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Preserving liposomal anthracycline exposure and reconsidering radiotherapy in frontline therapy of older adults with advanced-stage classical Hodgkin lymphoma. Comment on: "Nivolumab with doxorubicin, vinblastine, and dacarbazine in older adults with classic Hodgkin lymphoma: do S1826 results hold up in the real world?"

by Claudia Giordano and Marco Picardi

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Preserving liposomal anthracycline exposure and reconsidering radiotherapy in frontline therapy of older adults with advanced-stage classical Hodgkin lymphoma. Comment on: "Nivolumab with doxorubicin, vinblastine, and dacarbazine in older adults with classic Hodgkin lymphoma: do S1826 results hold up in the real world?"

Claudia Giordano[1] and Marco Picardi[1]

[1]Department of Clinical Medicine and Surgery, Federico II University Medical School, Via Sergio Pansini, 5, Naples, 80131, Italy

Author contributions

C.G. drafted the manuscript. Both authors critically revised the manuscript for important intellectual content, approved the final version, and agree to be accountable for all aspects of the work.

Disclosures

The authors declare no conflicts of interest.

Correspondence: Dr Claudia Giordano, Department of Clinical Medicine and Surgery, Federico II University Medical School, Via S. Pansini 5, 80131 Naples, Italy.
Tel. +390817462068; Fax +390817462165; E-mail: claudiagiordano91.cg@gmail.com

Dear Editor,

We read with interest the retrospective study by Torka et al. evaluating nivolumab combined with doxorubicin, vinblastine, and dacarbazine (N-AVD) in 81 older adults with advanced-stage (AS) classical Hodgkin lymphoma (cHL).[1] Their findings support the effectiveness of this frontline regimen beyond clinical trials. However, we believe that two aspects warrant further consideration in the upfront therapy of elderly: the cardiac implications of conventional doxorubicin exposure and the potential contribution of selective consolidation radiotherapy.

N-AVD represents an important therapeutic advance, supported by the randomized S1826 trial and its older-patient analysis.[2] Nevertheless, incorporating nivolumab does not remove the dose-dependent cardiotoxicity of conventional doxorubicin. Six full-dose AVD cycles entail a cumulative doxorubicin hydrochloride exposure of 300 mg/m². This is clinically relevant in older adults, whose cardiovascular comorbidities and reduced cardiac reserve may increase susceptibility to myocardial injury.[3] Data from oncology literature indicate that about 5% of patients receiving >210 mg/m^2 of cumulative anthracycline will develop overt heart failure 10-20 years after treatment.[4] ESC (European Society of Cardiology) guidelines classify conventional doxorubicin exposure of 250 mg/m² as an early high-risk feature in adult survivors.[5] Accordingly, favourable short-term tolerability should be complemented by systematic assessment of subclinical dysfunction and longer-term cardiac outcomes.

Our real-life multicenter experience on elderly AS cHL provides a complementary perspective, with median follow-up of 60 months (range, 2-86 months).[6] For the entire cohort, five-year PFS and OS rates were 81.6% and 87.5%, respectively. Briefly, fifty patients with a median age of 69 years (range, 60-89), received non-pegylated liposomal doxorubicin, vinblastine, and dacarbazine (MVD), followed by selective irradiation of residual nodal masses. At baseline over two-third of patients (80%) had at least two

