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Anthracycline Cardiotoxicity

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1. Introduction

Cancer patients who are undergoing chemotherapy have an increased risk of developing cardiovascular complications, and the risk is even greater if there is a known history of heart disease. A wide range of chemotherapy agents have been associated with cardiotoxicity. Among the serious cardiac complications related to chemotherapy, there are arrhythmias, myocardial necrosis causing a dilated cardiomyopathy and vasoocclusion or vasospasm resulting in angina or myocardial infarction.

The anthracyclines and related compounds (doxorubicin, idarubicin, epirubicin, and the anthraquinone mitoxantrone) are some of the most frequently implicated agents. Anthracyclines, including doxorubicin, are widely used in the treatment of cancer. Although topoisomerase II inhibition remains the most persuasive mechanism to explain the antitumor activity of anthracyclines, clinically relevant concentrations of anthracyclines were shown to induce apoptosis through additional mechanisms that were not bound to the topoisomerase II - p53 machinery.

However, their use is limited by cardiotoxicity and increasing survivors' susceptibility to treatment-related complications that can remarkably affect their quality of life. Surviving patients have an increased rate of heart failure, coronary artery disease, and cerebrovascular accidents compared to the general population. The specific mechanisms of anthracycline cardiotoxicity are complex and still remain unclear. Hence, determining the factors that may increase propensity to cardiotoxicity is of great importance, as is monitoring patients during and after treatment. Additionally, treatment and prevention options, such as limiting cumulative dosage, liposomal anthracyclines, and dexrazoxane, continue to be explored.

Liposomal doxorubicin has been developed with the aim of improving the therapeutics index of doxorubicin by reducing the drug's cardiotoxicity. Two liposomal formulations are currently available: non-pegylated liposomal doxorubicin (NPLD) (Myocet®, Cephalon, USA) and pegylated liposomal doxorubicin (PLD) (Caelix®/Doxil®, Schering-Plough/Orto Biothech, USA).

In this chapter, we will analyze the cardiac complications caused by the use of anthracyclines, and the potential benefit of substituting these drugs with their liposomal counterpart. Acute and chronic cardiac toxicities, together with risk factors will also be

discussed. Guidelines for monitoring and drug discontinuation will be another point to be analyzed in this chapter.

2. Pharmacology

The anthracyclines represent a broad family of antibiotics that exhibit activity in numerous tumours. The first anthracyclines, doxorubicin (DOX) and daunorubicin (DNR), were isolated from Streptomyces var. Peucetius; they were shown to be composed of a tetracyclic ring system with adjacent quinone-hydroquinone moieties, a short side chain with a carbonyl group, and an aminosugar bound to the C-7 of the four-ring system. DOX and DNR only differed in the side chain terminus (–CH_2OH in DOX vs –CH_3 in DNR). Second generation anthracyclines, like epirubicin (EPI) and idarubicin (IDA), were obtained after minor chemical modifications of DOX or DNR, respectively.

When injected by standard i.v. infusion, anthracyclines show a rapid distribution phase, a high distribution volume at steady state (~15 l/kg), a slow elimination phase (successive plasma half-lives of ~ 5 minutes, ~1 hour and ~30 hours). Anthracyclines are excreted mostly through bile, which imposes special care in patients with hepatic dysfunction (Robert & Gianni, 1993). In comparison with DOX, EPI is characterized by an unique glucuronidation that accelerates its systemic body clearance and imposes administering EPI at doses 1.5 times higher than those of DOX (Innocenti F et al., 2001).

Anthracyclines have long been known to kill tumor cells by inhibiting topoisomerase II. Anthracyclines act by stabilizing a reaction intermediate in which DNA strands are cut and covalently linked to topoisomerase II, eventually impeding DNA resealing. Anthracycline intercalation into DNA plays a role in this reaction; in fact, anthracycline rings that do not intercalate into DNA probably stabilize the complex between topoisomerase II and the DNA that it has nicked (Menna et al., 2008). Anthracycline- and topoisomerase II-mediated DNA damage is followed by growth arrest in G1 and G2 and apoptosis. This is usually, but not always, relayed by p53 and the consequent induction of the WAF1/CIP1 p21 gene product, a strong inhibitor of cyclin-dependent kinases that favour cell cycle progression through the G1 to S transition (Minotti et al., 2008).

Although topoisomerase II inhibition remains the most persuasive mechanism to explain the antitumor activity of anthracyclines, clinically relevant concentrations of anthracyclines were shown to induce apoptosis through additional mechanisms that were not bound to the topoisomerase II - p53 machinery. These mechanisms include, among others, i) the activation of neutral sphingomyelinases, followed by ceramide formation and converse activation of cell death effectors (c-Jun N-terminal kinase) or down-regulation of survival pathways (Akt/protein kinase B) ii), mitochondrial dysfunction, followed by cytochrome c release and apoptosome formation iii), induction of lipid peroxidation and formation of malondialdehyde-DNA adducts, followed by the reduced activity of cyclin E- and cyclin B-associated kinase activities and growth arrest in both p53-proficient and p53-deficient cells iv), inhibition of the proteasome, followed by an accumulation of undegraded ubiquinated proteins which signal apoptosis. The mechanisms i-iii) are triggered by reactive oxygen species (ROS), that are major byproducts of anthracycline metabolism. ROS may also enable anthracyclines to damage and shorten telomeres, long sequences of base repeats that otherwise would delay cell senescence and apoptosis by preventing the degradation and ligation of the end of chromosomes; however, anthracycline-induced telomere damage and dysfunction would be relayed to apoptosis through p53 (Minotti et al, 2004).

Anthracycline treatment may be accompanied by the acquisition of a resistance phenotype through a combination of pharmacokinetic and pharmacodynamic mechanisms. On pharmacokinetic grounds, tumor resistance is caused by the reduced accumulation and/or an altered distribution of anthracyclines in tumor cells, usually mediated by overexpression of drug transporters that belong to the ATP-binding cassette family of proteins and are collectively referred to as ABC proteins (P-glycoprotein/Pgp, multidrug resistance protein 1/MRP1, breast cancer resistance protein/BCRP). On pharmacodynamic grounds, tumor resistance may be caused by such diverse mechanisms as topoisomerase II mutation or redundancy, overexpression and preferred nuclear localization of proteasome α-type subunits (leading to a anomalous degradation of topoisomerase II), genetic deletion or loss-of-function mutations of p53, overexpression of ROS-detoxifying enzymes, overexpression of Bcl-2 (leading to a diminished cytochrome c release), etc. When taken in isolation, however, none of these factors would universally predict anthracycline-resistance in a given tumor or another (Minotti et al., 2008).

3. How do anthracyclines damage the heart

The problem of anthracycline-induced cardiomyopathy and congestive heart failure (CHF) has been around for some 40 years. On ultrastructural grounds, all of the approved anthracyclines share a pattern of damage that is characterized by loss of myofibrils, dilation of the sarcoplasmic reticulum, cytoplasmic vacuolization, swelling of mitochondria, and increased number of lysosomes; however, safety threshold may differ from one anthracyclines to another. In the case of DOX, the incidence of cardiomyopathy and congestive heart failure (CHF) averages below 5% if the cumulative dose did not exceed 400-450 mg/m^2 (Swain et al., 2003) ; EPI induces CHF at doses slightly higher than equiactive to DOX (~800-900 mg/m^2). Safety limits for DNR and IDA are less firmly established because of different regimens and schedules adopted in induction or consolidation treatment of myeloproliferative disorders. With that said, cardiac events may develop at reportedly safe cumulative doses if patients presented with hypertension, arrhythmias, valvular or coronary disease, or metabolic disorders; Moreover, children and the elderly are more vulnerable than the young-adult (Minotti et al., 2010). Perhaps more importantly, we now know that subthreshold doses of anthracyclines, as commonly adopted in many oncologic settings, may cause the development of cardiotoxicity months to years after completing chemotherapy, as if "safe doses" of anthracyclines primed the heart to a subclinical damage liable to a delayed clinical manifestation (Minotti et al., 2010). Mechanisms of anthracycline cardiotoxicity should therefore be reconciled with the concept of a lifetime risk of cardiotoxicity.

