Cardiovascular adverse events in patients treated with the (R-)CHOP regimen – a systematic review and meta-analysis in the era of cardio-oncology

Marijke Linschoten*, Janine AM Kamphuis*, Anna van Rhenen, Laurens P Bosman, Maarten J Cramer, Pieter A Doevendans, Arco J Teske†, Folkert W Asselbergs†

* Shared first authorship

† Shared last authorship

Department of Cardiology, Division of Heart and Lungs, University Medical Centre Utrecht, University of Utrecht, The Netherlands (M Linschoten MD; JAM Kamphuis MD; LP Bosman MD; MJ Cramer MD; Prof PA Doevendans MD; AJ Teske MD, Prof FW Asselbergs MD)
Department of Haematology, Cancer Centre, University Medical Centre Utrecht, University of Utrecht, the Netherlands (A van Rhenen MD)
Netherlands Heart Institute, Utrecht, The Netherlands (Prof PA Doevendans MD; Prof FW Asselbergs MD)
Central Military Hospital, Utrecht, The Netherlands (Prof PA Doevendans MD)
Health Data Research UK and Institute of Health Informatics, University College London, London, UK (Prof FW Asselbergs MD)
Institute of Cardiovascular Science, Faculty of Population Health Sciences, University College London, London, UK (Prof FW Asselbergs MD)

Correspondence to:
Marijke Linschoten, MD
University Medical Centre Utrecht
Internal postal address E03.511
PO Box 85500, 3508 GA UTRECHT
Phone number: +31 88 755 5555
Fax number: +31 88 75 556 60
E-mail: m.p.m.linschoten@umcutrecht.nl

Total word count: 4,657

Summary

Background: Patients treated for Non-Hodgkin Lymphoma's (NHL) are at risk of cardiovascular adverse events (CVAEs), with the risk of heart failure (HF) being particularly high. (R-)CHOP, the standard treatment for aggressive NHL, contains doxorubicin and cyclophosphamide, both associated with left ventricular (LV) dysfunction. The aim of this study was to delineate the cardiovascular toxicity of this regimen.

Methods: We systematically searched PubMed, EMBASE, and the Cochrane Library from inception to 03/06/2019 for clinical trials and observational studies in adult NHL patients that received first-line treatment with (R-)CHOP. Studies reporting on CVAEs and treatment-related cardiovascular mortality were included. Abstracts and articles not written in English were excluded. The main outcomes were the proportion of patients with grade 3+4 CVAEs and HF. Meta-analyses of one-sample proportions were carried out. Subgroup analyses on summary estimates were performed to determine the effect of number of (R-) CHOP cycles, cycle interval, age and sex.

Findings: Of 2,314 entries identified, 137 studies were eligible (median follow-up 39.0 months [IQR 25.5-52.8]). Fifty-three (39%) out of 137 studies were rated as high risk of bias for incomplete outcome data and 54 (39%) out of 137 for selective reporting. The pooled proportion for grade 3+4 CVAEs was 2.35% [95%CI 1.81-2.93](77 studies, n=14,351 patients; heterogeneity test: Q=326.21; τ^2=0.0042; I^2=71.40%; p< 0.001), with female sex and older age (≥65 years, RR 3.18 [95%CI 2.54; 3.98]) being associated with an increased risk. For HF (38 studies, n=5,936 patients; heterogeneity test: Q=527.33; τ^2=0.0384; I^2=95.05%; p<0.001), the pooled proportion was 4.62% [95%CI 2.25-7.65%], with a significant increase in reported HF from 1.64% [95%CI 0.82-2.65] to 11.72% [95%CI 3.00-24.53] when cardiac function was evaluated post-chemotherapy (p=0.017).

Interpretation: The considerable increase of reported HF with cardiac monitoring, indicates that this complication often remains unnoticed. Our findings are of importance to raise the awareness of this complication among clinicians treating NHL patients and stresses the need for cardiac monitoring during-

and post-chemotherapy. Prompt initiation of HF treatment in the pre-symptomatic phase can mitigate the progression to more advanced heart failure stages.

Funding: None.

