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ORIGINAL PAPER

Transplantation

Cardiovascular diseases after high-dose chemotherapy and autologous stem cell transplant for lymphoma: A Danish population-based study

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Summary

Cardiovascular diseases, especially congestive heart failure (CHF), are known complications of anthracyclines, but the risk for patients undergoing high-dose chemotherapy and autologous stem cell transplant (HDT-ASCT) is not well established. With T-cell therapies emerging as alternatives, studies of long-term complications after HDT-ASCT are warranted. Danish patients treated with HDT-ASCT for aggressive lymphoma between 2001 and 2017 were matched 1:5 on sex, birth year and Charlson comorbidity score to the general population. Events were captured using nationwide registers. A total of 787 patients treated with HDT-ASCT were identified. Median follow-up was 7.6 years. The risk of CHF was significantly increased in the HDT-ASCT population compared to matched comparators with an adjusted hazard ratio (HR) of 5.5 (3.8–8.1). The 10-year cumulative incidence of CHF was 8.0% versus 2.0% ($p < 0.001$). Male sex, ≥2 lines of therapy, hypertension and cumulative anthracycline dose (≥300 mg/m^2) were risk factors for CHF. In a separate cohort of 4089 lymphoma patients, HDT-ASCT was also significantly associated with increased risk of CHF (adjusted HR of 2.6 [1.8–3.8]) when analysed as a time-dependent exposure.

Joachim Baech and Simon Husby—Shared authorship.

HDT-ASCT also increased the risk of other cardiac diseases. These findings are applicable for the benefit/risk assessment of HDT-ASCT versus novel therapies.

KEYWORDS
cardiology, cytotoxicity, epidemiology, high-dose therapy, lymphoma

INTRODUCTION

High-dose therapy followed by autologous stem cell transplant (HDT-ASCT) has been used as consolidation therapy for patients with relapsed/refractory (R/R) aggressive lymphoma for decades.[1] It is also standard consolidation in first line for chemosensitive mantle cell lymphoma (MCL) and peripheral T-cell lymphoma (PTCL).[2,3] Lymphoma survivors have increased risk of cardiovascular disease (CVD), especially congestive heart failure (CHF), compared with the general population,[4–7] but the contribution of salvage chemotherapy and HDT-ASCT to the CVD risk is poorly understood. In a cross-sectional study of 274 Norwegian patients assessed by echocardiography at a median of 12 years after HDT-ASCT, the prevalence of left ventricular dysfunction was 16%.[5] There is a lack of population-based longitudinal data on CVD risk after HDT-ASCT for lymphoma of various subtypes. Previous studies were limited by single-centre or cross-sectional designs, or had narrow focus on one lymphoma subtype.[8,9] Due to the emergence of CAR-T with curative potential in R/R aggressive B-cell lymphoma and use of upfront BTK inhibitors combined with immunochemotherapy in MCL, the use of HDT-ASCT is expected to decrease substantially in coming years.[10–12] Moreover, several novel therapies have shown promising results in the R/R lymphoma setting and have already received or been recommended for marketing authorization, such as bispecific CD20×CD3 antibodies[13] and CD79b antibody-drug conjugates.[14] In pivotal phase III CAR-T trials in early high-risk R/R diffuse large B-cell lymphoma (DLBCL), the 12-month event-free survival rate was impressive 47%–57% after CAR-T therapy versus 17%–23% with HDT-ASCT.[10,15] However, in late relapse of DLBCL, the optimal use of new therapies (such as CAR-T) against conventional HDT-ASCT remains to be determined, particularly in light of known more favourable outcomes with the latter in the late relapse setting.[16] In fact, the choice between conventional HDT-ASCT and novel immunotherapies may eventually not be driven by superior efficacy of one therapy over the other but a total benefit/risk assessment, that also includes considerations of early and late toxicities.

In this national population-based matched cohort study, the short- and long-term risks of CHF and non-CHF CVD after HDT-ASCT were investigated and compared to the risks in a matched general population. The isolated contribution of HDT-ASCT on the risk of CVD among patients who were eligible to HDT-ASCT was also explored in analyses where HDT-ASCT was a time-dependent exposure.

MATERIALS AND METHODS

Study populations

Three cohorts were analysed in this study; (1) patients treated with HDT-ASCT (main HDT-ASCT cohort), (2) matched comparators from the general population and (3) a separate cohort of patients with newly diagnosed aggressive lymphoma who was eligible for later HDT-ASCT (HDT-ASCT eligible cohort).

The main HDT-ASCT cohort consisted of adult (≥18 years) Danish patients with DLBCL, Hodgkin lymphoma (HL), MCL and PTCL treated with HDT-ASCT between 2001 and 2017. Patients were identified in the Danish National Lymphoma Registry (LYFO). LYFO has been nationwide since 2000 and 98.4% of patients in Denmark referred for lymphoma treatment are captured in the register.[17] Reports on clinicopathological features, treatment, response and relapses are prospectively entered. The data quality of LYFO has been validated and positive predictive values of more than 98% have been reported for the evaluated variables used in this study.[17] HDT-ASCT treatment was identified by a LYFO registration of HDT-ASCT. If HDT-ASCT dates were missing in LYFO, they were retrieved from procedure codes in the Danish National Patient Register (DNPR), which has been described elsewhere.[18] Patients were excluded if HDT-ASCT dates could not be retrieved.

