

STATE-OF-THE-ART REVIEW

Cardiovascular and Oncologic Considerations in Adult Hodgkin Lymphoma



JACC: CardioOncology State-of the-Art Review

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ABSTRACT

Classic Hodgkin lymphoma is a highly curable lymphoma that affects primarily younger patients. The therapeutic landscape has evolved and generally consists of varying combinations of chemotherapy and immunotherapy as well as radiation in selected cases. Although most patients are cured of their lymphoma, there is a risk for late treatment-related cardiotoxicity that affects long-term survival and quality of life in this population. Careful consideration of baseline cardiac function and risk factors should be undertaken prior to proceeding with anthracycline-based therapies or thoracic radiation, as adjuvant cardiac-focused efforts may serve to mitigate the risk for cardiovascular dysfunction in this population. This review outlines the evidence supporting current recommendations for assessing baseline cardiotoxicity risk, implementing risk reduction strategies and treatment modifications, the role of multidisciplinary evaluation in high-risk patients, and strategies for long-term cardiac monitoring to minimize treatment-related cardiac morbidity and mortality. (JACC CardioOncol. 2025;7:781-799) © 2025 The Authors. 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/>).

Classic Hodgkin lymphoma (cHL) is a lymphoid neoplasm arising from B cells that represents approximately 10% to 15% of lymphomas. It is associated with a bimodal age distribution, with most patients diagnosed at 20 to 30 years and older than 55 years.¹ Up to 80% of patients with cHL can now be cured in the frontline setting, in part because of recent advances incorporating novel therapies and improved radiation

techniques with a standard chemotherapy backbone. Given the young age of most patients at diagnosis, late treatment-related toxicities must be considered alongside therapeutic efficacy. Notably, cardiovascular (CV) complications related to cHL treatment are relatively common and remain a leading cause of death in cHL survivors.² Older patients diagnosed with cHL are particularly at risk given the increased prevalence of pre-existing heart failure (HF) and

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ABBREVIATIONS AND ACRONYMS

ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine

ABVE = doxorubicin, bleomycin, vinristine, and etoposide

ASCT = autologous stem cell transplantation

AVD = doxorubicin, vinblastine, and dacarbazine

BrECADD = brentuximab-vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone

BV = brentuximab-vedotin

cHL = classic Hodgkin lymphoma

CMT = combined modality treatment

CT = computed tomography

CV = cardiovascular

GVD = gemcitabine, vinorelbine, and liposomal doxorubicin

GVHD = graft-vs-host disease

HF = heart failure

HL = Hodgkin lymphoma

ICI = immune checkpoint inhibitor

LVEF = left ventricular ejection fraction

MHD = mean heart dose

N-AVD = nivolumab, doxorubicin, vinblastine, and dacarbazine

PET = positron emission tomography

PFS = progression-free survival

R/R = relapsed or refractory

RT = radiation therapy

SCT = stem cell transplantation

other cardiac comorbidities. As such, all cHL patients benefit from careful pretreatment evaluation, therapy selection, and post-treatment monitoring, often in a multidisciplinary setting, to limit these toxicities. Here we review the important cardio-oncologic considerations and strategies to mitigate CV complications in the context of the modern treatment paradigm for adult patients with cHL.

CASE PRESENTATION

A 26-year-old man with mild cerebral palsy presented to his primary care physician with a persistent cough lasting longer than 1 month with drenching night sweats that were increasing in frequency. Chest computed tomography (CT) revealed a large lobulated mass in the right perihilar region >10 cm in size along the transverse axis. Biopsy revealed cHL, nodular sclerosis subtype. Fluorine-18 fluorodeoxyglucose positron emission tomography (PET)/CT revealed fluorodeoxyglucose-avid disease in the mediastinum and bilateral axillary lymphadenopathy with no other sites of disease. Laboratory studies were notable for an erythrocyte sedimentation rate of 60 mm/h and mild lymphopenia. In the setting of his bulky mediastinal involvement, B symptoms, and elevated erythrocyte sedimentation rate, the patient was diagnosed with Lugano classification stage IIB disease³ with an unfavorable prognosis on the basis of both the German Hodgkin Study Group and the European Organization for Research and Therapy in Cancer classification criteria.⁴ The patient's Eastern Cooperative Oncology Group performance status was 0.

STANDARD FRONTLINE TREATMENT OPTIONS FOR cHL

The standard approach to curative treatment for adults with cHL is determined by the extent of disease involvement, prognostic clinical characteristics, and underlying comorbidities. The primary consideration in therapy selection is the presence of early-stage (stages I and II; lymph nodes localized to one side of the diaphragm) or advanced-stage (stages III and IV) disease as determined using the Lugano staging system.³ The commonly used frontline treatment regimens are outlined in Table 1 and discussed in further detail as follows.

HIGHLIGHTS

- Most cHL patients can be cured with anthracycline-based regimens ± RT.
- cHL mostly affects younger patients and treatment-related cardiotoxicity is a risk.
- Pretreatment evaluation and optimization of cardiovascular risk factors are crucial.
- Post-treatment echocardiography is recommended in patients receiving anthracyclines.

EARLY-STAGE DISEASE. Outcomes in early-stage cHL are generally excellent, and clinical and laboratory characteristics are used to risk stratify patients with favorable and unfavorable disease. Although there are multiple risk stratification systems for early-stage cHL, all incorporate the presence of bulky mediastinal disease, B symptoms, elevated erythrocyte sedimentation rate, and number of nodal groups.^{5,6} Therapeutic options for patients with early-stage cHL require balancing long-term disease control with possible treatment-related complications, including but not limited to cardiotoxicity, pulmonary disease, and secondary malignancies.^{1,7}

Historically, combined modality treatment (CMT) with both radiation therapy (RT) and chemotherapy consisting of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) has been the preferred approach for early-stage cHL, with 5-year event-free survival rates >90%.^{8,9} Although CMT is highly effective in treating patients with cHL, late treatment effects related to radiation remain a key consideration in treatment selection.^{1,10} The decision to omit RT is nuanced and often influenced by several patient-specific factors. Generally, RT is avoided in young patients and those with CV risk factors who have disease in the chest given the increased risk for late cardiac toxicity.¹¹ In addition, RT is associated with increased risk for secondary malignancies including breast cancers in women treated younger than 30 to 35 years.^{7,12} Although CMT yields superior progression-free survival (PFS) compared with ABVD alone, studies have not yet demonstrated a difference in overall survival, in part because of these late toxicities.⁷

Encouragingly, RT techniques have significantly evolved since the era of mantle-field radiation, which exposed cardiac and chest wall tissue to high doses, with mean heart doses (MHDs) that could be >30 Gy (Figure 1).¹³ Improvements in radiation targeting

TABLE 1 Frontline Treatment Regimens for Hodgkin Lymphoma

Study	Stage	Systemic Therapy	Radiation	Efficacy	Cardiac Events
HD10 ⁹	Early favorable	ABVD × 2	20 Gy	10-y PFS 87.2%	1% cardiac-related mortality
H10F ¹⁸	Early favorable	ABVD × 3	30 Gy	10-y PFS 98.8%	4.6% long-term toxicity
H10U ¹⁸	Early unfavorable	ABVD × 4	30 Gy	10-y PFS 91.4%	12.7% long-term toxicity
RATHL ¹²⁹	Early unfavorable	AVD or ABVD × 6	None	7-y PFS 84.7%	1% cardiac-related mortality
ECHELON-1 ²⁶	Advanced	BV-AVD × 6	None	7-y PFS 82.3%	None reported
S1826 ²⁹	Advanced	N-AVD × 6	None	2-y PFS 92%	2.4% any cardiac events
HD21 ²⁸	Advanced	BrECADD × 4-6	None	4-y PFS 94.3%	1% grade ≥3 cardiac events

All listed regimens are included in current National Comprehensive Cancer Network guidelines.
 ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; AVD = doxorubicin, vinblastine, and dacarbazine; BV = brentuximab-vedotin; BrECADD = brentuximab-vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; ECHELON-1 = A Frontline Therapy Trial in Participants With Advanced Classical Hodgkin Lymphoma; PFS = progression-free survival; RATHL = Risk-Adapted Therapy in Hodgkin Lymphoma.

