SPOTLIGHT REVIEW ARTICLE

Sequencing of cellular therapy and bispecific antibodies for the management of diffuse large B-cell lymphoma

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Abstract

Historically, the management of relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) following first-line chemo-immunotherapy has been second-line chemotherapy, followed by high-dose chemotherapy and consolidative autologous hematopoietic stem cell transplantation (HSCT), resulting in durable remissions in approximately 40% of patients. In 2017, chimeric antigen receptor (CAR) T-cell therapy changed the landscape of treatment for patients with R/R DLBCL, with complete response rates ranging from 40-58% and long-term disease-free survival of >40% in the highest risk subgroups, including patients who relapsed after autologous HSCT. Since that time further studies have demonstrated improved overall response rates and survival outcomes in patients with primary refractory or early-relapsed (relapse within 1 year) DLBCL treated with CAR T-cell therapy compared with autologous HSCT, advancing CAR T-cell therapy into the second-line setting. However, >50% of patients will relapse in the post-CAR T-cell setting. In the past 2 years, two CD20 x CD3 bispecific antibodies were approved by the Food and Drug Administration for the treatment of R/R DLBCL after two or more lines of systemic therapy. These bispecific antibodies have demonstrated overall response rates exceeding 50% and durable remissions at >2 years of follow-up. Additionally, a notable treatment advantage of bispecific antibodies is their ability to be administered in the community setting, making treatment more accessible for patients. The development and advancement of these novel therapies raise questions regarding the ongoing role of HSCT in the management of R/R DLBCL and the best sequence of cellular and bispecific therapies to optimize patients' outcomes.

Introduction

Non-Hodgkin lymphoma is a heterogeneous group of lymphoid neoplasms that originate from B cells, T cells, or natural killer cells.[1] Mature B-cell lymphomas rank as the 11th most common cancer worldwide, with more than 80,000 new cases diagnosed in the United States each year, and accounting for >60% of all hematopoietic neoplasms.[2,3] Diffuse large B-cell lymphoma (DLBCL) is the most common and prototypical aggressive B-cell lymphoma accounting for approximately 30% of cases.[1] In the rituximab era, administration of anti-CD20-containing chemoimmunotherapy regimens, such as R-CHOP, DA-R-EPOCH, and POLA-R-CHP, has become the standard-of-care, front-line treatment for DLBCL with complete response rates ranging from 75-80%.[4-6] However, 30-40% of these patients will be refractory to front-line treatment or experience relapse within 5 years.[7]

Since 1995, management for relapsed or refractory (R/R) DLBCL has been second-line chemotherapy, followed by high-dose chemotherapy and consolidative autologous (auto) hematopoietic stem cell transplantation (HSCT), resulting in durable remission rates in 30-40% of patients.[8,9] However, auto-HSCT is associated with acute and long-term treatment-related toxicities and many patients are thought not to be good candidates for transplantation due to advanced age or other pre-existing comorbid conditions.[10] Novel therapies such as chimeric antigen receptor (CAR) T-cell therapy and bispecific antibodies (BsAb) have demonstrated durable treatment responses in the management of R/R DLBCL with tolerable side-effect profiles, even for those patients of advanced age or with comorbidities. These developments in cellular therapy raise questions regarding the role of HSCT in the management of R/R DLBCL going forward and how to integrate these novel therapies into clinical practice.

Autologous stem cell transplantation

The PARMA study, published by Philip *et al*. in *The New England Journal of Medicine* in 1995, demonstrated superior overall response rates for patients treated with intensive chemotherapy followed by consolidative auto-HSCT compared to those given four additional cycles of chemotherapy (84% *vs*. 44%). Long-term follow-up data showed a superior 5-year overall survival of 53% in the auto-HSCT group compared with 32% in the group treated with intensive chemotherapy alone, and established auto-HSCT as the standard of care for chemotherapy-sensitive, relapsed non-Hodgkin lymphoma.[9] The CORAL study further validated these findings in 2010, albeit in the post-rituximab era, and demonstrated a 3-year progression-free survival of 37% and a 3-year overall survival of 49% in patients with R/R DLBCL treated with second-line chemotherapy followed by auto-HSCT. However, this study showed an inferior 3-year progression-free survival of 23% in those patients whose disease relapsed early, defined as relapse within less than 12 months after diagnosis, treated with second-line chemotherapy followed by auto-HSCT.[8,11] Hamadani *et al*. further investigated the use of auto-HSCT in those patients with early relapsed disease in a large, multicenter, retrospective analysis of 516 patients with R/R DLBCL treated with second-line chemotherapy followed by auto-HSCT. This study demonstrated inferior progression-free and overall survival in those patients with early relapsed disease compared with patients who relapsed >12 months after diagnosis.[12] In addition, studies examining the use of auto-HSCT in patients with DLBCL harboring a *MYC* gene rearrangement with *BCL2* and/or *BCL6* gene rearrangements, also referred to as high-grade B-cell lymphomas, have demonstrated particularly bad outcomes with a 2-year overall survival <10%.[13] These studies highlight the limitations of second-line chemotherapy + auto-HSCT for the management of R/R DLBCL in higher risk groups of patients.

