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Safety and efficacy of Non-pegylated Liposomal Anthracyclines in the treatment of lymphomas: the experience of the Hematology Clinic

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Abstract

Background: Anthracyclines are a cornerstone of first-line lymphoma therapy. The efficacy is tempered by cardiotoxicity, particularly in elderly patients and those with cardiac disease. Non-pegylated liposomal doxorubicin (NPLD) demonstrates comparable efficacy to conventional anthracycline while mitigating the risk of cardiotoxicity.

Purpose: The primary endpoint was incidence of cardiac events, heart failure (HF) or acute coronary syndrome (ACS), measured as event-free probability (EFP). Secondary endpoints were therapeutic response, overall survival (OS) and progression free survival (PFS).

Methods: We retrospectively collected data of patients with diagnosis of lymphoma treated with NPLD at the Hematology Clinic of our Institution. Patients with no cardiological evaluation were excluded. The baseline cardiovascular (CV) toxicity risk was assessed using the HFA-ICOS risk assessment tool.

Results: Our study included 199 patients with diffuse large cell lymphoma (DLBCL), indolent non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma (HL) and other type of lymphomas **(**127, 43, 14 and 15 respectively). 114 (56.15%) were male. The median age was 73 (IQR 66-78). Based on HFA-ICOS risk, 44% of patients have high/very high risk and 48% has intermediate risk. Most of the patient 85% completed all 6 cycle of therapy. About 12% of subjects developed major cardiotoxic events including HF (N = 16), and ACS (N=8). The EFP at 5 years was 80% (95% CI: 72-89). Developing a major cardiac event did not impact on OS and PFS. Among patients with DLBCL the ORR was 87%, 78% of patients achieved a complete remission (CR). Similar response was noted in indolent lymphoma (ORR 88%; CR 71%). 85% of HL achieved RC. As expected the others lymphomas shows lower response rate (ORR 80%, CR 40%). In the context of DLBCL the 3, 5 years OS rates were 60% (95% CI: 45-80%) and 55% (95% CI: 39-77%) for IPI high risk respectively; PFS was 55% (95% CI: 41-75%) at 3 and 5 years. For DLBCL Low/Intermediate risk OS were 71% (95% CI; 62-82%) at 3 years and 60% (95%; 48-74%) 5 at years, PFS was 67% (95% CI; 58-78%) and 52% (95 CI, 40-66%) respectively. For indolent lymphomas the 3- and 5-years OS were 81% (95% CI: 69-

93%) and 72% (95% CI: 58-89%), PFS was 72% at 3 years (95% CI: 59-88%) and 68% (95% CI: 54-85%) at 5 years. In HL the 3- and 5-years OS was 85% (95% CI: 69-100%). In contrast 3 and 5 OS rates were lower for others 51% (95% CI: 30-85%) and 34% (95% CI: 13-88%) respectively with PFS rate at 3 and 5 years 38% (95% CI: 20-74%) and 19% (95% CI: 4-74%). A total of 67 (33%) patients died from all causes including progression of lymphoma (57%), infection disease (22%) unknown causes (19%), or second neoplasia (1.49%). There was no death for cardiotoxicity.

Conclusions: Our findings support that NPLA is an effective treatment in LNH at high risk of cardiac events, even within the DLBCL high-IPI risk subgroup. Results in HL are less consistent with the strong limitation of the small sample size and potential selection bias among elderly with HL. The NPLD-containing regimen was well tolerated, with 85% of patients completing the chemotherapy schedule. In our study the crude incidence of CV events (12%) was higher than previously reported studies. However, our cohort included not only hospitalized HF cases but also instance of worsening “ambulatory” HF during cardio-oncological follow-up. Furthermore, the EFP was similar at 5year (80%, IC 72-89%). Notably, the occurrence of CV events did not appear to impact PFS and OS. Conversely, a significant decline in OS was observed in association with treatment interruption. Our findings indicate that NPLD are both effective and safe, even in negatively selected populations.

Indice

INTRODUCTION

Anthracyclines play a pivotal role in the treatment of lymphoproliferative disorders, both non-Hodgkin lymphoma (NHL) within the R-CHOP regimen and Hodgkin lymphoma (HL) within the ABVD regimen.

Particularly in diffuse large B cell lymphoma (DLBCL) CHOP regimen has demonstrated its superiority over many other treatment protocols. The combination of the monoclonal anti-CD20 antibody rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (the R-CHOP regimen) has notably enhanced the regimen's effectiveness, making R-CHOP the standard frontline treatment for DLBCL nowadays.

However, anthracyclines are associated with cardiotoxicity, primarily manifesting as congestive heart failure (CHF), which can occur during treatment (acute toxicity) or several years later (chronic toxicity). The cardiotoxicity reduces the therapeutic potential of anthracyclines.

The two main determinants of toxicity are the cumulative dose of anthracyclines and the cardiac conditions at the time of the initiation of induction chemotherapy.

Indeed, anthracycline-related toxicity is dose-dependent, with a cumulative dose of 550 mg/m² linked to a 30% risk of cardiovascular disease. Furthermore, early clinical and subclinical signs of cardiotoxicity have been observed at a lower cumulative dose of 200 mg/8m² (1).

As for cardiac conditions that may pose a risk of cardiotoxicity, those with the greatest clinical impact are senile heart, left ventricular dysfunction, and increases in ventricular volume or pressure load, particularly regarding hypertensive, coronary, and valvular heart disease. Age also influences the risk of developing doxorubicin cardiomyopathy. Very Young and very old individuals are more prone to develop this complication.

Using induction treatments that exclude anthracyclines to reduce cardiovascular risk has been linked to less effective disease control and lower survival rates, suggesting that it is not feasible to recommend a first-line therapy without anthracyclines when the aim of treatment is cure.

Various strategies have been employed to mitigate the risk of cardiotoxicity. One of those is represented by the reduction of anthracyclines dosage: the R-miniCHOP is a valid option only in very elderly patients (> 80 years old), because it has a better safety profile, whereas is associated with worse outcome due to the reduction of all active agents (2).

Another option is to include the use of a cardioprotective agent, such as Dexrazoxane, in the induction treatments. The use of this drug is limited to a small percentage of patients due to concerns that it may interfere with antitumor activity and increase the risk of second neoplasms (3). Furthermore, its cardioprotective effects have been demonstrated in the pediatric population but not in adults (4).

Another strategy in order to mitigate cardiotoxicity is the use of liposome-encapsulated anthracyclines.

Myocet is a non-pegylated liposomal form of doxorubicin that has a shorter circulation time compared to its pegylated version. This unique pharmacokinetic profile leads to several advantages, including decreased myelosuppression, lower gastrointestinal toxicity, and a reduced risk of cardiotoxicity when compared to standard formulations.

Non pegylated liposomal anthracyclines (Myocet) were firstly used in the treatment of patients affected by breast cancer, where it has already demonstrated a lower risk of cardiotoxicity (5). Additionally, the safety and efficacy of non-pegylated liposomal doxorubicin as a substitute for conventional doxorubicin in the CHOP regimen have been studied in newly diagnosed patients with aggressive non-Hodgkin lymphoma (NHL). The combination proved to be an effective treatment option that was generally well tolerated, with myelosuppression identified as the primary side effect. Several studies in the Hematology setting confirmed in high risk and highly selected populations the efficacy and particularly the safety of the COMP Scheme (6).

1.1 Anthracycline-induced cardiotoxicity

Anthracyclines are well-established and highly effective antineoplastic agents employed in the treatment of various adult and pediatric malignancies, including solid tumors, mainly cancer of breast, lungs, thyroid gland and osteosarcoma and hematologic malignancies such as lymphoproliferative disorders and leukemias (7).

Despite the therapeutic efficacy of doxorubicin, its clinical application is often limited by several adverse effects, including hematopoietic suppression, nausea, vomiting, extravasation, and alopecia. Among these, cardiotoxicity remains the most concerning complication. The onset of this cardiotoxicity can be delayed, manifesting 10 to 15 years after the conclusion of chemotherapy. It encompasses a wide array of clinical presentations, ranging from asymptomatic electrocardiographic (ECG) alterations to pericarditis and decompensated cardiomyopathy. While the risk of developing cardiomyopathy is predominantly dose-dependent, it is important to note that cardiotoxic effects can also arise at lower doses in individuals with heightened susceptibility.

The multi-decade experience in the use of anthracyclines has led to the identification of several individual risk factors that promote the development of cardiomyopathy.

Gender disparities have been identified as a significant risk factor contributing to the toxic effects of doxorubicin. Indeed, females experience more pronounced cardiotoxicity, characterized by greater reductions in contractile function (8). Age also emerges as a critical risk factor, with individuals over 65 years and children under 4 years exhibiting an increased susceptibility to doxorubicin-induced cardiotoxicity (8-9).

Furthermore, chronic health issues like hypertension, diabetes mellitus, liver disease, and a history of heart disease may also elevate the risk of cardiotoxicity.

Four categories of anthracycline-induced cardiotoxicity are identified: acute, subacute, chronic, and late-onset.

Acute Cardiotoxicity: occurring in 0.4–41% of patients, acute cardiotoxicity can present during or shortly after anthracycline administration, characterized by electrocardiographic abnormalities such as atypical repolarization, diminished QRS voltage, sinus tachycardia, and QT interval prolongation (7). Symptoms are often mild or asymptomatic, resolving

within hours to weeks after treatment. Rarely, persistent symptoms such as decreased QRS voltage may occur. Notably, sudden cardiac death, linked to arrhythmias, has been reported in less than 1% of doxorubicin-treated patients, particularly in those with electrolyte imbalances.