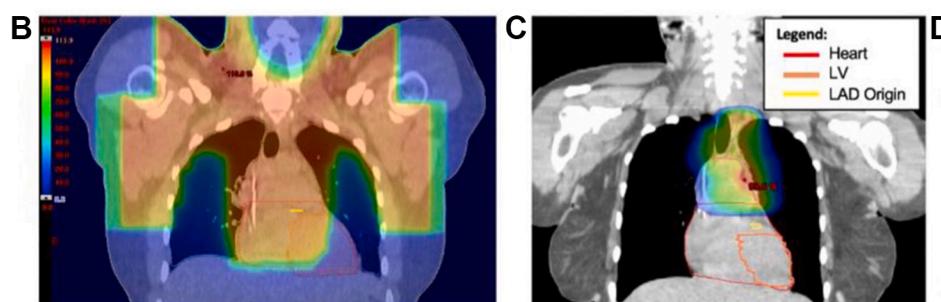
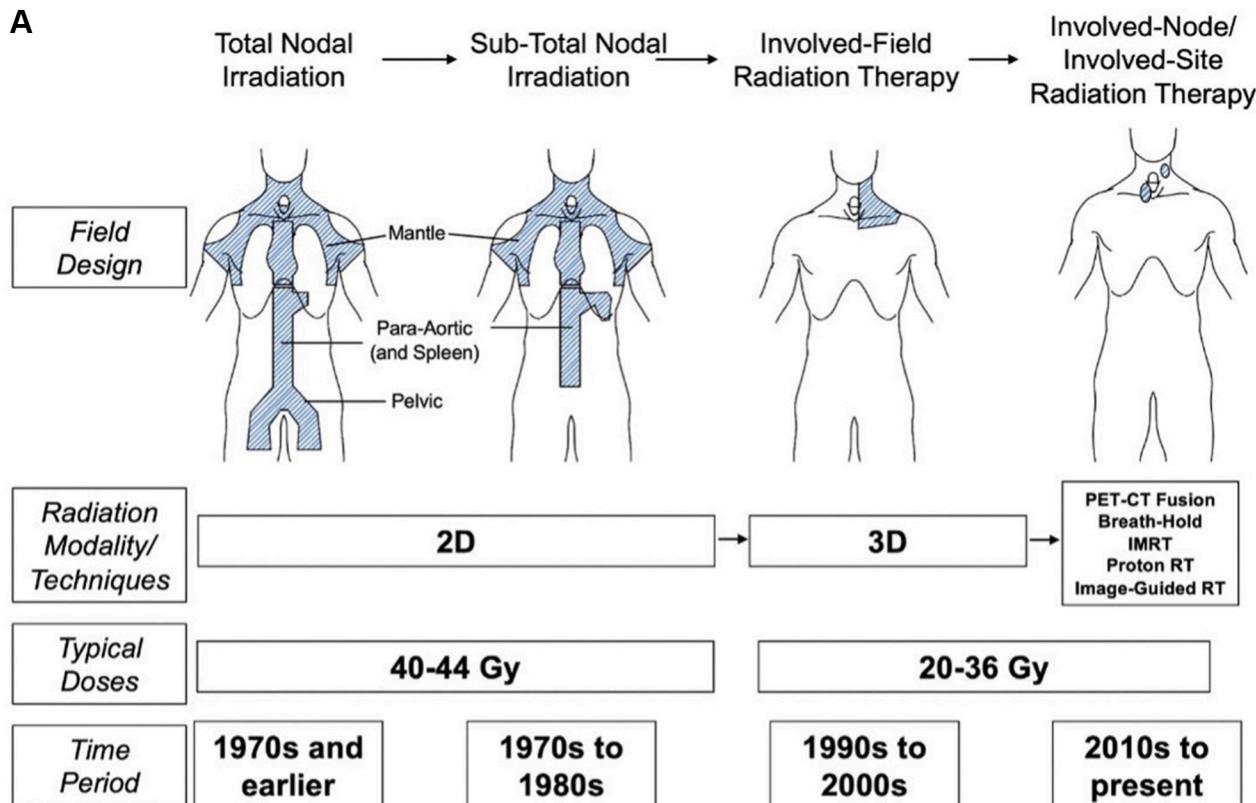
through involved node/site RT, daily image guidance, and breath-hold and respiratory gating techniques in conjunction with newer modalities such as 3-dimensional conformal therapy, intensity-modulated RT, and/or proton therapy have shown promise in sparing normal tissue while maintaining therapeutic doses to target regions.^{14,15} Indeed, in the modern era, the estimated MHD during CMT therapy has fallen to <10 Gy.^{13,14} However, although newer radiation techniques offer greater precision and reduce exposure to normal tissues, their long-term toxicity remains unclear.¹⁶

In patients who are not ideal candidates for CMT, the incorporation of interim PET/CT allows the identification of patients who are likely to experience long-term remission with chemotherapy alone. Recent clinical trials have tested these response adapted strategies using PET/CT after 2 cycles of therapy, assigning patients with negative findings to chemotherapy alone and including radiation with or without intensified systemic therapy in those with positive results.¹⁷⁻²⁰ However, without RT, the RAPID (PET Scan in Planning Treatment in Patients Undergoing Combination Chemotherapy For Stage IA or Stage IIA Hodgkin Lymphoma) trial demonstrated that an abridged chemotherapy course led to inferior PFS compared with CMT, underscoring the need to consider additional chemotherapy even after negative results on interim PET/CT after 2 cycles of therapy.²⁰

Advances in the understanding of the unique biology of cHL have spurred investigation of targeted systemic therapies in combination with conventional chemotherapy to improve outcomes and further reduce the likelihood of therapy-related toxicity. The characteristic CD30 expression on Hodgkin and Reed-Sternberg cells led to the development of brentuximab-vedotin (BV), an anti-CD30 antibody-drug conjugate. Additionally, Hodgkin and Reed-

Sternberg cells frequently express PD-L1 through genomic amplification of the 9p24.1 locus and constitutive JAK-STAT activation, providing therapeutic rationale for the incorporation of checkpoint inhibition in cHL.²¹ These novel targeted therapies, which are discussed in further detail later, have not yet fully supplanted ABVD in frontline treatment of early-stage cHL; however, there are several ongoing trials examining their efficacy in this space, with preliminary data leading to the inclusion of these agents in national guidelines ahead of U.S. Food and Drug Administration approval.²²⁻²⁴ Of note, the ongoing AHOD2131 (A Study to Compare Standard Therapy to Treat Hodgkin Lymphoma to the Use of Two Drugs, Brentuximab Vedotin and Nivolumab) phase III trial investigating the addition of BV and PD-1 blockade compared with standard chemotherapy in early PET-negative patients and CMT in PET-positive patients will likely provide further clarity on the role of targeted therapies in early-stage cHL.²²

ADVANCED-STAGE DISEASE. In contrast to early-stage disease, radiation is typically not used in advanced-stage cHL given the extent of disease involvement with the rare exception of localized residual disease after the completion of systemic therapy. Although treatment with ABVD for 6 cycles was the gold standard for more than 2 decades in North America,²⁵ the relatively recent incorporation of novel therapeutic agents has supplanted this regimen in the frontline setting. The addition of BV to doxorubicin, vinblastine, and dacarbazine (AVD) in patients with advanced-stage cHL improved 6-year overall survival from 89% to 93% compared with ABVD in the ECHELON-1 (A Frontline Therapy Trial in Participants With Advanced Classical Hodgkin Lymphoma) trial.²⁶ Although the German Hodgkin Study Group had previously established the efficacy of

