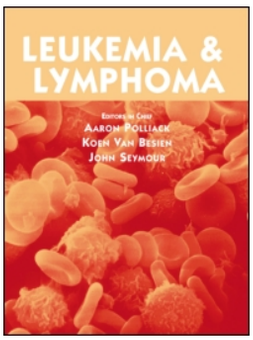

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ORIGINAL ARTICLE

Relapsed/refractory diffuse large B-cell lymphoma patients. A multicenter retrospective analysis of eligibility criteria for car-T cell therapy

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ABSTRACT

Anti-CD19 chimeric antigen receptor (CAR) T cells represent the first approved third-line therapy associated with long-term remissions in patients with refractory/relapsed (R/R) diffuse large B-cell lymphoma (DLBCL). Eligibility criteria to identify patients who can successfully receive CAR-T are still debated. For this reason, the aim of this study was to identify factors influencing eligibility and define a realistic patient estimate. Of 1100 DLBCL patients, 137 were included. Based on the Juliet trial inclusion criteria, only 64 patients (46.7%) would be eligible. Median overall survival (OS) was 8.04 months in eligible *vs* 3.23 in non-eligible patients ($p < 0.001$). Multivariate analysis identified stage III-IV ($p = 0.017$) and ECOG ≥ 2 ($p < 0.001$) as significant independent prognostic factors for OS. Moreover, only 64/1100 (5.8%) DLBCL patients would be truly eligible for CAR-T. Our real-life data confirm that with a longer waiting time patients with advanced stage and poor ECOG are less likely to be eligible for CAR-T cell infusion.

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Diffuse large B-cell lymphoma; CAR-T cells; relapse-refractory disease; CAR-T cell eligibility

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma (NHL), representing 25–35% of all newly diagnosed cases. The combination of rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) is the standard first-line therapy for patients with DLBCL, leading to 5-year progression-free (PFS) and overall survival (OS) rates of approximately 60% and 65% [1]. Despite these results, 20–40% of patients have a primary refractory disease or will experience a relapse [2]. High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) is considered the best second-line therapy in this setting. However, only about 50% of R/R DLBCL patients are able to undergo an ASCT due to a lack of response to salvage treatment or to comorbidities [2–5]. Patients with DLBCL refractory to second-line therapy or relapsed after an ASCT have a very poor clinical outcome with a median OS of 5 and 8–10 months, respectively [5,6]. Treatment options for these patients have focused on experimental drugs, with very limited results. An allogeneic stem cell transplant (SCT) represents a valid therapeutic option for this subset of patients, offering a chance of an improved long-term OS. However, only a small and highly selected group of patients who remain chemosensitive and with an available donor (less than 20%) can undergo a SCT [7] and the procedure is associated with notable side effects and a transplant-related mortality of 25% at 1 year [7,8].

The anti-CD19 chimeric antigen receptor T (CAR-T) cell therapy is a promising approach for the management of R/R DLBCL, associated with sustained complete remissions and long-term survivals in a large proportion of patients in the two pivotal clinical trials Zuma1 and Juliet [9,10]. This has led to the rapid approval by the Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) of CAR-T cells for the third-line treatment of R/R DLBCL. Currently, tisagenlecleucel (Kymriah™, Novartis) and axicabtagene ciloleucel (axi-cel, Yescarta™, Gilead) are registered in this setting and a third product,

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lisocabtagene maraleucel (liso-cel, Celgene), has generated promising preliminary data [11]. The clinical benefits of tisagenlecleucel and of the axi-cel product have been confirmed at the last ASH meeting by the Center of International Blood and Marrow Transplant Research (CIBMTR), indicating that real-life results are comparable to those of the clinical trials in terms of efficacy and safety [12,13].

Despite its efficacy, CAR-T cell therapy is associated with unique toxicities – namely the cytokine release syndrome (CRS) and neurotoxicity - which require an intensive monitoring strategy and a close interaction with the intensive care unit (ICU).

A highly debated issue is how to better identify patients who can successfully undergo CAR-T cells, taking into account the possible toxicities as well as the manufacturing complexity and time associated with the procedure. In addition, the financial implications of this innovative therapeutic strategy cannot be ignored, particularly in view of the number of R/R DLBCL patients potentially eligible to CAR-T cell therapy around the world.

There are no validated baseline clinical parameters capable of predicting the efficacy and toxicity of CAR-T cells in R/R DLBCL. The pretreatment evaluation has therefore become a pre-requisite step to determine patients' eligibility to CAR-T cells.

