Interim ^{18}F-FDG PET in Diffuse Large B-Cell Lymphoma: Emerging Worldwide?

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Over the last decade, the disease that has benefited the most from the introduction of anti-CD20 immunotherapy has been diffuse large B-cell lymphoma (DLBCL). The most widely used regimen for DLBCL today is immunochemotherapy combining cyclophosphamide, adriamycin, vincristine, and prednisone with rituximab (namely R-CHOP), although other regimens have shown superiority in molecular subtypes of the disease (*1*). Overall, R-CHOP is highly efficient, with event-free survival in excess of 75% at 2 y regardless of patient age (*2*). However, these results need to be optimized in patients with refractory disease that does not respond to initial therapy and requires a rapid shift toward more aggressive regimens. Such intensified treatments, including autologous transplantation, may in turn increase the risk of non–lymphoma-related morbidity and mortality. Defining the prognosis in the individual patient as early as possible is therefore of paramount importance. Age-adjusted International Prognostic Index, tissue phenotype, and gene expression are well-known prognostic factors at diagnosis but provide little information during the early phase of treatment and lead to few validated therapeutic changes.

^{18}F-FDG PET is currently used in DLBCL for staging, assessment of remission and recurrence, and evaluation of therapeutic efficacy at various time points. The prognostic value of end-of-treatment ^{18}F-FDG PET (ePET) in aggressive non-Hodgkin lymphoma remained unchallenged since its first report in 2001 (*3*). The value of interim PET (iPET) proved variable, and enthusiastic conclusions were tempered by more cautious recommendations (*4,5*).

Carr et al., in the December 2014 issue of *The Journal of Nuclear Medicine* (*6*), presented a large, multicentric study in a quite homogeneous population. They confirmed the high accuracy of ePET as a prognosticator but failed to fully reproduce previous results with iPET performed after 2 or 3 cycles of R-CHOP. The study, sponsored by a Coordinated Research Project of the International Atomic Energy Agency (IAEA), managed to collect data from 9 countries over 5 United Nations geographic areas, including countries with high income (105 patients), upper-middle income (170 patients), and low-middle income (52 patients). Patients were treated locally according to a standard R-CHOP regimen. iPET and ePET data were prospectively collected between 2008 and 2011. Treating physicians were aware of the iPET results, but modification of the planned treatment was not permitted unless progression required early escalation (3 patients). Heterogeneity analysis did not show significant differences between countries, with the exception of Chile. Analyzable data were available for 327 of 383 patients after exclusion of 22 patients who did not meet the inclusion criteria and patients from one country that failed to provide PET data for central revision. This successful recruitment resulted in the largest study that has yet investigated the prognostic role of iPET with visual analysis.

An important contribution of the study was to demonstrate the global applicability of PET data generated in the Western world. The lack of heterogeneity between countries based on clinical risk factors and the highly consistent prediction of outcome across participating countries showed that the diversity of health care systems is not a hurdle to internationally applying methodologies originating from developed countries in daily oncology practice. It also showed that with relatively limited funding dedicated to data collection and analysis, structured international efforts are prone to assess the value of a specific diagnostic methodology across the world, including emergent countries. The support of international sponsors such as, but not only, the International Atomic Energy Agency is highly recommended in future trials as they may provide worldwide exchange of data, training, and expertise.

iPET is currently widely used in DLBCL and considered by many clinicians to be a key tool in patient care. Nonetheless, the predictive value of iPET has not been consistent throughout the numerous studies published since 2002 (*4,7*). This is true both for the negative predictive value—that is, the capacity of a negative iPET result to predict favorable outcome in terms of either progression-free or overall survival—and for the positive predictive value. The few first reports were positive and suggested that ^{18}F-FDG PET performed early after initiation of therapy served as an in vivo marker of tumor sensitivity. Many methodologic issues arose, the most relevant being the definition of *interim,* namely 2, 3, or 4 cycles of chemotherapy; the heterogeneity of the patient population; the retrospective nature of the data; the definition of *response* and *residual disease*; and, recently, the addition of semiquantitative data. The approximately 70 reports found in a February 1, 2015, search of PubMed using the key words {interim and PET and DLBCL} demonstrate a wide heterogeneity in patient selection and evaluation criteria. In view of this heterogeneity, most studies are therefore valid but hardly comparable.

