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PRIMERS IN CARDIO-ONCOLOGY

How to Treat Diffuse Large B-Cell Lymphoma

Oncologic and Cardiovascular Considerations

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ABSTRACT

Anthracycline-containing therapy is the cornerstone of frontline treatment for diffuse large B-cell lymphoma (DLBCL), and autologous stem cell transplantation, and more recently, chimeric antigen receptor T-cell therapy are the primary treatment options for relapsed refractory DLBCL. Given these therapies are all associated with cardiovascular toxicities, patients with underlying cardiac comorbidities are severely limited in treatment options. The focus of this review is to outline the cardiotoxicities associated with these standard treatments, explore strategies developed to mitigate these toxicities, and review novel treatment strategies for patients with underlying cardiovascular comorbidities. DLBCL patients with underlying cardiac complications are a high-risk patient population who require complicated management strategies that utilize a multidisciplinary approach with collaboration between cardiologists and oncologists. (J Am Coll Cardiol CardioOnc 2023;5:281–291) © 2023 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Lymphoma is a heterogenous disease with over 70 subtypes. The frontline treatment of most patients with diffuse large B-cell lymphoma (DLBCL), the most common type of non-Hodgkin lymphoma (NHL), traditionally incorporates doxorubicin, an anthracycline, that is associated with cardiovascular toxicities including cardiomyopathy and may be contraindicated in patients with pre-existing cardiac comorbidities,[1] and cyclophosphamide, a nitrogen mustard alkylating agent, that can also rarely cause cardiotoxicity.[2] In this review, we discuss the management of DLBCL in patients with underlying cardiac conditions and the role of multidisciplinary care in assessing and treating these patients.

CASE PRESENTATION

A 75-year-old man with history of hypertension, diabetes, and NYHA functional class III heart failure presents with palpable axillary and inguinal lymphadenopathy, fevers, chills, night sweats, shortness of breath, and weight loss of 20 pounds in the last month. Biopsy of the left axillary lymph node revealed DLBCL. Positron emission tomography/computed tomography scan showed lymphadenopathy both above and below the diaphragm as well as pulmonary involvement (stage IV disease). Labs were notable for a lactate dehydrogenase of 400 U/L and hemoglobin of 8 g/dL. Patient had an ECOG (Eastern

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ABBREVIATIONS AND ACRONYMS

AE = adverse event

allo-SCT = allogeneic stem cell transplantation

auto-SCT = autologous stem cell transplantation

BR = bendamustine and rituximab

CAR-T = chimeric antigen receptor T-cell therapy

CR = complete remission

CRS = cytokine release syndrome

CVD = cardiovascular disease

DLBCL = diffuse large B-cell lymphoma

LVEF = left ventricular ejection fraction

NHL = non-Hodgkin lymphoma

ORR = overall response rate

OS = overall survival

PFS = progression-free survival

R-CEOP = rituximab-cyclophosphamide-etoposide-vincristine-prednisone

R-CHOP = rituximab-cyclophosphamide-vincristine-doxorubicin-prednisone

R-COMP = rituximab, cyclophosphamide, nonpegylated liposomal doxorubicin, vincristine, and prednisone

R-CVP = rituximab, cyclophosphamide, vincristine, and prednisone

R-GCVP = rituximab-gemcitabine-cyclophosphamide-vincristine-prednisone

R/R = relapsed/refractory

SCT = stem cell transplantation

HIGHLIGHTS

- Standard frontline treatment for DLBCL is anthracycline-containing chemotherapy, and standard treatments for relapsed/refractory DLBCL are autologous stem cell transplantation and chimeric antigen receptor T-cell therapy, all of which are associated with potential cardiovascular toxicities.
- For patients with cardiovascular comorbidities, non–anthracycline-containing regimens in the frontline setting, including R-CEOP and R-GCVP, may be considered.
- Novel agents including targeted therapies and immunotherapies have emerged that are associated with fewer cardiac complications.
- Collaboration between oncologists and cardiologists is important to identify, monitor, and manage cardiovascular risk factors, cardiovascular disease, and treatment-associated cardiotoxicities.

Cooperative Oncology Group) Performance Status of 1.

