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CORRESPONDENCE

Predictive Value of Interim [^{18}F]Fluorodeoxyglucose–Positron Emission Tomography in Advanced-Stage Hodgkin Lymphoma Is Not Well Established

TO THE EDITOR: We read with interest the study by Press et al[1] that included 331 patients with stage III or IV Hodgkin lymphoma (HL) who underwent interim [^{18}F]fluorodeoxyglucose (FDG) –positron emission tomography (PET) after two cycles (PET2) of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine). PET2-negative patients received four additional cycles of ABVD, whereas PET2-positive patients were switched to escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) for six cycles. Importantly, no control arm was used to determine the additional value of this treatment strategy compared with continuation of standard ABVD treatment in terms of progression-free (PFS) and overall survival (OS). After two cycles of ABVD, 271 (82%) of 331 patients acquired FDG-PET–negative status, whereas PET2 was positive in 60 (18%) of 331 patients. The 2-year estimate of PFS for 271 PET2-negative patients was 82%, with 58 patients experiencing treatment failure, and the 2-year estimate of PFS for the 60 PET2-positive patients was 64%, with 20 patients experiencing treatment failure. During follow-up, 17 deaths were reported, including six resulting from HL. Press et al concluded interim FDG-PET response-adapted therapy to be promising, considering the 2-year PFS of 64% for PET2-positive patients, which was described to be much higher than the historically observed 2-year PFS of 15% to 30%.

However, we disagree with the conclusion of Press et al.[1] Their claim that a positive interim FDG-PET results in a dismal prognosis in case of continuation of standard treatment was not supported by a recent meta-analysis on this topic.[2] This meta-analysis showed mixed results among studies, including the subgroup of patients with advanced-stage HL.[2] In particular, studies reporting that a positive interim FDG-PET in advanced-stage HL resulted in low PFS were methodologically flawed, because these studies did not use histopathology or did not report whether histopathology was used to confirm residual disease and instead determined disease relapse by means of follow-up imaging studies.[3,4] Considering the high false-positive rate of follow-up FDG-PET,[5,6] the prognostic value of a positive interim FDG-PET result was likely thoroughly overestimated. Indeed, results of the large-scale HD15 trial[7] that included 191 patients with advanced-stage HL whose FDG-PET scans indicated persistent disease after six to eight cycles of BEACOPP showed that these patients had a good 4-year PFS of 86.2% after being additionally treated with radiation therapy. These findings imply one of the following: HL that even persists after the entire BEACOPP regimen does not require treatment intensification beyond radiation therapy, or FDG-PET during or after antilymphoma treatment is prone to a high false-positive rate (the latter has already been demonstrated by studies in non-HL showing an unacceptably high biopsy-proven false-positive proportion among FDG-avid residual lesions[8,9]). Furthermore, administering a more intensified treatment is only justified when FDG-PET–positive patients have both a proven dismal PFS and OS. Applying intensified therapies to the entire group of interim FDG-PET–positive patients, even though a considerable proportion of patients would have been cured with standard treatment, should be avoided. The fact that only six HL-related deaths were reported among the group of 78 patients with relapsed or refractory disease after first-line therapy underlines that second-line therapies are able to cure a majority of patients with persistent disease after standard therapy. As such, only patients with persistent disease after first-line therapy should be exposed to intensified therapies.

Another important finding is that the 2-year PFS in the PET2-negative group after continuation of standard ABVD treatment was only 81%, which is also much lower than that reported in the historical cohorts.[2-4] The fact that only 60 patients were PET2 positive and the finding that 58 patients in the PET2-negative group experienced disease relapse indicate that at least approximately half of patients who might have benefited from treatment intensification had negative PET2 results. Note that the volume of FDG-active lymphomatous tissue decreases rapidly after treatment initiation.[2,10] As a result of the limited spatial resolution of current PET systems, small residual lymphomatous deposits cannot be detected. This hypothesis is supported by the fact that patients with HL in the palliative setting treated with noncurative therapies or patients with incurable indolent non-HL treated with noncurative chemotherapy may achieve FDG-PET–negative status.

In conclusion, the claim that patients with positive interim FDG-PET scans have a dismal prognosis has not convincingly been proven, and because a control arm in the study by Press et al[1] was lacking, the benefit of treatment intensification for interim FDG-PET–positive patients in terms of PFS and OS remains unknown. Furthermore, at least 50% of patients whose disease will persist after first-line therapy have interim FDG-PET–negative results. Therefore, interim FDG-PET–adapted therapy may not be effective in improving outcome in advanced-stage HL.

Hugo J.A. Adams
University Medical Center Utrecht, Utrecht, the Netherlands

Thomas C. Kwee
University Medical Center Groningen, Groningen, the Netherlands

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Hugo J.A. Adams
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Thomas C. Kwee
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