FIGURE 1 Evolution of RT in HL

(A) Schematic representation of field design, radiation therapy (RT) doses, and radiation techniques for adult Hodgkin lymphoma (HL) as they have evolved over time. (B, C) RT plan comparison of an HL patient treated with involved-site RT to the mediastinum including color wash dose distribution. Recreated historical mantle field (B), anterior-posterior technique, treated to a dose of 40 Gy, vs involved-site RT using intensity-modulated radiation therapy (IMRT) (C), with deep-inspiration breath hold (note expansion of lungs and elongation of mediastinal structures, displacing lungs and heart away from target volume) with arms down on inclined board (further displacement of heart inferiorly), treated to 30 Gy with a 6-Gy boost to a level 5 node. (D) Dosimetric comparison of plans in (B) and (C). CT = computed tomography; LAD = left anterior descending coronary artery; LV = left ventricular; PET = positron emission tomography. Adapted with permission from Bergom et al.¹⁴

escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone,²⁷ a regimen used in patients younger than 60 years in Europe, the HD21 trial demonstrated an improvement in efficacy and a reduction in toxicity with the addition of BV to etoposide,

cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone (BrECADD) in comparison with escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone, with 4-year PFS of 94%.²⁸ Recently, the Southwest Oncology Group S1826 trial compared the

TABLE 2 Summary of Cardiovascular Effects of Hodgkin Lymphoma Therapies

Agent	Cardiovascular Effects	Estimated Incidence	Risk Modifiers
Anthracyclines	Heart failure ^a	1%-10%	Patient factors: older age, LVEF < 55%, CAD, valve disease (moderate or greater), HTN, DM, obesity Therapy factors: lifetime cumulative dose and combination with thoracic radiation
	Atrial/ventricular arrhythmias	1%-5%	
Immune checkpoint inhibitors	Myocarditis	~1%	Combination therapy with CTLA-4 and PD-1/PD-L1
	Heart failure	1%-5%	
	Atrial/ventricular arrhythmias	1%-5%	
	Pericarditis	<1%	
	Accelerated CAD	Unknown	
Thoracic radiation	Vasculitis	<1%	Patient factors: tobacco use, HTN, DM Therapy factors: radiation doses to the heart and cardiac substructures Combination anthracycline and thoracic radiation
	Atrial arrhythmias	5%-10%	
	Heart failure ^a	1%-10%	
	Pericarditis/pericardial effusion	1%-5%	
	Coronary artery disease ^a	1%-10%	
Autologous SCT	Valvular disease ^a	1%-10%	Patient factors: HTN, DM, CHIP Therapy factors: prior anthracycline dose
	Arrhythmias	1%-10%	
Allogenic SCT	Heart failure ^a	5%-10%	Patient factors: HTN, DM, tobacco use, age Therapy factors: prior anthracycline dose, prior thoracic radiation, GVHD
	Coronary artery disease ^a	5%-10%	
	Arrhythmias	10%-15%	

^aRisk varies strongly according to known patient- and therapy-related risk factors, and predicted risk is much higher in some subgroups of patients.

CAD = coronary artery disease; CHIP = clonal hematopoiesis of indeterminate potential; DM = diabetes mellitus; GVHD = graft-vs-host disease; HTN = hypertension; LVEF = left ventricular ejection fraction; SCT = stem cell transplantation.

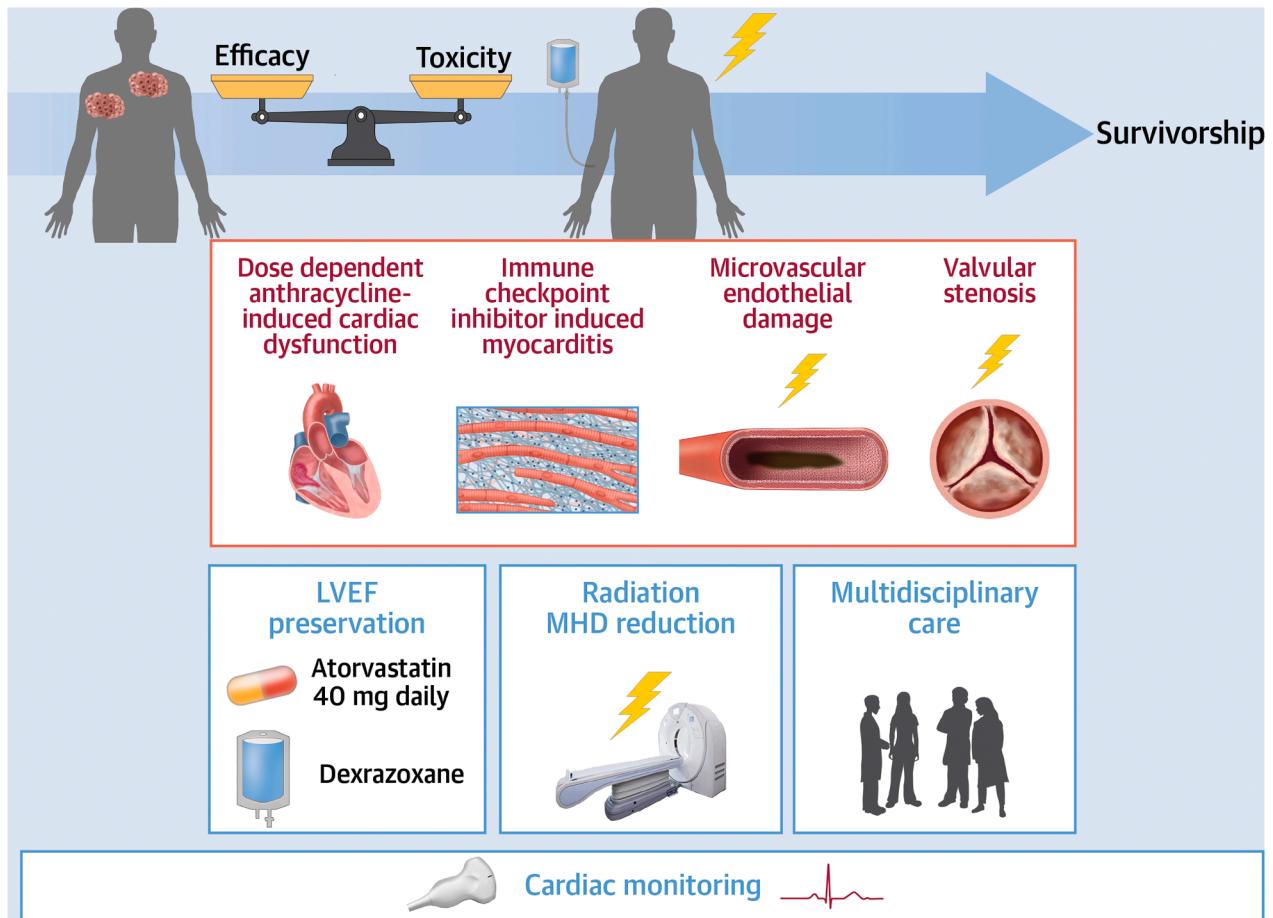
substitution of BV with nivolumab, an anti-PD-1 checkpoint inhibitor, in combination with AVD (N-AVD) in patients with advanced-stage disease and demonstrated 2-year PFS of 92% compared with the 83% in the BV plus AVD arm.²⁹ As BrECADD and N-AVD have not yet been directly compared, the comparative efficacy and toxicity of these 2 regimens remains unknown.³⁰ Currently, both N-AVD (in North America) and BrECADD are the preferred frontline treatment approaches for eligible patients with advanced-stage cHL.

CARDIOTOXICITY CONSIDERATIONS WITH FRONTLINE HODGKIN LYMPHOMA TREATMENTS

In devising a treatment plan and a long-term management plan for patients with Hodgkin lymphoma (HL), it is crucial to understand the CV risks of treatment (Table 2, Central Illustration). CV disease is a significant cause of morbidity and mortality in patients with HL and is the leading cause of death in long-term survivors of stage I and stage II cHL.² Anthracyclines and radiation are the major contributors to cardiotoxicity, with both early and late treatment effects, although there are also important considerations for immunotherapy and other cancer agents.