To address this issue, in this multicenter retrospective study we have examined data of R/R DLBCL patients in order to: 1) better identify the characteristics and outcome of a cohort of patients potentially eligible for CAR-T cell therapy; 2) define factors influencing CAR-T cell eligibility; 3) make a realistic estimate of patients eligible for CAR-T cells.

Methods

Study design and participants

This is a cohort study using clinical data on consecutive DLBCL patients with refractory disease or who have relapsed after ASCT, managed between 2010 and 2018 at four Italian centers. All patients had received anti-CD20 and anthracycline-based immunochemotherapy as first-line treatment. This cohort of R/R DLBCL was reviewed under IRB approval to determine the potential eligibility to CAR-T cell therapy by applying the Juliet clinical trial inclusion/exclusion criteria, reported in Table 1, that are very similar to the eligibility criteria reported by the Italian drug agency (AIFA) except for the age limit [10].

Eligible patients were $\geq$18 years, with a diagnosis of DLBCL according to the WHO 2016 classification, including transformed follicular lymphomas and high-grade lymphomas, managed between 1 January 2010 and 31 May 2018. All patients had undergone at least two previous lines of anti-CD20 containing chemotherapy regimens, or had relapsed after an ASCT. Patients with primary central nervous system lymphoma, primary mediastinal lymphoma, Richter syndrome, diffuse cutaneous large B- or T-cell/histiocyte-rich lymphoma were excluded. Relapsed disease was defined as a recurrence of the disease after having obtained a complete or partial response to the last line of chemotherapy including ASCT. Refractory disease was defined according to the SCHOLAR-1 study criteria [14]: progressive disease after $\geq$4 cycles of first-line therapy followed by stable disease after 2 cycles of salvage treatment or a relapse at $\leq$12 months from ASCT.

The clinical data recorded at the time of the second relapse or of second-line therapy failure were: ECOG ($<$2), hematology laboratory parameters, organ function, evaluation of central nervous system involvement.

Table 1. Juliet trial's key inclusion/exclusion criteria.

Juliet key inclusion criteria
• Age $\geq$ 18
• ECOG 0–1
• R/R disease after ASCT or ineligible for ASCT
Juliet key exclusion criteria
• Active Central Nervous System (CNS) involvement by malignancy
• Prior allogeneic HSCT
• Concurrent use of steroids
• Prior radiation therapy within 2 weeks of infusion
• Active replication of or prior infection with hepatitis B or active hepatitis C
• Uncontrolled acute life threatening bacterial, viral or fungal infection
• Cardiac arrhythmia not controlled with medical management
• Patients on oral anticoagulation therapy
• Patients with active neurological auto immune or inflammatory disorders

Aims of the study

The primary endpoint was the identification of the characteristics and outcome of a cohort of R/R DLBCL patients potentially eligible, according to the approval criteria, for CAR-T cell therapySecondary endpoints included the definition of factors influencing CAR-T cell eligibility and making a realistic real-life estimate of patients truly eligible for CAR-T cells.

Statistical analysis

Patients characteristics were summarized using relative frequencies for categorical variables, median and IQR for continuous variables. For the purposes of our analysis, OS was defined as the time from second relapse until death from any cause or last follow-up for

censored patients. OS curves were estimated with Kaplan-Meier product-limit estimator and compared using the log-rank test. Univariate and multivariable analyses were carried out using the Cox proportional hazard model [15]. Model selection was performed in a stepwise fashion, by minimizing the Akaike Information Criterion. Conditional survival at the threshold of 28 days was predicted using the final multivariate Cox regression model, after estimation of the baseline hazard through a Nelson-Aalen estimator. Significance was fixed at the 0.05 level. All analyses were performed by using R version 3.5.1.

Results

Among the 1100 patients registered in the database of newly diagnosed DLBCL from four centers, 156 (14.2%) experienced a second or further relapse or progression as of September 2019. Of these, 137 (90.4%) were included in our analysis; 15 patients were excluded because they had not received two previous lines of therapy, while 4 patients were diagnosed as indolent lymphoma at relapse. Median age was 63.0 years (IQR 54.7–71.2), 66/137 (48.1%) were ≥65 years; 54 (38.2%) were male. We collected the clinical data of the 137 patients who failed two lines or more of therapy: 108 (78.8%) were ECOG 0-1 and 29 (21.2%) ECOG ≥2; 34 (25%) patients had an Ann Arbor stage I-II and 103 (75%) a stage III-IV; 15 (10.9%) had normal lactate dehydrogenase (LDH) values and 90 (65.7%) had increased levels, while and this information was not available for 32 patients.