A cohort of matched comparators from the Danish general population was identified to compare the risks of cardiovascular diseases to that of the background population. Patients from the main HDT-ASCT cohort were matched on exact values of birth year, sex and Charlson comorbidity index score to individuals from the Danish general population in a ratio of 1:5 (matched comparators). Matched comparators were sampled from the entire Danish general population identified in the Danish Civil Registration System, which contains information on all individuals in Denmark.[19] Matching was done with incidence density sampling without replacement, and matched comparators had to be alive and living in Denmark at the time of inclusion. Although more matched comparators were available, the number of matched comparators was limited to five random individuals within the matching criteria for each patient.

A third cohort of newly diagnosed HDT-ASCT eligible lymphoma patients (HDT-ASCT eligible cohort) was identified to assess the excess rates of CHF and non-CHF CVD associated with treatment with HDT-ASCT compared to those who only received conventional chemotherapy treatment. This cohort included all patients with DLBCL or HL between

age 18 and 65 and with performance status 0–2 at lymphoma diagnosis. Patients were chosen for their assumed eligibility for transplant at first relapse. Patients were followed from lymphoma diagnosis, and the associations between CVD and HDT-ASCT were analysed with HDT-ASCT as a time-dependent exposure.[20]

In all cohorts, individuals with CVD prior to the index date were excluded.

Information on highest completed educational level at time of diagnosis was retrieved from the Danish Population Education Register[21] and stratified as low or high (Data S1, educational level). Comorbidities, which were identified as possible confounders a priori, were identified via the DNPR and/or the Danish prescription registry. Full comorbidity definitions can be found in Data S1 (comorbidities).

Outcomes

Outcomes of interest were CHF and non-CHF CVD. CHF was defined by ICD-10 codes for CHF and cardiomyopathy in the DNPR. Non-CHF CVD was identified by ICD-10 codes for ischaemic heart disease (IHD), pericarditis, restrictive cardiomyopathy, valvular disease, atrial fibrillation (AF) and flutter or malignant arrhythmias as well as with procedure codes for coronary artery bypass grafting or percutaneous coronary intervention. Full definitions are available in Data S1 (CVD events).

Statistical analysis

Patients with lymphoma in the main HDT-ASCT cohort were followed from the date of ASCT, and matched comparators were followed from the day of inclusion of the index patient. All included individuals were followed until the event of interest (CHF or non-CHF CVD), death, emigration or administrative censoring on 31 December 2018. Median follow-up was calculated using the reverse Kaplan–Meier method.

Univariable and multivariable Cox regressions were performed to provide crude and adjusted cause-specific hazard ratios (HRs) for CHF and non-CHF CVD. In the adjusted Cox model, the HR was adjusted for sex, age, educational level and comorbidities. The Cox proportional hazards assumption was assessed visually using Schoenfeld residuals and was not satisfied for analyses of both CHF and non-CHF CVD. To compensate for this, the time-varying HR was plotted over time using flexible parametric modelling with two degrees of freedom for the main effect and two degrees of freedom for the interaction with time.[22]

Cause-specific cumulative incidences (from here on referred to as cumulative risk) of CHF and non-CHF CVD with death before CVD as competing event were estimated for patients and comparators using the Aalen–Johansen estimator. Differences in cumulative risks between the groups, for the entire follow-up, were tested using Gray's test. The overall survival was estimated using the Kaplan–Meier method.

To identify risk factors for CHF and non-CHF CVD among the main HDT-ASCT cohort, a multivariable Cox regression analysis, adjusted for age and sex, was performed. Risk factors investigated in this analysis included age, sex, educational level, comorbidities, lymphoma subtype, performance status (stratified as 0–1 or ≥2), number of treatment lines prior to treatment with HDT-ASCT (1 or ≥2), cumulative dosage of anthracycline prior to HDT-ASCT (stratified as <300 or ≥300 mg/m^2; estimated on the basis of number of treatment cycles and an assumption of full dose per cycle in a relatively young and healthy HDT-ASCT cohort) and radiotherapy (information on radiation field was not available in LYFO). The count of treatment lines before the HDT-ASCT procedure was defined as follows: One line if HDT-ASCT was used as consolidation in first-line treatment; two or more lines if HDT-ASCT was used as consolidation for relapsed/refractory disease following one or more lines of salvage therapy. The HDT-ASCT procedure was not counted as a treatment line.

In the HDT-ASCT eligible cohort, the multivariable Cox regression analysis of HDT-ASCT as a time-dependent exposure was adjusted for age and sex, and stratified on lymphoma subtype.[20]

A descriptive analysis of IHD and AF occurring after HDT-ASCT but before CHF was performed to investigate the cardiovascular pathways leading to CHF for patients in the main HDT-ASCT cohort versus matched comparators.

The study was registered in the North Denmark Region (study ID: 2021-150).

RESULTS

In the main HDT-ASCT cohort, a total of 787 patients treated with HDT-ASCT (34% DLBCL, 29% MCL, 22% PTCL and 15% HL) were included and matched to 3935 matched comparators (Table 1). The median age was 57 years and median follow-up was 7.6 years for patients. Five-year overall survival was 67% (95% CI: 64–71) for patients treated with HDT-ASCT and 96% (95% CI: 66–97) for matched comparators (Figure S1). Among included patients, 54% ($n = 426$) received HDT-ASCT as part of first-line therapy. Of the patients treated with HDT-ASCT in first line, the majority had MCL or PTCL subtypes (81%), while only 1% had HL and 18% had DLBCL. Of the patients with DLBCL treated with HDT-ASCT in first line, 90% had transformed lymphoma (co-existing new indolent lymphoma at first diagnosis of DLBCL).

