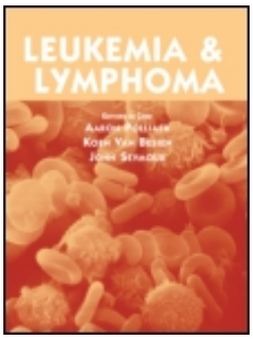

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COMMENTARY

Bendamustine: a bridge to longer term solutions in heavily treated Hodgkin lymphoma

Alison Moskowitz

Memorial Sloan-Kettering Cancer Center, New York, NY, USA

It was only a few years ago when the treatment choices for patients with Hodgkin lymphoma (HL) who failed autologous stem cell transplant (ASCT) were extremely limited. The short list of options included MOPP (mechlorethamine, vincristine, procarbazine and prednisone), gemcitabine-based regimens, radiation therapy and allogeneic stem cell transplant if chemosensitive disease could be established. The median survival for ASCT failures at that time was estimated to be 2 years [1]. With the advent of new drugs and, as is the case with bendamustine, the discovery of old drugs with promising activity in HL, treatment options have expanded, and the median survival for patients who fail ASCT at this point in time is likely considerably longer. One of the most important changes to the management of relapsed and refractory (rel/ref) HL has come with the approval of brentuximab vedotin (BV), the anti-CD30 antibody–drug conjugate. This drug achieved overall and complete response (CR) rates of 75% and 34%, respectively, and the median response duration for patients who entered CR was 20.5 months [2]. Clearly, this drug alters the previously expected survival for these patients. Given its excellent tolerability and efficacy, many studies are under way looking to incorporate BV into the front-line, second-line and post-transplant settings for HL; however, at this time, many patients with rel/ref HL have already received BV-based therapy and more options are still needed.

Bendamustine was first developed in East Germany in the 1960s, but it was not until 2008 that it was Food and Drug Administration (FDA) approved for chronic lymphocytic leukemia and indolent non-Hodgkin lymphoma in the USA. Since then, it has been widely used for these entities. Based upon anecdotal reports and small studies suggesting activity of bendamustine in HL, a single-center phase II study in rel/ref HL was initiated in 2008 at Memorial Sloan-Kettering Cancer Center (MSKCC) [3,4]. This study enrolled 36 heavily pretreated patients with rel/ref HL and demonstrated an overall response rate of 53%, with 33% patients achieving complete responses. Although five patients on this study proceeded to allogeneic stem cell transplant, the median progression-free survival was only 5.2 months, demonstrating that bendamustine typically works transiently. In this issue of ***Leukemia and Lymphoma***, Ghesquières and colleagues expand upon the published experience with bendamustine in HL with a retrospective analysis of 28 patients with rel/ref disease who received bendamustine on a compassionate use program [5]. This analysis provides insight regarding the efficacy of bendamustine in a real-world setting. Despite the inherent bias associated with retrospective analyses, the results reported by Ghesquières are quite similar to those observed at MSKCC, with overall response and CR rates of 50% and 29%, respectively, thus confirming its efficacy in this patient population. As seen in the MSKCC series, median response duration is disappointing at 5.7 months, indicating that as a single agent, bendamustine is unlikely to impact the overall survival for patients with rel/ref HL.

Given its reasonably high efficacy in heavily pretreated patients coupled with short remission duration, we have considered bendamustine to function best as a bridge to longer-term consolidative strategies, such as allogeneic stem cell transplant (alloSCT). Unfortunately, in these cases, highly dependable consolidative strategies do not exist in the post-ASCT setting. The role of alloSCT in rel/ref HL is controversial given that long-term remission rates are unsatisfactory at 24–39% [6–8]. Results are consistently better for patients transplanted in chemosensitive states, and therefore more effective induction regimens, either with novel drugs or new drug combinations, may result in better outcomes for these patients. Several studies are currently under way evaluating bendamustine combinations in HL, including bendamustine plus BV (NCT01657331), bendamustine with lenalidomide (NCT01412307) and bendamustine and gemcitabine (NCT01535924). These combinations may improve the response rate and response duration of single-agent bendamustine, and potentially bridge more patients to alloSCT. Relapse, however, continues to be the major reason for alloSCT failure. Among patients in CR prior to alloSCT, 50% will still relapse; therefore, better consolidative strategies

Correspondence: Alison Moskowitz, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA. Tel: 212-639-4839. E-mail: moskowia@mskcc.org

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are needed to improve the overall survival for patients with rel/ref HL who fail ASCT [8]. It is possible that donor source may impact the efficacy of alloSCT, as seen in a retrospective analysis by Burroughs *et al*. showing reduced relapse rates with haploidentical donors [9]. In addition, maintenance therapies following bendamustine-based therapy, either instead of transplant or following transplant, may perhaps prolong remission. Prospective studies are clearly needed to test these treatment strategies in this group of patients. At this point in time, for patients with rel/ref HL who fail both ASCT and BV-based therapy, bendamustine is a good option provided that consolidative treatment plans are already in place.

Potential conflict of interest: A disclosure form provided by the author is available with the full text of this article at www.informahealthcare.com/lal.

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