reporting.

Table 14
Long term follow-up after day 100: Shared care management and transitional care.

Long term follow-up after day 100: Shared care management and transitional care		N (%)
If there is a shared care arrangement, how often are patients seen in the centre that delivered the CAR T-cell therapy?	Not applicable	9 (22)
	Once monthly	6 (15)
	Three times monthly	7 (17)
	Six-monthly	4 (10)
	Yearly	2 (5)
	Don't know	2 (5)
If there is a shared care arrangement, how often are stable patients formally followed up (i.e. planned review, not reactive/ad hoc) in the centre that referred the patient for the CAR T-cell therapy?	Not applicable	10 (24)
	Once monthly	6 (15)
	Three times monthly	4 (10)
	Six-monthly	3 (7)
	Yearly	2 (5)
If you have a paediatric programme for CAR T-cells, how is long-term follow-up transitioned to patients who underwent CAR T-cell therapy in the local paediatric facility (i.e. transitional care)?	Not applicable	15 (37)
	Referral to a dedicated adult unit with experience in CART	5 (12)
	Referral to an adult HSCT unit	3 (7)
	Referral to an adult haematology-oncology unit	2 (5)
	Referral to an adult general haematology unit	1 (2)
If you have an adult programme for CART cells, how is long-term follow-up delivered to patients who underwent CAR T-cell therapy in the local paediatric facility (i.e. transitional care)?	Not applicable	10 (24)
	In a dedicated adult HSCT outpatient clinic	9 (22)
	In a haematology-oncology outpatient clinic	8 (20)
	In a general haematology outpatient clinic	0 (0)
	In a dedicated adult late effects outpatient clinic	1 (2)
	By the referring consultant (close to home)	2 (5)

Table 15
Health promotion information and measures taken for regulatory compliance.

Health promotion information and measures taken for regulatory compliance		N (%)
Other than discussions with clinicians (medical and nursing) before sending patients home after CAR T-cell therapy, what objective educational and health promotion information do you routinely provide to patients to alert them to the possible late complication following CAR T-cell therapy and the importance for long term follow-up	Written leaflets	26 (63)
	Patient website	8 (20)
	Copies of patient letters	15 (37)
What measures have been taken to assure compliance with EMA/FDA and other regulatory requirements for the long-term follow-up of recipients of CAR T-cell therapies? (Please tick all that apply)	None	1 (2)
	Informal arrangements	5 (12)
	Formally incorporated in an SOP for long term follow-up of CAR T-cell recipients	15 (37)
	Formally incorporated in the duties of HCT data managers	15 (37)
	The MDT review and document late complications/adverse events in previously treated patients and report to data managers	9 (22)
	There are mechanisms, such as an SOP, that enable referral centres to communicate late complications and adverse events	8 (20)

Measures have been taken to assure compliance with EMA/FDA and other regulatory requirements for the long-term follow-up

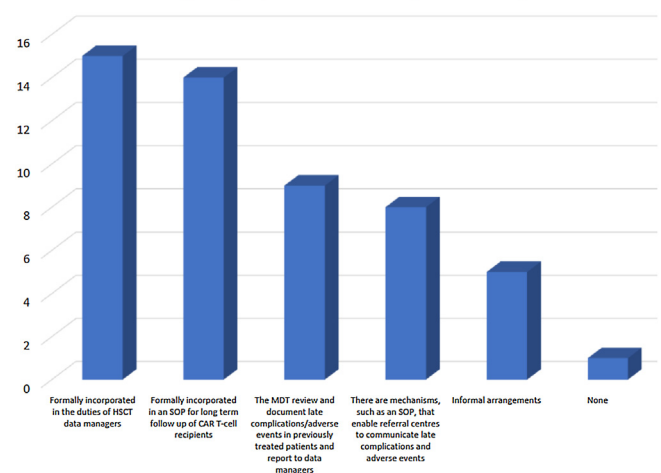


Fig. 2. Responses regarding measures taken to ensure compliance with regulatory requirements.