Subacute Cardiotoxicity: This form is rare and manifests insidiously days to weeks after treatment, primarily presenting as pericarditis-myocarditis syndrome (11).

Chronic cardiotoxicity: Observed in 0.4-23% of patients, chronic cardiotoxicity can lead to severe congestive heart failure weeks to months post-chemotherapy, mainly affecting the left ventricle. Electrocardiograms typically show signs of ventricular overload and low QRS voltage. Symptoms include reduced exercise capacity, dyspnea, cardiomegaly, and decreased left ventricular ejection fraction. Pharmacological interventions can improve quality of life, but mortality rates remain high (27-61%). Early onset of symptoms post-chemotherapy is associated with poorer prognosis, while pediatric patients fare better (20% mortality). Cardiotoxicity incidence correlates with cumulative doxorubicin dosage, with risks escalating beyond thresholds of 550 mg/m². However, cases of anthracycline-induced cardiomyopathy have been documented at lower doses.

Late Cardiotoxicity: This occurs several years after chemotherapy, affecting both children and adults, even at lower cumulative doxorubicin doses (<480 mg/m²). Clinically, it may present as congestive heart failure, arrhythmias, and conduction abnormalities, with second-degree atrioventricular block being common. Echocardiographic assessments indicate a reduced left ventricular ejection fraction in 18% of patients treated within the last ten years versus 38% in those treated over ten years ago (12).

1.2 Pathogenetic mechanism of anthracycline cardiotoxicity

The precise causal pathways leading to anthracycline-induced cardiomyopathy remain to be fully elucidated. Indeed, the cardiotoxicity associated with anthracyclines appears to involve multiple concomitant pathogenic mechanisms. First of all, the involvement of free radicals seems to play a significant role. The chemical composition of doxorubicin facilitates the generation of reactive oxygen species, which subsequently contributes to oxidative stress that correlates with myocardial cellular damage. In particular, in metabolic

processes, doxorubicin undergoes reduction to semiquinone, which is subsequently oxidized to primary quinone in the presence of oxygen, resulting in the formation of reactive hydrogen peroxide (13). Oxygen undergoes reduction to form the superoxide radical ($O2\cdot-$). The superoxide anion react with two protons ($2H^+$) to produce hydrogen peroxide ($H2O2$). Hydrogen peroxide can subsequently be reduced to the hydroxyl radical ($\cdot OH$) via several pathways: it can be catalyzed by the superoxide radical in the presence of trace amounts of iron (Haber-Weiss reaction), by reduced iron (Fe^{2+}) in the Fenton reaction, or under low oxygen conditions, akin to those in tumor cells, facilitated by the doxorubicin semiquinone. The hydroxyl radical is a highly reactive and short-lived species that can inflict damage on DNA through proton abstraction and induce lipid peroxidation. It is likely that this radical represents the ultimate damaging entity in the context of doxorubicin-induced free radical generation. The harmful effects of oxygen-derived radicals are counteracted by various cellular defense mechanisms. These include superoxide dismutase, which converts superoxide to hydrogen peroxide; catalase and glutathione peroxidase, which transform hydrogen peroxide into water and molecular oxygen; and an array of endogenous free radical scavengers, such as vitamin E. Together with their reductive capabilities, these cellular defenses significantly influence the chemosensitivity of various cell lines or tissues to free radical exposure.

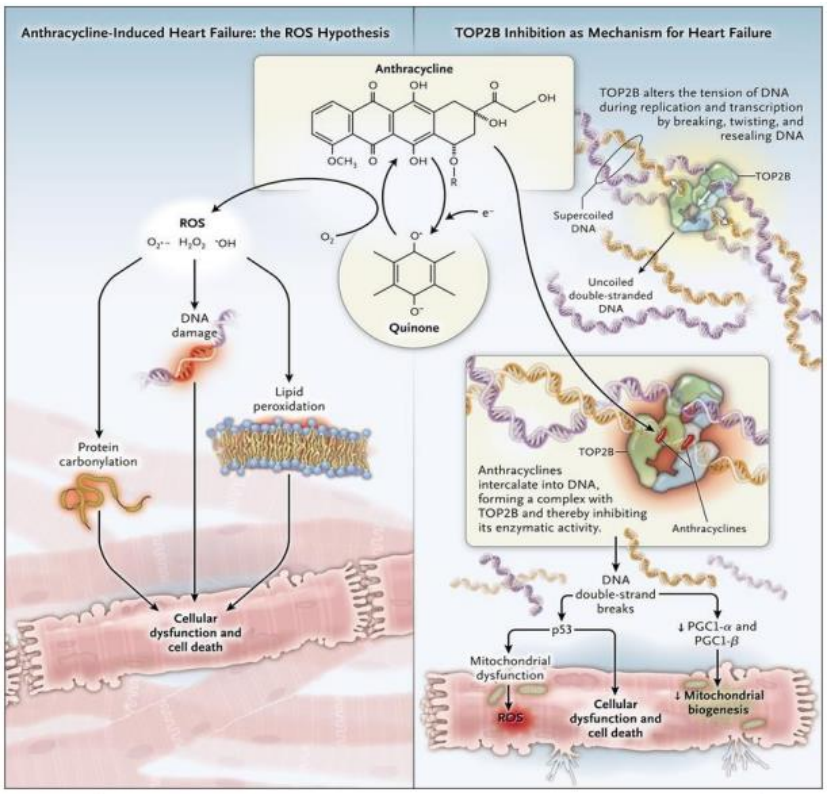
Hydroxyl radicals, the primary mediators of anthracycline-induced cardiotoxicity, are generated. These radicals contribute to lipid peroxidation of cell membranes, which leads to mitochondrial respiratory chain dysfunction, DNA fragmentation, collagen and hyaluronic acid degradation, and impairment of sulfhydryl-containing enzymes (13).

Moreover, the administration of doxorubicin has been linked to a reduction in the levels of endogenous antioxidants, which are crucial for the neutralization of free radicals. This decline in antioxidant capacity, coupled with an increase in oxidants, culminates in heightened oxidative stress. The resultant imbalance between oxidative agents and the antioxidant defense system is a key factor in the pathogenesis of cardiomyopathy and contributes to the subsequent onset of heart failure.

An additional pathogenic mechanism underlying cardiotoxicity has been linked to the inhibition of nuclear topoisomerase II beta activity.

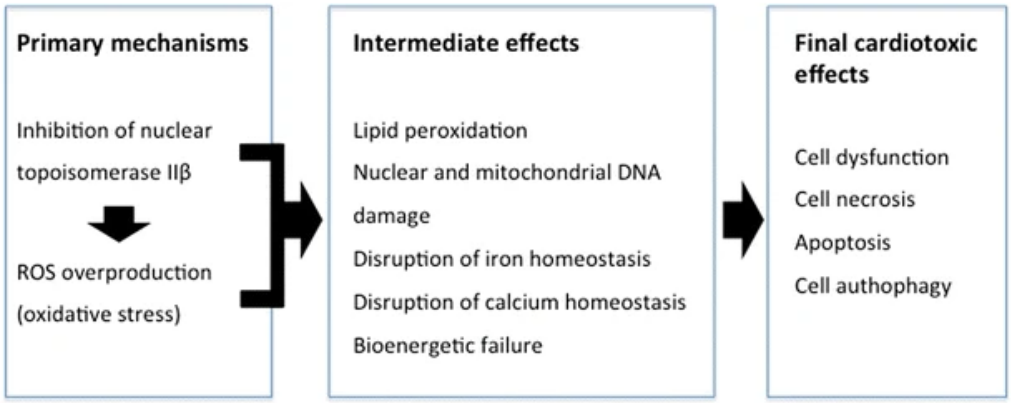
Topoisomerase II alpha is an essential enzyme that plays a critical role in DNA topology management during various cellular processes, such as replication, transcription, and chromosome segregation. It functions by introducing double-strand breaks in the DNA helix, allowing for the passage of another DNA segment through the break before re-ligating the ends. This action alleviates torsional strain and resolves tangles and knots that can arise during DNA metabolism. Topoisomerase II alpha-mediated DNA damage is then followed by cell growth arrest in G1 and G2, and programmed cell death eventually occurs (14). For this reason topoisomerase II alpha is a target of the antitumor activity of anthracycline, which exploits its mechanism to induce DNA damage in rapidly dividing cancer cells.

Topoisomerase II enzymes are categorized into two types: topoisomerase II alpha and topoisomerase II beta. The alpha variant is predominantly found in rapidly proliferating cells, such as tumor cells, and is recognized as a primary target for the anticancer effects of anthracyclines. In contrast, topoisomerase II beta is expressed in quiescent cells, including cardiomyocytes. Inhibition of this enzyme by anthracyclines results in DNA double-strand breaks, alterations in the transcriptome, and the production of reactive oxygen species (15).



Currently, the alcoholic metabolites of anthracycline are considered fundamental to the pathogenesis of the cardiotoxicity (CTX). These metabolites can induce CTX through both iron-dependent and iron-independent mechanisms, which disrupt iron and calcium homeostasis, leading to intracellular calcium overload.

