CD19-directed CAR T cells as first salvage therapy for large B-cell lymphoma: towards a rational approach

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Lancet Haematol 2023; 10: e1006–15

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The approval of CD19-directed chimeric antigen receptor (CAR) T-cell therapies for the second-line treatment of high-risk large B-cell lymphoma (LBCL) has greatly affected salvage algorithms for this condition, and such therapies could have the potential to improve the course of relapsed or refractory LBCL. In this Review, we provide guidance for a rational management approach to the use of commercial CD19-directed CAR T cells in the second-line treatment of LBCL, addressing crucial questions regarding eligible histologies; age, comorbidity, and tumour biology restrictions; the handling of very aggressive tumour behaviour; and holding and bridging therapies. The guidance was developed in a structured manner and, for each question, consists of a description of the clinical issue, a summary of the evidence, the rationale for a practical management approach, and recommendations. These recommendations could help to decide on the optimal management of patients with relapsed or refractory LBCL who are considered for second-line CAR T-cell treatment.

Introduction

The CD19-directed chimeric antigen receptor (CAR) T-cell therapies axicabtagene ciloleucel (axi-cel) and lisocabtagene maraleucel (liso-cel) have been approved over the past 15 months for the second-line treatment of patients with high-risk large B-cell lymphoma (LBCL), and have had a substantial effect on current algorithms for the salvage treatment of the disease.[1] In many European countries, CAR T-cell therapy is now the standard second-line approach for eligible patients with LBCL in whom first-line chemoimmunotherapy was unsuccessful or disease relapse occurred within 12 months of completing treatment. Although the principal indication of CAR T cells in these patients is well defined, several questions regarding the practical implementation of this treatment need to be considered. In this Review, we propose management strategies for these crucial issues, thereby providing guidance for a rational approach to the use of commercial CD19-directed CAR T cells in the second-line treatment of LBCL.

Process of content building

A working group comprising nine experts met on Sept 19, 2022 (PD, JGG, MJ, MJK, FM, and AV met in person; PC, AS, and PLZ attended virtually), agreed on the concept of the project, and discussed the individual questions to be addressed. Although this meeting was funded by Kite Gilead, the manufacturer of axi-cel, all other steps were conducted without any company support. Kite Gilead had no access to any further part of the process, draft versions, or the final version of this manuscript.

Two coordinating authors (PD and AS) were appointed by the group, who in turn confirmed the remainder of the panel, including the appointment of two additional expert members (BG and AM). Proposals for subtopics were drafted by the coordinating authors, and discussed and agreed upon by the whole panel by email or in virtual meetings (appendix p 2).

Because of the paucity of valid evidence for most of the questions posed, the objective was not to conduct a systematic review or to develop a formal consensus on treatment algorithms. Therefore, we did not use evidence grading or formally structured consensus building approaches. Instead, after conducting a thorough literature search, the coordinating authors developed a working draft containing suggestions for each individual question posed, following a structure comprising a description of the clinical issue, a summary of evidence and lack of evidence, the rationale for a practical approach, and recommendations. This draft was then discussed and further elaborated by the whole working group. All definitions and conclusions required endorsement from all working group members to be included in the final manuscript.

Recommendations

All recommendations are summarised in the panel.

Eligible histologies

Clinical issue

Axi-cel has received approval from the European Medicines Agency for the second-line therapy of diffuse large B-cell lymphoma (DLBCL) or high-grade B-cell lymphoma (HGBCL) in the case of either primary refractory disease or disease that relapses within 12 months of completion of first-line therapy, but it is not formally approved for other clinically relevant LBCLs. Liso-cel has received a similar approval, although it also includes primary mediastinal B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (now known as follicular large B-cell lymphoma [FLBL], according to the 2022 WHO classification).[2] However, of patients treated with CAR T-cell therapy in the TRANSFORM trial,[3] only seven (8%) of 92 patients had PMBCL and one (1%) of 92 patients had FLBL, and both

lymphoma subtypes were excluded from the ZUMA-7 trial.[4] As such, the benefit of second-line CAR T-cell therapy in PMBCL, FLBL, and also transformed indolent lymphoma is poorly documented.

Evidence

Transformed lymphoma, PMBCL, and FLBL largely follow the same therapeutic indications as DLBCL in current clinical practice. Despite the poor representation of these histologies in trials of second-line therapy and also in the pivotal trials of CAR T-cell therapies for use beyond second-line,[5,6] evidence from larger real-world cohorts in which such therapies were used beyond second-line shows that outcomes of patients with transformed follicular lymphoma and PMBCL are not inferior to those observed in DLBCL.[7,8] In fact, transformed follicular lymphoma and PMBCL had a significantly reduced risk of early treatment failure compared with DLBCL in one study.[8] Consistent with this, the 64% (95% CI 49–84) 12-month progression-free survival observed in 33 patients with PMBCL who were treated with axi-cel in a registry study suggested favourable efficacy of CAR T cells in this lymphoma subtype.[9] Comparative real-world studies from 2023 suggest that PMBCL could have a better outcome after axi-cel treatment than DLBCL, not otherwise specified (DLBCL-NOS).[10,11]