Anthracycline cardiotoxicity correlates directly with drug's peak plasma concentration (Minotti et al., 2004) but correlates inversely to the levels and activity of ABC proteins that eject drugs from endothelial cells of the blood-heart barrier (Sissung et al., 2011). Once inside cardiomyocytes, much of anthracycline toxicity seems to depend on bioactivation events.

The quinone moiety of anthracyclines undergoes one-electron reduction by a number of reductases, primarily located to mitochondria; oxidation of the so-formed semiquinone with molecular oxygen regenerates the parent quinone and exposes the cell to higher than physiological levels of ROS like superoxide anion ($O_2^{\cdot -}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($^{\cdot}OH$). Bimolecular reaction of $O_2^{\cdot -}$ with nitric oxide also generates peroxynitrite endowed with noticeable prooxidant activities. In comparison to other cell types cardiomyocytes are very rich in mitochondria, but relatively poor in ROS-detoxifying

enzymes; it follows that cardiomyocytes would readily succumb to a sustained generation of ROS that eventually induced sarcomere degradation, mitochondrial dysfunction and DNA damage, disruption of cardiac-specific gene expression programs, necrotic or apoptotic death (Minotti et al., 2004). This "oxidative stress" hypothesis of cardiotoxicity gained popularity over the years and was successfully probed in transgenic mice that overexpressed antioxidant defense systems like catalase, mitochondrial manganese-dependent superoxide dismutase, metallothioneins; Interestingly, however, robust doses of antioxidants like vitamin E or N-acetylcysteine neither delayed nor mitigated cardiotoxicity induced in patients by cumulative doses of DOX (Minotti et al., 2004). The only compound consistently found to be cardioprotective in clinical settings is the iron chelator, dexrazoxane. Iron chelation would mitigate free radical reactions that otherwise caused cardiotoxicity. Another caveat in the "oxidative stress hypothesis" is the lack of a clear-and-cut relation with the lifetime risk of cardiotoxicity. Once inside cardiomyocytes anthracyclines can diffuse back toward extracellular fluids, making the intracellular drug levels decrease to below a threshold of toxic concern (Salvatorelli et al., 2009). Some investigators suggested that DOX caused an oxidative mitochondriopathy that self-maintained after DOX had been cleared from cardiomyocytes; however, self-maintaining mitochondriopathy was documented with DOX but not EPI (Lebrecht & Walker, 2007), in spite of that EPI clearly retained a potential for inducing cardiotoxicity. On balance, anthracyclines do form ROS in the relatively unprotected cardiac tissue, but compelling evidence for a cause-and-effect relationship between oxidative stress and chronic cardiomyopathy is lacking.

The lifetime risk of cardiotoxicity from anthracyclines could be better reconciled with their conversion to secondary alcohol metabolites, formed after two electron reduction of their side chain carbonyl group. Being more polar than their parent drugs, secondary alcohol metabolites are poorly cleared from cardiomyocytes and accumulate to become a long-lasting anthracycline toxic signature in the heart (Menna et al., 2008); times more potent than their parent anthracyclines at inactivating Ca^{2+}-handling proteins of the contraction-relaxation cycle or key regulators of energy metabolism and redox balance, such as cytoplasmic aconitase. Therefore, secondary alcohol metabolites may cause cardiotoxicity both during and well after the course of chemotherapy.

In clinical settings, a retrospective study of patients enrolled in the Childhood Cancer Survivor Study suggests that the V244M polymorphism of carbonyl reductase 3 associated with a higher risk to develop CHF, presumably because the methionine244 isoform of carbonyl reductase 3 shows a greater catalytic specificity toward carbonyl substrates (Blanco et al., 2008). Most recent reports suggest that gain of function CBR polymorphisms could be invoked to particularly explain CHF development in patients exposed to subthreshold cumulative doses of anthracyclines .

There are, of course, some caveats in the alcohol metabolite hypothesis of cardiotoxicity. EPI forms fewer amounts of its alcohol metabolite as compared to DOX, which is consistent with CHF developing at cumulative doses of EPI higher than equiactive to DOX (Salvatorelli et al., 2007). In contrast, DNR and IDA generate more alcohol metabolites than DOX in spite of that their cardiotoxicity was ranked similar to or less severe than that of DOX, respectively (Minotti et al., 2004). Once again, the different modalities of administration of DNR or IDA in the settings of myeloproliferative disease could be invoked to explain such discrepancy.

4. How to prevent anthracycline induced cardiotoxicity

Anthracycline cardiotoxicity coud be prevented by replacing bolus administration with slow infusions that generate lower anthracycline plasma peaks and thus mitigate a pharmacokinetic determinant of cardiotoxicity. The benefit of replacing bolus administration (5-15 min infusion) with slow infusions (24-48 h) is quite evident in adult settings but not in pediatric settings. The current thinking is that children are more vulnerable by anthracyclines; the protective benefit obtained by lowering plasma peak concentrations would therefore be offset by damage due to the longer cardiac exposure to anthracyclines (Lipshultz et al., 2002).

The notion that anthracycline-related cardiotoxicity may develop long after completing chemotherapy suggests that drugs used to treat clinically evident cardiotoxicity should be used much earlier to protect the heart against subclinical cardiotoxicity. Unfortunately, active cardiac prevention by beta-blockers, angiotensin I-converting enzyme inhibitors, or angiotensin II receptor blockers, has been explored in only few limited studies. Prophylactic commencement of angiotensin I-converting enzyme inhibitors prevented decrements of Left Ventricular Ejection Fraction (LVEF) in patients receiving high-dose chemotherapy (Cardinale et al, 2006), while prophylactic commencement of angiotensin II receptors blockers prevented transient elevations of brain natriuretic peptide in patients receiving one cycle of standard-dose chemotherapy for non-Hodgkin lymphoma (Nakamae et al., 2005). Unfortunately, prophylactic commencement of cardiovascular medications was not prospectively assessed in patients scheduled to receiving multiple cycles of standard-dose chemotherapy. The reported protective efficacy of carvedilol, mixed a1-2-b1 blocker, was observed in patients treated with anthracycline cumulative doses higher than recommended (Kalay et al., 2006) this likely amplified the protective signal of any drug that had been administered (Florenzano & Salman, 2007). Outside of these limited exploratory studies, prophylactic commencement of cardiovascular medications is uncommon or disregarded because of concerns about class-related effects such as hypotension, bradicardia, fluid retention, cough, or other discomfort.

As already mentioned, dexrazoxane was the only compound that consistently proved effective in preventing anthracycline-related cardiotoxicity. The chemical structure of dexrazoxane consists of a *bis*-ketopiperazine that diffuses in cardiomyocytes and then undergoes stepwise hydrolysis of the two piperazine rings to form one-ring open intermediates. This one-ring intermediate hydrolyses to give a diacid-diamide (code-named ADR 925) which is structurally reminiscent of EDTA and chelates iron bound to low molecular weight cellular ligands or coordinated within 3:1 anthracycline:Fe complexes (Minotti et al., 2004). When administered by intravenous push or slow infusion some 15 to 30 min before DOX at dose ratios up to 10:1 to DOX, dexrazoxane did not interfere with DOX distribution or metabolism or excretion, but reduced the incidence of cardiotoxicity. In a randomized clinical trial, women with metastatic breast cancer who received dexrazoxane prior to DOX could be treated with more cycles and higher cumulative doses of DOX (700-1,000 mg/m^2 or more) than patients in the control group. Moreover, cardiac protection was observed in patients with or without risk factors such as e.g., prior chest wall irradiation (reviewed in Minotti et al., 2004). As a matter of fact, the pharmacological properties and clinical readouts of dexrazoxane have been widely challenged. In the pharmacological field, there have been reports that dexrazoxane could protect by mechanisms other than iron chelation, like e.g., inhibition of topoisomerase II-mediated formation of DNA double-