Risk of CHF

The crude and adjusted HRs for CHF were 5.0 (95% CI: 3.5–7.2) and 5.5 (95% CI: 3.8–8.1), respectively, for patients treated with HDT-ASCT (main HDT-ASCT cohort) relative

TABLE 1 Baseline characteristics of patients from the main HDT-ASCT cohort and matched comparators.

Variable	Level	Patients treated with HDT-ASCT ($n=787$)	Matched comparators ($n=3935$)
Age (median, IQR)		57 (47, 63)	57 (47, 64)
Sex	Male	503 (63.9)	2515 (63.9)
	Female	284 (36.1)	1420 (36.1)
Educational level	Low	549 (70.7)	2792 (72.2)
	High	228 (29.3)	1075 (27.8)
	Missing	10	68
Lymphoma subtype	MCL	225 (28.6)	
	DLBCL	270 (34.3)	
	PTCL	173 (22.0)	
	cHL	119 (15.1)	
Number of treatment lines	1	426 (54.1)	
	≥2	361 (45.9)	
Radiotherapy	Yes	113 (14.4)	
Anthracycline dose	<300 mg/m^2	276 (35.1)	
	≥300 mg/m^2	511 (64.9)	
Ann Arbor stage	1–2	164 (20.8)	
	3–4	623 (79.2)	
Performance status at diagnosis	0–1	722 (91.7)	
	≥2	65 (8.3)	
Thyroid diseases	Yes	21 (2.7)	105 (2.7)
Hypertension	Yes	106 (13.5)	676 (17.2)
Diabetes mellitus	Yes	42 (5.3)	221 (5.6)
Renal diseases	Yes	17 (2.2)	71 (1.8)

Abbreviations: cHL, classic Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; HDT-ASCT, high-dose chemotherapy and autologous stem cell transplant; MCL, mantle cell lymphoma; PTCL, peripheral T-cell lymphoma.

TABLE 2 Crude and adjusted hazard ratios for congestive heart failure (CHF) and cardiovascular diseases not defined as congestive heart failure (non-CHF CVD) for patients treated with high-dose chemotherapy and autologous stem cell transplant compared to matched comparators.

	Crude hazard ratio (95% CI)	*p*-Value	Adjusted hazard ratio (95% CI)	*p*-Value
CHF	4.97 (3.45–7.18)	<0.001	5.52 (3.79–8.06)	<0.001
Non-CHF CVD	2.09 (1.66–2.62)	<0.001	2.22 (1.76–2.81)	<0.001

Note: Crude analyses were based on all 4722 individuals from the main cohort and the comparator cohort, and the adjusted analyses were based on 4644 patients due to missing data.

Abbreviations: CI, confidence interval; CHF, Congestive heart failure; CVD, Cardiovascular diseases.

to matched comparators (Table 2). The time-varying HR estimates (Figure 1A) showed highest risk immediately after HDT-ASCT (HR ~8.9 at 3 months) and subsequent decline to a plateau at HR ~3.6 after 10 years. The cumulative risk of developing CHF was higher in patients treated with HDT-ASCT (main HDT-ASCT cohort) as compared to matched comparators ($p<0.001$ for the whole period, Figure 2). After 5 years, the cumulative risk of CHF for patients was 4.3% (95% CI: 2.8–5.8) as compared to 1.0% (95% CI: 0.7–1.3) for matched comparators. After 10 years, the cumulative risk was 8.0% (95% CI: 5.7–10.3) as compared to 2.0% (95% CI: 1.5–2.5) respectively. The risk difference between patients and matched comparators was highest for males (10-year cumulative risk 10.2% [95% CI: 6.8–13.6] vs. 2.7% [95% CI: 1.9–3.4], $p<0.001$ for the whole period, Figure S2A) and less for females (10-year cumulative risk 4.4% [95% CI: 1.8–7.0] vs. 0.9% [95% CI: 0.2–1.5], $p<0.001$ for the whole period, Figure S2B). The risk of CHF was significantly higher in patients treated HDT-ASCT after ≥2 prior lines of therapy when compared to patients treated with HDT-ASCT after one prior line of therapy (Figure S3, $p=0.02$).

A total of 116 individuals developed CHF during follow-up (49 patients from the main HDT-ASCT cohort and 67 matched comparators). CHF occurred more often without any prior clinically identified IHD or AF in the HDT-ASCT setting (80% vs. 43%, $p<0.001$). Patients with CHF

