PET-guided, BEACOPP$_{escalated}$ therapy in advanced Hodgkin lymphoma

The authors of the AHL2011 trial[1] should be applauded for reducing BEACOPP$_{escalated}$ (defined as increased bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) cycles for most patients (346 [84%]) while maintaining similar outcomes to the standard of care group. However, the choice of upfront therapy in a de-escalation model for advanced Hodgkin lymphoma remains a point of debate. Over the past several years, upfront doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) PET-adapted strategies have largely been adopted as standard of care in the USA in an attempt to balance toxicities with adequate lymphoma control.

The SWOG S0816 trial[2] is the most comparable of the upfront ABVD PET-adapted trials to the AHL2011 trial in terms of patients' baseline characteristics (48% stage IV, exclusion of patients with lower risk stage II disease, which comprised 13% of the AHL2011 cohort). Although 5-year progression-free survival is 11·7% higher in the AHL2011 cohort than in the SWOG S0816 trial (86% [95% CI 81–89] *vs* 74% [69–79]), the most important endpoint, overall survival, is similar between trials (95% [95% CI 91–97] *vs* 94% [91–96]) at 5 years.[3] Similar overall survival are reflective of highly effective salvage regimens that are being optimised with newer combinations involving brentuximab vedotin, bendamustine, and nivolumab.[4]

We agree that it is appropriate to caution use of cross-trial comparisons and we understand the difficulty in changing practice based on secondary outcomes, such as overall survival. However, 317 (94%) of 336 patients in S0816 were still alive at 5 years, most of whom only received ABVD and were not exposed to BEACOPP$_{escalated}$ toxic effects. By contrast, upfront BEACOPP$_{escalated}$, even with a PET-adapted strategy, exposes all patients to at least two cycles of BEACOPP$_{escalated}$. To illustrate the impact on side-effect profile, grade 3 or worse haematological toxic effects were higher in patients with negative scans after two cycles of chemotherapy (PET2) AHL2011 than those with PET2-negative scans in SWOG S0816, with more anaemia (24% *vs* <5%) and thrombocytopenia (36% *vs* <5%).[2] Although reported secondary malignancies in AHL2011 only account for 1%, a longer follow-up is needed to assess the true frequency. Ultimately, clinicians are left with a challenging question: do you overtreat for an 11·7% progression-free survival benefit or underexpose in favour of reducing toxicity exposure given no difference in overall survival?

Thus, we respectfully disagree with the authors' conclusion that "PET-driven strategies after ABVD showed inferior results to those after upfront escalated BEACOPP."[1] Admittedly, more refined prognostic tools and molecular markers are required to improve early identification of patients likely to fail upfront ABVD and need upfront BEACOPP$_{escalated}$. However, until a randomised trial comparing PET-adapted upfront ABVD versus PET-adapted upfront BEACOPP$_{escalated}$ shows an overall survival benefit, we should first do no harm and opt for less intensive upfront regimens.

We declare no competing interests.

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