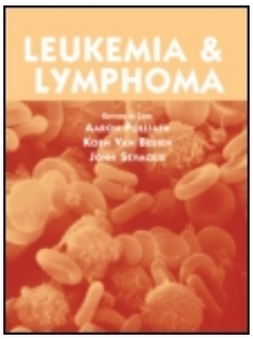

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COMMENTARY

Bendamustine: more ammunition in the battle against mantle cell lymphoma

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While mantle cell lymphoma (MCL) outcomes appear to have improved in the last decade, it remains an incurable disease in the majority of cases. Generally speaking, the more “ammunition” one has to combat an incurable disorder, the better it is for patients and their treating physicians. Bendamustine has been available for several decades in Europe following its development in 1963 in the German Democratic Republic, but only more recently has it been made available for investigation in the USA [1]. The efficacy of bendamustine has been demonstrated in chronic lymphocytic leukemia [2] and indolent non-Hodgkin lymphoma (NHL) [3], with several studies including smaller subsets of MCL. Based on these reports, bendamustine is emerging as a new therapeutic option for MCL, in both the frontline and relapsed settings.

The report by Warsch *et al.* provides an analysis of the multicenter experience with bendamustine for treatment of MCL [4]. Although the conclusions that can be drawn from these data are limited by the small sample size and retrospective nature of the analysis, the reported outcomes provide a better understanding of response rates and tolerability with this agent. Previous reports of bendamustine activity in MCL were derived from trials including multiple NHL histologies, with only small fractions represented by MCL. The overall response rate (ORR) of 83% and complete response (CR) rate of 50% observed in this study [4] are consistent with other data. Robinson *et al.* observed an ORR of 92% and CR or unconfirmed CR rate of 59% among the subgroup of patients with relapsed MCL [5]. Data regarding progression-free survival (PFS) are somewhat more difficult to compare in this retrospective analysis. Here, Warsch *et al.* observed a time-to-treatment failure of 16.2 months in this predominantly relapsed population [4], while Robinson *et al.* reported a higher median PFS of 23 months, but with this endpoint reported for the entire cohort of indolent NHL and MCL [5].

Toxicity appears acceptable in this series, particularly considering that this is a relatively heavily pretreated population [4]. Rates of grade 3–4 infections were observed in 10% of treated patients, and neutropenic fever occurred in only 7% of patients. Thrombocytopenia is common with bendamustine, and 20% of patients experienced grade 3–4 thrombocytopenia, although notably without significant bleeding complications observed. These toxicity data are compatible with prior reports of bendamustine + rituximab (BR) in indolent NHL and MCL. In the report by Robinson *et al.*, 66 patients with relapsed indolent NHL or MCL (18%) were treated with BR, with 36% of patients experiencing grade 3–4 neutropenia but only 10% of patients experiencing grade 3–4 infections. Thrombocytopenia was manageable, with only 9% of patients experiencing grade 3–4 thrombocytopenia [5].

Current therapy options for relapsed MCL are limited. Bortezomib is the solitary Food and Drug Administration (FDA)-approved regimen for relapsed MCL in the USA, with a primary dose-limiting toxicity being sensory neuropathy. The risk for sensory neuropathy with bortezomib is further exacerbated by frequent exposure to vincristine in many up-front MCL regimens. The PINNACLE trial observed an ORR of 33% with single-agent bortezomib in patients with relapsed MCL after no more than two prior therapies, with a median duration of response of 9.2 months and time-to-progression (TTP) of 6.2 months [6]. Other agents with reported activity in MCL have similarly demonstrated reasonable rates of objective response but with disappointing PFS. For example, in a phase II study with cladribine + rituximab in 29 patients with previously untreated MCL, a CR rate of 52% was achieved but with a median TTP of 12.1 months [7]. Although bendamustine has not been compared with other standard regimens in a randomized trial in relapsed MCL, comparisons of available data suggest that bendamustine may provide improved outcomes in the setting of relapsed disease.

Emerging data are also suggestive of high rates of durable response in newly diagnosed MCL. The StIL (Study Group Indolent Lymphomas) trial reported by Rummel *et al.* also observed a more favorable toxicity profile with BR compared

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with R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) in previously untreated indolent NHL, including a subset of patients with MCL (18% of enrolled patients) [8]. Compared with R-CHOP chemotherapy, there were significantly fewer infectious events and significantly less grade 3–4 neutropenia (10.7% with BR vs. 46.5% with R-CHOP). In the patients with MCL, Rummel *et al*. also found a significant improvement in PFS in favor of BR (33 months) compared with R-CHOP (22 months) [8]. In addition, the lack of cardiac toxicity associated with anthracycline-based regimens may allow bendamustine-based regimens to be administered even among patients with cardiovascular co-morbidities. These promising results with BR in up-front treatment of MCL are the basis for the planned intergroup study E1411 comparing BR-based induction chemotherapy with or without concurrent bortezomib followed by a second randomization to rituximab with or without lenalidomide. Ultimately, BR may prove to be a more efficacious and less toxic alternative for older and less fit patients with MCL.

There are several unanswered questions about the role of bendamustine in both previously untreated and relapsed/refractory MCL. The incorporation of novel targeted agents with bendamustine will continue to be an area of active research. Ongoing clinical studies are already investigating bendamustine with or without rituximab in combination with temsirolimus (mammalian target of rapamycin [mTOR] inhibitor) [9], lenalidomide [10] and ofatumumab [11]. Other targeted agents emerging with impressive activity in MCL include the oral PI3Kδ inhibitor CAL-101 and the oral Bruton's tyrosine kinase (BTK) inhibitor PCI-32765. A recent phase I dose-escalation study with CAL-101 included 16 evaluable patients with MCL, with an observed overall response rate of 62% [12]. A phase II study of the oral BTK inhibitor PCI-32765 reported an overall response rate of 67% among 24 evaluable patients with relapsed or refractory MCL [13]. It is hoped that combinations of novel targeted agents, on the optimal chemoimmunotherapy platform, will make a significant impact in this disease.

Chemoimmunotherapy for MCL is not curative. More weapons are needed to combat this difficult lymphoma subtype. Bendamustine offers a significant advance in the treatment of MCL, and the optimal combination regimen with novel agents will continue to be developed.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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