Interim positron emission tomography in limited-stage diffuse large B cell lymphoma: A modern will-o'-the-wisp?

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Fox Chase Cancer Center, Temple University School of Medicine, Philadelphia, Pennsylvania; Department of Pathology, Mayo Clinic, Scottsdale, Arizona; Section of Hematology/Oncology, University of Chicago, Chicago, Illinois, USA.) Positron emission tomography-directed therapy for patients with limited-stage diffuse large B-cell lymphoma: Results of Intergroup National Clinical Trials Network Study S1001. *J Clin Oncol* 2020;**38:**3003–11.

SUMMARY

In the S1001 trial published in the *Journal of Clinical Oncology*, the authors show the use of an interim positron emission tomography and computed tomography (PET-CT) adapted approach after three cycles of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (RCHOP) in limited-stage diffuse large B cell lymphoma (DLBCL). In this phase 2 trial, 132 patients received three cycles of RCHOP and underwent interim PET-CT on days 15–18 of the third cycle. Those with interim PET-negative scan received one more cycle of RCHOP (a total of four cycles), whereas those with an interim PET-CT-positive result received radioimmunoconjugate ibritumomab tiuxetan plus involved-field radiation therapy (IFRT) as consolidation treatment.

A majority of patients (89%) had an interim PET-CT-negative scan. Only 12 of 132 patients received augmented consolidation therapy. In RCHOP-only arm, 5-year progression-free survival was 89% (95% CI 80%–94%), and in the ibritumomab arm, it was 86% (95% CI 54%–96%); both arms did remarkably well. Six patients relapsed, 4 of whom had no evidence of disease on interim PET-CT. As we reviewed this interesting study, a pertinent question arose: Is interim PET-CT meaningful in the management of limited-stage DLBCL, or could four cycles of RCHOP be the standard approach without actually doing an interim PET-CT.

COMMENT

The controversy surrounding interim PET-CT encompasses all its aspects: timing, method of assessment, relevance to prognosis, and value to guiding therapy. In a study by Moskowitz *et al.*,[1] 33 of 38 patients with interim PET-CT positivity had biopsy negative for the presence of disease and prognosis was equivalent to those whose interim PET-CT was negative. There was no histopathological confirmation of an interim PET-positive result in the S1001 trial. Given the high possibility of a high false-positive rate of interim PET-CT in DLBCL,[2] we cannot rule out that the 12 patients who went on to receive IFRT plus ibritumomab tiuxetan were over-treated. Pregno *et al*. found that 12 of 19 patients, who had evidence of disease in the interim PET-CT done after two cycles, became negative in the PET-CT evaluation done after completion of four cycles of therapy, thereby questioning the appropriateness of its timing.[3] Trials of interim PET-CT assessment are further confounded by different methods of ascertaining PET-positivity: Deauville 5-point scale, change in maximum standardized uptake or the older International Harmonization Project (IHP), which make correlation among different studies difficult.[4]

Limited-stage DLBCL without bulky disease did remarkably well with four cycles of RCHOP followed by two cycles of rituximab in the recent FLYER trial,[5] which along with 89% of patients from S1001 trial suggests the likelihood of four cycles of chemo-immunotherapy being sufficient for most patients. Six patients in the S1001 trial progressed, 4 of whom were showing no evidence of disease in the interim PET-CT; the remaining 2 were insufficiently treated due to patient refusal. This raises a question of whether the strategy of escalation of therapy with radioimmunotherapy in limited-stage DLBCL used in this study was applied to the appropriate patient population, given that interim PET-CT-positivity did not predict for relapse. The limited number of events in the S1001 trial makes it difficult to conclude that the adaptive approach with escalation of therapy by adding ibrutumomab tiuxetan is beneficial. Indeed, limited-stage DLBCL has distinct biology; it shows a pattern of late and continuous relapses distant from the original site of disease.[6] Thus, IFRT, which plays a role in preventing locoregional relapse, may not be able to address the question of late relapses. The short median follow-up of 4.92 years in the S1001 study precludes us from interpreting the impact of ibritumomab, a novel therapy, on prolonging the disease-free survival in limited-stage DLBCL.

Modification of therapy based on interim PET-CT is well established in Hodgkin lymphoma[7] but is regarded experimental in DLBCL. Dührsen *et al*. used interim PET-CT modified therapy after two cycles in aggressive lymphomas (>70% of whom were DLBCL), with randomization either to Burkitt protocol or continuation of four cycles of RCHOP based on interim PET-CT-positivity by △SUVmax; they found interim PET-CT-positivity in 12.5% of patients and failure of escalated therapy to improve outcomes with increased toxicity.[8] The French group, GELA, administered patients with high-risk DLBCL either of two induction therapies: RCHOP or rituximab doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone, followed by consolidation based on interim PET-CT adapted method: Positive PET-CT after two cycles received autologous stem cell transplant (ASCT). Evaluated either by the IHP criteria or by △SUVmax, patients having positive interim PET-CT after two cycles failed to show benefit of ASCT.[2]

Interim PET-CT assessment at best helps in identifying chemosensitive disease in those who test negative. Once we exclude the false-positives from the interim PET-CT-positive subset, we are left with chemorefractory patients, a small fraction of the total, who do not seem to respond to any form of escalation therapy. This is true for limited-stage and advanced-stage DLBCL. Perhaps, four cycles of RCHOP may be considered as standard in all limited-stage DLBCL without the need for an interim PET-CT.

Unlike CT scan, which has become ubiquitous, PET-CT as an imaging modality is scarce in India. Notably, PET-CT is also an expensive modality of investigation, limiting its use in resource-constrained settings. There is an added burden of unnecessary radiation exposure. Ibritumomab is an experimental, scarcely available, expensive modality and requires special expertise for its administration. The current study does not provide enough evidence for it to be considered in our armamentarium to treat limited-stage DLBCL. Until we have better treatment options for these non-responders, the role of interim PET-CT determined therapy in clinical practice will remain controversial.

Conflicts of interest. None declared

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