Introduction

Non-Hodgkin lymphoma's (NHL) comprise a wide variety of neoplasms arising from the lymphoid tissues. With an estimated 509,600 new cases in 2018, NHL accounts for approximately 3% of all cancer cases worldwide[1]. Over the last four decades, the survival rate of patients with these malignancies has improved markedly and currently, 72% of patients survive up to 5-years after the diagnosis[2]. In line with these developments, the management and prevention of treatment-related side effects is becoming increasingly important.

There is accumulating evidence that the risk of cardiovascular disease (CVD) is considerably raised in NHL patients and survivors[3,4]. The reasons behind this observation are believed to be multifactorial, driven by amongst others shared risk factors between cancer and CVD[5] as well as toxic cardiovascular effects of antineoplastic drugs[6]. In particular, the risk of heart failure (HF) is substantially elevated, with an adjusted hazard ratio of 1.77 [95% CI 1.50-2.09][4] and a standardized incidence ratio of 5.4 [95% CI 4.1-6.9] when compared to the general population[3]. Moreover, set side by side to patients treated for other malignancies, the risk of HF appears especially high in this patient population[4]. It is conceivable that the chemotherapeutic regimens used to treat these neoplasms play an important role herein.

The CHOP regimen (cyclophosphamide 750mg/m^2, doxorubicin 50mg/m^2, vincristine 1.4mg/m^2 (maximal dose 2mg) and prednisone) was first introduced in 1976, and soon evolved to become the golden standard for the treatment of patients with aggressive NHL[7,8]. In patients with B-cell NHL, CHOP is combined with the anti-CD20 monoclonal antibody rituximab (375mg/m^2)(R-CHOP) after the LNH98-5 trial showed overwhelming benefit[9,10]. (R-)CHOP contains two agents associated with a high risk of left ventricular (LV) dysfunction, namely the anthracycline doxorubicin and the alkylator cyclophosphamide[11]. The dose-dependent incidence of HF in patients treated with doxorubicin has with time resulted in a

restriction of the maximum cumulative dose to 450 mg/m^2, correlating with a ~5% incidence of symptomatic HF[6]. Nevertheless, as some patients develop severe HF at much lower doses[12] it appears there is no 'safe' dose and individual tolerability is, for a large part, also dependent on patient-related related risk factors[13,14]. In comparison to anthracyclines, the causal link between cyclophosphamide and LV dysfunction has received far less attention. Cyclophosphamide-induced cardiotoxicity mostly occurs within days of treatment initiation, and can lead to HF (2-38%)[15—20] and/or (myo)pericarditis (9-27%)[15,20,21].

Despite the combination of these two highly cardiotoxic agents within (R-)CHOP, the incidence of cardiovascular adverse events (CVAEs) in patients treated with this regimen has been poorly established. An important limitation of previous studies is the inclusion of patients that have received different first line chemotherapeutic regimens with varying doses of cardiotoxic agents[22—24]. Additionally, the larger studies have only captured cases of symptomatic HF leading to hospital contact[23,24], thereby potentially underestimating the true incidence of LV dysfunction. Since it is the expectation that CHOP will remain the backbone in the treatment of aggressive NHL for the upcoming years, insight into the incidence of CVAEs in patients treated with this specific regimen is of great importance. Furthermore, identification of factors predisposing NHL patients to CVAEs can aid in individual risk stratification. With this systematic review and meta-analysis, we aimed at determining the proportion of NHL patients developing CVAEs after receiving (R-)CHOP as a first-line treatment and identify factors modulating this risk.

Methods

This systematic review and meta-analysis was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)(appendix p2)[25].

The literature search was performed by two independent researchers (ML, JAMK) in PubMed, EMBASE, and the Cochrane Library (CENTRAL) from inception of each database to 03/06/2019. The complete search string is provided in the appendix (p3). We selected clinical trials and observational studies in adult patients with NHL that received first-line treatment with (R-)CHOP. Reviews, letters, commentaries, case reports, conference abstracts, preclinical studies, and articles not written in English were excluded. Also studies in which (R-)CHOP was combined with other chemo- or immunotherapeutic

agents were removed. In case other chemotherapeutic agents were administered sequentially, the study was deemed eligible only if (R-)CHOP toxicity reports were available prior to the initiation of other agents. If articles were based on the same trial, we selected the most recent article with the longest follow-up or the article reporting the most complete toxicity data.