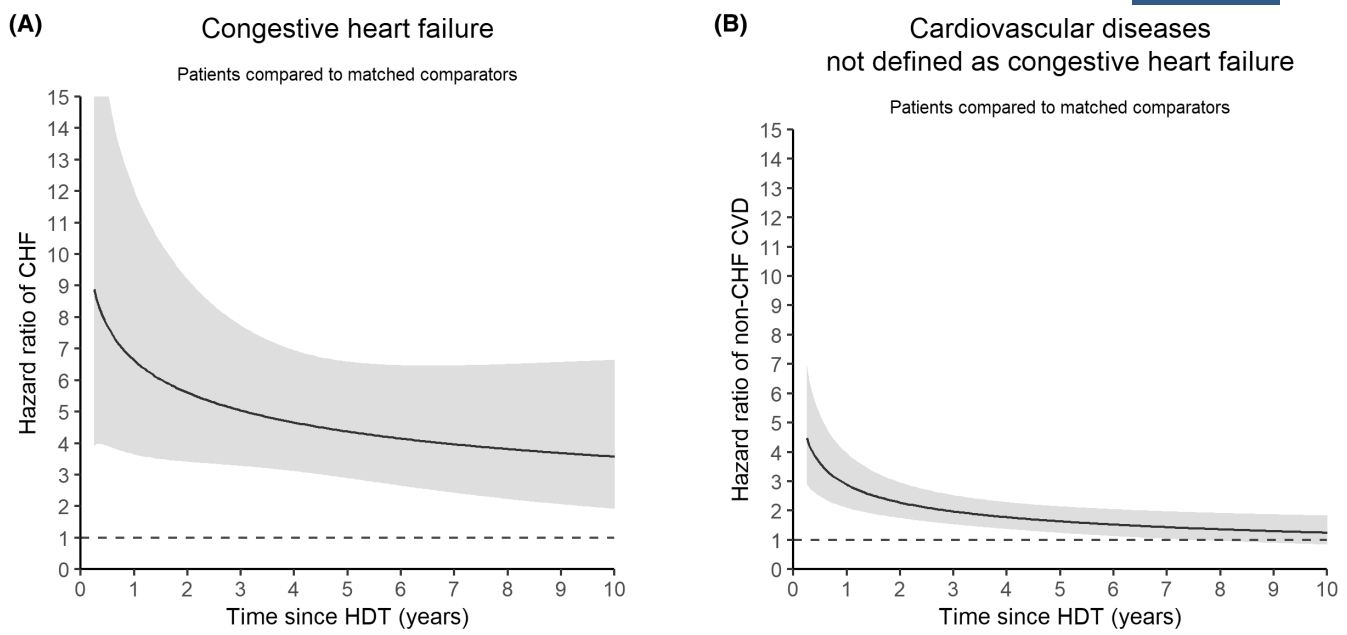

FIGURE 1 Time-varying hazard ratio from a flexible parametric model for (A) congestive heart failure (CHF) and (B) cardiovascular diseases not defined as congestive heart failure (non-CHF CVD) as function of follow-up time. HDT, high-dose therapy.

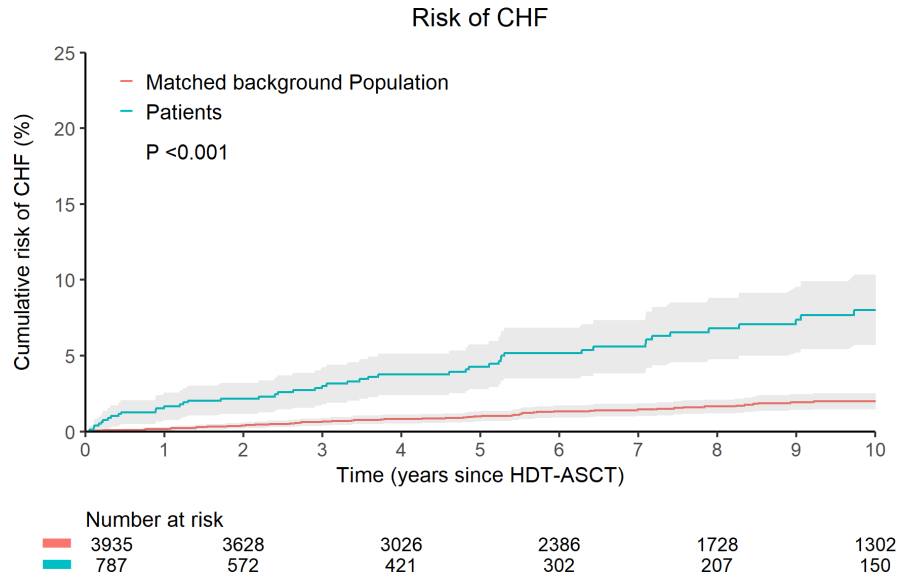

FIGURE 2 Cause-specific cumulative risk of congestive heart failure (CHF) in lymphoma patients treated with high-dose chemotherapy and autologous stem cell transplant (HDT-ASCT) and matched comparators from the general population.

after HDT-ASCT were younger than matched comparators at the time for first CHF diagnosis (55 vs. 60 years).

Risk factors for the development of CHF among the main HDT-ASCT cohort were male sex (HR of 2.1 [95% CI: 1.1–4.2]), treatment with two or more lines of therapy prior to HDT-ASCT (HR of 2.7 [95% CI: 1.5–4.9]), hypertension (HR of 2.0 [95% CI: 1.0–4.1]) and treatment with ≥300 mg/m^2 cumulative dosage of anthracycline compared to <300 mg/m^2 (HR of 2.1 [95% CI: 1.1–4.0]) (Table 3).

In the HDT-ASCT eligible cohort, a total of 4089 patients with DLBCL and HL were included in the multivariable Cox regression with HDT-ASCT as a time-dependent exposure. The HR for CHF associated with HDT-ASCT exposure was 2.6 (95% CI: 1.8–3.8), $p < 0.001$, after adjusting for age and sex and stratifying on lymphoma subtype.

Risk of non-CHF CVD

The crude and adjusted HRs for non-CHF CVD, mainly ischaemic heart disease and atrial fibrillation, after HDT-ASCT (main HDT-ASCT cohort) were 2.1 (95% CI:

TABLE 3 Risk factors for congestive heart failure (CHF) and cardiovascular diseases not defined as congestive heart failure (non-CHF CVD) among patients treated with high-dose chemotherapy and autologous stem cell transplant.