At the time of data collection, 101/137 (74%) patients were chemorefractory and 16 of these (16%) had undergone an ASCT; 36 (26%) patients relapsed after two lines of chemotherapy, 18 (50%) after an ASCT. The median lines of therapy was 3 (range 2–8). All clinical and pathologic characteristics are reported in Table 2.

Table 2. Patients' characteristics at second relapse.

Characteristic	Patients ($N = 137$)	%
Gender		38.7
Male	53	61.3
Female	84	
Age (years)		
Mean (range)	62 (21–87)	
Age > 65	66	48.1
Ann Arbor stage		
I - II	34	24.8
III - IV	103	75.2
Symptoms B		27.7
Yes	38	51.8
No	71	20.5
Missing	28	
HCV/HBV serology		78.8
Negative	108	19.7
Positive	27	1.5
Missing	2	
ECOG		
0	45	32.8
1	63	46.0
2	17	12.4
3	12	8.8
Missing	0	0
Histology		
DLBCL	120	87.6
tFL	17	12.4
Missing	0	0
Lines of therapy		
2	23	16.8
≥3	113	82.5
Missing	1	0.7
ASCT		
Yes	34	25.8
No	103	75.2
ECOG		
≥2	29	21.2
LDH ≥ ULN		65.7
Yes	90	10.9
No	15	23.4
Missing	32	

Eligibility to CAR-T cell therapy

Based on the Juliet clinical trial inclusion/exclusion criteria, 64 of the 137 patients (46.7%) would be defined as eligible and 73 (53.3%) as not eligible to CAR-T cells, for the following reasons: 20 (27.4%) because of an ECOG ≥2 (among these, 14 had also another ineligibility criteria), 21 (28.8%) had at least one severe comorbidity, 13 (17.8%) were positive for hepatitis serology, 19 (26.0%) had organ dysfunction, such as renal impairment (serum creatinine levels >1.5 ULN) or elevated transaminases levels (GOT/GPT >2 ULN). Twelve CAR-T ineligible patients had also an active CNS disease involvement and 25 (34.2%) had more than one exclusion criteria for CAR-T.

Patients eligible for CAR-T cell therapy had a median age of 62 years (range 21–87 yrs), while the median age of non-eligible patients was 64 (range 21–83), (p-value 0.822). In our analysis, we have evaluated also patients >70 years who represented 31.4% of the case series (43/137). Among these patients, the CAR-T eligible and not eligible patients were 22 and 21, respectively ($p = 0.559$).

Outcome and clinical prognostic factors

The median OS of the entire cohort of R/R DLBCL was 5.41 months (95% CI: 4.19–7.55). The 1-year and 2-year OS rates were 27.4% (95% CI: 20.4–36.8) and 17.1% (95% CI: 11.1–26.4), respectively (Figure 1). The median OS was 8.04 months (95% CI: 5.74–21.43) in eligible patients *vs* 3.23 months (95% CI: 2.14–5.27) in non-eligible patients ($p < 0.001$) (Figure 2).

