

Interim PET Assessment of Advanced Hodgkin Lymphoma: Is It Sufficient?

TO THE EDITOR: We would like to draw attention to accumulating evidence on the additional role of end-of-treatment PET/CT in advanced Hodgkin lymphoma (HL) (1,2).

Stephens et al. reported the results of long-term follow-up of HL patients included in the Southwest Oncology Group S0816 trial (1). This trial, which included stage III (52%) and IV (48%) HL patients, aimed to evaluate the benefit of a tailored therapy based on the results of interim ¹⁸F-FDG PET/CT evaluation after 2 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) (PET-2) (3). If PET-2 was positive (Deauville scores 4–5), treatment was switched to 6 cycles of escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP). If PET-2 was negative (Deauville scores 1–3), ABVD chemotherapy was continued for 4 additional cycles. No radiotherapy was planned. An end-of-treatment PET/CT scan was also performed 6–8 wk after the end of chemotherapy (3).

This study showed that a PET-2–driven strategy of personalized therapy is beneficial. The 5-y overall survival of all patients from the Southwest Oncology Group trial was 94% (95% confidence interval, 91%–96%), which is superior to previous cohorts of advanced HL (4). The overall survival of PET-2–negative and PET-2–positive patients was 96% (95% confidence interval, 93%–98%) and 86% (95% confidence interval, 74%–93%), respectively (1). Other prospective trials have also shown that the use of PET-2 as a decisional tool for therapy escalation improves the survival of PET-2–positive advanced-HL patients treated with ABVD, as these patients are historically known to have a poor prognosis (1,5–7).

Centrally reviewed PET-2 scans in Southwest Oncology Group S0816 were negative in 82% of patients (270/331). In this last update, the median follow-up was 5.9 y (1). About a quarter of the patients with negative PET-2 results (64/270) had experienced relapse, highlighting an unsatisfying negative predictive value for PET-2, with an estimated 5-y progression-free survival of 76%. Most relapses (49/64; 77%) occurred during the first 2 y after treatment, with 36% (23/64) occurring less than 8 mo after the last cycle of chemotherapy. Therefore, one may assume that at least 36% of relapses were or could have been detected earlier by end-of-treatment PET/CT. Unfortunately, end-of-treatment PET/CT results for relapsing and nonrelapsing patients are not available (1).

This study, however, echoes the results of the GITIL 0607 trial, which also included stages IIB to IVB HL and started therapy with ABVD (7). Patients with a negative PET-2 result after 2 cycles underwent 4 more cycles of ABVD and were then assessed by end-of-treatment PET/CT. Patients with a positive PET-2 result proceeded to an intensified chemotherapy with 4 cycles of escalated BEACOPP and randomization to additional rituximab versus no rituximab (7). The authors showed that in patients with a negative PET-2 result, obtaining an end-of-treatment PET/CT examination was able to detect more than half the cases of refractory disease or relapse that occurred (47/81; 58%) (7).

Furthermore, Rigacci et al. recently published an interesting study focusing on clinical characteristics and outcomes

of PET-2–negative patients with a positive end-of-treatment PET/CT result who were included in the HD0801 trial (2). In that trial, ABVD-treated advanced-HL patients with a positive PET-2 result were switched to intensification and autologous stem cell transplantation. Patients with a negative PET-2 result continued on 4 more cycles of ABVD and were then assessed by end-of-treatment PET/CT. In total, 395 patients had a negative PET-2 result, of whom 39 (10%) were positive on the end-of-treatment PET/CT. Two patients progressed before end-of-treatment PET/CT could be performed. The pathology results were positive for 15 of 16 performed biopsies, and 38 of 39 patients underwent salvage therapy.

There is now a large body of evidence supporting that we cannot rely solely on a negative PET-2 result to predict the outcome of patients with advanced HL (1–3,6–8). Because a negative PET-2 result in these patients is not synonymous with cure, an end-of-treatment PET/CT examination remains necessary in order to promptly deliver salvage treatment when needed. Patients with primary refractory disease or with early relapse need to be treated without delay, as these patients have a worse prognosis than do advanced-HL patients with late relapse (9).

Thus, both PET-2 and end-of-treatment PET are key procedures for the treatment of advanced HL (stages IIB–III and IV). Interim PET is essential for the early detection of high-risk patients, contributing to their improved survival. Additional evaluation at the end of treatment is a highly important safety net for depicting primary refractory patients that need prompt delivery of salvage therapy.

