B-cell binding of PF4/heparin/complement complexes be important in explaining aspects of this clinical heterogeneity? Here, Khandelwal et al showed that among 16 patients receiving heparin at usual therapeutic doses, approximately one-third (6/16, or 37%) exhibited binding of PF4/heparin complexes to their B cells. This phenomenon was heparin-dependent, because it was only demonstrable after commencing the heparin infusion; moreover, at very high heparin concentrations (sufficient to raise the activated partial thromboplastin time to >300 seconds), the antigen complexes no longer bound to B cells. These fascinating observations point to future investigations: is the subset of patients whose B cells bind PF4/heparin complexes the same patient population that subsequently form high levels of anti-PF4/heparin antibodies? Unlike the majority of immune-mediated adverse drug reactions affecting blood cells, which are rare, the anti-PF4/heparin immune response is common, and even clinical HIT occurs often enough that a future study that systematically evaluates the predictivity of PF4/heparin binding to B cells among individuals patients in determining their subsequent immune response, would likely be feasible.

As an aside, the authors also noted that protamine (PRT)/heparin complexes exhibited similar features of preferential B-cell binding; although not the focus of their current paper, these observations could provide insights into the high frequency of formation of anti-PRT/heparin complex antibodies, a recently recognized immune response that, like the anti-PF4/heparin immune response, is common, rapid, and relatively transient.10

The high degree of binding of PF4/heparin complexes to B cells from many normal individuals suggested to Khandelwal et al that a non–antigen-specific mechanism must be operative, and indeed the authors showed that PF4/heparin binding to B cells in vitro required the presence of complement. Further, B cells isolated from heparin-treated patients showed that for those whose B cells bound PF4/heparin complexes, C3 and C4 also could be detected on their B cells, whereas those patients whose B cells did not bind PF4/heparin complexes, these complement system components could not be detected either. Using a variety of techniques, the authors convincingly showed that binding of PF4/heparin/complement complexes occurred via CD21 on B cells, otherwise known as CR2.

The authors propose the following early steps during the pathogenesis of the anti-PF4/heparin immune response. Administration of pharmacologic heparin displaces PF4 from platelets and endothelium, raising its concentration ~10-fold, and leading to the formation of PF4/heparin ULCs that bind complement and thereby bind preferentially to B cells via CR2 (see figure). This general mechanism could explain several of the known features of the anti-PF4/heparin immune response, including its high frequency (because near ubiquitous binding to B cells in many individuals seems likely to trigger B-cell response against the PF4/heparin complexes) and greater frequency of immunization triggered by unfractonated heparin (UFH) vs low molecular weight heparin (LMWH) (because the authors found lower dose requirements for UFH vs LMWH for producing ULCs capable of activating complement). These exciting studies represent a real breakthrough in understanding how it is that heparin can trigger so often an immune response, and provides further insights into how the innate and adaptive immune systems interact in explaining certain adverse drug effects.

Conflicts of interest disclosure: T.E.W. has received lecture honoraria from Pfizer Canada and Instrumentation Laboratory, royalties from Taylor & Francis (Informa), consulting fees and research funding from W.L. Gore & Instrumentation Laboratory, and has provided expert witness testimony relating to HIT.

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*** CLINICAL TRIALS AND OBSERVATIONS

Comment on Albertsson-Lindblad et al, page 1814

Combined therapy in MCL: less may be more?

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In this issue of Blood, Albertsson-Lindblad et al report on the efficacy of a bendamustine (B)/lenalidomide (LEN)/rituximab (R) combination in first-line therapy of mantle cell lymphoma (MCL). Essentially, this combination achieved high response rates (complete response, 64%; molecular remission, 36%) and a prolonged median progression-free survival (PFS) of 42 months, but rate of infections (42%) and secondary malignancies (16%) were significant.1 So how should we evaluate these results in light of other trials?

Based on 2 phase 3 studies on both sides of the Atlantic, bendamustine-rituximab (B-R) became the standard approach in elderly MCL patients achieving long-term remissions at least comparable to conventional rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) but being better tolerated2-3 (see table1-6). However, further analysis revealed an unexpected increased rate of atypical infections based on reduced CD4 counts for a prolonged period. Accordingly, with regard to anti-infectious comedication, some authors have suggested the use of antimicrobial prophylaxis (review in Dreyling and Subklewe). Although there was also concern of a potential increased rate of secondary malignancies, randomized trials did not confirm an increased risk. In multiple myeloma, a similar concern of an increased rate of secondary malignancies in LEN-treated patients was shown to be most likely due to alkylating agents given with LEN. Excellent results have been published for a LEN-R combination in a small oligocentric first-line trial (see table). Most frequent adverse events were grade 3-4 neutropenias, but overall the regimen was tolerated better than conventional chemotherapy.

