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Is it time to increase the liposomal doxorubicin dosage for frontline therapy in young adults and adults with classic Hodgkin lymphoma? Comment on: “Is it time to reduce the doxorubicin dosage in Hodgkin lymphoma therapy?”

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Comment to the Editor

Frontline treatment with ABVD for Young adults and Adults (Ya&A) with advanced-stage cHL is unsatisfactory. In this setting, novel therapies are reshaping treatment, *i.e.*, ECHELON-1 examining brentuximab vedotin (BV) plus AVD, HD21 examining BV plus etoposide, cyclophosphamide, adriamycin, dacarbazine, dexamethasone (BrECADD), and SWOG S1826 examining nivolumab (N) plus AVD. These treatments have improved therapy cure rates, reducing the need for consolidative radiotherapy (c-RT). However, conventional anthracycline exposure has occurred, with patients having received a cumulative doxorubicin hydrochloride dose of 300 mg/m^2 for both BV+AVD and N+AVD, and 200 mg/m^2 (range, 160-240 mg/m^2) for BrECADD. The most common clinical manifestation of cardiotoxicity is a dose-dependent cardiomyopathy (CMP) leading to chronic heart failure (HF). Recent reports[1,2] set the cardiotoxicity threshold at 210 mg/m^2. While about 15% of patients exceeding this dose develop overt heart failure within 20-30 years after treatment, this likely underestimates true incidence, since over 50% show some degree of cardiac dysfunction after initial hydroxydoxorubicin doses.[3,4] The 2022 Task Force for Cancer Treatments and Cardiovascular Toxicity of the European Society of Cardiology (ESC) Guidelines[5] strongly recommend systematic echocardiographic monitoring, including strain rate imaging with measures of global radial and circumferential strain (global longitudinal strain [GLS]) in addition to left ventricular ejection fraction (LVEF) for exploring subclinical signs of impaired ventricular function. Normal thresholds were defined as GLS ≥–20% and LVEF ≥50%. The authors advocate to diagnose anthracycline-induced CMP in early phase, i.e, at the onset when GLS declines ≥15% from baseline and/or LVEF falls ≥10% to 40-49%.[5]

We read with interest the editorial by Dann E.J. published in *Haematologica* 2026[6] reporting on a key question in the current HL management, *i.e.*, whether the cumulative doxorubicin hydrochloride dose in the AVD-based therapy for patients with negative FDG

PET-2 could be safely reduced to mitigate cardiotoxicity. Novel molecular tools, such as plasma cell-free DNA, offer greater specificity than PET-2 for detecting minimal residual disease, enabling treatment adjustments and reduced cumulative chemotherapy. The authors also evaluated dexrazoxane and atorvastatin to mitigate doxorubicin-induced myocardial and endothelial damage. As highlighted by Dann E.J., HL treatment-related cardiotoxicity remains an unresolved challenge.

In our tertiary hospital in southern Italy (Federico II University, Medical School, Naples), 2D echocardiography and speckle tracking echocardiography for standard echocardiography and strain measurements has been implemented as a routine procedure for patients with hematological diseases by cardiologist experts in echocardiography of the cardioncology units.[7,8] Myocet™ is doxorubicin encapsulated in a non-pegylated liposomal membrane of phosphatidylcholine and cholesterol. [9] Initially used in breast cancer, non-pegylated liposomal doxorubicin (NPLD) spares healthy tissues with tight capillary junctions, such as the heart.[3,4] Consequently, NPLD-based regimens (e.g., MBVD) are recommended over standard ABVD for elderly or cardiopathic c-HL patients.[10] MBVD scheme resulted as a safe option, with activity profile comparable to historical ABVD data. High-dose liposomal doxorubicin may offer pharmacokinetic and pharmacodynamic advantages,[11] rapidly accumulating in tumor-associated macrophages and the reticuloendothelial system of spleen, liver, lung, and bone. In real-life, this benefits c-HL patients with high tumor burden, regardless of age or comorbidities. There is a clear need to maintain the high efficacy of the front-line therapy of HL with anthracycline-based regimens while minimizing treatment-related adverse events, underscoring the importance of developing truly efficacy- and safety-oriented therapeutical strategies. We recently published a preliminary phase II report,[12] and demonstrated this concept in a small cohort (n = 28) of patients (median age 40 years, with a range of 22-64 years) with untreated, advanced-stage c-HL in which ABVD scheme was modified by replacing conventional doxorubicin with NPLD at