STANDARD FRONTLINE TREATMENT OPTIONS FOR DLBCL. R-CHOP, a chemotherapy regimen that includes rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, has been the standard frontline treatment for DLBCL for over the past 20 years. The initial trial that demonstrated the benefit of adding rituximab to standard CHOP chemotherapy regimen was the LNH-98.5 trial performed by the Groupe d'Etudes des Lymphomas de L'Adulte (GELA).[3] There have been a variety of trials that have attempted to improve upon the outcomes of R-CHOP with the addition various targeted agents such as bortezomib in PYRAMID (Study to Assess the Effectiveness of RCHOP With or Without VELCADE in Previously Untreated Non-Germinal Center B-Cell-like Diffuse Large B-Cell Lymphoma Patients),[4] lenalidomide in ROBUST (Efficacy and Safety Study of Lenalidomide Plus R-CHOP Chemotherapy Versus Placebo Plus R-CHOP Chemotherapy in Untreated ABC Type Diffuse Large B-cell Lymphoma),[5] or ibrutinib in PHOENIX (A Study of the Bruton's Tyrosine Kinase Inhibitor, PCI-32765 (Ibrutinib), in Combination With Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Patients With Newly Diagnosed Non-Germinal Center B-Cell Subtype of Diffuse Large B-Cell Lymphoma).[6] However none of these targeted agents have led to a significant benefit in outcomes. The recent POLARIX trial (A Study Comparing the Efficacy and Safety of Polatuzumab Vedotin With Rituximab-Cyclophosphamide, Doxorubicin, and Prednisone [R-CHP] Versus Rituximab-Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone [R-CHOP] in Participants With Diffuse Large B-Cell Lymphoma), however, was a landmark phase III trial comparing polatuzumab vedotin in combination with chemoimmunotherapy (pola-R-CHP) to R-CHOP that demonstrated a 6.5% benefit in progression-free survival (PFS) at 2 years with pola-R-CHP, without an increase in toxicity. Pola-R-CHP is now approved as standard frontline treatment for DLBCL in Europe and awaiting Food and Drug Administration approval in the United States.[7]

Given the limited success of intensification of R-CHOP with the addition of targeted agents in improving outcomes of patients with high-risk clinical and molecular features, da-R-EPOCH (dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) emerged as a new treatment backbone specifically for high-risk DLBCL cohorts such as high grade B-cell lymphoma with double-hit or triple-hit lymphoma, primary mediastinal B-cell lymphoma, HIV-associated DLBCL, and gray zone lymphoma. The phase III randomized study CALGB 50303 study, however, failed to show improvement in survival outcomes in DLBCL with da-R-EPOCH compared with R-CHOP.[8] Thus for the majority of patients with DLBCL, R-CHOP remains the standard choice of treatment without benefit in intensification of therapy. In patients over 80 years of age, dose reduction of chemoimmunotherapy with R-mini-CHOP has been demonstrated to be safe and effective, with a substantial proportion of elderly/frail patients being cured with this regimen.[9]

CARDIOTOXICITIES ASSOCIATED WITH STANDARD FRONTLINE TREATMENT OF DLBCL. Although anthracyclines are the single most effective component of R-CHOP, the frontline treatment for DLBCL, it is also associated with significant cardiotoxicities especially among those with pre-existing cardiovascular disease (CVD) such as cardiomyopathy.[1]

TABLE 1 Frontline DLBCL Treatment Regimens for Cardiac Frail Patients

First Author	Therapy	N	Age, y	CR, %	PFS	OS	LVEF Change
Moccia et al.[13a]	R-CEOP	81	73 (34-93)	–	5-y TTP 57%	5 y 49%	
Fields et al.[16a]	R-GCVP	62	76.5 (52-90)	38.7	2 y 49.8%	2 y 55.8%	
Herbrecht et al.[17]	R-CPOP	61	68 (38-88)	75	Median PFS not reached	3-y OS 69%	2% with ≥20% declines in EF
Luminari et al.[21]	R-COMP	50	76 (53-90)	56	3 y 38%	3 y 50%	Decline: 6% Median unchanged
Oki et al.[24]	R-COMP	80	69 (61-92)	78	3 y 60%	3 y 74%	Decline: 14% Median unchanged
Corazzelli et al.[25]	R-COMP	41	73 (62-82)	68	4 y 77%	4 y 67%	Decline: 32% Median unchanged
Laribi et al.[18]	R-CVP	43	83 (80-93)	37.2	Median 11.2 mo	2 y 31.9%	–

[a]Preferred treatment options.

CR = complete remission; DLBCL = diffuse large B-cell lymphoma; EF = ejection fraction; LVEF = left ventricular ejection fraction; OS = overall survival; PFS = progression-free survival; R-CEOP = rituximab-cyclophosphamide-etoposide-vincristine-prednisone; R-COMP = rituximab, cyclophosphamide, nonpegylated liposomal doxorubicin, vincristine, and prednisone; R-CPOP = rituximab, cyclophosphamide, pixantrone, vincristine, and prednisone; R-CVP = rituximab, cyclophosphamide, vincristine, and prednisone; R-GCVP = rituximab-gemcitabine-cyclophosphamide-vincristine-prednisone; TTP = time to progression.

