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Primary Cardioprotection Reduces Mortality in Lymphoma Patients with Increased Risk of Anthracycline Cardiotoxicity, Treated by R-CHOP Regimen

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Keywords
Cardio-oncology · Cardioprotection · Cardiotoxicity · Doxorubicin · Lymphoma

Abstract
Background: Advances in anti-lymphoma therapy prolong overall survival, making late adverse effects, like doxorubicin-related cardiotoxicity, an even more important clinical issue. The effectiveness of cardioprotective strategies with close monitoring, angiotensin-converting enzyme inhibitors and/or β-blockers as well as liposomal doxorubicin are still unconfirmed in clinical practice. ***Methods:*** This study evaluated the role of a primary cardioprotection strategy in preventing cardiovascular mortality and heart failure occurrence in non-Hodgkin lymphoma (NHL) patients with a high risk of anthracycline cardiotoxicity. Thirty-five NHL patients were subjected prospectively to ramipril and/or bisoprolol at NHL diagnosis, before implementing doxorubicin-containing regimens. Additionally, patients with a diagnosis of asymptomatic/mild heart failure received the liposomal form of doxorubicin. The clinical outcome and frequency of all serious cardiac events were compared with the results in a historical cohort of 62 high-risk cases treated without primary cardioprotection. ***Results:*** NHL patients with a primary cardioprotection strategy did not experience cardiovascular deaths in contrast to the retrospective control group where cardiovascular mortality was 14.5% at 3 years ($p < 0.05$). Primary cardioprotection also decreased the frequency of new cardiotoxicity-related clinical symptoms (2.8 vs. 24.1%; $p < 0.05$) and prevented the occurrence of cardiac systolic dysfunction (0 vs. 8.5%, respectively; $p < 0.05$). Although the study was not planned to detect any survival benefit, it demonstrated a trend towards increased response rates (complete response 82 vs. 67%; p not significant) and prolonged survival (projected 5-year overall survival 74 vs. 60%; $p < 0.05$) for patients treated with primary cardioprotection. ***Conclusions:*** A primary personalized cardioprotection strategy decreases the number of cardiac deaths and may potentially prolong overall survival in NHL patients with increased risk of anthracycline cardiotoxicity.

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Introduction

Recent advances in anti-lymphoma therapy prolong overall survival (OS), making long-term adverse effects of cytostatics more relevant. The CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisone, with [R-CHOP] or without rituximab) is the backbone of the first-line therapy in nearly half of non-Hodgkin lymphoma (NHL) patients. The efficacy of CHOP depends largely on the use of doxorubicin, an anti-cancer anthracycline antibiotic known for marked cardiovascular toxicity. Doxorubicin-related heart failure (HF) and premature cardiac deaths may influence the outcome of oncological treatment [1, 2].

Early manifestations of doxorubicin-induced cardiotoxicity, like heart rhythm disturbances or diastolic dysfunction, are often observed [3]. Systolic dysfunction and decreased left ventricular ejection fraction (LVEF), even if detected by echocardiography before the occurrence of clinical signs and symptoms, are probably progressive and irreversible. Once developed, the prognosis of cardiomyopathy is dismal. Although the existence of risk factors for cardiovascular diseases increases the probability of doxorubicin cardiotoxicity, it is difficult to predict which individuals will develop acute HF on a case-by-case basis [4, 5].

The major objective of this study was to analyse the efficacy of implemented primary cardioprotective strategies in high-risk patients based on clinical outcome.

Methods

Study Cohort

The study group comprised 97 white Caucasian NHL patients with increased risk of anthracycline cardiotoxicity treated at the Department of Haematology of Jagiellonian University Hospital, Krakow, Poland. Increased cardiotoxicity risk was defined as the existence of at least one risk factor identified as important in a previous multicentre PLRG (Polish Lymphoma Research Group) study on 610 cases [6]. In our previous analysis, patients with coronary artery disease, arterial hypertension, obesity, dyslipidaemia or diabetes concomitantly with lymphoma, and/or a medical history of cigarette smoking, myocardial infarction, arrhythmia, valvular heart disease or stroke had a significantly higher incidence of premature cardiovascular deaths.