		CHF		Non-CHF CVD	
Variable	**Level**	**Hazard ratio (95% CI)**	***p*-Value**	**Hazard ratio (95% CI)**	***p*-Value**
Sex	Male	2.14 (1.09; 4.21)	0.03	1.45 (0.93; 2.27)	0.10
Age per decade		1.01 (0.99; 1.03)	0.47	1.06 (1.03; 1.08)	<0.001
Performance status >2		0.25 (0.03; 1.81)	0.17	1.41 (0.73; 2.72)	0.30
Previous radiotherapy		0.90 (0.40; 2.02)	0.80	1.38 (0.83; 2.31)	0.22
Number of treatment lines ≥2		2.69 (1.48; 4.90)	<0.001	1.65 (1.10; 2.48)	0.01
Diabetes mellitus		0.74 (0.18; 3.05)	0.67	1.75 (0.88; 3.50)	0.11
Thyroid diseases		1.27 (0.17; 9.43)	0.81	1.53 (0.48; 4.93)	0.47
Renal diseases		0.88 (0.12; 6.41)	0.90	2.10 (0.85; 5.20)	0.11
Hypertension		2.04 (1.00; 4.13)	0.05	1.62 (0.99; 2.66)	0.05
Anthracycline ≥300 mg/m^2		2.06 (1.07; 3.99)	0.03	1.86 (1.19; 2.91)	0.01
Lymphoma subtype	cHL	Reference			
	DLBCL	1.80 (0.74; 4.39)	0.19	1.48 (0.71; 3.10)	0.30
	MCL	0.37 (0.12; 1.18)	0.09	0.70 (0.31; 1.55)	0.38
	PTCL	1.17 (0.44; 3.15)	0.75	1.42 (0.64; 3.15)	0.38

Note: All models were adjusted for age and sex (except for the age model and the sex model respectively). Analyses were based on all 787 individuals from the HDT-ASCT-treated cohort.

Abbreviations: cHL, classic Hodgkin lymphoma; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; HDT-ASCT, high-dose chemotherapy and autologous stem cell transplant; MCL, mantle cell lymphoma; PTCL, peripheral T-cell lymphoma.

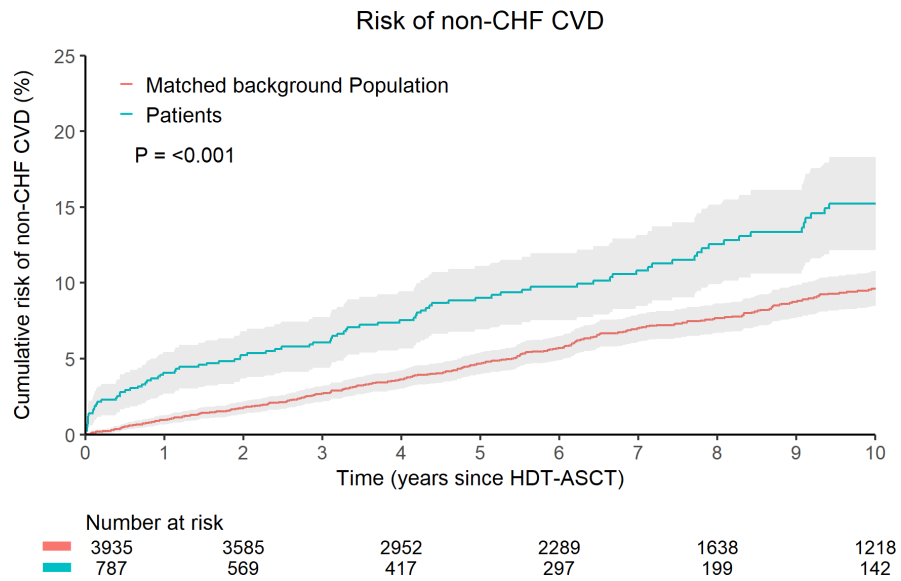

FIGURE 3 Cause-specific cumulative risk of cardiovascular diseases not defined as congestive heart failure (non-CHF CVD) in lymphoma patients treated with high-dose chemotherapy and autologous stem cell transplant (HDT-ASCT) and matched comparators from the general population.

1.7–2.6) and 2.2 (95% CI: 1.8–2.8), respectively, compared to matched comparators (Table 2). The risk of non-CHF CVD was highest immediately after HDT-ASCT (HR ~4.5 at 3 months) and declined to a plateau of HR ~1.2 at 10 years (Figure 1B). The cumulative risk of developing non-CHF CVD was increased in patients treated with HDT-ASCT (main HDT-ASCT cohort) as compared to matched comparators ($p < 0.001$ for the whole period, Figure 3). After 5 years, the cumulative risk of non-CHF CVD was 9.0% (95% CI: 6.9–11.1) for patients and 4.7% (95% CI: 4.0–5.4) for matched comparators. After 10 years, the cumulative risk was 15.2% (95% CI: 12.2–18.3) for patients and 9.6% (95% CI: 8.5–10.8) for matched comparators. For males, risk of non-CHF CVD was statistically significantly different for HDT-ASCT-treated patients and matched comparators (10-year cumulative risk 17.7% [95% CI: 13.6–21.9]

for patients vs. 11.7% [95% CI: 10.1–13.3] for comparators, $p = 0.01$ for the whole period, Figure S4A). Female patients had increased risk of non-CHF CVD (11.0% [95% CI: 6.7–15.3] for patients vs. 6.2% [95% CI: 4.7–7.7] for matched comparators, $p < 0.001$ for the whole period, Figure S4B). The risk of non-CHF CVD was similar in patients treated HDT after ≥2 prior lines of therapy compared to patients treated with HDT-ASCT after one prior line of therapy (Figure S5, $p = 0.55$).