Rationale

Although evidence is scarce and is restricted to patients treated beyond second-line, the available information consistently suggests that patients with transformed follicular lymphoma or PMBCL benefit from axi-cel treatment at least to the same extent as those with DLBCL. The benefits of CAR T-cell therapy might also be extended to rare disease subsets, such as FLBL and DLBCL transformed from other indolent lymphomas, because of their close biological and clinical similarities with DLBCL-NOS.[2,12,13] The situation is less clear for orphan lymphoma subtypes such as rare DLBCL and T-cell/histiocyte-rich LBCL,[14] and also for related lymphoma subtypes that were explicitly excluded from the approval trials, in particular primary CNS lymphoma (PCNSL)[15] and DLBCL transformed from chronic lymphocytic leukaemia (Richter transformation),[13,16] in which the efficacy of CAR T cells might be affected by the immunosuppressive properties of the underlying chronic lymphocytic leukaemia clone (appendix p 3).[17] Conversely, accumulating evidence suggests that secondary CNS involvement in systemic DLBCL does not affect the outcome of CAR T-cell therapy.[15,18] Finally, it should be kept in mind that trial eligibility, and therefore approval, rely on the 2016 edition of the WHO classification of diseases.[19]

Recommendation

In addition to DLBCL-NOS and HGBCL, the use of anti-CD19 CAR T-cell therapy as a second-line standard of care seems to also be appropriate for PMBCL, DLBCL transformed from indolent lymphoma, FLBL, and DLBCL with secondary CNS involvement. By contrast, second-line CAR T-cell therapy for PCNSL, Richter transformation, and T-cell/histiocyte-rich LBCL should preferably be administered only within clinical trials.

Age and comorbidity restrictions and transplantation-ineligibility

Clinical issue

The ZUMA-7 and TRANSFORM trials included only patients who were deemed eligible for autologous haematopoietic cell transplantation (HCT) by the treating physicians. Although this criterion was not defined further, patients with cardiac, renal, hepatic, cerebral, or severe pulmonary dysfunction were ineligible. No upper age limit was used in ZUMA-7, in which patients up to the age of 80 years were enrolled, whereas an age limit of 75 years was set in TRANSFORM. It might therefore be questioned whether patients who have one or more of the comorbidities mentioned, are older, or are generally considered as not capable of withstanding autologous HCT should be routinely treated with CAR T cells as second-line therapy.

Evidence

As the median age at diagnosis with DLBCL is 66 years, and almost 30% of patients are diagnosed when older than 75 years,[20] age compatibility is an important requirement for therapies targeted to change the natural history of the disease. 28% (n=51 of 180) of patients in ZUMA-7 and 39% (n=36 of 92) of patients in TRANSFORM were aged at least 65 years, and being older than 65 years did not affect the event-free survival benefit of the CAR T-cell group in either study.[3,4,21]

Toxicity is a major concern in older patients. Regarding settings beyond second-line therapy, a subanalysis of the ZUMA-1 trial in 108 patients focusing on age effects found that patients aged 65 years or older had higher rates of grade 3–4 immune effector cell-associated neurotoxicity syndrome (44%; n=12 of 27) than younger patients (28%; n=23 of 81).[22] Furthermore, in real-life settings, higher rates of immune effector cell-associated neurotoxicity syndrome, severe cytokine release syndrome, and infections were observed in patients aged 65 years or older treated with axi-cel or tisa-cel than in younger patients,[23–25] translating into increased non-relapse mortality in this age group.[25] Despite this drawback, survival outcomes of older patients treated with anti-CD19 CAR T cells have been shown to be at least similar to those of younger patients.[21,24–26] This finding is clearly related to patient selection; however, with this caveat in mind, an upper age limit for CD19 CAR T-cell therapy in LBCL cannot be defined at present.[25]

Regarding comorbidities, a common clinical challenge is the presence of renal insufficiency. In a 2022 study