The first cohort consisted of 62 cases evaluated retrospectively (abbreviated from here onwards as "retrospective patients" [RPs]), who were treated between 2002 and 2011. The unsatisfactory cardiac outcome of these patients became the impetus for implementing primary cardioprotection strategies in accordance with the current guidelines of the European Society for Medical Oncology [7]. The next 35 patients were observed prospectively ("prospective patients" [PPs]) and treated with primary cardioprotection in the period 2012–2017. Demographic and other clinical characteristics of both cohorts are summarised in Table 1. RPs had fewer risk factors of anthracycline cardiotoxicity and more favourable International Prognostic Index (IPI) scores; otherwise, the groups were fully comparable.

Table 1. Clinical characteristics of the study population

Characteristics	Retrospective group (n = 62)	Prospective group (n = 35)	p
Age, years			
Median	59.5	53	ns
Quartiles	53–68	38–68	
Range	22–85	20–83	
Female	26 (42)	22 (63)	<0.05
Male	36 (58)	13 (37)	
ECOG performance status			
<2	53 (85)	27 (77)	ns
≥2	9 (14)	8 (23)	
Clinical stage of lymphoma			
I/II	11 (18)	12 (34)	ns
III/IV	51 (82)	23 (66)	
IPI score at diagnosis			
Median	2	3	<0.05
Quartiles	2–3	2–4	
Range	0–4	1–4	
Number of cardiovascular risk factors			
Median	1	3	<0.05
Quartiles	1–2	2–4	
Range	1–4	1–8	
Coronary artery disease at baseline	1 (1.61)	5 (14.29)	<0.05
Arterial hypertension	33 (53)	26 (74)	<0.05
Obesity	26 (42)	5 (14)	<0.05
Dyslipidaemia	18 (29)	16 (46)	ns
Diabetes	9 (14)	4 (11)	ns
Smoker	7 (11)	23 (66)	<0.05
Myocardial infarction in PMH	1 (2)	2 (6)	ns
Arrhythmia in PMH	5 (8)	10 (29)	<0.05
Valvular heart disease in PMH	0 (0)	2 (6)	ns
Stroke in PMH	1 (2)	2 (6)	ns

Values are n (%) unless otherwise indicated. ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; PMH, past medical history; ns, not significant.

Oncological Status and Treatment

The diagnosis of NHL was histopathologically confirmed in all cases. Diffuse large B-cell lymphoma was most common (n = 74, 76%), followed by indolent lymphoma subtypes (n = 9, 10%), mantle cell lymphoma (n = 7, 7%) and peripheral T-cell lymphoma (n = 7, 7%).

All patients received 6 (R)-CHOP cycles as the first-line therapy, with 50 mg/m^2 doxorubicin per cycle (cumulative dose of 300

mg/m^2). Supportive treatment, including prevention of tumour lysis syndrome, prophylactic antibacterial, antiviral and antifungal therapy and transfusions of red blood cells, platelets or other blood products, was implemented as required. Possible effects of consolidation strategies and subsequent therapy lines in relapsing patients were taken into account in this analysis, as they were evenly distributed in the 2 compared cohorts.

Cardiac Assessment

Anthracycline cardiotoxicity risk factors were determined at diagnosis based on a physical examination and patients' past medical history. Cardiovascular events were assessed according to the guidelines of the European Society of Cardiology. Hypertension was recognized according to the guidelines of the European Society of Hypertension. In the retrospective study, available archival data were used.

Serious clinical cardiotoxicity was defined as cardiovascular death or typical symptoms of HF (orthopnoea, fatigue, weakness, significantly reduced exercise tolerance, nocturnal dyspnoea and peripheral oedema), or acute symptoms related to ischemic heart disease: unstable angina or myocardial infarction.

