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by Marc S. Hoffmann

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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
E-mail: mhoffmann@kumc.edu

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

One area of ongoing controversy for 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 that form the basis for current treatment recommendations. 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 FLYER 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 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 in this issue of Haematologica (9). The authors analyzed 112 patients treated at 13 academic centers with Stage I-E or Stage II-E primary bone lymphoma in the post-rituximab era between 2005-2019. Stage II-E patients were only included if they had loco-regional adenopathy amenable to radiation therapy in a single field. OS and RFS outcomes were obtained with multi-variate analysis comparing RT vs no RT and also comparing RT <36Gy or ≥36Gy. The results were clear: there was no significant difference in OS or PFS between the two arms. Additionally, higher doses of RT (≥36Gy) were not associated with improved outcomes compared to doses <36Gy. Not surprisingly, given the choices between regimens, the CMT arm received fewer doses of systemic therapy compared to the chemotherapy alone arm (4.5 vs 5.6 cycles). The only group that appeared to potentially benefit from CMT arm were
the 6 patients in that arm who achieved a PR after induction therapy. Regrettably disease bulk was not reported.

This study provides the best available data regarding outcomes of 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 (n = 112), early stage primary bone lymphomas constitute a rare presentation of DLBCL and we are unlikely to see larger studies. Given generally favorable outcomes there has been little appetite in industry to study limited stage DLBCL and these retrospective data sets will guide therapy choices. Indeed, it is a testament to the paucity of data that, in spite of the FDA approval of rituximab as a component of R-CHOP in 2006, we are only now seeing post-rituximab era data sets in 2023.

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

These data allow the treating physician to use radiation more selectively in 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 due to durable remissions for the low-grade component of disease seen with radiation therapy (10). In contrast, patients who may require post-treatment surgical interventions, whose fields will include gastrointestinal or mucosal surfaces, and younger patients at higher risk of secondary malignancies an approach with systemic therapy alone may be preferred.
References:


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<th>Study</th>
<th>Critical Inclusion Criteria</th>
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<td>ECOG 1484</td>
<td>Stage I Bulky (&gt;10cm)</td>
<td>Addition of XRT to CHOP x 8 improved PFS but not OS</td>
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<td>Stage I-E, II or II-E</td>
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<tr>
<td>SWOG 8736</td>
<td>Stage I, Stage I (bulky, ≥10cm)</td>
<td>CHOP x 3 -&gt; XRT equivalent to CHOP x 8</td>
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<tr>
<td>SWOG 0014</td>
<td>Stage I, I-E</td>
<td>R-CHOP x 3 -&gt; XRT has 84% 2-yr PFS</td>
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<td>Stage II, II-E (&lt;10cm)</td>
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<tr>
<td>SWOG 1001</td>
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<td>Stage II non-bulky (&lt;10cm)</td>
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<td>FLYER (8)</td>
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