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See **Online** for appendix

from Wood and colleagues,[27] 166 patients were treated with axi-cel or tisa-cel, comprising 17 with renal insufficiency (defined as an estimated glomerular filtration rate <60 mL/min/1·73 m²; including two receiving dialysis) and 149 with normal renal function. 17 out of 166 CART-treated patients had renal insufficiency (including 2 patients on dialysis). No significant differences in progression-free survival or overall survival were observed between the two groups; however, patients who developed acute kidney injury after infusion had poor outcomes irrespective of their baseline renal function. Similar conclusions were drawn from a retrospective single-centre study by Ahmed and colleagues.[28] CAR T-cell therapy might even be feasible in kidney transplantation recipients.[29] On the contrary, an analysis of 1297 patients selected from the data registry of the Center for International Blood and Marrow Transplant Research, who were receiving axi-cel for beyond-second-line treatment of LBCL, showed that moderate-to-severe renal comorbidity (defined as defined as serum creatinine >2 mg/dL, being on dialysis, or previous renal transplantation) was associated with a significantly increased risk of overall mortality (hazard ratio [HR] 2·1 [95% CI 1·3–3·4]). Other comorbidities that were significantly associated with excess mortality were hepatic disorders (defined as liver cirrhosis, bilirubin >1·5× upper limit of normal, or aspartate aminotransferase to alanine aminotransferase ratio >2·5× upper limit of normal; HR 2·7 [1·7–4·2]), cardiac diseases (defined as any history of coronary artery disease, congestive heart failure, or myocardial infarction, or ejection fraction ≤50%; HR 1·4 [1·1–1·8]), and a score of 2 or higher on the Eastern Cooperative Oncology Group performance status scale. By contrast, pulmonary comorbidities and age had no effect.[26] Notably, a similar analysis in 2022, involving 968 patients who were receiving tisa-cel beyond the second line, did not show any effect of comorbidities on mortality outcomes.[30]

Regarding eligibility for autologous HCT, preliminary evidence is provided by the ALYCANTE and PILOT trials.[31,32] In these prospective phase 2 studies, axi-cel (ALYCANTE) and liso-cel (PILOT) were administered as second-line therapies to patients with LBCL who were deemed to be ineligible for transplantation. Response rates and toxicities were similar to those observed in the CAR T-cell groups of the ZUMA-7 and TRANSFORM trials, with fewer high-grade neurotoxicities (5% in PILOT and 20% in ALYCANTE) and non-relapse deaths (7% in PILOT and 12% in ALYCANTE) with liso-cel than with axi-cel. Although definite conclusions cannot be drawn, the results suggest that second-line CD19 CAR T-cell therapy could be administered in this vulnerable patient group with an acceptable efficacy-to-toxicity ratio.

Rationale

Transplant eligibility is hard to define and might differ from axi-cel eligibility (which, in turn, might differ from liso-cel eligibility). Therefore, eligibility for axi-cel or liso-cel treatment, rather than for transplantation, should be the basis of indication for second-line CAR T-cell therapy in LBCL. Although the available evidence does not support a distinct upper age limit for second-line CAR T-cell therapy, some data suggest detrimental effects of particular comorbidities on outcomes after axi-cel therapy in patients with relapsed or refractory LBCL.

Recommendation

Higher chronological age in itself should not be an exclusion criterion for second-line CAR T-cell therapy in patients with LBCL. By contrast, renal, hepatic, and cardiovascular comorbidities could affect mortality risk and should therefore be considered alongside other variables known to affect outcome, such as performance status, tumour parameters, geriatric assessment,[20] and—where validated—biomarker scores such as HAEMATOTOX and the Endothelial Activation and Stress Index.[33–35] In any case, the patient and their relatives should be thoroughly informed about their individual risk–benefit profile and should be involved in the final decision-making process.

Should holding and bridging or salvage therapies be used before second-line CAR T-cell therapies?

Detailed descriptions of holding, bridging, and salvage therapies are provided in table 1. Holding and bridging can be defined as treatment interventions primarily aimed at keeping the patient stable during the time required for organising a production slot and leukapheresis (holding) and for manufacturing CAR T-cell products (bridging). Keeping stable means maintaining control of tumour-related symptoms and preventing tumour-related effects on performance status and organ functions that could jeopardise the feasibility or outcome of CAR T-cell therapy. In patients with bulky disease, the time needed for leukapheresis preparation and CAR T-cell manufacture might also be used to reduce the tumour burden, which could, in turn, decrease the risk of severe toxicity and increase the success rate of CAR T-cell therapy. However, all holding and bridging therapies should be applied in such a way that extension of indication-to-leukapheresis and leukapheresis-to-product-infusion times is avoided.

By contrast, the primary goal of salvage therapy is response induction, with the aim of minimising the tumour load and the associated pro-inflammatory milieu before CAR T-cell therapy, making the patient eligible for CAR T-cell therapy by improving tumour-related performance status impairment and organ dysfunction, and abrogating the mass effects of the tumour. Salvage therapy can be administered before and after leukapheresis, can require multiple cycles and even multiple regimens, and can result in considerable prolongation of the indication-to-leukapheresis and leukapheresis-to-product-infusion times.