Risk factors for non-CHF CVD among the main HDT-ASCT cohort were age (HR per decade of 1.6 [95% CI: 1.3–1.8]), treatment with two or more lines of therapy prior to HDT-ASCT (HR of 1.7 [95% CI: 1.1–2.5]), hypertension (HR 1.6 [95% CI: 1.0–2.7]) and treatment with ≥300 mg/m^2 cumulative dosage of anthracycline compared to <300 mg/m^2 (HR of 1.9 [95% CI: 1.2–2.9]) (Table 3).

In the HDT-ASCT eligible cohort with HDT-ASCT as time-dependent exposure in a multivariable Cox regression, the HR for non-CHF CVD associated with HDT-ASCT was 1.9 (95% CI: 1.4–2.6), $p < 0.001$.

DISCUSSION

To the best of our knowledge, this is the first study to separately address CHF and non-CHF CVD risk associated with HDT-ASCT in lymphoma in a population-based setting. HDT-ASCT increased the risk of CVD events relative to a matched general population despite possible healthy patient selection bias and higher competing risk of death without CVD among patients. HDT-ASCT was also a risk factor when analysed as a time-dependent exposure among HDT-ASCT eligible lymphoma patients. Male sex, treatment with two or more lines of therapy prior to HDT-ASCT, estimated ≥300 mg/m^2 cumulative anthracycline dose and hypertension were associated with increased risk of CHF after HDT-ASCT.

The estimated 10-year risk of CHF in HDT-ASCT-treated patients was 8.0% in the present study, which is lower than the 10.6% symptomatic cases identified in a cross-sectional Norwegian study.[5] In the latter, all patients were invited to echocardiography at a median of ~11 years after HDT-ASCT. The use of echocardiography enabled the identification of both symptomatic and asymptomatic CHF (10.6% and 5.1%, respectively, in the Norwegian study) in contrast to the present study, which only included formally diagnosed CHF in hospital/outpatient registers. In addition, the cross-sectional study investigated only living patients who were healthy enough to travel to a tertiary hospital (69% of the invited patients alive), potentially underestimating the true prevalence of CHF in this population.

Cumulative anthracycline dose of ≥300 mg/m^2 was associated with increased CHF risk in the present study (HR 2.1), consistent with previous findings.[5,8,9,23,24] The aforementioned Norwegian cross-sectional study reported similar association between CHF and cumulative anthracycline dose ≥300 mg/m^2 (odds ratio [OR] of 3.3).[5] Two retrospective case–control studies also found significantly increased CHF risk in patients treated with cumulative doses ≥300 mg/m^2, with, respectively, a relative risk of 2.93[23] and OR of 3.2[9] (the latter study being in solely HDT-ASCT-treated patients and having a cut-off anthracycline dose of ≥250 mg/m^2). Anthracyclines are known to cause CHF, with a clear dose–response relationship among patients with DLBCL undergoing first-line R-CHOP therapy.[24]

The present study provided CVD risk estimates in a population that is similar agewise to those receiving HDT-ASCT in recent trials of second-line CAR-T versus HDT-ASCT.[10] The age of patients considered eligible for HDT-ASCT has increased substantially during recent decades and likely influence observed toxicity patterns after HDT-ASCT. The data provided are more reflective of a contemporary HDT-ASCT patient population in contrast to three prior studies of CVD risk of HDT-ASCT where mean age was below 45 years.[5,8,25] However, in the present cohort, age at time of HDT-ASCT was not an independent risk factor for CHF. This was in contrast to a US single-centre case–control study of 882 HDT-ASCT-treated patients with lymphoma that found that patients above 55 years at the time of HDT-ASCT had higher risk for CHF with an adjusted relative risk of 4.1.[8]

The risk of CHF in HDT-ASCT-treated patients remained higher than in the general population throughout follow-up. Similar results were seen in a Dutch study of 4919 patients with HL; excess cardiovascular mortality and CHF risk (over the general population) were evident as long as 40 years after treatment with a standardized circulatory system-specific mortality ratio of 5.5, although these results may primarily have been driven by radiotherapy exposure.[6,7] It is not fully elucidated why the risk remains increased many years after end of treatment, but there are several mechanisms through which anthracyclines can damage the heart muscle. They include direct myocyte death in the short term and permanent disruption of sarcomere structure in the long term.[26]

Interestingly, we found that most patients with CHF after HDT-ASCT did not experience IHD or AF prior to CHF in contrast to matched comparators, where only 40% developed CHF without previous IHD or AF.

Among the strengths of the present study are the prospective data collections in LYFO and administrative registers used for capturing CVD events. Only a very small proportion of the included patients and comparators emigrate, and national follow-up including event capture is complete. Therefore, attrition bias is considered minimal compared to the cross-sectional and case–control studies. In addition, we were able to perform a comparison of CHF risk in HDT-ASCT patients and patients with lymphoma treated with standard immunochemotherapy only (i.e. typically R-CHOP/ABVD/BEACOPP) to isolate the additional contribution of salvage regimens and HDT-ASCT to CVD risk. There were several weaknesses inherent to the dependence on register data. No data on smoking, sedentary lifestyle, increased body mass index and hypercholesterolemia was available. As a proxy for these factors, information on educational level was included in the analyses, which has been found

to be inversely correlated to these covariates.[27] Patients and comparators had very similar educational levels, which indicates possible balance in these risk factors (smoking, sedentary lifestyle, increased body mass index). There is a risk of surveillance bias as patients with lymphoma have more frequent contact to health-care professionals and access to diagnostic work-up. This could overestimate CVD risk associated with HDT-ASCT. However, our study showed that the time-varying HR for CHF was increased for patients during the entire follow-up period and not only during the period where patients were seen frequently as part of lymphoma follow-up. Confirming a genuine increase in risk, HDT-ASCT was also associated with CHF and non-CHF CVD when analysing patients only.

