EDITORIAL

Routine consolidation of early stage primary bone lymphoma with radiation therapy does not improve outcomes

Marc S. Hoffmann

Division of Hematologic Malignancies and Cellular Therapeutics, University of Kansas Cancer Center, Kansas City, KS, USA

Correspondence: M. S. Hoffmann
mhoffmann@kumc.edu

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Since the discovery that radiation therapy could be delivered with curative intent to a subset of patients with lymphoma, such therapy has been an important part of the management of lymphoproliferative disorders. However, with improvements in systemic therapy and recognition of long-term adverse effects,[1] radiation therapy has played an ever smaller role in the treatment of diffuse large B-cell lymphoma (DLBCL). As an example, in the large, randomized MInT study that accrued over 800 patients and helped to establish that the addition of rituximab to cyclophosphamide, doxorubicin, vincristine and prednisone chemotherapy (R-CHOP) chemotherapy improved survival, radiation therapy was given as protocol-planned consolidation therapy to all sites of extranodal and bulky disease.[2] In contrast, essentially all modern studies in the treatment of advanced stage DLBCL consider administration of radiation therapy to be an event denoting progression. We have moved from planned consolidative radiation therapy to delivering radiation therapy more selectively.

One area of ongoing controversy regarding the role of radiation therapy in DLBCL management is in the setting of limited stage disease. Table 1 summarizes outcomes from selected, prospective studies in early stage DLBCL which form the basis for current treatment recommendations.[3-8] These existing data can leave the treating physician in a quandary regarding optimal treatment for an individual patient with early stage DLBCL. If a patient otherwise meets criteria for the FLYER study but is 68 years old, do those data apply? Would a patient with stage II disease and a primary mass measuring 10.5 cm be eligible for combined modality therapy (CMT) or is that patient obligated to have a longer course of systemic therapy? Does the site of disease matter?

Enter the study by Rezazadeh *et al.*, published in this is-

Table 1. Outcomes in selected prospective studies in early stage diffuse large B-cell lymphoma.

Study (ref)	Critical inclusion criteria	Critical outcomes
ECOG 1484[3]	Stage I bulky (>10 cm) Stage I-E, II or II-E	Addition of RT to CHOP x 8 improved PFS but not OS
SWOG 8736[4,5]	Stage I, stage I (bulky, ≥10 cm) Stage II (non-bulky, <10 cm)	CHOP x 3 → RT equivalent to CHOP x 8
SWOG 0014[6]	Stage I, I-E Stage II, II-E (<10 cm) IPI of at least 1	R-CHOP x 3 → RT 2-yr PFS was 84%
SWOG 1001[7]	Stage I regardless of bulk Stage II non-bulky (<10 cm)	R-CHOP x 4 5-yr PFS of 87% in pts with CR on interim PET/CT after 3 cycles
FLYER[8]	Stage I or stage II non-bulky (<7.5 cm) IPI = 0	R-CHOP x 4 → R x 2 non-inferior to R-CHOP x 6 with 3-yr PFS of 96%

ECOG: Eastern Cooperative Oncology Group; RT: radiation therapy; CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone; PFS: progression-free survival; OS: overall survival; SWOG: Southwest Oncology Group; IPI: International Prognostic Index; R-CHOP: rituximab plus CHOP; yr: year; pts: patients; CR: complete response; PET: positron emission tomography; CT: computed tomography; ref: reference.

sue of *Haematologica*.[9] The authors analyzed 112 patients with stage I-E or stage II-E primary bone lymphoma in the post-rituximab era who were treated at 13 academic centers between 2005-2019. Stage II-E patients were only included if they had loco-regional adenopathy amenable to radiation therapy in a single field. Overall and relapse-free survival outcomes were obtained with multivariate analysis comparing radiotherapy *versus* no radiotherapy and also comparing <36 Gy or ≥36 Gy radiotherapy. The results were clear: there was no significant difference in overall or progression-free survival between the two arms. Additionally, higher doses of radiotherapy (≥36 Gy) were not associated with improved outcomes compared to doses <36 Gy. Not surprisingly, given the choices between regimens, patients in the CMT arm of the study received fewer doses of systemic therapy compared to patients in the arm receiving chemotherapy alone (4.5 *vs.* 5.6 cycles, respectively). The only group that appeared to potentially benefit from CMT was formed of the six patients in that arm who achieved a partial response after induction therapy. Regrettably disease bulk was not reported.

The study by Rezazadeh provides the best available data regarding outcomes of patients with early stage primary bone lymphoma in the post-rituximab era. As the authors duly note in their conclusion, rituximab use was limited in previously published literature and is therefore not reflective of modern practice. While the sample size at first glance appears somewhat small (112 patients), early stage primary bone lymphomas constitute a rare presentation of DLBCL and we are unlikely to see larger studies. Given the generally favorable outcomes there has been little appetite in industry to study limited stage DLBCL and retrospective datasets will guide therapy choices. Indeed, it is a testament to the paucity of data that, in spite of Food and Drug Administration approval of rituximab as an addition to CHOP in 2006, we are only now, in 2023, seeing post-rituximab era datasets.

So how should we incorporate these data into clinical practice? First, routine consolidation with radiation in early stage primary bone lymphoma does not appear to improve outcomes in patients who achieve a complete response with systemic therapy. Second, doses of radiation >36 Gy are not more effective than lower doses and consequently should be avoided. Finally, the greater exposure to chemotherapy in the systemic therapy arm suggests that giving a sufficient number of doses of chemotherapy may be necessary to achieve adequate results.

These data enable treating physicians to use radiation more selectively in the management of early stage primary bone lymphoma. Patients who present with disease in a field with low risk of short- and long-term toxicity, such as a distal extremity lesion, may be preferentially managed with CMT to lessen chemotherapy exposure. Additionally, in a patient who presents with disease transformation from a low-grade follicular lymphoma, CMT may be preferred because of the durable remissions of the low-grade component of disease seen with radiation therapy.[10] In contrast, in patients who may require post-treatment surgical interventions, whose fields will include gastrointestinal or mucosal surfaces, and in younger patients at higher risk of secondary malignancies, an approach with systemic therapy alone may be preferred.

Disclosures

MSH has provided consultancy services for ADC Therapeutics, Abbvie, Janssen, Pharmacyclics, BeiGene, and AstraZeneca.

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