strand breaks in cardiomyocytes (Lyu et al., 2007). Accordingly, preclinical studies showed little or no cardiac protection by dexrazoxane analogues that chelated iron but failed to inhibit toposomerase II (Sterba et al. J Pharmacol Exp Ther 2006). In the clinical setting, the risk/benefit ratio of dexrazoxane was questioned in terms of hemathologic toxicities and interference with anthracycline activity. An exacerbation of anthracycline-related myelotoxicity (usually in the form of grade 3 or 4 neutropenia) is a well- known complication of the use of dexrazoxane, but other studies raised a concern that children treated with dexrazoxane were at a higher risk for second malignancies including, among others, acute myelogenous leukaemia and myelodysplastic syndrome. This latter concern was dispelled by two authoritative studies of childhood cancer survivors who had been randomized to receive anthracyclines with or without dexrazoxane as cardioprotectant (Barryet al., J Clin Oncol. 2008; Vrooman et al., Eur J Cancer. 2011). Other concerns were raised in relation to a possible interference of dexrazoxane with anthracycline activity. One single study suggested that dexrazoxane reduced response rates in women who received DOX for the treatment of advanced breast cancer (Swain et al., J Clin Oncol 1997) but many other clinical studies showed that this was not the case in either pediatric or adult settings (Swain and Vici, J Cancer Res Clin Oncol. 2004; van Dalen et al., Cochrane Database Syst Rev. 2011). In spite of the overwhelming evidence for its safety and preventative activity in a number of oncologic settings, the American Society of Clinical Oncology, Chemotherapy, and Radiotherapy Expert Panel maintained and recommended using dexrazoxane only in patients who had received more than 300 mg of DOX/m^2 and could benefit from continuing on DOX or EPI (Schuchter et al., 2002). It is our opinion that dexrazoxane should be used with less restrictions; current limitations to using it in a prophylactic manner are not supported by available evidence.

In a similar manner, oncologists should be encouraged to use liposomal formulations of DOX. These formulations approach very high peak plasma levels and longer circulating time than conventional DOX but release little or no free anthracycline in the bloodstream. Moreover, the liposomes are small enough to diffuse through the discontinuous "leaky" endothelium of tumors, but they are big enough not to diffuse through the normal microvasculature of the heart. Liposomal formulations therefore deliver high amounts of DOX in tumors but not in the heart. One liposomal DOX (Caelyx®) has polyethylene glycol embedded in the lipid layers; another formulation (Myocet®) adopts an uncoated liposome. Regardless of obvious pharmacokinetic and toxicokinetic differences between the two formulations, both proved remarkably cardiac tolerable and allowed administering high to very high cumulative doses of anthracycline. in a number of clinical settings. A recent Cochrane Intervention Review raises caution against using liposomal doxorubicin in pediatric settings or in patients diagnosed with leukaemia, but it is quite strong in concluding that liposomal formulations should be favoured in adults with a solid tumor (van Dalen et al., 2010). Despite this authoritative recommendation, clinical use of liposomal anthracycline formulations remains quite limited, primarily because of cost-related concerns. It is our opinion that liposomal doxorubicin should remain a must in certain approved settings (like e.g., ovary cancer in the case of Caelyx) and first choice in any other patients presenting with cardiovascular risk factors (as it is the case for Myocet in high risk or older patients with non Hodgkin lymphoma) (Visani & Isidori, 2011).

Preventing the risk of anthracycline-related cardiotoxicity during the lifetime means to reshape the pharmacological management of cancer survivors. Preexisting comorbidities or

unfavorable lifestyle choices (hypertension, diabetes, hyperlipidemia, reduced physical activity) had long been known to increase the risk of cardiotoxicity in patients scheduled to receiving anthracyclines. The available evidence suggests that this picture should also be viewed the other way around. In comparison to siblings or age-matched subjects from the general population, previously healthy cancer survivors tend in fact to develop more comorbidities or to reduce physical activity (De Bruin et al., 2009; Jones et al., 2007). It follows that sublinical cardiotoxicity from "safe doses" of anthracyclines may progress to symptomatic events by overlapping with risk factors that matured after ending chemotherapy. This is the so-called multiple-hit hypothesis, according to which late onset cardiotoxicity originates from pharmacological and non pharmacological sequential injuries (Minotti et al, 2010). These concepts call for a new dimension of preventative cardiology, in a sense that in cancer survivors any comorbidity or unfavourable lifestyle choice should be treated earlier or more vigorously than in the general population.

5. Monitoring

There is no universally accepted guideline for monitoring patients receiving anthracyclines. Table I provides a tentative schedule that follows on suggestions by Ewer and colleagues mainly based on widely used criteria such as cumulative dose, time elapsed after chemotherapy, presence or absence of cardiovascular risk factors or preexisting cardiac disease, concerns (or symptoms) calling for unscheduled visits and cardiological inspection, dosability in any clinical center (measurements of LVEF only).

Planned Cumulative Dose (mg/m^2)	**During treatment**		**After treatment**	
	No risk factors or Preexisting Cardiac Disease	One or more risk factors, Preexisting Cardiac disease	No risk factors or Preexisting Cardiac Disease	One or more risk factors, Preexisting Cardiac disease
Baseline	yes	yes		
<300	At the physician's discretion	Recommended after two-three cycles	Approx 1, 6, and 12 months after ending therapy, and then every two years unless symptoms occur	Approx 1, 6, and 12 months after ending therapy, and then every year unless symptoms occur
300-450	At the physician discretion; recommended anytime patients report on symptoms	Recommended every two cycles	Approx 1, 6, and 12 months after ending therapy, and then every year unless symptoms occur	Approx 1 month after ending therapy, and then every six months unless symptoms occur
>450	Recommended at midtherapy or earlier if symptoms occur	Recommended every two cycles or more often if symptoms occur	Approx 1 month after ending therapy, and then every six months unless symptoms occur	Approx 1 month after ending therapy, and then every six months unless symptoms occur

Table 1. General principles for monitoring LVEF in patients receiving doxorubicin. Modified after Ewer and Benjamin (2006).

Whereas the reported timetable is intrinsically correct and doable in everyday clinical practice, there are at least two disturbing points that need to be kept in mind if one wished to improve the caring of cancer patients and survivors. First, we now know that as little as 100 mg of DOX/m^2 may cause an increased risk of asymptomatic abnormalities at non-invasive cardiac tests, whereas 270 mg of DOX/m^2 introduces a measurable 4.5-fold excess risk of such abnormalities (Hudson et al, 2007). The second point is that dilative cardiomyopathy and systolic failure (reduced LVEF) have been considered for long time the only (or prevailing) clinical phenotypes of chronic cardiotoxicity from anthracyclines. Therefore, serial measurements of LVEF (whether by echocardiography or MUGA) have been adopted to measure the cardiac function of patients treated with anthracyclines. Keeping this in mind, we now know that asymptomatic diastolic dysfunction is seen in many cancer survivors with a history of prior exposure to anthracyclines. Anthracyclines, in fact, could cause diastolic elevated $[Ca^{2+}]_I$ and impaired left ventricle relaxation (stiffness) by a number of mechanisms (inhibition and/or reduced expression levels of the Ca^{2+}-ATPase that sequesters Ca^{2+} in sarcoplasmic reticulum, inhibition of the energy build-up that assists Ca^{2+} loading in mitochondria, inappropriate opening of the Ca^{2+}-gated Ca^{2+} release channel of the sarcoplasmic reticulum (ryanodine receptor 2) (Minotti et al, 2004). Long lasting diastolic dysfunction eventually increases interstitial pressure, thereby diminishing coronary conductance and causing ischemia that further aggravates Ca^{2+} overload and left ventricle wall tension (Hale et al., 2008). Reciprocal interactions between diastolic dysfunction and ischemia may remain asymptomatic for many years but eventually surface in the form of symptomatic ischemic disease and myocardial infarction. The risk of myocardial infarction in previously nonischemic Hodgkin's lymphoma survivors therefore correlated with their prior exposure to anthracyclines (Swerdlow et al., 2007). Furthermore, diastolic dysfunction and reduced coronary conductance would render the heart more vulnerable by comorbidities that diminish coronary flow or increased oxygen demand, like e.g. premature atherosclerosis or hypertension. All such concepts call for reshaping current modalities of follow up of cancer survivors. Serial measurements of LVEF should no longer be considered adequate to identify patients at risk for symptomatic cardiac events. Moreover, careful inspection of diastolic function (e.g., transmitral flow) is equally important and much needed, not to mention myocardial perfusion imaging techniques that show hypoperfusion under stress conditions. These approaches are less doable in clinical practice, leaving many patients with normal LVEF at risk for sudden or slowly developing cardiac events.

