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CAR-T cell therapy in older adults with relapsed/refractory LBCL: benefits and challenges

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ABSTRACT

Patients with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) have poor prognosis with a high unmet need for efficacious treatment options. Most patients with r/r large B-cell lymphoma (LBCL) are elderly, which adds to the complexity of choosing the appropriate and effective therapy in these patients. Recently approved therapies, such as CD19-targeted chimeric antigen receptor-T cell therapy, have shown improvements in the outcomes of patients with r/r DLBCL. Several real-world studies also support the use of these newer therapies in elderly patients. However, given the frailty, variability in the risk factors in each elderly patient, and the increased susceptibility for adverse events, a comprehensive geriatric assessment and a multidisciplinary approach could be helpful in guiding the management and treatment choices for these vulnerable patients. Individualized care can aid in giving elderly patients with r/r LBCL the best possible outcome with their chosen treatment regimen.

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma (NHL), with an incidence of about 5 out of 100,000 people yearly in the USA.[1 2] DLBCL commonly affects older patients (median age at diagnosis in the USA is 66 years), resulting in suboptimal outcomes with standard therapy; complete response (CR) rates and overall survival (OS) decrease with age while toxicities are increased in the elderly.[3–6] Overall, the prognosis for patients with relapsed or refractory (r/r) DLBCL is poor, and there is a need for additional safe and effective treatments that improve long-term outcomes in this patient population.[7]

Currently, the combination of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) and the combination of polatuzumab vedotin and R-CHOP are considered the first-line (1L) standard of care (SOC) for patients with DLBCL.[8–11] However, about one-third of patients subsequently relapse after an initial response or are refractory to the initial treatment.[9] Currently, a standard second-line (2L) treatment for r/r DLBCL is salvage chemotherapy followed by high-dose consolidation chemotherapy supported with autologous stem cell transplantation (ASCT), which can provide durable outcomes.[10 12] However, it is not as effective in patients with refractory disease who have already undergone chemotherapy, and its utility is primarily limited to younger and physically fit patients.[13] The American Society of Transplantation and Cellular Therapy Clinical Practice Recommendations for Transplantation and Cellular Therapies now recommend cluster of differentiation (CD)19-targeted chimeric antigen receptor (CAR)-T cell therapy as a 2L therapy option in r/r DLBCL based on the event-free survival (EFS) and OS benefits reported in head-to-head trials versus SOC chemoimmunotherapy followed by ASCT in responders.[14]

Axicabtagene ciloleucel was approved in 2017 for the treatment of patients with r/r large B-cell lymphoma (LBCL) following disease progression after ≥2 systemic therapies.[15–17] Another CD19-targeting CAR-T cell therapy, tisagenlecleucel, was approved in 2018 for patients with r/r LBCL after ≥2 prior therapies.[18 19] Lisocabtagene maraleucel is the most recently approved (2021) CAR-T cell therapy for r/r LBCL in the 3L setting.[20–22] Axicabtagene ciloleucel and lisocabtagene maraleucel were also approved for patients with 2L high-risk LBCL based on improved EFS, and better OS with axicabtagene ciloleucel, compared with SOC salvage chemotherapy and ASCT.[22–26] All three CD19-targeting CAR-T cell therapies have shown acceptable safety profiles in these patient populations.[16 18 20]

CAR-T CELL THERAPY: CLINICAL TRIAL EVIDENCE IN OLDER ADULTS

Axicabtagene ciloleucel

Results from ZUMA-1, a study in 111 patients with r/r LBCL, were the basis for regulatory approval of axicabtagene ciloleucel in the

3L setting for adults with r/r LBCL.[15 16 27] The post hoc 2-year follow-up subgroup analysis showed that there were no apparent age-related differences in overall efficacy and safety outcomes among patients age ≥65 and <65 years (table 1).[20 26 28–31] Of note, patients age ≥65 years had a higher CR rate and longer median duration of response (mDOR) and median progression-free survival (mPFS), compared with those age <65 years (CR: 75% vs 53%, mDOR: 12.0 vs 8.1 months, mPFS: 13.2 vs 5.6 months, respectively); however, 24-month OS was similar for both age groups (54% vs 49%, respectively). Adverse events (AEs) were tolerable for both age groups at 2 years' follow-up; grade ≥3 cytokine release syndrome (CRS) events were reported in 7% for patients ≥65 years of age and in 12% of patients<65 years of age. Grade ≥3 immune effector cell-associated neurotoxicity syndrome (ICANS) was noted in 44% of patients ≥65 years of age and in 28% of patients <65 years of age.[28] The 5-year follow-up reported durable OS and no new safety signals in the overall patient population.[32] Regulatory approval of axicabtagene ciloleucel in 2L LBCL was based on outcomes from the ZUMA-7 study.[17 23 25] The 5-year survival analysis of ZUMA-7 demonstrated the superiority of axicabtagene ciloleucel compared with SOC.[23 33] A separate preplanned subgroup analysis of ZUMA-7 in older patients (≥65 years of age) with r/r LBCL found that 2L axicabtagene ciloleucel resulted in significantly higher overall response rate (ORR) compared with SOC (88% vs 52%, respectively; p<0.0001) (table 1),[20 26 28–31] including among patients ≥70 years of age (88% vs 41%, respectively; p<0.001).[30] Patients ≥65 years of age who received axicabtagene ciloleucel also had a significantly longer median EFS compared with SOC (21.5 vs 2.5 months, respectively).[30] The incidence and management of CAR-T-associated AEs such as CRS and ICANS were consistent with previous reports. Overall, patients ≥65 years of age who received axicabtagene ciloleucel experienced improved clinical benefits over the SOC as in the overall patient population.[30]