Studies were included in the systematic review if at least one of the following variables could be extracted: (1) numbers of patients experiencing CVAEs reported in grades, preferably with the use of a well-established toxicity grading system to quantify the severity of the adverse events (e.g. World Health Organization (WHO) Toxicity Grading Scale, or the Common Terminology Criteria for Adverse Events (CTCAE) of the US National Cancer Institute, etc.), (2) number of patients who died due to CVAEs stated to be (possibly) treatment-related and (3) number of patients with clinical (symptomatic) and, if available, subclinical HF (i.e. asymptomatic LV dysfunction). We here use the term 'overall HF' as an umbrella term for both clinical- and subclinical HF. If CVAEs were not reported, only studies explicitly mentioning that no such events occurred where included. In addition, only when all causes of deaths were specified, we assumed no treatment-related cardiovascular deaths had occurred.

Data extraction

We extracted the following counts from all studies found eligible: number of patients included in the toxicity analysis, proportion of patients with grade 1 (mild), 2 (moderate), 3 (severe) and 4 (life-threatening) CVAEs, number of patients with cardiomyopathy or HF, number of patients who discontinued treatment due to treatment-related cardiomyopathy or HF and number of (possibly) treatment-related cardiovascular deaths (grade 5 toxicity). In addition, the number of patients who died at the end of study follow-up (i.e. all-cause mortality) were gathered. The data extraction was performed independently by two researchers (ML, JAMK). In case of discrepancies, the study was re-evaluated and a consensus was reached.

Risk of bias

For the assessment of bias in individual studies the Cochrane Risk of Bias Tool was used[26]. Nevertheless, almost all studies compared the neoplastic efficacy of (R-)CHOP to another

chemotherapeutic regimen and thereby, information on the occurrence of AEs was only extracted for the group of patients receiving (R-)CHOP. Subsequently all these 'single-arms' of different studies were pooled. For this reason, after careful consideration, we judged that random sequence generation, allocation concealment and blinding of participants, personnel and outcome assessment was not likely to introduce bias. Incomplete outcome data and selective reporting were however viewed as important potential sources of bias and these were assessed for all studies. A quality assessment on the reporting of safety data was done using the CONSORT extension for harms checklist[27]. As a vast majority of studies were primarily conducted to evaluate the efficacy of (R-)CHOP and not to determine the incidence of CVAEs, we deemed the risk of publication bias negligible. For this reason, we did not perform the traditional publication bias modelling tool.

Statistical analysis

Meta-analyses of one-sample proportions were carried out for the proportion of patients developing grade 1+2 CVAEs, grade 3+4 CVAEs, HF, treatment discontinuation due to HF, and cardiovascular death. A double-arcsine transformation was applied on the proportions to establish a normal distribution appropriate for pooling[28]. Weights for each study in the analysis were based on the inverse of their variance. Heterogeneity between studies was estimated using the Q-statistic, I^2 and τ^2. Heterogeneity was classified as low (25%), moderate (50%) and large (75%), respectively[29]. The fixed-effect model was used to pool the summary proportions when the heterogeneity was <50%, otherwise, the random-effects model was used. Pre-specified subgroup analyses were performed for grade 3+4 CVAEs and HF. These subgroups involved the categorical outcomes 'R-CHOP vs. CHOP' and 'cardiac screening after chemotherapy', and the continuous outcomes 'number of cycles', 'interval between cycles', 'age' and 'sex'. All statistical analyses were performed in R version 3.5.1 (R Foundation, Vienna, Austria), with the aid of the 'metafor' package version 2.1-0[30]. Statistics were performed in collaboration with an independent clinical epidemiologist (LPB).

Role of the funding source

There was no funding source for this study. The funding sources of individual researchers that contributed to the study did not have any role in the study design, data collection, data analysis, data interpretation, or writing of the report. ML, JAMK and LPB had access to the raw data. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Results

