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PET response–guided radiotherapy for advanced DLBCL?

Andrew Wirth[1] and N. George Mikhaeel[2] | [1]Peter MacCallum Cancer Centre; [2]Guy's & St. Thomas' NHS Trust

In this issue of *Blood*, Freeman and colleagues report long-term outcomes in a large, population-based cohort of 723 patients with advanced diffuse large B-cell lymphoma (DLBCL) treated with 6 to 8 cycles of rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) and a consistent policy of end-of-therapy (EOT) positron emission tomography (PET)-guided radiotherapy (RT).[1] EOT PET-negative patients did not receive RT and had an 83% 3-year time to progression (TTP), with the authors suggesting such patients may reasonably be spared RT. A second key finding was that selected patients who received RT to nonprogressive, anatomically suitable EOT PET-positive sites had outcomes comparable to those in the PET-negative cohort.

This study provides a robust benchmark for outcomes of EOT PET-negative patients after R-CHOP without adjuvant radiation. Based on the 83% 3-year TTP and subset analyses showing near identical outcomes for patients with or without bulky disease (>10 cm), or with or without skeletal disease at diagnosis, the authors recommend that RT should be routinely avoided for such patients. However, this recommendation requires careful consideration, particularly as this was not a randomized trial addressing that question. Although the 83% 3-year TTP for PET-negative patients was good, an eventual progression rate of at least 25% was observed (Figure 1A in Freeman et al), consistent with previous reports of a 70% to 75% progression-free survival (PFS) for EOT PET-negative patients.[2] With 25% of EOT PET-negative patients experiencing treatment failure, potentially effective adjuvant therapies, including RT, remain a relevant consideration. This is particularly important given the very poor outcome of relapsed DLBCL post–R-CHOP, even in the chimeric antigen receptor T-cell era.

The benefit of adjuvant RT for bulky/advanced DLBCL has been debated for 2 decades. "Proof of principle" for the efficacy of RT was provided by Eastern Cooperative Oncology Group-1484, a randomized trial in which RT following CHOP increased PFS by 16%.[3] In the R-CHOP era, the only randomized trial of RT for bulky DLBCL, "UNFOLDER," was not PET-guided and has been reported only in abstract form. This study reported a 16% increase in event-free survival (EFS) ($P = .0001$), including an 8% higher PFS ($P = .221$), with RT. As EFS included RT given for residual masses (which do not always represent disease), applicability in the PET era is not straightforward.[4] Notable among nonrandomized studies, the RICOVER trial reported a 26% higher EFS with RT after R-CHOP for elderly patients with bulky disease (per protocol analysis) and an MDACC study reported a 15% higher 5-year PFS associated with the addition of RT in 295 patients in complete response (CR) after R-CHOP.[5,6] These data, together with multiple other nonrandomized and population-based studies, consistently suggest a possible overall benefit of up to 15% associated with adjuvant RT after R-CHOP.

The key question in the PET era is how the reported benefits of RT are distributed across EOT PET-positive and -negative populations. The observational design of the study reported by Freeman et al does not allow a benefit of RT in PET-negative patients to be quantified (or excluded, particularly in patient subsets). Similarly, the nonrandomized "OPTIMAL" study limited RT to PET-positive patients following R-CHOP–like therapy and used the RICOVER trial as a historical comparator, making it difficult to draw definitive conclusions about the benefit of RT.[5,7]

Given the heterogeneity of EOT PET-negative patients, it may be helpful to consider whether specific disease characteristics, such as initial bulk, disease stage/distribution, and the presence of a residual mass, may help select patients potentially benefiting from adjuvant RT. Bulk has been reported to be a prognostic factor and traditionally been considered an indication for RT.[5] Freeman et al did not identify bulk as a prognostic factor in PET-negative patients and infer from this that patients with bulky disease cannot benefit from RT. However, it is important to distinguish the prognostic and potential predictive value of bulk. Although patients with and without bulk may have similar total tumor burdens (and prognoses), some patients with bulk may have much (or for stage I to II, all) of their tumor burden located locoregionally. For such patients, improved local control conferred by RT may translate to improved overall outcomes.