The findings of this study are important in light of alternative therapies to HDT-ASCT for patients with lymphoma.[10,13,28] CVD, and in particular CHF, risks should be considered when deciding for HDT-ASCT in patients where alternative and equally effective (or better) therapies exist. Risk factors for CHF (male sex, number of treatment lines, hypertension and cumulative anthracycline dose) could be considered before allocating patients for HDT-ASCT or novel immunotherapies. However, it should be noted that CAR-T therapy can also lead to cardiac adverse events in as many as 16% of patients, especially in relation to cytokine release syndrome.[29] Furthermore, a report found that CAR-T therapy could induce a lasting decrease in left ventricular ejection fraction in roughly 3% of recipients.[30]

In summary, we find that the risk of CHF was significantly increased for HDT-ASCT-treated patients compared to both a matched general population and patients treated with first-line therapy without consolidating HDT-ASCT, despite likely selection of healthy patients to HDT-ASCT. Both the risk of CHF and non-CHF CVD were significantly increased in patients treated with HDT-ASCT and major risk factors for CHF were male sex, two or more prior treatment lines, ≥300 mg/m^2 cumulative dosage of anthracycline and hypertension. The results presented advocate a low threshold for referring HDT-ASCT-treated patients with cardiovascular symptoms to relevant diagnostic work-up.

AUTHOR CONTRIBUTIONS

Joachim Baech, Simon Husby, Trine Trab and Tarec C. El-Galaly contributed to the conception and design of the study. Joachim Baech and Simon Husby performed the management and coordination of responsibilities. Joachim Baech, Simon Husby, Peter Brown, Trine Trab, Jette S. Gørløv, Judit M. Jørgensen, Sif Gudbrandsdottir, Marianne Tang Severinsen, Kirsten Grønbæk, Thomas Stauffer Larsen and Tarec C. El-Galaly contributed to acquisition of data. Joachim Baech, Simon Husby and Lasse Hjort Jakobsen performed data analysis. Joachim Baech, Simon Husby, Lasse Hjort Jakobsen and Tarec C. El-Galaly directly accessed and verified the data. Joachim Baech and Simon Husby drafted the manuscript. All authors contributed to interpretation of the results and revised the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

KG and TT received research support from Janssen and is on the advisory board of Nanexa and GSK. JB, SH, KK, PB, JSG, JMJ, SG, MTS, TSL, TW, SE, KBS, LHJ and TCE-G declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are not available, as it is not allowed to share individual participant data from Statistics Denmark, according to rules set forth by the Danish Authorities.

ETHICS STATEMENT

Ethical approval and written informed consent were not needed according to Danish law on retrospective studies based on data from registers.

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REFERENCES

1. Philip T, Guglielmi C, Hagenbeek A, Somers R, van der Lelie H, Bron D, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med. 1995;333(23):1540–5. https://doi.org/10.1056/NEJM199512073332305
2. Zelenetz AD, Gordon LI, Chang JE, Christian B, Abramson JS, Advani RH, et al. NCCN guidelines® insights: B-cell lymphomas, version 5.2021. J Natl Compr Canc Netw. 2021;19(11):1218–30. https://doi.org/10.6004/jnccn.2021.0054
3. d'Amore F, Gaulard P, Trümper L, Corradini P, Kim WS, Specht L, et al. Peripheral T-cell lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(June):v108–15. https://doi.org/10.1093/annonc/mdv201