The literature search yielded a total of 2,314 records, from which 426 duplicates were removed (**Figure 1**). Based on abstract screening 1,534 irrelevant studies were excluded. After assessing the full-text of 354 articles, we eventually included 137 studies in the systematic review (21,211 patients) published between April 1984 and June 2019. Of these, 26 studies made a comparison between different subgroups of (R-)CHOP treatment. Thereby, a total of 165 subgroups were available for the meta-analysis. Standard doses of doxorubicin (50 mg/m^2 per cycle), cyclophosphamide (750 mg/m^2 per cycle) and vincristine (1.4 mg/m^2 (max. 2mg)) were given in 136 (82.4%) out of 165 subgroups. Eighty-five subgroups were treated with CHOP, 76 with R-CHOP and in 4 studies both CHOP and R-CHOP were used without a subdivision in separate groups. Most studies investigated the efficacy of (R-)CHOP for the treatment of high-grade NHLs (n=136 subgroups covering 18,535 patients in total). The mean interval between cycles was 19.9±3.4 days and the mean number of cycles was 6.3±1.3. Overall, the median follow-up of the included studies was 39.0 months [IQR 25.5-52.8]. In total, 133 studies had a prospective study design and 4 studies were of retrospective nature. An overview of study characteristics and the types of NHL patients were treated for can be found in the appendix (p4). Of all 137 studies, 103 (75%) reported AEs using a well-established toxicity grading system and 29 (21%) did report AEs in grades without further specification on which grading system was used. In total, 85 studies reported on the occurrence of CVAEs. Only 6 (4.4%) out of 137 studies specified the incidence of HF or cardiomyopathy as a primary or secondary outcome.

Ninety-six subgroups were derived from 77 studies that reported on the proportion of patients with high-grade (III-IV) CVAEs. A total of 14,351 patients were included in the meta-analysis, for which a random effects model was used (heterogeneity test: $Q=326.21$; $\tau^2=0.0042$; $I^2=71.40\%$; $p< 0.001$). The proportion of grade 3+4 CVAEs ranged from 0% up to 15.1% with a pooled proportion of 2.35% [95% CI

1.81-2.93](**Figure 2**). Subgroup analysis showed a significant influence of age (regression coefficient 0.39; p<0.0001) where studies that included patients with a median age ≥65 years had a relative risk (RR) of 3.18 [95% CI 2.54-3.98] compared to studies including patients with a median age <65 years (**Table 1;** appendix p10). The variable "sex", expressed as percentage of females, showed a significant effect, with a higher proportion of patients with high grade CVAEs in studies with a larger percentage of females (regression coefficient 0.24; p=0.0023)(appendix p10). Other pre-specified subgroup analyses (i.e. whether or not cardiac screening was performed after the completion of chemotherapy, CHOP vs. R-CHOP, number of cycles and interval between cycles) did not generate any significant results on the percentage of patients with grade 3+4 CVAEs (**Table 1**).

There were 38 studies, covering 47 subgroups and 5,936 patients, that reported on the occurrence of HF. According to the random effects model (heterogeneity test: Q=527.33, τ^2=0.0384; I^2=95.05%; p< 0.001) the pooled proportion of HF was 4.62% [95% CI 2.25-7.65]. Subgroup analysis showed a significant difference in the reported proportion of patients with HF when active screening of cardiac function was performed after (R-)CHOP treatment had been finalized (screening: 11.72% [95% CI 3.00-24.53]; no screening 1.64% [95% CI 0.82-2.65]; p=0.017 (**Table 1, Figure 3**). Furthermore, we did observe an effect of the number of (R-)CHOP cycles (i.e. cumulative doxorubicin dose) on the number of patients with HF (regression coefficient: 4.99, p=0.024), with a greater proportion when more (R-)CHOP cycles were given. There was no effect of R-CHOP vs. CHOP, interval between cycles, age and sex. We also found no relation between the reported incidence of HF and time of follow-up (r=-0.104, p=0.50)(appendix p11).

Based on a meta-analysis of 30 subgroups (n=4,688 patients), the pooled proportion of grade 1+2 CVAEs was 8.52% [95% CI 5.58-11.96%]. Cause of death was specified in 134 subgroups (n=15,055 patients), in which the proportion of (possible) treatment-related cardiac death ranged from 0 up to 5.6%. Based on a fixed effect model, the pooled proportion was 0.03% [95% CI 0-0.10%]. Treatment discontinuation due to HF showed similar results, with a proportion of <0.0001% [95% CI 0-0.05%], based on a meta-analysis of 56 subgroups (n=3,802 patients), performed with a fixed effects model. No relation between the incidence of treatment-related cardiac death and time of follow-up was

detected (r=-0.081, p=0.37)(appendix p11). The outcome of all meta-analyses using both the fixed-effect and random-effects model are presented in the appendix (p12).