Anthracycline-induced cardiotoxicity is generally dose-dependent, seen especially at doxorubicin dosages >250 mg/m^2.[10] It is recommended that the cumulative, lifetime dose of doxorubicin not exceed 400 mg/m^2.[11] Beyond the cumulative doses, several studies have investigated risk factors associated with doxorubicin-induced cardiotoxicity. A SEER (Surveillance, Epidemiology, and End Results) database study demonstrated that doxorubicin was associated with a 29% increase in risk of heart failure, and the risk was associated, not only with the exposure to the agent, but also with increasing age, prior heart disease, comorbidities, diabetes, and hypertension.[1] Another large retrospective study of newly diagnosed DLBCL patients demonstrated a 1-year and 3-year cumulative incidence of 9.7% and 14.7% cardiovascular events, respectively. Multivariable analysis revealed age >60 years, BMI >30 kg/m^2, and history of chronic renal failure as significant risk factors for developing cardiovascular events.[12] The majority of cardiac complications occur early within 1 year of diagnosis and treatment, and have a significant effect on long-term survival.[12] The challenge with DLBCL management is that it primarily affects older patients with a median onset of 70 years, but older patients and patients with underlying cardiac comorbidities are at highest risk of developing toxicities with anthracycline-containing therapy.

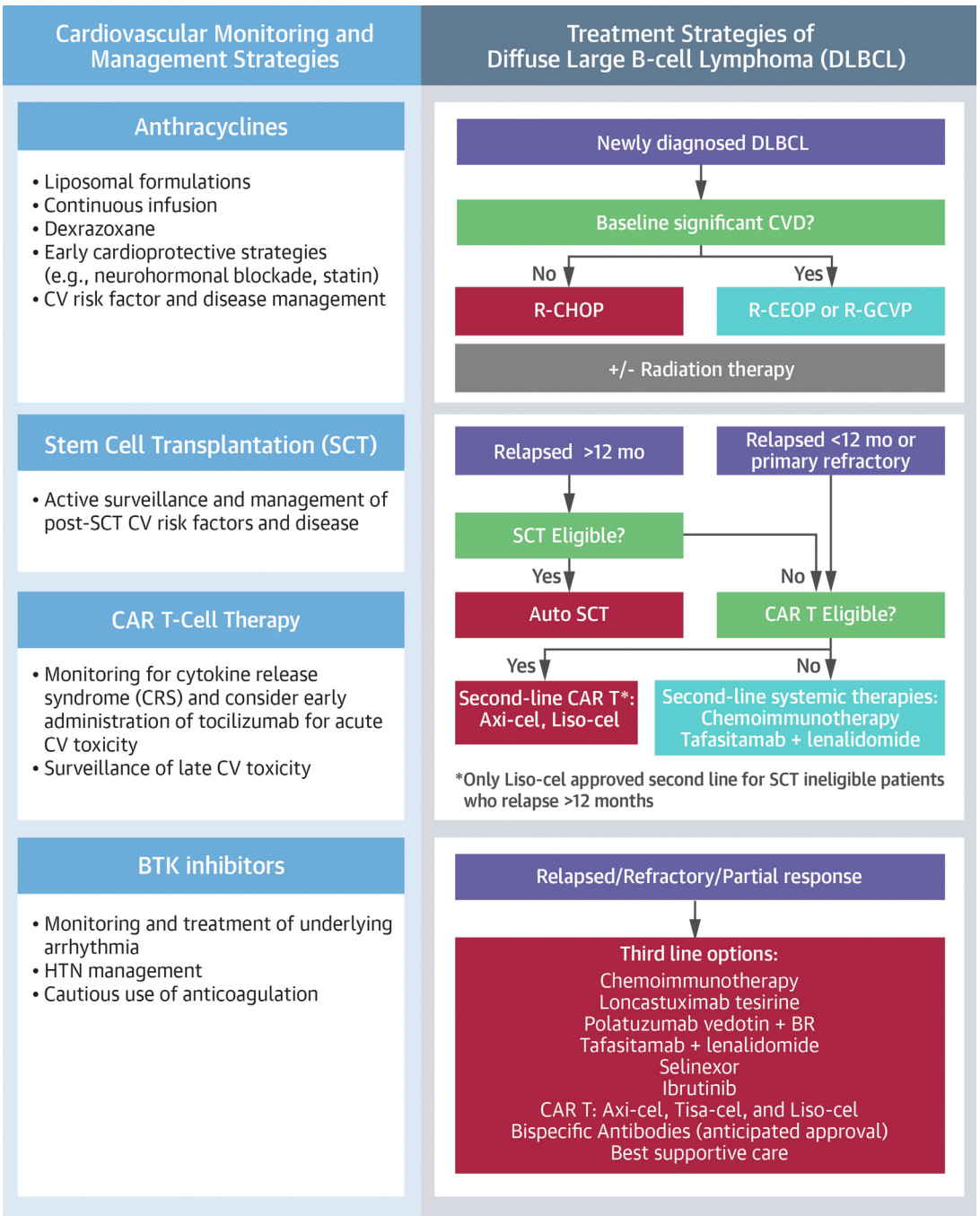
NON-ANTHRACYCLINE-CONTAINING FRONTLINE TREATMENT OPTIONS FOR DLBCL. Upon clinical evaluations, some patients may be deemed to be at too high risk for anthracycline-based therapies; patients with pre-existing heart failure with reduced ejection fraction, patients with a decline in left ventricular ejection fraction (LVEF) >10% following cancer treatment, and any patients with active heart failure symptoms and/or need for heart failure therapy. There are several frontline treatment options that have been developed for DLBCL patients with underlying cardiac comorbidities and contraindications to receiving anthracyclines (Table 1) that involve substituting doxorubicin in R-CHOP with an alternative, less-toxic chemotherapeutic agent such as etoposide (R-CEOP) or gemcitabine (R-GCVP). R-CEOP has been demonstrated to be a useful frontline treatment alternative with curative potential in DLBCL, though most studies have shown it is not as effective as R-CHOP. A recent study evaluated the 10-year outcomes of frontline R-CEOP in DLBCL patients with contraindications to receiving an anthracycline-containing regimen. Outcomes in patients treated with R-CEOP were compared with a 2:1 case-matched (age, stage, and international prognostic index score) control group treated with R-CHOP. This study demonstrated that although time to progression and disease-specific survival were not statistically significantly different between R-CEOP and R-CHOP, the 10-year overall survival was lower in the R-CEOP group (30% vs 49%; $P = 0.002$).[13] Deaths due to toxicity were similar between the groups (4% in each cohort). Over a median follow-up of >12 years, there appears to be a plateau on the R-CEOP disease-specific survival curve, suggesting curative potential with this non-anthracycline-based regimen.[13] A multicenter "real-world" study demonstrated that R-CEOP had significantly inferior 4-year PFS, overall survival (OS), and disease-specific survival compared with R-CHOP (32% vs 52%, 39% vs 59%, and 48% vs 69% respectively).[14] Another retrospective study of elderly DLBCL patients demonstrated that patients who receive R-CHOP or R-EPOCH had significantly longer 3-year failure-free survival than those who