Tisagenlecleucel

Tisagenlecleucel was approved in the treatment of patients with r/r LBCL after two or more lines of therapy based on the findings from the JULIET trial, which showed durable responses and an acceptable safety profile.[18 29 34] After a median follow-up of 40.3 months, the best ORR was 49.4% among patients <65 years of age and 65.4% for patients ≥65 years of age, and mDOR was not reached in either age group (table 1).[20 26 28–31] In the overall patient population, AEs were similar to the previous report, with no treatment-related deaths or unexpected events reported.[29]

Lisocabtagene maraleucel

The TRANSCEND study led to the approval of lisocabtagene maraleucel for treatment of patients with r/r LBCL in the ≥3L setting, and the TRANSFORM and PILOT studies led to approval in the ≥2L setting.[20 21 24 35] In the TRANSCEND NHL 001 study, subgroup analyses by patient age demonstrated numerically higher ORR among patients ≥65 years of age versus <65 years of age, with durable PFS and OS in both age groups (table 1).[20 26 28–31] In addition, rates of grade ≥3 CRS and ICANS were similar in both age groups.[20] In the TRANSFORM trial, lisocabtagene maraleucel showed similar EFS benefits compared with SOC both in patients <65 years of age and in those between 65 and 75 years of age.[26] The PILOT study assessed the antitumor activity and safety of lisocabtagene maraleucel as ≥2L treatment in adults with r/r LBCL who were ineligible for hematopoietic stem cell transplantation (HSCT) because of poor performance status (PS) (Eastern Cooperative Oncology Group PS (ECOG PS) 2), reduced organ function, or older age (≥70 years).[31 36] In the PILOT study, the median patient age was 74 years and most patients (79%) were ≥70 years of age; many patients had preexisting comorbidities (renal 25%, pulmonary 7%, cardiac 2%). In the final analysis of PILOT, with 23.1 months' median follow-up, mDOR was 23.3 months, median OS was not reached, and rates of grade ≥3 CRS and ICANS were low (table 1).[20 26 28–31]

Although data are somewhat limited, subgroup analyses from the clinical trials of currently approved CAR-T therapies for 2L and 3L r/r LBCL have shown high response rates with acceptable safety profiles in patients ≥65 years of age (table 1).[20 26 28–31] Across the three CAR-T cell therapy clinical trials in the 3L r/r LBCL setting, ORRs were numerically higher in patients ≥65 years of age compared with those <65 years of age, and durability of response was similar or better among patients aged ≥65 years in some studies. Overall, rates of key CAR-T cell-associated grade ≥3 AEs (CRS, ICANS) were generally similar across age groups, although more data are needed. Overall, CAR-T cell therapies offer a viable therapy option for older patients with r/r LBCL.

UNIQUE CHALLENGES FOR TREATING ELDERLY PATIENTS AND PATIENTS WITH COMORBIDITIES

Older age is a known risk factor for developing DLBCL and increases the risk of disease relapse and mortality in these patients.[37 38] Unfortunately, elderly patients (>65 years of age) are often considered ineligible for CAR-T cell therapy due to lower PS than younger patients, comorbidities, and increased vulnerability for treatment-related AEs such as CRS and ICANS.[37] CAR-T cell therapy-related toxicities, including CRS and ICANS, represent a challenge when treating patients with pre-existing comorbidities.[37] Overall, there are limited data regarding CAR-T cell therapy outcomes in high-risk populations, including patients age ≥65 years and those with comorbidities or central nervous system involvement.

Comorbidities can influence CAR-T cell therapy outcomes

Underlying disease pathology and comorbidities can affect the outcomes in patients with hematologic malignancies. Several comorbidities should be considered in

Table 1 Clinical trials of CAR-T cell therapy in 2L and 3L r/r LBCL—outcomes by age subgroup

	Axicabtagene ciloleucel[28] (ZUMA-1)		Tisagenlecleucel[29] (JULIET)		Lisocabtagene maraleucel[20] (TRANSCEND-NHL)		Axicabtagene ciloleucel[30] (ZUMA-7)		Lisocabtagene maraleucel[26] (TRANSFORM)		Lisocabtagene maraleucel[31] (PILOT)
Indication	≥3L r/r LBCL		≥3L r/r DLBCL		≥3L r/r LBCL		≥2L r/r LBCL		≥2L r/r LBCL		≥2L r/r LBCL
Median follow-up, months	27.1		40.3		18.8		24.3		17.5		18.2
Median age, years (range)	55 (23–64)	69 (65–76)	56 (IQR 46–64)		63 (IQR 54–70)		69 (65–81)		60 (20–74)	58 (26–75)	74 (53–84)
Age subgroup, years	<65	≥65	<65	≥65	<65	≥65	≥65		–		–
Efficacy set, n	77	24	89	26	148	108	Axi-cel 51	SOC 58	Liso-cel 92	SOC 92	61
ORR, %	81	92	49.4	65.4	70.3	75.9	88	52	–	–	80
CR, %	53	75	–	–	48	60.2	75	33	–	–	54
Median DOR, months	8.1	12	NR	NR	NR	13.3	–	–	–	–	23.3
Median PFS, months	5.6	13.2	–	–	7.4	5.9	21.5	5	–	–	9
Median OS, months	–	–	–	–	21.1	17.1	–	–	–	–	NR
2-year OS, %	49	54	–	–	–	–	64	51	–	–	–
Safety set, n	81	27	–	–	–	–	49	55	92	91	61
CRS											
Grade ≥3, %	12	7	–	–	3	1	8	0	–	–	2
ICANS											
Grade ≥3, %	28	44	–	–	10	11	27	2	–	–	5

