Non-Hodgkin's Lymphoma in the Elderly: A Tale of Successes and Future Challenges

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As noted in part 1 of this two-part article, non-Hodgkin's lymphoma is one of a few malignancies that have been increasing in incidence over the past several decades. Likewise, these disorders are more common in elderly patients, with a median age of occurrence of 65 years. Therapy in elderly patients may be affected by multiple factors, especially attendant comorbidities. The approaches to management of these patients, with either indolent or aggressive disease processes, have been based on prospective clinical trial results, many of which have included a younger patient population. Fortunately over the past decade, results of treatment trials that have targeted an older patient population have emerged. The disease incidence and treatment approaches for both follicular (part 1) and diffuse aggressive (part 2) histologies in elderly patients are reviewed, as well as the impact of aging on the care of these patients.

Given ongoing demographic changes, when we care for the patient with non-Hodgkin's lymphoma (NHL), we are more than likely caring for the older person. Based on recent data from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program, the incidence of NHL continues to increase, with a median age of 65 and over one-third of all patients older than 70 years. Furthermore, the increasing incidence is greatest in patients over 60 years of age—a fact compounded by population predictions that the number of people living longer than 65 years will double over the next 50 years, with a near quadrupling of those over 80. Against this backdrop, the article by Dr. Morrison is both a timely and germane review of a problem all oncologists will face.

Age as a Prognostic Marker
Across histologies, age has repeatedly been one of the most important prognostic factors, figuring prominently in the international prognostic index (IPI), follicular lymphoma IPI (FLIPI), and, importantly, in Hodgkin's disease.[1-3] As oncologists have become more adept at designing trials specifically for the older patient with diffuse large B-cell lymphoma (DLBCL), they frequently find themselves evaluating a group of patients uniformly over 60. In these cases, the age-adjusted IPI (aIPI)[2] is an effective and important prognostic tool, but it reflects pre-rituximab (Rituxan) risk modeling. More recently, prognostic models developed from modern era immunochemotherapy programs such as Eastern Cooperative Oncology Group (ECOG) 4494 and the German High-Grade Lymphoma Study Group (GHGLSG) studies have demonstrated that an age cutoff of 70 now functions as a dichotomous variable for prognosis.[4,5] Utilizing these modifications to the IPI will be essential as we assess and design prospective trials in the elderly and in the analysis of treatment populations from recent trials demonstrating improved outcomes over those achieved with CHOP-21 (cyclophosphamide, doxorubicin HCl, vincristine [Oncovin], prednisone).

Diffuse Large-Cell Lymphomas: Current Success in Context
Treatment of the older patient with DLBCL is frequently complicated by the presence of significant comorbidities, impaired organ function as a result of aging, and alterations in pharmacokinetics. Additionally, the patient generally has only a single chance at curative outcome. For these reasons, designing trials for the older patients is essential.
For the better part of 2 decades, CHOP chemotherapy remained the standard of care for patients of all ages with diffuse large-cell lymphoma (DLCL), proving to be superior in numerous randomized clinicals trials on the basis of greater or maintained efficacy with less toxicity. In the past, a litany of attempts to maintain or improve outcomes by decreasing toxicity with anthracycline substitutions, dose reductions, or omissions fell short of standard-dose CHOP (see Table 3 in part 1 of the Morrison article, August ONCOLOGY, page 1107). Thankfully, efforts to address the specific needs of the older DLCL patient did not cease. In fact, recent efforts have not only demonstrated the feasibility of carrying out well designed trials in the older patient, but have resulted in the first survival benefits over CHOP chemotherapy in roughly 20 years[b]benefits that have now been extended to the younger patient as well.
The recent randomized studies documenting improvements in overall survival have added the monoclonal antibody rituximab to CHOP (R-CHOP) and/or utilized more dose-intensive schedules (Table 1). R-CHOP chemotherapy administered every 21 days, as reported by the Groupe d'Etude des Lymphomes de l'Adulthe (GELA) is the current standard of care for the patient over 60.[6,7] In the pre-rituximab era, the GELA also demonstrated an improvement in survival by employing a dose-intensive ACVBP program (doxorubicin [Adriamycin], cyclophosphamide, vindesine, bleomycin, prednisone) compared with CHOP in elderly patients with at least one risk factor.[8] In a similar vein, the GHGLSG NHL-B2 study evaluated dose-dense (every 14 day) CHOP-14 vs standard schedule CHOP-21 (every 21 days), with and without etoposide.[5] In this analysis, the dose-dense regimen was superior, but immunotherapy with rituximab was not included.