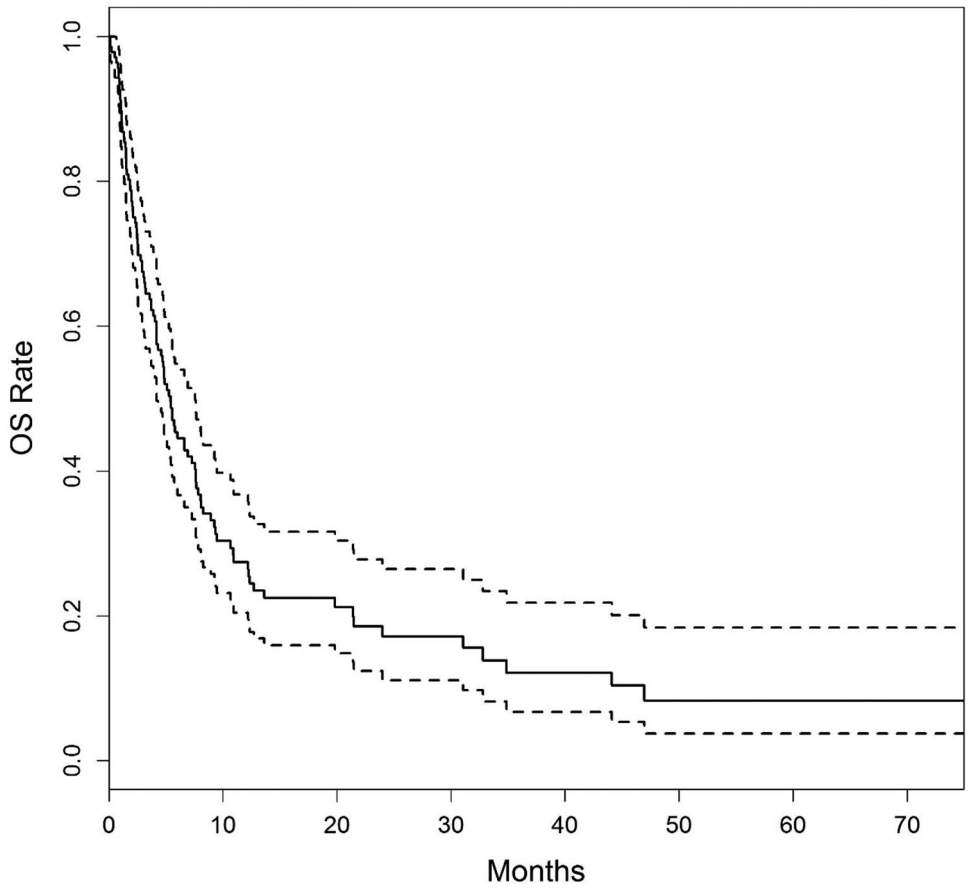

Figure 1. Overall survival of all R/R DLBCL patients.

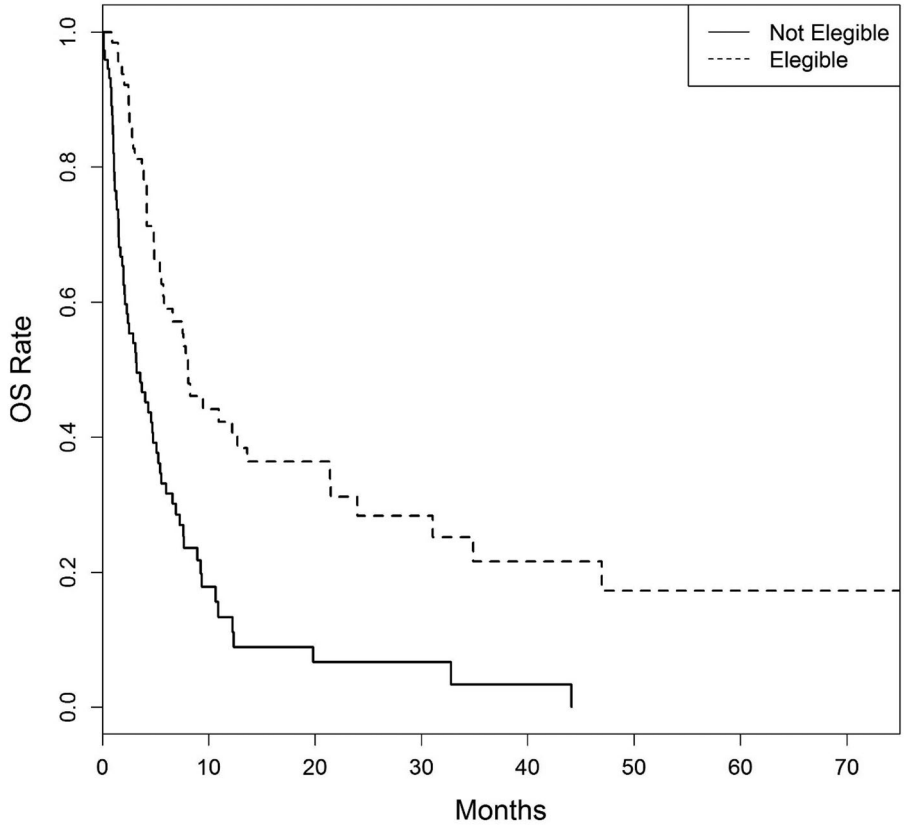

Figure 2. Overall survival of CAR-T cell eligible vs not-eligible R/R DLBCL patients.

