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Preserving anthracycline-containing treatment in older patients with classical Hodgkin lymphoma: a role for liposomal doxorubicin. Comment on: "Age, anthracycline and mortality in 28,000 classic Hodgkin lymphoma patients: cohort study of a complete population"

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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.

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We read with interest the population-based study by Barrett and colleagues, “Age, anthracycline and mortality in 28,000 classic Hodgkin lymphoma patients”. Their analysis provides consistent evidence regarding the persistent survival disadvantage of older patients with classical Hodgkin lymphoma (cHL) and the association between anthracycline-containing treatment and improved lymphoma-specific survival. The substantial geographical variation in anthracycline prescribing is particularly noteworthy, suggesting that treatment selection reflects differences in clinical practice alongside patient characteristics. These findings raise a practical question: how can anthracycline-containing treatment be delivered to older patients when concerns about tolerability may otherwise lead to its omission?

The observation that lymphoma remains the predominant cause of death is central to this discussion. Although comorbidities and treatment toxicity complicate management, preserving effective disease control remains a major objective. Among patients aged 60–79 years, Barrett et al. reported an adjusted 5-year lymphoma-specific survival of 79.7% with anthracycline-containing regimens versus 59.8% with regimens omitting anthracyclines. Although residual confounding related to treatment selection cannot be excluded, these findings provide a rationale for exploring strategies that preserve anthracyclines while tailoring treatment to patients’ individual vulnerabilities. Our previously published multicentre experience with non-pegylated liposomal doxorubicin offers complementary evidence relevant to this objective.

In our retrospective study, 50 patients aged ≥ 60 years with newly diagnosed stage III or IV cHL received frontline non-pegylated liposomal doxorubicin, vinblastine and dacarbazine (MVD), with consolidation radiotherapy for selected residual nodal masses. The median age was 69 years, ranging from 60 to 89; 17 patients were aged 70–79 and six were ≥ 80 . Half of the cohort had baseline nodal masses exceeding 5 cm. This population therefore

included patients with substantial disease burden and individuals beyond the age range usually associated with favourable treatment tolerance, although eligibility criteria necessarily selected patients considered suitable for curative-intent therapy.

MVD consisted of non-pegylated liposomal doxorubicin 25 mg/m², vinblastine 6 mg/m² and dacarbazine 375 mg/m² on days 1 and 15 of each 28-day cycle, for six cycles. Bleomycin was omitted throughout treatment. Patients routinely received granulocyte colony-stimulating factor and antimicrobial prophylaxis, alongside serial cardiac assessment incorporating left ventricular ejection fraction and global longitudinal strain. The strategy combined modification of the anthracycline formulation with supportive care and cardiac surveillance, seeking to facilitate treatment delivery while retaining the principal cytotoxic components of an AVD-like regimen.

Forty-nine patients (98%) completed all six planned cycles; one died from COVID-19 during induction. Following chemotherapy and before consolidation radiotherapy, 45 of 50 patients (90%) achieved a complete metabolic response. Seventeen patients (34%) subsequently received radiotherapy to residual nodal masses measuring ≥ 2.5 cm. At a median follow-up of 60 months, estimated 5-year overall survival was 87.5% (95% confidence interval [CI], 78.7–97.4), and progression-free survival was 81.6% (95% CI, 71.4–93.2). These outcomes describe the complete treatment strategy and should not be attributed exclusively to liposomal doxorubicin.

The high treatment completion rate is particularly relevant to the findings of Barrett et al. In their cohort, 68.6% of patients aged 60–79 years completed chemotherapy as planned, highlighting treatment delivery as an important challenge. Direct comparison with our selected cohort would be inappropriate. Nevertheless, our experience suggests that evaluating how treatment can be completed is a useful complement to evaluating which

regimen is prescribed. Furthermore, Barrett et al. found no association between chemotherapy dose reduction and inferior adjusted lymphoma-specific survival among anthracycline recipients. Together, these observations support prospective investigation of individualised approaches that preserve effective treatment while accommodating tolerability.

Safety findings require consideration alongside feasibility. Eleven patients (22%) experienced grade ≥ 3 adverse events. Cardiovascular events included grade ≥ 3 atrial fibrillation in two patients and grade < 3 left ventricular systolic dysfunction in five. Two fatal COVID-19 infections occurred, one during induction and one after chemotherapy. Thus, successful treatment delivery did not imply an absence of clinically relevant toxicity. Moreover, baseline left ventricular ejection fraction $\geq 50\%$ was required for inclusion. Our findings therefore support further evaluation in selected older patients but cannot establish safety in those with significant pre-existing systolic dysfunction or demonstrate reduced cardiotoxicity relative to conventional doxorubicin.

Radiotherapy provides another connection between the studies. Barrett et al. observed better adjusted survival among patients receiving radical-dose radiotherapy alongside curative chemotherapy, while acknowledging substantial potential for selection bias. In our study, consolidation radiotherapy was administered to residual nodal masses after MVD, including patients who had achieved complete metabolic response. The favourable outcomes provide a rationale for examining this combined-modality approach further, but do not establish the independent contribution of irradiation. Prospective studies should define the subgroup in whom additional local control justifies irradiation.

Several methodological distinctions are essential when interpreting these complementary observations. Barrett et al. analysed a population-based cohort with heterogeneous

disease stages, treatment choices and baseline fitness, whereas our series comprised patients with advanced-stage disease treated within a specific institutional strategy. Our study was retrospective, small and lacked a conventional doxorubicin comparator. Overall and progression-free survival are also different endpoints from lymphoma-specific survival. Accordingly, our results provide a feasibility signal and a rationale for prospective testing, without establishing comparative efficacy. Future studies should incorporate geriatric assessment, standardised cardiac endpoints, treatment completion, patient-reported outcomes and explicit criteria for radiotherapy.

Finally, the incorporation of novel agents into frontline cHL treatment makes the tolerability of the chemotherapy backbone an ongoing research priority. Barrett et al. discuss encouraging results with nivolumab plus AVD in older patients, an approach that retains doxorubicin. Whether liposomal substitution could preserve efficacy within such combinations while improving tolerability remains an unanswered question requiring prospective evaluation. Our experience supports investigating this possibility without assuming interchangeability between formulations. The broader implication of both studies is that older age should prompt careful assessment and treatment adaptation. Developing evidence-based ways to retain anthracycline-containing therapy may help extend curative-intent treatment to a wider, appropriately selected population.

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