Anthracycline-induced cardiotoxicity exhibits a significant mitochondrial component. Indeed, doxorubicin, once accumulated within the mitochondria (likely due to its high affinity for cardiolipin, a negatively charged phospholipid present in the inner mitochondrial membrane), can exert deleterious effects. These effects primarily include the stimulation of reactive oxygen species production, inhibition of oxidative phosphorylation, and interaction with mitochondrial DNA. In particular, anthracyclines increase mitochondrial calcium accumulation, which causes damage to mitochondrial membranes. Moreover, the accumulation of anthracyclines induces mitochondrial DNA lesions, leading to a progressive decline in cellular energy production capacity and cellular dysfunction. Finally, the reduction of cardiac progenitors by anthracyclines, which play a crucial role in cardiac repair, may compromise the ability of cardiac tissue to regenerate following minor injuries (17).



1.3 Primary prevention strategies for anthracycline cardiotoxicity

Pharmacokinetic manipulations of cardiac exposure to anthracyclines

Anthracycline cardiotoxicity is a multifactorial process influenced by various molecular mechanisms. Pharmacokinetic factors play a significant role, with evidence suggesting that slow infusion (24–96 hours) of anthracyclines reduces cardiotoxicity compared to bolus administration. This strategy is based on the differential relationship between anthracycline pharmacokinetics and their effects: while the anti-tumor activity correlates with total plasma exposure (area under the curve, AUC), cardiotoxicity is linked to peak plasma concentration (C_max) and cardiac tissue penetration. Slow infusions do not significantly alter AUC but effectively lower C_max and reduce anthracycline accumulation in cardiac tissue (15, 19).

In some settings, slow infusions can enable the administration of cumulative doses that would typically induce heart failure (HF).

However, these benefits are offset by increased patient discomfort during prolonged hospitalization and exacerbated exposure-related effects, such as myelotoxicity, mucositis,

and alopecia. Furthermore, slow infusions may not fully mitigate HF risk in survivors of childhood malignancies.

Concerns also arise from findings in breast cancer patients receiving doxorubicin through slow infusions, who exhibited increased DNA-oxidized base accumulation in peripheral blood mononuclear cells, potentially due to prolonged oxidative stress from anthracycline redox cycling. If such DNA damage occurs in cardiomyocytes or cardiac stem cells, patients may remain at risk for HF. Additionally, DNA damage in hematopoietic precursors could elevate the risk of secondary hematologic malignancies.

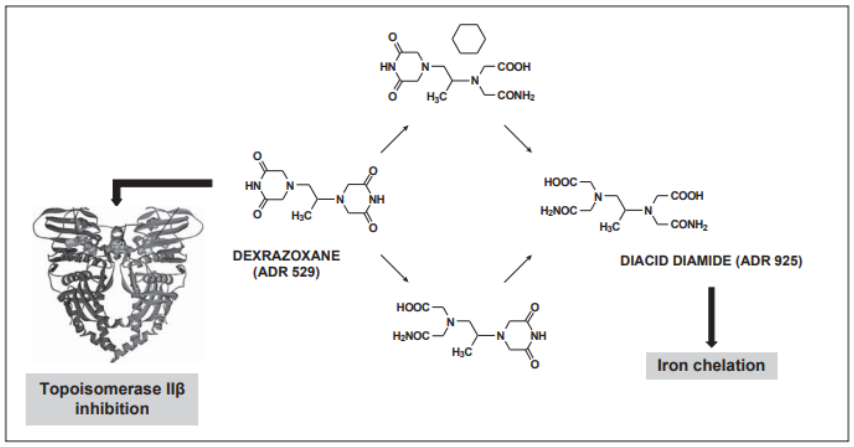
Coadministration of cardioprotective agents

Alternative approaches to mitigate anthracycline-induced cardiotoxicity involve the concurrent administration of pharmacological agents that enhance the protective mechanisms of cardiomyocytes against oxidative stress.

The only drug demonstrated to confer cardioprotective effects in both preclinical and clinical settings is dexrazoxane (DRZ). This is a bis-diketopiperazine, which penetrates cardiomyocytes and undergoes a sequential hydrolysis of its piperazine moieties ending in the release of a diacid diamide. This metabolites effectively chelates iron, preventing its conversion of superoxide anions (O2–) and hydrogen peroxide (H2O2) into more reactive hydroxyl radicals or equally reactive iron-oxygen complexes

The myocardial uptake of DRZ occurs at an exceptionally rapid time, reaching peak concentrations within one minute, which facilitates prompt exposure of cardiomyocytes to this drug. For this reason DRZ could be administered immediately before the infusion of anthracyclines.

The DRZ acts on both pathogenic mechanisms of cardiotoxicity. On one hand, through ferrochelation, it reduces the production of reactive oxygen species (ROS) and consequently oxidative stress. On the other hand, it inhibits the blockade of topoisomerase II beta by anthracyclines. Indeed, DRZ has the capability to compete for the ATP-binding site of topoisomerase IIβ. This interaction compels topoisomerase IIβ to adopt a closed-clamp conformation, which inhibits the formation of anthracycline-DNA-topoisomerase IIβ complexes. Consequently, DRZ serves to mitigate DNA damage and the resulting apoptosis of cardiomyocytes (15).



Dexrazoxane has demonstrated efficacy in mitigating anthracycline-induced cardiotoxicity across numerous clinical trials involving both pediatric and adult oncology patients. This protective effect has frequently enabled the administration of anthracyclines at cumulative doses associated with heart failure (HF) induction.

However, the clinical applicability of DRZ is limited by a singular report suggesting its potential interference with antitumor activity in metastatic breast cancer (16). This interaction may be mediated by the binding of DRZ to topoisomerase IIα, which raises theoretical concerns regarding its detrimental impact on tumor response. Nevertheless, a substantial body of evidence indicates that such interference either does not occur or is of minimal clinical significance. Despite this compelling data, the American Society of Clinical Oncology, along with the Chemotherapy and Radiotherapy Expert Panel, adopts a cautious stance, recommending the use of DRZ only under specific circumstances—particularly in patients who have received more than 300 mg/m² of doxorubicin for metastatic breast cancer and who may derive benefit from ongoing anthracycline treatment.

Another reason that has limited the use of DRZ is the concern that it may be associated with an increased risk of developing secondary malignancies. Particularly, this was noted in young patients with Hodgkin lymphoma who underwent treatment with a combination of doxorubicin and etoposide. It is important to emphasize that, like doxorubicin and DRZ, etoposide also acts by inhibiting topoisomerase. Consequently, these patients received a triple inhibition of topoisomerase, which may have led to genetic instability that could

explain the higher incidence of secondary tumors. Due to such apprehensions, the European Medicines Agency issued a formal warning contraindicating the use of DRZ in pediatric populations. Nevertheless, similar to the concerns regarding potential interference with antitumor efficacy, assertions about an increased risk of secondary malignancy have been alleviated in several investigations (17). Thus, a risk-benefit analysis and pharmacological rationale advocate for the unrestricted clinical use of DRZ in children and adolescents, with the sole exception of those few patients who are candidates for etoposide-anthracycline combinations (18) .

Cardiovascular prophylaxis

The management of comorbidities and cardiovascular risk factors (hypertension, systolic dysfunction, metabolic disorders), as well as the modification of certain unhealthy habits (such as smoking, overweight, and reduced physical activity), plays a crucial role in preventing the development of cardiotoxicity in patients exposed to anthracyclines.

Over the past two decades, fueled by scientific evidence regarding the efficacy of certain cardiovascular drugs in preventing the cardiac remodeling, the focus of cardio-oncologists has shifted towards investigating the use of beta-blockers and angiotensin-converting enzyme (ACE) inhibitors in the oncology setting in patients without risk factors in order to mitigate the toxic effects associated with cardiotoxic agents like anthracyclines.

Numerous studies have evaluated the efficacy of cardioprotective medications in the oncological setting with a specific focus on breast cancer. The phase 3 randomized study, SAFE, aimed to assess the effectiveness of bisoprolol, ramipril, or both drugs compared to placebo in patients with non-metastatic breast cancer. Cardio protection was continued for one year following the initiation of therapy. The most effective tools for assessing subclinical cardiac damage, particularly in identifying signs of ventricular remodeling and global longitudinal strain (GLS), were found to be three-dimensional echocardiography and speckle tracking echocardiography. This study demonstrated a significant decline in ejection fraction in the placebo group, with a reduction of 4%, compared to 1.3% reduction in the group receiving cardio protection, particularly among those treated with both ramipril and bisoprolol. However, it is essential to note that the study population was characterized as low-risk, with a median age of 48 years and no cardiovascular risk factors.

Consequently, this cohort of patients, despite exposure to anthracyclines, is unlikely to develop significant cardiotoxicity (20). Moreover, the implementation of primary cardiovascular prophylaxis is influenced by the potential side effects associated with cardiovascular medications, such as bradycardia, hypotension, and fluid retention. These adverse effects can compound the discomfort experienced by patients undergoing antitumor therapy and reduce the compliance to the therapy.

While several studies have investigated the use of prophylactic cardio protection based upon anthracycline exposure alone, others have proposed risk-guided approaches targeting patients at higher risk of development of cardiotoxicity (21). This strategy may facilitate the identification of a subset of patients who are likely to derive the most significant benefit from primary preventive measures.

Various risk stratification methodologies have been proposed, including troponin-guided and strain-guided strategies.