In the subgroup of elderly patients (≥65 years), the survival assessment showed that the median OS of patients considered eligible for CAR-T cell therapy was 7.85 months compared to 9.45 months of the eligible young patients ($p = 0.2$) (Figure 3(A)). Worldwide, CAR-T cell therapy has been approved without age limits, while the Italian medicine agency (AIFA) defines 70 as the age limit for CAR-T cells. The analysis of eligible

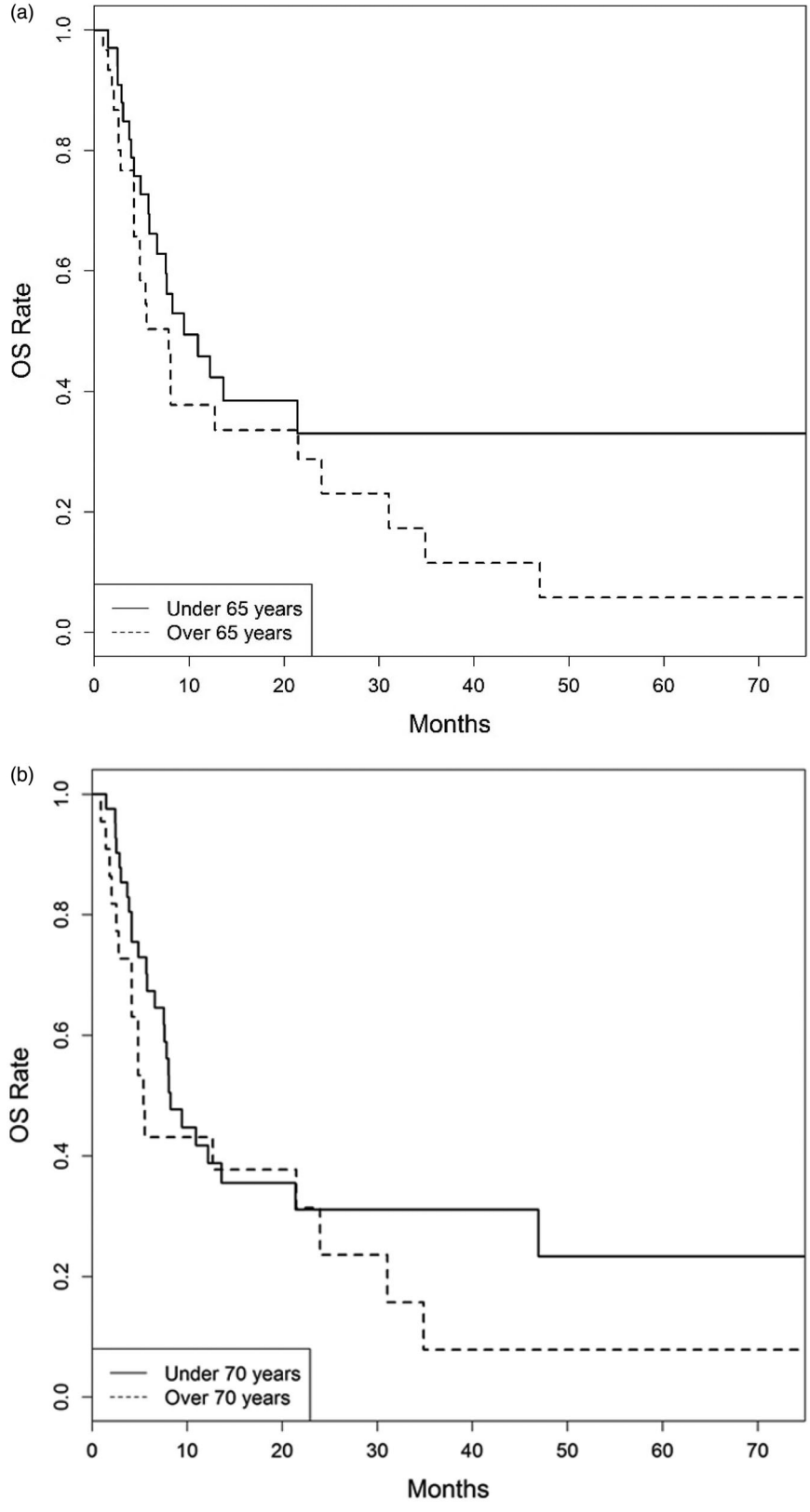

Figure 3. (A) Overall survival of CAR-T-cell eligible patients stratified by age; (B) Overall survival of CAR-T cell eligible patients stratified according to AIFA's upper age limit.

patients stratified for AIFA age limit showed that there are no statistical differences in terms of median OS between patients under and over 70: 8.27 months and 5.41 months, respectively ($p = 0.3$) Considering 70 years as a cutoff, the results were similar: the 1-year OS was 43.1% (95% CI: 26.2–70.8) for patients >70 and 41.7% (95% CI: 28.4–61.3) for patients <70 years (Figure 3(A)).