Current limitations in the monitoring of patients at risk for anthracycline related cardiotoxicity could be obviated by measuring pre- and post- infusional levels of circulating troponin (TnI), marker of toxic or ischemic cardiomyocyte necrosis. Persistent elevations of TnI were shown to anticipate LVEF decrements and other cardiac events in otherwise asymptomatic childhood cancer patients (Lipshultz et al., 1997) or in adults receiving high-dose chemotherapy (Cardinale et al., 2006). More recently, elevations of TnI were shown to anticipate LVEF decrements in women who had received sequential adjuvant chemotherapy and immunologic treatment with the anti-Erbb2 monoclonal antibody trastuzumab for the treatment of $Erbb2^+$ early breast cancer (J Clin Oncol., 2010, 28:3910-6). Unfortunately, TnI measurements are uncommon outside of limited exploratory studies; there is a lack of studies that prospectively evaluated TnI in large cohort of patients and firmly established laboratory ranges that should guide the physicians in making decisions such as adjusting

the dose of anthracycline or commencing prophylactic cardiovascular medications. Similarly uncommon is the measurement of circulating natriuretic peptides, markers of left ventricular diastolic tension. On treatment elevations of natriuretic peptides were reported to anticipate chemotherapy-induced diastolic dysfunction, but such elevations were seen in patients treated with high-dose chemotherapy or in patients receiving just one cycle of standard-dose chemotherapy (Gianni et al., 2008, J. Clin. Oncol. 26; Nakamae et al., 2005). There is little information on the prognostic value of natriuretic peptides elevations during the course of cumulative standard-dose chemotherapy and at follow-up.

6. Liposomal formulations of doxorubicin

Daunorubicin (DNR) as the cell cycle non-specific anthracycline antibiotics is highly effective in treating a wide range of cancer diseases [5-7]. Its antineoplastic mechanisms are through DNA topoisomerase II inhibition, DNA intercalation, RNA synthesis inhibition, cell membranes interaction, free radicals production and induction of apoptosis [8-10]. However, the clinical use of daunorubicin is hampered by two major problems: cardiotoxicity [11] and drug resistance, as daunorubicin is a substrate for P-glycoprotein (MDR1; ABCB1) [12] and breast cancer resistance protein (BCRP;ABCG2) [13]. This limits of standard doxorubicin have moved forward the development of new liposomal formulations of the drug, which gained increasing interest in the therapy of onco-hematological malignancies and, in particular, for the treatment of breast cancer and B-cell lymphomas. In the early 1980s, liposomes were discovered to be good anthracycline carriers, reducing toxicity while retaining potent antitumor activity and therefore improving the therapeutic index of anthracyclines [14]. Liposomal formulations of doxorubicin have indeed been developed with the aim of improving the therapeutic index of doxorubicin by reducing the drug's cardiotoxicity. Nevertheless, liposomal conjugation of doxorubicin results in preferential distribution of the drug in the tumor compared with normal tissue.

Two liposomal formulations are currently available: non-pegylated liposomal doxorubicin (NPLD) (Myocet®, Cephalon, USA) and pegylated liposomal doxorubicin (PLD) (Caelix®/Doxil®, Schering-Plough/Orto Biothech, USA)

NPLD is a liposome encapsulated formulation of doxorubicin, which differs from pegylated liposomal doxorubicin, as well as from unencapsulated, conventional doxorubicin, resulting in an alteration in the pharmacokinetics and biodistribution. This results in a higher area under the curve, a smaller volume of distribution and a preferential distribution to liver, spleen, and lymphatics, when compared with conventional doxorubicin. Pre-clinical studies comparing equal doses of liposome-encapsulated doxorubicin and conventional doxorubicin showed that the use of nonpegylated liposomal doxorubicin resulted in a significantly lower cardiac and gastrointestinal toxicity, with similar anti-tumor efficacy.

The other liposomal compound, pegylated liposomal doxorubicin (PLD) (Caelix®/Doxil®, Schering-Plough/Orto Biothech, USA), is a liposomal formulation with a distinct pharmacokinetic profile characterized by an extended circulation time and a reduced volume of distribution [22]. Biodistribution animal studies indicate superior accumulation of PLD into various implanted mouse-human tumors, with an augmentation of liposomal drug tumor levels compared with free drugs [22]. The extended circulation time of pegylated liposomes and their ability to extravasate through the leaky vasculature of tumors results in the increased delivery of liposomal drug and/or radiotracers to the tumor site in patients

with cancer. Pegylated liposomal doxorubicin has been approved for clinical use in a variety of cancer types due to its antitumor efficacy. However, the safety profile needs further improvement, as long as hand-foot syndrome remains a dose-limiting toxic effect of Doxil, maybe due to the considerable amount of drug being delivered to the skin owing to the drug's long circulation in the bloodstream.

7. Non-Pegylated Liposomal Doxorubicin (NPLD)

NPLD is a doxorubicin citrate complex encapsulated in a liposome, an aqueous dispersion of egg Phosphatydilcholine
and cholesterol, sterile, non-pyrogenous that traps doxorubicin by pulling it into the interior of the vesicle (TLC D-99 model) by the generation of an electropotential across the liposome membrane. This mechanism for remote loading involves the generation of a pH gradient between the inside and the extraliposomal buffer. At the end of the encapsulation process, the ratio of doxorubicin:lipid in NPLD is approximately 1:4 and the pH is in the range of 5.5–6.5. The maximum activity of doxorubicin and other anthracyclines manifests itself in the S phase of the cellular cycle.
The encapsulation of a cytostatic agent within a macromolecular vector such as a liposome reduces drastically its distribution volume, diminishing its diffusion in the organism and thus the toxicity for healthy tissues while increasing the concentration within the neoplastic tissue. In ideal conditions the drug can be transported in the circulatory system within the liposome's aqueous space and arrives to the site of the tumor in active form. Encapsulation in a liposome means the drug is protected from inactivation while in the blood stream and furthermore its diffusion through the healthy endothelium is limited, while it can diffuse through tumoral endothelium which would present discontinuities. Thus, NPLD should preferentially direct doxorubicin away from sites of potential toxicity, but leaves the tumor exposed.

7.1 Non-pegylated liposomal doxorubicin in breast cancer

NPLD was designed to reduce the cardiotoxicity of doxorubicin while preserving its antitumor efficacy. In the early 2000, the safety and efficacy of NPLD was tested in cancer patients, after the demonstration of a significantly lower cardiac and gastrointestinal toxicity, with similar anti-tumor efficacy showed by NPLD in pre-clinical studies.
The first studies were conduced in breast cancer patients. These phase III, randomized, multicenter trials were designed to test the hypothesis that NPLD, alone or in combination with other drugs, would result in significantly less cardiac toxicity than the same dose and schedule of conventional doxorubicin and other drugs, while providing comparable antitumor efficacy in first-line treatment of metastatic breast cancer.
Batist et al (Batist et al., 2001) randomized 297 patients with MBC and no prior chemotherapy for metastatic disease were randomized to receive either 60 mg/m^2 of NPLD or conventional doxorubicin (A), in combination with 600 mg/m^2 of cyclophosphamide (C), every 3 weeks until disease progression or unacceptable toxicity. Antitumor efficacy of MC versus AC was comparable: objective response rates, 43% versus 43%; median time to progression, 5.1% versus 5.5 months; median time to treatment failure, 4.6 versus 4.4 months; and median survival, 19 versus 16 months (Batist et al., 2001).
Cardiotoxicity was a primary end point parameter in all treated patients (Batist et al., 2001). Cardiac toxicity, sufficient for removal of a patient from study, was defined as a decrease in

resting LVEF of ≥ 20 ejection fraction (EF) units from baseline to a final value of ≥ 50%, or a decrease of ≥ 10 EF units from baseline to a final value of less than 50%, or clinical evidence of CHF. LVEFs were assessed using serial Multigated blood-pool imaging (MUGA) scans, which have been shown to be a reliable and serially reproducible method of evaluating cardiac function in patients receiving anthracycline therapy.