Note: because of differences in patient populations and trial designs, cross-trial comparisons should not be made. Data provided here are for information only.
Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; ICANS, immune effector cell-associated neurotoxicity syndrome; 2L, second-line; 3L, third-line; LBCL, large B-cell lymphoma; Liso-cel, lisocabtagene maraleucel; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; r/r, relapsed or refractory; SOC, standard of care.

the decision-making process when evaluating a patient for CAR-T cell therapy. For example, CAR-T-induced cardiotoxicities in patients with existing cardiovascular risk factors may be transient in younger patients but could result in fatal events in elderly patients.[39] Patient nutritional status and recent weight loss are also important factors to evaluate. Two single-center retrospective studies examined the effects of malnutrition and cachexia prior to CAR-T cell therapy and found that poor nutritional status and weight loss prior to treatment were associated with worse efficacy outcomes including lower response rates and worse OS and EFS.[40 41] Baseline renal function was not associated with renal adverse effects or efficacy outcomes post CAR-T therapy; however, patients who developed acute kidney injury related to CRS secondary to CAR-T therapy had worse clinical outcomes.[42 43]

Assessing the impact of comorbidities on treatment outcomes can be challenging. The modified Cumulative Illness Rating Scale (CIRS) is a comorbidity score originally used to predict mortality in hospitalized elderly patients. Recent evidence suggests that CIRS can also predict outcomes in patients with chronic lymphocytic leukemia and NHL.[44 45] Assessment of comorbidities using the CIRS and ECOG PS can be used to predict survival outcomes in patients with r/r DLBCL who receive CAR-T cell therapy.[45] Among possible comorbidities, the presence of severe comorbidities in the respiratory, upper gastrointestinal, hepatic, and renal systems was associated with worse survival post CAR-T therapy.[46]

In a retrospective, multicenter study of patients with r/r DLBCL, a total CIRS score ≥7 or a severity score of CIRS-3+ was associated with a statistically significant decrease in OS.[45] However, multivariable analyses revealed that ECOG PS was the only baseline characteristic that was a significant predictor of PFS and OS.[45] Another retrospective analysis found that high CIRS scores (≥7) were also associated with worse OS in patients with DLBCL who received CAR-T cell therapy.[46] Overall, both studies found that patients with comorbidities derived benefit from CAR-T cell therapy compared with other available treatment options, and highlighted the need for assessment and mitigation of comorbidities when making treatment decisions.

CAR-T CELL EFFICACY AND SAFETY IN PATIENTS WITH COMORBIDITIES AND ELDERLY PATIENTS: REAL-WORLD DATA

Efficacy and safety in patients with comorbidities

In a retrospective analysis of data from the US Lymphoma CAR-T Consortium, real-world evidence on the efficacy and safety of axicabtagene ciloleucel in patients with r/r LBCL was comparable with the outcomes from the ZUMA-1 trial.[47] Around 43% of the patients in the real-world study had comorbidities at the time of leukapheresis and would have been ineligible for ZUMA-1.[16] Despite the large percentage of patients with comorbidities, ORR and CR were 82% and 64%, respectively (table 2).[47–51] The subset of patients with comorbidities experienced shorter mPFS and mOS than patients without comorbidities, although these patients still achieved a 12-month OS rate similar to that of the ZUMA-1 trial (58% vs 59%, respectively). Rates of grade ≥3 CRS and neurotoxicity were slightly higher among patients with comorbidities (10% and 36%, respectively) compared with 7% and 31% of patients overall. In addition, real-world data from the Center for International Blood and Marrow Transplant Research (CIBMTR) registry have evaluated patients with preexisting comorbidities that would have made them ineligible for clinical trials who were treated with axicabtagene ciloleucel (table 2).[47–51] Multivariable analyses demonstrated worse ORR among patients with moderate-to-severe pulmonary disease, and worse DOR, PFS, and OS in patients with moderate-to-severe hepatic disease.[48] In addition, multivariable analysis of patients who received axicabtagene ciloleucel found that moderate-to-severe hepatic disease was associated with an increased risk of experiencing grade ≥3 CRS.[48] In the same study, patients with an ECOG PS ≥2 had worse ORR, DOR, PFS, and OS, and had an increased risk for experiencing CRS and ICANS.[48] Together, these real-world data show that patients with preexisting comorbidities may still benefit from CAR-T cell therapy, but clinicians should also consider the risks of AEs (ie, CRS and ICANS) along with treatment failure when making therapeutic decisions.[47 48]