All studies were individually evaluated regarding risk of bias and quality of reporting of harms (appendix p13; p20). Conservatively, we judged all studies for which we could not extract complete information on all AEs to be at risk of selective reporting and incomplete outcome data. Fifty-three (39%) out of 137 studies were rated as high risk of bias for incomplete outcome data and 54 (39%) out of 137 for selective reporting (appendix p13). The quality assessment revealed that the reporting of harms was of good quality in 28 (20%) studies, moderate in 98 (72%) and poor in 11 (8%) out of the total 137 studies (appendix p20). In three meta-analyses, the Q-test for heterogeneity was significant, supporting the use of a random effects model. As a sensitivity analysis, the results of a fixed effects model are provided in the appendix (p12).

Discussion

To our knowledge, this is the first study to comprehensively evaluate the proportion of patients that develop CVAEs in the context of the (R-)CHOP regimen. Previous work within the field has mainly focused on unravelling the cardiovascular toxicity of individual agents, which are often not used as monotherapy. We believe that it is beneficial to assess the toxicity of complete treatment regimens, due to their increasing complexity as well as possible toxic synergistic interactions between agents. The most important findings of this work are: (1) the reported proportion of patients that develop severe CVAEs is relatively low, with a pooled proportion of 2.35% (2) female sex and older age (≥65 years) are independently associated with an increased risk of severe CVAEs (3) the reported proportion of patients with HF increased significantly from 1.64% to 11.72% when cardiac function was screened actively at the end of treatment and (4) discontinuation of (R-)CHOP due to treatment-related HF is rare.

In previous studies among paediatric cancer survivors, female sex has repeatedly been associated with an increased risk of anthracycline-related LV dysfunction[31]. In adults, this relation has been inconclusive, probably because a majority of studies concerning cardiotoxicity have been performed in female breast cancer patients. Moreover, we confirmed that elderly are more prone to develop high-grade CVAEs. This elevated risk might be provoked by a high prevalence of cardiovascular risk factors in

this patient population as illustrated in a large series of lymphoma patients ≥65 years, where 73% of patients had hypertension, 54% hyperlipidaemia and 32% diabetes mellitus[23]. It is possible that the patients that did develop severe CVAEs in our meta-analysis had pre-existing or ongoing cardiac disease, that increased their susceptibility of developing these unintended effects in the context of a 'second-hit' like phenomenon[13,14,32]

Considering the increasing prevalence of NHL with age, less cardiotoxic alternatives in these patients could be considered. Historically, the antineoplastic potency of anthracycline agents has been assumed to be proportional to the acute hematologic toxicity and by extension to toxic effects on other organs, including the heart[33,34]. From this assumption, conversion factors for the cardiotoxicity of the various different anthracyclines have been derived. This validity of this assumption was recently investigated in a large cohort of childhood cancer survivors, which estimated the conversion factor of epirubicin to doxorubicin at 0.8, indicating that this agent is indeed associated with reduced cardiotoxicity[34]. The first trial comparing (R-)CEOP70 (70 mg/m2 epirubicin) to standard (R-)CHOP in 348 adults with diffuse large B-cell lymphoma (DLBCL) did however not report a difference in the proportion of patients with ≥10% decline in left ventricular ejection fraction (LVEF)(15.0% vs. 16.1%) albeit the number of patients with raised troponin levels differed significantly in favour of (R-)CEOP (20.4% vs. 42.0%)[35]. The oncologic efficacy of these regimens was comparable. A recent large multicentre phase 3 randomized controlled trial conducted in China, randomized young patients (≤60 years)(n=404) to R-CHOP50, R-CEOP70 or R-CEOP90 and older patients (61-80 years)(n=244) to R-CHOP50 or R-CEOP70[36]. The 2-year progression-free survival for these regimens was 72.5% [95% CI 66.6–77.6], 72.4% [95%CI 66.5–77.5] and 88.8% [95%CI 82.1–93.1] respectively. In this trial, 13% of patients randomized to R-CEOP70 developed an LVEF decline of >10%, compared to 29% in the R-CHOP50 group at 3-years after remission. Young patients that received the R-CEOP70 or R-CEOP90 also were less likely to develop an LVEF decline, 11% and 13% compared to 26% in patients treated with R-CHOP50. Additional studies with longer follow-up are necessary to determine the impact of substituting doxorubicin with epirubicin on the incidence of hard clinical endpoints, including symptomatic HF.