In univariate analysis, OS was significantly reduced in patients with: Ann Arbor stage III-IV (HR = 2.41 95% CI: 1.38–4.20, $p = 0.002$), ECOG ≥2 (HR = 3.20 95% CI: 2.00–5.13, $p < 0.001$), receiving more than three lines of therapy (HR = 0.83 95% CI: 0.71–0.98, $p = 0.024$), elevated LDH (HR = 1.002 95% CI: 1.001–1.003, $p < 0.001$) and gender (HR = 0.56 95% CI: 0.37–0.85, $p = 0.007$) (Table 3). Multivariate analysis identified Ann Arbor stage III-IV (HR = 2.01 95% CI: 1.13–3.57, $p = 0.017$) and ECOG ≥2 (HR = 2.83 95% CI: 1.66–4.84, $p < 0.001$) as significant independent prognostic factors for OS. The OS stratified for prognostic factors is shown in Figure 4. Patients with both unfavorable

Table 3. Univariate and multivariable analysis of OS in relation to second relapse variables.

Variable	Univariate models HR (95% CI)	*p* value	Multivariable model HR (95% CI)	*p* value
Gender Male	0.559 (0.366–0.852)	0.007		
Age	1.006 (0.993 – 1.018)	0.379		
Ann Arbor stage III – IV	2.408 (1.381–4.199)	0.002	2.011 (1.133–3.569)	0.017
Symptoms B	0.849 (0.528–1.364)	0.499		
Hepatitis serology	1.424 (0.901–2.251)	0.13		
ECOG				
1	2.265 (1.420–3.612)	<0.001		
2	3.971 (2.051–7.686)	<0.001		
3	9.671 (4.542–20.597)	<0.001		
Comorbidity	1.105 (0.753–1.624)	0.61		
LVEF	0.6 (0.024–14.942)	0.755		
N° of treatment	0.833 (0.71–0.976)	0.024		
ECOG				
≥2	3.201 (1.998–5.128)	<0.001	2.833 (1.660–4.837)	<0.001
LDH ≥ ULN	2.006 (0.993–4.056)	0.052		

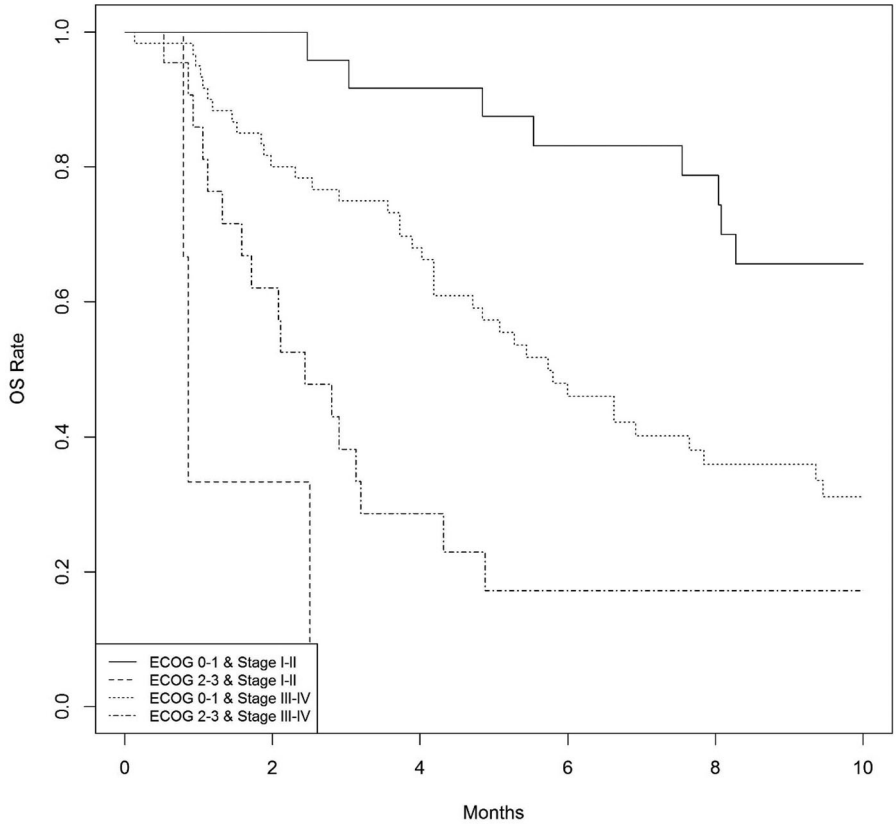

Figure 4. Overall survival of CAR-T cell eligible patients stratified by ECOG and stage.