Additional real-world data from the CIBMTR registry showed that in patients with r/r DLBCL, tisagenlecleucel had similar efficacy with a more favorable safety profile than was observed in the JULIET trial.[18 52] Of note, more than half of the patients in the CIBMTR registry had comorbidities that would have made them ineligible for the JULIET trial[18 52] (table 2).[47–51] Nevertheless, response rates were similar among JULIET-ineligible patients in the CIBMTR registry (ORR: 55.7%; CR: 41.6%), the overall CIBMTR registry population (ORR: 57.4%; CR: 42.4%), and the JULIET trial (ORR: 53.0%; CR: 39.1%).[18 52] 12-month PFS rates were also similar between JULIET-ineligible patients in the CIBMTR registry (34.2%) and the overall CIBMTR population (33.1%); both were similar to the 12-month PFS rate reported in JULIET (34.6%). Furthermore, 12-month DOR rates were similar among JULIET-ineligible patients in the CIBMTR registry (56.5%; 95% CI: 48.5% to 63.8%), the overall CIBMTR population (53.5%; 95% CI: 46.9% to 59.7%), and the JULIET trial (62.6%; 95% CI: 48.5% to 73.9%). Key CAR-T cell therapy-associated safety outcomes were better in the CIBMTR registry, with grade ≥3 CRS being reported less in the CIBMTR registry than in JULIET (8.0% vs 13.5%, respectively), as well as grade ≥3 ICANS (7.7% vs 12.6%, respectively[52]; table 2).[47–51] However, it is important to note that this difference between the real-world and the clinical trial data could have been affected by the use of different CRS and ICANS grading systems, as well as earlier management of CRS in the real-world setting.[53 54] With more patients and longer-term follow-up

Table 2 Real-world data for CAR-T cell therapy in r/r LBCL

Data source	US lymphoma CAR-T consortium[47]	CIBMTR registry[48]	CIBMTR registry[49]	Medicare claims database[50]	DRST registry[51]
CAR-T cell therapy	Axicabtagene ciloleucel	Axicabtagene ciloleucel	Tisagenlecleucel	CAR-T—various*	Tisagenlecleucel and axicabtagene ciloleucel
Indication	≥3L r/r LBCL	≥3L r/r LBCL	r/r DLBCL and HGBL	r/r DLBCL	LBCL†
Infused set, n	275	1297	1159	551	356
Median follow-up, months	12.9	12.9	20.9	11.9	11
Comorbidities, %					
Pulmonary	3.4	28	26.3	–	–
Cardiovascular	13.8	13	16.0	–	–
Hepatic	2.4	2	10.4	–	–
Renal	7.0	2	3.1	–	–
Efficacy set, n	275	1297	968	–	344
ORR, %	82	73	59.5	–	65
CR, %	64	56	44.5	–	37
Median DOR, months	NR	NR	27.6	–	–
12-month DOR, %	–	64	56.9	–	–
Median PFS, months	8.3	8.6	4.1	–	–
12-month PFS, %	47	47.3	34.1	–	30
Median OS, months	NR	21.8	16.4	17.1	–
12-month OS, %	68	62.3	59.7	–	52
Median EFS, months	–	–	–	7.2	–
12-month EFS, %	–	–	–	–	–
Safety set, n	275	1297	990	–	356
CRS, %	91	83	58.2	–	73
Grade ≥3, %	7	8	6.0	–	12
ICANS, %	69	55	22.5	–	33
Grade ≥3, %	31	24	7.4	–	11

Note: because of differences in patient populations and study designs, cross-study comparisons should not be made. Data provided here are for information only.
*Individual CAR-T cell therapies not specified.
†71% of the population was ≥3L LBCL.
CAR, chimeric antigen receptor; CIBMTR, Center for International Blood and Marrow Transplant Research; CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; DRST, Deutsches Register für Stammzelltransplantation (German Registry for Stem Cell Transplantation); EFS, event-free survival; HGBL, high-grade B-cell lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome; 3L, third-line; LBCL, large B-cell lymphoma; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; r/r, relapsed or refractory.

in the CIBMTR real-world setting (median follow-up of ~2 years), durable efficacy and a favorable safety profile of tisagenlecleucel continued to be observed.[49] Overall, efficacy and safety data were similar to those seen in earlier reports (ORR: 59.5%; 24-month PFS: 28.4%; 24-month DOR: 52.6%).[49] Importantly, patients with comorbidities composed a large proportion (~44%) of this real-world patient population, with efficacy and safety outcomes among patients with comorbidities that were similar to the overall population.[49]

Efficacy and safety in elderly patients

In elderly patients with r/r DLBCL, CAR-T cell therapy has been shown to be a potentially curative treatment, with up to 40% of patients achieving long-term remission.[15 29 37] An analysis of real-world data from the US Lymphoma CAR-T Consortium reported that patients ≥60 years of age who received axicabtagene ciloleucel achieved efficacy outcomes that were generally better than patients <60 years old, but had slightly increased risk of CRS and ICANS, including grade ≥3 events (table 3).[37 47 50 51 55]

Table 3 Real-world data—efficacy and safety outcomes in r/r LBCL by patient age groups

Data source	US lymphoma CAR-T consortium[47]		DLBCL CAR-T surveillance database[37]		Medicare claims database[50]			DRST registry[51 55]	
CAR-T cell therapy	Axicabtagene ciloleucel		Tisagenlecleucel and axicabtagene ciloleucel		CAR-T cell therapy*			Tisagenlecleucel and axicabtagene ciloleucel	
Indication	≥3L r/r LBCL		≥3L r/r DLBCL		r/r DLBCL			LBCL†	
Median follow-up, months	12.9		7		11.9			11	
Age group, years	<60	≥60	<70‡	≥70	65–69	70–74	≥75	<65	≥65
Efficacy set, n	–	–	41	41	202	176	173	216	140
ORR, %	–	–	78	63	–	–	–	58	69
CR, %	55§	72§	59	46	–	–	–	31	43
Median PFS, months	–	–	NR	3.6	–	–	–	–	–
12-month PFS, %	42	51	54	32	–	–	–	26	36
Median OS, months	–	–	NR	NR	17.2	20.1	13.4	–	–
12-month OS, %	66	70	53	69	57	64	54	51	55
Median EFS, months	–	–	–	–	6.5	12.6	5.3	–	–
12-month EFS, %	–	–	–	–	43	52	34	–	–
Safety set, n	–	–	41	41	–	–	–	–	–
CRS, %	–	–	69.3	69.3	–	–	–	–	–
Grade ≥3, %	6	8	7.3	9.8	–	–	–	13	10
ICANS, %	–	–	17.1	27.5	–	–	–	–	–
Grade ≥3, %	30	32	4.9	2.5	–	–	–	9	16

