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Is it time to reduce the doxorubicin dosage in in Hodgkin lymphoma therapy?

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Declaration of Interests:

The author declares no competing interests.

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The treatment of Hodgkin lymphoma (HL) has dramatically advanced over the past two decades, facilitating deep and durable responses, with the current 4-year progression-free survival (PFS) being close to 90%. Given that the median age of HL patients is 32 years, their post-treatment life expectancy nowadays reaches five decades, which renders the issue of late toxicity crucial. It is demonstrated that 2-3 decades after the end of treatment, cardiac morbidity becomes the dominant problem[1,2]. Moreover, the most prevalent nonmalignant cause of death in HL survivors is established to be cardiac[3,4]. The estimated relative risks (RR) of cardiac mortality at 15-20 years of follow-up are ranging between 2.8-6.8, whereas absolute excess risks are varying between 12.3-54/10000 person-years of follow-up[3]. While analyses performed 15-30 years after therapy completion do provide data on long-term toxicity, this information may be not entirely pertinent to the current therapeutic approaches. For instance, the awareness of the radiation therapy (RT) toll on the incidence of secondary malignancies and cardiac disease has led to profound transformations in RT techniques, used dosage and the radiation field size, which has changed from the mantle field to the involved-site or involved nodal RT, performed using intensity-modulated RT. These modifications have resulted in 90% reduction in cardiac exposure to RT[4].

In the current issue of Haematologica, Marr et al from the British Columbia Cancer Center presented interesting findings on 804 adolescent and young adult HL patients, aged 15-39 years during treatment, who were followed for 15-30 years[1]. The cumulative incidence of cardiovascular disease in this cohort was compared to that documented in the British Columbia general population registry. The heart failure (HF) rate among HL survivors was 4.3% versus 0.8% in the control group, with the corresponding values of ischemic heart disease (IHD) amounting to 8.3% versus 2.8%, respectively. The relative risk (RR) of combined cardiovascular disease was 2.88, with RR of 5.18 for HF and 2.38 for IHD. Notably, the RR of HF was particularly increased in patients carrying comorbidities, including diabetes mellitus, hypertension or chronic obstructive pulmonary disease (COPD) (3.34, 3.09, 5.8, respectively). These findings emphasize the need for long-term and aggressive treatment of the aforementioned comorbidities in this patient population, incurring increased HF and IHD risk 2-3 decades after therapy. Another key finding is the reduction in IHD RR owing to the introduction of PET/CT-guided therapeutic approaches, applying RT only to patients with positive interim PET (PET-2). These modifications have resulted in significant decrease in the percentage of patients exposed to RT (from 56% to 14.9%). Consequently, IHD rates in these patients have dramatically declined, with RR not significantly differing from that observed in the control group.

On the other hand, no changes in the HF pattern have been demonstrated (Figure 3C), which highlights the need for further cardiotoxicity reduction in these patients. Nowadays, the backbone of

HL therapy is still based on the adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine (ABVD) regimen, introduced by the late Dr. Gianni Bonadonna in the 1970s, with several modifications implemented later to reduce bleomycin-related pulmonary toxicity[5]. In a recent randomized ECHELON-1 trial, demonstrating improved PFS and OS, patients with advanced-stage HL were treated with the regimen containing brentuximab vedotin (A-AVD) instead of bleomycin (ABVD)[6]. Treatment in another randomized study, S1826, that recruited patients aged ≥12 years with stage III-IV HL, was also based on the AVD backbone with an addition of the immune checkpoint inhibitor nivolumab (Nivo-AVD) in one arm and A-AVD in the other[7]. Notably, Nivo-AVD was associated with significantly improved 24-month PFS. However, as specified in the discussed article by Marr et al, in both these pivotal studies, patients continued to be exposed to 300 mg/m^2 of adriamycin, a well-established cardiotoxic agent, whose toxicity is dose- and age-dependent[2]. Remarkably, the use of immune checkpoint inhibitors is also associated with elevated risk of cardiovascular disease, e.g., atherosclerosis[8] and acute myocarditis[4].

Despite major benefits of the AVD-based therapy, late cardiotoxicity, particularly an increased rate of HF even 30 years post-treatment, can take a heavy toll on these patients. Several study groups have addressed this highly important issue. In their seminal work, Engert et al., from the German Hodgkin Study Group, reported a non-inferior 5-year freedom-from-treatment-failure despite the reduction in the number of ABVD cycles from 4 to 2 and a dose of involved-field RT from 30 to 20 Gy in patients with early-stage favorable HL[9]. For patients with advanced-stage HL, from 1998 to 2011, the standard of care was 8 cycles of escalated BEACOPP, indicating exposure to 280 mg/m^2 of adriamycin, while 70% also received RT. Nowadays, patients demonstrate improved results following PET-2-guided treatment with 4-6 cycles of the brentuximab vedotin-based protocol (brentuximab vedotin, etoposide, cyclophosphamide, adriamycin, dacarbazine, dexamethasone BrECADD), which is more efficient and less toxic than BEACOPP. The majority of such patients receive a cumulative adriamycin dose of 160 mg/m^2 only[10].