Echocardiography was performed in all RPs who developed clinical signs or symptoms of cardiac failure, as an element of standard clinical practice, and at least 3 times (at diagnosis, mid-therapy and after its completion) in all patients in the prospectively observed cohort. In the echocardiographic assessment, serious cardiotoxicity was identified as cardiac left ventricle (LV) systolic dysfunction: decline in LVEF by >10 percentage points from baseline to a final value of LVEF below 50% [8]. The impairment of the LV diastolic function was evaluated [8]. The grading scheme was implemented from the current echocardiographic guidelines published by the European Association of Echocardiography and the American Society of Echocardiography: grade I (mild) – impaired LV relaxation; grade II (moderate) – pseudo normal LV filling; and grade III (severe) – restrictive LV filling [9].

Primary Personalized Cardioprotection Strategy

Patients in the prospective cohort were subjected to primary cardioprotection with a maximum tolerated dose of angiotensin-converting enzyme (ACE) inhibitors (ramipril) and/or β-blockers (bisoprolol or similar). Cardioprotection was initiated with ramipril, except in women with childbearing potential. It was administered at an initial dose of 1.25 mg once daily and gradually increased to 10 mg once daily in 4 steps by doubling the dose at an interval of 7 days. In case of persistent hypotension, the dose was reduced to the highest tolerated level. After setting the ramipril dose, bisoprolol was added and titrated from an initial dose of 1.25 mg to 10 mg daily by incrementing the dose as above. 15/35 (42.8%) patients who were already on ACE inhibitors and/or β-blockers other than ramipril and/or bisoprolol were substituted with equivalent doses of ramipril and/or bisoprolol. Cardioprotection was always started before implementing doxorubicin-based chemotherapy; however, in some cases, it was fully adjusted after the first cycle of (R)-CHOP.

Non-pegylated liposomal doxorubicin (NPLD) was administered to selected PPs when there were contraindications to conventional doxorubicin, defined as diagnosis of HF before chemotherapy or occurrence of systolic and/or diastolic dysfunction of the LV during its course. Echocardiography was performed in PPs at diagnosis, at mid-therapy and after its completion.

Follow-Up

The study encompassed the period of active chemotherapy treatment (6 months), close cardiovascular monitoring with clinical and echocardiographic assessments (first 12 months after completing chemotherapy) and further follow-up for survival. Response to treatment was assessed according to Cheson criteria. In order to determine OS and progression-free survival, all patients or their families were contacted to confirm survival status or cause of death and to obtain information concerning symptoms of HF or cardiac death.

Statistical Analysis

Univariate analyses were carried out using the χ^2 test or Fisher's exact test for categorical variables and the Mann-Whitney test for continuous variables. Kaplan-Meyer curves were used to determine OS. Differences in survival of the population subgroups were tested by the Cox test. Results were considered statistically significant if $p < 0.05$. All statistical analyses were performed using Statistica software.

Results

Cardiovascular diseases and anthracycline cardiotoxicity risk factors were determined at diagnosis based on physical examination and medical history. PPs, subjected to primary cardioprotection, had significantly more risk factors of cardiotoxicity compared to RPs (Fig. 1; Table 1). Both ramipril and bisoprolol were effectively dosed in 26 of 35 (74%) patients: 13 women and 13 men. Due to contraindications, monotherapy with bisoprolol was used in the other 8 women and ramipril alone in 1 case.

Patients were treated with a standard dose of anthracycline-containing chemotherapy: R-CHOP and CHOP (in 90 and 7 cases, respectively). Conventional doxorubicin was the most often used anthracycline in the whole study (100% of RPs and 48.5% of PPs). NPLD was administered in 52.5% ($n = 16$) of patients in the PP group, together with an ACE inhibitor and/or a β-blocker. In 6 patients, Myocet was given at diagnosis due to contraindications for conventional doxorubicin: HF with preserved ($n = 4$) or mid-range impairment ($n = 2$) of LVEF. A further 10 patients received NPLD after the 4th course of chemotherapy: 1 patient who developed cardiovascular syncope due to arrhythmia with no subsequent differences in EF, and 9 asymptomatic patients with new diastolic dysfunction on echocardiographic examination. All newly recognized cases of diastolic dysfunction were in grade I, which meant impaired LV relaxation, and this occurred only in patients with pre-existing arterial hypertension.