cardiac risk factors, such as hypertension, obesity, tobacco use, diabetes mellitus, hyperlipidemia, and/or history of heart disease. The planned cumulative liposomal doxorubicin dose was 300 mg/m², administered intravenously at 25 mg/m² on days 1 and 15, along with standard vinblastine and dacarbazine, for a total of 6 cycles. Forty-nine patients completed six cycles, and 46 received full-dose treatment. Therapy delivery was supported by systematic antimicrobial prophylaxis with trimethoprim–sulfamethoxazole and acyclovir, together with primary G-CSF prophylaxis with lipegfilgrastim, which may have contributed to treatment completion.[6] Cardiac tolerability was evaluated through serial echocardiography incorporating global longitudinal strain (GLS) alongside left ventricular ejection fraction (LVEF). Complete assessments at baseline, interim, treatment completion, and six months thereafter were available for 45 patients. Median GLS was −20% at baseline and −21% at each subsequent assessment; corresponding median LVEF values were 60%, 60%, 59%, and 60%. These findings support overall preservation of myocardial function despite frequent baseline cardiovascular risk factors. Thus, favourable cardiac findings were observed with substantial anthracycline exposure, rather than systematic dose attenuation. This does not imply an absence of cardiac toxicity. Four patients had GLS deterioration meeting the study's ≥15% threshold; six patients had LVEF reductions meeting its ≥10% threshold. Nevertheless, the overall echocardiographic measurements trajectory suggested that liposomal delivery could facilitate clinically meaningful anthracycline exposure with an acceptable cardiac function profile in older patients. This distinction is relevant when interpreting the study by Torka et al.[1] Although their results are encouraging (PFS and OS were 91.5% and 98.6%, respectively), median follow-up was 12.6 months, and serial GLS assessment by echocardiographic scans was not reported. Consequently, the study cannot fully characterize subclinical or delayed conventional anthracycline-related myocardial injury. The reported immune-mediated myocarditis also highlights the importance of distinguishing checkpoint inhibitors toxicity

from anthracycline-associated dysfunction. Prospective comparisons incorporating new tools for cardiac surveillance would help determine whether anthracycline formulation can further improve treatment delivery and safety. Systematic echocardiographic monitoring, including strain rate imaging with measures of global radial and circumferential strain in addition to LVEF is able for early exploring subclinical signs of impaired ventricular function.[3,4] The second issue concerns consolidation radiotherapy. Because of incomplete regression of nodal masses at initially involved sites, 17 of 50 patients (34%) in our study received localized radiotherapy (approximately 30 Gy) to residual nodal masses in mediastinal (n=3) or extra-mediastinal (n=14) sites. Residual FDG uptake corresponded to Deauville scores of 3 in 13 patients (FDG uptake >mediastinum but ≤liver) and in 4 cases with FDG uptake moderately or markedly >liver (three in the category of DS 4 scores and one in the category of DS 5 score at PET scans). The clinical value of local disease control deserves consideration in older patients, in whom relapse may necessitate treatments that are difficult to deliver because of comorbidities and limited physiological reserve. In this setting, selective irradiation of residual nodal masses (especially in extra-mediastinal sites) could complement systemic therapy and potentially reduce the subsequent need for salvage treatment. The balance between disease control and radiation toxicity should therefore be individualized, considering anatomical location, anticipated organ exposure, baseline cardiovascular status, and life expectancy. Our findings support prospective evaluation of this approach, while acknowledging that the contribution of radiotherapy cannot be isolated from the overall treatment strategy. These results support further investigation of selective radiotherapy in older adults, particularly when preventing relapse could reduce the need for poorly tolerated salvage treatment. On the other hand, persistent uptake after checkpoint inhibition also requires caution because inflammation may mimic residual lymphoma; biopsy should be considered when feasible before additional treatment. As discussed in our study, non-pegylated liposomal encapsulation

modifies doxorubicin biodistribution, favoring delivery through the disrupted tumor microvasculature while limiting penetration into myocardial tissue with intact capillary endothelium. Preclinical studies have shown approximately 30–40% lower peak and overall myocardial drug concentrations compared with conventional doxorubicin, providing a pharmacological rationale for reduced cardiotoxicity.[8] Moreover, the accumulation of therapeutic liposomal nanoparticles inside tumor microenvironment theoretically enhances the susceptibility to chemotherapy and/or radiotherapy of cancer cells, by hampering pro-tumor activities of CD68-positive tumor-associated macrophages.[8]

In conclusion, the results of Torka et al.[1] strengthen the evidence for N-AVD in older patients eligible for anthracycline-based therapy. Our experience suggests that further progress may also come from optimizing anthracycline delivery and selectively integrating consolidation treatment.[6] In elderly with untreated AS cHL, prospective studies should assess liposomal anthracycline, standardized GLS monitoring by echocardiography scans, and carefully selected radiotherapy alongside contemporary systemic regimens.[6-8]

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