received R-CEOP or R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone), with 3-year failure-free survival rates of 63% for R-CHOP, 74% for R-EPOCH, and 23% for R-CEOP or R-CVP, with the limitation that patients in the R-CEOP or R-CVP cohorts had worse performance status and a higher comorbidity index.[15] These studies suggest that substituting doxorubicin with etoposide may result in poorer long-term survival, but a sizable minority of patients appear to experience durable remission. These studies also reflect the impact of underlying comorbidities and frailty on response to treatment in DLBCL. Substituting doxorubicin with gemcitabine in DLBCL patients with underlying cardiac comorbidities has also been studied in a phase II multicenter trial of R-GCVP. With a median follow-up of 25 months in 61 patients, R-GCVP yielded an overall response rate (ORR) of 61.3%, 2-year PFS of 49.8%, and 2-year OS of 55.8%.[16] Fifty-six percent of patients experienced grade ≥3 hematologic toxicity. There were 15 cardiac events, of which 7 were grade 1 to 2, 5 were grade 3 to 4, and 3 were fatal, reflecting the poor cardiac status of the study population.[16] Another option for patients with cardiac comorbidities is substitution of doxorubicin with pixantrone, an azaanthracenedione (R-CPOP). A study assessing safety and efficacy of R-CPOP compared with R-CHOP demonstrated moderately lower response rates (75% vs 84%) but similar PFS and event-free survival and fewer cardiac events.[17]

Simply omitting doxorubicin is not as effective from an oncologic standpoint. A retrospective study evaluating the efficacy of omitting doxorubicin and using R-CVP as frontline treatment demonstrated safety and efficacy of this regimen in elderly, frail patients with contraindications to anthracycline. However, this regimen has poor outcomes compared with those historically seen with R-CHOP, with an ORR of 58.1%, 2-year OS rate of 59%, and median OS of 12.6 months, and is considered a palliative therapy option.[18] Studies have also investigated the role of bendamustine and rituximab (BR) in frontline setting for patients not eligible for R-CHOP, and although BR can induce high response rates, the OS rates are generally low, rendering this a palliative treatment.[19,20] The role of nonpegylated liposomal doxorubicin in place of conventional doxorubicin in standard R-CHOP (R-COMP) has also been assessed.[21-25] A randomized phase III trial comparing R-COMP to standard R-CHOP in patients with newly diagnosed DLBCL and normal cardiac function suggested significant differences in LVEF <50% in the R-COMP arm (4.6%) compared with the R-CHOP arm (15.8%) ($P < 0.001$) at the beginning of treatment cycles vs 4 to 8 weeks after the last cycle. Additionally, there were fewer elevations in NT-proBNP with R-COMP ($P = 0.013$). Clinical heart failure at the end of treatment was not statistically different between the 2 groups, but was numerically greater with R-CHOP (17.5% in R-COMP vs 30.8% in R-CHOP; $P = 0.6$).[22] Dose-reduced R-CHOP (R-mini-CHOP) is a commonly used regimen for patients who are too frail for R-CHOP, but is still not typically recommended in patients with cardiac conditions posing a contraindication to anthracyclines.[9]