Chimeric antigen receptor T-cell therapy

In 2017, CAR T-cell therapy changed the landscape of treatment for patients with refractory DLBCL or relapse following auto-HSCT. The ZUMA-1, JULIET, and TRANSCEND NHL 001 clinical trials, targeting patients who progressed after at least two lines of therapy, including auto-HSCT, demonstrated overall response rates of 52-83%, with complete responses in 40-58%, and long-term overall survival ranging from 36-42%.[14-16] These studies led to the approval of axicabtagene ciloleucel (axi-cel; Yescarta), tisagenlecleucel (tisa-cel; Kymriah), and lisocabtagene maraleucel (liso-cel; Breyanzi) by the US Food and Drug Administration (FDA) in the third- or later-line setting for R/R DLBCL. The subsequent ZUMA-7 and TRANSFORM clinical trials evaluated CAR T-cell therapy as an earlier line of therapy for patients with primary refractory DLBCL or early relapsed disease compared with standard-of-care chemoimmunotherapy + auto-HSCT. The ZUMA-7 clinical trial enrolled 359 patients with DLBCL, 74% with primary refractory disease, and 26% with early relapsed disease.[17] Only 64 patients (36%) in the standard-of-care arm achieved at least a partial response after second-line chemotherapy and went on to undergo auto-HSCT compared with 170 patients (94%) who received axi-cel infusion.[17] ZUMA-7 demonstrated a superior overall response rate (83% *vs*. 50%), complete responses (65% *vs*. 32%), and median event-free survival (8.3 months *vs*. 2 months) with axi-cel compared with standard-of-care treatment.[17] The TRANSFORM study randomized patients to standard-of-care chemotherapy followed by auto-HSCT or liso-cel and enrolled 184 patients. Ninety-one (99%) of the patients randomized to liso-cel received the liso-cel infusion while only 43 (46.7%) patients in the standard-of-care arm underwent auto-HSCT, with progression of disease cited as the most common reason for inability to proceed with auto-HSCT. The TRANSFORM study produced similar results to those of ZUMA-7. Patients who were randomized to liso-cel compared with standard-of-care chemoimmunotherapy + auto-HSCT had overall response rates of 86% *versus* 46%, complete response rates of 66% *versus* 39%, and median event-free survivals of 10.1 months *versus* 2.3 months, respectively.[18] Recent long-term follow-up data from the ZUMA-7 study at a median follow-up of 47.2 months showed superior overall survival among patients treated with axi-cel compared with those in the standard-of-care treatment arm.[19] These studies led to FDA approval of axi-cel and liso-cel for second-line treatment of patients who relapsed within 1 year of remission or who never achieved remission after first-line therapy.

Autologous hematopoietic stem cell transplantation compared with chimeric antigen receptor T-cell therapy

Auto-HSCT is associated with treatment-related toxicities such as febrile neutropenia, opportunistic infections, and cardiovascular events, with ≥ grade 3 cardiovascular toxicity occurring in 29% of patients within the first 100 days after auto-HSCT and in nearly 60% of patients 70 years of age or older.[9,10,20] Although CAR T-cell therapies are associated with their own unique toxicity profile, namely cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and hypogammaglobulinemia, the PILOT study (a phase II, open-label, multicenter clinical trial) demonstrated the safety and efficacy of liso-cel as second-line therapy in patients who did not experience early relapse (relapsed after >1 year) but were considered

not to be candidates for auto-HSCT based on age or other co-morbid conditions.[21] In this study, the overall response rate with liso-cel was 80% and 54% of the patients had complete responses.[21] Long-term follow-up data show that with a median follow-up of 18.5 months, the median duration of response was 23 months, and for patients in complete remission the median duration of response was not reached.[21] Taken together, these studies establish CAR T-cell therapy as the second-line treatment option for patients with primary refractory or early relapsed disease and patients who relapse any time after remission but are deemed to be poor candidates for auto-HSCT based on advanced age or the presence of co-morbid medical conditions.