One of the key questions in the current HL management is whether the cumulative adriamycin dose in the AVD-based therapy for patients with negative PET-2 could be safely reduced to mitigate cardiotoxicity. The emergence of novel molecular tools that are more specific than PET-2, such as the plasma cell-free DNA (ctDNA) analysis, may assist detecting minimal residual disease (MRD), allowing for treatment adjustment and ultimate decrease in cumulative chemotherapy dosage. One of such eagerly anticipated studies is being currently conducted by Kurts D. et al at the University of Washington (NCT06745076). In this study, MRD-negative patients, both according to PET-2 and ctDNA, are randomized to a total of 4 cycles versus standard 6 cycles of Nivo-AVD, which could

reduce exposure to adriamycin to 200 mg/m^2. Another approach to decreasing myocardial and endothelial damage associated with adriamycin is the use of dexrazoxane and atorvastatins.

Overall, the present study by Marr et al, along with others, provides a strong argument that the chapter of HL treatment-related cardiotoxicity remains unfinished. The fact that the 30-year risk of cardiac morbidity among HL survivors is currently predicted to be as high as 7% calls for rigorous consideration of this issue in upcoming trials.

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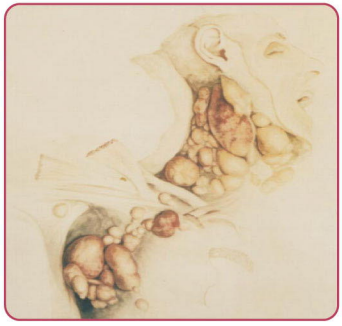
Figure 1. Current first-line treatments for Hodgkin lymphoma and causes of associated cardiac damage

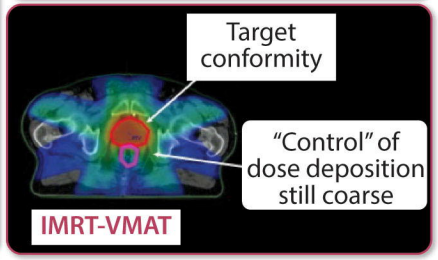


Treatment potency versus toxicity

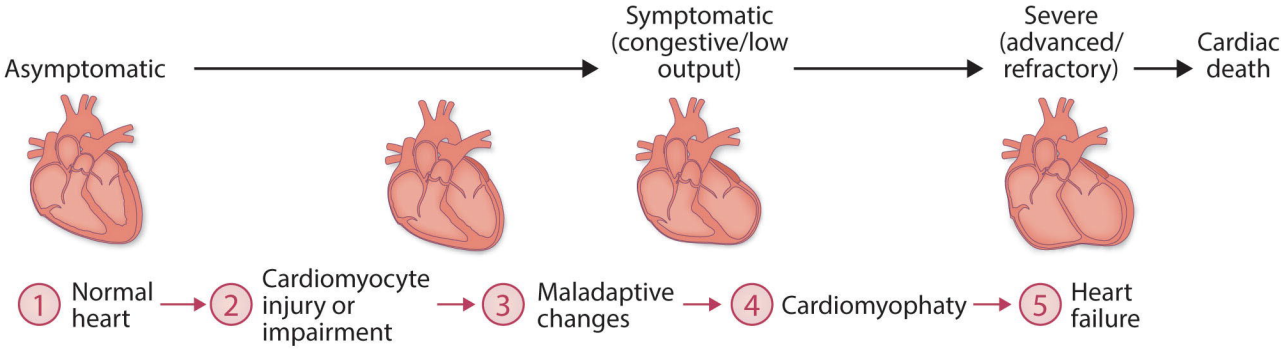
Adriamycin cumulative dose in various regimens:

- ABVD: 2-6 cycles ± RT (Adria 100-300 mg/m^2)
- BrECADD: 4-6 cycles (Adria 160-240 mg/m^2)
- Bv-AVD: 6 cycles (Adria 300 mg/m^2)
- Nivo-AVD: 6 cycles (Adria 300 mg/m^2)

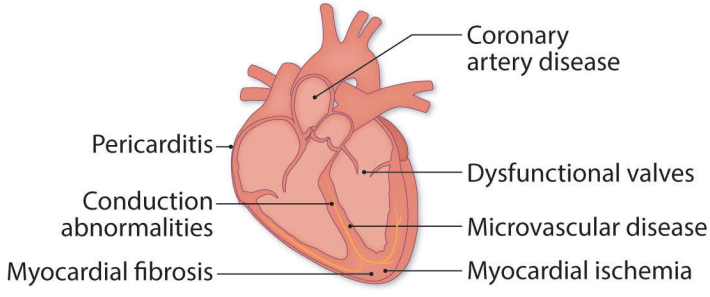
Current radiation techniques



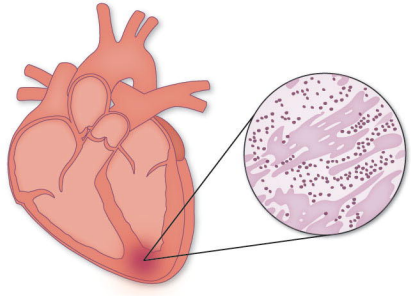
Dose-dependent adriamycin-induced cardiac dysfunction



Radiation-induced damage is dependent on mean heart dosage exposure



Anti-PD1 induced myocarditis



Mitigation of damage and care of coexisting morbidities: dexrazoxane, atorvastatin, management of hypertension, diabetes mellitus, hyperlipidemia, cessation of smoking.