Besides epirubicin, pixantrone an analogue of mitoxantrone, is also believed to be less cardiotoxic than doxorubicin. This agent has been conditionally approved by the European Medicine

Agency (EMA) in 2012 and is currently indicated as monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive B-cell NHL. Thus far, only one trial has investigated this agent as first-line therapy, comparing R-CPOP to R-CHOP in 140 patients with DLBCL[37]. In this setting, patients treated with R-CPOP had slightly lower response rates (CR/CRu rate 75% vs. 84%) but similar progression- and event-free survival. The R-CPOP regimen was substantially less cardiotoxic, with 2% of patients developing an LVEF decline of ≥20% and 0% symptomatic HF compared to 17% and 6% in the R-CHOP respectively. In the light of these results, the authors suggested that pixantrone might be alternative in patients at high risk of cardiotoxicity. At the moment, this is being investigated in a phase II trial in elderly patients with DLBCL and decreased cardiac function (EudraCT number: 2014-005069-60).

The pooled proportion of patients developing HF (4.62%) in this meta-analysis is in line with previous studies reporting on the development of symptomatic HF, with a 3-5% incidence at a cumulative doxorubicin dose of 400 mg/m^2 [12,38]. Many patients in these studies had also received concomitant treatment with cyclophosphamide, complicating the interpretation of the association of this individual agent with LV dysfunction. However, a large cohort study in lymphoma patients comparing the 5-year cumulative risk of symptomatic HF between patients treated with (n=1994) or without anthracyclines (n=446), found that the risk was only 0.8% in the patients not exposed to anthracyclines vs. 4.5%-7.9% in the anthracycline group. Patients treated without anthracyclines had received similar cyclophosphamide doses as incorporated in (R-)CHOP, indicating that this alkylator at these relatively low doses does not contribute considerably to the toxicity of (R-)CHOP. From the small number of studies that have described an association between cyclophosphamide and LV dysfunction, especially doses of >1.5g/m^2/day seem associated with a high risk of HF[16].

Cardiac dysfunction was a common exclusion criteria for (R-)CHOP, applied in 58 out of 137 studies (42%). However, strikingly, only 38 (28%) of the studies reported on the incidence of HF and an even smaller number performed active cardiac screening pre- and post- chemotherapy to determine whether LV dysfunction had been induced. The significant increase in the reported proportion of patients with cardiac dysfunction from 1.64% to 11.72% when patients received cardiac follow-up post chemotherapy, is suggestive of a widespread under-diagnosis of this complication. We believe that an important contributing factor to this under-diagnosis is the common practice to solely report the incidence

of high-grade AEs in phase 3 clinical trials, that are collected during a limited period of time[39]. In the current CTCAE v5.0, only patients with HF symptoms at rest or patients with a symptomatic drop in the LVEF are counted as severe. This is problematic, as HF symptoms can easily be misattributed to noncardiac AEs in cancer patients[40] and HF symptoms are known to correlate poorly with the LVEF. In other words, a considerable decline in cardiac contractility can be evoked by cardiotoxic chemotherapeutics without the immediate onset of symptomatic HF. A great majority of patients develop this decline within the first year of anthracycline-containing therapy[41]. Systolic dysfunction can thereafter progress silently for years by the activation of various compensatory mechanisms, including peripheral vasoconstriction and activation of the renin-angiotensin aldosterone system (RAAS)[42].

Indeed, we found that onset of symptomatic HF during (R-)CHOP treatment, leading to the necessity of treatment discontinuation is very rare. In addition, the proportion of patients with LV dysfunction was limited to 1.64% in studies that did not evaluate cardiac function after chemotherapy. Clinical HF predominantly is of concern on the long-term, as indicated by other studies in lymphoma survivors, with an increasing cumulative risk from 1.0-4.0% at 1-year to 8.1-9.4% at 8-years[24]. Patients that have developed clinical HF due anthracyclines generally have a poor prognosis with a 9% and 24% cardiovascular mortality rate at 5- and 10 years respectively[43], up to even more dramatic outcomes of a 60% mortality at 2-years[44]. An early discovery of a decline in cardiac function in the pre-symptomatic phase and immediate initiation of conventional HF therapy gives the greatest chance of complete functional recovery[45], preventing the progression to more advanced HF stages. Treatment involves management according to standard HF guidelines with the administration of ACE-inhibitors and beta-blockers, both targeting RAAS to counteract adverse cardiac remodelling[46].

