An Integrated Approach to Cardio-Protection in Lymphomas.

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Summary (150 words)

In curable cancers, long-term survival depends on the successful treatment of the malignancy but also on the risks associated with treatment-related toxicity, especially cardiotoxicity. Malignant lymphomas affect both young and elderly patients, with acute and late toxicity risks that may have a severe impact on morbidity, mortality and quality of life. While our understanding of chemotherapy and radiotherapy-related cardiovascular disease has advanced considerably over the last years, new drugs with potential cardiotoxicity have been introduced for the treatment of lymphomas.

In this review, we summarise the mechanisms of treatment-related cardiac injury, available clinical data and current protocols for optimizing cardio-protection in lymphomas. We also focus on ongoing research strategies to further advance our knowledge of the molecular basis of drug and radiation-induced toxicity. Finally, we emphasise the potential for personalised follow-up and early detection including the role of biomarkers and novel diagnostic tests, highlighting the role of the cardio-oncology team.

Introduction

Hodgkin (HL) and non-Hodgkin lymphomas (NHL) are curable malignant neoplasms. For HL, 10-year survival rates currently exceed 80% [1]. For NHLs, over 70% of patients now survive up to 5 years after diagnosis[2]. In line with these improvements in survival, the management and prevention of treatment-related side effects is becoming increasingly important.

Treatment for HL has been associated with adverse late effects, such as increased risks of secondary malignant neoplasms and cardiovascular diseases. Late cardiovascular complications may arise as a consequence of radiotherapy and chemotherapy, and cause substantial excess morbidity and mortality in long-term HL survivors[3–5]. In adults, van Nimwegen et al detected a cumulative incidence of cardiovascular events at 40 years of 50%[6]. For patients treated before 25 years of age, cumulative incidences at 60 years or older were 20%, 31%, and 11% for coronary heart disease (CHD), valvular heart disease (VHD), and heart failure (HF) as first events. Mediastinal radiotherapy increased the risks of CHD (hazard ratio [HR], 2.7; 95% CI, 2.0-3.7), VHD (HR, 6.6; 95%CI, 4.0-10.8), and HF (HR, 2.7; 95%CI, 1.6-4.8), and anthracycline-containing chemotherapy increased the risks of VHD (HR, 1.5; 95%CI, 1.1-2.1) and HF (HR, 3.0; 95%CI, 1.9-4.7) as first events compared with patients not treated with mediastinal radiotherapy or anthracyclines, respectively[7]. Mediastinal radiotherapy and anthracyclines showed additive effects[8]. The risk of late cardiovascular events is strongly

related to the cumulative dose of anthracyclines, to the heart volume exposed to RT and to the mean RT dose to the heart in either pediatric[9] or adult HL patients [5,10].

Growing evidence also indicates that the risk of cardiovascular disease is considerably raised in survivors of NHL[11]. In particular, the risk of heart failure is substantially elevated, with an adjusted hazard ratio of 1·77 (95% CI 1·50–2·09)[12]. A regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone, with (R-CHOP) or without (CHOP) rituximab is the standard first-line treatment in adult aggressive non-Hodgkin lymphoma, and doxorubicin and cyclophosphamide are both associated with left ventricular dysfunction. Moreover, for HL and NHL as well, salvage strategies may include high-dose chemotherapy with stem cell transplant, immunotherapy, antibody-drug conjugates, and targeted biological agents. All these therapies may have an impact on cardiac function, and on the risk of late complications.

In The Lancet Haematology, a systematic review and meta-analysis by Linschoten and colleagues analyzed 137 clinical studies (with over 21 000 adult patients) on cardiovascular toxicity in NHLs[13]. In this meta-analysis, the incidence of reported left ventricular dysfunction increased from 1·64% to 11·72% (p=0·017) in studies that performed cardiac monitoring of asymptomatic patients. These findings suggest that there are potentially many patients with undiagnosed cardiotoxicity resulting from lymphoma treatment, and that the implementation of appropriate screening and administration of cardioprotection for lymphoma patients is still in its infancy.