To ensure accuracy and objectivity, each center was required to have its equipment and methodology used for MUGA scans reviewed and certified by a cardiologist at the Core Laboratory at Yale University before enrolling patients. During the trial, all MUGA scans were sent to the Core Laboratory at Yale, where they were read by the same cardiologist blinded to the patient's treatment (Batist et al., 2001). To minimize the risk of CHF, all scans were read in real time and results provided to the site before the next scheduled dose of anthracycline therapy. CHF was determined on the basis of a treatment-blinded review of records from patients for whom the investigator had made a diagnosis of CHF, as well as patients who had a LVEF of ≤ 30%. LVEF ≤ 30% was selected as the cutoff because these patients are at significant risk for CHF (Batist et al., 2001). The blinded review was conducted by a second cardiologist at Yale University noted for his expertise in doxorubicin-induced cardiotoxicity. All MUGA scan data were interpreted and LVEF values were estimated at a core laboratory on a blinded basis. Nine patients (6%) treated with MC developed protocol-defined cardiotoxicity compared with 33 patients (21%) treated with AC (log-rank *P* = .0001). Five cases of CHF, all in the AC arm (log-rank *P* = .02), were observed after cumulative lifetime doses ranging from 360 to 480 mg/m². Four of the five patients with CHF were anthracycline-naive before this study; one patient had 240 mg/m² of prior adjuvant doxorubicin. All other patients with cardiotoxicity had an asymptomatic decrease in LVEF of ≥ 10 EF units from baseline to a final value less than 50%. The estimated (Kaplan-Meier) median cumulative lifetime dose of doxorubicin at the first occurrence of protocol-defined cardiac toxicity was more than 2,220 mg/m² for the MC arm versus 480 mg/m² for the AC arm. The hazard ratio of 4.8 shows that patients treated with MC were 80% less likely to develop cardiotoxicity with respect to patients treated with AC.

Similarly, there was a highly significant difference in the time to onset of cardiotoxicity when measured from the start of protocol therapy. The estimated median onset of protocol-defined cardiotoxicity was more than 22 months for MC versus 10 months for AC (log-rank P = .0003). There was a gradual increase in the median change from baseline LVEF to the last posttreatment LVEF among patients treated with either regimen, but this was more pronounced in the AC-treated group (Batist et al., 2001).

In the subset of patients with recognized risk factors for cardiac toxicity, the hazard ratio was increased to 16, indicating that these patients were more than 90% less likely to develop cardiac toxicity with MC relative to AC. Four percent of MC-treated patients developed a protocol-defined cardiac event versus 22% of AC-treated patients (Batist et al., 2001). The median lifetime cumulative dose of doxorubicin at onset was 480 mg/m2 for AC versus more than 2,220 mg/m2 for MC (P = .0001) (Batist et al., 2001). Four of the five patients with CHF were in this subgroup with increased risk of cardiac toxicity (Batist et al., 2001).

In conclusion, the improved therapeutic index for NPLD predicted by the preclinical data and indicated by the phase I/II clinical trials was confirmed in this phase III, randomized, multicenter trial. Statistically significantly fewer patients treated with NPLD in combination with cyclophosphamide experienced cardiac toxicity defined by reductions in LVEF or clinical CHF (Batist et al., 2001).

Another interesting study was carried on by Harris et al (Harris et al, 2002). Two hundred twenty-four patients with MBC and no prior therapy for metastatic disease were randomized to receive either TLC D-99 (75 mg/m2) or doxorubicin (75 mg/m2) every 3 weeks, in the absence of disease progression or unacceptable toxicity. The primary efficacy endpoint was response rate. The primary safety endpoint was cardiotoxicity.

Electrocardiograms and MUGA scans were done at baseline, and after reaching a lifetime cumulative doxorubicin dose of 300, 400, 500 mg/m², and before each subsequent dose, at off-study, and at 3-month follow-up. All MUGA scan data were transferred electronically to a core laboratory for blinded interpretation and estimation of LVEF (Harris et al, 2002). Before the first interim analysis, endomyocardial biopsies were performed at a selected number of institutions after lifetime cumulative doxorubicin dose of 425 mg/m². All patients whose LVEF declined by greater than 10% to a value of greater than or equal to 50%, or by greater than 6% to a value of less than 50% were to have cardiac biopsies regardless of lifetime cumulative doses (Harris et al, 2002). All biopsies were read by a core pathologist, and the results were scored according to the Billingham scale. The purpose of biopsies was to validate the results of MUGA scans. After the first interim analysis, it was determined that MUGA scans were adequate to monitor cardiac function and cardiac biopsies were discontinued (Harris et al, 2002). All MUGA scan data were sent to an independent central laboratory for estimation and interpretation of LVEF values without knowledge of treatment arm.

Cardiac events, sufficient for removal of a patient from study, were more than twice as frequent in doxorubicin-treated patients than TLC D-99–treated patients (29% vs. 13%, log-rank P = 0.0001) (Harris et al, 2002). With the increasing lifetime cumulative dose of doxorubicin and TLC D-99, there was a gradual increase in the median change from baseline LVEF to the first post-treatment LVEF among patients treated with either agent, but this was more pronounced in the doxorubicin group (Harris et al, 2002). A Kaplan–Meier estimate of the probability of the first onset of a cardiac event as related to the lifetime cumulative dose of doxorubicin or TLC D-99 showed that risk of cardiotoxicity was much higher with doxorubicin treatment than TLC D-99 (HR = 3.56) (P = 0.0001) (Harris et al, 2002). Two patients (2%) on TLC D-99 developed clinical CHF. One patient, after 13 cycles of TLC D-99 and a cumulative dose of 1110 mg/m², had a decrease of 14 EF units in her LVEF to 46% and was taken off-study. Two months after the last dose she presented with shortness of breath and bilateral pleural effusions and was hospitalized for CHF. Another patient, with prior adjuvant doxorubicin dose of 290 mg/m² and prior chest wall irradiation, received five cycles of TLC D-99 for a total lifetime doxorubicin dose of 785 mg/m², and went off-study for PD. Four months after the last dose, a MUGA scan showed a LVEF of 46% (a 16-point decrease from baseline). Later, the patient received five cycles of a mitomycin plus mitoxantrone, and 11 months after the last study treatment she received a diagnosis of CHF (Harris et al, 2002). Nine patients (8%) on doxorubicin developed clinical CHF at lifetime doses of 525–765 mg/m². Three patients had CHF within 30 days of the last dose of study treatment, including one who died of CHF after 585 mg/m². All nine cases were attributed to study drug treatment (Harris et al, 2002).

Before the first interim analysis, 51 patients were treated at 8 participating institutions performing endomyocardial biopsies. Of those, 36 patients qualified for the procedure, and all 36 patients had cardiac biopsies. All biopsies were read by a core pathologist, blinded to treatment assignment, and the results were scored according to the Billingham scale. There

was a significant difference between the two treatment groups favoring TLC D-99 and the number of patients who had a score of greater than or equal to 2.5 (26% vs. 71%; *P* = 0.02) (Harris et al, 2002).

Regarding efficacy, the overall response rate was 26% in both treatment groups. The median TTP was 2.9 months on TLC D-99 versus 3.1 months on doxorubicin. Median survival was 16 versus 20 months with a non significant trend in favor of doxorubicin (P = 0.09).

