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Guideline

ASTCT Clinical Practice Recommendations for Transplantation and Cellular Therapies in Diffuse Large B Cell Lymphoma

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A B S T R A C T

Autologous hematopoietic cell transplantation (auto-HCT) has long been the standard approach for patients with relapsed/refractory (R/R) chemosensitive diffuse large B cell lymphoma (DLBCL). However, the advent of chimeric antigen receptor (CAR) T cell therapy has caused a paradigm shift in the management of R/R DLBCL patients, especially with the recent approval of CD19-directed CAR-T therapy in the second-line setting in high-risk groups (primary refractory and early relapse [≤12 months]). Consensus on the contemporary role, optimal timing, and sequencing of HCT and cellular therapies in DLBCL is lacking; therefore, the American Society of Transplantation and Cellular Therapy (ASTCT) Committee on Practice Guidelines undertook this project to formulate consensus recommendations to address this unmet need. The RAND-modified Delphi method was used to generate 20 consensus statements with a few key statements as follows: (1) in the first-line setting, there is no role for auto-HCT consolidation for patients achieving complete remission (CR) following R-CHOP (rituximab, cyclophosphamide,

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adriamycin, vincristine, and prednisone) or similar therapy in non-double-hit/triple-hit cases (DHL/THL) and in DHL/THL cases receiving intensive induction therapies, but auto-HCT may be considered in eligible patients receiving R-CHOP or similar therapies in DHL/THL cases; (2) auto-HCT consolidation with thiotepa-based conditioning is standard of care for eligible patients with primary central nervous system lymphoma achieving CR with first-line therapy; and (3) in the primary refractory and early relapse setting, the preferred option is CAR-T therapy, whereas in late relapse (>12 months), consolidation with auto-HCT is recommended for patients achieving chemosensitivity to salvage therapy (complete or partial response), and CAR-T therapy is recommended for those not achieving remission. These clinical practice recommendations will serve as a tool to guide clinicians managing patients with newly diagnosed and R/R DLBCL.

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL), the most common form of non-Hodgkin lymphoma (NHL), presents with rapidly evolving nodal and/or extranodal disease and frequently requires immediate treatment [1]. Although first-line chemoimmunotherapies are effective, DLBCL poses a therapeutic challenge because ~40% of patients are refractory to or relapse after initial treatment [2]. The standard approach to relapsed/refractory (R/R) DLBCL has been salvage platinum-containing chemoimmunotherapy followed by high-dose therapy and autologous hematopoietic cell transplantation (auto-HCT) in patients deemed eligible with chemosensitive disease [3–5], including those with early chemoimmunotherapy failure [6–9]. However, the advent of CD19-directed chimeric antigen receptor (CAR) T cell therapies has changed this therapeutic paradigm. For the purpose of these guidelines, the term "DLBCL" includes DLBCL not otherwise specified (NOS), high-grade B cell lymphoma (HGBCL) NOS, and HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangement (unless otherwise specified).

Three CD19-directed CAR-T therapies for R/R DLBCL after 2 prior lines of therapy have been approved since 2017 (Supplementary Table S1) [10–12]. Recently, three phase 3 randomized studies compared standard salvage chemotherapy followed by auto-HCT versus CAR-T therapy in R/R DLBCL in the second-line setting (Supplementary Table S2) [13–15]. Two of these trials, ZUMA-7 (axicabtagene ciloleucel [axi-cel]) [13] and TRANSFORM (lisocabtagene maraleucel [liso-cel]) [15], met their primary event-free survival endpoint in favor of CAR-T therapy, leading to approval by the US Food and Drug Administration and other regulatory agencies for second-line treatment for patients with DLBCL that are primary refractory or relapsed within 12 months. For an in-depth analysis of the 3 trials, refer to the American Society of Transplantation and Cellular Therapy (ASTCT) position paper by Perales et al. [16].