Troponin-guided strategy for cardio protection: is based on the evidence of a correlation between elevated troponin levels before and during the treatment and the onset of chemotherapy-related cardiotoxicity, supporting their role in identifying patients at high risk.

A key study led by Cardinale et al. (22) compared the use of enalapril as c cardioprotective agent in all patients in the preventive arm, while the other arm only received it after a troponin elevation detection. Outcomes, including the incidence of troponin elevation and cardiotoxicity defined by LVEF reduction, showed no significant differences between the two groups. The researchers proposed that ACEI provides cardio protection post-injury by mitigating neuro hormonally-mediated adverse remodeling, as troponin release occurs concurrent with cardiomyocyte injury, unaffected by ACEI.

The Cardiac-CARE trial (23) further investigates this troponin-guided approach in breast cancer and non-Hodgkin patients receiving anthracycline chemotherapy. Elevated troponin I levels during the treatment lead to randomization for either standard care or a combination of beta-blockers and ARBs. The result of this study did not demonstrate a cardioprotective effect of the combination of candesartan and carvedilol in patients receiving anthracycline and with high risk cardiac troponin concentrations. Indeed, the

overall decline in left ventricular ejection fraction occurred, at the 6 months post chemotherapy evaluation, regardless of changes in cardiac troponin concentrations during chemotherapy.

Echocardiographic strain-guided strategy for cardio protection: it is based on the evidence that global longitudinal strain (GLS) is a robust and sensitive marker of left ventricular dysfunction and that it may also serve as a criterion for identifying patients at high risk for chemotherapy-induced cardiotoxicity. This strategy was used in several studies for guiding the initiation of cardioprotective therapies in patients exposed to anthracycline.

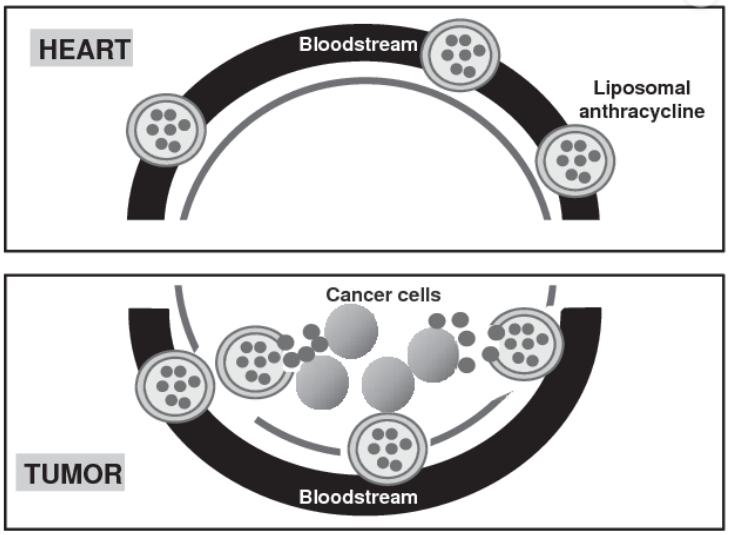
An important multicenter randomized study uses the GLS-guided strategy in order to stratify patients to receive cardioprotective therapy during anthracyclines treatments. The results of this study support the use of GLS in surveillance for anthracycline-induced cardiotoxicity (24).

1.4 Mechanism of action of liposomal anthracyclines

In order to mitigate cardiotoxicity an effective approach involves substituting conventional anthracyclines with liposome-encapsulated formulations.

Liposomal anthracyclines are large enough to prevent passage through the gap junctions of endothelial cells in the heart and other healthy tissues. This steric hindrance reduces the diffusion of anthracyclines in extravascular spaces, resulting in a higher maximum concentration (C_max) and lower distribution volume and clearance compared to conventional formulations. Consequently, most circulating anthracyclines remain encapsulated within the liposomal vesicles, leading to minimal exposure to "free" drugs and thereby reducing cardiac risk. However, these liposomal formulations can still navigate the irregular and permeable microvasculature that characterizes tumors microenvironment. Once extravasated, they accumulate within tumors due to inadequate lymphatic drainage and increased interstitial pressure, a phenomenon known as the "enhanced permeability and retention effect " (25).

The tumor microenvironment can destabilize liposomal vesicles through mechanisms such as low pH, the release of lipases from necrotic cells, or oxidizing agents from inflammatory cells. Resident macrophages may also degrade the vesicles and release free anthracyclines.



There are three liposomal doxorubicin formulations approved in Europe: Caelyx® Myocet® and DaunoXome®. The former is pegylated liposomal doxorubicin (PLD) and, compared to the non-pegylated formulation (NPLD), demonstrates a longer circulation time and a smaller volume of distribution. However, PLD is associated with cutaneous toxicity, and up to 25% of patients may experience hand-foot syndrome (HFS), characterized by erythema and dysesthesia of the palms and soles; this is not an adverse effect associated with NPLD. Preclinical studies have demonstrated that liposomal formulations can deliver substantial amounts of anthracycline to tumors while minimizing doxorubicin exposure in cardiac tissue relative to conventional formulations.

In some animal models, liposomal formulations may even provide higher levels of free anthracycline to tumor cells compared to standard formulations.

1.5 Use of liposomal anthracyclines in lymphomas

Anthracyclines represent a fundamental treatment for lymphoproliferative syndromes, particularly for Hodgkin and non-Hodgkin lymphomas. Despite the advent of immunotherapy, anthracyclines continue to be an integral component of first-line therapeutic protocols. Specifically, they are included in the R-CHOP and polatuzumab-CHP regimens for the treatment of non-Hodgkin lymphomas, and in the MBVD regimen for Hodgkin lymphomas.

Since the discovery of liposomal anthracyclines, various clinical studies have aimed to demonstrate the role of liposomal anthracyclines in the primary prevention of cardiovascular events and to compare their antitumor efficacy with that of conventional anthracyclines. Most of the studies are single arm, while others have compared the R-COMP and R-CHOP regimens.

The multicenter phase II study conducted by Luminary et al (26) in 2009 involving 72 elderly patients with DLBCL analyzed the efficacy and cardiotoxicity of liposomal anthracyclines. Patients receiving R-COMP were recruited based on age (>60 years) and had an LVEF >50% (mean LVEF 61%); more than half of the patients had pre-existing cardiovascular diseases. The results showed a complete response (CR) rate and an overall response rate (ORR) lower than those obtained from R-CHOP in previous work, but without correlation to worse outcomes: in fact, the three-year overall survival (OS) was higher. The results were considered promising given that the median age of patients was 72 years, which is higher than that of trials studying R-CHOP. From a cardiological perspective, pre-existing cardiovascular diseases did not affect CR or three-year failure-free survival (FFS); there was no statistically significant reduction in LVEF, and the rate of severe cardiac events was among the lowest recorded in trials involving elderly patients with DLBCL.

Following this study, additional studies were conducted, all monocentric with small sample sizes, regarding the use of liposomal anthracyclines in the setting of lymphomas in elderly patients or those at high cardiovascular risk, yielding similar results.

A more recent multicenter and retrospective study by Rigacci et al. (27), examined the incidence of cardiovascular events and the efficacy of Myocet within the R-COMP regimen in a total of 946 elderly patients with DLBCL or with cardiac comorbidities at diagnosis. Cardiovascular events were observed in only 5% of the population. Regarding antitumor efficacy, R-COMP demonstrated an ORR of 85.2% with a CR of 72%, and a five-year OS of 72%. The authors concluded that R-COMP is safe and effective in the elderly population with cardiovascular risk factors.

Comparative studies of R-COMP versus R-CHOP are less common in the literature.

One of those is the multicenter retrospective study of Mian et al. (28) that involved 364 patients, where 60% received R-CHOP and the remaining portion received R-COMP. No assessment of cardiovascular effects was performed, but the antitumor efficacy of the two regimens was evaluated. The CR was comparable between the two groups, but patients treated with NPLD had a significantly lower relapse-free survival and a shorter progression-free survival (PFS) compared to the other arm. OS was also found to be lower. However, when analyzing the data for patients who received more than four cycles, it was observed that the number of cycles administered affected PFS and OS, rather than the type of regimen; furthermore, the R-COMP group comprised significantly older patients (median age of 76 years vs. 63) and consequently had more cardiovascular diseases (70% vs. 40%).

Another randomized multicenter Phase II trial conducted on 91 patients over 60 years old with DLBCL or grade 3b follicular lymphoma compared R-COMP with R-CHOP. The efficacy of the two therapeutic regimens was found to be comparable, both in terms of ORR and CR, which were similar between the two arms.

A recent study by the Italian Lymphoma Foundation (29) compared the use of the aforementioned therapeutic regimens in a total of 1163 patients with DLBCL. Patients treated with R-COMP had a higher age (median 76 vs. 71) and a greater number of cardiac comorbidities. The three-year PFS was similar in the two groups, R-CHOP and R-COMP (70% and 64%), as was the three-year OS (77% and 71%, respectively)

PATIENTS AND METHODS

In this single-center retrospective study, we report data on the use of non-pegylated liposomal anthracyclines (NPLD) in patients with newly diagnosed or relapsed lymphoma both Hodgkin and non-Hodgkin.

According to Italian law 648/96, from 2007, in Italy NPLD could be used in the setting of non-Hodgkin lymphoma in elderly patients (over 65 years) or in cardiopathic patients at a dosage of 50 mg/m2. As regards Hodgkin lymphoma in Italy NPLD can be used only off-label.