In another randomized study, Chan et al tried to ascertain the efficacy and tolerability of NPLD and epirubicin combined with cyclophosphamide in the first-line treatment of patients with metastatic breast cancer (Chan et al., 2004). One hundred and sixty anthracycline-naïve metastatic breast cancer patients were randomised to receive NPLD (M; 75 mg/m2) or epirubicin (E; 75 mg/m2) in combination with cyclophosphamide (C; 600 mg/m2), every 3 weeks for up to eight cycles. Cardiotoxicity was low in both treatment groups: nine patients on MC and eight on EC had asymptomatic LVEF reductions at comparable cumulative doses . For MC there were two cases at 100–299 mg/m2, four at 300–399 mg/m2 and three at 500–599 mg/m2; for EC there was one case at 200–299 mg/m2, four at 300–399 mg/m2 and three at 400–499 mg/m2. There was no clinical evidence of CHF in any patient. Overall response rates were 46% and 39% for MC and EC treatment, respectively (P=0.42). MC was superior to EC with respect to median time to treatment failure (5.7 versus 4.4 months; P=0.01) and median time to disease progression (7.7 versus 5.6 months; P=0.02). Median survival times were 18.3 and 16.0 months for MC and EC, respectively (P=0.504). Unsurprisingly, the results from this study (Chan et al., 2004) suggested that, at equimolar doses, in combination with cyclophosphamide, NPLD has modest but significant advantages over epirubicin for some efficacy end points and a non-significant trend towards improvement in others. Given the well established correlation between dose and therapeutic effect for doxorubicin, and in light of the uncertainty surrounding the optimal therapeutic dose of epirubicin, NPLD offers clinicians the opportunity to make clinical use of a drug that combines the dose/effect reliability of doxorubicin with the level of safety provided by epirubicin.

In conclusion, two studies (Batist et al., 2001; Harris et al., 2002; Chan et al, 2004) clearly demonstrated reduced cardiotoxicity of NPLD when compared to standard doxorubicin, with a superimposable antitumor efficacy of the two drugs. The third study showed a trend of higher efficacy fot NPLD with respect to epirubicin, with equal cardiotoxicity.

7.2 Non-pegylated liposomal doxorubicin in non-Hodgkin lymphoma

The first study testing the safety and efficacy of NPLD in non-Hodgkin lymphoma NHL (AIDS-related) was conducted by Alexandra Levine and coworkers in 2004 (Levine et al., 2004). The study enrolled 24 patients with newly diagnosed AIDS-related NHL (median age: 43 years). Sixty-seven percent of patients had a high or high-intermediate International Prognostic Index (IPI) scores at diagnosis. Serum LDH was high in 17 patients (71%). A total of 21 patients (88%) had extranodal disease, and 12 patients (50%) had 2 or more sites of extranodal involvement.

The primary objective of the study was to evaluate the safety and efficacy of NPLD when substituted for doxorubicin in the CHOP in patients with newly diagnosed AIDS-related non-Hodgkin's lymphoma (AIDS-NHL). NPLD at doses of 40, 50, 60, and 80 mg/m2 was given with fixed doses of cyclophosphamide (750 mg/m2), vincristine (1.4 mg/m2) and

prednisone (40 mg/m2) every 21 days. The maximum tolerated dose (MTD) of NPLD was defined as the dose at which less than half of the patients on a cohort experienced a dose-limiting toxicity. No dose escalations were allowed in individual patients. The MTD of NPLD was not reached at the 80 mg/m2 dose. As a high complete response (CR) rate was seen at all dose levels, a dose of 50 mg/m2 of NPLD was chosen for the phase II portion of the trial, which was expanded to a total of 24 patients, including 10 on the initial phase I dose-escalation portion. All patients received highly active antiretroviral therapy while on chemotherapy.

The results of the study were encouraging. No dose-limiting toxicities were observed at any level, with myelosuppression being the most frequent toxicity (grade 4 neutropenia in 75% of patients, neutropenic fever in 12% and neutropenic sepsis in 8%). Overall response rate was 88%, with a CR rate of 75%, and a partial response (PR) rate of 13%. The median duration of CR was 15.6 months (range, 1.7 to 43.5 months).

Moreover, 16 out of 24 AIDS-related NHL patients were evaluated for multidrug resistance (MDR-1) expression on their hystological samples. The Authors demonstrated that this NPLD-based regimen was equally effective in both MDR-1–positive and MDR-1–negative cases. The Authors postulated that the efficacy of this regimen was eventually related to the ability of NPLD to overcome excessive drug efflux due to P-gp (MDR-1) overexpression. The MDR-1 expression did not correlate with response in this study, suggesting that NPLD might evade this resistance mechanism.

In terms of potential cardiac toxicity, left ventricular ejection fraction (LVEF) was obtained at baseline and at study termination in 19 patients. No patient developed a decline in LVEF to below normal (45%). Fourteen patients had no significant change in LVEF over time, while 5 patients (26%) experienced a 10% or greater decline, though their LVEF values still remained within normal range. None of these five patients had any signs or symptoms of cardiac dysfunction, and the values returned to baseline levels in the two patients who had follow-up cardiac studies performed, 3 months after completion of chemotherapy.

Starting from that background, the same group of the Keck School of Medicine designed in 2006 a phase I-II trial to evaluate the safety of the same regimen (NPLD, cyclophosphamide, vincristine, and prednisone every 21 days) in the treatment of newly diagnosed aggressive NHL patients (Tulpule et al., 2006).

Forty-seven patients (median age: 55 years) were enrolled in the study. The vast majority of the patients had diffuse large B-cell NHL (37/47). Liposomal doxorubicin at doses of 40 mg/m2, 50 mg/m2, 60 mg/m2, and 80 mg/m2 was given with fixed doses of cyclophosphamide (750 mg/m2), vincristine (1.4mg/m2) and prednisone (40 mg/m2). Chemotherapy cycles were repeated every 21 days.

No dose-limiting toxicities were observed at any level. Reversible grade 3/4 neutropenia was the most common toxicity (95.8%). Most non-hematologic side effects were nausea, vomiting fatigue and fever and were primarily grade 1/2 in severity. Stomatitis of mild or moderate severity was reported in 23% of patients.

Two out of 47 patients (4%) developed clinically silent cardiac toxicity, with a decline in LVEF of 20% each. None of the patients presented any symptoms of cardiotoxicity. The decline in LVEF occurred in one patient after a cumulative NPLD dose of 240mg/m2 and in the other one after a cumulative NPLD dose of 640 mg/m2. In both patients the declines returned to baseline 2 months and 6 months from discontinuation of NPLD, respectively.

Complete remissions were documented in 31 of 46 evaluable patients (67.4%) and partial remissions in 7 (15.2%), for an overall major response rate of 82.6%. Responses were attained after a median of 4 cycles of therapy. Patients with T-cell lymphomas fared poorly with this regimen, with none of them achieving a CR lasting more than 6 months.

The median duration of complete remission was 27.7 months (range, 2.4 months to 59.8 months). Reported median follow-up was 3.1 years. Median survival was not reached at the time of publication. The 2-year estimated overall suvival (OS) probability was 65% (95% CI, 50-77%), with a 3-year estimated OS probability of 59% (95%CI, 44%-73%). Nineteen patients had died at the time of publication.

Regarding the relationship between MDR-1 expression and outcome, MDR-1-related p-glycoprotein expression was assessed in lymphoma tissues from 27 patients. Eight patients (30%) was MDR-1 positive at diagnosis. No difference in CR rates were observed when comparing patients whose tumors expressed MDR-1 versus those who did not (63% in MDR-1-positive and 74% in the MDR-1-negative lymphomas, P = 0.66), indicating that NPLD might overcome MDR-1 in vivo.

Rigacci and collaborators (Rigacci et al., 2007) designed a prospective study to assess the efficacy and safety of the combination of NPLD with cyclophosphamide, vincristine, prednisone and Rituximab (R-COMP) in patients with aggressive non-Hodgkin's B-cell lymphomas and concurrent cardiac disease or pre-treated with anthracyclines.