Allogeneic HCT (allo-HCT) is another potentially curative option in R/R DLBCL [17–19] that can provide durable disease control, even after auto-HCT relapse, with a therapeutic mechanism attributed mainly to the graft-versus-lymphoma effect [17,20,21]. The use of reduced-intensity conditioning (RIC) with allo-HCT has significantly expanded access to allo-HCT [17,22-26]; however, similar to auto-HCT, the advent of CAR-T therapy has led to a recent decline in allo-HCT, effectively relegating allo-HCT for patients whose DLBCL progresses after CAR-T therapy [27].

Consensus on the contemporary role, optimal timing, and sequencing of HCT and cellular therapies in DLBCL is lacking. Clinical practice recommendations addressing areas of clinical ambiguity not only can aid transplantation and cellular therapy physicians, but also can inform the practice of lymphoma experts and community hematologists who refer these patients to transplantation and cell therapy programs. Therefore, the ASTCT undertook this project to formulate consensus recommendations to address this unmet need.

METHODS

Panel Composition

The development of practice recommendations was approved by the ASTCT Committee on Practice Guidelines. As an initial step, a Steering Committee was formed comprising 8 members, including 2 project leaders, 5 subject matter experts, and an independent methodologist with expertise in systematic reviews, meta-analysis, and the RAND-modified Delphi method. The Steering Committee was responsible for drafting the protocol plus the preliminary consensus statements, based on clinical expertise and clinical practice considerations, and for setting up the expert panel [28]. The aim was to put together an expert panel with a balanced distribution of "DLBCL" and "cellular therapy and transplantation" experts, to have broad expertise and to cover a wide spectrum of views while keeping administrative efforts manageable, as previously recommended [29,30]. The panel of experts comprised physicians with diverse geographical representation and expertise in the field, as demonstrated by their track record of peer-reviewed publications, leadership on clinical trials relevant to the consensus project, and involvement in national and international lymphoma or HCT organizations. A physician representing a community-based practice (S.A.A.) was also included, as previously recommended [28].

The final Consensus Panel comprised 25 physicians, including the 7 physician members of the Steering Committee. Of note, the (nonclinical) independent methodologist (A.K.) did not have a vote (see below).

Consensus Methodology

The RAND-modified Delphi method [28,29] was used to generate consensus statements addressing the sequencing, timing, and role of HCT and CAR-T therapies in patients with newly diagnosed and R/R DLBCL. In the Delphi method, participants rate the statements anonymously in generally 2 rounds of voting. In the modified version of the method, a face-to-face meeting with presentation of the results precedes the second round of voting (if needed) [28–30]. Details of the systematic step-by-step approach used in this project are provided in Table 1.

After the panel selection, a Baseline Demographics and Scope (BD&S) Survey was developed to determine the scope of the project. Participants were invited to submit their suggestions regarding the scope of the consensus project and provide input about the clinical issues relevant to clinical practice (details in Supplementary Appendix). After the finalization of the scope of the consensus project (Supplementary Table S3), the Steering Committee formulated preliminary consensus

Table 1
Steps Involved in the RAND-Modified Delphi Methodology

Step	Representation*	Description	Method
Concept development and approval	Steering Committee	Approved and endorsed by ASTCT CoPG, March 2020	Teleconference
Protocol development	Steering Committee	Protocol development according to the modified Delphi method Identify and invite potential members of the Consensus Panel, including academic experts plus a community practice representative	Email and electronic communication
Baseline Demographics and Scope (BD&S) Survey	Consensus Panel	(i) Obtain demographic details of the participants and (ii) determine the clinical scope of the project, ratings along with written feedback, September 2022	Online survey (100% panel response rate)
Review of BD&S results	Steering Committee, Consensus Panel	(i) Results compiled by the Steering Committee and shared with the Consensus Panel in October 2022 (ii) Questions pertaining to the sequence of cellular therapy (including auto-HCT, allo-HCT, and CAR-T) and practice scenarios generated for the First Voting Survey (Steering Committee)	Email Email
First Voting Survey	Consensus Panel	(i) Rate clinical practice recommendation statements on a Likert scale, January 2023	Online survey (100% panel response rate)
Review of First Voting Survey results	Steering Committee/ Consensus Panel	(i) Results compiled and reviewed by the Steering Committee (ii) Results shared with the Consensus Panel in February 2023	Email Email
Second Voting Survey*	NA	NA	NA
Final evaluation of consensus and manuscript	Steering Committee/ Consensus Panel	Ratings are accepted if a consensus is reached based on the predefined threshold. If no consensus was reached, statements were noted as "consensus could not be reached." Results compiled as manuscript and first draft written by the Steering Committee and shared with the Consensus Panel for review and editing.	Email