The study involved an analysis of all patients who received liposomal non-pegylated anthracyclines therapy between 2007 and 2023 at the Hematology Clinic of Polyclinic San Martino Hospital in Genoa.

Inclusion criteria required a diagnosis of either Hodgkin Lymphoma (HL), Non-Hodgkin Lymphoma (NHL) or T cell lymphoma, as well as having attended at least one cardiac evaluation. Patients treated during this period with NPLD who had not undergone a cardiovascular assessment were excluded from the study. The final population includes 199 patients.

The baseline evaluation encompassed various parameters including age, sex, B symptoms, International Prognostic Index (IPI) and follicular International Prognostic Index (FLIPI).

The baseline cardiovascular toxicity risk stratification was performed using the HFA-ICOS (Heart Failure Association International Cardio-Oncology Society) risk assessment tool. At the standard criteria were added the evaluation of moderate aortic stenosis as M2 risk, moderate aortic and mitral insufficiency as M1 risk and previous CAD as M2 risk.

Cardiac function was assessed prior to the initiation of treatment through a comprehensive review of medical history, physical examination, electrocardiographic analysis, and two-dimensional echocardiography.

2.1 Aims

The primary endpoint was the a composite incidence of heart failure (HF) or acute coronary syndrome (ACS) calculated as event-free probability (EFP). Secondary endpoints were response to therapy, overall survival (OS) and progression free survival (PFS).

2.2 Treatments

Patients with a diagnosis of non- Hodgkin lymphoma received outpatient treatment with the R-COMP regimen every three weeks for a total of six cycles. The R-COMP regimen was based on the standard R-CHOP protocol, with doxorubicin replaced by Myocet.

Specifically, the treatment consisted of cyclophosphamide at a dose of 750 mg/m² on day 1, vincristine at 1.4 mg/m² on day 1 (with a maximum allowable dose of 2 mg), Myocet at 50 mg/m² on day 1, and prednisone at 100 mg/day 1 to 5.

Among patients with non-Hodgkin indolent lymphoma there were 5 mantle cell lymphoma who underwent first line treatment with 3 cycles of R-COMP alternated with 3 cycles of R-DAHOX.

Patients with a diagnosis of Hodgkin lymphoma received outpatient treatment with the MBVD regimen every 28 days for a total of six cycles. The MBVD regimen was based on the standard ABVD protocol, with doxorubicin replaced by Myocet. The treatment consisted of vinblastine at a dose of 6 mg/m2 on day 1 and 15, dacarbazine 375 mg/m2 on day 1 and 15, bleomycin at a dose of 10.000 UI/m2 on day 1 and 15 and Myocet at 50 mg/m2 on day 1 and 15. Supportive care, including the use of prophylactic antibiotics, antiviral and antiemetics, was permitted based on the treating physician's clinical judgment. Granulocyte colony-stimulating factor (G-CSF) could also be administered.

Patients affected by T cell lymphoma received outpatient treatment with COMP regimen as mentioned before, without the somministration of Monoclonal antibody against CD20 (rituximab).

2.3 Efficacy and safety response

The overall response rate (ORR) was determined as the sum of complete and partial response rates. Overall survival (OS) was recorded from the date of diagnosis to the last follow-up. Progression free survival (PFS) was calculated from diagnosis to the date of progression or death from any cause or last clinical contact for censored patients.

Event-free probability (EFP) was evaluated in relation to significant cardiac events, including heart failure, acute coronary syndrome and left ventricular dysfunction.

To assess cardiotoxicity, we utilized the percentage of cardiovascular events occurring during and after therapies, as well as the cardiovascular risk profile of patients who experienced such events. We defined cardiovascular events as: heart failure (HF) and coronary syndrome (ACS). We also evaluated the left ventricular dysfunction (LVD) independently.

For the patients who experienced a cardiovascular event, we evaluated whether this led to the discontinuation of therapies or resulted in patient mortality.

2.4 Statistical analysis

Descriptive statistics were reported in terms of absolute frequencies and percentages. Distribution of data regarding continuous variables was described in terms of a median value and range.

Survival analysis was estimated by the Kaplan-Meier method, with a 95% confidence interval (95% CI). The influence of covariates was quantified as the hazard ratio (HR). The P-value <0.05 was considered as statistically significant. The statistical analysis was conducted using the R software. Cox proportional-hazard ratio was used to compare curves in subgroups.

RESULTS

3.1 Clinical characteristics of the study population

Between 2007 and 2023, 342 patients received treatment with liposomal non-pegylated anthracycline at the Hematology Clinic of Policlinic San Martino Hospital in Genoa. Of these, 199 underwent pre and post treatment cardiological evaluation, and were included in the present study.

Demographic and clinical characteristics of the study population are listed in **Table 1.**

Table 1. Demographic and clinical characteristics of the study population

Variable	All patients (N= 199)
Demographics	
Age (median, years)	73
Male gender (%)	112 (56.28)
Histology	
DLBCL (%)	127 (63.81)
IPI (%)	
Low (0-1)	11 (8.66)
Intermediate (2-3)	69 (54.33)
High (4-5)	35 (27.55)
Indolent LNH (%)	43 (21.60)
HL (%)	14 (7.03)
Others (%)	15 (7.53)
Treatment	
R-COMP	172 (86.43)
R-COMP/ R-DHAOX	4 (2.01)
MBVD	13 (6.53)
COMP	2 (1)
Myocet	4 (2.01)

The study population was composed predominantly of male (56%), with an advanced age, the median age was 73 years.

One hundred seventy (85.42%) had non-Hodgkin lymphoma, 14 patients (7.03%) had Hodgkin lymphoma, while 15 patients (7.53%) had other type of lymphoma (8/15 PTCL-NOS, 5/15 Sezary syndrome, 1/15 PTLD, 1/15 BPDCN).

Among non-Hodgkin lymphoma, 74.70% of the subject (127/170) had diffuse large B-cell lymphoma (DLBCL), 25.29% (43/170) had indolent non hodgkin lymphoma, of whom 65.11% (28/43) had follicular lymphoma, while the others 37.20% (16/43) had indolent lymphoma other than follicular (9/16 marginal zone lymphoma, 7/16 had mantle cell lymphoma).

Based on IPI classification, as regards DLBCL patients, more than half (54.3%) of the patients were at intermediate risk and 27.5% of patients were at high risk.

As regards cardiovascular risk stratification assessed on the HFA-ICOS criteria, the patients were classified into four risk categories: 5 patients were identified as very high risk, 84 as high risk, 96 as intermediate risk, and 14 patients as low risk **(Table 2).**

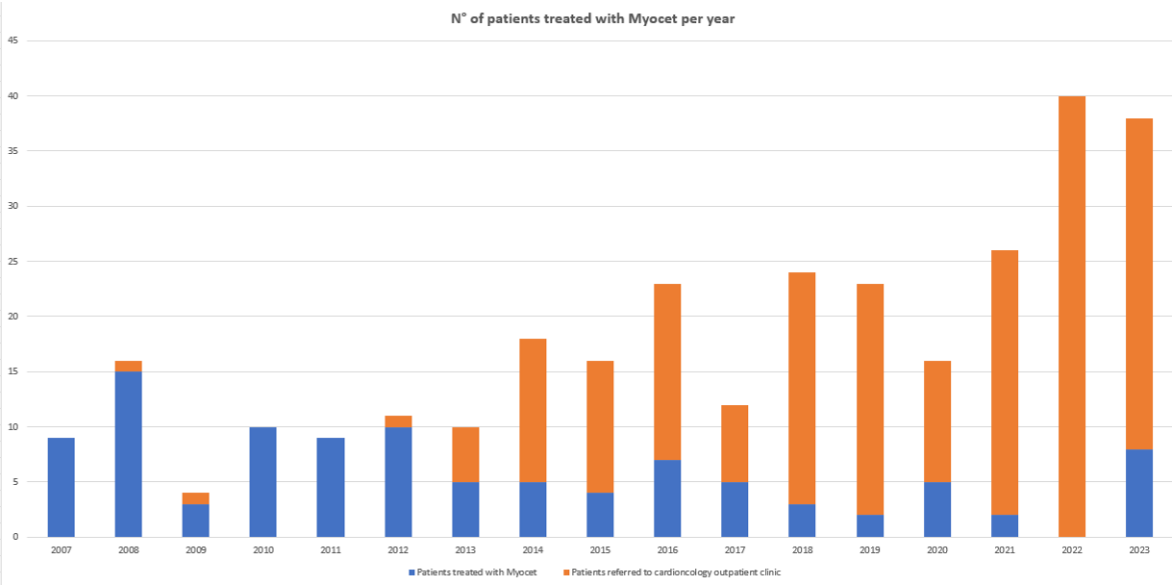
Table 2. Cardiovascular toxicity risk stratification based on ICOS criteria

CV risk	All patients (N= 199)
Low	14
Intermediate	96
High	84
Very High	5

The median follow up from the diagnosis was 30 months (range 13.4-61.5), mean follow up was 41 months (DS +/- 33).

The reason for treatment with NPLD was older age for 59% of patients (119/199), 17.58% of patient pre-existing cardiac morbidity (35/119), 6.5% for previous anthracycline therapy (13/199) and 16.11% of patients for other causes not specified (32/199).