Twenty-one patients were selected for the presence of cardiac comorbidity and/or previous treatment with anthracycline-based regimens. NPLD at a dose of 50 mg/m2 was administered in association with cyclophosphamide (750 mg/m2), vincristine (1.4mg/m2), prednisone (40 mg/m2) and rituximab (375 mg/m2) every 21 days for 4 to 6 cycles unless progression or unacceptable toxicity occurred. CR rate was 76%, whereas PR rate was 14%, with an overall response rate (ORR) of 90%. Two patients (10%) did not respond to therapy. After a median follow-up of 13 months (range 2–36 months), 2/16 CR patients relapsed, with a cumulative disease-free survival (DFS) rate of 78%.

Regarding toxicities, the Authors observed only a congestive heart failure (CHF) in one patient, among a total of 115 chemotherapy cycles administered. LVEF was evaluated after the 3rd cycle and at the end of treatment in all but one patient, who developed CHF with LVEF 20% after the first cycle of R-COMP. Between the 20 evaluable patients, median LVEF was 60% (range 38%–74%) after three cycles and 60% (range 40%–69%) at the end of the treatment. There was no significant difference between LVEF at baseline, after the 3rd cycle, and at the end of study in patients with cardiac comorbidity (52, 58 and 60%, respectively), in those without cardiac diseases (62, 61 and 60%, respectively) and in those previously treated with anthracyclines. Patients were evaluated every 6 months after the end of the study. Among the 15 patients who were followed-up for at least 12 months after the end of therapy, none of them presented any cardiac dysfunction or significant decrease of LVEF.

The Authors stated that Rituximab plus NPLD-based regimen was well tolerated and highly effective in inducing clinical responses in this group of patients at high risk for cardiac toxicity or previously treated with anthracyclines. The tolerability profile was favorable, with a low incidence of cardiac events (1/21 patients).

Visani and coworkers (Visani et al., 2008) conduced a pilot study to assess the toxicity and efficacy of the combination of NPLD with cyclophosphamide, vincristine, prednisone and

Rituximab (R-COMP) in frail and elderly patients with aggressive non-Hodgkin's B-cell lymphomas.

NPLD at a dose of 50 mg/m2 was administered in association with cyclophosphamide (750 mg/m2), vincristine (1.4mg/m2), prednisone (40 mg/m2) and rituximab (375 mg/m2) every 21 days for 4 to 6 cycles unless progression or unacceptable toxicity occurred.

Twenty frail patients (median age: 73 years), as defined by Balducci & Extermann (Balducci & Extermann,2000) with diffuse large B cell or grade IIIb follicular lymphoma, either at diagnosis (15 patients) or relapsed (5 patients), were prospectively enrolled.

Thirteen out of 20 NHL patients (65%) had a complete response (CR) and an additional 5 patients (25%) achieved a partial response (PR), with an overall response rate of 90% (ORR). Notably, the median age of the study population (73 years) was the oldest ever reported in literature of patients treated with this combinations. As a matter of fact, this population consisted of particularly elderly and frail patients with advanced disease at the time of study entry. These patients had indeed an extremely high probability of being unable to complete one of the standard anthracyclines-based regimens or to suffer from cardiotoxicity.

The treatment was relatively well-tolerated. Grade 3 or 4 neutropenia occurred in 26% of cycles and febrile neutropenia in 5%. There was no significant difference between LVEF at baseline, after the 3rd cycle, and at the end of study in 16/19 patients. Notably, 2 patients presented a CHF (NYHA 3) after 1 and 3 cycles of R-COMP, respectively and were shifted to receive an anthracycline-free regimen while in CR after R-COMP. In these 2 patients, the Authors observed a 20% decrease of the LVEF which partially recovered after medical therapy. The cumulative percentage of cardiovascular complications was 15%, higher than that reported for elderly patients treated with R-CHOP 21 or 14. However, this patient population consisted only of frail patients having a poor WHO performance status and important comorbidities.

This study demonstrated for the first time the safety and efficacy of the R-COMP 21 regimen in frail and elderly patients with aggressive NHL. Cardiotoxicity was low and a promising response rate was observed in this setting patients.

Another interesting study regarding the safety and the efficacy of the R-COMP combination was recently published (Luminari et al., 2010). Seventy-five elderly patients with diffuse large B-cell lymphoma (DLBCL) were studied. Only patients with left ventricular ejection fraction (LVEF) > or =50% were allowed. R-COMP regimen was administered every 3 weeks for three cycles, followed by additional five cycles in case of complete response (CR) or partial response.

Seventy-five patients with a median age of 72 years were registered, and 72 were evaluable for response assessment. Fifty-six percent of patients had high or high-intermediate International Prognostic Index score. Median LVEF at baseline was 61%. Thirty-eight patients had history of abnormal cardiovascular conditions. The overall response rate was 71%, with a CR rate of 57%. After a median follow-up of 33 months, the 3-year overall survival, failure-free survival, and progression-free survival rates were 72%, 39%, and 69%, respectively. Neutropenia (54%) was the most frequent grade 3-4 adverse event; 21% of patients experienced cardiac adverse events, graded as 3-4 in 4% of the cases.

8. Pegylated Liposomal Doxorubicin (PLD)

Pegylated liposomal doxorubicin (PLD) is doxorubicin confined in liposomes that have been sterically stabilized by grafting polyethylene glycol onto the surface (Stealth Liposome"). PLD has a circulation half-life of approximately 73.9 h, whereas doxorubicin has a half-life of <10 min. Prolonged circulation facilitates greater uptake of PLD liposomes by tumor tissue. PLD accumulates selectively in metastatic breast carcinoma tissue, resulting in 10-fold higher intracellular drug concentrations compared with adjacent normal tissue (Symon et al., 1999). Pegylated liposomal encapsulation also reduces plasma levels of free doxorubicin and may reduce drug delivery to normal tissue, which may reduce toxicity. Studies of PLD suggest that a dose of 45 to 50 mg/m2 every 4 weeks is well tolerated with little nausea or vomiting, mild myelosuppression, minimal alopecia, and very little cardiotoxicity.

8.1 Pegylated liposomal doxorubicin in breast cancer

The first randomized, multicenter, phase III study was designed to demonstrate that efficacy in terms of progression-free survival of pegylated liposomal doxorubicin HCl (PLD) was non-inferior to doxorubicin with significantly less cardiotoxicity in first-line treatment of women with metastatic breast cancer (MBC) (O'Brien et al., 2004). Women (*n* = 509) with MBC and normal cardiac function were randomized to receive either PLD 50 mg/m^2 (every 4 weeks) or doxorubicin 60 mg/m^2 (every 3 weeks). Cardiac event rates were based on reductions in left ventricular ejection fraction as a function of cumulative anthracycline dose.

In this open-label, multicenter trial, patients were randomized in a 1:1 ratio by an independent central third party according to a computer-generated randomization program. Patients received either PLD [50 mg/m2 intravenous (i.v.) infusion for up to 60 min every 4 weeks] or doxorubicin [60 mg/m2 i.v. infusion for 60 min every 3 weeks]. Patients were prospectively stratified based on three criteria to balance major prognostic risk factors between treatment groups: prior adjuvant anthracycline exposure; presence of bone metastases as only site of disease; presence of at least one cardiac risk factor (O'Brien et al., 2004). Cardiac risk factors were defined as prior mediastinal irradiation, age ≥65 years, history of heart disease (previous myocardial infarction, arrhythmia or angina, not requiring treatment) or hypertension, or diabetes requiring medical treatment.

Regarding cardiotoxicity, MUGA scans were performed to measure LVEF before onset of treatment, after 300 mg/m2 cumulative anthracycline exposure, and after every additional 100 mg/m2 of PLD and every 120 mg/m2 of doxorubicin. Compliance with the protocol on performing MUGA evaluations was high. Of the 283 patients who reached doses ≥300 mg/m2 cumulative anthracyclines, all but 20 patients (nine PLD, 11 doxorubicin) had a baseline MUGA evaluation and at least one follow-up MUGA evaluation during treatment (O'Brien et al., 2004).

