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Who needs bleomycin in classic Hodgkin lymphoma? Comment on: "Bleomycin omission in limited-stage classic Hodgkin lymphoma with negative PET scan after two cycles of ABVD"

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Who needs bleomycin in classic Hodgkin lymphoma? Comment on: "Bleomycin omission in limited-stage classic Hodgkin lymphoma with negative PET scan after two cycles of ABVD"

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Comment to the Editor

We read with interest the report by Yang et al. on PET-adapted bleomycin omission in limited-stage classic Hodgkin lymphoma (cHL).[1] Their real-world experience provides reassuring evidence that patients with a negative FDG-PET scan after two cycles of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) can complete treatment with doxorubicin, vinblastine and dacarbazine (AVD) without an apparent loss of disease control. Among patients completing four cycles of chemotherapy, 5-year progression-free survival (PFS) was 96.7% after 4 cycles of ABVD versus 95.0% after 2 ABVD cycles followed by 2 AVD cycles (P= 0.60).[1] These findings further strengthen the rationale for minimizing unnecessary bleomycin exposure in patients demonstrating an early favourable metabolic response.[2,3] However, their observations may raise a question that extends beyond PET-adapted de-escalation: should bleomycin omission necessarily wait for PET2-scans?

The success of PET2-guided omission relies on the principle that patients who have already demonstrated treatment sensitivity may not require further exposure to a potentially toxic drug. This strategy substantially reduces cumulative bleomycin exposure. Yet, it cannot prevent toxicity occurring during the first two ABVD cycles. This limitation is particularly evident in the experience reported by Yang et al.: although bleomycin pulmonary toxicity was markedly reduced after implementation of PET2-guided omission, pulmonary toxicity still occurred during cycle 2 (4 patients of 121). The authors themselves appropriately suggest that this observation supports ongoing investigation into the omission of bleomycin altogether.[1] This distinction between early discontinuation and upfront avoidance deserves consideration. PET2 is an excellent tool for deciding whether bleomycin should be continued, but it cannot answer whether every patient needed to receive bleomycin in the first place. Consistent with several publications, the use of bleomycin sulfate especially in the adults and elderly appears prohibitive: bleomycin-

induced lung toxicity is frequent and is diagnosed in up to 18% of older patients receiving this compound.[4] Bleomycin binds to DNA and produces free radicals, which then cause DNA strand breaks and cell death. Bleomycin is inactivated by bleomycin-hydrolase, which has markedly decreased activity in lung tissue. Although the exact mechanism is unknown, it seems that bleomycin-induced cell injury in the lung stimulates an inflammatory response with recruitment of inflammatory cells and an increase in cytokine production. Routine evaluations of the diffusing capacity of the lung for carbon monoxide (DLco) show measurements diminished already following the first exposures to bleomycin.[5] Noteworthy, in about 40% of these patients, bleomycin lung toxicity is judged severe and potentially life-threatening. The mortality rate due to bleomycin-related pulmonary damage ranges between 4% and 24%.[4] However, historical evidence understandably argues against indiscriminate omission. In the GHSG HD13 trial, AVD failed to demonstrate non-inferiority to ABVD in early-stage favorable cHL, with a small but significant impairment in tumor control when bleomycin was omitted. Thus, the available evidence does not support simply replacing ABVD with AVD for all patients with limited-stage disease. However, HD13 preceded contemporary PET-guided treatment and addressed universal drug omission rather than biologically or clinically selected omission.[2,3]

The therapeutic landscape has also substantially changed. Bleomycin-free treatment is no longer confined to de-escalation after PET2. Brentuximab vedotin plus AVD has established an effective frontline regimen completely devoid of bleomycin, including in older patients,[6] and more recently nivolumab plus AVD has further reinforced AVD as a highly effective bleomycin-free backbone in advanced-stage cHL.[7] These regimens clearly cannot be directly extrapolated to limited-stage disease, particularly because the activity of the novel agents may compensate for bleomycin omission. Nevertheless, they have changed an important conceptual assumption: effective frontline treatment of cHL does not necessarily require exposure to bleomycin. This issue may be particularly relevant in older

patients, in whom bleomycin-related pulmonary toxicity can substantially compromise the feasibility of curative-intent treatment. Contemporary real-world experience also suggests increasing use of AVD-based bleomycin-free approaches in this population.[8] In this setting, the balance between a potential gain in disease control and the risk of severe pulmonary toxicity may differ substantially from that observed in younger, fit patients with limited-stage disease.

A similar principle has been explored using alternative cytotoxic backbones. In a multicenter real-world study, we treated 50 older adults with advanced-stage cHL using upfront MVD—non-pegylated liposomal doxorubicin, vinblastine and dacarbazine—completely avoiding bleomycin. In addition, relatively low dose, consolidation radiotherapy targeted only to residual nodal masses with size ≥2,5 cm in the initial bulky site, including areas with FDG uptake ≥mediastinum (Deauville score 3 or higher at PET scans) was administered in a minority of patients. Ninety percent achieved complete metabolic response after chemotherapy, with 5-year PFS and overall survival of 81.6% and 87.5%, respectively.[9] The feasibility observed in an older population with exclusively stage III-IV disease is particularly noteworthy, although these findings cannot establish the oncologic equivalence of upfront bleomycin omission in the limited-stage setting investigated by Yang *et al.* Conventional doxorubicin was also simultaneously replaced by its non-pegylated liposomal formulation, and the absence of a randomized comparator prevents attribution of outcomes specifically to bleomycin omission. Nevertheless, together with contemporary experience with other bleomycin-free regimens, our findings provide clinical proof of feasibility for a curative-intent cytotoxic strategy completely avoiding bleomycin from treatment initiation. Importantly, this should not be interpreted as supporting universal replacement of ABVD with AVD. The small but significant loss of tumor control observed with AVD in HD13 remains an important warning, particularly given the exceptionally high cure rate of limited-stage cHL.[1–3] Any strategy aimed at eliminating bleomycin from cycle 1

should therefore be prospectively validated and demonstrate preservation of disease control, rather than merely a reduction in toxicity. The question raised by the findings of Yang *et al.* may instead be one of patient selection. PET2 can identify patients in whom further bleomycin exposure is unnecessary, but it cannot prevent toxicity occurring during the first two cycles.[1] Future studies should therefore investigate whether baseline clinical characteristics, particularly age and pulmonary vulnerability, together with early markers of treatment response, could identify patients in whom bleomycin can safely be avoided *ab initio*. PET2 can pinpoint whether bleomycin can be stopped. The next challenge is to determine who needs to start it at all.

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