Future Challenges

Despite these advances, there remain major hurdles to overcome for the older patient with lymphoma. The majority of older patient with DLBCL present with high-risk disease (defined as two or three aaIPI factors), yet this group derives a smaller incremental survival benefit from the addition of rituximab.[9,10] The patient populations are complementary, in part, as the RICOVER-60 patients tended to be relatively younger with less high-risk disease, while the HOVON study enrolled an older population with more high-risk features. In both, although there was associated toxicity with the programs, this did not offset a survival benefit to the patient. In the appropriate patients, dose-dense programs may confer incremental survival benefit. Unfortunately, we lack data comparing a dose-dense R-CHOP-14 to R-CHOP-21, but such a study is being performed by the GELA and will hopefully better define the role of dose density.

Table 1

<table>
<thead>
<tr>
<th>Trial</th>
<th>Median Age/Range</th>
<th>Advanced Stage (III/IV)</th>
<th>ECOG Performance Status &gt; 1</th>
<th>High Risk (HI/H)</th>
</tr>
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<tbody>
<tr>
<td>GELA</td>
<td>69 yr/60-75 yr</td>
<td>47%</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>ECOG 4494</td>
<td>69 yr/60-92 yr</td>
<td>49%</td>
<td>74%</td>
<td>15%</td>
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<tr>
<td>GHGLSG NHL-B2</td>
<td>61-75 yr</td>
<td>22%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>51%</td>
<td>18%</td>
</tr>
<tr>
<td>RICOVER-60</td>
<td>61-80 yr</td>
<td>36%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>51%</td>
<td>14%</td>
</tr>
<tr>
<td>HOVON</td>
<td>73 yr/65-85 yr</td>
<td>&gt;50%</td>
<td>87%</td>
<td>32%</td>
</tr>
</tbody>
</table>

<sup>a</sup>70 yr.

<sup>ECOC = Eastern Cooperative Oncology Group; GELA = Groupe d'Etude des Lymphomes de l'Adulthe; GHGLSG = German High-Grade Lymphoma Study Group; HI/H = high-intermediate/high risk; HOVON = Dutch-Belgian Hemato-Oncology Association; NHL = non-Hodgkin's lymphoma; RICOVER-60 = Rituximab with CHOP Over 60.</sup>

Two subsequent randomized studies have compared dose-dense approaches in the setting of chemoimmunotherapy with R-CHOP. The Rituximab with CHOP Over 60 (RICOVER-60) and Dutch Hemato-Oncology Association (HOVON) studies have both demonstrated improved survival for R-CHOP-14 over the nonrituximab dose-dense CHOP regimen based on early reports.[9,10] The patient populations are complementary, in part, as the RICOVER-60 patients tended to be relatively younger with less high-risk disease, while the HOVON study enrolled an older population with more high-risk features. In both, although there was associated toxicity with the programs, this did not offset a survival benefit to the patient. In the appropriate patients, dose-dense programs may confer incremental survival benefit. Unfortunately, we lack data comparing a dose-dense R-CHOP-14 to R-CHOP-21, but such a study is being performed by the GELA and will hopefully better define the role of dose density.

Future Challenges

Despite these advances, there remain major hurdles to overcome for the older patient with lymphoma. The majority of older patient with DLBCL present with high-risk disease (defined as two or three aaIPI factors), yet this group derives a smaller incremental survival benefit from the addition of rituximab on longer follow-up, overall survival is not significantly improved in this group on the GELA study, and survival remains below 50%. Efforts to integrate new agents into the R-CHOP program and to consolidate therapy with radioimmunotherapy are being explored with hopes of aiding this population. Additionally, how to best treat older patients with comorbidity or organ impairment that precludes CHOP chemotherapy is not well defined. Efforts to incorporate comprehensive geriatric assessments into our thought process and therapeutic decision-making are just beginning to be explored. For the ever more prevalent octogenarian with newly diagnosed lymphoma, the applicability of randomized data is limited by the smaller percentage of these patients on trials. Specific efforts in the "old, old" are needed, with criteria for evaluation based on
improved functional assessments rather than just numeric age.

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**References:**


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