	Salvage therapy	Holding therapy	Bridging therapy
Time (relative to leukapheresis)	Before and after leukapheresis	Before leukapheresis	After leukapheresis
Primary aim	Response induction, to make the patient eligible for CAR T-cell therapy (by improving tumour-related performance status impairment and organ dysfunction and abrogating tumour mass effects) and to minimise tumour load before CAR T-cell therapy	To keep the patient stable by controlling symptoms, preventing tumour mass effects, and avoiding organ dysfunction and tumour-related deterioration in performance status	Similar to holding therapy
Intended outcome	Response	Symptom control and non-deterioration	Similar to holding therapy
Determinant of time delay	Reaching best response	Time needed to organise production slot and leukapheresis	CAR T-cell production time
Expected duration of time delay	>6 weeks	<2 weeks	4 weeks
Opportunities	Response probability 30–40%	Reduction of tumour load; downregulation of pro-inflammatory environment	Similar to holding therapy
Threats	Non-response, clonal evolution, or breakthrough proliferation; T-cell toxicity; haematotoxicity; other toxicity or infections	T-cell toxicity (with bendamustine); inefficacy; delay due to infections or other toxicity	Inefficacy; delay due to infections, haematotoxicity, or other toxicity

CAR=chimeric antigen receptor.

Table 1: **Definitions for types of treatment given before CAR T-cell therapy**

Salvage therapies

Clinical issue

Similar to other cellular therapies used in patients with relapsed or refractory LBCL, such as autologous or allogeneic HCT,[36,37] inducing a status of disease responsiveness or minimising the pre-intervention tumour load could be associated with improved outcomes of second-line CAR T-cell therapies.

Evidence

Although individual tumour activity or volume indicators—such as lactate dehydrogenase (LDH) serum concentrations and the sum of product diameters—did not have a significant effect on progression-free survival in the axi-cel group of the ZUMA-7 trial,[38] high metabolic tumour volume, as a more comprehensive aggregate of tumour burden and proliferation, predicted for inferior outcome in this group.[38] In the TRANSFORM trial, no interaction was found between treatment group and either LDH concentrations or the sum of product diameters for the primary endpoint of event-free survival, although analyses of the effect of these parameters within the liso-cel group are not available.[39] Some circumstantial evidence comes from real-world studies on commercial CD19 CAR T-cell therapy beyond second-line, which concordantly reported that active disease at lymphodepletion had detrimental effects on outcomes.[8,26,40–42]

Rationale

Although the data are conflicting, there is some evidence—albeit weak—and some plausibility that lymphoma control before second-line CAR T-cell therapy might be beneficial. However, these considerations do not mean that attempting to reach a status of disease control is a reasonable treatment goal in this setting. Whether successful tumour debulking by salvage therapy is a contributor to favourable CAR T-cell treatment outcome in itself, or just a surrogate marker of less aggressive tumour biology, is unclear. Moreover, data from beyond-second-line CAR T-cell treatments,[40,42] from the standard-of-care groups of the three phase 3 second-line approval trials,[4,39,43] and from earlier studies exploring salvage therapies before second-line autologous HCT[44,45] suggest that response-induction attempts are successful in only a minority of patients—implying that, at least in two-thirds of patients, salvage therapy provides nothing more than toxicity and potential evolution of tumour resistance. The risks of salvage attempts could therefore substantially exceed their theoretical benefits. The disappointing results from the tisa-cel group of the BELINDA trial, which had the most intensive bridging efforts and by far the longest leukapheresis-to-product-infusion times in comparison with ZUMA-7 and TRANSFORM, are in keeping with this hypothesis.[43]

Recommendation

Salvage strategies aimed at minimising tumour load or activity should not be used before intended second-line CAR T-cell therapy in LBCL if such treatment would delay CAR T-cell infusion or could jeopardise the feasibility of CAR T-cell therapy, for example by inducing infectious or haematopoietic toxicity.

Holding and bridging therapies

Clinical issue

In many patients, symptoms or imminent complications caused by lymphoma proliferation require adequate management to keep the patient stable during the CAR T-cell production period.

Evidence

Although patients undergoing beyond-second-line CAR T-cell therapy for relapsed or refractory LBCL without

previous bridging appear to have favourable outcomes in some retrospective studies,[40,42,46,47] these findings could just reflect a more favourable tumour biology, a lower tumour burden, or both. Prospective studies comparing bridging with non-bridging strategies before CAR T-cell therapy in LBCL are not available. Patients in the CAR T-cell group of the TRANSFORM study (63% [n=58 of 92] of whom received bridging therapy) tended to show higher complete response rates and better event-free and overall survival outcomes than patients in this group of the ZUMA-7 study, despite similar risk profiles in both studies (appendix p 4).[1,4,39] A subset analysis of the liso-cel group of TRANSFORM did not suggest inferior outcomes for patients receiving bridging therapy; in fact, 18-month event-free survival was 54% (95% CI 40–69) in patients with PET-positive disease after bridging, 67% (36–98) in those with PET-negative disease after bridging, and 47% (30–64) in those who did not receive bridging therapy.[39]

Rationale

Although prospective comparisons are absent, the results from the CAR T-cell group of TRANSFORM do not suggest detrimental effects from a single cycle of platinum-based bridging therapy—on the contrary, bridging could help to mitigate lymphoma-related symptoms and stabilise the patient such that they begin CAR T-cell therapy in a more promising condition or even when they otherwise might not be eligible. Moreover, bridging could result in a reduction of tumour load, thereby increasing the probability of a successful CAR T-cell therapy outcome in terms of both efficacy and safety.[48] For the same reasons, considering holding therapy in cases in which access to CAR T-cell production is delayed seems plausible, although evidence is scanty.