CoPG indicates American Society of Transplantation and Cellular Therapy Committee on Practice Guidelines; NA, not applicable.

* The Steering Committee comprised 8 members including 2 project leaders, 1 statistical expert (independent nonvoting member), and 5 experts. The Consensus Panel (n = 25) comprised the 7 Steering Committee members (except the statistical expert) plus 17 academic experts and 1 community representative.†All statements achieved consensus (≥75% agreement), and thus a Second Voting Survey was not conducted.

statements based on expert opinion for the first round of voting (Supplementary Table S4).

The First Voting Survey included 20 consensus statements. Panel members rated each statement electronically. The Steering Committee methodologist analyzed and summarized the results while keeping the individual ratings anonymous. A specific statement was defined as having achieved formal consensus if ≥75% of the panel members voted to agree with the proposed statement.

All surveys were administered online using www.Qualtrics.com (Qualtrics, Provo, UT), and results were reviewed and collated independently by the methodological expert. At each step of the process, the electronic survey also allowed the participating members to provide written feedback and comments about each statement. Collated results were shared via email with the Consensus Panel members in real time after each step was completed, to ensure transparency of the process. The final consensus statements were graded based on the strength and level of supporting evidence, according to the Agency of Healthcare Research and Quality grading scheme [31]. The final determination of the grade for each consensus statement was based on the voting by Steering Committee members and should have achieved a simple majority (>50%).

RESULTS

Member Participation

The demographics of the consensus panel members are outlined in Table 2. Included were transplantation and cellular therapy physicians (>75% of practice time in HCT), non-cellular therapy academic physicians, mixed practitioners, and a community-based practitioner. A mixed practice was defined as practitioners devoting approximately 50% of clinical time to HCT and non-cellular therapy-related lymphoma, each. In general, panelist participation and response rates were excellent. During the voting process, 100% (n = 25) panel member participation was noted for the BD&S and First Voting Surveys.

First Voting Survey

The First Voting Survey consisted of 20 statements specific to the roles of auto-HCT, CAR-T therapy, and allo-HCT in eligible newly diagnosed DLBCL patients (7 statements), primary refractory and early relapsed DLBCL patients (4 statements), and late relapsed DLBCL patients (9 statements). All statements achieved consensus by predefined criteria (Supplementary Table S4). The results of the First Voting Survey were shared electronically with all panel members.

Second Voting Survey

Because all statements achieved consensus (≥75% agreement), a Second Voting Survey was not conducted. The final consensus recommendations on auto-HCT, allo-HCT, and CAR-T therapy for upfront and R/R DLBCL consisting of 20 consensus statements are provided in Tables 3, 4, and 5.

DISCUSSION

In this project, an ASTCT-endorsed panel broadly representing experts in lymphoma, transplantation, and cellular therapy with diverse practice experience and geographical representation was convened to provide 20 consensus recommendations on the roles of auto-HCT, allo-HCT and CAR-T therapy for newly diagnosed and R/R DLBCL. This project was conceived to offer rational clinical guidance on treatment sequencing to inform the choice between auto-HCT in patients with chemosensitive R/R DLBCL and the recent approval of CAR-T therapy for second-line therapy for R/R DLBCL.