Table 4. Survival prediction at 17, 40 and 54 days from time of relapse, stratified by ECOG and stage, both at time of second relapse.

Time	Ecog <2 & Stage I–II	Ecog <2 & Stage III–IV	Ecog ≥ 2 & Stage I–II	Ecog ≥ 2 & Stage III–IV
17	99.3%	98.6%	98.0%	96.0%
40	94.1%	88.6%	84.3%	70.9%
54	92.4%	85.3%	80.0%	63.8%

factors have a very poor prognosis compared to those with no risk factors. We could not consider the difference in prognosis between patients with only one risk factor because there were only 3 patients with a poor performance status and a limited stage, and all had a rapid disease progression and death.

We also estimated the survival of our patients considering the waiting time to the CAR-T cell infusion. We have analyzed the rate of survival at different median waiting times: 17 days as reported in the Zuma trial, 54 days as in the Juliet trial and 40 days as reported in the real-life French experience presented at the last EHA congress [16]. We could estimate that patients with a limited stage and an ECOG <2 had a 17-day OS of 99.3%, a 54-day OS of 92.4% and a 40-day OS of 94.1%. On the contrary, patients with advanced stage and an ECOG ≥ 2 had a 17-day OS of 96%, a 54-day OS of 63.8% and a 40-day OS of 70.9% (Table 4).

Estimate of patients eligible for CAR-T cells

At the time of this analysis, 34/137 (25%) patients were alive and 12 (35.3%) of them were considered eligible for CAR-T therapy. One patient was lost to follow-up and would have been considered eligible for CAR-T cells. One hundred and two (74.4%) patients died; among these, 64 (60.4%) would have been considered eligible for CAR-T cell therapy. Overall, of the initial 1100 newly diagnosed DLBCL collected over 8 years, the rate of cases considered truly eligible for CAR-T cell therapy was 5.8% (64/1100).

Discussion

Our study is a retrospective analysis of a real-life cohort of 137 consecutive patients with DLBCL relapsed after at least two lines of chemotherapy or chemorefractory. This study, with the limits of a retrospective database, defines the clinical characteristics of R/R DLBCL patients potentially eligible to a CAR-T cell treatment according to the currently approved disease indications by FDA and EMA. The aim was to describe the outcome of these patients who have a dismal prognosis with no other therapeutic options in the pre-CAR-T era. Moreover, we wanted to identify the clinical factors that impacted on the eligibility of R/R DLBCL to the cellular therapy and to estimate a realistic number of patients potentially eligible to CAR-T cell therapy.

Our results confirm that R/R DLBCL patients have a very poor outcome showing that 27.4% and 17.1% of patients are alive at 1 year and 2 years, respectively, with a median OS of 5.4 months in line with published data [14]. There is therefore an urgent need to develop new effective therapeutic strategies for the difficult to treat patient population.

CAR-T cell therapy is the only newly approved third-line therapy that has been able to improve the prognosis of this cohort of patients. However, this treatment is limited by different aspects: its unique specific toxicities (CRS and neurotoxicity), the waiting time associated with the manufacturing procedure and quality controls, the need for the CAR-T center to have a dedicated multidisciplinary team, the costs and the overall production capabilities.

The waiting time from the selection of a patient to the infusion of the CAR-T cells is a critical point: R/R DLBCL is a very aggressive disease and because of a possible chemorefractory status they may not respond to bridging chemotherapy, so that the production time may preclude the administration of the CAR-T cells. Patients' selection becomes essential to allow the optimal infusion of the product and best long-term outcome likelihood.

In 2017, FDA first approved tisagenlecleucel and axicabtagene ciloleucel, and one year later also EMA granted the approval for both products. However, within the international community, there is no consensus on the selection criteria, and individual countries apply different patient selection algorithms. One model to select patients is to follow the inclusion and exclusion criteria used in the pivotal clinical trials, ZUMA-1 and Juliet, where there was no upper age limit. Patients enrolled in these trials had a similar median age of 59 and 65 years, respectively, with about 25% of patients over the age of 65. In our cohort study, we have used the eligibility criteria of the Juliet study to divide our population into eligible versus non-eligible patients, including also the elderly population. The median age was very similar in the two groups and the rate of patients over age 65 was

48.1%. Overall, 53.3% of patients were considered non-eligible; among these, most patients (24.1%) had more than one exclusion criteria and 13% of patients were excluded due to a poor performance status (ECOG $\geq$2). These results are very similar to another retrospective analysis of eligibility presented at the last EHA and ASH meetings by Paillassa et al. who reported that 77/215 patients (36%) were considered non-eligible [16–18].