Recommendation

Holding and bridging treatments intended for symptom control, patient stabilisation, or tumour debulking during the leukapheresis preparation and CAR T-cell production periods should be administered to all patients with dynamic tumour growth or high tumour volume.

How to bridge

Clinical issue

Classic platinum-based salvage chemoimmunotherapies can exert considerable haematopoietic and organ toxicity and are effective in only a minority of patients with LBCL who are refractory to R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone).

Evidence

Prospective trials have shown that platinum-based chemoimmunotherapies—such as R-DHAP (rituximab plus dexamethasone, high-dose cytarabine, and cisplatin), R-ICE (rituximab plus ifosfamide, carboplatin, and etoposide), and R-GDP (rituximab plus gemcitabine, dexamethasone and cisplatin)—can induce objective responses in 30–50% of patients if administered as a second-line treatment to those for whom R-CHOP induction was not successful.[43–45] Similar results were reported for the CD79b-targeting immunotoxin antibody polatuzumab vedotin in combination with rituximab either with or without bendamustine in patients with relapsed or refractory LBCL (table 2).[49–51] Considering also that the patients receiving polatuzumab vedotin were older and tended to have a higher score on the International Prognostic Index than those receiving platinum-based therapies, and that they mostly received the study treatment beyond second-line, polatuzumab vedotin-based bridging could be a reasonable alternative to platinum-containing standard regimens. Indeed, polatuzumab vedotin was the most effective bridging regimen in beyond-second-line real-world analyses from Germany[40] and the UK.[47] However, regarding holding therapies, the risks of manufacturing failure when using bendamustine as a standard combination partner for polatuzumab vedotin before leukapheresis should be considered.[52]

Tafasitamab is a humanised anti-CD19 monoclonal antibody licensed for the treatment of relapsed or refractory DLBCL in combination with lenalidomide. Although promising responses were observed in the approval trial involving 81 patients with relapsed or refractory DLBCL (overall response rate 60%, complete response 43%),[53] preliminary real-world experience was less encouraging.[54] Moreover, as tafasitamab has the same antigen target as CAR T cells, potential interference between these therapies is a concern, even though anecdotal cases of the successful sequential use of tafasitamab and axi-cel have been reported.[55] This concern might also be relevant for loncastuximab terisine,[56] which is not yet licensed for second-line treatment.

CD20-targeting, T-cell-engaging antibodies—such as epcoritamab and glofitamab—are known as bispecific antibodies and are emerging as a novel immunotherapeutic approach for LBCL.[57–59] However, none of these agents have yet been licensed for second-line use, and administering them as a bridge to CAR T-cell therapy could be detrimental because both approaches use T cells, potentially leading to interactions in terms of efficacy and immunosuppressive adverse effects. However, preliminary evidence from the use of CD20×CD3 bispecific antibodies before CAR T-cell therapy, and vice versa, does not support these theoretical concerns.[58,60,61]

Ibrutinib monotherapy has shown some activity in some LBCL subtypes, such as activating B-cell-like DLBCL and double-expressor lymphoma,[62,63] and has therefore been used anecdotally for off-label bridging to CAR T-cell therapy.[40] Although responses are infrequent and usually short-lived, ibrutinib has the advantage of low toxicity, especially haematoxicity, in addition to the

	NCIC LY.12[44]		ORCHARRD[45]		BELINDA SOC[43]	GO29365 plus extension[49]	Polatuzumab vedotin real-world studies (bridging to cellular therapy)[50,51]	
	R-GDP (n=310)	R-DHAP (n=309)	R-DHAP (n=223)	O-DHAP (n=222)	Platinum-based (n=158)	Pola-BR (n=152)	Pola-BR or Pola-R (n=51)	Pola-BR (n=40)
Age, years	55 (19–71)	55 (23–74)	56 (18–79)	58 (23–83)	58 (26–75)	69 (22–94)	61 (22–82)	67 (29–87)
ECOG performance status score ≥2	42 (14%)	42 (14%)	16 (7%)	20 (9%)	0	20 (13%)	NA	7 (18%)
IPI high-intermediate/high risk group	100 (33%)	98 (32%)	87 (39%)	89 (40%)	NA	94 (62%)	NA	25 (63%)
First failure ≤12 months from first-line	224 (73%)	222 (71%)	157 (70%)	159 (72%)	158 (100%)	97 (64%)*	NA	NA
Beyond second-line	0	0	0	0	0	102 (67%)	51 (100%)	39 (97%)
Intended cellular therapy	Autologous HCT	Autologous HCT	Autologous HCT	Autologous HCT	Autologous HCT	..	CAR T-cell or allogeneic HCT	CAR T-cell
Overall response rate	140 (45%)	136 (44%)	94 (43%)	84 (38%)	NA	>61 (>42%)	14 (27%)	16 (40%)
Complete response	NA (14%)	NA (15%)	48 (22%)	34 (15%)	NA	>58 (>39%)	1 (2%)	7 (18%)
Progression	95 (31%)	105 (34%)	60 (27%)	69 (34%)	76 (48%)	40 (27%)	NA	16 (40%)
Discontinued owing to toxicity	9 (3%)	15 (5%)	23 (10%)	22 (10%)	21 (13%)	..	≤4 (≤8%)	1 (3%)
Proceeded to cellular therapy	158 (51%)	151 (49%)	83 (37%)	74 (33%)	52 (33%)	..	35 (67%)	31 (78%)