Note: because of differences in patient populations and study designs, cross-study comparisons should not be made. Data provided here are for information only.
*Individual CAR-T cell therapies not specified.
†71% of the population was ≥3L LBCL.
‡Matched patients as the control group.
§Best CR at 12 months.
CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; DRST, Deutsches Register für Stammzelltransplantation (German Registry for Stem Cell Transplantation); EFS, event-free survival; ICANS, immune effector cell-associated neurotoxicity syndrome; 3L, third-line; LBCL, large B-cell lymphoma; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; r/r, relapsed/refractory.

A retrospective analysis compared the efficacy of commercial CAR-T cell therapy in a population of elderly patients (≥70 years; n=41) with r/r DLBCL with matched younger patients (<70 years; n=41) (table 3).[37 47 50 51 55] Response rates, incidence of grade ≥3 CRS, grade ≥3 neurotoxicity, and duration of hospitalization were similar among elderly and younger patients.[37] Using the US Food and Drug Administration (FDA) Adverse Events Reporting System, a large-scale postmarketing study compared the treatment-related AEs among patients age <65 and ≥65 years infused with tisagenlecleucel or axicabtagene ciloleucel.[56] The most common AE reported in both age groups was CRS. Some manifestations of CRS were more common among the younger patients, such as fever (33% vs 23%; p<0.01), tachycardia (10% vs 5%; p<0.01), and thrombocytopenia (4% vs 2%; p=0.03). However, the older patients had a higher proportion of neurological AEs, including ICANS (8% vs 4%; p=0.03). Outcomes from this postmarketing study, coupled with clinical trial safety data, may help guide treatment decisions for patients who are being considered for CAR-T cell therapy.[56]

Several other real-world studies have shown that increased age alone is not a risk factor for poor outcomes after CAR-T cell therapy. A study using data from Medicare from 2015 to 2020, specifically assessing patients with DLBCL who received CAR-T cell therapy from 2018 to 2020, showed a median OS of 17.1 months. However, there was no significant difference in the 12-month OS between those age 65–69 years, 70–74 years, and ≥75 years[50] (57%, 64%, and 54%, respectively; table 3).[37 47 50 51 55] Median EFS was 7.2 months and the differences between the median EFS and 12-month EFS across age groups were significant but did not have a pattern with regard to older age (65–69 years: 6.5 months, 43%; 70–74 years: 12.6 months, 52%; ≥75 years: 5.3 months, 34%).[50] Another study by the German Lymphoma Alliance using the German Registry for Stem Cell Transplantation showed that older age was not associated with reduced PFS or OS.[51]

In elderly patients, the most prevalent AEs that may cause concern about the use of CAR-T cell therapy are CRS and ICANS.[48 57] In a CIBMTR multivariable analysis of patients who received axicabtagene ciloleucel, patients

≥65 years of age experienced favorable efficacy outcomes but also had an increased risk of CRS and ICANS.[48] A meta-analysis analyzed the safety of CAR-T cell therapy in elderly versus younger patients with r/r DLBCL.[57] In that study, age did not seem to affect the risk of patients developing CRS after CAR-T cell therapy. The range in incidence of CRS across studies was similar between the two age groups (elderly: 36–84%; younger: 34–83%). However, older patients had a higher incidence of ICANS compared with younger patients (elderly: 27–65%; younger: 8.5–47%).[57] Overall, the authors recommend that CAR-T cell therapy be used with caution in patients ≥65 years old, especially for patients who already have a neurological impairment at baseline. However, recent data suggest that preventative management may reduce the incidence, severity, and duration of CRS and ICANS. A cohort of patients in ZUMA-1 who received prophylactic or earlier corticosteroids and/or tocilizumab showed a reduced incidence of grade ≥3 CRS and achieved durable efficacy.[58] This proactive management strategy could help make CAR-T cell therapy more accessible for elderly patients and those with comorbidities by minimizing the risk of severe CRS.

In a retrospective study, tisagenlecleucel was used more often in older, more heavily pretreated patients than axicabtagene ciloleucel.[59] Tisagenlecleucel was associated with lower rates and severity of CRS and ICANS events compared with axicabtagene ciloleucel. One key objective of a post-CAR-T cell therapy management strategy is to reduce the frequency and severity of CRS and ICANS.[60]