ANTHRACYCLINES. Anthracyclines are most strongly linked to myocardial toxicity, with HF from anthracycline chemotherapy being first described in 1973, shortly after this class of highly effective cancer therapies was discovered. In addition to left ventricular systolic dysfunction, anthracyclines are also associated with increased risk for diastolic dysfunction, arrhythmias, and QT interval prolongation (Table 2). Doxorubicin leads to cardiotoxicity in a dose-dependent manner through multiple mechanisms that include oxidative stress, mitochondrial damage, and calcium dysregulation. The risk for doxorubicin cardiotoxicity is significantly increased in patients who also receive radiation as well as patients with hypertension or other CV risk factors.³¹

Over the past 5 decades, HF risk has been reduced by efforts to decrease cumulative anthracycline dose, substantially reduce radiation dose to the heart, improve monitoring, and manage cardiac risk factors such as hypertension and diabetes. In addition, dextrazoxane, a cardioprotectant given with anthracycline infusions, is used more commonly by pediatric providers and is associated with favorable echocardiographic and cardiac biomarker profiles, which likely translates into reduced long-term risk for clinical HF.³² With current frontline cHL therapy, most patients receive approximately 200 to

CENTRAL ILLUSTRATION Treatment and Long-Term Cardio-Oncology Considerations in Hodgkin Lymphoma

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Arrows indicate relationships. Therapy selection in classical Hodgkin lymphoma requires careful consideration of efficacy and toxicity. Anthracyclines, immune checkpoint inhibitors, and radiation therapy all pose unique cardiac risks. Pre- and post-treatment cardiac evaluation along with the strategies illustrated may mitigate treatment-related cardiac toxicities. LVEF = left ventricular ejection fraction; MHD = mean heart dose.

300 mg/m² doxorubicin for early-stage disease and 300 mg/m² doxorubicin for advanced-stage disease.²⁴ Even with these changes, population-based estimates suggest that cHL survivors continue to have higher cardiac-related mortality than age- and sex-matched noncancer control subjects.³³ Although estimates of absolute HF risk vary widely according to the presence of other CV risk factors, age at the time of treatment, and use of dexrazoxane, the 30-year risk for severe or fatal cardiac disease for a teenager treated with doxorubicin 300 mg/m²

without RT is estimated to be 6.2% (95% CI: 2.7%-10.9%) on the basis of simulation studies using S1826 treatment (N-AVD) and estimates of cardiac late effects from these treatments in the CCSS (Childhood Cancer Survivor Study).³⁴

RT. RT causes microvascular endothelial damage, capillary loss, inflammation, and fibrosis and can affect all structures of the heart.³⁵ The late CV effects of RT are diverse and can include coronary artery disease, valvular stenosis or regurgitation, arrhythmias, constrictive pericarditis, restrictive

cardiomyopathy, and HF with preserved or reduced ejection fraction.³⁶⁻³⁹ MHD and doses to cardiac substructures (left ventricle, coronary arteries, heart valves) are predictive of CV risk.^{36,38-43} As mentioned earlier, the use of RT in cHL treatment is decreasing overall, and improvements in technology and techniques are associated with much lower radiation doses to normal structures including the heart⁴⁴⁻⁴⁶ (**Figure 1**). Although extended mantle RT has not been used for more than 25 years, given the long latency prior to clinically evident heart disease coupled with the high cure rates of cHL, it is important that clinicians be cognizant of the late effects of more extended RT fields.

IMMUNE CHECKPOINT INHIBITORS. Immune checkpoint inhibitors (ICIs) are best known for the risk for associated myocarditis, a rare but serious complication occurring in <1% of patients receiving PD-1 inhibitors, with a high fatality rate of 27.6%.⁴⁷⁻⁴⁹ Other CV complications associated with checkpoint inhibitors include acute coronary syndrome (1.73%), stroke (2.17%), tachyarrhythmia (3.15%), HF (3.4%), pericardial effusions (3.98%), and CV death (0.67%).⁴⁹ Observational and preclinical studies also suggest that PD-1 inhibition may be associated with accelerated atherosclerosis.^{50,51} The risks of these toxicities from ICI-containing HL regimens have not been quantified, and the impact of short-term PD-1 inhibition as part of N-AVD is uncertain. In the N-AVD trial, immune-mediated adverse events were infrequent, and no cases of myocarditis were reported, though longer term follow-up to monitor the incidence of delayed cardiac toxicities on immunotherapy-based cHL regimens is needed.⁵²

ABSOLUTE RISK ESTIMATES AFTER cHL TREATMENT. Estimating CV risk with current HL therapies is challenging because of the long latency period and young age at the time of cHL diagnosis (often <40 years). However, multivariable risk calculators based on longitudinal cohort studies of patients treated many decades ago can help estimate the long-term risk for HF, ischemic heart disease, and stroke.^{40,41,53,54} The CCSS models were derived from longitudinal follow-up of patients diagnosed before 21 years of age, treated from 1970 to 1986, and surviving at least 5 years postdiagnosis. Of the CCSS cohort, 13% had HL. The models estimate risk for HF, ischemic heart disease, and stroke through 50 years of age, with good discrimination in independent validation cohorts, on the basis of age at diagnosis, sex, and cancer treatment data, including cumulative anthracycline and RT doses.^{40,41} The CCSS models have since been updated to include hypertension,

diabetes, and hyperlipemia, on the basis of self-reported medication use, performing well with internal CCSS validation. External validation has not yet been reported for the updated models.⁵³ The CCSS risk calculators are available online at <https://ccss.stjude.org/resources/calculators/cardiovascular-risk-calculator.html>.

Another prediction model specific to patients 18 to 50 years of age at time of cHL diagnosis was developed using a cohort of 1,433 5-year HL survivors treated between 1965 and 2000 in the Netherlands. This model includes age at HL diagnosis, sex, smoking status at the time of HL diagnosis, RT, and anthracycline dose and predicts 20- and 30-year risks for coronary heart disease and HF on the basis of Common Terminology Criteria for Adverse Events 3 to 5 (severe or fatal) definitions and medical record review with good discrimination of the coronary heart disease model in external validation. An online calculator is available at evidencio.com.⁵⁴

PRETREATMENT EVALUATION AND CONSIDERATIONS FOR PATIENTS WITH PREVALENT CARDIAC DISEASE OR MULTIPLE CARDIAC RISK FACTORS. The aforementioned risk models were developed among 5-year survivors of cHL and do not include baseline echocardiographic results or pre-existing CV disease. Although most patients with cHL are young, with a low likelihood of pre-existing CV disease, approximately 20% are older than 65 years and have more prevalent cardiac comorbidities.⁵⁵ The 2022 European Society of Cardiology guidelines on cardio-oncology recommend the use of cancer therapy-specific risk stratification schemas that account for patient and therapy risk factors with specific criteria for categorizing patients as “very high risk,” “high risk,” “moderate risk,” or “low risk” prior to the initiation of cancer therapy.⁵⁶ For example, patients receiving anthracycline chemotherapy would be categorized as “very high risk” in the setting of pre-existing HF or cardiomyopathy or as “high risk” with any 1 high-risk factor (severe valvular heart disease, coronary artery disease, angina, age \geq 80 years, chest RT) or >5 moderate risk factors.⁵⁶

The 2017 American Society of Clinical Oncology guideline for the prevention and monitoring of cardiac dysfunction in adult cancers define combinations of patient and therapy risk factors that categorize patients as “increased risk for cardiac dysfunction” including cumulative anthracycline dose, radiation dose, cardiac risk factors, and baseline echocardiography.⁵⁷ Both the 2022 European Society of Cardiology guidelines and the 2017 American Society of Clinical Oncology guidelines include

recommendations for cardio-oncologic evaluation, multidisciplinary discussion about the benefits and harms of different cancer treatment strategies, optimization of CV risk factors, consideration of cardioprotective strategies and monitoring in patients at higher risk for cardiac events, especially in patients with pre-existing HF or cardiomyopathy. The recommendations for CV monitoring in patients undergoing treatment with potentially cardiotoxic therapies are shown in **Table 3**. Most recommendations stem from expert consensus informed by non-randomized retrospective studies and registry data. This summary presents guidance from leading oncologic and cardio-oncology societies to support readers in selecting an appropriate surveillance strategy.

SUMMARY.

- Frontline treatment for cHL is highly dependent on disease involvement and typically includes anthracycline-based chemotherapy, with selective incorporation of novel therapies such as PD-1 inhibitors and targeted use of radiation.
- Anthracyclines and RT are key contributors to CV toxicity, primarily presenting as cardiomyopathy, coronary artery disease, and valvular dysfunction, though modern dose limits and improved radiation precision have reduced these risks.
- All patients receiving anthracyclines should undergo pretreatment echocardiography and cardiac risk stratification on the basis of history, physical examination, and echocardiographic results, with multidisciplinary input in those at high risk for cardiac dysfunction.