Data are mean (range) or n (%). CAR=chimeric antigen receptor. ECOG=Eastern Cooperative Oncology Group. HCT=haematopoietic cell transplantation. IPI=International Prognostic Index. NA=not available. O-DHAP=ofatumumab plus dexamethasone, high-dose cytarabine, and cisplatin. Pola-BR=polatuzumab vedotin plus bendamustine and rituximab. Pola-R=polatuzumab vedotin plus rituximab. R-DHAP=rituximab plus dexamethasone, high-dose cytarabine, and cisplatin. R-GDP=rituximab plus dexamethasone, gemcitabine, and cisplatin. *Primary refractory only.

Table 2: **Comparison of platinum-based and polatuzumab vedotin-based salvage regimens before CAR T-cell therapy**

theoretical advantage of enhancing the efficacy of CAR T-cell therapy by improving T-cell function.[64]

Finally, radiotherapy might be a convenient and effective option for both holding and bridging purposes in cases of localised tumour activity or tumour bulk.[46,47,65]

Rationale

Current evidence supports the use of polatuzumab vedotin-based bridging as an alternative to standard platinum-containing regimens. Whether the use of polatuzumab vedotin as part of first-line therapy could decrease its efficacy in subsequent lines of treatment remains to be established.[66] If used as a holding therapy, polatuzumab vedotin should be administered without bendamustine; however, bendamustine could be added after leukapheresis. The use of bispecific antibodies in holding and bridging therapies should be preferentially explored in clinical trials. Although ibrutinib is often ineffective, its rapid onset of efficacy and low toxicity render it easy to explore as a therapeutic option, and therefore it might be administered in individual settings despite not yet being licensed for this indication.

Recommendation

Platinum-based standard salvage regimens and combinations containing polatuzumab vedotin should be the first therapies considered for bridging purposes before second-line CAR T-cell therapy in LBCL. By contrast, CD19-targeting agents should be avoided. Holding therapies should have low myelosuppressive activity and low T-cell toxicity and should not include bendamustine. Radiotherapy can be a useful alternative to both holding and bridging in patients with localised tumour activity.

What to do in the case of good response to bridging therapy

Clinical issue

Whether CAR T-cell therapy is superior to autologous HCT for patients with chemosensitive disease—ie, those who reach complete or partial response after bridging therapy, or who are referred for second-line CAR T-cell treatment after responding to salvage therapy administered in the referring centre—is unclear.

Evidence

Unfortunately, the three phase-3 approval trials of CAR T-cell therapy were not designed to answer this important question. Circumstantial evidence comes from the TRANSFORM trial, in which the nine patients from the liso-cel group who reached complete metabolic response after one cycle of bridging therapy had a remarkably good outcome, with 18-month estimates for progression-free survival of 67% (36–98) and overall survival of 78% (51–100).[39] Unfortunately, these values were not compared with the survival outcomes of patients who responded to

salvage therapy in the standard-of-care group in this study. A registry analysis by the Center for International Blood and Marrow Transplant Research found that chemosensitive patients with relapsed or refractory DLBCL who were treated with CAR T cells had a higher risk of relapse than those treated with autologous HCT.[67] However, the two cohorts were poorly balanced—the CAR T-cell group had a shorter time from diagnosis to cellular therapy, more extensive pretreatment, a higher tumour load, a poorer performance status, and a more recent treatment period—therefore precluding definite conclusions. Finally, although not conclusive, some evidence can be deduced from the small series of patients who are receiving beyond-second-line therapy with axi-cel or tisa-cel without measurable disease, suggesting promising CAR T-cell expansion and efficacy in this setting.[68–70]

Rationale

Although evidence for the superiority of CAR T-cell therapy over autologous HCT in patients who responded to second-line salvage therapy is insufficient, there is also no sound evidence for the inferiority of axi-cel or liso-cel in this setting. According to registry analyses, the long-term progression-free survival of patients with DLBCL for whom first-line therapy failed within the first year and who receive autologous HCT with sensitive disease can be estimated at 35–45%.[36,71] This value is not superior to the long-term progression-free survival observed with axi-cel in the ZUMA-7 trial across all risk profiles.[72] Another argument in favour of CAR T-cell consolidation in patients who respond to bridging therapy is the inferior quality-of-life outcomes reported in both the ZUMA-7 and TRANSFORM trials for patients who remain event-free on the standard-of-care group.[73,74] Moreover, if the type of cellular therapy to be administered is decided only after the response to bridging therapy has been established, parallel preparation for both CAR T-cell therapy and autologous HCT would be required, therefore substantially increasing resource consumption and logistical efforts.