Conclusion

The advent of CAR T therapies represents a significant advance in the treatment of haematological malignancies and there is widespread interest in starting institutional programmes [14,15]. However, experience remains limited and providing this immune effector cell therapy to patients requires the coordinated work of physicians, apheresis facilities, cryobiology laboratories and pharmaceutical companies. Tisagenlecleucel (Kymriah™) and Axicabtagene ciloleucel (Yescarta™) are now commercially available in many countries and the results of this survey of forty-one experienced physicians demonstrates the heterogeneity of current clinical practice.

One of the strengths of this survey is the relatively large number of participants for what remains a new therapeutic class. The survey was emailed to 50 clinicians and 41 replied within a relatively short timeframe of two weeks. Although a small proportion of recipients declined to answer specific questions, this often usefully highlights the lack of certainty in a given area.

Any conclusions drawn from this study can only be, at best, tentative. Although the respondents come from a wide range of centres in several countries, they were chosen based on their involvement in international societies such as EBMT or ASTCT (American Society for Transplantation and Cellular Therapy) and not all responded. Some degree of inadvertent selection bias may therefore apply.

In conclusion, our survey provides a snapshot of current practice as this promising new therapy class moves from clinical trials to routine clinical use. The difficult choices facing physicians when trying to balance the benefits and risks involved in using these novel therapies are reflected in the different thresholds chosen by these forty-one experienced physicians, both when selecting patients and when judging acceptable levels of comorbidities. The findings also illustrate the embryonic nature of current follow-up arrangements and the need for centres to address this current deficit. Finally, the survey has informed the forthcoming EBMT recommendations on the management of adults and children undergoing autologous CAR-T cell therapy.

Conflict of interest

Submitted online.

Funding

This study was entirely funded by the Chronic Malignancies Working Party of EBMT.

Acknowledgments

The chronic malignancies working party (CMWP) of the EBMT would like to thank all participants for their timely responses to this survey: **Mahmoud Aljurf** (King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia); **Merav Bar** (FHRC, University of Washington, Seattle, USA); **André Baruchel** (Hôpital Robert Debré, Paris, France); **David Beauvais** (CHU de Lille, France); **Nicolas Boissel** (hôpital Saint-Louis, Paris); **Michael Byrne** (Vanderbilt University Medical Center - Nashville, TN, USA); **Miguel A. Canales** (La Paz University Hospital – Madrid, Spain); **Andy Chen** (Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA); **Christof Scheid** (University Hospital of Cologne, Germany); **Fabio Ciceri** (Ospedale San Raffaele, Milan, Italy); **Marco Davila** (H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida, USA); **Hermann Einsele** (Universitätsklinikum Würzburg, Germany) ; **Rawan Faramand** (H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida, USA); **Jordan Gauthier** (FHRC, University of Washington, Seattle, USA) ; **Armin Ghobadi** (Washington University in St. Louis, USA) ; **Stephan Grupp** (CHOP, Philadelphia, USA); **Shahrukh K. Hashmi** (Mayo Clinic, Rochester, Minnesota, USA and Riyadh, Saudi Arabia); **He Huang** (Zhejiang University. School of Medicine, Hangzhou, China); **Michael Jain** (Moffitt Cancer Center, Florida, USA); **Marie José Kersten** (Lymphoma and Myeloma Center Amsterdam, The Netherlands); **Mohamed A. Kharfan-Dabaja** (Mayo Clinic, Jacksonville, Florida, USA); **Nicolas Kröger** (University Hospital Hamburg-Eppendorf, Germany); **Jürgen Kuball** (University Medical Center, Utrecht, The Netherlands); **Richard Maziarz** (Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA); **John Murray** (Christie Hospital NHS Foundation Trust, Manchester, UK); **Sarah Nagle** (Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA); **Arnon Nagler** (Chaim Sheba Medical Center, Israel); **Antonio Pagliuca** (King's College Hospital and King's College, London, UK); **Miguel-Angel Perales** (Memorial Sloan Kettering Cancer Center, New York, NY, USA); **José María Ribera** (Institut Català d'Oncologia, Hospital Germans Trias i Pujol de Badalona, Spain); **Peter Riedell** (The University of Chicago, IL, USA); **Stephen Robinson** (University Hospitals Bristol, Bristol, UK); **Annalisa Ruggeri** (Ospedale Bambino Gesù in Roma, Italy); **Gilles Salles**