STRATEGIES TO MITIGATE CARDIOTOXICITY

CV RISK OPTIMIZATION. In all patients receiving potentially cardiotoxic therapies, CV risk factors should be identified and optimized before, during, and after cancer treatment (**Central Illustration**).⁵⁶ Risk factors can significantly potentiate the risk for cardiotoxicity. The onset of hypertension, specifically, increases the risk for developing HF 19-fold in childhood cancer survivors.⁵⁸

PREVENTION OF ANTHRACYCLINE CARDIOTOXICITY. Combined with efforts to minimize cumulative anthracycline doses and RT delivered to the mediastinum in modern treatment protocols, there are several additional cardioprotective strategies that may further reduce the risk for anthracycline cardiotoxicity.

STATINS. In preclinical studies of anthracycline cardiotoxicity, atorvastatin reduced markers of oxidative stress and cell death and attenuated declines in left ventricular ejection fraction (LVEF).^{59,60} The STOP-CA (Statins to Prevent the Cardiotoxicity From Anthracyclines) trial was a randomized, placebo-controlled trial of atorvastatin 40 mg/d or matching placebo in adult patients (≥ 18 years of age) with lymphoma and planned anthracycline treatment.⁶¹ Of the 300 enrolled participants, 27% had cHL and 73% had non-Hodgkin lymphoma, with a median doxorubicin dose of 300 mg/m^2 . The primary endpoint, a reduction in LVEF of $\geq 10\%$ from baseline to a value $< 55\%$ by cardiac magnetic resonance imaging, occurred in 9% in the atorvastatin arm and 22% in the placebo group ($P = 0.002$). Symptomatic HF events were numerically lower with atorvastatin, although this was not statistically significant, and the trial was not powered for this endpoint. Two smaller randomized trials of atorvastatin starting prior to anthracycline treatment had neutral primary outcome results and both enrolled a combination of patients with breast cancer and lymphoma, with the majority of patients having breast cancer and thus receiving a lower cumulative anthracycline dose.^{62,63} All 3 studies demonstrated reassuring safety with no difference in liver function tests or myositis between the atorvastatin and placebo arms with atorvastatin 40 mg starting prior to multiagent chemotherapy.⁶¹⁻⁶³

DEXRAZOXANE. Dexrazoxane inhibits DNA topoisomerase IIb-anthracycline-mediated double-stranded DNA breaks and reduces oxygen free radical formation in cardiomyocytes.⁶⁴ Randomized studies in adult patients with metastatic breast cancer treated with high-dose anthracyclines showed that dexrazoxane significantly reduced the risk for HF (risk ratio: 0.22; 95% CI: 0.11-0.43), with no significant difference in oncologic outcomes and no signal for an increase in other adverse events.⁶⁵ The Food and Drug Administration indication for dexrazoxane reflects this evidence, and dexrazoxane is specifically approved for patients with metastatic breast cancer who have already received more than 300 mg/m^2 doxorubicin and who would benefit from ongoing doxorubicin therapy.⁶⁶ There are no randomized studies of dexrazoxane in adult patients with cHL. There were 2 randomized trials of dexrazoxane in children and adolescents with cHL up to 21 years of age, P9426 ($n = 294$, treated with doxorubicin, bleomycin, vincristine, and etoposide [ABVE]

TABLE 3 Cardiovascular Monitoring Recommendations for Patients With Anthracycline Exposure

Exposure	Timing	ASCO ⁵⁷	ESC ⁵⁶	NCCN ^{130,131}	NCCN ²⁴ /COG ¹³²
Anthracyclines	Baseline (pretreatment)	• TTE with LVEF ± GLS	• TTE with LVEF + GLS • Troponin/NT-proBNP as adjuncts	• TTE with LVEF ± GLS	• TTE with LVEF
	During treatment	• TTE in symptomatic patients or in asymptomatic patients based on clinical judgement	• TTE every 2 cycles in high-risk/very high-risk patients • Troponin/NT-proBNP as adjuncts	• TTE in symptomatic patients	• TTE with LVEF
	After treatment	• TTE within 6-12 mo in high-risk patients	• TTE within 12 mo in all patients • TTE after doxorubicin dose ^a ≥250 mg/m ² in moderate-risk patients • TTE within 3 mo in high-risk patients • Troponin/NT-proBNP as adjuncts	• TTE within 12 mo in high-risk patients	• TTE with LVEF at completion
	Long-term follow-up	• Annual CV assessment in high-risk patients with imaging as clinically indicated	• Life-long follow-up in high-risk survivors • TTE every 1-5 y based on risk • Prepregnancy or first-trimester cardiac evaluation	• Annual CV assessment in high-risk patients with imaging as clinically indicated	• Lifelong follow-up in moderate- to high-risk survivors • TTE every 2 y in high-risk and every 5 y in moderate-risk patients • Prepregnancy or first-trimester cardiac evaluation in high-risk survivors
	High-risk definition	• Doxorubicin dose ≥250 mg/m ² , doxorubicin dose <250 mg/m ² + cardiac RT, any doxorubicin dose + any of the following: age ≥60 y, LVEF 50%-55%, MI, moderate or greater valvular heart disease, or ≥2 CV risk factors	• Doxorubicin dose ^a ≥250 mg/m ² , doxorubicin dose ^a ≥100 mg/m ² + RT with MHD ≥5 Gy, any doxorubicin + any of the following: history of HF cardiomyopathy, severe valvular heart disease, symptomatic CAD/angioplasty, age ≥80 y, multiple moderate risk factors (score ≥5)	• Doxorubicin dose ^a ≥250 mg/m ² , any doxorubicin dose ^a + any of the following: age >65 y, LVEF 50%-54%, pre-existing CVD, or CV risk factors	• Doxorubicin dose ^a ≥250 mg/m ² , doxorubicin dose ^a ≥100 mg/m ² + chest RT ≥15 Gy, any doxorubicin + chest RT ≥30 Gy
Thoracic radiation	Baseline (pretreatment)	• TTE with LVEF ± GLS	• Baseline estimate of 10-y CVD risk • Consider baseline TTE	Not addressed in these guidelines	Not addressed in these guidelines
	During treatment	• TTE in symptomatic patients or in asymptomatic patients based on clinical judgement	No recommendations		Not addressed in these guidelines
	After treatment	• TTE within 6-12 mo in high-risk patients	• TTE within 12 mo in all patients		Not addressed in these guidelines
	Long-term follow-up	• Annual CV assessment in high-risk patients with imaging as clinically indicated	• Lifelong follow-up in high-risk survivors • TTE every 1-5 y based on risk • Noninvasive screening for CAD every 5-10 y if MHD >15 Gy starting 5 y after RT • Carotid ultrasound every 5 y if neck RT starting 5 y after RT • Prepregnancy or first-trimester cardiac evaluation		• Lifelong follow-up in moderate- to high-risk survivors • TTE every 2 y in high-risk and every 5 y in moderate-risk patients • CAD evaluation 5-10 y after RT • Carotid ultrasound 10 y after RT if RT >40 Gy to neck • Prepregnancy or first-trimester cardiac evaluation in high-risk survivors
	High-risk definition	• RT ≥30 Gy if heart is in the treatment field • Any combination of anthracycline and cardiac radiation regardless of doses (as above)	• Very high risk: MHD >25 Gy or MHD >15 Gy + doxorubicin dose ^a ≥100 mg/m ² • High risk: MHD > 15 to 25 Gy or MHD 5-15 Gy + doxorubicin dose ^a ≥100 mg/m ²		• Chest RT ≥30 Gy • Chest RT ≥15 Gy + doxorubicin dose ^a ≥100 mg/m ²