During the lymphoma treatment, 15 (24%) RPs and only 1 (3%) PP experienced new cardiological symptoms.

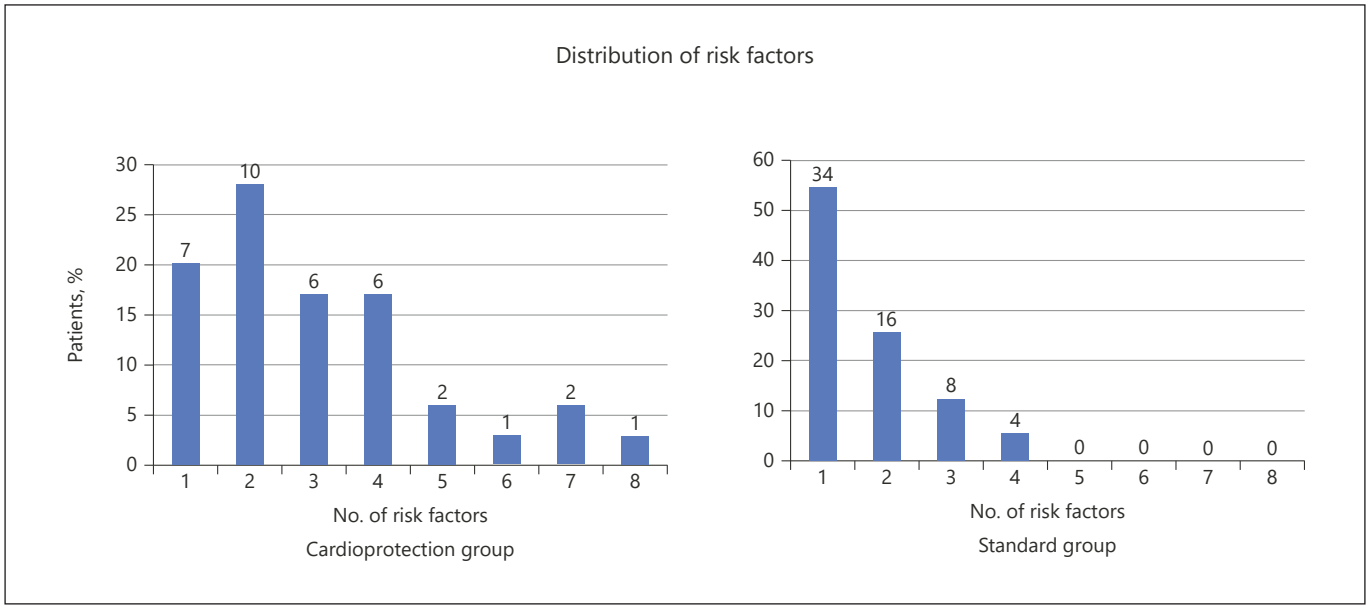

Fig. 1. Distribution of the number of anthracycline cardiotoxicity risk factors in the study groups: historical group with standard management (retrospective cohort) and modern group with cardioprotection (prospective cohort) ($p = 0.0058$). Values above columns are numbers of patients.