REFERENCES

- Stephens DM, Li H, Schoder H, et al. Five-year follow-up of SWOG S0816: limitations and values of a PET-adapted approach for stage III/IV Hodgkin lymphoma. *Blood*. 2019;134:1238–1246.
- Rigacci L, Puccini B, Broccoli A, et al. Clinical characteristics of interim-PET negative patients with a positive end PET from the prospective HD08-01 FIL study. *Ann Hematol*. 2020;99:283–291.
- Press OW, Li H, Schoder H, et al. US intergroup trial of response-adapted therapy for stage III to IV Hodgkin lymphoma using early interim fluorodeoxyglucose-positron emission tomography imaging: Southwest Oncology Group S0816. *J Clin Oncol*. 2016;34:2020–2027.
- Moccia AA, Donaldson J, Chhanabhai M, et al. International prognostic score in advanced-stage Hodgkin's lymphoma: altered utility in the modern era. *J Clin Oncol*. 2012;30:3383–3388.
- Gallamini A, Hutchings M, Rigacci L, et al. Early interim 2-[¹⁸F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. *J Clin Oncol*. 2007;25:3746–3752.
- Johnson P, Federico M, Kirkwood A, et al. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. *N Engl J Med*. 2016;374:2419–2429.
- Gallamini A, Tarella C, Viviani S, et al. Early chemotherapy intensification with escalated BEACOPP in patients with advanced-stage Hodgkin lymphoma with a positive interim positron emission tomography/computed tomography scan after two ABVD cycles: long-term results of the GITIL/FIL HD 0607 trial. *J Clin Oncol*. 2018;36:454–462.
- Mesguich C, Cazeau AL, Bouabdallah K, et al. Hodgkin lymphoma: a negative interim-PET cannot circumvent the need for end-of-treatment-PET evaluation. *Br J Haematol*. 2016;175:652–660.
- Sibon D, Morschhauser F, Resche-Rigon M, et al. Single or tandem autologous stem-cell transplantation for first-relapsed or refractory Hodgkin lymphoma: 10-year follow-up of the prospective H96 trial by the LYSA/SFGM-TC study group. *Haematologica*. 2016;101:474–481.

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Reply: Interim PET Assessment of Advanced Hodgkin Lymphoma: Is It Sufficient?

REPLY: Mesguich et al. (1) commented on our publication, which reported the long-term outcome of patients with advanced-stage Hodgkin lymphoma undergoing interim ¹⁸F-FDG PET (after 2 cycles of chemotherapy; PET2) and PET2 response-adapted change in therapy in the SWOG S0816 trial (2,3). Their letter emphasizes the importance of the end-of-treatment PET (PET3). Of the 270 patients with a negative PET2 scan result from the S0816 study, 244 patients (90%) underwent PET3 and 35 of these 244 patients (14%) had a positive PET3 scan result (3). Unfortunately, our study did not mandate biopsy after positive PET3, so we are not able to confirm that all 35 of these patients actually had residual disease. At the time of positive PET3, 13 of the 35 patients were officially categorized as disease progression. Nineteen of the 35 patients initiated salvage therapy shortly after the PET3 scan. Therefore, it remains possible that some of the positive PET3 scans represent a false-positive result. However, we agree with the assessment that the PET3 scan can be a useful tool to identify pri-

mary refractory patients requiring expedited salvage therapy. Nevertheless, PET2 remains very important in the early detection of high-risk patients treated with standard chemotherapy regimens, who are unlikely to show a complete response to therapy, which may justify intensification of treatment at that time, contributing to improved survival (2). In addition, we note that when novel targeted agents such as brentuximab vedotin and nivolumab are used in combination with standard chemotherapy agents, PET2-based responses are not used to alter therapy. As such, the ongoing national SWOG S1826 study compares brentuximab vedotin or nivolumab in combination with adriamycin, vinblastine, and dacarbazine and does not modify therapy based on the PET2 scan results (NCT03907488).

REFERENCES

1. Mesguich C, Bouabdallah K, Bordenave L, Milpied N, Hindié E. Interim PET assessment of advanced Hodgkin lymphoma: is it sufficient? *J Nucl Med.* 2020; 61:1694–1695.
2. Press OW, Li H, Schoder H, et al. US intergroup trial of response-adapted therapy for stage III to IV Hodgkin lymphoma using early interim fluorodeoxyglucose-positron emission tomography imaging: Southwest Oncology Group S0816. *J Clin Oncol.* 2016;34:2020–2027.
3. Stephens DM, Li H, Schöder H, et al. Five-year follow-up of SWOG S0816: limitations and values of a PET-adapted approach with stage III/IV Hodgkin lymphoma. *Blood.* 2019;134:1238–1246.

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