Recommendations in the Front-Line Setting

The panel does not recommend auto-HCT consolidation for patients with DLBCL (regardless of the International Prognostic Index [IPI] score) when a complete response (CR) is achieved after first-line R-CHOP chemotherapy (grade A recommendation; Table 3, #1) [31] or when positron emission tomography (PET)-negative CR is achieved after DA-R-EPOCH (dose-adjusted

Table 2
Demographic Information of Members of the Consensus Panel

Member Demographic		No. (%)
Sex	Male	15 (60%)
	Female	10 (40%)
Race	White	11 (44%)
	African American	2 (8%)
	Asian	8 (32)
	Others*	4 (16)
Practice setting	University/teaching hospital	23 (92%)
	Community	2 (8%)
Years of clinical experience in lymphoma and/or HCT practice	>10	19 (76%)
	6-10	5 (20%)
	≤5	1 (4%)
Description of clinical practice	Nontransplantation lymphoma practice	2 (8%)
	Primarily HCT and/or cellular therapy practice	12 (48%)
	Combined lymphoma and HCT/cellular therapy practice	11 (44%)
Region of practice	United States	23 (92%)
	Canada	1 (4%)
	Australia	1 (4%)
Estimated number of newly diagnosed lymphoma patients seen by individual members annually	>75	6 (24%)
	51-75	5 (20%)
	26-50	10 (40%)
	≤25	4 (16%)
Estimated number of DLBCL patients seen by individual members annually	>40	6 (24%)
	31-40	6 (24%)
	21-30	9 (36%)
	≤20	4 (16%)
Estimated annual transplantation volume at respective programs (number of autologous plus allogeneic HCTs)	>300	12 (48%)
	201-300	3 (12%)
	101-200	7 (28%)
	51-100	0
	≤50	2 (8%)
	Don't know/unsure	1 (4%)
Estimated annual autologous HCT performed at respective centers for lymphoma (Hodgkin plus non-Hodgkin)	201-300	3 (12%)
	101-200	2 (8%)
	51-100	7 (28%)
	≤50	11 (44%)
	Don't know/unsure	2 (8%)
Estimated annual CAR-T therapies performed at respective centers for lymphoma (on or off clinical trial)	>20	20 (80%)
	16-20	2 (8%)
	10-15	1 (4%)
	<10	2 (8%)

Statistical expert A.K. did not participate in the voting process.
* Others include Pakistani, n = 2; Arab race, n = 1; mixed ethnicity, n = 1.

rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and adriamycin) or similar high-intensity regimens in HGBCL with *MYC/BCL2* and/or *BCL6* rearrangement (grade B recommendation; Table 3, #2) [32]. Auto-HCT consolidation may be considered in patients with HGBCL with *MYC/BCL2* and/or *BCL6* rearrangement achieving a CR following first-line R-CHOP chemotherapy (grade B recommendation; Table 3, #3), given the relatively poor survival outcomes for these patients, while acknowledging the limited available data in this setting [32]. This recommendation is based in part on findings from the retrospective analysis by Landsburg et al. suggesting that auto-HCT consolidation can provide a benefit in patients treated with R-CHOP but not in patients receiving more intensive induction therapies [32,33]. The panel does not recommend CAR-T therapy in the frontline setting for high-risk DLBCL regardless of IPI score or the presence of *MYC, BCL2,* or *BCL6* gene rearrangements outside the setting of a clinical trial (grade C recommendation; Table 3, #4). The panel recommends consolidation with auto-HCT for eligible patients with (non-HIV) primary central nervous system (CNS) lymphoma achieving a CR (grade A recommendation; Table 3, #6) [34–36] and recommends a thiotepa-containing conditioning regimen in this setting (grade B recommendation; Table 3, #7) [37]. However, the panel cautions against extrapolating these recommendations to HIV-positive patients with primary CNS lymphoma. Given the poor outcomes associated with DLBCL and secondary CNS involvement, auto-HCT may be considered for eligible patients achieving a CR with undetectable CNS disease after first-line therapy (grade C recommendation; Table 3, #5) [38,39]. It is important to acknowledge that this is a data-free area of clinical practice, and that this recommendation reflects the expert opinion of panel members.