Interim PET response and the presence of a residual mass have also been reported to identify patients potentially benefiting from RT. For example, progression has been reported to occur at positive sites on interim (but not EOT) PET.[8] At least 2 studies suggested a benefit of RT for patients failing to achieve a CR on computed tomography following chemotherapy in the pre-PET era.[5,9] Even in the PET era, a residual mass may confer an increased relapse risk and plausibly identify a patient subset that might benefit from RT.[10]

Emerging PET parameters, such as metabolic tumor volume, indices of disease distribution, and quantitative markers of response, may have potential to identify patients likely to benefit from RT. Large (ideally randomized) trials with careful documentation of all these variables are needed to more robustly identify factors predicting a benefit from RT in EOT PET-negative patients.

RT toxicity considerations are of course important in clinical decision making. However, the acute toxicity of small

involved-site RT volumes and doses of 30 Gy or less is typically mild, and major long-term morbidity (even in head and neck and thoracic locations) is very uncommon using modern planning techniques. There is little evidence for elevated second malignancy risk following RT in the age range commonly affected by DLBCL. Thus, toxicity concerns should not unduly deter the use of RT when clinical benefit is expected.

Freeman and colleagues also report that selected patients who were EOT PET-positive and received RT had better than expected outcomes. The occurrence of false-positive PET results is of course well recognized, but it is likely that a proportion of these patients had residual disease eradicated by RT. This finding is supported by the OPTIMAL trial, among others. These results suggest that for patients who are PET-positive after R-CHOP, the use of salvage RT may be considered for localized, nonprogressive PET abnormalities, particularly when a confirmatory biopsy is difficult, and for patients unfit for salvage therapy and autologous stem cell transplant.

Freeman and colleagues' data confirm that a policy of no radiation in EOT PET-negative patients delivers acceptable results for many patients. This is important information for both current practice and for guiding further research into the selection of patients for additional therapies. As treatment failure occurs in 1 in 4 PET-negative patients with bulky/advanced DLBCL after R-CHOP, and aggressive salvage therapies are toxic, often ineffective, and not suitable for frail or elderly patients, there remains significant room for improvement. Up to 15% of all patients treated with R-CHOP for bulky/advanced DLBCL may benefit from RT, and a proportion of these patients are likely within the EOT PET-negative cohort. Although further research is required to resolve uncertainties regarding the potential benefit of adjuvant RT for patient subsets as noted above, the available evidence provides a reasonable basis on which to consider the use of modern RT for appropriately selected patients with DLBCL.

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LYMPHOID NEOPLASIA

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BiTtEn by Src inhibitors

Philippe Rousselot | Centre Hospitalier de Versailles; Université Versailles Saint-Quentin-en-Yvelines et Paris-Saclay; UMR1184

In this issue of *Blood*, Leonard et al report that the dual Src/ABL inhibitors dasatinib and ponatinib inhibit in vitro blinatumomab-induced T-cell activation in blood samples from patients with Philadelphia chromosome positive acute lymphoblastic leukemia (Ph^+ ALL).[1]

Patients with Ph^+ ALL are typically treated with the combination of conventional chemotherapy and a tyrosine kinase inhibitor (BCR-ABL1 inhibitors). This approach is supported by a significant improvement in survival compared with chemotherapy alone.[2] All available tyrosine kinase inhibitors (TKIs) have been evaluated from imatinib to second- and third-generation TKIs. No improvement in survival has been formally demonstrated favoring 1 TKI over the others. However, second- and third-generation TKIs induce a deeper reduction in minimal residual disease (MRD) levels after induction or during consolidation and ponatinib remains the only option if the T315I BCR-ABL1 kinase domain mutation is detected. The choice of the chemotherapeutic regimen will depend on age and fitness and ranges from full dose to reduced intensity regimens.[3,4]

Blinatumomab is a bispecific T-cell engager approved for relapsed or refractory ALL, including Ph^+ ALL, and for treatment of MRD positivity after chemotherapy. The combination of blinatumomab and TKIs is a reasonable next step to pave the way toward chemo-sparing therapy in Ph^+ ALL for induction or salvage therapy. Our enthusiasm for this approach may be tempered by the results presented here by Leonard et al. Using primary B cells from Ph^+ ALL patients, they investigated whether dasatinib or ponatinib would prevent T-cell activation