Table 2. Cardiovascular events during active chemotherapy (first 6 months) and 1 year after completion of chemotherapy

	Total ($n = 97$)	Retrospective ($n = 62$)	Prospective ($n = 35$)	p
Cardiovascular deaths	9 (9.3)	9 (14.5)	0 (0)	
First 6 months	5	5	0	<0.05
7–18 months	4	4	0	<0.05
19–36 months	0	0	0	ns
Clinical cardiotoxicity symptoms (first 18 months)	16 (16.5)	15 (24.2)	1 (2.9)	<0.05
Angina pectoris	4 (4.1)	4 (6.5)	0 (0)	ns
Myocardial infarction	2 (2.1)	2 (3.2)	0 (0)	ns
Dyspnoea	13 (13.4)	13 (21)	0 (0)	<0.05
Ankle oedema	9 (9.3)	9 (14.5)	0 (0)	<0.05
Nycturia	6 (6.2)	6 (9.7)	0 (0)	ns
Arrhythmia requiring treatment	5 (5.2)	4 (6.5)	1 (2.9)	ns
Cardiovascular syncope	1 (1)	0 (0)	1 (2.9)	ns

Values are *n* (%). ns, not significant.

They are summarised in Table 2: in the RP group, angina pectoris was diagnosed in 4 (6.5 %) patients and myocardial infarction in 2 (3%) patients. The other symptoms occurring in RPs included significant exertional dyspnoea in 13 (21%), ankle oedema in 9 (14.5%), nycturia in 6 (10%) and arrhythmia in 4 (6.5%) patients.

Echocardiography confirmed LV systolic dysfunction in 12.9% of RPs (8 of those 15 who experienced new cardiological symptoms). It was regarded as important in 2 patients, where LVEF decreased by 16 and 26%. Diastolic dysfunction was not assessed in the RPs. No important impairment of LVEF on echocardiography was detected

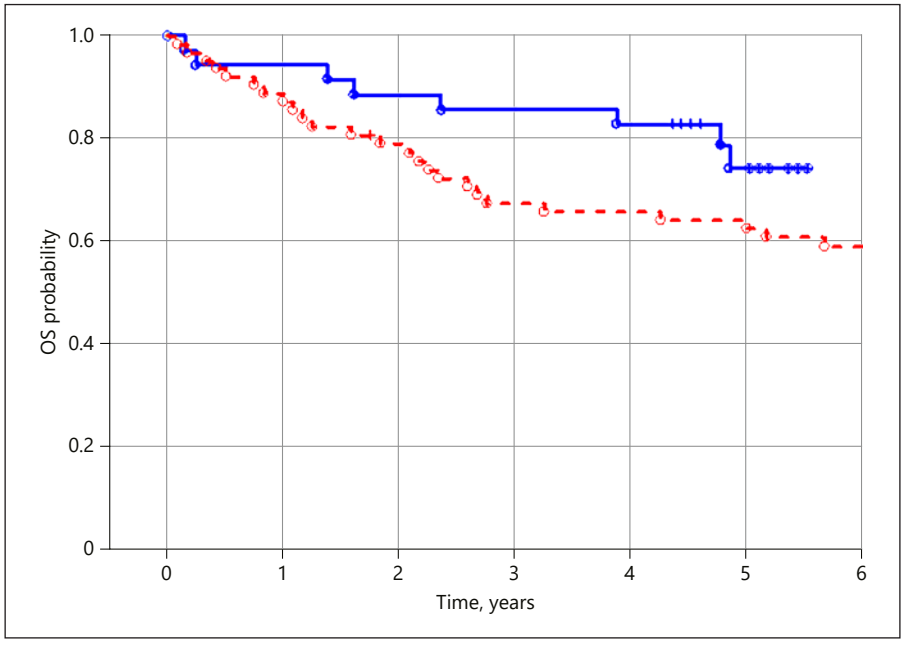

Fig. 2. Comparison of overall survival (OS): patients from the prospective cohort treated with cardioprotection (blue line) are compared to the historical group with standard management (red line) (F Coxa test: T1 = 13.70390; T2 = 21.29610; $F(16, 52)$ = 2.091354; p = 0.02340).

in the PP group; mild diastolic dysfunction occurred in 9 cases and did not progress after switching the treatment to liposomal doxorubicin.