Recommendations in the Primary Refractory and Early Relapse Setting (≤12 Months)

The panel recommends CAR-T therapy (axi-cel or liso-cel) [13,15,40] as a standard of care option in DLBCL refractory to first-line chemoimmunotherapy or relapsed within 12 months of first-line chemoimmunotherapy (grade A recommendation; Table 4, #1). Two phase III randomized trials showed superior event-free survival [13,15,40] and, more recently, an overall survival (OS) benefit [41] in patients with primary refractory and early relapse (relapsed within 12 months) DLBCL receiving CAR-T therapy compared to attempting salvage therapy (and offering auto-HCT to those responding to salvage attempts).

For DLBCL patients with early treatment failure but established disease responsiveness to salvage treatments, careful consideration of the pros and cons of CAR-T therapy versus auto-HCT consolidation is warranted. It has been previously shown that patients achieving chemoresponsive disease to salvage therapy may experience durable remission following auto-HCT, including those with early chemoimmunotherapy failure [3,6,8]. In studies comparing standard salvage chemotherapy with auto-HCT versus CAR-T therapy in the second-line setting in R/R DLBCL, a smaller proportion of patients in the standard of care arm underwent auto-HCT compared to those who received CAR T-cell therapy (Supplementary Table S2) [13–15]. In addition, the data on chemosensitivity prior to auto-HCT has been reported in only one study (BELINDA) [14], in which 31% of patients achieved chemosensitivity prior to auto-HCT [14]. Although CAR-T therapy provides superior outcomes relative to standard salvage therapy in the second-line setting, the most appropriate strategy (auto-HCT versus CAR-T therapy) in patients with R/R DLBCL achieving chemosensitivity was not determined in these trials. In a recent analysis, Shadman et al. [42] found that auto-HCT was associated with a lower incidence of relapse and superior OS compared with CAR-T therapy in patients achieving a partial response (PR) after salvage therapy [42] while acknowledging a potential reporting bias, as this was not an intention-to-treat analysis but rather an analysis of patients who had received infused cells. Keeping these data in perspective for patients with R/R DLBCL achieving chemoresponsive disease (CR or PR) to salvage therapy, the panel considers auto-HCT an acceptable therapeutic option in eligible patients (grade B

Table 3
Final Clinical Practice Guidelines Consensus Statements for Transplantation and CAR-T Therapy following First-Line Chemoimmunotherapy in DLBCL

Consensus Statement	Grading of Recommendations*	Percentage of Panelists in Agreement
1. The panel does not recommend autologous HCT in DLBCL (regardless of IPI score) as consolidation in complete remission after first-line (R-CHOP or similar) therapy.	A	96%
2. The panel does not recommend autologous transplantation in HGBCL with *MYC*/*BCL2* and or *BCL6* rearrangement as consolidation therapy in PET negative complete remission after DA-R-EPOCH or similar high-intensity regimens.	B	100%
3. Autologous HCT may be considered in eligible patients with HGBCL with *MYC*/*BCL2* and or *BCL6* rearrangement as consolidation therapy in PET-negative complete remission after first-line R-CHOP or similar therapy.	B	80%
4. The panel does not recommend CAR-T therapy in the frontline setting for high-risk DLBCL (regardless of IPI score or presence of *MYC*, *BCL2*, or *BCL6* gene rearrangements), outside the setting of a clinical trial.	C	96%
5. Autologous HCT may be considered for eligible patients with DLBCL with secondary CNS involvement at diagnosis achieving complete remission and with undetectable CNS disease after first-line therapy.	C	100%
6. The panel recommends consolidation with autologous HCT for eligible primary CNS lymphoma patients in CR1.	A	96%
7. The panel recommends a thiotepa-containing conditioning regimen when using autologous HCT consolidation for eligible primary CNS lymphoma patients in CR1.	B	100%

* Agency of Healthcare Research and Quality grading of recommendations based on level of evidence [15]:A: There is good research-based evidence to support the recommendation.B: There is fair research-based evidence to support the recommendation.C: The recommendation is based on expert opinion and panel consensus. X: There is evidence of harm from this intervention.

recommendation; Table 4, #2,3). In DLBCL patients with early relapse who achieve a CR or PR to salvage therapy, the panel considers CAR-T therapy an acceptable therapeutic option (grade B recommendation; Table 4, #4) [43,44].