COMPLICATIONS AND RISKS AFTER CAR-T CELL THERAPY

Severe cytopenia

The development of prolonged cytopenias after CAR-T cell therapy is common but the mechanism is poorly understood, and data are lacking for elderly patients with r/r DLBCL.[61 62] A single-center, retrospective analysis of 63 patients with r/r LBCL who received CAR-T cell therapy reported that grade ≥3 cytopenias were not associated with patient age, sex, number of prior lines of chemotherapy, prior HSCT, bone marrow involvement, CRS, neurotoxicity, baseline platelet count, or baseline C-reactive protein levels.[63] However, a meta-analysis of 68 studies across multiple indications found that age, sex, disease type, number of prior therapies, and CAR-T cell molecule and viral vector can influence cytopenia.[64] In this analysis, patients <60 years of age with r/r B-cell NHL were more likely to experience leukopenia.[64] The management of treatment-induced cytopenias post CAR-T cell therapy focuses on symptomatic relief with the use of transfusions and therapy with colony-stimulating factor but lacks age-specific recommendations.[61 62] In patients who are considered at high risk for cytopenias, use of prophylactic granulocyte-colony stimulating factor, along with antiviral and antifungal prophylaxis, and close monitoring for infections postinfusion are recommended. After cytopenias develop, granulocyte-colony stimulating factor or thrombopoietin-receptor agonists may be considered in patients with low cell counts.[65] The CAR-HEMATOTOX model uses predictive biomarkers such as platelet count, hemoglobin, ferritin, absolute neutrophil count, and C-reactive protein to stratify a patient's risk of hematotoxicity following CAR-T cell therapy.[66] Patients with high CAR-HEMATOTOX scores had a higher incidence of long-duration neutropenia and severe thrombocytopenia and anemia compared with patients with a low score. This scoring system can be used for risk-adapted cytopenia management.[66]

Real-world data from the European Society for Bone and Marrow Transplantation CAR-T registry showed that severe cytopenias following CAR-T cell therapy were associated with worse PFS and a higher relapse rate, but did not significantly affect OS.[67] Factors that may influence the risk of CAR-T cell-associated cytopenia include age, bone marrow reserve status, tumor burden and stage of disease, and severity of CRS and neurotoxicity.[62]

Cardiovascular events

Short-term cardiovascular events have been observed in 12–16% of patients undergoing CAR-T cell therapy in clinical trials or the retrospective setting,[68–70] which is similar to the long-term (5-year) cumulative incidence of cardiovascular events experienced by patients who received autologous HSCT and allogeneic HSCT (12% and 16%, respectively).[71] Several risk factors were found to be associated with an increased risk of developing cardiovascular events post CAR-T cell infusion, such as older age (≥60 years) and the presence of comorbidities (eg, diabetes, hypertension, hyperlipidemia) that are more commonly seen in elderly patients.[68 69 72] These cardiac events could potentially result in prolonged hospital stay or admission to the intensive care unit for vasopressor support and should be taken into consideration when evaluating patients for CAR-T cell therapy.[68] Typically, vasopressor support is provided in the context of hypotension in patients experiencing CRS, and recent evidence suggests that prophylactic management with tocilizumab and corticosteroids can reduce the incidence and severity of CRS and presumably the related cardiovascular events.[58] Furthermore, patients who experience severe cardiovascular events, such as myocardial infarction and clinical heart failure, are at increased risk of mortality.[72] Additional long-term prospective studies are needed to better understand the extent of potential impacts of CAR-T cell therapy on cardiac function.

However, not considering patients for CAR-T cell therapy solely due to cardiac comorbidities may be inappropriate for treatment selection. It is recommended to closely monitor elderly patients and patients with underlying cardiovascular disease who are undergoing CAR-T cell therapy.[68] It will be important for future studies to investigate biomarker detection and early treatment options that could lessen cardiovascular risks associated with CAR-T cell infusion.[72] A multidisciplinary approach including referral to a cardiac oncologist group for optimization of heart function before CAR-T cell infusion is

widely used to optimize care for patients with cardiovascular risk factors.

DISCUSSION

Patient selection and overcoming misperceptions about CAR-T cell use in elderly populations

Over the years, elderly patients with age-related comorbidities have often been excluded from or under-represented in clinical trials that served as the basis for FDA approval of the current standards of care for advanced cancer.[73 74] However, age-related conditions, such as comorbidities and disabilities, are highly prevalent in the elderly patients routinely treated by oncologists in the community setting.[74] This reasoning may limit the accessibility of CAR-T cell therapy among elderly patients with comorbidities. Regardless of the misconceptions about the toxicity of CAR-T cell therapy, it has been widely used in multiple indications with thousands of patients reaping its benefits. However, a thorough benefit/risk assessment of CAR-T cell therapy should be conducted on an individual patient basis.[46] Despite the strict eligibility criteria used in clinical trials, efficacy outcomes in the real-world setting seem to mirror the results reported in the pivotal studies, with an improved safety profile observed in the real-world setting.[75] Complete coverage for CAR-T cell therapy for patients with Medicare has been proposed and approved, emphasizing the need for more effective treatment options in the elderly patient population.[76 77] A study comparing the toxicities and outcomes of younger versus elderly patients who received CAR-T cell therapy reported similar safety profiles between both groups.[37] Taking into consideration the similar efficacy and safety across age groups and different levels of impairment, the elderly and more vulnerable patients should be equally considered for CAR-T cell therapy. However, additional data are needed to better understand the potential impact of CAR-T cell therapy-associated CRS and ICANS on long-term cognitive function.[78]

Recent studies have shown that CAR-T cell therapy can have a significant benefit in patient-reported quality of life.[79 80] Non-oncological geriatric issues should be appropriately managed, and care should be individualized for each patient, using a multidisciplinary team approach to improve patient PS and enhance the likelihood of a successful outcome with CAR-T cell therapy. A comprehensive geriatric assessment along with organ function evaluation may enhance identification of elderly patients who would have significant benefits with this potentially curative therapy.[37 76]

