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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

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Comment to the Editor

In patients of 18-59 years of age, *i.e.*, Young adults and Adults (Ya&A), with advanced-stage classical Hodgkin lymphoma (cHL), frontline treatment landscape is rapidly changing with novel therapies integration. The global, phase III ECHELON-1 trial compared brentuximab vedotin (BV) in combination with adriamycin, vinblastine, and dacarbazine (BV+AVD) *versus* adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) in patients with newly diagnosed stage III/IV cHL.[1] Ya&A received either BV+AVD (n = 580) or ABVD (n = 568): at 7-year follow-up, the Kaplan-Meier curve of progression free survival (PFS) for BV+AVD was 86% *versus* 79% for ABVD (hazard ratio [HR] 0.667; 95% confidence interval [CI]: 0.486-0.914; *P*= 0.011).[2] A phase III randomized trial (SWOG S1826) examining the frontline use of nivolumab in combination with AVD (N-AVD) in patients with advanced-stage cHL, now closed to enrollment with 2-year PFS data reported and ongoing longer follow-up.[3] Considering Ya&A, in the N-AVD arm (n = 321) the outcome was better than the BV+AVD one (n = 318), with PFS rates of 92% and 86% respectively (HR 0.59; 95% CI: 0.36-0.95; *P*=0.03). These treatments have improved front-line therapy cure rates, reducing drastically the need for consolidative irradiation, which may further influence cardiovascular disease. However, anthracycline exposure has occurred, with patients with advanced-stage disease having received a cumulative doxorubicin hydrochloride dose of 300 mg/m^2. The most common clinical manifestation of cardiotoxicity is a dose-dependent cardiomyopathy (CMP) leading to chronic heart failure (HF). According to recent reports,[4,5] the cut-off to prevent cardiotoxicity is 210 mg/m^2. Data from oncology literature indicates that about 5% of patients receiving >210 mg/m^2 of cumulative anthracycline will develop overt HF 10-20 years after treatment.[6] However, this incidence is likely underestimated, since over half of patients show some degree of cardiac dysfunction.[4,5] The 2022 Task Force for Cancer Treatments and Cardiovascular Toxicity of

the European Society of Cardiology (ESC) Guidelines[7] 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 asymptomatic phase, *i.e.*, at the onset when GLS declines ≥15% from baseline and/or LVEF falls ≥10% to 40–49%, allowing early modern HF treatment.[4,5,7]

We read with interest the retrospective study by Marr et al. published in *Haematologica* 2025[8] reporting late side effects of 806 adolescent and young adults (ages 16-39 years) with cHL treated frontline with ABVD or ABVD-like regimens between 1992 and 2013 and identified in the British Columbia Cancer Lymphoid Cancer Database. At a median follow-up of 17 years from initial diagnosis, the incidence of HF among patients with advanced-stage disease — who underwent a median cumulative anthracycline dose of 300 mg/m² — was 5.2%. Among those diagnosed at age 30 years or older, the incidence of HF increased to 7.4% (95% CI, 3.1–11.6). The authors underline the need for refining monitoring strategies and screening guidelines for cardiotoxicity in adolescent and young adult cHL survivors, applying similar diagnostic work-up of pediatric patients, *i.e.*, echocardiogram surveillance extension beyond the pediatric age group. Evaluations of survivorship guidelines in lymphoma suggest a wide variation in screening approaches when comparing pediatric and adult recommendations, as well as across guidelines. Pediatric guidelines recommend lifelong surveillance with 2-D echocardiogram for early identification of asymptomatic heart disease to prevent or delay disease progression, with screening every 2-5 years based on risk stratification by anthracycline dose and/or mediastinal irradiation.[8]

In four tertiary hospitals in southern Italy, 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.[9,10] Recently, we carried out a real-life analysis from the registry databases of the four Units to evaluate the PFS in 18-59 years aged patients who were scheduled to receive six BV+AVD courses for newly diagnosed advanced-stage cHL.[11] In addition, the study focused on cardiac toxicity profile as detected by serial echocardiography evaluations. We reviewed clinical charts of 150 patients between November 2021 and December 2024. Median dose intensity of BV+AVD regimen was 100%. Four patients (2.7%) received consolidation radiotherapy (residual nodal masses at mediastinum, in 3 cases). At 2-year median follow-up, the PFS of the entire population was 91% (95% CI, 0.864-0.958). Overall, any grade heart-toxicity (according to the National Cancer Institute Common Terminology Criteria for Adverse Events) was reported in 16% of patients (n = 23) with grade 1 in 48% (n = 11) and grade ≥2 in 52% (n = 12). Complete GLS and LVEF evaluations were available for 59 patients (39%), at baseline, interim, end-of-treatment (EoT), and 6 months follow-up. At baseline (chemotherapy start), there were 9 patients (15%) with measurements of GLS worse than −20% and three patients (5%) experienced a ≥10% decrease in LVEF; the echocardiographic assessment showed median result of GLS of −20.8% and median result of LVEF of 59.5%. At the interim assessment, the median result of GLS was −21% and the median result of LVEF was 59%. At EoT assessment, the median result of GLS was −21% and the median result of LVEF was 58%. At 6-month follow-up, the median result of GLS was −21% and the median result of LVEF was 60%. Among the remaining 91 patients, who had at least two echocardiographic evaluations (baseline and EoT), a reduction in myocardial strain was observed in 11 patients. Based on these findings, twenty-three patients underwent cardiological toxicity early treatment included angiotensin-

converting enzyme inhibitors (5 cases), angiotensin receptor blockers (6 cases), beta-blockers (8 cases), and/or anti-arrhythmic drugs (4 cases); all patients improved myocardial ventricular function with medical management during follow-up.

Although anthracycline-based chemotherapy provides the best outcomes for HL patients, specific echocardiography and speckle tracking echocardiography monitoring for standard and strain measurements should be considered for Ya&A HL survivors, to early detect and treat doxorubicin hydrochloride-induced cardiac dysfunction as underlined by Marr et al.[8]

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