STRATEGIES TO MITIGATE CARDIOTOXICITY AMONG DLBCL PATIENTS UNDERGOING FRONTLINE THERAPIES. In a recent study leveraging longitudinal data from the SEER-Medicare registry from 1999 to 2016, Upshaw et al[26] reported that pre-existing heart failure was common (13.9%) among patients with DLBCL and those with preexisting heart failure were less likely to be treated with an anthracycline (OR: 0.55; 95% CI: 0.49-0.61) with higher lymphoma-related mortality, emphasizing the importance of cardiovascular risk management and effective lymphoma treatment. For treatment-naive DLBCL patients with underlying cardiac concerns (eg, preexisting heart failure), there are several ways to mitigate cardiovascular risk related to anthracycline administration.[27-29] These include using a dose-reduced regimen (eg, R-mini-CHOP), liposomal formulation of doxorubicin (doxil) to reduce myocardial drug accumulation,[30] infusional anthracycline (continuous/slow intravenous infusion instead of bolus infusion),[31] and finally, concomitant administration of dexrazoxane, which may provide cardioprotection through several suggested mechanisms, most notably via the inhibition of doxorubicin-topoisomerase-IIβ interaction and the chelation of iron, thereby decreasing cytosolic iron accumulation.[29] Available meta-analyses of studies comparing liposomal vs nonliposomal doxorubicin thus far suggest reduced rates of cardiotoxicity associated with liposomal formulations.[32] Similarly, continuous infusion of doxorubicin has been associated with a lower rate of clinical and subclinical cardiotoxicity compared to bolus administration. Regarding dexrazoxane, a recent randomized trial comparing treatment with vs without dexrazoxane in 537 pediatric patients with hematologic malignancies demonstrated that treatment with dexrazoxane conferred significant cardioprotection, as evidenced by a smaller reduction in

FIGURE 1 **Schema Outlining Treatment Strategies for DLBCL and Cardiovascular Considerations**



This figure displays treatment strategies for patients with cardiac dysfunction or significant cardiac comorbidities as well as outlines the cardiac complications of treatments including anthracycline, auto stem cell transplantation (SCT), chimeric antigen receptor T-cell therapy (CAR T), and other therapies in the relapsed setting. CRS = cytokine release syndrome; CV = cardiovascular; CVD = cardiovascular disease; DLBCL = diffuse large B-cell lymphoma; HTN = hypertension; R-CEOP = rituximab-cyclophosphamide-etoposide-vincristine-prednisone; R-CHOP = rituximab-cyclophosphamide-vincristine-doxorubicin-prednisone; R-GCVP = rituximab-gemcitabine-cyclophosphamide-vincristine-prednisone; SCT = stem cell transplantation.

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left ventricular fractional shortening, without a compromise in antitumor efficacy.[33] It is, however, important to note that the current Food and Drug Administration indications for the use of dexrazoxane are only for women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m^2 and who will continue to receive doxorubicin therapy to maintain tumor control.[34] Additionally, there have been small studies that have investigated the cardioprotective effects of neurohormonal modulators such as the use of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, aldosterone antagonists, and β-blockers.[36] These studies, as well as a recent meta-analysis, have shown some benefits of these therapies in preventing declines in LVEF, although there were no statistically significant differences in overt heart failure or other clinical cardiovascular outcomes.[35] Thus far, expert consensus recommends the prophylactic use of angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers and β-blockers as primary prevention in high- and very high-risk patients receiving anthracyclines. If patients develop declines in LVEF, guideline-directed medical therapy for heart failure with reduced ejection fraction should be implemented.[35] Additionally, there has been a recent report of the potential beneficial effects of statins in reducing doxorubicin-related cardiac dysfunction among lymphoma patients. The STOP-CA (Statins to Prevent the Cardiotoxicity From Anthracyclines) trial randomized 300 patients with lymphoma undergoing anthracycline treatment to atorvastatin 40 mg daily treatment vs no atorvastatin treatment for 12 months, those on atorvastatin experienced a significantly lower rate of LVEF decline (≥10% to <55%) compared with placebo (9% vs 22%; $P = 0.002$).[37] Although further validation of such findings is warranted, statins may also provide cardioprotection against doxorubicin in lymphoma patients. Finally, it is critical to involve cardiologists/cardio-oncologists upfront to collaboratively assess cardiovascular risk among lymphoma patients, implement the aforementioned cardioprotective strategies among those deemed to be at high risk, and monitor and manage any cardiovascular complications (**Figure 1**).