Recommendation

Proceeding with the intended second-line CAR T-cell treatment in patients who respond to bridging therapy or who are referred with responsive disease should be preferred over switching to an autologous HCT strategy.

Panel: **Summary of recommendations on the use of CD19-directed CAR T cells as first salvage therapy for LBCL**

Eligible histologies

In addition to DLBCL-NOS and HGBCL, the use of anti-CD19 CAR T-cell therapy as a second-line standard of care seems to also be appropriate for PMBCL, DLBCL transformed from indolent lymphoma, FLBL, and DLBCL with secondary CNS involvement. By contrast, second-line CAR T-cell therapy for PCNSL, Richter transformation, and T-cell/histiocyte-rich LBCL should be preferably be administered only within clinical trials.

Age

Higher chronological age in itself should not be an exclusion criterion for second-line CAR T-cell therapy in patients with LBCL.

Comorbidities

Renal, hepatic, and cardiovascular comorbidities could affect mortality risk and should therefore be considered alongside other variables that are known to affect outcome, such as performance status, tumour parameters, geriatric assessment, and—where validated—biomarker scores such as HAEMATOTOX and Endothelial Activation and Stress Index. The patient and their relatives should be thoroughly informed about their individual risk–benefit profile and should be involved in the final decision-making process regarding second-line CAR T-cell therapy.

Salvage therapies

Salvage strategies aimed at minimising tumour load or activity should not be used before intended second-line CAR T-cell therapy in LBCL if such treatment would delay CAR T-cell infusion or could jeopardise the feasibility of CAR T-cell therapy, for example by inducing infectious or haematopoietic toxicity.

Holding and bridging therapies

Holding and bridging treatments intended for symptom control and patient stabilisation, or tumour debulking during the leukapheresis preparation and CAR T-cell production periods should be administered to all patients with dynamic tumour growth or high tumour volume.

How to bridge

Platinum-based standard salvage regimens and combinations containing polatuzumab vedotin should be the first therapies considered for bridging purposes before intended second-line CAR T-cell therapy in LBCL. By contrast, CD19-targeting agents should be avoided. Holding therapies should have low myelosuppressive activity and low T-cell toxicity and should not include bendamustine. Radiotherapy can be a useful alternative for both holding and bridging in patients with localised tumour activity.

Implications of response to bridging

Proceeding with the intended second-line CAR T-cell treatment in patients who respond to bridging therapy or who are referred with responsive disease should be preferred over switching to an autologous HCT strategy.

Immediate need for therapy

The requirement for urgent therapy should not preclude the initiation of second-line CAR T-cell treatment in patients with LBCL.

CAR=chimeric antigen receptor. DLBCL-NOS=diffuse large B-cell lymphoma-not otherwise specified. FLBL=follicular large B-cell lymphoma. HCT=haematopoietic cell transplantation. HGBCL=high-grade B-cell lymphoma. LBCL=large B-cell lymphoma. PCNSL=primary CNS lymphoma. PMBCL=primary mediastinal B-cell lymphoma.

Search strategy and selection criteria

We searched PubMed for articles published in English since Jan 1, 2017, containing the term "B-cell lymphoma" and either or both of the terms "axicabtagene" or "lisocabtagene". The search was first conducted on Dec 10, 2022, and later updated on June 29, 2023. We also reviewed abstract databases from the 2021 and 2022 annual meetings of the American Society of Hematology and the American Society of Clinical Oncology. All members of the author panel were then asked to indicate any appropriate citations that were of interest but had not been detected by the search strategy. The final reference list was generated on the basis of relevance to the specific focus of this Review.

Very aggressive disease

Clinical issue

The ZUMA-7 trial excluded patients with "requirement for urgent therapy due to tumour mass effects";[4] however, such a requirement is quite frequent in patients with high-risk relapsed or refractory LBCL. Because such patients represent a poor risk selection, whether the results from ZUMA-7 can be extrapolated to this population is not known.