We observed a progressive increase in the usage of NPLD from 2007 to nowadays. Indeed in 2007 only 9 patients received a NPLD treatment, while in 2022 40 patients underwent treatment with NPLD. Moreover we noted that there was a improvement among the years of cardiac evaluation of patients before and after chemotherapy treatment **(Graph1).**



Graph 1. Number of patients treated per year

3.2 Cardiotoxicity

During a median follow up of 30 months, about 12% (n = 24) of subjects developed major cardiotoxic events including 16 heart failure (HF) and 8 acute coronary syndrome (ACS). Two patients developed left ventricular dysfunction (LVD) during follow-up.

Deep vein thrombosis and pulmonary embolism have not been considered within the context of cardiovascular events, they were considered independently. Deep vein thrombosis occurred in 5 patients, while pulmonary embolism occurred in 9 patients (9/199).

The overall probability of not experiencing a major cardiac event, including HF and ACS, after 5 years was 80% (IC 72-89%.) **(Figure 1-2).**

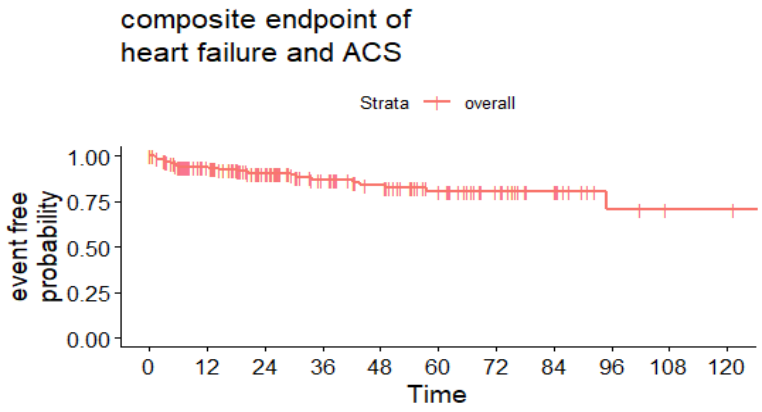


Figure 1. Event free probability of major cardiac event (HF or ACS)

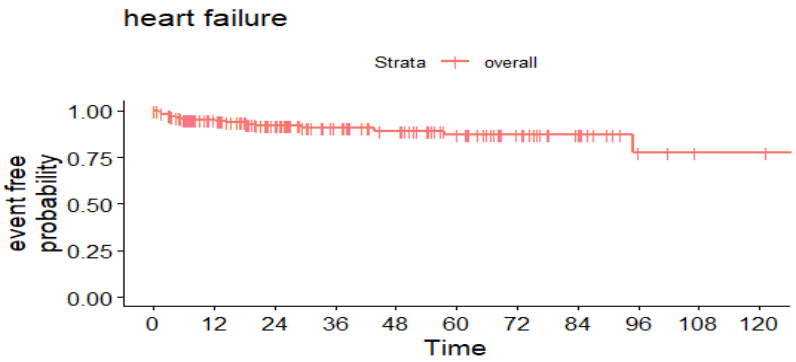


Figure 2. Event free probability of developing HF

As expected, we observe that age greater than 75 years (n =) affect the probability of event-free condition (*P* = 0.02) **(Figure 3).**

Additionally, examining the probability of developing a major cardiac event within the ICOS groups, a statistically significant difference is observed between patients categorized as high and very high risk and those classified as moderate risk (*P value* = 0.003) **(Figure 4).**

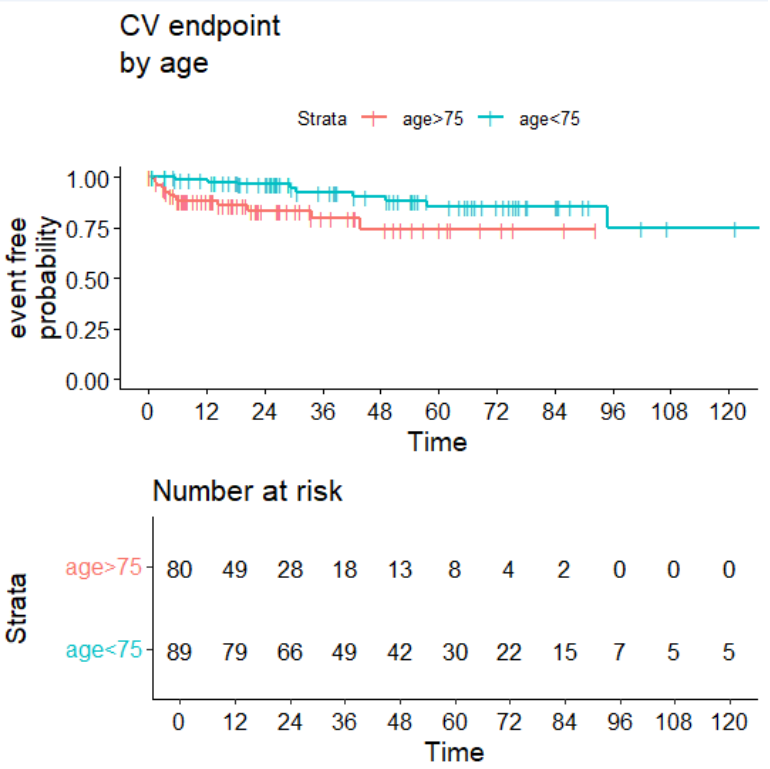


Figure 3. Event free probability by age

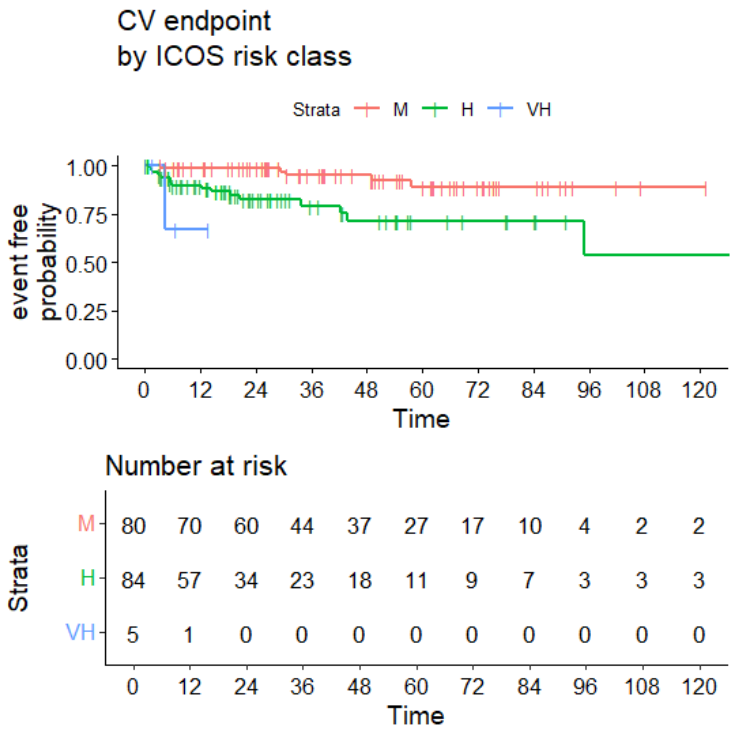


Figure 4. Event free probability by ICOS group

3.3 Survival and causes of death

A total of 67 (33.66%) patients died from all causes including progression of lymphoma (56.71%, N = 38), infectious disease due to therapy (22.38%, N=15) unknown causes (19.40%, N = 13), or second neoplasia (1.49%, N = 1).

Overall survival (OS) and Progression-free survival (PFS) was evaluated for each histological diagnosis **(Figure 5-6).**

In the context of diffuse large B-cell lymphoma (DLBCL), high-risk International Prognostic Index (IPI) and low/intermediate-risk groups were assessed separately.

The 3-year and 5-year OS rates for high-risk DLBCL patients were 60% (95% CI: 45–80%) and 55% (95% CI: 39–77%), respectively. For patients categorized as low or intermediate risk, the 3-year and 5-year OS rates were 71% (95% CI: 62–82%) and 60% (95% CI: 48–74%), respectively. For indolent lymphoma, the 3-year and 5-year OS rates were 81% (95% CI: 69–93%) and 72% (95% CI: 58–89%), respectively. In Hodgkin lymphoma, the 3-year and 5-year OS rates were 85% (95% CI: 69–100%), while for patients with other histological subtypes, the 3-year and 5-year OS rates were significantly lower, at 51% (95% CI: 30–85%) and 34% (95% CI: 13–88%), respectively.

The 3-year and 5-year PFS rates for high-risk DLBCL patients were 55% (95% CI: 41-75%). In contrast, for patients classified as low/intermediate risk, the 3-year and 5-year PFS rates were 67% (95% CI: 58-78%) and 52% (95% CI: 40-66%), respectively.

The 3- and 5-year PFS for indolent lymphoma were 72% (95% CI: 59-88%) and 68% (95% CI: 54-85%), respectively. For patients with Hodgkin lymphoma, the 3- and 5-year PFS rates were 71% (95% CI: 51-95%). In contrast, the 3- and 5-year PFS rates for patients with other histological diagnoses were significantly lower, at 38% (95% CI: 20-74%) and 19% (95% CI: 4-74%), respectively.