the dose of 35 mg/m^2 in cycles 1 and 2 for improving negative interim (i)-PET cases incidence. In the subsequent cycles (3 through 6), the patients were scheduled to receive MBVD consisting of outpatient intravenous Myocet™ administered at a de-escalated dose of 25 mg/m^2 on day 1, in combination with standard dose of bleomycin, vinblastine and dacarbazine on days 1 and 14 of each 28-day course. In this treatment strategy, the planned cumulative dose of NPLD for patients with c-HL was 140 mg/m^2 achieved by administering 35 mg/m^2 per cycle, and 200 mg/m^2 over cycles 3 to 6, delivered at the standard dose of 25 mg/m^2 per cycle. According to this treatment strategy, the dose intensity of liposomal doxorubicin in cycles one and two of the planned series of MBVD-DI (dose intensified) was increased to 140% of the standard dose, whereas the cumulative dose over six cycles (two courses of MBVD-DI + four courses of MBVD) was restricted to 340 mg/m^2 (113% of standard dose). The mean (range) dose-intensity was 94% (91%-100%) for all 28 patients. At i- and end-of-treatment (EoT) PET, 27 patients obtained complete metabolic response; only one (3%) had positive FDG-PET scans. Altogether, 6 patients (21%) received c-RT (mediastinal field, one). After a median follow-up of 61 months (range, 57-78 months), the 5-year PFS was 89.3% (95% CI, 78.6%-100%). A complete echocardiographic evaluation (including measurements of GLS and LVEF performed at baseline, interim, EoT and during follow-up) was available for 27 patients. At study entry, the echocardiographic assessment showed median result of GLS of -21% and median result of LVEF of 61%. At i-assessment, the median result of GLS was -21% and the median result of LVEF was 61%. At EoT assessment, the median result of GLS was -21% and the median result of LVEF was 60%. At 60-month follow-up, the median result of GLS was −22% and the median result of LVEF was 61%, respectively. There were very small changes (according to the definition of anthracycline-induced cardio-toxicity for cancer treatment of ESC),[5] *i.e.*, <10 percentage points reductions in values of GLS and

LVEF at each time point compared with the baseline. None of the patients required hospitalization to manage treatment-related adverse events.

Our data suggest that a large prospective, multicenter trial is warranted to assess the feasibility of liposomal doxorubicin as frontline therapy in YA&A patients with high-risk cHL, with the goal of improving clinical outcomes.

References

1. Cardinale D, Colombo A, Lamantia G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. J Am Coll Cardiol. 2010;55(3):213-220.

2. De Vries S, Haaksma ML, Jóźwiak K, et al. Development and validation of risk prediction models for coronary heart disease and heart failure after treatment for Hodgkin lymphoma. J Clin Oncol. 2023;41(1):86-95.

3. Minotti G, Menna P, Salvatorelli E, Cairo G, Gianni L. Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. Pharmacol Rev. 2004;56(2):185-229.

4. Renu K, Abilash VG, Tirupathi Pichiah PB, Arunachalam S. Molecular mechanism of doxorubicin-induced cardiomyopathy – An update. Eur J Pharmacol. 2018;818:241-253.

5. Lyon AR, López-Fernández T, Couch LS, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J. 2022;43(41):4229-4361.

6. Dann EJ. Is it time to reduce the doxorubicin dosage in in Hodgkin lymphoma therapy? Haematologica. 2026 Feb 26. doi: 10.3324/haematol.2025.289210. [Epub ahead of print]

7. Picardi M, Vincenzi A. Systematic echocardiogram surveillance to early detect and treat doxorubicin hydrochloride-induced cardiomyopathy in young adults and adults with classical Hodgkin lymphoma. Comment on: Long-term cardiac morbidity in adolescent and young adult survivors of classical Hodgkin lymphoma: the British Columbia experience. Haematologica. 2026 Mar 12. doi: 10.3324/haematol.2025.300167. [Epub ahead of print]

8. Picardi M, Vincenzi A, Pugliese N, et al. Liposomal doxorubicin in place of doxorubicin hydrochloride to prevent anthracycline-induced cardiomyopathy in elderly patients with Hodgkin lymphoma. Hemasphere 2025;9(10):e70240.

9. Leonard RCF, Williams S, Tulpule A, Levine AM, Oliveros S. Improving the therapeutic index of anthracycline chemotherapy: Focus on liposomal doxorubicin (Myocet^{TM}). Breast. 2009;18(4):218-224.

10. Salvi F, Luminari S, Tucci A, et al. Bleomycin, vinblastine and dacarbazine combined with nonpegylated liposomal doxorubicin (MBVD) in elderly (≥70 years) or cardiopathic patients with Hodgkin lymphoma: a phase-II study from Fondazione Italiana Linfomi (FIL). Leuk Lymphoma. 2019;60(12):2890-2898.

11. Miller MA, Zheng Y-R, Gadde S, et al. Tumour-associated macrophages act as a slow-release reservoir of nano-therapeutic Pt(IV) pro-drug. Nat Commun. 2015;6(1):8692.

12. Picardi M, Giordano C, Pugliese N, et al. Liposomal doxorubicin supercharge-containing front-line treatment in patients with advanced-stage diffuse large B-cell lymphoma or classical Hodgkin lymphoma: Preliminary results of a single-centre phase II study. Br J Haematol. 2022;198(5):847-860.