CASE PRESENTATION CONTINUED

This patient was treated with R-CEOP × 6 cycles and achieved complete remission but unfortunately developed lymphadenopathy and night sweats a few months later. Positron emission tomography/computed tomography at this time revealed lymphadenopathy in the mediastinal, axillary, and inguinal areas, and lymph node biopsy confirmed relapsed DLBCL.

TREATMENT OPTIONS FOR RELAPSED/REFRACTORY DLBCL. Autologous stem cell transplant and CD19 chimeric antigen receptor T-cell therapy. About one-third of DLBCL patients develop refractory or relapsed (R/R) disease.[38] Standard treatment options for these patients are salvage chemotherapy followed by high-dose chemotherapy with carmustine, etoposide, cytarabine, and melphalan (BEAM) and autologous hematopoietic cell transplantation (auto-SCT) consolidation or chimeric antigen receptor T-cell therapy (CAR-T), which are both associated with sustained remission in a subset of patients. Salvage chemotherapy followed by auto-SCT was traditionally the standard second-line treatment for R/R DLBCL. Unfortunately, one-half of patients are ineligible for transplantation due to an ineffective response to salvage therapy, and another one-half of patients will relapse after auto-SCT. A multicohort retrospective NHL research (SCHOLAR-1) study evaluating outcomes of salvage therapies in R/R DLBCL showed an ORR of 26% (complete remission [CR] 7%) with a median OS of 6.3 months.[39] The CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) study was a phase II multicenter, randomized trial that compared the efficacy of R-ICE or R-DHAP cycles followed by auto-SCT with or without rituximab maintenance in patients with R/R DLBCL. The 48-month OS was 48%. Early relapse and prior exposure to rituximab during first-line treatment were associated with a worse outcome, with an ORR of 46% with the salvage regimen and 2-year PFS of 20%.[40] CD19 CAR-T was historically the standard third-line option based on the pivotal ZUMA-1 (Study Evaluating the Safety and Efficacy of KTE-C19 in Adult Participants With Refractory Aggressive Non-Hodgkin Lymphoma),[41] JULIET (Study of Efficacy and Safety of CTL019 in Adult DLBCL Patients),[42] and TRANSCEND (Study Evaluating the Safety and Pharmacokinetics of JCAR017 in B-cell Non-Hodgkin Lymphoma)[43] trials leading to approval of axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel), and lisocabtagene maraleucel (liso-cel), respectively. The 5-year OS rate from ZUMA-1 was 42.6%, demonstrating curative potential of CD19 CAR-T in a subset of patients.[44] Given the poor outcomes of DLBCL with early relapse and prior exposure to rituximab, 3 pivotal trials ZUMA-7 (Efficacy of Axicabtagene Ciloleucel Compared to Standard of Care Therapy in

Subjects With Relapsed/Refractory Diffuse Large B Cell Lymphoma),[45] BELINDA (Tisagenlecleucel in Adult Patients With Aggressive B-cell Non-Hodgkin Lymphoma),[46] and TRANSFORM (A Study to Compare the Efficacy and Safety of JCAR017 to Standard of Care in Adult Subjects With High-risk, Transplant-eligible Relapsed or Refractory Aggressive B-cell Non-Hodgkin Lymphomas)[47] were conducted to evaluate second-line CD19 CAR-T for patients with primary refractory or relapse within 12 months of initial chemoimmunotherapy. Based on these trials, both lisa-cel and axi-cel were approved in the second-line setting for high-risk DLBCL patients, demonstrating responses in 40% of patients. Based on these results, CD19 CAR-T has now become the standard second-line treatment for high-risk DLBCL patients with primary refractory and/or early relapse disease. For patients with late relapse, standard treatment is salvage chemotherapy followed by auto-SCT. For frail, transplant-ineligible patients with late relapse, second-line liso-cel has become the treatment of choice based on the phase II PILOT (Lisocabtagene maraleucel as second-line therapy in adults with relapsed or refractory large B-cell lymphoma who were not intended for hematopoietic stem cell transplantation) study.[48]

Cardiotoxicities and cardiovascular optimization of auto-SCT and CD19 CAR-T. However, both auto-SCT and CD19 CAR-T are associated with potential cardiotoxicities. The high-dose chemotherapy administered with SCT is associated with significant risk of developing CVD, such as heart failure and accelerated coronary artery disease, and late morbidity and mortality.[49-51] Notably, the risk of CVD-related mortality among SCT survivors is more than twice that of the general population. As such, the ability to predict who is at risk for developing CVD is critical in managing patients after SCT. Armenian et al[50] has recently published a CVD risk score for those treated with SCT and free of clinically evident CVD 1-year post-SCT. Risk scores included age, anthracycline dose, chest radiation, hypertension, diabetes, and smoking. Patients in the high-risk group were at a 7.8-fold risk of developing CVD compared with those considered at low risk.