Continued on the next page

TABLE 3 Continued

Exposure	Timing	ASCO ⁵⁷	ESC ⁵⁶	NCCN ^{130,131}	NCCN ²⁴ /COG ¹³²
Immune checkpoint inhibitors	Baseline (pretreatment)	Not addressed in these guidelines	<ul style="list-style-type: none"> Baseline clinical assessment, ECG, troponin, and NP in all patients Baseline TTE in high-risk patients Can consider troponin and ECG during treatment based on risk and duration of ICI treatment 	<ul style="list-style-type: none"> Consider baseline ECG, troponin, and NP 	Not addressed in these guidelines
	During treatment			<ul style="list-style-type: none"> Consider periodic testing for those with abnormal baseline or those with symptoms 	
	After treatment		No recommendations	No recommendations	
	Long-term follow-up		No recommendations	No recommendations	
	High-risk definition		Any of the following: dual ICI, combination ICI and cardiotoxic therapy, ICI-related non-CV adverse events, prior CTRCD or CVD	No recommendations	
Stem cell transplantation	Baseline (pretreatment)	Not addressed in these guidelines	<ul style="list-style-type: none"> TTE, ECG, NP, comprehensive clinical assessment, CPET in select patients No recommendations TTE at 3 and 12 mo post-transplantation in high-risk patients Annual lifelong follow-up with comprehensive clinical assessment, ECG, and NP in high-risk survivors TTE in select patients 	<ul style="list-style-type: none"> Not addressed in these guidelines 	Not addressed in these guidelines
	During treatment				
	After treatment				
	Long-term follow-up				
	High-risk definition		Any of the following risk factors: allogenic (vs autologous), pre-existing CVD, multiple uncontrolled CV risk factors, prior mediastinal RT, doxorubicin dose ^a ≥250 mg/m ² , alkylating agents, conditioning with TBI or alkylating agents, GVHD		

^aDoxorubicin equivalent. Multiply by 0.6 for daunorubicin and by 10.5 for mitoxantrone. No established conversion equivalents for epirubicin and idarubicin.¹³³

ASCO = American Society of Clinical Oncology; COG = Childhood Oncology Group; CPET = cardiopulmonary exercise testing; CTRCD = chemotherapy-related cardiac dysfunction; CV = cardiovascular; CVD = cardiovascular disease; ECG = electrocardiography; ESC = European Society of Cardiology; GLS = global longitudinal strain; HF = heart failure; ICI = immune checkpoint inhibitor; MHD = mean heart dose; MI = myocardial infarction; NCCN = National Comprehensive Cancer Network; NP = natriuretic peptide; RT = radiation therapy; TBI = total body irradiation; TTE = transthoracic echocardiography; other abbreviations as in Table 2.

and radiation) and P9425 ($n = 216$; treated with ABVE with prednisone and cyclophosphamide and radiation).^{67,68} In patients on ABVE with prednisone and cyclophosphamide, randomization to dexamethasone was associated with higher rates of myelosuppression and infections,⁶⁷ while combined analysis of both pediatric HL trials showed concern for secondary malignancies with dexamethasone, including secondary acute myeloid leukemia.⁶⁹ The higher rates of secondary malignancies were not seen in other studies of dexamethasone in pediatric acute

lymphoblastic leukemia,^{70,71} with the possible difference being the inclusion in the HL trials of etoposide, an additional topoisomerase inhibitor. Long-term outcome analyses of randomized dexamethasone studies, including these 2 HL studies, have not suggested increased long-term risks for mortality or secondary malignancies with dexamethasone but have shown improvement in long-term cardiac outcomes.^{32,72,73} In a median of 18-year follow-up of patients treated in 5 studies incorporating dexamethasone, including the 2 cHL studies, patients who

received dexrazoxane prior to anthracycline therapy had higher LVEFs and lower N-terminal pro-brain natriuretic peptide with lower odds of left ventricular systolic dysfunction, defined as LVEF <50% or fractional shortening <30%.³² The cardiac benefit was observed primarily among patients receiving >250 mg/m² doxorubicin.³² A more recent study using simulation models and data from 4 recent HL Children's Oncology Group clinical trials has argued that both the use of dexrazoxane and decrease in mediastinal RT has significantly lowered the estimated 30-year cumulative incidence of severe or fatal cardiac disease in HL survivors, with an expected estimate of 6.2% for patients in the recent N-AVD trial (S1826), as mentioned previously.³⁴

LIPOSOMAL ANTHRACYCLINES. Liposomal anthracycline formulations reduce drug delivery to tissues with tight capillary junctions, including the heart, and also reduce the risk for cardiotoxicity in patients with metastatic breast cancer receiving high-dose anthracyclines (OR: 0.46; 95% CI: 0.23-0.92).⁷⁴ Pegylated liposomal doxorubicin (Doxil/CAELYX, Janssen Pharmaceuticals) is currently Food and Drug Administration approved for ovarian cancer, Kaposi sarcoma, and multiple myeloma.⁷⁵ The combination of gemcitabine, vinorelbine, and liposomal doxorubicin (GVD) has been studied in the setting of relapsed HL after an initial course of doxorubicin containing regimens and is included in the National Comprehensive Cancer Network guidelines as an option for second-line therapy in relapsed or refractory (R/R) disease.^{24,76} There are limited studies of the use of liposomal anthracyclines for first-line therapy in cHL.

CONTINUOUS DOXORUBICIN INFUSION. Randomized trials of doxorubicin given as a continuous infusion instead of bolus dosing for adult patients with sarcoma, breast cancer, or ovarian cancer have demonstrated reduced cardiotoxicity.^{77,78} However, continuous doxorubicin infusion was not found to improve echocardiographic measures of cardiotoxicity in children with acute lymphoblastic leukemia over a 10-year follow-up.⁷⁹ Notably, dexrazoxane cannot be given in conjunction with continuous anthracycline infusions. Continuous doxorubicin infusion is incorporated into the inpatient regimen of rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin that is used in non-Hodgkin lymphoma; however, continuous doxorubicin infusion to limit cardiotoxicity has not been studied in cHL regimens and is not typically incorporated into standard cHL regimens.

NEUROHORMONAL ANTAGONIST THERAPY. Randomized trials of neurohormonal antagonist therapy for the primary prevention of anthracycline cardiotoxicity have been mixed.⁸⁰ Some trials have demonstrated modest benefit⁸¹⁻⁸³; however, many studies have been neutral.⁸⁴⁻⁸⁶ Most studies enrolled patients with breast cancer and excluded patients already taking these classes of medications for other indications such as hypertension, so the study cohorts tend to have lower risk for cardiotoxicity. Although there is insufficient evidence to recommend neurohormonal antagonist therapy for all patients, patients with low-normal LVEFs or with hypertension may benefit from consideration of these agents. In patients with reduced LVEFs or HF with preserved ejection fraction, standard HF therapies should be prescribed according to the 2022 American College of Cardiology/American Heart Association/Heart Failure Society of America HF guidelines.⁸⁷

LIFESTYLE INTERVENTIONS. The American Heart Association's Life's Essential 8 provides an approach to assessing and promoting CV health and includes recommendations for healthy diet, physical activity, nicotine avoidance, sleep health, healthy weight, blood lipids, blood glucose, and blood pressure.⁸⁸ Regular physical activity is associated with improved CV health and longevity in the general population.⁸⁸⁻⁹⁰ Structured physical activity as part of cardiac rehabilitation improves outcomes in patients with coronary artery disease, atrial fibrillation, and HF.⁹¹⁻⁹³ Higher self-reported physical activity was associated with lower incident CV events in adult survivors of childhood HL.⁹⁴ Randomized trials of structured exercise interventions have shown improved functional capacity assessed by cardiopulmonary exercise stress testing and favorable effects on health related quality of life, symptoms, and measures of vascular function.^{95,96} Ongoing studies are investigating novel strategies to increase physical activity in adolescent and young adult cancer survivors.⁹⁷

MINIMIZING RADIATION-RELATED CARDIOTOXICITY. Modern RT techniques are associated with much lower radiation doses to normal structures, including the heart (Figure 1), and are expected to reduce long-term cardiotoxicity associated with RT.⁴⁴⁻⁴⁶ Patients who received prior RT with MHDs >25 Gy or MHDs of 5 to 25 Gy plus cumulative doxorubicin exposure ≥100 mg/m² are considered very high risk for cardiotoxicity, while those who received MHDs of 15 to 25 Gy or MHDs of 5 to 15 Gy with doxorubicin exposure ≥100 mg/m² are considered high-risk

patients.⁵⁶ Primary prevention strategies should focus on optimizing lifestyle and cardiac risk factors according to the American Heart Association's Life's Essential 8, as described previously.⁸⁸ When the MHD is not available, total radiation exposure is used as a surrogate when the heart may have been in the radiation treatment field. In these cases, higher risk patients are those treated with >35 Gy or with 15 to 34 Gy plus doxorubicin exposure $\geq 100 \text{ mg/m}^2$. Statins and other lipid-lowering agents should be considered to reduce atherosclerotic CV disease risk, with shared decision-making discussions informed by risk models that include radiation dosimetry when this information is available.^{41,54}

SUMMARY.