Evidence

Unlike in ZUMA-7, an immediate need for treatment was not an exclusion criterion in the TRANSFORM trial, in which 63% of patients (n=58 of 92) assigned to the liso-cel group received platinum-based salvage chemoimmunotherapy after leukapheresis. Of these, 40% (n=23) received bridging because of rapid tumour growth and 48% (n=28) because of high tumour burden.[3] As described earlier, the overall outcome of patients receiving bridging therapy, including those who did not respond, was similar to that of patients proceeding to liso-cel therapy without bridging, suggesting that the requirement for urgent therapy might not preclude successful CAR T-cell treatment. This finding is consistent with follow-up data from the ZUMA-7 trial, which showed that neither increased LDH serum concentrations nor tumour burden, measured by the sum of radiological product diameters, significantly affected event-free survival.[38]

Rationale

Translating the data from the TRANSFORM trial to the axi-cel setting seems plausible, suggesting that an urgent need for treatment does not preclude second-line CAR T-cell therapy unless disease-related performance status deterioration or other factors render a successful outcome unlikely.

Recommendation

An immediate need for therapy should not preclude the initiation of second-line CAR T-cell treatment in patients with LBCL.

Conclusions

CAR T-cell therapy has revolutionised the treatment of relapsed or refractory LBCL and other B-cell malignancies. However, the optimal management of CAR T-cell application in the second-line setting requires careful consideration of various patient-related and treatment-related factors, and the suggestions given here could be helpful in this regard. Nonetheless, because the treatment of LBCL is so rapidly advancing—both in terms of CAR T-cell and other therapies—new evidence should continuously be incorporated to enable LBCL management algorithms to be adapted to scientific progress, thereby improving outcomes for this patient population.

Contributors

All authors jointly designed the concept and developed the contents. PD, AM, and AS drafted the manuscript. All authors further elaborated the manuscript and approved the final version.

Declaration of interests

PC reports consultancy for BMS, Celgene, Gilead Sciences, Janssen Pharmaceuticals, Novartis, Sanofi, and BeiGene; participation on speakers' bureaus for BMS, Gilead Sciences, and Novartis; and travel grants from Janssen Pharmaceuticals, Roche, Gilead Sciences, and Novartis. PD reports consultancy for AbbVie, AstraZeneca, BeiGene, BMS, Gilead Sciences, Miltenyi Biotec, Novartis, and Riemser; participation on speakers' bureaus for AbbVie, AstraZeneca, BeiGene, BMS, Gilead Sciences, Novartis, Riemser, and Roche; and research support from Riemser, all to his institution. BG reports consultancy for BMS and Roche and research funding from Riemser. JGG reports consultancy for AbbVie, Amgen, AstraZeneca, BMS/Celgene, Janssen Pharmaceuticals, Kite Gilead, and Novartis; and research funding from AstraZeneca, BMS/Celgene, and Janssen Pharmaceuticals. MJ reports consultancy for AbbVie, AstraZeneca, Autolus, Genmab, Gilead Sciences, Janssen Pharmaceuticals, Novartis, Pierre Fabre, and Roche; and research support from AbbVie, AstraZeneca, Gilead Sciences, Janssen Pharmaceuticals, and Roche. MJK reports honoraria from BMS/Celgene, Kite/Gilead, Novartis, and Roche; consulting or advisory roles for BMS/Celgene, Kite Gilead, Miltenyi Biotec, Novartis, Takeda Pharmaceuticals, and Adicet Bio; and research funding from Kite Gilead, all to her institution. FM reports consulting fees from Roche, Gilead Sciences, Novartis, BMS, AbbVie, Genmab, Miltenyi Biotec, Allogene Therapeutics, AstraZeneca, and Janssen Pharmaceuticals. AM reports consultancy for BMS, Jazz Pharmaceuticals, Merck, and Takeda Pharmaceuticals; and research funding from Kite Gilead. AS reports consultancy for BMS, Celgene, Gilead Sciences, Janssen Pharmaceuticals, MSD, Novartis, Sanofi, and Takeda Pharmaceuticals; participation on speakers' bureaus for BMS, MSD, and Takeda Pharmaceuticals; and travel grants from BMS, Celgene, Janssen Pharmaceuticals, Roche, Sanofi, and Takeda Pharmaceuticals. AV reports consultancy for AbbVie, Gilead Sciences, Novartis, BMS, Roche, and Amgen; honoraria from Roche, Gilead Sciences, BMS, and AbbVie; and travel grants from Roche, Gilead Sciences, and AbbVie. PLZ reports consultancy for ADC Therapeutics, AstraZeneca, BeiGene, BMS, Celltrion, EUSA Pharma, Incyte Kyowa Kirin, Novartis, Gilead Sciences, MSD, Roche, Sandoz, Secura Bio, Servier Laboratories, and Takeda Pharmaceuticals; and participation on speakers' bureaus for AstraZeneca, BeiGene, BMS, Celltrion, EUSA Pharma, Incyte Kyowa Kirin, Novartis, Gilead Sciences, MSD, Roche, Servier Laboratories, and Takeda Pharmaceuticals.

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