Early detection of cardiac dysfunction enables timely initiation of heart failure treatment, which has been shown to increase the chance of complete recovery[14], whereas delay is likely to result in the transition from asymptomatic left ventricular dysfunction to clinically overt heart failure with progressive and irreversible heart damage. Strategies for cardioprotection alongside baseline risk stratification, stringent surveillance screening and early treatment of cardiotoxicity are therefore of outmost importance for HL and NHL patients who have a relatively good prognosis and long disease-specific survival [15].

However, cardioprotection strategies are not fully implemented in clinical practice nor in clinical trials. We lack specific guidelines and validated risk stratification calculators using blood and imaging biomarkers for screening by age, type of lymphoma, type of therapy received and co-existing risk factors. Moreover, we have new imaging modalities such as global longitudinal strain assessment using echocardiography, and cardiovascular MRI, but their role is not yet defined. In this narrative review, we aim to provide a multidisciplinary perspective on cardioprotection for lymphoma patients, and in particular: A) an overview of the reported excess cardiac morbidity and mortality associated with the use of chemotherapy

and mediastinal radiotherapy, B) an overview of clinical manifestations following single and multi-modality treatments, and C) a focus on treatment optimization, best follow-up practices and early detection strategies. The available evidence considered for this review included recent published guidelines, prospective and retrospective clinical studies as well as radiotherapy planning studies published to date.

Mechanisms and clinical manifestation of drug-induced heart injury

Anthracyclines are the most cardiotoxic drugs among first-line therapies for haematological malignancies. Although the cardiac side effects of anthracyclines can appear early after infusion, primarily in the form of electrocardiogram abnormalities, cardiotoxicity more commonly manifests later as left ventricular dysfunction which may be asymptomatic or symptomatic. This is classified as an absolute fall in left ventricular ejection fraction (LVEF) of >10% to <50%[16]. This latter form of chronic cardiotoxicity can be either early-onset, typically affecting adults within one year from therapy conclusion[14], or may, particularly in paediatric patients, be detected years after completion of chemotherapy[17]. Anthracycline cardiotoxicity is dose-dependent and progresses through different stages, beginning with a subclinical myocardial cell damage that progressively evolves into an asymptomatic LVEF decline and, ultimately, into heart failure with severely reduced LVEF where recovery is uncommon[18]. At cellular and molecular level, the cardiac toxicity of anthracyclines has been ascribed to their ability to promote the production of cytotoxic reactive oxygen species (ROS) through multiple mechanisms, including DNA topoisomerase inhibition and activation of the DNA damage response as well as disruption of mitochondrial biogenesis and of mitochondrial iron metabolism[19].

In contrast to anthracyclines, whose cardiotoxicity has been extensively characterised through four decades of preclinical and clinical research, cardiovascular complications of newer anti-cancer drugs including targeted therapies such as tyrosine kinase inhibitors, immune check-point inhibitors (ICI) and Chimeric antigen receptor (CAR)-T cell therapies, are less well defined. Cardiotoxicity is also not limited to left ventricular dysfunction, and arrhythmias are common with some lymphoma treatments. Ibrutinib, an irreversible inhibitor of Bruton's tyrosine kinase (BTK) that has revolutionised the treatment for several B-cell malignancies in the adult setting, increases the risk of atrial fibrillation (AF) with a cumulative incidence of 6-16%[20]. Sudden cardiac death and ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation, have also been reported shortly after starting therapy with ibrutinib[21]. Although the molecular mechanisms behind ibrutinib-induced AF are still

undefined, a recent report suggested that this might be due to off-target inhibition of C-terminal Src kinase (CSK)[22], and the incidence of arrhythmias with other BTK inhibitors such as acalabrutinib appears to be lower[23].