More recently, there have been increasing reports of cardiovascular events also associated with CD19-directed CAR-T therapy including hypotension, pulmonary edema, heart failure, arrythmia, and cardiac arrest.[52-56] Acute cardiotoxicity occurs mostly in the context of cytokine release syndrome (CRS), which is caused by surge in cytokines due to the activation of immune cells themselves as well as the resultant tumor-cell lysis. The rate of cardiotoxicity generally correlates with the severity of CRS,[54] and a recent study showed lower rates of cardiotoxicity when there was a shorter time between the start of CRS and the administration of IL-6 inhibitor tocilizumab. More recently, a study found that the cumulative incidence for major cardiac events was 17% at 30 days, 19% at 6 months, and 21% at 12 months following CD19 CAR-T infusion, suggestive of not only immediate but also a longer-term risk of cardiovascular events with CAR-T.[57] Similarly, based on a multicenter registry of 202 patients receiving anti-CD19 CAR-T, Mahmood et al[55] reported that 16.3% (33/202) of the patients suffered from severe cardiovascular events defined as a composite of heart failure, cardiogenic shock, or myocardial infarction. A study by Alvi et al[58] reported that an elevated troponin post-CAR T was associated with an increased risk for cardiovascular complications. In summary, relapsed DLBCL patients with significant cardiovascular comorbidities would benefit from cardiac consultation and comanagement by cardiologists/cardio-oncologists to further assess cardiac risk and determine eligibility for intensive therapies such as auto-SCT and CAR-T-cell therapy. Additionally, continued efforts to identify at-risk cohorts as well as to strategies to minimize cardiovascular risk are warranted.

OTHER NOVEL TREATMENT OPTIONS AND THEIR CARDIOTOXICITIES. There are a variety of targeted agents and immunotherapy options for R/R DLBCL that could be considered for transplant-ineligible or CAR T-ineligible patients with underlying cardiac comorbidities (**Table 2**). Loncastuximab tesirine (Lonca), an antibody drug conjugate targeting CD19, has demonstrated efficacy with an ORR of 48.3%, CR rate of 24.1%, and median duration of response of 10.3 months.[59] Serious adverse events (AEs) occurred in 28% of patients, with those occurring in ≥2% being febrile neutropenia, pneumonia, edema, pleural effusion, and sepsis.[59] Given the risk for edema and pleural effusions, loncastuximab tesirine should be used cautiously in patients with underlying cardiac issues. Polatuzumab vedotin (Pola), an antibody drug conjugate targeting CD79b, in combination with BR has also been approved for R/R DLBCL in transplant-ineligible patients with a CR rate of 40% and median PFS of 9.5 months and median OS of 12.4 months. Main treatment-related AEs with this combination include cytopenias and peripheral neuropathy.[60] Tafasitamab, a monoclonal antibody targeting CD19, in combination with lenalidomide has also demonstrated a CR rate of 43% in transplant-ineligible patients, with the most common toxicity being cytopenias. However, it is important to note that serious AEs did occur in 51% of

TABLE 2 Cardiotoxicities of DLBCL Therapies

Treatment Regimen	Cardiovascular Toxicities
R-CHOP	Any cardiotoxicity (21%-45%), symptomatic heart failure (13%), cardiovascular death (2%)[1,3]
CD19 CAR T	Cardiomyopathy (10%), clinical heart failure (6%), myocardial infarction (5%)[57,58,76]
Hematopoietic stem cell transplant	Cumulative incidence of cardiovascular disease (8%), heart failure (4%), myocardial infarction (0.9%), coronary artery stenosis (1%)[50]
Loncastuximab tesirine	Hypertension (5%), hypotension (8%), QT prolongation (4%), pericardial effusion (3%), myocardial infarction (1%)[59]
Polatuzumab vedotin-bendamustine-rituximab	None reported[60]
Tafasitamab-lenalidomide	Peripheral edema (22%), hypertension (9%), atrial fibrillation (4%), syncope (3%), heart failure (2%), atrial flutter (1%), cardiac failure (1%), myocardial ischemia (1%), myositis (1%)[61]
Selinexor	Hypotension (13%), peripheral edema (12%), dyspnea (12%)[77]
Ibrutinib	Hypertension (78%), atrial fibrillation (13%), any cardiac arrhythmias (up to 20%)[78,79]
Bispecifics	Hypotension (24%-31%), tachycardia (16%-21%), atrial fibrillation (5%)[68,69]

CAR T = chimeric antigen receptor T-cell; other abbreviations as in Table 1.

