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

Authors' reply

We are delighted that Anthony Perissinotti and colleagues acknowledge in our AHL2011 study[1] that BEACOPP$_{escalated}$ exposure can be reduced in 346 (84%) of 410 patients with negative PET assessment after two cycles of treatment (PET2)without loss of lymphoma control. However, they criticise exposing all patients to at least two cycles of BEACOPP$_{escalated}$ instead of PET-driven upfront ABVD treatments and conclude that starting treatment with the more toxic BEACOPP$_{escalated}$ regimen is useless. This assertion is questionable: haematological immediate toxicity of the first two cycles of BEACOPP is manageable and only two patients (0·4%) died from adverse events in the AHL2011 PET-driven group; secondary primary malignancies frequency was also low (five [1·2%]), even if we acknowledge that a longer follow-up is warranted; and the increased risk of gonadal toxic effects related to BEACOPP compared with ABVD was shown only beyond two cycles.[2] They minimise the fact that starting with BEACOPP$_{escalated}$ provides better disease control in both patients who are PET2 negative or positive, even if no direct, randomised comparison of these approaches is available. Fewer patients were required to be exposed to salvage therapy and transplantation, and also encumbered an increased risk of immediate and long-term toxicity. Perssinotti and colleagues did not mention that most patients chose to receive treatment with curative intent as first-line treatment,[3] which places lymphoma control as a major endpoint for patients, haematologists, and oncologists. Because patients with low international prognosis score also benefit from BEACOPP$_{escalated}$[4] and the biological characteristics of the tumour[5] did not identify which patients require more intense treatment than ABVD, no baseline factor helps in making individual decisions for upfront chemotherapy. Therefore, we estimate that AHL2011's strategy offers a better balance between disease control and treatment toxicity than upfront ABVD PET-adapted treatments in advanced Hodgkin lymphoma.

We agree with Charles Mesguish and colleagues that PET2 assessment alone is insufficient to accurately stratify patients with different outcomes, and to our knowledge, AHL2011 is the first study showing prospectively the added prognosis value of PET4, which improved patients' stratification independently of their PET2 results. Indeed, in a multivariate analysis, the tandem interim PET evaluation after two and four cycles of chemotherapy overcomes the prognosis value of the international prognosis score. On the basis of the available data, it is difficult to affirm that end of treatment could still refine the interim PET-based prognosis assessment in a substantial subset of patients. In the GHSG HD18 study,[6] 188 (13%) of 1439 treated patients had a hypermetabolic residual mass of 2·5 cm or greater, including 155 (35%) of 434 patients in the positive PET2 group and 33 (3%) of 1005 in the negative PET2 group, and received radiation therapy. However, we do not know how many of these patients would had positive PET4. In AHL2011, all relapses in the PET2 and PET4 negative group except one and 12 (80%) of the 15 relapses in the PET2 positive and PET4 negative group occurred after the end of treatment evaluation so were not identified at the end of treatment PET. Altogether, these results suggest that PET4 is probably more suitable than end of treatment PET for the management of patients and early identification of patients who need salvage therapy.

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