This study has a number of limitations. Most importantly, we did not have access to individual patient data (IPD) that has a number of benefits over pooling aggregate data[47]. In the absence of IPD, it was not possible to perform competing risk analyses nor determine the effect of known cardiovascular risk factors, including smoking, diabetes, hypertension and chest radiation on CVAE incidence. However, we did observe that female sex and older age were associated with an increased risk of severe CVAEs in the subgroup analysis. Albeit some caution is required when interpreting these results that are based on

summary estimates, significant findings detected with aggregate data are replicated in 95% of IPD meta-analyses[48].

Despite using well-defined inclusion criteria for this meta-analysis, some level of heterogeneity was expected due to differences in study designs and populations. Based on the Q-test, significant heterogeneity was present in three meta-analyses (appendix p12). Because this test can be too sensitive when used to analyse results from a large number of studies, the random effects model was selected based on visual evaluation of the heterogeneity in the forest plot, in combination with the τ^2 and I^2 statistics. Thirdly, due to the risk of bias induced by selective reporting of adverse events, studies could have been excluded from the meta-analyses even though CVAEs did- or did not occur. Out of the 60 studies that were not included in the grade 3 + 4 CVAE meta-analysis, 30 studies did not completely report on adverse events, leading to a risk of underreporting of estimated proportion. Also, in 27 out of these 60 studies it was unclear whether the reporting of AEs was complete, which can also lead to biased estimates. Fourthly, the outcome of this meta-analysis is likely influenced by the inconsistency of toxicity grading systems in CVAE grading. For example, with the CTCAE, a (large) asymptomatic decline in cardiac function can be reported as grade 0-3 depending on the entry chosen by the researcher[40]. Furthermore, cardiotoxicity is used as an umbrella term for all manifestations of cardiovascular toxicity by some while others use this term only for chemotherapy-induced LV dysfunction. Due to poor CVAE specification (appendix p13), a limited number of studies could be included in the meta-analysis of HF and a separate analysis for subclinical- vs clinical HF nor other CVAEs was possible. The discrepancy between the proportion of patients with high-grade CVAEs and HF is likely to be partly explained by these subclinical HF cases. We hypothesized that, the studies that did perform cardiac screening pre- and post-chemotherapy might have included patients at a higher risk of HF. However, based on the summary estimates we did not find any differences between the studies that could explain the large difference in the proportion of patients reported with LV dysfunction (appendix p25). There were also no differences in the proportion of patients with CVAEs in the studies that handled cardiac dysfunction as an exclusion criteria and studies that did not (appendix p25). Moreover, we could not establish a relationship between overall survival and the incidence of CVAEs, presumably due to the short period that clinical trials record

AEs and the varying prognosis of different NHL subtypes. Lastly, we did not contact authors of the original studies to assess the accuracy and veracity of our extracted data.

We believe that the findings of this study are important in raising the awareness of CVAEs in NHL patients treated with (R-)CHOP. Our results can presumably also be generalized to NHL patients receiving DA-EPOCH(-R), since the regimen contains comparable doses of doxorubicin. To reduce the burden of CVD in cancer patients and survivors, close multidisciplinary collaborations between (hemato)oncologists and cardiologists are currently coordinated by the implementation of cardio-oncology clinics worldwide[49,50]. These clinics will provide more insight into the burden of CVAEs in a real-world setting and aid in the implementation of targeted strategies for their primary- and secondary prevention. It is plausible that the optimal strategy varies per cancer type, as often the prognosis of the malignancy is the dominant factor. Serial echocardiographic assessment is currently the cornerstone in the detection of early changes in LVEF, due to its availability and versatility[51]. In patients exposed to anthracyclines, the duration of cardiac monitoring should be at least one year, as almost all patients that will develop LV dysfunction display an important decline in cardiac function within the first year[45]. Additional to standard LVEF measurements, deformation imaging by means of global longitudinal strain has shown promising results to detect early changes in myocardial contractility in this setting[52]. Other screening methods include biomarkers, of which the most promising is troponin with a negative predictive value of 93%[53]. For primary prevention, ACE-inhibitors and beta-blockers have been studied in breast cancer patients in a small number of trials with limited sample size[54,55]. Moreover, the bisdioxopiperazine agent dexrazoxane warrants further investigation. A Cochrane meta-analysis pooling data from eight trials showed a highly significant and clinically relevant benefit in favour of dexrazoxane for the prevention of clinical HF (RR 0.18,95% CI 0.10 to 0.32, P<0.00001), and overall HF (RR 0.29, 95% CI 0.20 to 0.41, P<0.00001)[56].