Even more importantly, 9 patients from the RP group (14.5%) compared to none (0%) of the PP group died due to cardiac complications during either active chemotherapy or within 30 months of its completion (Table 2). In the RP cohort, 5 patients died due to cardiovascular causes within the first 6 months (angina and myocardial infarction in 2 cases, dyspnoea and HF in 2 cases and rhythm disturbances in 1 case) and a further 4 patients during the next 12 months of follow-up (as a consequence of HF in 2 patients, pulmonary embolism in 1 patient and HF with coexisting thrombosis in 1 patient).

The study was not designed to detect any differences in response rates and OS. In both cohorts, there were no significant differences in complete response (82 and 68% of complete response in the PP and RP cohorts, respectively; p not significant). As there were no cardiac deaths in patients treated with primary cardioprotection, Kaplan-Meier analyses revealed important OS differences: in both cohorts, the median OS was not reached; a projected 5-year OS was 74 and 60% for PPs and RPs, respectively (Cox test; $p < 0.05$; Fig. 2). The trend for an increased complete response rate and prolonged OS in the PP cohort was observed although patients had a significantly higher IPI (median 3 vs. 2; $p < 0.05$) and more cardiotoxicity risk factors (median 3 vs. 1; $p < 0.05$) than the RP cases.

Discussion

Premature cardiovascular mortality has become one of the main problems in oncology. The identification of patients with individual susceptibility as well as finding effective primary prevention strategies for cardiac damage is essential in lymphoma patients. Our previous analysis of 610 patients performed by the PLRG revealed that premature cardiovascular mortality in lymphoma patients treated with doxorubicin-based chemotherapy is the second most common cause of death, responsible for 30% of all deaths (5% of all cases) during the treatment and follow-up phase [6].

A number of risk factors may predispose a patient to cardiotoxicity caused by anthracyclines. Patients with a medical history of heart diseases, especially those with arterial hypertension, are at particular risk [10]. Selection of high-risk patients based on the results of the physical examination and past medical history proved to be very effective; in the RP cohort the cardiovascular mortality (n = 9, 14.5%) was nearly 3 times higher compared to 5% in the PLRG observational study. Among PPs, the number of risk factors was even higher (median 3 vs. 1 in RPs; $p < 0.05$). Furthermore, patients with 5 or more risk factors were present only in the PP group (6 of 35 patients, 17%; Fig. 1). Despite a very high risk of developing doxorubicin-related cardiotoxicity, our primary cardiopro-

tection protocol implemented in all PPs reduced the number of cardiac deaths to 0.

Doxorubicin cardiotoxicity has a direct effect on the myocardium, limiting its use in patients with heart diseases. NPLD, thanks to a specific biodistribution and pharmacokinetic properties, shows similar efficacy and less cardiac toxicity [11]. The mechanism of antitumor activity of the liposomal and conventional form is similar, whilst NPLD is less toxic, as shown by animal studies [12]. Liposomes do not penetrate the healthy tissue through the wall of normal capillaries but cross capillaries of inflamed tissue, leading to the preferential release of doxorubicin into the tumour [13]. Several clinical studies have confirmed the usefulness of NPLD in metastatic breast cancer treatment [14–16]. There is only 1 small phase III trial indicating the cardiac advantage of the COMP scheme in comparison to CHOP in lymphoma patients [17]. Similar conclusions come from the PLRG retrospective observation demonstrating the beneficial effects of liposomal doxorubicin in lymphoma patients with coexisting cardiovascular disorders [18].

ACE inhibitors and/or β-blockers may reduce the cardiac toxicity of doxorubicin during cancer treatment, which is suggested by different guidelines [19, 20] and still examined in many clinical observations [21, 22]. The results of prospective randomised studies confirmed the role of ACE inhibitors and β-blockers in cardioprotection [23–25]. However, only 1 of these studies demonstrated prolonged OS.