Based on the favorable tolerability and the benefit of maintenance therapy in MCL, these 2 approaches have been combined in patients who do not tolerate high-dose cytotoxic-containing regimens. As initial phase 1 trials suggested increased myelotoxicity, subsequent guidelines recommended dose reductions of the B-L-LEN combinations. Currently, 2 phase 2 studies have been reported in MCL. The Italian study group explored this combination in relapsed disease. Tolerability with a reduced bendamustine dose (70 mg/m²) was reasonable, and a response rate of 79% with a median PFS of 20 months has been observed. In the study reported in this issue, the LEN dose had to be held during cycle 1 and given at a reduced dose (10 mg) afterward due to rash and infectious complications; with such a modified scheme, grade 3/4 infections were still observed in 42% of patients, mostly during induction. In comparison with the different first-line strategies, it appears that the combined BR-LEN regimen seems to be superior to the immunotherapy regimen2,3 but showed no benefit in comparison with the R-LEN approach of the New York group (see table). However, MCL is an especially heterogeneous disease, and such comparisons are hampered by that heterogeneity.10

We have to address the same dilemma as in multiple myeloma: is it worthwhile to move on to triple or quadruple regimens or might it be beneficial to spare various options for sequential strategies? Surveying local MCL patients, a median of >3 therapeutic regimens have been given, and the armamentarium of targeted approaches is likely to extend during the new few years. Especially for the BR-LEN combination, we have to carefully balance the observed side effects to the high efficacy of this regimen.

Thus, we may have to challenge the dogma of such mixed approaches, as the “nonchemotherapy” component may add significant toxicity. On the other hand, we have to realize that chemotherapy-based strategies achieve long-term remissions in first-line therapy of MCL. However, today we already have a spectrum of targeted drugs registered in the United States or Europe (bortezomib, ibrutinib, temsirolimus, LEN), and promising additional approaches (including dual phosphatidylinositol 3-kinase, BCL-2, or cdk inhibitors) are in early clinical evaluation. In this regard, the high response rates, especially of the Bruton tyrosine kinase inhibitor ibrutinib, may challenge the future predominance of chemotherapy-based regimens.10 If current clinical studies confirm recent preclinical data regarding the high efficacy of complementary ibrutinib combinations, we will finally have the opportunity to challenge chemotherapy-based approaches even in first-line therapy of MCL, a disease which used to have a dismal outcome only 2 decades ago. In this way, the study of Albertsson-Lindblad et al represents an important milestone to reconsider our clinical standards.

Conflict-of-interest disclosure: M.D. has received honoraria for scientific advisory boards and speaker’s honoraria from Celgene and Roche.

REFERENCES

Table: B/LEN-R combinations in MCL (phase 2/3 trials >20 patients)

<table>
<thead>
<tr>
<th>Ref</th>
<th>Regimen</th>
<th>Study type, phase</th>
<th>Line of therapy</th>
<th>Patient no.</th>
<th>OR, %</th>
<th>CR, %</th>
<th>PFS</th>
<th>OS</th>
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<tbody>
<tr>
<td>2</td>
<td>6×BR</td>
<td>3</td>
<td>First line</td>
<td>46</td>
<td>93</td>
<td>40</td>
<td>Median: 35.4 mo</td>
<td>N/A</td>
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<tr>
<td>3</td>
<td>6×BR</td>
<td>3</td>
<td>First line</td>
<td>36</td>
<td>94</td>
<td>50</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>1</td>
<td>6×BR + LEN</td>
<td>2</td>
<td>First line</td>
<td>51</td>
<td>80</td>
<td>64</td>
<td>Median: 42 mo</td>
<td>73% (36 mo)</td>
</tr>
<tr>
<td>4</td>
<td>6×BR + LEN</td>
<td>2</td>
<td>Relapse</td>
<td>42</td>
<td>79</td>
<td>58</td>
<td>Median: 20 mo</td>
<td>67% (24 mo)</td>
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<tr>
<td>5</td>
<td>R + LEN</td>
<td>2</td>
<td>First line</td>
<td>38</td>
<td>87</td>
<td>61</td>
<td>85% (2 y)</td>
<td>97% (24 mo)</td>
</tr>
<tr>
<td>6</td>
<td>R + LEN</td>
<td>2</td>
<td>Relapse</td>
<td>44</td>
<td>57</td>
<td>36</td>
<td>Median: 11.1 mo</td>
<td>Median: 24.3 mo</td>
</tr>
</tbody>
</table>

CR, complete response; N/A, not available; OR, overall response; OS, overall survival; Ref., reference/citation number.

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