ICI have been found to cause a rare but fulminant presentation of myocarditis, characterised by ventricular arrhythmias and conduction abnormalities, and which may be fatal[24]. The mechanistic basis of ICI-mediated myocarditis is still vague, but the prevailing view is that myocyte death is driven by myocardial infiltration of CD4+ and CD8+ T lymphocytes and macrophages[25]. While it is recognised that fulminant myocarditis occurs early after treatment, the long-term and late-onset cardiovascular effects of ICIs, particularly ischemic events, remain incompletely understood and future studies are awaited to shed light on this point[26]. On the other hand, other new drugs seem to have a low cardiotoxicity profile. This is the case for Brentuximab Vedotin, a selective inhibitor of the CD30 antigen largely used in relapsed/refractory HL, which is well tolerated with no increase in cardiac events for treated patients[27].

Mechanisms and clinical manifestation of stem cell therapy

Haematopoietic cell transplantation (HCT), especially autologous HCT, is a curative option for patients with lymphoma who have relapsed after frontline multi-agent therapy[28]. Patients who undergo autologous HCT receive a combination of high-dose chemotherapy to eradicate resistant cells, followed by stem cell reinfusion and a prolonged period of immunodeficiency due to marrow recovery. For many, this is in addition to cardiotoxic therapeutic exposures (chemotherapy, radiation) they may have received before HCT. Studies in large cohorts of autologous HCT survivors have shown how multiple sequential organ system and metabolic impairments sustained prior to, during, or after HCT result in a greater than four-fold risk of cardiovascular disease (CVD), compared to the general population[29]. Cardiovascular complications, such as myocardial infarction and cardiomyopathy/heart failure, are not only more common in HCT survivors, but they occur earlier than in the general population and more frequently in survivors exposed as children [29,30]. The findings from these studies suggest that there may be an accelerated cardiovascular aging phenotype in HCT survivors that is initiated by pre-HCT and HCT-related therapeutic exposures, and worsened by post-HCT complications such as de novo risk factors (e.g. hypertension, diabetes), and lifestyle behaviors (e.g. physical deconditioning)[30,31].

Mechanisms and clinical manifestation of radiation-induced heart disease

The pathogenetic and clinical picture of radiation-induced heart disease (RIHD) is painted by a number of different and interacting pathways including endothelial dysfunction, oxidative stress, and pro-inflammatory pathways impacting nearly every aspect of cardiac function.

Cardiac endothelial cells are highly sensitive to radiation. Within minutes of exposure, endothelial dysfunction results, with vasodilatation, an influx of inflammatory cells, and the release of cytokines and thrombotic mediators such as IL-1, -6, -8, thrombomodulin and tumour necrosis factor alpha (TNF-a). The persistent inflammatory environment over the following days promotes the release of pro-fibrotic cytokines including transforming growth factor B (TGF-β), amongst many others. TGF-β has a pivotal role in the development of fibrosis, central to almost all late cardiac toxicity. It recruits fibroblasts and promotes differentiation to myofibroblasts resulting in autocrine production of TGF-β[32]. This allows fibrosis to continue for some time after the initial exposure. Oxidative stress also contributes ROS through several pathways[33]. This further enhances release of proinflammatory mediators and adhesion molecules, and decreases nitric oxide production, which is important for endothelial stabilization. The end-result of these converging pathways is damage to both the cardiac micro- and macrovasculature, leading to loss of endothelial capillaries, and to large vessels that are more susceptible to stress. The resultant fibrosis can affect all cardiac substructures and may progress for years following exposure. Especially, fibrosis of the tunica intima and smooth muscle layer reduces elasticity of the vessel, worsening any stenosis and increasing the risk of acute coronary events within approximately 10 years of RT[10].

Valvular disease may present in approximately 2 – 17% of patients receiving mediastinal RT for HL. The left-sided valves are most frequently impacted[34]. There is a latency of several decades between treatment and presentation.

The myocardium has a rich microvascular blood supply. The inflammation brought about by RT-induced damage to this capillary network results in patchy areas of ischaemia[35]. Fibrosis results, leading to reduced distensibility of the ventricles, raising end diastolic pressures and causing diastolic heart failure[36].