Recommendations in the Late Relapse Setting (≥12 Months)

In DLBCL patients with late relapse, the panel recommends auto-HCT in eligible patients who have achieved a CR or PR after second-line therapies (grade A recommendation; Table 5, #1). The standard of care for R/R DLBCL remains auto-HCT consolidation in those who achieve a chemoresponsive state (CR or PR) based on the results of the pivotal PARMA study that compared auto-HCT with further cycles of salvage chemotherapy in patients achieving a CR or PR after the initial salvage attempt [3]. These results were further corroborated in the rituximab era in the CORAL study [6]. Furthermore, patients who achieve a CR to salvage therapy, especially those with a negative post-salvage PET scan (PET-CR), have the best outcomes after auto-HCT (3-year progression-free survival [PFS] >80% with PET-CR versus ≤35% with positive PET) [4,45,46]. These data underscore the role of auto-HCT consolidation in R/R DLBCL patients achieving a CR or PR to salvage therapy.

The panel recommends CAR-T therapy in patients with late relapse who have not achieved remission after second-line therapies (grade A recommendation; Table 5, #2) or have R/R disease after 2 or more lines of systemic therapy (grade A recommendation; Table 5, #4). In the SCHOLAR-1 study, the CR rate was 7% and the median OS was 6.3 months with the use of existing therapies in patients who had aggressive B cell NHL that was resistant to chemotherapy or who experienced a relapse within 12 months after auto-HCT [47]. In contrast, results from the 3 single-arm phase 2 pivotal CAR-T trials, ZUMA-1, JULIET, and TRANSCEND, which established its utility in patients with multiply-relapsed DLBCL (summarized in Supplementary Table S1) showed relatively better outcomes [10–12]. All 3 CAR T cell products demonstrated the ability to induce durable remissions in approximately one-third of treated patients (including those not achieving a durable remission with a prior auto-HCT) and have received US Food and Drug Administration approval for treating R/R DLBCL after at least 2 lines of therapy. The recently published 5-year follow-up analysis of ZUMA-1 continues to demonstrate sustained OS and disease-specific survival [48].

The panel recommends CAR-T therapy in those who are not eligible for auto-HCT because of comorbidities or age regardless of the timing of relapse (grade B recommendation; Table 5, #3) [49,50]. The panel does not consider secondary CNS involvement a contraindication for administering CAR-T

Table 4
Final Clinical Practice Guidelines Consensus Statements for Transplantation and CAR-T Therapy in Primary Refractory and Early Relapse (Relapse Within 12 Months of First-Line Chemoimmunotherapy) DLBCL

Consensus Statement	Grading of Recommendations*	Percentage of Panelists in Agreement
1. The panel recommends CAR-T therapy as a standard of care option in patients with DLBCL who have refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy.	A	96%
2. In DLBCL patients with early relapse who achieve a complete remission with salvage therapy, the panel considers autologous HCT an acceptable consolidation therapy in eligible patients.	B	88%
3. In DLBCL patients with early relapse who achieve a partial remission with salvage therapy, the panel considers autologous HCT an acceptable consolidation therapy in eligible patients.	B	96%
4. In DLBCL patients with early relapse who achieve a complete remission or partial remission to salvage therapy, the panel considers CAR-T therapy an acceptable therapeutic option.	B	84%

* Agency of Healthcare Research and Quality grading of recommendations based on level of evidence [15]:A: There is good research-based evidence to support the recommendation.B: There is fair research-based evidence to support the recommendation.C: The recommendation is based on expert opinion and panel consensus. X: There is evidence of harm from this intervention.