Overall, 339 patients (152 PLD and 187 doxorubicin) had electronic MUGA scan data for evaluation of cardiotoxicity (baseline and at least one scan during treatment) and were included in the analysis. Patients in the PLD arm had a median cumulative anthracycline dose of 398 mg/m2 (including prior anthracycline exposure). Patients in the

conventional doxorubicin arm had a median cumulative anthracycline dose of 421 mg/m2 (including prior anthracycline exposure). Fifty-eight patients (10 PLD, 48 doxorubicin) met the protocol-defined LVEF criteria for cardiotoxicity during treatment and/or follow-up. The risk of developing cardiotoxicity was significantly higher for patients receiving doxorubicin than for those receiving PLD (P <0.001, HR = 3.16 for comparison of cumulative anthracycline dose at the first, protocol-specified, cardiac event) (O'Brien et al., 2004). The increase in risk of developing cardiotoxicity on doxorubicin versus PLD was observed in all subgroups analyzed, including those at high risk for developing CHF. In the subgroup that received prior adjuvant anthracycline therapy, the risk of developing cardiotoxicity was seven-fold higher with doxorubicin than with PLD. None of the 10 PLD-treated patients who had cardiotoxicity by LVEF criteria developed clinical signs or symptoms of CHF, whereas 10 of 48 doxorubicin-treated patients who had cardiotoxicity by LVEF criteria developed signs or symptoms of CHF. Two patients in each group developed clinical CHF but did not have a corresponding decrease in LVEF. As expected with doxorubicin, the mean percentage change from baseline in LVEF was positively correlated with the increase in cumulative anthracycline dose. However, with PLD, only a 2–3% mean decrease in LVEF was observed as the cumulative anthracycline dose increased. At cumulative doses at or above 450 mg/m2, a seven-fold greater mean percentage decrease in LVEF was observed with doxorubicin versus PLD (–17.2% versus– 2.3%; mean percentage change from baseline in LVEF in doxorubicin-treated and PLD-treated patients, respectively) (O'Brien et al., 2004).

Regarding efficacy, PLD and doxorubicin were comparable with respect to PFS (6.9 versus 7.8 months, respectively) and to OS (21 and 22 months for PLD and doxorubicin, respectively. Palmar-plantar erythrodysesthesia (48% versus 2%), stomatitis (22% versus 15%) and mucositis (23% versus 13%) were more often associated with PLD than doxorubicin. In conclusion, in first-line therapy for MBC, PLD provides comparable efficacy to doxorubicin, with significantly reduced cardiotoxicity (O'Brien et al., 2004).

Another multicentric, randomized trial was published on the same year (Keller et al., 2004). This trial was designed to compare the efficacy of pegylated liposomal doxorubicin (PLD) with that of a common salvage regimen (comparator) in patients with taxane-refractory advanced breast cancer. Following failure of a first- or second-line taxane-containing regimen for metastatic disease, 301 women were randomly assigned to receive PLD (50 mg/m2 every 28 days); or comparator-vinorelbine (30 mg/m2 weekly) or mitomycin C (10 mg/m2 day 1 and every 28 days) plus vinblastine (5 mg/m2 day 1, day 14, day 28, and day 42) every 6 to 8 weeks (Keller et al., 2004). Changes in LVEF values were only assessed in patients receiving PLD. Cardiac toxicity was defined as either a decrease of ≥ 15 points from baseline or a ≥ 5-point decrease from baseline with a level below the lower limit of normal for the institution. Twenty-two patients developed LVEF changes consistent with cardiac toxicity. However, decreases in LVEF did not correlate with cumulative anthracycline dose and none of these patients developed clinical congestive heart failure. The majority (n = 14) discontinued due to progressive disease. There were four patients who discontinued treatment due to cardiac toxicity (LVEF decrease), three patients who discontinued due to noncardiac adverse events, and one patient who discontinued due to noncompliance. Progression-free survival (PFS) and overall survival (OS) were similar for PLD and comparator (Keller et al., 2004).

8.2 Pegylated liposomal doxorubicin in non-Hodgkin lymphoma

Pegylated liposomal doxorubicin has been substituted for conventional doxorubicin in the CHOP regimen in a number of trials. In phase II studies in elderly patients with diffuse large B-cell lymphoma, ORR of approximately 65% was achieved: 50% CR and 15% PR, an estimated 1-year OS of 55%, and an estimated 2-year event-free survival of 45%. Neutropenia was the only grade III-IV toxicity observed [23,24].

Cutaneous T-cell lymphoma (CTCL) is a specific niche in which PLD has proven to be very active at low doses in a similar fashion to Kaposi sarcoma [25]. A response rate of 88% (44% CR) with mean OS of 18 months was observed in a retrospective analysis of 31 patients receiving PLD at doses varying from 20-40 mg/m2 every 4 weeks. These patients had recurrent or unresponsive disease, or rapidly progressive disease [25].

Indeed, PLD has been shown to have equal efficacy and a better safety profile in the treatment of multiple myeloma, when compared with conventional doxorubicin combinations. In controlled clinical trials, PLD combined with vincristine and dexamethasone provided response rates comparable with the doxorubicin-based standard vincristine/doxorubicin/dexamethasone) therapy, but the former required less hospitalization, no central venous catheter, with a reported lower toxicity in terms of alopecia and severe leukopenia [26]. There are ongoing studies trying to establish the usefulness of newer compounds in combination with liposomal anthracyclines for the therapy of multiple myeloma.

9. Conclusions

New acquisitions, particularly in terms of pathogenetical mechanisms, have considerably changed the perception of anthracycline cardiotoxicity in patients cured after a cancer diagnosis. From a " cumulative dose" era, where caution to further treatments with anthracyclines was linked more to a mere calculation of global administered dose, we are now shifting to a more prudential approach, that considers a persistent biological damage due to anthracycline administration, and prompts us toward a better definition of measures able to control, in particular, late cardiac toxicity. One item is becoming evident: a strict cohoperation between cardiologists and oncologists/hematologists could significantly improve the life expectancy and reduce the risks of major CHF in anthracycline pretreated patients, simply not underevaluating concurrent risk factors for CHF, that must be addressed early and consistently with adequate "cardiological" therapies.

On the other hand, the pharmacological research has in some way met the challenge to reduce the toxicity of the therapy with anthracyclines, both designing new, safer, anthracycline analogues, such as liposomal compounds, and reshaping the way to use protective compounds, such as dexrazoxane, during anthracycline therapy. The possible role (and optimal way of use) of iron chelators, such as deferasirox, is still under evaluation.

Cost related issues have up to now limited the use of liposomal derivatives, except for niches of fragile patients; it should be considered, anyway, if the global,high impact on costs of cardiotoxicity in cancer survivors(in terms of disability and related treatments) could justify,expecially in the long run, the costs of an optimized treatment,with modified anthracyclines or with cardioprotectants, potentially able to reduce, in particular, the frequency of late cardiac toxicity.

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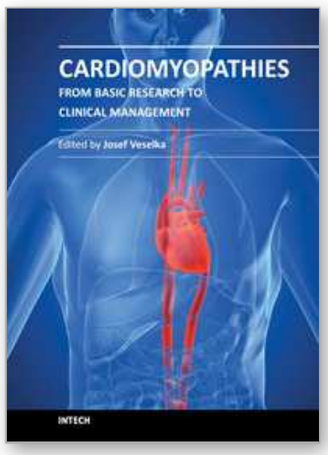

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Cardiomyopathy means "heart (cardio) muscle (myo) disease (pathy)". Currently, cardiomyopathies are defined as myocardial disorders in which the heart muscle is structurally and/or functionally abnormal in the absence of a coronary artery disease, hypertension, valvular heart disease or congenital heart disease sufficient to cause the observed myocardial abnormalities. This book provides a comprehensive, state-of-the-art review of the current knowledge of cardiomyopathies. Instead of following the classic interdisciplinary division, the entire cardiovascular system is presented as a functional unity, and the contributors explore pathophysiological mechanisms from different perspectives, including genetics, molecular biology, electrophysiology, invasive and non-invasive cardiology, imaging methods and surgery. In order to provide a balanced medical view, this book was edited by a clinical cardiologist.

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