When considering treatment for R/R DLBCL it is important to consider the financial implications associated with each subsequent line of therapy. In the USA, the estimated cost of anti-CD19 CAR T-cell therapy ranges from $373,000-$1,600,000 compared with $140,000-$150,000 for auto-HSCT.[22-25] Several financial analyses have justified the high price tag of CAR T-cell therapy, finding that when accounting for life-years gained due to improved overall survival with the use of CAR T-cell over intensive chemotherapy for R/R DLBCL, the cost of each quality-adjusted life year ranged from $58,146-$82,400.[22,25,26] Nevertheless, it is important to acknowledge that the cost of CAR T-cell therapy may preclude the adoption of this novel therapy over auto-HSCT for management of R/R DLBCL world-wide.

CAR T-cell therapy has also demonstrated remarkable efficacy for the treatment of high-grade B-cell lymphomas in the third-, second-, and more recently, first-line settings. The TRANSCEND NHL-001 and ZUMA-1 trials included 13% and 15% of patients with high-grade B-cell lymphomas with complete response rates of 60.6% and 67%, respectively.[14,15] The ZUMA-7 and TRANSFORM clinical trials also demonstrated superior clinical event-free survival in patients with primary refractory or early relapsed high-grade B-cell lymphomas treated with CAR T-cell therapy compared with standard-of-care chemoimmunotherapy + auto-HSCT.[17-19] A subsequent multicenter, phase II clinical trial, ZUMA-12, which examined the use of axi-cel following two cycles of chemoimmunotherapy for the front-line treatment of high-grade B-cell lymphomas, demonstrated superior response rates to those historically reported in the literature with an overall response rate of 89% and a complete response rate of 78%.[27] Randomized trials (e.g., ZUMA-23) comparing first-line CAR T-cell therapy with standard chemotherapy in high-risk patients are ongoing.

Recently, the FDA announced an investigation into reports of increased rates of subsequent malignant neoplasms, in particular T-cell lymphomas, following CAR T-cell therapy.[28] Historically, rates of subsequent malignant neoplasms after auto-HSCT for the treatment of R/R DLBCL have been reported to range from 6-20%.[20] Following the FDA's announcement, multiple, large, multicenter, retrospective analyses have documented similar rates of subsequent malignant neoplasms in the post-CAR T-cell setting, ranging from 0.9-12.9%, including T-cell neoplasms in <0.2%.[28-30] Thus, it is not clear yet whether subsequent malignant neoplasms are a result of CAR T-cell therapy or the extensive prior treatment these patients have received. Further investigation is needed to evaluate the presence of remnant viral vector genes and CAR transgenes in subsequent malignant neoplasms arising in the post-CAR T-cell setting.

Is there still a role for autologous stem cell transplantation in B-cell lymphoma?

The superior outcomes demonstrated with the use of axi-cel and liso-cel compared with standard-of-care chemoimmunotherapy + auto-HSCT in ZUMA-7 and TRANSFORM raise the question as to whether there is still a role for auto-HSCT in the management of R/R DLBCL. The current literature and consensus guidelines support the use of auto-HSCT in patients with chemotherapy-sensitive disease (able to achieve at least a partial response to second-line chemotherapy) who relapse >12 months after completion of first-line chemoimmunotherapy and are deemed fit enough to proceed with auto-HSCT.[31] This approach allows for a curative treatment option in about 40% of patients treated with auto-HSCT.[11] In addition, it is important to note that ZUMA-1, TRANSCEND NHL-001, and JULIET included 25-49% of patients who were previously treated with auto-HSCT, and a subgroup analysis of these studies demonstrated the efficacy of CAR T-cell therapy after treatment failure with auto-HSCT with overall response rates ranging from 52-78%.[14-16] Conversely, there are few data available regarding the role of auto-HSCT following CAR T-cell relapse. Speigel *et al*. reported particularly bad outcomes with salvage chemotherapy in patients who progressed following axi-cel therapy, with an overall response rate of 29%, 17% with complete responses, and a median progression-free survival of only 55 days.[32] Therefore, for those patients with R/R DLBCL who are deemed candidates for and proceed with auto-HSCT in the second-line setting, CAR T-cell therapy remains a viable third-line treatment option. It is partly for this reason that auto-HSCT remains a viable approach for those patients who relapse >1 year after front-line chemotherapy and are fit enough to proceed with transplantation