Pericardial complications may be acute or chronic and include pericarditis, pericardial effusion, pericardial thickening and constrictive pericarditis. These complications are rare and mostly asymptomatic in patients treated with modern techniques but may occasionally present as constrictive pericarditis if severe. Conduction abnormalities also can develop from damage to or fibrosis of the conducting system. Up to 75% of patients have some abnormality on routine ECG after mediastinal RT. The majority have little clinical significance, but in severe cases may require intervention.

In Figure 1, we summarise the effects of chemotherapy and radiotherapy on heart substructures.

Mechanisms and clinical manifestation of CAR-T mediated cardiovascular damage

Chimeric antigen receptor (CAR)-modified T cells targeting CD19, an antigen that is frequently over-expressed in various haematological malignancies, has rapidly become a promising treatment option for leukemias and lymphomas. Long-term cardiac follow-up is, thus far, not available, however, data from prospective clinical trials as well as retrospective case series are accumulating [37]. It is important to realise that patients with pre-existing/recent cardiac events were excluded in the pivotal trials leading to CAR-T cell approval[38], however, many patients had prior exposure to anthracyclines, radiotherapy, and/or stem cell transplant in previous lines of therapy, all of which are associated with cardiotoxicity.

A significant contributor to cardiovascular toxicity following CAR-T cell therapy is cytokine release syndrome (CRS) which may occur as a consequence of massive myeloid cell activation, triggered by T cells activation upon engagement of CAR by CD19. Its variable clinical presentation ranges from high fever and fatigue to severe septic shock and cardiac dysfunction. Alongside CRS, troponin elevation, left ventricular dysfunction and arrhythmias have also been reported following CAR-T[39], which overlap with CRS in 68% of cases. The pathophysiology of cardiovascular damage is currently not fully understood, however capillary leak syndrome or nonspecific stress-induced cardiomyopathy could play a major role[40].

In the paediatric ELIANA trial (for acute lymphoblastic leukemia) [32], CRS requiring ICU admission occurred in 47% patients and 25% required vasopressors because of severe hypotension. In retrospective paediatric series, up to one third of patients had shock or hypotension requiring vasopressors,[33] although all had recovered their cardiac function by 6 months[41], with no fatal cardiac events.

In the first adult, retrospective study by Alvi et al. on 137 patents receiving CAR-T, six cardiac deaths, six heart failures, and 5 new onset supraventricular tachycardias were reported, all of which were associated with increased troponin levels and CRS > grade 2[42]. After CRS recognition, an earlier administration of tocilizumab was associated with a reduction in cardiovascular events[42].

Methods for personalised risk stratification and cardio-protection

Systemic therapies

Prior to administration of any potentially cardiotoxic cancer therapy, formal baseline risk factor stratification should be conducted with published tools available for each individual treatment

group[43]. In addition, guidelines suggest screening for cardiac dysfunction prior to initiation of potentially cardiotoxic therapies along with aggressive management of modifiable risk factors (e.g. hypertension, diabetes) during cancer treatment[44]. To date, several meta-analyses have been performed demonstrating the efficacy of cardioprotective strategies, especially regarding anthracycline therapy (e.g., coadministration of dexrazoxane, use of liposomal formulation, continuous infusion)[45]. However, many of the RCTs included in these meta-analyses were limited to adult patients with advanced-stage or metastatic solid malignancies. Therefore, any information regarding the potential cardioprotective effect of these agents should be considered in the context of differences in treatment exposures, the lifetime dose of anthracycline delivered to an individual as well as the individual's age and disease stage. Studies evaluating other cardioprotective strategies (e.g., use of angiotensin-converting enzyme [ACE] inhibitors, □-blockers, or angiotensin receptor blockers [ARBs] in normotensive patients or statins in patients without dyslipidemia), also conducted mostly in patients with solid malignancies have been limited by small sample size, lack of long-term measures of clinical efficacy (e.g., reduction in the risk of symptomatic cardiac dysfunction), or use of non-randomised study design [46]. There is increased recognition about the importance of integrating cardiac biomarkers into CVD risk determination prior to delivery of potentially cardiotoxic therapies to patients with haematologic malignancies, allowing for primary or secondary prevention in high risk individuals. A recent study in patients >18 years with acute leukemia found that a comprehensive (clinical risk factors, cardiotoxic exposures, echocardiographic) 21-point risk score could reliably identify patients at low- (1%), moderate- (13.6%), and high-risk (35.0%) of developing cardiac dysfunction within 1-year of diagnosis [47]. The study highlighted the important prognostic role of baseline low left ventricular ejection fraction (EF <50%) and global longitudinal strain (GLS >-15%), setting the stage for novel primary prevention strategies that target patients at highest risk for cardiovascular complications. It remains to be seen whether a cardiac biomarker-based prevention strategy can result in clinically meaningful reduction in cardiovascular disease risk during treatment. A recent randomised trial in patients who mostly had breast cancer suggested there may be some short-term benefit (e.g. preservation of EF during treatment) to cardiac imaging-guided intervention [48] but the long-term efficacy (e.g. reduction of clinical heart failure risk) of this approach has yet to be determined.