Prospective registries are necessary for the identification of risk factors predisposing patients to CVAEs, optimization of cardiologic screening strategies and determination of the progression rate from asymptomatic to clinical HF. For future clinical trials within the field of oncology, it is of great importance that the type of CVAEs are specified in more detail, since their therapeutic management, reversibility and prognosis varies. The CONSORT extension for harm can aid researchers herein[27]. Furthermore, we

believe that revisions of the CTCAE is of paramount importance to assure consistent CVAE grading. Preferably, these revisions should also reflect the duration, reversibility and multiplicity of AEs[39,57].

Our systematic review and meta-analysis demonstrates that the proportion of patients that develop severe CVAEs after (R-)CHOP treatment is limited during the AE registration period, with a pooled proportion of 2.35%. Women and the elderly appear to have a particular high risk of severe CVAEs, and cardiologic screening in these patients is warranted. Despite the well-established association of doxorubicin with cardiomyopathy, cardiac function is seldom monitored. However, if assessed post-chemotherapy, cardiac dysfunction is reported in >10% of NHL patients suggesting this is a common AE that often remains undetected.

Research in context

Evidence before this study

Survivors of non-Hodgkin lymphoma's (NHL) are at risk of cardiovascular disease (CVD) which is believed to be related to toxic effects of antineoplastic treatment. (R-)CHOP has been the regimen of first-choice for the treatment of aggressive NHLs for decades, but the proportion of patients developing cardiovascular adverse events (CVAEs) after treatment has not been comprehensively evaluated. Previous work within the field has mainly focused on unravelling the cardiovascular toxicity of individual agents, which are often not used as monotherapy. We searched PubMed, EMBASE and the Cochrane Library using a broad search string including the words "lymphoma", "CHOP" and "R-CHOP" from inception, with the last search on the 3rd of June 2019. Among 1,888 unique hits, we found no meta-analysis assessing the occurrence of CVAEs in NHL patients receiving (R-)CHOP.

Added value of this study

Our analysis summarizes the occurrence of CVAEs in patients treated with (R-)CHOP as a first-line regimen across 137 studies. In contrast to previous work, we focused on the cardiovascular toxicity of a complete treatment regimen, rather than individual agents. Moreover, to our knowledge, this is the first

study that specifically evaluates the consequences of serial cardiac assessment on the reported number of patients with heart failure or left ventricular dysfunction following treatment with (R-)CHOP.

Implications of all the available evidence

Clinicians should be aware that chemotherapy-related cardiac dysfunction is common after treatment with (R-)CHOP and often does not immediately result in symptomatic heart failure. Our findings stress the importance of close multidisciplinary collaboration between (haemato)oncologists and cardiologists for the early detection of cardiovascular complications in the pre-symptomatic phase, enabling targeted prevention strategies to improve long-term cardiac outcome in NHL survivors.

Contributors

ML and JAMK contributed equally to the literature search, study design, data collection, data analysis, data interpretation and writing the manuscript. AR and AJT contributed to the study design and writing the manuscript. LPB contributed to statistical analysis, data interpretation and writing of the manuscript. MJC and PAD contributed to writing the manuscript. FWA was the principal investigator who supervised the study. All authors critically reviewed the manuscript and provided important intellectual content. The final manuscript was approved by all authors.

Declaration of interests

All authors declare no competing interests.

Acknowledgements

ML is supported by the Alexandre Suerman Stipend of the University Medical Centre Utrecht. FWA is supported by UCL Hospitals NIHR Biomedical Research and CVON 2015-12 eDETECT.

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Figure legends

Figure 1 Study selection.

Figure 2 Forest plot of the pooled proportion of patients with grade 3+4 CVAEs.

Figure 3 Forest plot of the pooled proportion of patients with overall heart failure, sorted by studies with- (bottom) and without (top) cardiac screening after therapy.