Bispecific antibodies

CD20 x CD3 bispecific T-cell engaging monoclonal antibodies (BsAb) are immunological agents that cross-link the CD20 surface marker expressed on malignant B cells to the CD3 surface marker expressed on both cytotoxic

and helper T cells to induce potent T-cell-mediated cytotoxic activity against the CD20-positive malignant B cells. Both epcoritamab and glofitamab (two novel BsAb) have demonstrated remarkable efficacy for the management of heavily pre-treated patients with DLBCL.

A phase I/II, multi-institutional study of epcoritamab for the management of large B-cell lymphoma following at least two prior lines of chemoimmunotherapy included 157 patients previously treated with a median of three lines of therapy; 61.1% of the patients had primary refractory disease.[33] Patients received CRS prophylaxis with prednisone, diphenhydramine, and acetaminophen and epcoritamab was administered using a step-up dosing with a priming dose of 0.16 mg on day 1 of the first 21-day cycle, followed by an intermediate dose of 0.8 mg on day 8 of the first cycle, and then the full 48-mg dose on day 15 of the first cycle and day 1 of all subsequent cycles until disease progression or unacceptable toxicity.[33] Treatment with epcoritamab produced an overall response rate of 63.1% with complete responses in 38.9% of patients and a median duration of response of 12 months. Treatment was well tolerated with four patients experiencing grade 3 CRS following epcoritamab infusions (no patients experienced grade 4 or 5 CRS) and ten patients experiencing ICANS (of any grade), with only one patient with possible grade ≥3 ICANS (this patient was also noted to have multiple brain infarcts, making it unclear whether the neurological changes were related to epcoritamab).[33]

A phase II study of glofitamab included 155 heavily pre-treated patients with DLBLC, 60% of whom had received three or more prior lines of therapy and 90% of whom had refractory disease.[34] Patients included in this study received B-cell-depleting therapy with 1,000 mg of obinutuzumab 7 days prior to the initial glofitamab infusion. Glofitamab was then administered via step-up doses on day 8 (2.5 mg) and day 15 (10 mg) of the first 21-day cycle, followed by a dose of 30 mg on day 1 of cycles 2 through 12.[34] Treatment with glofitamab resulted in an overall response rate of 52% and a complete response rate of 39%. Of those patients who achieved a complete response, 67% remained in complete remission at 18 months of follow-up.[35] Although only 4% of patients developed ≥3 grade CRS, 44 patients required admission to hospital for management of CRS. The rate of ICANS was low, since the syndrome occurred in only 12 patients, and was grade ≥3 in 3% of patients.[34] Similar findings were also reflected in real-world data from patients treated with glofitamab in a compassionate use setting in Turkey, published by Birtas Atesoglu *et al*. This study included 43 patients who received at least one dose of glofitamab and showed an overall response rate of 37% including 21% of patients who were able to achieve a CR.[36] Based on these studies, in the late spring of 2023, both epcoritamab and glofitamab were approved by the FDA as additional treatment options for patients with R/R DLBCL.

How to sequence these therapies

Despite overall response rates surpassing 80% with CAR T-cell therapy in the second-line setting, more than 30% of patients will not achieve a complete response, and at a median follow-up of 12.9 months nearly 36% of patients who do achieve a complete response will experience progression after CAR T-cell therapy.[32,37] Historically, patients relapsing after CAR T-cell therapy have had poor outcomes with a median overall survival of 5-6 months; however, BsAb have demonstrated efficacy in the treatment of this heavily pre-treated population of patients.[33,34]