Radiotherapy

Cardiac sparing is paramount to reduce the risk of RIHD and to improve the quality of life in the high proportion of long-term survivors. Heart sparing in RT can be achieved through the following approaches: 1) treating smaller volumes with lower doses; 2) adopting modern RT planning and delivery techniques to increase conformality of RT dose; 3) using motion management to keep the heart out of the treated volume; 4) optimizing the RT planning on prioritised cardiac substructures through an iterative process.

RT fields have evolved in the past decades, starting with HL patients, first with a reduction from extended-field and mantle field to involved field RT and, next, to the modern concepts of involved-site (ISRT) and involved node RT (INRT)[49,50]. At the same time, the integration of RT with systemic agents and the advent of positron emission tomography (PET)-CT for staging have allowed for a significant de-escalation in the RT doses in the consolidative setting from 40-45 Gy to 20-30 Gy in many adult HL patients[51,52]. This combination of smaller volumes and lower doses has led to a significant reduction of the dose received by healthy tissues and, consequently, of the risk of long term complications compared to older approaches [53,54]. Figure 2 shows the timeline of treatment evolution (with a main focus on RT) in HL patients.

Likewise, the transition from 3-Dimensional conformal RT (3DCRT) to highly conformal RT techniques such as intensity modulated RT (IMRT) and rotational therapy (VMAT) has led to a reduction in the dose delivered to the heart but at the price of an increased exposure of breasts and lungs to low-doses, with a potential increase in the risk of second cancers[55]. However, second generation studies have tested new VMAT solutions to better tailor the RT treatment to the clinical needs of each patient in term of heart sparing while limiting the exposure of other organs (primarily breasts and lungs)[56].

The most recent innovation in RT planning and delivery is proton therapy (PT). PT, with its peculiar physics properties favouring a low entrance dose and a steep fall-off of the dose at the end of the beam range ("Bragg peak"), offers a great opportunity to further minimise the risk of RIHD, particularly when cardiac constraints cannot be achieved with photons[57]. Comparative studies conducted on mediastinal HL patients have demonstrated lower RT doses to all cardiac structures (chambers, valves, coronary arteries) with PT planning compared to 3DCRT and VMAT plans[53,58], without any additional risk of second cancers. The benefit of PT is greatest in patients with lower mediastinal and/or cardiophrenic node involvement[59].

Deep inspiration breath holding (DIBH) is another advanced heart-sparing strategy which compensates for breathing motion: during deep-inspiration the heart is separated from the lymphoma with a consequent reduction in dose exposure. In mediastinal HL patients, the

combination of modern photon solutions (IMRT or VMAT) or PT with DIBH ensure the most effective heart-sparing with a reduction in the risk of cardiovascular complications[60] (Figure3). The detailed contouring of all cardiac substructures (coronary arteries, chambers, valves)[61,62] may further improve the dosimetric profile not only of the whole heart but even of the individual cardiac substructures[63]. In fact, the combination of detailed contouring with modern and highly conformal RT techniques may effectively prevent the generation of "hot spots" to prioritised cardiac substructures through optimised and iterative processes.