- In addition to optimizing CV risk factors and promoting lifestyle changes before treatment, moderate dose atorvastatin and the use of dexamethasone may limit the risk of HF, although long-term data in cHL remain limited.
- Modified anthracycline delivery methods, such as liposomal formulations and continuous infusions, have demonstrated moderate reductions in cardiotoxicity in solid tumors but are not routinely used in frontline cHL treatment.

CASE PRESENTATION CONTINUED

The patient initiated ABVD with plans to de-escalate to AVD if interim PET/CT after 2 cycles of ABVD demonstrated a complete metabolic response. CMT was not initially planned because of his young age and bulky mediastinal disease, in an effort to mitigate long-term cardiac and oncologic complications. At treatment start, atorvastatin 40 mg/d was initiated for cardioprotection. PET/CT after 2 cycles of ABVD demonstrated ongoing response, and treatment was de-escalated to AVD for the remaining 4 cycles. Shortly after completing his fifth cycle, the patient presented to the clinic with progressive shortness of breath, sinus tachycardia, and radiographic imaging consistent with pulmonary edema. Transthoracic echocardiography revealed newly reduced systolic function, with a decline in LVEF from a baseline of 50% to 37%. Cardio-oncology believed that the decrement in systolic function was probably related to anthracycline therapy. Following multidisciplinary discussion, weighing the risk for exacerbating cardiomyopathy while proceeding with curative intent, the plan was made to repeat imaging to assess disease status and to sequentially initiate guideline-directed medical therapy for HF to optimize cardiac function in order to maximize lymphoma-directed

therapy. Subsequent PET/CT unfortunately showed a new fluorodeoxyglucose-avid mediastinal lesion consistent with refractory cHL.

TREATMENT OF PATIENTS WITH R/R cHL

Despite the efficacy of frontline regimens, 10% to 25% of cHL patients will experience primary R/R disease.¹ Nonetheless, second-line therapy in this population is approached with curative intent in patients who are eligible for high-dose chemotherapy and autologous stem cell transplantation (ASCT).

SALVAGE THERAPY PRIOR TO ASCT. The general approach to second-line chemotherapy for most patients consists of a inhibitor in combination with chemotherapy or BV. In contrast to the frontline approach, there is no standard chemotherapy backbone for cHL in the R/R setting, as direct prospective comparisons of regimens have not been undertaken. Generally, second-line regimens have incorporated various chemotherapeutic agents, including but not limited to cytarabine, cisplatin, gemcitabine, ifosfamide, etoposide, vinorelbine, and bendamustine.⁹⁸ The combination of ifosfamide, carboplatin, and etoposide as well as GVD are commonly used second-line regimens prior to ASCT and have demonstrated tolerability and efficacy, with initial response rates ranging from 70% to 88%.^{99,100} As both checkpoint inhibition and BV have considerable single-agent efficacy in the R/R setting,^{101,102} there has been recent momentum to incorporate these novel agents as part of standard second-line therapy. The combinations of BV and bendamustine and of BV and nivolumab followed by ASCT in eligible patients have been highly effective, with rates of long-term PFS >70%.^{103,104} A phase II study of pembrolizumab and GVD followed by ASCT consolidation demonstrated significant efficacy, further supporting the incorporation of novel agents in the R/R setting.⁷⁶

ASCT. The role of ASCT as consolidation in R/R cHL was established more than 20 years ago on the basis of 2 randomized European trials that showed a significant PFS benefit over chemotherapy alone.^{105,106} Currently, ASCT is considered in patients who achieve a response by PET/CT to at least 2 cycles of chemotherapy. Determining eligibility for ASCT is a complex consideration, but ASCT is generally reserved for fit patients up to 70 to 75 years of age.¹⁰⁷ High-dose chemotherapy with carmustine, etoposide, cytarabine, and melphalan prior to stem cell rescue is the most common ASCT regimen given the relatively lower risk for treatment-related mortality compared with other conditioning regimens.¹⁰⁸ In the era of incorporating PD-1 inhibitors in second-

line chemotherapy, outcomes after ASCT have improved significantly compared with chemotherapy alone with or without BV with 2-year PFS >90% for patients undergoing ASCT in a large multicenter retrospective analysis.¹⁰⁹ In patients in whom ASCT is contraindicated, maintenance with either checkpoint inhibitors or BV following initial salvage therapy has been shown to be effective for long-term disease control.^{101,103,110}

ALLOGENEIC STEM CELL TRANSPLANTATION. The majority of patients with R/R disease are effectively treated in the second-line setting, however in multiply-relapsed patients, allogeneic stem cell transplantation (SCT) remains a potential option. In contrast to ASCT, allogeneic SCT offers the potential of long-term adoptive immunity with a graft-vs-lymphoma effect following engraftment. Careful selection of patients is essential, as there is significant risk for treatment-related complications due to the conditioning regimens as well as the risk for graft-vs-host disease (GVHD).¹ Randomized studies in this context are lacking, but relatively recent examination of allogeneic SCT in the era of novel cHL treatments (including PD-1 inhibition) has shown a 1-year PFS of 76% and treatment-related mortality of 11%.¹¹¹

RT. The role of RT in the R/R setting has primarily been as an adjunct to systemic therapy, particularly in patients with persistent foci of bulky disease that have not fully resolved on PET/CT during treatment. In the frontline setting, patients with bulky disease that has largely but not completely responded to systemic therapy may be candidates for subsequent involved-site RT with doses ≥ 30 Gy.^{112,113}

CV CONSIDERATIONS IN R/R cHL

Patients with R/R cHL will have both intermediate- to long-term risk from their frontline therapy as well as potentially additive risks from their second-line treatment. Given these combined risks, extra care should be taken to maximize cardioprotective efforts when indicated. Patients undergoing stem cell transplantation (SCT) will be receiving high-dose cytotoxic therapy that can trigger an extensive inflammatory response and exacerbate underlying comorbidities. As the patient case highlights, some patients will have established CV disease that is best managed by a multidisciplinary team.

MULTIDISCIPLINARY CONSIDERATIONS. It is not uncommon to encounter patients with CV disease, including left ventricular dysfunction, at the time of

relapse or progression or even at initial presentation. A multidisciplinary approach is key to maximizing cancer therapy while minimizing potential CV toxicity.¹¹⁴ No absolute contraindications have been clearly defined for a given cancer therapy, but the overall risk/benefit ratio may shift toward an alternative regimen in certain conditions. As an example, patients with LVEFs <40% may very well benefit from an alternative to anthracyclines for their conditioning regimen. In some cases, though, a strategy of permissive cardiotoxicity can be pursued, whereby some level of left ventricular dysfunction or other CV toxicity may be tolerated if the benefit of the cancer therapy is clear.¹¹⁵ In most cases, patients will be more likely to die of their lymphoma, and care should be taken prior to withholding potentially lifesaving cancer therapy. In all cases, patients should be optimized fully for both their CV disease and their CV risk factors regardless of treatment pursued. Patients with LVEFs <40% can potentially tolerate SCT but should be well compensated and on maximum tolerated guideline-directed medical therapy before initiating treatment. There may be some utility to cardiopulmonary exercise testing for further risk stratification in select patients in whom the benefit/risk ratio of SCT is less clear, though more research is needed.¹¹⁶

SALVAGE THERAPY PRIOR TO ASCT. Although alternative regimens are increasingly used, patients may be re-exposed to anthracyclines, which carry a risk for dose-dependent toxicity, as previously mentioned. In the GVD regimen, the liposomal form of doxorubicin does help lower the cardiac risk for additional anthracycline exposure. With checkpoint inhibition, there is a theoretical concern for atherosclerotic progression, though a dose effect has not yet been identified.