A phase I/II clinical trial, published by Thieblemont *et al*., which examined the use of epcoritamab for the management of R/R DLBCL included 61 patients previously treated with CAR T-cell therapy (75.4% of whom progressed within 6 months following CAR T-cell infusion).[33] The subset analysis of this patient population showed an overall response rate of 54.1% and a complete response rate of 34.3%, similar to the response rates seen in the overall study population. In addition, of those patients who achieved a compete response, 88% remained in complete remission at follow-up at both 6 and 9 months.[33] A phase II study of glofitamab included 52 patients previously treated with CAR T-cell therapy and reported a complete response rate of 35%, similar to that reported with epcoritamab.[34] Although the efficacy of BsAb following CAR T-cell therapy progression has been documented in both prospective and retrospective studies, the efficacy of CAR T-cell therapy following treatment with BsAb is unknown as none of the prospective studies examining CAR T-cell therapy in either the third-, second-, or first-line setting has included patients previously treated with BsAb.[33,34] Studies have suggested that the lymphoma microenvironment and T-cell activity play vital roles in the efficacy of CAR T-cell therapy for the management of DLBCL.[38] Although data are limited, there is a theoretical concern that continuous BsAb treatment could lead to T-cell exhaustion, decreasing the proliferative capacity and antitumor activity of CAR T cells in patients previously treated with BsAb.[39] In a retrospective analysis, Rentsch *et al*. monitored the kinetics of CAR T-cell-specific DNA in peripheral blood before, during, and after glofitamab treatment in nine patients previously treated with CAR T-cell therapy.[40] Of these patients, five patients had detectable CAR T-cell-specific DNA prior to the glofitamab infusions. Two patients had a continued decrease in CAR T cells following glofitamab; however, three patients experienced a re-expansion of CAR T cells in the peripheral blood after glofitamab with peak expansion occurring a median of 35 days following the start of the glofitamab infusions.[40] These data suggest that treatment with BsAb following CAR T-cell therapy may not only be an effective treatment modality but may also enhance residual CAR T-cell activity.

When to consider allogeneic stem cell transplantation for B-cell lymphoma

Allogeneic (allo) HSCT was the first form of immunotherapy to demonstrate clinical efficacy and potential cure in the treatment of leukemia and lymphoma and, indeed, can be considered the first cellular therapy and forerunner of the cellular therapy we have been discussing. In 1957, Thomas *et al*. first described the ability to harness the T cells and natural killer cells of the donor's immune system against a recipient patient's leukemia.[41] This graft-*versus*-tumor effect has served as the foundation for the development of alternative cellular and immunotherapies, such as CAR T-cell therapy. However, despite the efficacy of allo-HSCT and the benefits of the graft-*versus*-tumor effect in the management of R/R DLBLC, resulting in complete respons-