The study by Carr et al. (*6*) included a relatively homogeneous population of patients and standardized treatment, with the exception of the 14% of the patients who did not receive rituximab (interestingly, those patients did not behave differently from the rest of the cohort). A composite index was used for analysis that, using current semantics, can be translated into a score of 4 or 5 for positive

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^{18}F-FDG PET findings, 1 or 2 for definitely negative findings, and 3 for complete response with minimal residual uptake. Patients who had a score of 3 were later aggregated with patients who had a score of 1 or 2 after it was shown that these 2 groups had a similar outcome. Most patients were scanned at interim after cycle 2 or 3, and this timing may be substantially different from the scanning at cycle 4 done in other studies. Assuming that each cycle of immunochemotherapy has a similar effect (i.e., first-order kinetics)—let us say, 1 log per cycle—after 2 cycles 1% of the initial 10^{11} neoplastic cells would remain viable (a detectable number) whereas after 4 cycles only 0.01% of the initial neoplastic cells would survive (a number below the detection limit of 10^7 cells) (*8*). iPET at cycle 2 shows a mix of residual cancer cells and possible inflammation; iPET at cycle 4 may show resistant cells and potential tumor regrowth. Clinically, this finding confirms the excellent negative predictive value of iPET at cycle 2/3 and, at the same time, the suboptimal positive predictive value of iPET. The data of Carr et al. nicely illustrate this by identifying a significant subgroup of patients who were iPET-positive/ePET-negative and who eventually had an outcome closer to that of iPET-negative/ePET-negative patients than to that of ePET-positive patients. These "slow responders," though, have approximately double the risk of developing further events. It is not surprising that the proportion of patients with bulky disease was larger in this subgroup than in the entire cohort. These findings clearly indicate the need for other prognostic factors to stratify patients on the basis of iPET. As previously reported, performance status (i.e., according to the scoring systems of the World Health Organization and the Eastern Cooperative Oncology Group) and raised lactate dehydrogenase level were found in a multivariate analysis to be the only predictors of late outcome; iPET results were not. However, performance status and lactate dehydrogenase level did not distinguish well between iPET-positive patients who eventually had a good outcome and those who had a poor outcome, as illustrated by the 84% overall survival at 2 y in the 39% of the subjects with iPET-positive and -negative prognostic factors. On the basis of published literature, it is tantalizing to use iPET to reorient treatment earlier. The International Conference on Malignant Lymphoma Imaging Working Group recently issued recommendations on the use of iPET (*7*). Their statement that "currently, it is not recommended to change treatment solely on basis of iPET unless there is a clear evidence of progression" is fully supported by the findings of Carr et al. Ongoing clinical trials are evaluating the role of ^{18}F-FDG PET in response-adapted therapy.

Semiquantitative measures might be capable of improving visual analysis of response assessment in DLBCL, but further validation in clinical trials is required (*7*). For historical and technical reasons, the international cohort study published by Carr et al. did not use quantification (i.e., change in maximum standardized uptake value). When the study commenced, there was only initial evidence that quantification might be useful. To overcome the lack of reproducibility of visual interpretation (*9*), accurate and reproducible quantitative data are mandatory. Harmonized and strict acquisition protocols are thus required, especially with regard to time elapsed between ^{18}F-FDG injection and scanning, thorough validation of the scanner, and use of standardized reconstruction processes. These requirements could hardly have been met in this study. With extended access to modern scanners, these requirements can soon be met. Such a trial would reinforce the strength of the many valuable efforts dedicated to more reliable early assessment of tumor response using quantitative tools (*10*). The combination of clinical indices, visual data, and semiquantitative data was shown to better discriminate patients at interim evaluation (*11*). The ultimate goal should be to identify potential slow responders, namely those patients with a Deauville 5-point score of more than 3 at cycle 2, a substantial change in maximum standardized uptake value (the threshold of which still needs to be defined), and clinical markers of disease aggressiveness at baseline. These patients are probably those who deserve a second iPET study at cycle 4. A large (worldwide) consortium is needed to assess this hypothesis and better stratify patients at cycle 2 iPET. Procedure guidelines such as those provided by the Society of Nuclear Medicine and Molecular Imaging and the European Association of Nuclear Medicine should be strictly followed, and accreditation of the scanners is recommended using EANM Research Ltd. or the North American Quantitative Imaging Biomarker Alliance (*12*). With these requirements being met, we are confident that such a study is feasible and could shortly provide the missing link in therapeutic stratification of DLBCL.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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