4. Schaapveld M, Aleman BM, van Eggermond AM, Janus CP, Krol AD, van der Maazen RW, et al. Second cancer risk up to 40 years after treatment for Hodgkin's lymphoma. N Engl J Med. 2015;373(26):2499–511. https://doi.org/10.1056/NEJMoa1505949
5. Murbraech K, Smeland KB, Holte H, Loge JH, Lund MB, Wethal T, et al. Heart failure and asymptomatic left ventricular systolic dysfunction in lymphoma survivors treated with autologous stem-cell transplantation: a national cross-sectional study. J Clin Oncol. 2015;33(24):2683–91. https://doi.org/10.1200/JCO.2015.60.8125
6. van Nimwegen FA, Schaapveld M, Janus CPM, Krol AD, Petersen EJ, Raemaekers JM, et al. Cardiovascular disease after Hodgkin lymphoma treatment: 40-year disease risk. JAMA Intern Med. 2015;175(6):1007–17. https://doi.org/10.1001/jamainternmed.2015.1180
7. de Vries S, Schaapveld M, Janus CPM, Daniëls LA, Petersen EJ, van der Maazen RWM, et al. Long-term cause-specific mortality in Hodgkin lymphoma patients. J Natl Cancer Inst. 2021;113(6):760–9. https://doi.org/10.1093/jnci/djaa194
8. Armenian SH, Sun CL, Shannon T, Mills G, Francisco L, Venkataraman K, et al. Incidence and predictors of congestive heart failure after autologous hematopoietic cell transplantation. Blood. 2011;118(23):6023–9. https://doi.org/10.1182/blood-2011-06-358226
9. Armenian SH, Sun CLL, Francisco L, Steinberger J, Kurian S, Wong FL, et al. Late congestive heart failure after hematopoietic cell transplantation. J Clin Oncol. 2008;26(34):5537–43. https://doi.org/10.1200/JCO.2008.17.7428
10. Locke FL, Miklos DB, Jacobson CA, Perales MA, Kersten MJ, Oluwole OO, et al. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. N Engl J Med. 2022;386(7):640–54. https://doi.org/10.1056/nejmoa2116133
11. Younes A, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. J Clin Oncol. 2012;30(18):2183–9. https://doi.org/10.1200/JCO.2011.38.0410
12. Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med. 2015;372(4):311–9. https://doi.org/10.1056/NEJMoa1411087
13. Dickinson MJ, Carlo-Stella C, Morschhauser F, Bachy E, Corradini P, Iacoboni G, et al. Glofitamab for relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2022;387(24):2220–31. https://doi.org/10.1056/nejmoa2206913
14. Sehn LH, Hertzberg M, Opat S, Herrera AF, Assouline S, Flowers CR, et al. Polatuzumab vedotin plus bendamustine and rituximab in relapsed/refractory DLBCL: survival update and new extension cohort data. Blood Adv. 2022;6(2):533–43. https://doi.org/10.1182/bloodadvances.2021005794.Quali
15. Abramson JS, Solomon SR, Arnason JE, Johnston PB, Glass B, Bachanova V, et al. Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study. Blood. 2023;141(14):1675–84. https://doi.org/10.1182/blood.2022018730
16. Maurer MJ, Jakobsen LH, Mwangi R, Schmitz N, Farooq U, Flowers CR, et al. Relapsed/Refractory International Prognostic Index (R/R-IPI): an international prognostic calculator for relapsed/refractory diffuse large B-cell lymphoma. Am J Hematol. 2021;96(5):599–605. https://doi.org/10.1002/ajh.26149
17. Arboe B, El-Galaly TC, Clausen MR, Munksgaard PS, Stoltenberg D, Nygaard MK, et al. The Danish National Lymphoma Registry: coverage and data quality. PLoS One. 2016;11(6):e0157999. https://doi.org/10.1371/journal.pone.0157999
18. Lynge E, Sandegaard JL, Rebolj M. The Danish national patient register. Scand J Public Health. 2011;39(7):30–3. https://doi.org/10.1177/1403494811401482
19. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol. 2014;29(8):541–9. https://doi.org/10.1007/s10654-014-9930-3
20. Fisher LD, Lin DY. Time-dependent covariates in the cox proportional-hazards regression model. Annu Rev Public Health. 1999;20(6):145–57. https://doi.org/10.1146/annurev.publhealth.20.1.145
21. Jensen VM, Rasmussen AW. Danish education registers. Scand J Public Health. 2011;39(7):91–4. https://doi.org/10.1177/1403494810394715
22. Liu XR, Pawitan Y, Clements M. Parametric and penalized generalized survival models. Stat Methods Med Res. 2018;27(5):1531–46. https://doi.org/10.1177/0962280216664760
23. van Nimwegen FA, Ntentas G, Darby SC, Schaapveld M, Hauptmann M, Lugtenburg PJ, et al. Risk of heart failure in survivors of Hodgkin lymphoma: effects of cardiac exposure to radiation and anthracyclines. Blood. 2017;129(16):2257–65. https://doi.org/10.1182/blood-2016-09-740332
24. Baech J, Hansen SM, Lund PE, Soegaard P, Brown PN, Haaber J, et al. Cumulative anthracycline exposure and risk of cardiotoxicity; a Danish nationwide cohort study of 2440 lymphoma patients treated with or without anthracyclines. Br J Haematol. 2018;183(5):717–26. https://doi.org/10.1111/bjh.15603
25. Hertenstein B, Stefanic M, Schmeiser T, Scholz M, Göller V, Clausen M, et al. Cardiac toxicity of bone marrow transplantation: predictive value of cardiologic evaluation before transplant. J Clin Oncol. 1994;12(5):998–1004. https://doi.org/10.1200/JCO.1994.12.5.998
26. Sawyer DB, Peng X, Chen B, Pentassuglia L, Lim CC. Mechanisms of anthracycline cardiac injury: can we identify strategies for cardioprotection? Prog Cardiovasc Dis. 2010;53(2):105–13. https://doi.org/10.1016/j.pcad.2010.06.007
27. Hoeymans N, Smit HA, Verkleij H, Kromhout D. Cardiovascular risk factors in relation to educational level in 36 000 men and women in The Netherlands. Eur Heart J. 1996;17(4):518–25. https://doi.org/10.1093/oxfordjournals.eurheartj.a014903
28. Dreyling M, Doorduijn JK, Gine E, Jerkeman M, Walewski J, Hutchings M, et al. Efficacy and safety of ibrutinib combined with standard first-line treatment or As substitute for autologous stem cell transplantation in younger patients with mantle cell lymphoma: results from the randomized triangle trial by the European MCL network. Blood. 2022;140(Suppl 1):1–3. https://doi.org/10.1182/blood-2022-163018
29. Goldman A, Maor E, Bomze D, Liu JE, Herrmann J, Fein J, et al. Adverse cardiovascular and pulmonary events associated with chimeric antigen receptor T-cell therapy. J Am Coll Cardiol. 2021;78(18):1800–13. https://doi.org/10.1016/j.jacc.2021.08.044
30. Ganatra S, Redd R, Hayek SS, Parikh R, Azam T, Yanik GA, et al. Chimeric antigen receptor T-cell therapy-associated cardiomyopathy in patients with refractory or relapsed non-Hodgkin lymphoma. Circulation. 2020;142(17):1687–90. https://doi.org/10.1161/CIRCULATIONAHA.120.048100

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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