An optimal algorithm for echocardiography in cancer patients is still being discussed and has not yet been clearly defined in high-risk subgroups [26]. In the retrospective cohort, overt cardiotoxicity was diagnosed in patients based on clinical symptoms and 2D echocardiography evaluation of systolic dysfunction. This was the historical algorithm used in many oncological centres. The new protocol of echocardiographic surveillance implemented in the prospective cohort, evaluating the systolic and diastolic cardiac function in all patients, allowed switching from conventional to liposomal doxorubicin at the right time. In contrast to RPs, where both new acute symptoms of HF and echocardiographic impairment of LVEF were observed, none of these symptoms were diagnosed in PPs.

In this analysis, primary cardioprotection with maximum tolerated doses of an ACE inhibitor and/or a β-blocker (ramipril and/or bisoprolol) was used in all PPs, whereas NPLD was limited to PPs with concomitant contraindication for conventional doxorubicin. We confirmed the high efficacy of our strategy, especially in the elimination of cardiovascular deaths in PPs compared to the unfavourable outcomes of RPs not subjected to well-planned primary cardioprotection. It has been demonstrated that all cardiotoxic events, including all cardiovascular deaths, occurred either during the active 6 months of chemotherapy or during the first year after completing anthracycline-based chemotherapy [27] (Table 2). For this period, we evaluated the efficacy of cardioprotective procedures by analysing the incidence of cardiovascular events (deaths and symptomatic cardiotoxic effects) in high-risk patients in both groups. Despite a higher IPI and more risk factors of cardiotoxicity prior to chemotherapy, there were significantly fewer cardiotoxic complications in patients undergoing primary cardioprotection. Importantly, cardiovascular deaths were not observed in PPs, whilst several RPs died due to cardiovascular reasons (Table 2). Moreover, PPs had a better quality of life as they were free of cardiac symptoms.

The study was not designed to detect any response rate and OS differences. Prolonged OS, although confirmed by Cox statistics, should be interpreted with caution, as this is a comparison to a historical control group. However, it should be noted that the OS benefit was clear despite IPI imbalance favouring the control group (median 2 vs. 3 in PPs; $p < 0.05$).

The greatest limitation of our study is the lack of randomization. It should, however, be emphasized that there is an imbalanced distribution of risk factors favouring RPs. This analysis is a real-life experience, where we treat more and more high-risk patients (Fig. 1). More difficult patients require closer surveillance, as cardioprotection strategies should be individually tailored to each patient. Our study used personalized cardioprotection: ramipril and bisoprolol were chosen because they carry the lowest risk of hypotension as an adverse effect; β-blockers were favoured in women, and doxorubicin was switched to its liposomal form only in patients developing HF, as is recommended by international guidelines [19, 20].

Taken together, the use of cardioprotective drugs (ramipril and/or bisoprolol) in combination with NPLD can be successful in the treatment of patients with an increased risk of cardiovascular complications related to anthracyclines. The high efficacy of this treatment has been demonstrated by the complete elimination of cardiovascular deaths and LV systolic impairment as well as the improvement in quality of life by minimizing cardiac symptoms related to chemotherapy. Although the analysis was limited to a small group of patients and the follow-up is not long, the differences are significant enough for the proposed primary cardioprotection to be considered in lymphoma patients with high cardiovascular risk.

Statement of Ethics

The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Informed consent was obtained for experimentation with human subjects. This article does not contain any studies with animals performed by any of the authors.

Disclosure Statement

All authors declare no conflicts of interest.

Author Contributions

M.D.-D. performed the study and analysed the data; W.J. designed the study; M.D.-D. and W.J. had substantial contributions to the conception and design of the work; M.D.-D., A.M.G. and S.S. drafted the manuscript; W.J., S.S., A.O., T.O., M.S., A.J., K.K. and A.B.S. critically revised the manuscript for important intellectual content; and M.D.-D., W.J., A.M.G., S.S., A.O., T.O., M.S., A.J., K.K. and A.B.S. made substantial contributions to the acquisition, analysis and interpretation of data for the work. The authors had full access to data and take full responsibility for their integrity. All authors have read and agreed with the content of the manuscript as it was written.

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