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?"

Front-line treatment with ABVD for young adults and adults (YA&A) with advanced-stage classical Hodgkin lymphoma (cHL) is unsatisfactory. In this setting, studies of 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 leading to chronic heart failure. Recent reports[1,2] set the cardiotoxicity threshold at 210 mg/m^2. While approximately 15% of patients exceeding this dose develop overt heart failure within 20-30 years after treatment, this likely underestimates the 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 diagnosis of 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[6] published in *Haematologica* on the work by Marr *et al*.,[7] reporting on a key question in current HL management: 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. Marr *et al*. also evaluated dexrazoxane and atorvastatin to mitigate doxorubicin-induced myocardial and endothelial damage.[7] As highlighted by Dann, HL treatment-related cardiotoxicity remains an unresolved challenge.[6]

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 have been implemented as a routine procedure for patients with hematologic diseases by cardiologist experts in echocardiography of the cardioncology units.[8,9] Myocet™ is doxorubicin encapsulated in a non-pegylated liposomal membrane of phosphatidylcholine and cholesterol.[10] 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 cHL patients.[11]

The MBVD scheme has proved to be a safe option, with an activity profile comparable to historical ABVD data. High-dose liposomal doxorubicin may offer pharmacokinetic and pharmacodynamic advantages,[12] rapidly accumulating in tumor-associated macrophages and the reticuloendothelial system of spleen, liver, lung, and bone. In real-life, this benefits cHL 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[13] demonstrating this concept in a small cohort (N=28) of patients (median age: 40 years; range: 22-64 years) with untreated, advanced-stage cHL in which the ABVD scheme was modified by replacing conventional doxorubicin with NPLD at the dose of 35 mg/m^2 in cycles 1 and 2 to improve on the incidence of negative interim PET cases. 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 cHL 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 1 and 2 of the planned series of dose-intensified MBVD (MBVD-DI) was increased to 140% of the standard dose, whereas the cumulative dose over 6 cycles (2 courses of MBVD-DI + 4 courses of MBVD) was restricted to 340 mg/m^2 (113% of standard dose). The mean dose-intensity was 94% (range: 91-100%) for all 28 patients. At interim 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, 1). After a median follow-up of 61 months (range: 57-78 months), the 5-year progression-free survival 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 a median GLS of -21% and median LVEF of 61%. At interim assessment, median GLS was -21% and median LVEF was 61%. At EoT assessment, median GLS was -21% and median LVEF was 60%. At the 60-month follow-up, median GLS was –22% and median LVEF was 61%. Very small changes (according to the definition of anthracycline-induced cardio-toxicity for cancer treatment of the ESC)[5] were observed i.e., <10% reductions in GLS and LVEF values at each time point compared with 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 front-line therapy in YA&A patients with high-risk cHL, with the goal of improving clinical outcomes.

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Contributions

Both authors contributed equally.

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