Role of comprehensive geriatric assessment

In general, the majority of patients with hematologic malignancies who are candidates for HSCT and adoptive T-cell therapy are older adults.[81] Previously, assessing the fitness of elderly patients to undergo cell-based therapies depended on patient age, comorbidities, and PS; however, there was no system to improve elderly patients' physiologic status or to provide social support to enable them to undergo therapy.[81] Conducting a geriatric assessment provides actionable guidance for decisions regarding therapy and recommendations more suited for age-related conditions.[74] This comprehensive patient assessment tool includes a wide range of factors commonly seen in older adults, such as cognitive abilities, PS, behavioral conditions, comorbidities, social/economic support, nutritional status, and concurrent therapies.[81] In this study, all elderly CAR-T cell therapy candidates undergo a modified cancer-specific geriatric assessment aimed at understanding each patient's functional status and where deficits and vulnerabilities may lie. This information is then used to develop a comprehensive treatment plan tailored to each individual patient (figure 1). Geriatric assessment has been demonstrated to be an effective tool for estimating the life expectancy of elderly patients, as well as their tolerance for therapy.[81] In addition, geriatric assessment-guided management recommendations were shown to significantly reduce serious treatment-related toxicity in elderly patients, including those receiving CAR-T cell therapy.[82–84]

Benefits of using a multidisciplinary approach for managing treatment in elderly patients

Multidisciplinary team assessment of elderly patients has been proven to be valuable in other patients who undergo cellular therapy. A geriatric assessment-guided multidisciplinary team clinic was used to assess older patients (≥60 years and ≥70 years) who were candidates for HSCT and to create individualized plans to optimize care.[81] A patient who was a potential candidate for CAR-T cell therapy was referred to the multidisciplinary team clinic by the treating physician. In this study, the patient was then evaluated by the multidisciplinary team, the treating physician, a geriatric physician/oncologist, an infectious disease physician, a physical and/or occupational therapist, a dietician, and a social worker. Multidisciplinary team discussions focused on minimizing any limitations and optimizing strengths from the geriatric assessment, developing a plan for lessening the risk of AEs, and ultimately included the patient and caregivers in goal-setting.[81] The multidisciplinary team meetings allowed for real-time interactions between care providers and benefited from sharing experience. This optimization of care resulted in fewer inpatient deaths, shorter lengths of stay, and fewer discharges to nursing facilities compared with historical controls. It has also reduced early mortality and improved 1-year OS in elderly patients. These data support the use of a multidisciplinary approach to minimize age-related biases and ensure the safety of elderly patients needing cellular therapies.[81] A multidisciplinary approach may also improve the identification of patients who will benefit most from CAR-T cell therapy.[85–87]

Barriers to obtaining timely CAR-T cell therapy

Several barriers, such as out-of-pocket costs of getting therapy (including patient lodging and