(Hospices Civils de Lyon, France); **Fermin Sanchez-Guijo**, (Hospital Universitario de Salamanca, University of Salamanca, Spain); **Bipin Savani** (University Medical Center - Nashville, TN USA); **Levanto Schacter** (Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA); **Ana Sureda** (stitut Català d'Oncologia Hospitalet, Barcelona, Spain); **Catherine Thieblemont** (Hôpital Saint-Louis, Paris, France); **Cameron Turtle** (FHRC, University of Washington, Seattle, USA); **Ibrahim Yakoub-Agha** (Lille University Hospital, France) and undisclosed US city.

The number of names is more than 41 as some centers completed the survey once following local agreement on the responses.

References

- [1] June CH, Sadelain M. Chimeric antigen receptor therapy. *N Engl J Med* 2018;379(1):64–73.
- [2] Gauthier J, Yakoub-Agha I. Chimeric antigen-receptor T-cell therapy for hematological malignancies and solid tumors: clinical data to date, current limitations and perspectives. *Curr Res Transl Med* 2017;65(3):93–102.
- [3] Quesnel B. CAR T-cells: A John von Neumann legacy? *Curr Res Transl Med* 2018;66(2):35–6.
- [4] Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in children and young adults with B-Cell lymphoblastic leukemia. *N Engl J Med* 2018;378(5):439–48.
- [5] Grupp S. Beginning the CAR T cell therapy revolution in the US and EU. *Curr Res Transl Med* 2018;66(2):62–4.
- [6] Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-Cell lymphoma. *N Engl J Med* 2019;380(1):45–56.
- [7] Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel CAR T-Cell therapy in refractory large B-Cell lymphoma. *N Engl J Med* 2017;377(26):2531–44.
- [8] Ghobadi A. Chimeric antigen receptor T cell therapy for non-Hodgkin lymphoma. *Curr Res Transl Med* 2018;66(2):43–9.
- [9] Yakoub-Agha I. Clinical units to set up chimeric antigen receptor T-cell therapy (CAR T-cells): based on the recommendations of the Francophone Society of Bone Marrow Transplantation and Cellular Therapy (SFGM-TC). *Curr Res Transl Med* 2018;66(2):57–8.
- [10] Buitrago J, Adkins S, Hawkins M, Iyamu K, Oort T. Adult survivorship: considerations following CAR T-Cell therapy. *Clin J Oncol Nurs* 2019;23(2):42–8.
- [11] Callahan C, Barry A, Fooks-Parker S, Smith L, Baniewicz D, Hobbie W. Pediatric survivorship: considerations following CAR T-Cell therapy. *Clin J Oncol Nurs* 2019;23(2):35–41.
- [12] Rubin DB, Danish HH, Ali AB, Li K, LaRose S, Monk AD, et al. Neurological toxicities associated with chimeric antigen receptor T-cell therapy. *Brain* 2019.
- [13] 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):50–2.
- [14] Perica K, Curran KJ, Brentjens RJ, Giral SA. Building a CAR garage: preparing for the delivery of commercial CAR t cell products at memorial sloan kettering Cancer center. *Biol Blood Marrow Transplant* 2018;24(6):1135–41.
- [15] Taylor L, Rodriguez ES, Reese A, Anderson K. Building a program: implications for infrastructure, nursing education, and training for CAR T-Cell therapy. *Clin J Oncol Nurs* 2019;23(2):20–6.