patients, with those occurring in ≥2% being pneumonia, febrile neutropenia, pulmonary embolism, bronchitis, atrial fibrillation, and heart failure.[61] Selinexor, a selective inhibitor of XPO-1 nuclear export, was also approved in R/R DLBCL based on an ORR of 28% with the most common grade 3 to 4 AEs being cytopenias, fatigue, hyponatremia, and nausea, and most common serious AEs being pyrexia, pneumonia, and sepsis.[62] Other targeted therapy options include bruton tyrosine kinase inhibitors (BTKi) such as ibrutinib, an inhibitor of B-cell receptor signaling, that shows particular activity in non-GCB DLBCL, with an ORR of 37%. However, ibrutinib has been associated with significant cardiotoxicities including increased bleeding, hypertension, atrial fibrillation, and ventricular arrhythmia.[63] Although second-generation BTKi, such as acalabrutinib and zanubrutinib, appear to have an improved cardiovascular safety profile for the treatment of chronic lymphocytic leukemia, it remains unknown how safe they are from a cardiovascular perspective in treating relapsed lymphoma patients.[64] Finally, lenalidomide, an immunomodulatory agent, used as monotherapy or in combination with rituximab, is also well-tolerated with minimal cardiotoxicities and with efficacy in R/R DLBCL.[65] Although all of these treatment options have demonstrated efficacy in R/R DLBCL, most patients will not achieve a durable remission.

There are several ongoing clinical trials evaluating the role of novel therapies in DLBCL. Bispecific T-cell engagers are a new class of immunotherapy that enhances the patients' immune cells to attack tumors by retargeting T-cells (engaged by CD3) to tumor cells (engaged by CD20). Several bispecific antibodies are currently being investigated in DLBCL, including mosunetuzumab,[66] glofitamab,[67] epcoritamab,[68] and odronextamab.[69] Each of these agents has demonstrated promising early data, including in heavily pretreated patients who have progressed after CAR-T therapy. Bispecifics have a favorable toxicity profile when compared with CAR-T therapy, with lower rates of CRS and neurotoxicity, thus warranting further study in patients with underlying cardiac comorbidities. Ongoing trials are also evaluating novel combinations of targeted agents, chemotherapy with targeted agents, and bispecific antibodies with targeted agents.

While the role of allogeneic stem cell transplantation (allo-SCT) for R/R DLBCL has diminished in the modern era with the advent of variety of novel therapies, allo-SCT remains an important option for patients with multiple relapses of disease given the cytoreductive effect of conditioning regimen and graft-vs-lymphoma effect. Allo-SCT is associated with a high risk of mortality, with causes of death including relapse, infection, acute graft vs host disease, CVD, and multiorgan failure.[70,71]

RADIATION THERAPY. Radiation therapy has a role in DLBCL both in the frontline setting for patients with limited stage disease or bulky disease as consolidation, and in the relapsed setting as salvage therapy or bridging therapy for patients with localized symptoms or bulky disease at a focal site.[72] Cardiotoxicity is a side effect of radiation therapy particularly when delivered to the thoracic region. Cardiovascular side effects of radiation include short-term side effects such as pericarditis and pericardiac effusions, as well as long-term side effects including coronary artery disease, arrythmias, cardiomyopathy, valvular dysfunction, and heart failure.[73-75] Risk factors that increase the likelihood of radiation-induced

cardiovascular toxicity including higher doses of radiation, exposure to cardiotoxic chemotherapy, and presence of pre-existing CVD.[74]

CASE PRESENTATION CONTINUED

The patient was treated with medical therapy to optimize cardiac function and underwent CD19 CAR-T therapy with lisocabtagene maraleucel. He achieved complete remission 1 month post-CAR T but unfortunately 3 months later developed axillary lymphadenopathy with biopsy proven relapse. He is currently on single-agent loncastuximab tesirine.

CONCLUSIONS

DLBCL is a curable, but aggressive NHL. Current standard treatments carry a clinical risk of cardiovascular complications. Most DLBCL patients are older that 60 years of age and many have pre-existing cardiac comorbidities. These patients may require treatment modification and alternative treatment options with the goal of optimizing efficacy while minimizing cardiotoxicity. In the frontline setting, options for these patients include omitting or substituting doxorubicin for alternative agents that are less cardiotoxic while implementing cardioprotective therapies such as neurohormonal modulators and/or statins in collaboration with cardiologists. In the relapsed setting, auto-SCT and CD19 CAR-T are standard treatment options with curative potential but can be associated with cardiotoxicities, which therefore require careful cardiovascular risk assessment before the therapy as well as close monitoring and surveillance following the therapy. In the recent era, novel immune therapies and targeted therapies have emerged in recent years that are less toxic than intensive therapies such as auto-SCT and CAR-T therapy. These alternate treatment options, however, are not thought to be curative at this time, and long-term durability of responses remains to be seen. Hence, developing improved treatments for the DLBCL patients with cardiac conditions both in the frontline and relapsed setting is a significant unmet need. A multidisciplinary approach between cardiologists and oncologists is paramount in addressing reversible cardiac risk factors for DLBCL patients, medical optimization, and monitoring cardiotoxicities of these treatments. In DLBCL patients with cardiovascular risk factors, upfront cardiology involvement and management of cardiac risk factors and CVD in conjunction with oncology to maximize successful outcomes and minimize DLBCL treatment toxicity is critically important.

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