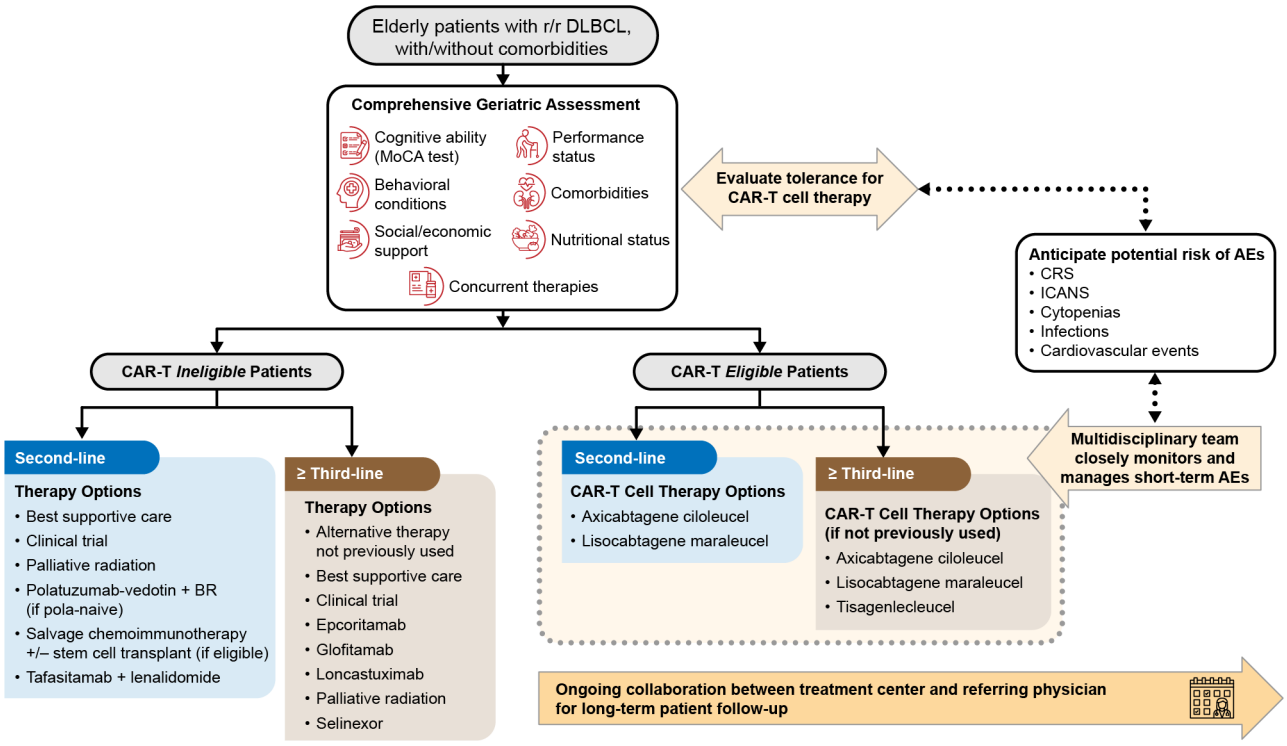

Figure 1 Guidance for CAR-T cell therapy in elderly patients with r/r DLBCL. A geriatric assessment, along with a multidisciplinary team approach, can be useful in evaluating patient eligibility for CAR-T cell therapy and for anticipating and proactively managing potential AEs following CAR-T cell infusion. AE, adverse event; BR, bendamustine and rituximab; CAR-T, chimeric antigen receptor T cell therapy; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome; MoCA, Montreal Cognitive Assessment; r/r, relapsed/refractory.

transportation), problems in the referral system (such as non-referrals and delays in referral), distance from the treatment centers, patient hesitancy, and lack of caregiver support, may prevent eligible patients from receiving CAR-T cell therapy.[88] Referral of patients late in their disease process and after multiple lines of therapy may result in ineligibility for CAR-T cell therapy due to rapidly progressing disease and low PS or increase in comorbidities.[88] Lack of awareness about the impact of prior therapies, such as recent bendamustine exposure, which reduces T cell function, may reduce CAR-T cell efficacy.[89 90]

Early and consistent communication between the community oncologist and treatment center can facilitate timely referral and treatment as well as postinfusion AE management and long-term follow-up.[88] Cost-effectiveness analyses have shown that CAR-T cell therapies are cost-effective as ≥2L therapy in patients with r/r LBCL based on efficacy and safety compared with the previous standards of care.[91–98] A few analyses suggest that one CAR-T cell therapy may be more cost-effective compared with the other available CAR-T cell therapies, but outcomes were dependent on assumptions used in each model and real-world data are needed to validate results.[98 99] Reducing delays in receiving CAR-T cell therapy may provide improvement in response rates by at least 10%.[100] Earlier access to CAR-T cell therapy also increased the number of patients who were deemed eligible for treatment. Removing these barriers to CAR-T cell therapy appears to reduce long-term costs and improve clinical outcomes.

Guidance for CAR-T cell therapy in elderly patients with r/r DLBCL

The advent of CAR-T cell therapy has improved clinical outcomes in elderly patients with r/r LBCL than the previous SOC. Early communication between the referring oncologist and the CAR-T cell treatment center is key to matching eligible patients with CAR-T cell therapy at the appropriate time. In addition, an initial geriatric assessment may be beneficial for determining eligibility for CAR-T cell therapy and can also help proactively identify potential challenges and evaluate risks for AEs that will need to be managed before and after therapy (figure 1). This comprehensive geriatric assessment typically includes assessment of the patient's cognitive ability using a screening tool such as the Montreal Cognitive Assessment, the patient's performance and nutritional status, any comorbidities and behavioral conditions, the availability of social and economic support, as well as current therapies. The healthcare team then evaluates the patient's overall eligibility for CAR-T therapy and provides the information to the patient/caregiver to allow for an informed treatment decision. A group at

the University of Chicago reported clinical outcomes based on an institution-specific multidisciplinary team geriatric assessment for elderly patients considering CAR-T cell therapy; this assessment has allowed their team to inform treatment decisions on a patient-by-patient basis without setting specific thresholds.[84] Given the complexity and nuances inherent with determining CAR-T cell therapy candidacy in elderly patients, we are not able to provide firm recommendations regarding minimal thresholds for parameters such as cognitive function, PS, comorbidities, or even social/economic support. We believe that each patient's case should be assessed on an individual basis and decisions regarding CAR-T cell therapy candidacy should be based on the collective decision-making of the multidisciplinary team. These decisions are aided by the geriatric assessment and take into consideration the level of decrements that each patient may have, and how and in what manner the multidisciplinary team might be able to mitigate risks while maximizing benefit. Recent reports by Derman *et al* and Yates *et al* provide a model of a geriatric assessment-guided multidisciplinary clinic and may be used as a guide when developing an institutional framework for the evaluation, management, and treatment of geriatric patients undergoing cellular therapy.[81 84] In practical terms, this framework should be tailored to each center's needs and influenced by programmatic infrastructure, center-specific practices, and institutional resources, among other factors.

The choice of CAR-T cell therapy may also be influenced by the patient's comorbidities, their relative risk for severe AEs, and the known safety profiles for each of the CAR-T cell therapy options. At this time, there are no prospective trials comparing CAR-T cell products in patients of advanced age, although in the absence of such data, the authors generally prefer using lisocabtagene maraleucel and tisagenlecleucel over axicabtagene ciloleucel due to their safety profiles. Ideally, future research focused on the use of CAR-T cell therapy in patients of advanced age will help to better inform product selection and toxicity management practices.

In summary, the treatment of elderly patients with r/r LBCL is very dynamic and dependent on the close coordination and partnership between the multidisciplinary team and each patient. Individualized treatment decisions based on patient-specific risk factors and response to treatment are necessary to achieve the best possible outcomes. An ongoing collaboration between the treatment center and the referring oncologist can help to optimize long-term outcomes and patient care.

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