In 2019, AIFA approved CAR-T cell therapy with specific eligibility criteria including an age limit under 70. Italy was the only country to approve CAR-T cells with an age limit. In our analysis, we have included also over 70 patients (31.4%) and did not find differences in terms of eligibility characteristics compared to the under 70. In our elderly case series, the median OS of patients considered eligible for CAR-T cell therapy was 7.85 months compared to 9.45 months for the eligible young patients. Also in univariate analysis, advanced age was not a predictive factor of survival and should not be considered an absolute exclusion criterion for CAR-T cell treatment. In fact, also in terms of toxicity, a recent study has reported that the efficacy and safety were comparable between elderly (>65 years) and younger (<65 years) patients following axi-cel therapy [12].

In univariate analysis, the predictive factors for OS were advanced stage, ECOG $\geq$2, more than three lines of therapy, elevated LDH and gender, while multivariate analysis identified stage III-IV and ECOG $\geq$2 as the only significant prognostic factors for OS. As expected, a high tumor burden and a poor performance status are indicative of patients with rapidly progressive disease who may not be ideal patients for a CAR-T cell program. Although the two pivotal clinical trials excluded patients with ECOG 2 or more, patients with a poor performance status have been treated with commercial CAR-T cells. In the real-world experience with tisagenlecleucel patients with ECOG >2 were only 3/70 (4.3%) [13], but Jacobson et al. [19] showed that ECOG performance status (p =.009), tumor bulk (p =.016), baseline CRP (p =.029) had a significant association with lack of response to treatment with axi-cel. However, at univariate analysis conducted for toxicity, the authors did not find an association between high grade of CRS or neurotoxicity and ECOG.

It is clear that patients with rapidly progressive disease cannot wait for the time period required to have the CAR-T cell product ready for infusion. There is always a gap of several weeks between the decision to treat and the hospitalization for the infusion, including the manufacturing time that is different in clinical trials [9,10] and continues to vary also in the real-life setting. In the Zuma-1 and Juliet studies, the median time from leukapheresis to infusion was 17 and 54 days, respectively. In the real-life, there are also different center and country logistic issues that could extend the waiting time. Considering the different delivery times, we have calculated the survival estimate stratified according to two prognostic factors: ECOG $\geq$2 and Stage III-IV. Our results confirm that with the longer waiting time patients with advanced stage and poor performance status are less likely to survive up to the infusion or be still eligible for the infusion. It is predicted that at 54 days from relapse, only 63.8% of patients with ECOG $\geq$2 and Stage III-IV would be infused compared to 92.4% of patients with ECOG = 0–1 and a limited disease stage.

Based on our results, we confirm that disease evaluation and the performance status of patients help to better select optimal candidates for a CAR-T cell therapy and, based on the waiting time to organize a bridging therapy following leukapheresis, for disease control during the CAR-T manufacturing process. It is important that logistic issues should be resolved at each center in advance in order to reduce the gap of several weeks considering also the time needed to have the product delivered.

In our overall study cohort of 1100 DLBCL patients, only 64 (5.8%) would have been eligible for CAR-T therapy based on the Juliet inclusion/exclusion criteria. To our knowledge, this is one of the first published studies that reports a realistic estimate of CAR-T cell eligibility among a large series of DLBCL patients. Due to the limited production capability and of the high costs of CAR-T cells, it is important that every country makes an estimate of the number of eligible patients per year who are truly likely to benefit from this innovative but complex treatment strategy in order to optimize the likelihood of success, as well as the costs on the health system. At a time of important financial constraints and hospital facility limitations, a refined patient identification becomes even more crucial.

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ADR designed and performed the research, analyzed data and wrote the paper. LP, DP, FR, MG provided samples and clinical data; MA and GDL analyzed the data and wrote the paper. GMR, FR, FM critically revised the paper. AF designed the research study and ADR performed statistical analysis. AC and RF supervised the study and critically revised the manuscript.

Disclosure statement

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