Additional agents that may be encountered in salvage therapy include carboplatin (part of the combination of ifosfamide, carboplatin, and etoposide) and gemcitabine (part of the GVD combination) as well as bendamustine. Carboplatin is overall well tolerated but has been associated with a risk for hypertension and a low risk for myocardial ischemia, similar to vinca alkaloids. Neither gemcitabine nor bendamustine has significant cardiotoxicity. Gemcitabine can rarely lead to capillary leak syndrome, which can mimic HF with noncardiogenic pulmonary edema and extremity swelling. Treatment is traditionally with corticosteroids.

SCT. Both ASCT and allogeneic SCT have been strongly associated with short- and long-term CV

effects. Because of the effects of their cumulative treatment regimen and potential for other CV risk factors, SCT survivors are at 2-fold risk for CV mortality and a 4-fold risk for developing CV disease compared with the general population over more than 10 years of follow-up.^{117,118} In a single-center analysis of 1,930 patients undergoing SCT (56% autologous, 38% lymphoma), risk factors for developing CVD included age >30 years, anthracycline dose >250 mg/m², chest radiation, and presence of any CV risk factor (hypertension, diabetes mellitus, and/or smoking).¹¹⁷

During the initial SCT hospitalization, atrial fibrillation or flutter occurs in 4% to 10% of patients, with a similar rate in autologous and allogenic SCT.^{119,120}

Patients who develop atrial fibrillation are at a significantly increased risk for mortality (13-fold higher risk in a study of allogeneic SCT patients).¹²¹ Other CV events such as HF and coronary events are less common acutely (<2%),¹²² though management during SCT is significantly more complex given comorbid thrombocytopenia or infection, which is often present. Notably, GVHD prophylaxis with post-transplant cyclophosphamide is becoming widely adopted, particularly in the ICI-exposed setting, and has been independently associated with a 2.7-fold higher risk for cardiac toxicity within the first 100 days.¹²³

Over intermediate- to long-term follow-up, SCT survivors remain at increased risk for atrial fibrillation or flutter while also having a 5% to 6% risk for HF and a 1.1% to 3.7% risk for myocardial infarction.¹²⁰ The CARE-BMT risk score helps assess the 1- and 5-year predicted incidence of CV risk in SCT survivors, incorporating age, race, transplantation type, anthracycline exposure, and comorbidities.¹²⁴ Allogeneic SCT patients have an overall higher risk for CV events relative to ASCT.¹²⁰ Patients undergoing allogeneic SCT are notably at risk for GVHD, which can rarely affect the myocardium directly or lead to coronary thrombosis. Treatments for GVHD are also known to contribute to hypertension and hyperlipidemia. Recommendations for CV monitoring in patients undergoing SCT are outlined in **Table 3**.

SUMMARY.

- In the salvage setting, cHL remains curable, with treatment involving combination chemotherapy plus immunotherapy or BV, followed by consolidation with ASCT in eligible patients.
- Because of cumulative cardiotoxic effects of therapy, patients with R/R cHL, especially those with

underlying cardiac dysfunction, should undergo multidisciplinary evaluation, including cardiology consultation, prior to therapy selection.

- SCT carries significant short- and long-term cardiac toxicity risks including atrial arrhythmias and CV disease, with increased incidence in those with prior exposure to anthracyclines and chest radiation.

CV MONITORING

All guidelines advise annual CV assessment for high-risk cancer survivors, including CV risk factor management and counseling on heart healthy lifestyle habits.

Surveillance for anthracycline cardiotoxicity in HL patients is essential given the well-established risk for dose-dependent toxicity (**Table 3**). All patients should undergo baseline echocardiography to assess LVEF, preferably with global longitudinal strain, before initiating anthracycline therapy. Monitoring during treatment is based on individual risk factors, including cumulative anthracycline dose, age, pre-existing CV risk factors or CV disease, and cardiac radiation dose. Troponin and N-terminal pro-brain natriuretic peptide levels may be measured to detect early myocardial injury. Depending on the patient's risk level (low, medium, or high), the patient may require only post-treatment echocardiography as opposed to more regular assessment of left ventricular function and biomarkers as often as every 2 cycles of anthracyclines.¹¹⁴

Although post-treatment surveillance guidelines vary by society, all recommend echocardiography within 1 year after the completion of anthracycline therapy in high-risk patients. This recommendation is based on data from a longitudinal, prospective study in 2,625 breast cancer patients demonstrating that the majority of cases (98%) with anthracycline cardiotoxicity present within the first year after completion of treatment.¹²⁵ Long-term monitoring is particularly important in childhood cancer survivors. An analysis from the DCOG-LATER (Dutch Childhood Oncology Group—Long-Term Effects After Childhood Cancer) cohort, which includes 6,165 5-year childhood cancer survivors diagnosed between 1963 and 2002, showed that the cumulative incidence of HF increased over time, reaching 4.4% at 40 years postdiagnosis, with no evidence of a plateau.¹²⁶ Accordingly, the Childhood Oncology Group long-term follow-up guidelines recommend lifelong echocardiographic monitoring, with the frequency based on underlying risk.

Long-term monitoring may be beneficial in patients with higher risk radiation exposures. Like anthracyclines, chest radiation causes dose-dependent cardiotoxicity that may not manifest until decades after treatment. In a nested case-control study of 2,617 5-year HL survivors, treated between 1965 and 1995, each 1-Gy increase in MHD was associated with a 7.4% increased risk for coronary artery disease, with a median onset of 19 years post-radiation.³⁶ Given this prolonged latency, guidelines recommend comprehensive CV surveillance, including echocardiography, stress testing, assessment of coronary calcium, and carotid ultrasound (in survivors treated with neck radiation), starting 5 to 10 years after completion of RT and then every 5 years thereafter in patients at increased risk for cardiotoxicity (**Table 3**).^{58,127}

Patients at increased risk for ICI cardiotoxicity include those receiving ICIs combined with other cardiotoxic therapies, those with pre-existing CV disease, and those with other immune-related adverse events. The 2022 European Society of Cardiology cardio-oncology guidelines recommend baseline electrocardiography and troponin for all patients starting ICI therapy, with baseline echocardiography advised for high-risk patients (**Table 3**).⁵⁶ As most ICI myocarditis cases occur within the first 3 months of ICI exposure,¹²⁸ electrocardiography and troponin monitoring before cycles 2, 3, and 4 of ICI therapy can be considered.⁵⁶

SUMMARY.

- In addition to baseline CV risk assessment and echocardiography, all patients receiving anthracyclines should undergo repeat echocardiography 1 year following treatment, with more frequent echocardiographic evaluation in high-risk patients and lifelong surveillance in pediatric patients.
- Patients receiving chest radiation are at risk for late-term cardiotoxicities and as such should have indefinite comprehensive cardiac evaluation, beginning 5 to 10 years after therapy completion.

- Immune checkpoint cardiac toxicity, although rare, primarily presents shortly after exposure to therapy and prompt assessment should be undertaken in symptomatic patients to improve outcomes.

CASE PRESENTATION FOLLOW-UP

Following biopsy confirmation of refractory mediastinal disease, the patient began second-line therapy with an anthracycline-free regimen of BV-nivolumab, with repeat imaging demonstrating ongoing response. His cardiac function has since recovered on guideline-directed medical therapy, and consolidation with ASCT is being considered.

CONCLUSIONS

With modern HL treatment, many patients will be cured of their lymphoma but will remain at an increased risk for short- and long-term cardiotoxicity. Interventions such as reducing cardiac radiation exposure, optimization of CV risk factors, appropriate screening protocols, and incorporation of cardioprotectants help mitigate these CV risks. Ultimately, patients are best served by a multidisciplinary approach that maximizes cancer treatment while minimizing cardiac risks.

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