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# To B or not to B, that is the question: the role of bleomycin in early stage Hodgkin lymphoma

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In the frontline treatment of classical Hodgkin lymphoma (cHL), bleomycin pulmonary toxicity (BPT) is a potentially life-threatening complication.[1] Efforts to optimize bleomycin utilization in ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) started with HD13, which randomized patients with favorable (by German Hodgkin Study Group criteria) early stage (ES) cHL to ABVDx2 or reduced-intensity variants omitting dacarbazine, bleomycin, or both, with all patients also receiving 30 Gy radiotherapy (RT).[2] While the predefined non-inferiority margin was exceeded by all reduced-intensity variants, complete bleomycin omission led to the smallest decrement, 3.9%, in 5-year freedom from treatment failure. This suggested bleomycin was the least crucial component of ABVD. However, as <1% of patients receiving ABVDx2 experienced BPT, investigators concluded, “omission of bleomycin for patients receiving only two cycles of ABVD…does not seem to be necessary for safety reasons.”

Given higher risk of BPT with longer ABVD courses, bleomycin optimization was further tested in RATHL, which enrolled patients with stage II (high risk by bulk, B symptoms, or ≥3 sites), III, or IV cHL and integrated positron emission tomography (PET) response-adapted therapy. Patients received ABVDx2 prior to interim PET (iPET) — patients with negative iPET (Deauville 1–3) were randomized to ABVD or AVD in cycles 3–6. The primary endpoint was non-inferiority of 3-year progression-free survival (PFS). Although the primary analysis of RATHL fell just short of the pre-specified 5% non-inferiority margin (absolute difference 1.6%; 95% confidence interval [CI] −3.2%–5.3%), 7-year follow-up met this target.[3] Bleomycin omission after negative iPET resulted in less BPT (1% vs. 3% grade 3+ pulmonary events). This approach was widely endorsed by

guidelines and adopted in practice. However, whether to extrapolate these findings to patients with lower risk ES cHL who do not typically receive 6 cycles of chemotherapy has remained unanswered until the important analyses by Yang et al. presented in this issue of *Haematologica*.[4]

In January 2016, the British Columbia (BC) lymphoma tumor group (LYTG) endorsed bleomycin omission for the remaining 2 cycles (AVD) for lower risk ES cHL (stage IA/IB/IIA without bulk >10 cm) and negative iPET after ABVDx2. Between December 2011 and January 2016 ('**ABVD era**') patients were intended to receive ABVDx2 followed by iPET, then RT alone for positive iPET or **ABVD**x2 without RT for negative iPET (Deauville 1–2). These patients were compared to patients diagnosed February 2016 to June 2024 ('**AVD era**') who were intended to receive ABVDx2 followed by RT for positive iPET or **AVD**x2 without RT for negative iPET. The major observations include no difference in 5-year PFS comparing all patients between eras irrespective of iPET result, and impressive 5-year PFS of 97% (ABVDx4) and 96% (ABVDx2/AVDx2) for the 88% of patients with negative iPET. Given the essentially equivalent cure rates between the two eras combined with the marked decrease in BPT with AVD (4/121, 3.3%) vs. ABVD (12/67, 17.9%), the authors conclude these efficacy and tolerability data support their practice change, bringing RATHL-style bleomycin de-escalation to all patients irrespective of stage.

Beyond the non-randomized nature of this analysis, several nuances influence interpretation of these data. Most obviously, the modest sample size limits any formal

statistical demonstration of non-inferiority. However, the key comparisons of 62 and 84 iPET negative patients in the as-treated analysis is likely large enough to reliably rule out a 'true' 5-year PFS difference of ~8–9% (compared to the observed 1.7% difference). This falls in the range of PFS differences observed in landmark randomized studies including RAPID and EORTC H10 in which no OS differences were observed,[5,6] providing reassurance the BC LYTG approach is not missing a survival signal due to sample size. Furthermore, one must consider the definition of negative iPET. Akin to many treatment de-escalation trials, the BC LYTG bleomycin omission guidance incorporated a centrally reported, conservative iPET threshold of Deauville 5-PS 1/2/X = negative vs. 5-PS 3/4/5 = positive. Rigid application of the recommended bleomycin omission after negative iPET in routine practice will require high quality PET interpretation to ensure rigorous distinctions between 5-PS 2 vs. 3, a real-world challenge considering upwards of one-third of patients with cHL do not undergo iPET restaging, and only half of those that do have Deauville 5-PS reported.[7]

Further questions exist regarding real-world applicability given current patterns of care. Several studies reported mortality from BPT as high as 10–20% in patients ≥60 years old, which exceeds the risk of death from ES cHL in the study by Yang et al. (1/188) and many clinical trials. As a result, our practice was already to omit bleomycin entirely when treating patients ≥60. Subsequent extrapolations also have to integrate these findings with pre-planned combined modality treatment approaches (e.g., H10-style ABVDx3 + 30 Gy RT for favorable risk, or HD11-style ABVDx4 + 30 Gy RT for unfavorable risk). Do the Yang et al. observations support omitting bleomycin after negative iPET in these

scenarios? The data suggest ‘probably’, but uptake of this practice may be slow and inconsistent given lacking scenario-specific data.

Looking to the future, the CD30-targeting antibody-drug conjugate brentuximab vedotin (BV) and anti-PD1 immune checkpoint inhibitors such as nivolumab are solidified as crucial components of advanced stage cHL regimens, but it remains unclear how they will be incorporated into ES cHL. Replacing bleomycin in ABVD with BV per ECHELON-1 or nivolumab per S1826 not only sought to eliminate the risk of BPT but also improve cure rates.[8,9] However, with less room for efficacy improvement in ES cHL, we must rigorously scrutinize toxicities when replacing bleomycin (or abbreviating the chemotherapy course) with BV and/or nivolumab. The only ongoing randomized clinical trial in ES cHL is AHOD2131 (NCT05675410), in which all patients receive ABVDx2 then are randomized after iPET to ABVDx2 or BV/nivolumabx4 if favorable risk and iPET negative (Deauville 1-3). Importantly, iPET-positive patients receive RT following escalated BEACOPP or BV/nivolumabx4 regardless of response. Substituting new agents for RT, instead of adding them to RT, should be explored given continued concerns of late effects in this young population, especially given ≥98% 3-year PFS seen in NIVAHL (nivolumab-AVDx4 + RT in unfavorable risk).[10]

Beyond newer (and better) drugs for cHL, recent studies of circulating tumor DNA (ctDNA) sequencing for measurable residual disease (MRD) testing are also poised to trigger overhauls of the entire response-adapted paradigm in cHL. Interim and end-of-treatment ctDNA MRD appears to outperform the prognostic value of PET, with rising

false positive PET risk as immunotherapies such as anti-PD1 checkpoint inhibitors are increasingly utilized.[11,12] Single-arm ctDNA-based response-adapted studies are underway, with randomized comparisons being planned for the near future that may eventually be entirely bleomycin-free.

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