Finally, an individualised approach is needed to ensure a proper selection and combination of strategies according to age, disease extension, comorbidities and risk profile of cardiac complications and secondary cancers[64].

Follow-up and early detection

There is a major unmet need to address relevant acute and/or chronic cardiovascular complications resulting from systemic therapy and mediastinal RT in lymphoma survivors and to effectively identify appropriate follow-up protocols for these patients[65]. It is accepted that the risk of major cardiovascular events is lifelong and proportionally related to the dose of anthracyclines and of the dose of RT received by the heart[10]. Prevention and treatment of cardiovascular events include both screening strategies to early detect acute complications during lymphoma-directed therapies and routine long-term surveillance after disease remission, so that appropriate cardioprotective agents can be initiated[44]. Echocardiography is a widely available and useful diagnostic tool in the assessment of acute and late cardiac toxicity. Modern 3D echocardiography provides accurate evaluation of left ventricular volumes and ejection fraction and allows an accurate longitudinal follow-up with limited inter-measurement variability[66].

Despite modern advances in left ventricular ejection fraction (LVEF) assessment, global longitudinal strain (GLS) is an innovative echocardiographic approach to assess systolic function. Allowing measurement of systolic deformation of myocardial fibers, GLS is a far more accurate and reproducible marker of early systolic dysfunction and a stronger predictor of long-term adverse outcomes in cancer patients[67]. In fact, subclinical left ventricular impairment may be more accurately and earlier detected by GLS reduction up to 6-12 months before the onset of an overt LVEF reduction[68]. A GLS reduction of >15% from baseline is considered an early marker of subclinical cardiac toxicity[16] and may suggest a timely start of cardioprotective treatment, to prevent the progression to overt systolic dysfunction. Interim results of the ongoing CARDIOCARE project (NCT 03480087) have showed a significant

correlation of the acute deterioration in average GLS with the dose of anthracyclines and the dose of radiation received by the left ventricle in adult lymphoma patients[69].

Cardiac magnetic resonance (CMR) is a second-level imaging test, with high accuracy and reproducibility in the assessment of cardiac structure and function. It may be useful in case of contradictory results or severe systolic dysfunction, despite high costs and limited availability[70]. CMR allows myocardial tissue characterization and assessment of the pericardium. Indeed, late gadolinium enhancement-CMR analysis is useful to differentiate ischemic and non-ischemic myocardial fibrosis, while T1- and T2-sequences may detect intracellular and interstitial edema[70,71].

To date, the usefulness of cardiac biomarkers (such as troponin and N-terminal pro-brain natriuretic peptide) is debated, with no evidence for their implementation in lymphoma patients[72]. Ongoing studies are investigating the potential role of miRNAs as modern circulating biomarkers of acute cardiovascular toxicity in breast cancer patients (BACCARAT study, NCT 02605512), but there is no evidence of similar studies in haematological patients.

Long-term cardiovascular surveillance is essential in lymphoma survivors and should include yearly outpatient visits, with prompt repetition of echocardiography in those with symptoms or signs of cardiovascular disease. In asymptomatic patients, screening echocardiograms, and exercise stress test in selected high risk patients, may be performed at least every 5 years, starting 5-10 years after the end of cancer treatments[16,73]. Second-level testing for coronary artery disease, such as coronary computed tomography angiography, stress cardiac magnetic resonance, stress echocardiography or nuclear perfusion imaging should be promptly offered in case of angina symptoms during follow-up, while their utility in asymptomatic patients is currently unclear[74]. A more intensive follow-up could be planned and tailored to the patient needs according to the risk of late cardiovascular toxicity considering the personal oncological history and pre-existing cardiovascular risk factors or comorbidities, on a case-by-case basis[74].