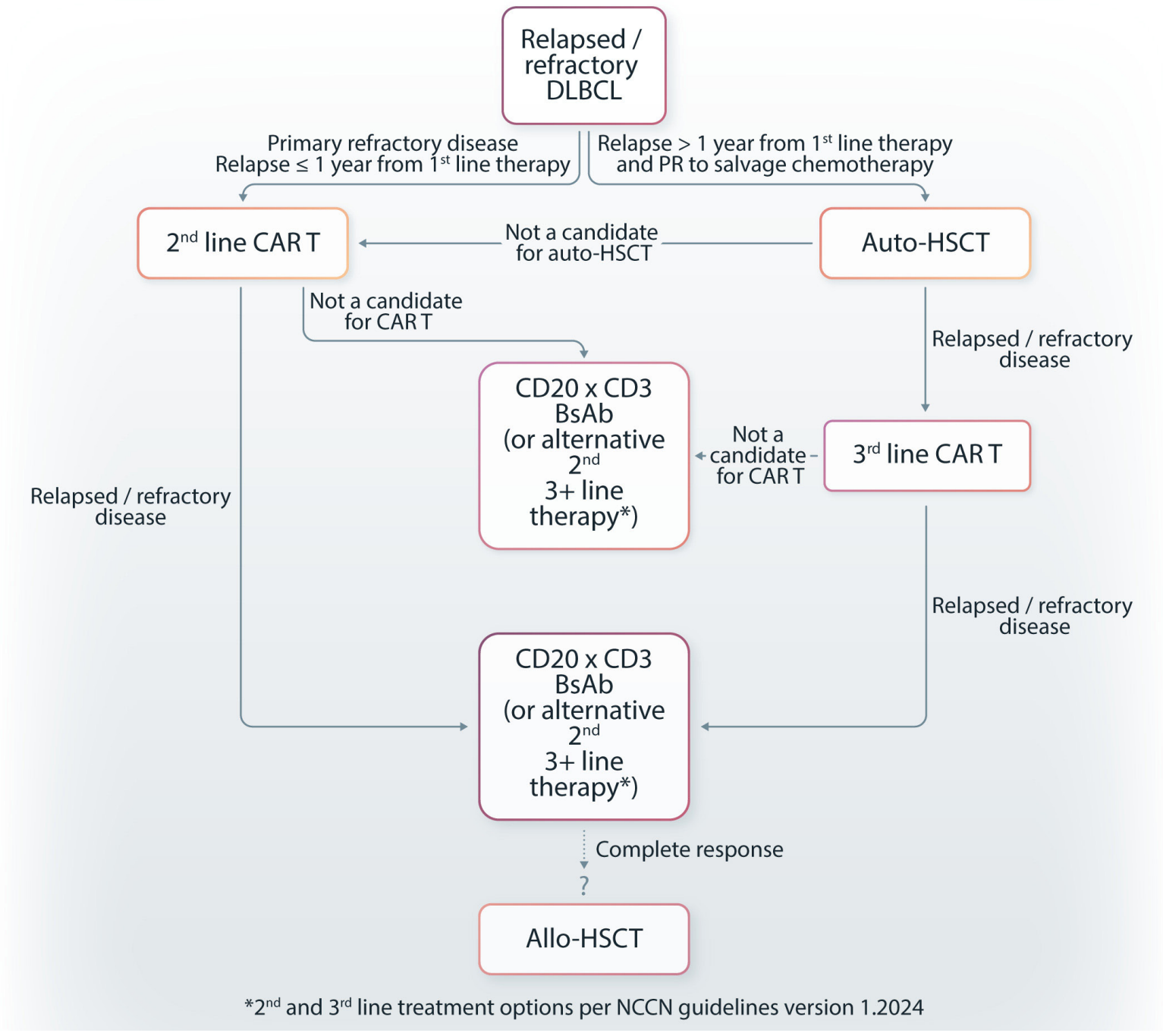

Figure 1. Proposed treatment algorithm for the management of relapsed/refractory diffuse large B-cell lymphoma. Patients whose disease relapses more than 1 year after first-line chemoimmunotherapy and who have chemotherapy-sensitive disease (able to achieve at least a partial response to second-line therapy) should be considered for autologous (auto) hematopoietic stem cell transplantation (HSCT). Those patients who are deemed not to be candidates for auto-HSCT or patients with primary refractory diffuse large B-cell lymphoma or early relapsed disease should be considered for chimeric antigen receptor (CAR) T-cell therapy in the second-line setting. For those patients deemed not to be candidates for CAR T-cell therapy (because of an underlying neurological condition or other comorbid condition) or who are unwilling to travel to a tertiary center to receive care, second- or third-line treatment options, according to the National Comprehensive Cancer Network (NCCN) guidelines version 1.2024, including bispecific antibodies (BsAb) which should be considered on a case-by-case basis. Patients who experience disease relapse after auto-HSCT should be considered for CAR T-cell therapy, and those patients who are thought not to be candidates for CAR T-cell therapy should proceed with third-line treatment options as per NCCN guidelines until treatment-related toxicity or disease progression. Those patients who experience disease relapse following CAR T-cell therapy in either the second- or third-line setting should be considered for treatment with BsAb or an alternative 3+ line treatment option as per NCCN guidelines. If patients can achieve a complete response with these subsequent lines of therapy, they should be considered for allogeneic HSCT. DLBCL: diffuse large B-cell lymphoma; PR: partial response; CAR T: chimeric antigen receptor T-cell therapy; allo-HSCT: allogeneic hematopoietic stem cell transplantation.

es in 50-60% of patients, it has historically been used in the third-line setting or beyond, following auto-HSCT, due to the increased treatment-related morbidity and mortality of allo-HSCT compared with auto-HSCT.[42,43] However, in the post-CAR T-cell therapy setting, Speigel *et al*. reported particularly poor outcomes in patients treated with salvage chemotherapy alone, suggesting that there may not be a role for consolidative auto-HSCT following CAR T-cell therapy and raising the question of whether patients may benefit from the graft-*versus*-tumor effect from allo-HSCT following CAR T-cell failure.[32]

