If systemic treatment is effective enough to reliably control not only microscopic but also bulky disease, there will be little role for radiotherapy. And if systemic treatment cannot even reliably control microscopic disease, let alone macroscopic disease, there will be little role for radiotherapy, either. However, there are patients who fall into neither of these categories, and in them radiotherapy may well have a role.

The role of radiotherapy (RT) for early/favorable diffuse large B-cell lymphoma (DLBCL) is not a simple binary yes-or-no issue, but rather is a function of the effectiveness of the systemic treatment. If systemic treatment is effective enough to reliably control not only microscopic but also bulky disease, there will be little role for RT. And if systemic treatment cannot even reliably control microscopic disease, let alone macroscopic disease, there will be little role for RT, either. However, there are patients who fall into neither of these categories, and in them radiotherapy may well have a role.

The role of RT has been evolving to complement chemotherapy since the establishment of the CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) regimen as the modern standard of care about 2 decades ago. Two phase III studies addressed the role of RT in the management of stage I and II DLBCL in the pre-rituximab (Rituxan) era. The SWOG study[1] compared 3 cycles of CHOP followed by involved field RT vs 8 cycles of CHOP alone. The ECOG study[2] compared observation vs consolidation RT for patients who had achieved a complete response (CR) with 8 cycles of CHOP. The advantage from adding RT—in terms of failure-free and overall survival—that was observed early in both trials disappeared with longer follow-up, but this was mainly due to systemic failures. This is particularly well demonstrated in the SWOG study, in which patients treated with 3 cycles of chemotherapy experienced more distant failures compared with the patients treated with 8 cycles.[1] Also, we now know that both of these studies, which were based mainly on the Ann Arbor stages, had somewhat heterogeneous patient populations compared with what might be seen in the current era of the International Prognostic Index (IPI).

The GELA LNH 93-1 and 93-4 trials included not only Ann Arbor stage I and II disease in the eligibility criteria, but also no IPI adverse prognostic factor. GELA LNH 93-1[3] compared ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone) followed by consolidation chemotherapy vs 3 cycles of CHOP followed by consolidation RT in patients ≤ 60 years of age and suggested that intensification of chemotherapy could reduce the role of RT. However, it leaves unresolved the further question of whether adding RT to the ACVBP regimen would have improved the outcome, since 41% of the failures involved the initial sites of the disease. GELA LNH 93-4[4] compared 4 cycles of CHOP with RT vs 4 cycles of CHOP without RT for patients > 60 years of age. Although this trial demonstrated no benefit from adding RT to 4 cycles of CHOP, it also left open the question of whether there was a potential benefit of RT in a subgroup of patients (such as those with bulky disease), since the study was not powered to detect such a benefit. Among the patients treated with CHOP alone whose disease recurred, the recurrence was in the initial site in 47%. Compare this with the 21% in-field recurrence rate among the patients treated with combined modality therapy whose disease recurred: these results again emphasize that a gain in local control with RT may be lost depending on the specifics of systemic treatment. It should be noted that both the GELA trials, LNH 93-1 and 93-4, were conducted before the rituximab era. An exploratory study of the MInT trial[5]
showed that the addition of rituximab reduced but did not eliminate the adverse prognostic effect of tumor bulk when patients aged 18 to 60 years with low IPI scores were treated with CHOP-like chemotherapy. The UNFOLDER study (DSHNHL 2004-3) is currently addressing the role of RT in patients aged 18 to 60 with an age-adjusted IPI score of 1, or an IPI score of 0 with bulky tumor (≥ 7.5 cm), when treated with 6 cycles of CHOP + rituximab (RCHOP)-21 or RCHOP-14.

A recent report from the German High-Grade Non-Hodgkin Lymphoma Study Group on patients aged 61 to 80 with DLBCL suggested that, after a median observation time of 17 months, the addition of RT to therapy for patients with bulky disease had no benefit for those who achieved CR with 6 cycles of RCHOP-14,[6] although there was a benefit for those who achieved a partial response. However, clinical trials that attempt to use a risk-adapted approach by utilizing interim FDG-PET have resulted in conflicting outcomes depending on the patient population and treatment regimen, making a categorical statement about the role of radiation therapy in this risk-adapted approach difficult at this time.

In summary, we need to weigh the potential risks and benefits of consolidation RT for each patient in the context of ever-evolving prognostic factors and the chemotherapy regimen used. We need to keep in mind that for the same involved field—for example, the right axilla—the risk/benefit ratio for consolidation RT is quite different when this involved field is in a 20-year-old woman compared with when it is in a 70-year-old man. We also need to consider that the therapeutic ratio of RT will continue to improve with advances in such technologies as IMRT, IGRT, and respiration-gated treatment. There will continue to be subsets of patients for whom the benefits of RT outweigh the risk, and the decision to add RT needs to be individualized for each patient.

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