Indolent and mantle cell
NHL: the future is BRIGHT

Nathan Fowler1  MD ANDERSON CANCER CENTER

In this issue of Blood, Flinn et al report a phase 3 study demonstrating similar complete response rates with bendamustine and rituximab compared with rituximab plus cyclophosphamide, Adriamycin, vincristine, and prednisone (R-CHOP) or rituximab plus cyclophosphamide, vincristine, and prednisone (R-CVP) in untreated indolent and mantle cell lymphomas.1

The treatment landscape for patients with newly diagnosed indolent non-Hodgkin’s lymphoma (NHL) and mantle cell lymphoma (MCL) is changing rapidly. The identification of druggable biologic targets and rediscovery and integration of existing agents into effective combination regimens have resulted in significant clinical improvements over the last several decades. These advances, coupled with improved supportive care techniques, have led to a progressive lengthening of the expected survival of patients with newly diagnosed indolent lymphoma.2

Bendamustine, a bifunctional alkylator, was first developed in East Germany 50 years ago as a potentially more effective and less toxic nitrogen mustard. Over the ensuing decades, the drug was explored in several phase 2 studies in patients with both solid tumors and hematologic malignancies, mainly in Germany. Recent preclinical studies demonstrated that bendamustine had a unique mechanism of action capable of inducing rapid and durable DNA damage, inhibiting DNA repair, and inducing mitotic catastrophe.3

Despite promising results, the agent remained in relative obscurity until recent larger phase 2 European and North American trials showed significant activity in relapsed NHL and chronic lymphocytic leukemia. In 2 single agent phase 2 studies, bendamustine induced overall responses of 75% to 77% in patients with rituximab-refractory indolent NHL.4,5 Combining bendamustine with rituximab, Robinson et al reported overall and complete response rates of 92% and 41%, respectively, in patients with relapsed indolent NHL and MCL.6 In 2008, bendamustine was approved in the United States for relapsed indolent NHL and chronic lymphocytic leukemia.

Table. Select clinical outcomes and adverse events reported with BR compared with R-CHOP/ R-CVP in untreated patients with indolent and mantle cell lymphoma

<table>
<thead>
<tr>
<th></th>
<th>BR</th>
<th>R-CHOP/R-CVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall response rate</td>
<td>97%</td>
<td>91%</td>
</tr>
<tr>
<td>Complete response</td>
<td>31%</td>
<td>25%</td>
</tr>
<tr>
<td>Partial response</td>
<td>65%</td>
<td>66%</td>
</tr>
<tr>
<td>Toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>63%</td>
<td>58%</td>
</tr>
<tr>
<td>Opportunistic infection</td>
<td>10-12%</td>
<td>7%</td>
</tr>
<tr>
<td>Rash</td>
<td>20-24%</td>
<td>12%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>9-14%</td>
<td>44%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>3-4%</td>
<td>51%</td>
</tr>
<tr>
<td>Neutropenia (Gr3 +)</td>
<td>39-49%</td>
<td>87%</td>
</tr>
<tr>
<td>Lymphopenia (Gr3 +)</td>
<td>61-63%</td>
<td>33%</td>
</tr>
<tr>
<td>Platelets (Gr3 +)</td>
<td>5-10%</td>
<td>12%</td>
</tr>
</tbody>
</table>

Adapted from Tables 2 and 4 in the article by Flinn et al that begins on page 2944.

On the basis of these and earlier studies, the German Study Group, Indolent Lymphoma (StiL), launched a phase 3 noninferiority trial to determine whether 6 cycles of bendamustine and rituximab (BR) were equivalent to one of the more common standards for frontline treatment of indolent NHL: 6 cycles of R-CHOP. Entry criteria included untreated advanced stage disease requiring therapy (rapid progression, disease related symptoms, bulk, or threatened organ function). The study enrolled 514 subjects between 2003 and 2008, randomizing patients 1:1 to each arm. Although the study was designed as a noninferiority trial, at a median follow-up of 45 months, the median progression-free survival was significantly longer in the BR arm (69.5 vs 31.2 months; P < .0001).7 Treatment with BR was associated with a higher complete response rate, and overall response rates were similar between the 2 groups. Fewer serious adverse events were reported in the BR arm compared with R-CHOP (19% vs 29%). Neutropenia, leukopenia, and serious infections were also less common following bendamustine.

Flinn and colleagues present the data of a follow-up/validation phase 3 clinical trial comparing bendamustine and rituximab with R-CHOP or R-CVP in patients with untreated indolent NHL or MCL. During screening, investigators preassigned patients to R-CHOP or R-CVP based on clinical condition and disease presentation. The primary objective of the trial was to demonstrate noninferiority of BR compared with R-CHOP/R-CVP with regard to complete response rate. Entry criteria were similar to the German STiL trial and included only patients with advanced stage disease and a requirement to initiate therapy. Patients with indolent NHL and MCL were randomized to receive 6 cycles of BR (n = 224) or R-CHOP/R-CVP (n = 223; 2 additional cycles were allowed at investigator’s discretion). Responses were assessed by study investigators and a blinded independent review committee. In the evaluable population, the reported complete response rate was similar between BR and R-CHOP/R-CVP (31% vs 25%, respectively, P = .0225 for noninferiority).1 Complete response rates in the 134 evaluable patients with MCL were higher in the BR arm (50% vs 27%, respectively). The toxicity profiles were unique and differed between treatment arms (see table). BR was associated
with a higher rate of significant lymphopenia, whereas R-CHOP/R-CVP was associated with increased neutropenia. BR was also associated with a slightly increased risk of opportunistic infections and nausea but decreased neuropathy and alopecia compared with R-CHOP/R-CVP. Follow-up is ongoing, and progression-free survival/overall survival data were not reported.

This report by Flinn et al confirms that the future of therapy for indolent NHL and MCL is increasingly bright, and bendamustine and rituximab are effective agents adding to the armamentarium of resources for patients with untreated disease. However, the potential superiority of a given combination will not be evident without longer follow-up and a comparison of progression-free survival, overall survival, and the incidence of long-term toxicities. Although complete and overall response rates were similar between combinations, each regimen was associated with its own unique toxicity profile. Furthermore, differences between the German StiL study and the current report possibly stem from differences in toxicity reporting and the use of an independent review committee. While we wait for the next report, the management of symptomatic indolent NHL and most MCLs should remain individualized, with continued emphasis on trial entry and management decisions based on close attention to comorbidities, cost, tolerability, and goals of therapy.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES


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CLINICAL TRIALS & OBSERVATIONS

Comment on Middeke et al, page 2960

Abnl(17p) in AML: who will guard the guardian?

Minoo Battiwalla1 1NATIONAL INSTITUTES OF HEALTH

In this issue of Blood, Middeke and colleagues highlight the poor outcome of the abnormal (17p) [abnl(17p)] subgroup of cytogenetically adverse-risk acute myeloid leukemia (AML) even after allogeneic hematopoietic stem cell transplantation (HSCT).1

Metaphase cytogenetics at the diagnosis of AML is routinely used to establish favorable, intermediate, and unfavorable prognostic categories. Unfavorable-risk cytogenetics is a standard indication for HSCT in first complete remission (CR1) for subjects with an available donor. Further dissection of the impact of individual cytogenetic abnormalities within the unfavorable-risk group is ongoing by retrospective analyses of registry studies. Eventually, it will be possible to identify patients who would unequivocally benefit from HSCT.

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