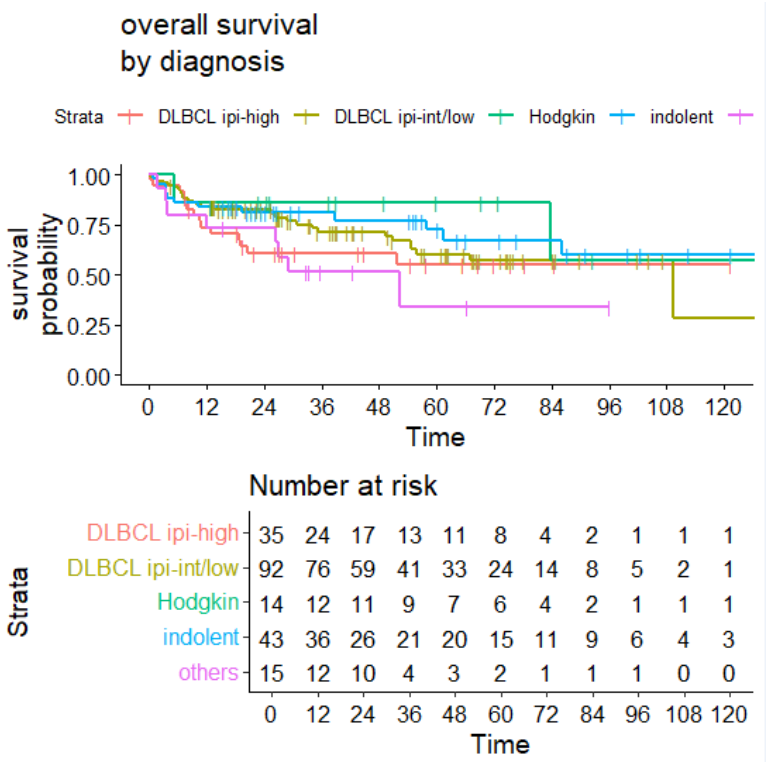


Figure 5. OS by Histological diagnosis

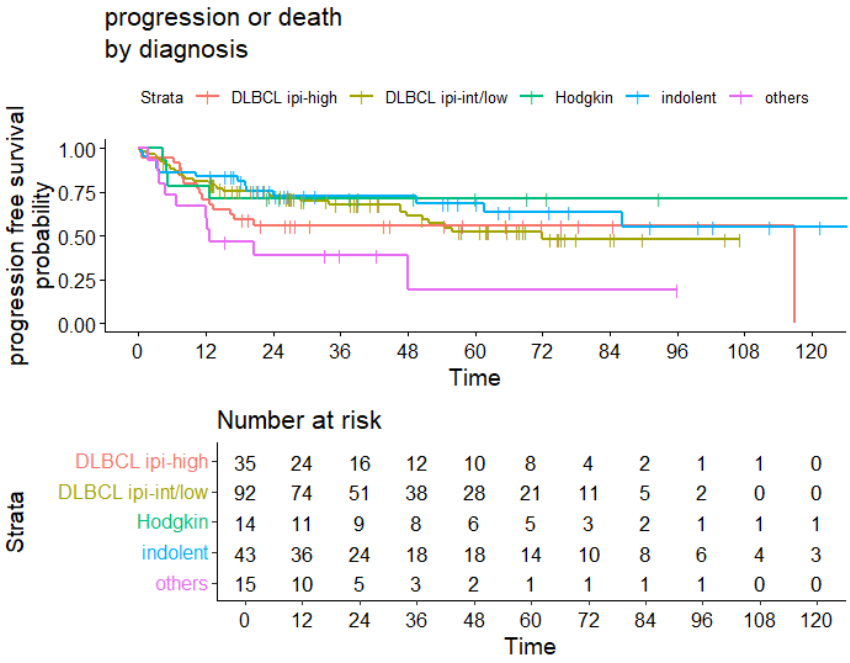


Figure 6. PFS by Histological diagnosis

As expected, there was a significant difference in PFS based on age, with patients younger than 75 years exhibiting a 3-year PFS rate of 73%, compared to 57% for those aged 75 years

or older [*p value* = 0.04] **(Figure 7).** Moreover, we did not observe statistically significant differences in PFS between high cardiovascular risk patients (ICOS High) and low/Intermediate risk (ICOS), although a worse survival trend was noted in the high-risk group [*P value* = 0.078] **(Figure 8)**.

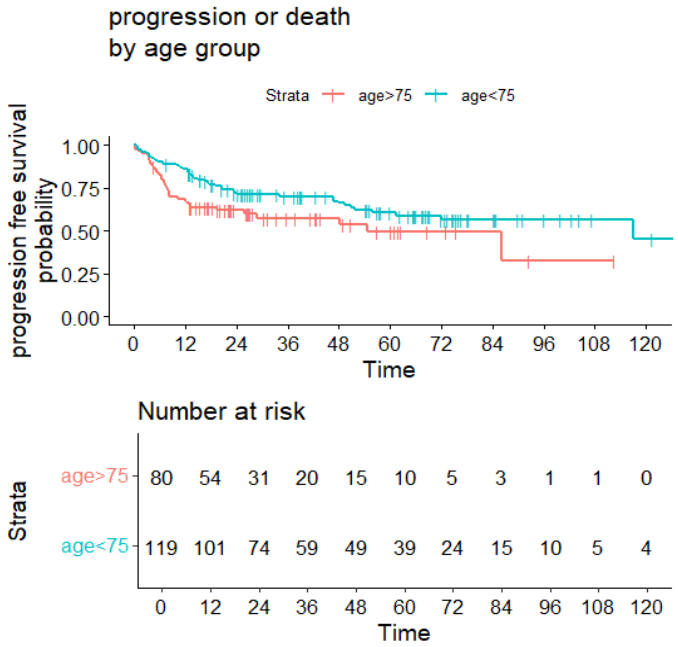


Figure 7. PFS by age

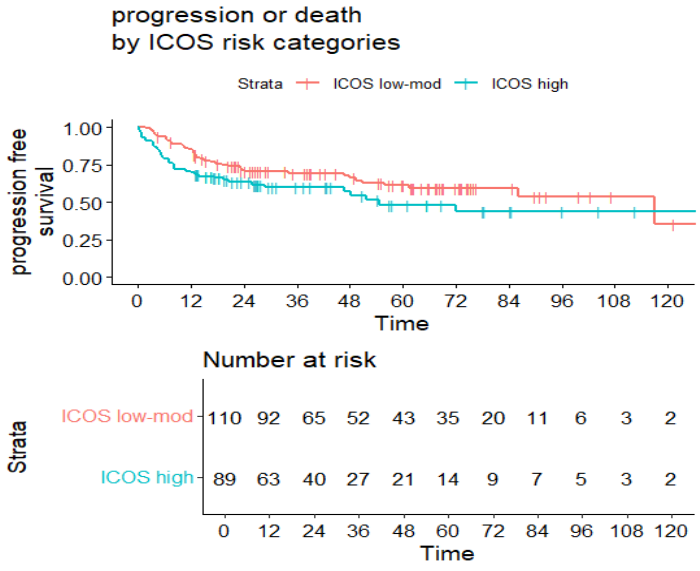


Figure 8. PFS by ICOS risk category

The PFS was also assessed in patients who developed a major cardiovascular event and those who did not, interesting no significant difference were observed between those groups **(Figure 9).**

Another interesting point that is been noted is the significant difference in OS between patients that completed therapy and those who did not. Indeed those one have a OS worst than the others **(Figure 10).**

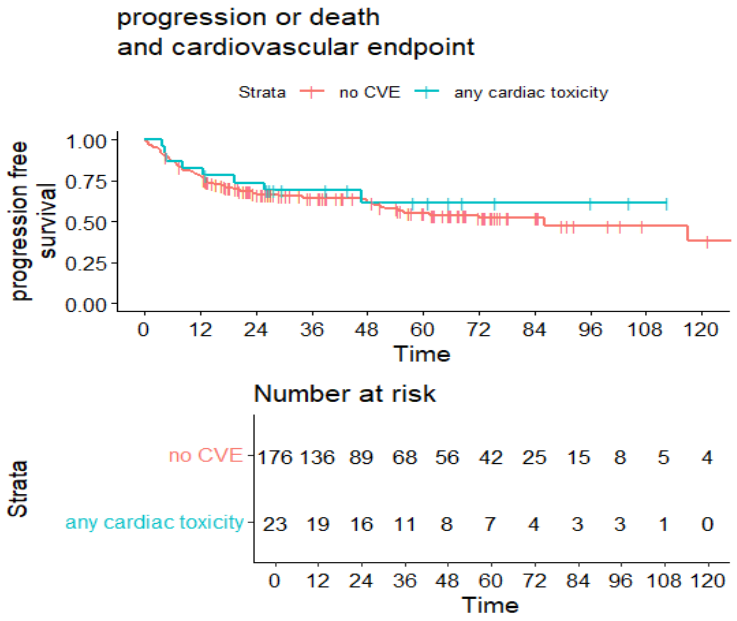


Figure 9. PFS by cardiovascular endpoint.