Discussion

Cardioprotection has become one of the most relevant medical issues when curing lymphoma patients in order to improve long-term patient outcomes. The toxic effects on the heart of chemotherapy and RT are quite well known, but the current therapeutic landscape for malignant lymphomas includes several new approaches that might contribute to the development of late complications. This review has focused on the pathogenetic mechanisms and clinical manifestations of multi-factorial cardiac damage, and strategies for prevention, as we depict in Figure 4.

Special considerations for lymphoma patients, in comparison with those affected with solid malignancies, are a) a relatively younger age at diagnosis with high chance of cure and hence importance of healthy survivorship, b) a high cure rate , with several decades of remaining life c) the use of anthracycline-based chemotherapeutic regimens which despite significant progress remains the cornerstone of treatment for both HL and NHL, d) the less frequent use of radiation, and at lower doses, but often directed to mediastinal targets close to sensitive cardiac sub-structures, e) the frequent use of high-dose chemotherapy and bone marrow transplantation, and f) the use of maintenance therapies, with long-term exposure to anti-CD20, immune checkpoint inhibitors or TKIs.

All these factors play a role in the complex pathogenetic scenario of cardiac complications. It is challenging to define direct cause-effect relationships, with subsequent uncertainties for early diagnosis, primary and secondary prevention strategies. For example, the use of cardioprotective agents for lymphoma patients during chemo-radiotherapy has not been demonstrated to have a clinical benefit in randomised trials, the same for more intensive follow-up strategies aimed at early diagnosis and treatment. However, the implementation of clinical recommendations, the broader availability of echocardiography and cardiac MRI, and a more conscious use of biomarkers are expected to reduce mortality over the following years. Part of these prevention strategies is also a more careful use of RT, incorporating all the modern definitions of target volumes and the use of highly conformal techniques. In HL, we are moving towards a progressive de-intensification of first-line therapies, reducing the number of chemotherapy cycles and the use of RT, with an entire risk-adapted and response-adapted approach, and we are introducing immunotherapy as first line treatment to test chemo-free protocols. We will also probably re-consider the use of so-called “consolidation” RT after chemo(immuno)-therapy for patients with bulky mediastinal presentations at diagnosis. For these cases, we will gradually implement a more personalized approach to RT, better taking into account the quality of response and other factors. A reduction in the use of anthracyclines is also expected for the most common forms of NHLs, such as diffuse large B-cell and follicular lymphomas, in parallel with increased indications to targeted agents and immunotherapy. These changes might lead to a reduction of cardiac morbidity and mortality secondary to chemo-radiation over the next years; however, new clinical manifestations may also emerge secondary to the use of novel agents. Lastly, clinicians should regularly evaluate patients after treatment and monitor cardiovascular risk factors, advising against unhealthy habits such as smoking and obesity. In fact, “heart-healthy” lifestyle, including the role of diet and exercise, should be a fundamental part of long-term follow-up care in lymphoma survivors [44].

In this very challenging field, a multi-disciplinary approach involving cardiologists from the beginning appears essential for reducing the risks and for preventing cardiac complications. The common goal should be to personalise our approach to patients during the treatment phase and in the follow-up period.

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Figures Legend

Figure 1: Overview of the cardiotoxic effects of systemic therapies and radiotherapy.

Figure 2: Timeline of radiation therapy evolution in Hodgkin lymphoma.

Figure 3: A) Coronal image showing the cranio-caudal shift of the heart achievable with deep inspiration breath holding (DIBH) compared to free breathing (FB). This allows to move the heart away from the RT target when it is located in the upper mediastinum (which is very often the case in Hodgkin lymphoma). B) Axial images of VMAT (Volumetric Modulated Arc Therapy) treatment plan for a representative patient: in DIBH (left) and in FB (right). The CT slices are at the same heart level, passing through the origin of the left coronary artery (left main trunk in white, left anterior descending in purple, circumflex in pink and right coronary artery in black), and show the impact of DIBH in reducing the intersection between the RT target (in yellow) and the heart (in red) and in lowering the RT dose to the cardiac substructures in the presented case (RT doses detailed in the boxes below the CT slices).

Figure 4: Integrated strategies to prevent cardiotoxicity and to apply a multi-disciplinary cardioprotection