Table 5
Final Clinical Practice Guidelines Consensus Statements for Transplantation and CAR-T Cell Therapy for Late Relapsed (Relapse Beyond 12 Months of First-Line Chemoimmunotherapy) DLBCL

Consensus Statement	Grading of Recommendations*	Percentage of Panelists in Agreement
1. In DLBCL patients with late relapse, the panel recommends autologous HCT consolidation therapy in eligible patients who have achieved a complete or partial remission after second-line therapies.	A	96%
2. In DLBCL patients with late relapse, the panel recommends CAR-T therapy in patients who have not achieved remission (complete or partial) after second-line therapies.	A	96%
3. In patients with DLBCL, the panel recommends CAR-T therapy in patients who are not eligible for autologous HCT (due to comorbidities or age) regardless of the timing of relapse.	B	96%
4. In patients with DLBCL, the panel recommends CAR-T therapy in those who have relapsed or refractory disease after 2 or more lines of systemic therapy.	A	96%
5. The panel does not consider secondary CNS involvement a contraindication for administering CAR-T therapy.	B	88%
6. In relapsed DLBCL patients with available access to CAR-T therapy, the panel recommends offering CAR-T therapy before proceeding with allogeneic HCT.	C	96%
7. The panel recommends allogeneic HCT in eligible DLBCL patients relapsing/progressing after CAR-T therapy if they achieve a complete or partial remission with subsequent antilymphoma therapies.	C	96%
8. The panel recommends allogeneic HCT in eligible relapsed or refractory DLBCL patients after autologous HCT failure in regions without access to CAR-T therapy, and in those with CAR T cell manufacturing failure, ideally after achieving a complete or partial remission with subsequent antilymphoma therapies.	C	96%
9. The panel recommends reduced-intensity conditioning or nonmyeloablative conditioning regimens for eligible patients undergoing allogeneic HCT.	B	92%

* Agency of Healthcare Research and Quality (AHRQ) grading of recommendations based on level of evidence [15]:A = There is good research-based evidence to support the recommendation.B = There is fair research-based evidence to support the recommendation.C = The recommendation is based on expert opinion and panel consensus.X = There is evidence of harm from this intervention.

therapy (grade B recommendation; Table 5, #5) [51,52]. If access to CAR T-cell therapy is available, the panel recommends offering CAR-T therapy before proceeding with allo-HCT (grade C recommendation; Table 5, #6).

The panel recommends allo-HCT in eligible DLBCL patients relapsing/progressing after CAR-T therapy if they achieve a CR or PR with subsequent antilymphoma therapies (grade C recommendation; Table 5, #7) and recommends RIC or nonmyeloablative conditioning regimens (grade B recommendation; Table 5, #9). The panel recommends allo-HCT for eligible R/R DLBCL patients after auto-HCT failure in regions without access to CAR-T therapy and in those with CAR-T product manufacturing failure (resulting in no CAR-T product available to infuse), ideally after achieving a CR or PR with subsequent antilymphoma therapies (grade C recommendation; Table 5, #8).

Allo-HCT may be necessary for patients who relapse after CAR-T therapy, given that allo-HCT can be potentially curative following failure of auto-HCT, especially in patients who achieve chemosensitivity [15]. In the CIBMTR analysis of 503 DLBCL patients who relapsed after auto-HCT and underwent subsequent allo-HCT, 31% were able to achieve long-term PFS at 3 years [15]. In a recent multicenter retrospective study of allo-HCT following CAR-T failure, the 1-year PFS and OS were 45% and 59%, respectively [53]. In both these studies, the single factor associated with superior outcomes was achieving chemosensitivity at the time of allo-HCT [15,53].

CONCLUSION

In clinical scenarios in which data from prospective studies are either scarce or unavailable, or in situations in which patient populations included in published trials are less relevant to contemporary clinical practice, formal consensus recommendations can be an invaluable resource to inform clinical decision making [54]. The promising data with bispecific antibodies (and eventual approval by regulatory agencies worldwide) suggest that these therapies will imminently further change the therapeutic landscape of R/R DLBCL. Additionally, both CAR-T and bispecific antibody therapies are now being studied in first-line therapy, and treatment algorithms will continue to evolve as data emerge from these studies. Meanwhile, we hope the clinical practice recommendations in this article can serve as a tool to guide clinicians managing patients with newly diagnosed and R/R DLBCL.

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SUPPLEMENTARY MATERIALS

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