One multicenter retrospective analysis of 88 patients who received allo-HSCT after failure of anti-CD19 CAR T-cell therapy demonstrated a 1-year progression-free survival of 45% and overall survival of 59%.[44] The median number of lines of therapy between CAR T-cell infusion and allo-HSCT was one (range, 1-7 lines). Multivariate analysis showed that receiving less than two lines of therapy between CAR T-cell therapy and allo-HSCT and the ability to achieve a complete response at the time of allo-HSCT were associated with better transplant-related outcomes.[44] These findings suggest that if a patient can achieve a complete response with subsequent lines of therapy after the failure of CAR T-cell therapy, early allo-HSCT should be considered if the patient is deemed to be a suitable candidate for such a transplant.

Given the novelty of CD20 x CD30 BsAb, there is a paucity of data surrounding the use of allo-HSCT after BsAb. Each of the two phase II clinical trials that examined the use of either glofitamab or epcoritamab for the treatment of R/R DLBCL included seven patients who went on to receive allo-HSCT after treatment with BsAb; however, the outcomes of these patient subgroups have not yet been published.[33,34] Additionally, a single-center retrospective analysis from Spain reported eight patients who received allo-HSCT after treatment with CD20 x CD3 BsAb (3 patients treated with epcoritamab and 5 with glofitamab). Patients received a median of ten doses of BsAb and six patients (75%) were in complete remission at the time of the transplant.[45] Five patients received haploidentical transplants, two patients had matched unrelated donors, and one had a matched related donor. All patients received graft-*versus*-host disease prophylaxis with post-transplant cyclophosphamide. At a median follow-up of 30 months (range, 23-37 months) after allo-HSCT, the 2-year overall survival was only 25%. Of the six patients who died during follow-up, one died from disease relapse, three died from infections, and two from complications of graft-*versus*-host disease.[45] Only two of the patients included in this analysis had previously been treated with CAR T-cell therapy.[45]

Conclusion

Based on the current literature, auto-HSCT should still be considered for a subset of patients with chemotherapy-sensitive, relapsed DLBCL who are deemed medically fit for auto-HSCT. Patients with primary refractory DLBCL or early relapsed disease, relapsed disease following auto-HSCT, or who are deemed not to be a candidate for auto-HSCT should be offered potentially curative and definite treatment with CAR T-cell therapy (Figure 1). BsAb should be utilized as a line of therapy following CAR T-cell therapy and as an earlier line of therapy in select patients on a case-by-case basis. These situations include those patients in the community who are unwilling or unable to travel to a larger academic center to receive auto-HSCT or CAR T-cell therapy, and those patients who do not wish to receive intensive cellular therapy. Higher rates of severe neurological toxicity have been noted in patients with underlying neurological deficits treated with CAR T-cell therapy.[46] In this subset of patients who are deemed to be at a higher risk for severe complications or toxicities with CAR T-cell therapy, it may be reasonable to consider treatment with BsAb without prior treatment with CAR T-cell therapy. However, these decisions should be based on an individualized conversation between the physician and the patient about the risks *versus* the benefits. There are limited data to support the use of auto-HSCT after failure of CAR T-cell treatment; however, allo-HSCT should be considered for those patients who are able to achieve a complete remission after CAR T-progression with either CD20 X CD3 BsAb or alternative regimens as suggested in National Comprehensive Cancer Network guidelines.[31] Ongoing clinical trials are currently investigating the use of both BsAb and CAR T-cell therapy in combination with chemoimmunotherapy in the front-line setting. As patients are exposed to these cellular therapies earlier in their disease and treatment course, it will be even more important to establish objective criteria and guidelines for the sequencing of these novel therapies.

Disclosures

LIG is a consultant for Ono Pharmaceuticals, sits on advisory boards for Bristol Meyers Squibb, Kite Pharmaceuticals, and Novartis and on a data and safety monitoring board for Janssen clinical trials, is a co-founder of Zylem Biosciences and holds patents regarding (i) nanoparticles for cancer therapy (HDL NP as inducers of ferroptosis in cancer, PCT/US2020/051549) and (ii) nanostructures for treating cancer and other conditions (PCT/US2013/027431).

Contributions

MM and LIG contributed equally to writing and editing this manuscript.

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