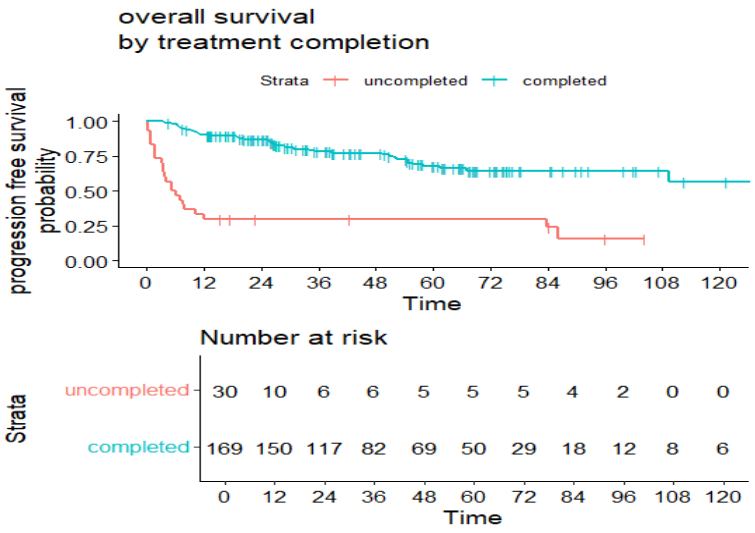


Figure 10. OS by treatment completion.

3.4 Response to therapy

Most of the patients (84.92%, n=169) completed all six cycles of therapy; 25 patients (12.56%) received 4 or 5 cycles and 5 patients (2.51%) less or equal to 3 cycles. The primary reason for treatment discontinuation was death (56.66%, N=17); 9 patients (30%) did not complete treatment due to progression of hematological disease, while 4 patients (13.33%) discontinued treatment due to the development of toxicity (1 patient due to cardiotoxicity).

Outcomes including ORR, CR and PR of the whole study population are listed in **Table 2.**

As regard DLBCL, ORR was attained in 87.40% (111/127) of subjects with CR in 77.95% (N = 99) and PR in 9.44% (N=12), respectively, whereas only 12.59% (N= 16) of patients did not respond to therapy, or were withdrawn because of premature death.

Among the study cohort, 27.55% of patients (35/ 127) had a high IPI score of 4-5, resulting in an ORR of 77.14%, with CR rate of 71.42% (25/35) and a PR rate of 5.71% (2/35). In the cohort of 69 patients (54.33% of the whole population) with an intermediate IPI score of 2-3, the ORR was 91.30% (63/69), with CR rate of 81.15% (56/69) and a PR rate of 10.14% (7/69). Subjects with a low IPI score of 0-1, representing 8.66% of the total population (11/127), had an ORR of 100% (11 out of 11), with a CR observed in 81.81% of patients (10/11) and a PR in 18.18% (2/11).

During follow-up, 17.32% (N = 22) of the patients with DLBCL that successfully responded to R-COMP regimen relapsed. Of those 18/22(81.81%) had achieved a CR, 4/22 (18.18%) had achieved a PR.

As regards indolent non-Hodgkin lymphoma, the ORR was 88.37% (38/43), with CR in 71.09% of patients (31/43) and PR in 16.27% (7/43). Only 5 patients out of 43 (11.62%) did not respond to therapy. During follow-up 6 subjects relapsed (13.95%).

Among Hodgkin lymphoma the ORR was attained in 92.85% of patients (13/14), with CR in 85.71% (12/14) and PR in 7.14% (1/14), only one patient was refractory to therapy (7.14%). During follow-up, only one patient that successfully responded to MBVD regimen relapsed (7.14%).

For what concern the others cases (PTCL-NOS, Sezary syndrome, PTLD and BPDCN) the ORR was 80% of (12/15), the CR was 40% (6/15) and the PR was 40% (6/15)

Table 3. Outcomes of the study population

Outcomes	
DLBCL	**All patients (N= 127)**
ORR (%)	111 (87.40)
RC (%)	99 (77.95)
RP (%)	12 (9.44)
Indolent LNH	**All patients (N= 43)**
ORR (%)	38 (88.37)
RC (%)	31 (71.09)
RP (%)	7 (16.27)
HL	**All patients (N= 14)**
ORR (%)	13 (92.85)
RC (%)	12 (85.71)
RP (%)	1 (7.14)
Others	**All patients (N= 15)**
ORR (%)	12 (80)
RC (%)	6 (40)
RP (%)	6 (40)

DISCUSSION

Anthracyclines continue to be a cornerstone included in the chemo-immunotherapeutic regimens for the first-line treatment of non-Hodgkin lymphoma, Hodgkin lymphoma, and T-cell lymphomas, even in the era of immunotherapy. The efficacy of anthracyclines is tempered by a contained but present risk of cardiotoxicity, which limits their use, particularly in elderly patients and those with pre-existing cardiac comorbidities. The two primary determinants of toxicity are cumulative dose and cardiac status at the initiation of chemotherapy. Over the years, several strategies have been explored to mitigate the cardiotoxic effects of anthracyclines while preserving their antitumor activity. These include modifying the pharmacokinetics of anthracyclines through prolonged infusions, co-administering cardioprotective agents like Dexrazoxane, utilizing novel formulations such as liposomal anthracyclines, and implementing cardiovascular prophylaxis. Recent studies over the past 10-20 years have particularly focused on cardiovascular prophylaxis, driven by promising findings related to novel cardiovascular drugs (beta-blockers and ACE inhibitors) in preventing cardiac remodelling in patients with heart disease. This focus has introduced a bias in population selection, as most studies have targeted healthy, low cardiovascular risk populations, which are less likely to develop anthracycline-induced cardiotoxicity.

Consequently, despite liposomal anthracyclines being in clinical use for over 20 years, there is a scarcity of studies assessing their efficacy and safety, with most being monocentric and involving very small patient populations.

The aim of our study was to investigate in a real life clinical setting the efficacy and safety of nonpegylated liposomal doxorubicin (NPLD) in patients diagnosed with lymphoma.

The study population was elderly, with a median age of 73 years, and exhibited a moderate to high cardiovascular risk. Notably, 45% of the patients were classified as having very high or high cardiovascular risk according to the HFA-ICOS criteria, 48% had an intermediate risk, and only 7% were considered to have a low cardiovascular risk.

The main reason for the choice of NPLD was advanced age in 59% of the patients, the presence of pre-existing cardiomyopathy in 18%, prior use of anthracyclines in 7%, while in the remaining 16% of patient there was no specific reason. Therefore, the study population represents a strongly negatively selected cohort characterized by elderly patients with multiple comorbidities. The efficacy of NPLD was evaluated across histological subtypes of lymphoma. As regards, non-Hodgkin lymphomas, we observed very high overall response rates and complete response rates in both aggressive and indolent lymphomas. Specifically, for diffuse large B-cell lymphoma (DLBCL), we noted an overall response rate of 87% and a complete remission rate of 77%, which are consistent with previous studies in literature on the use of R-CHOP, particularly considering that the patients in this study were elderly with multiple comorbidities who probably would not have been eligible for conventional anthracycline-based regimens. The 3- and 5-years overall survival (OS) rates were 60% and 55% for IPI high risk, and 71% and 60% for low/intermediate. Survival rates observed in our study are slightly lower than that reported in previous R-CHOP studies. However, the patients in our study were strongly negatively selected, indeed they are typically deemed ineligible for treatment with conventional anthracyclines and, therefore, do not fall within the cohorts of R-CHOP studies. In this patient population, survival curves tend to be very low, making our results promising in this context.

Outcomes in indolent non-Hodgkin lymphomas are similar to ones of the literature, with complete response rates of 71% and overall survival rates at 3 and 5 years of 81% and 72%, respectively. Results in Hodgkin lymphoma are less consistent with the strong limitation of the small sample size and a potentially strong selection bias in elderly with HL. Patients with other histological lymphoma diagnosis, as expected, have poorer outcomes and lower survival rates.

The use of NPLD has been generally well tolerated in the study population, with 85% of patients completing all six cycles of chemoimmunotherapy.

As regards cardiotoxicity, the incidence of major cardiological events, specifically heart failure (HF) and acute coronary syndrome (ACS), was 12%, with HF occurring in 8% and ACS in 4% of patients. The percentage of cardiological events observed in our study is higher than the values reported in the literature.

The study by Rigacci et al. (27) from 2020, which analyzes the safety and efficacy of NPLD in aggressive DLBCL lymphomas, reports an incidence of major cardiovascular events of 5.3%. Despite a difference in incidence of cardiovascular events, the event free probability at 5 years follow up in our study was similar to the one of Rigacci et al (80%, ci 72-89). It is important to emphasize that, in addition to being a strongly negatively selected population, our study considered heart failure not only for those events requiring hospitalization but also for subclinical cases managed on an outpatient contest. Indeed, analyses based on cardiovascular risk stratification using the HFA-ICOS score and by age show that high-risk patients and elderly patients were the ones most likely to develop a cardiovascular event. Furthermore, the study demonstrated that the occurrence of a cardiological event does not impact on overall survival (OS) and progression-free survival (PFS).

Another interesting finding that emerged from our study is that from 2007 to 2024, due to the safety and efficacy of liposomal anthracyclines, there has been a progressive and significant increase in the use of therapeutic regimens containing NPLD, particularly R-COMP and MBVD, in the context of lymphomas. Additionally, there has been an increasing focus on cardiovascular risk factors both pre- and post-treatment thanks to the cardi-oncology department.

In conclusion, the NPLD-containing regimen in our study exhibited a mild incidence of major cardiac events, even among a population at high cardiovascular risk, without compromising treatment efficacy. This finding is particularly important given the patient setting, as it allows the use of more effective therapeutic regimens for even the most fragile and complex patients. This means we can extend the best available treatments to a greater number of patients.

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