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EDITORIAL

20 Gy Versus 30 Gy: Will it Make a Difference?

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In the current issue of the Journal, Kelsey et al., report on a phase 2 trial evaluating the use of a lower than conventional dose (20 Gy) as consolidation therapy for patients with bulky or nonbulky stage I to IV diffuse large B-cell lymphoma (DLBCL) or mediastinal large B-cell lymphoma (MLBCL) who have achieved a complete response to 4 or more cycles of conventional chemoimmunotherapy.[1] The conventional dose in this setting has been 30 to 36 Gy.

The primary endpoint was freedom from local recurrence. With a median follow-up of 4+ years, only 1 patient developed disease progression within the radiation field. The local control rate was 98%, which is similar to reported outcomes in previous combined-modality therapy experience for DLBCL.[2,3]

Radiation therapy is the most effective single agent for the treatment of lymphoma. The continued challenge we have as radiation oncologists is to provide this therapy safely. We can accomplish that with reduction in field size and the use of advanced radiation therapy techniques such as intensity modulated radiation therapy/volumetric modulated arc therapy or proton therapy, as well as maneuvers such as deep inspiration breath hold. But perhaps the simplest approach is to reduce the radiation dose. Several trials in lymphoma have tested this possibility and confirmed the efficacy of lower doses in specific situations, including the German Hodgkin Study Group HD10 trial[4] and the British National Lymphoma Investigation/National Cancer Research Institute trial.[5]

For DLBCL, the British National Lymphoma Investigation/National Cancer Research Institute trial tested 30 Gy versus 40 to 45 Gy for a variety of scenarios for patients with DLBCL and concluded there was no difference. In large trials from the German non-Hodgkin lymphoma study group, a dose of 36 Gy was often used for patients with bulky or extranodal disease.[6] Based on these trials, 30 to 36 Gy has been adopted as the standard dose range in combined modality therapy for DLBCL by the National Comprehensive Cancer Network (NCCN).[7]

Interpretation of the current study and its utility moving forward is complicated by the diverse characteristics of the study population. Patient stage (I-II vs III-IV), histology (DLBCL vs MLBCL), number of cycles (4 vs 6) and type of chemotherapy (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP] vs dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin [DA-EPOCH-R]) are all important variables that will need to be considered in the clinical trial that the authors indicate is being planned. A multi-institutional trial would generate larger numbers which would permit focusing on more specific groups of patients. Because MLBCL is relatively uncommon compared with DLBCL, and because there are special considerations for MLBCL treated with R-CHOP versus DA-EPOCH-R, a purer study would be limited to DLBCL. Within this cohort there are 3 populations to consider: stage I to II nonbulky, stage I to II bulky, and stage III to IV bulky.

For patients with stage I to II nonbulky disease, the NCCN endorses 3 possible treatment programs: 3 cycles of R-CHOP followed by involved-site radiation therapy (ISRT) (30-36 Gy) (level 1 quality of evidence); 6 cycles of R-CHOP with or without ISRT (30-36 Gy); or 4 to 6 cycles of R-CHOP-14 with or without ISRT (30-36 Gy) (the "Lamy" regimen).[8] However, the study of Kelsey et al. included no patients who had only 3 cycles of chemotherapy. Will 20 Gy ISRT work as well with only 3 cycles of chemotherapy as it did with 4 to 6? If so, perhaps more

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oncologists would be willing to forgo the choice of 6 R-CHOP with or without ISRT in favor of 3 R-CHOP plus 20 Gy. This would be a much less toxic program, especially with respect to cardiotoxicity.[9] However, R-CHOP × 3 plus 20 Gy ISRT would still have to compete with the Lamy approach, in which patients who are positron emission tomography negative (Deauville 1-2) after just 4 cycles of R-CHOP-14 receive no consolidative irradiation. Here the trade off would be just 1 cycle of chemotherapy versus 20 Gy ISRT.

For patients with bulky stage II disease, the NCCN recommends R-CHOP × 6 with or without ISRT (30-36 Gy). Many oncologists already refer patients with bulky disease for consolidative irradiation. Will more do so if the radiation dose is reduced from 30 to 20 Gy?

For patients who have stage III to IV with bulk, after achievement of a complete response to chemotherapy, the NCCN suggests to "consider ISRT to initially bulky sites." In a prospective clinical trial for these patients, the eligibility criteria should be carefully defined and the ISRT should be restricted to initially bulky sites, as it was in the German trials, without an attempt to irradiate all initial sites of disease.

Should 20 Gy pass the muster as a consolidative treatment in these settings, it will decrease radiation-related risks for the patients we treat, which is commendable. However, will this 10 Gy reduction in dose result in more oncologists being willing to accept the added benefit that radiation provides and refer those patients for consolidative therapy? That is the important question, and only time will tell.

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