Is there a place for the combination of brentuximab vedotin and bendamustine in treatment of patients with relapsed/refractory Hodgkin lymphoma?

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This study by O'Connor and colleagues investigated the combination of brentuximab vedotin plus bendamustine in patients with relapsed/refractory Hodgkin lymphoma (HL). Both drugs have been studied as single agents in this setting; brentuximab vedotin was found to have an overall response rate (ORR) of 74% and complete response (CR) rate of 32% in a pivotal phase II trial (1). For single agent bendamustine an ORR of 53% and CR rate of 33% was reported (2). The clinical rationale of this study was to combine the two agents to increase their efficacy. However, no preclinical rationale was provided for this combination in this manuscript.

The phase 1 portion of the study did not yield significant toxicities that warranted stopping the trial. The combination of brentuximab vedotin and bendamustine was considered to be well tolerated in the phase 2 portion of the study, with some concerns regarding toxicities. Although this is not a randomized controlled trial, it seems that more adverse events were seen with the combination as opposed to with either drug alone. The increased incidence of infusion reaction and rash (11% and 32%, respectively in phase 2) were notable as neither drug alone had significant issues (3). The grade 3 lung infection rate of 14% in the phase 2 study serves to highlight that the combination does introduce more toxicities than either drug alone.

In the phase 2 portion of the study the ORR was 74% and CR rate was 43%. This combination seemed to have higher efficacy compared to brentuximab vedotin or bendamustine alone. However, given that this wasn't a randomized controlled trial, it is difficult to say the exact improvement this combination had over either drug alone. Brentuximab vedotin alone had an ORR of 74% and CR rate of 33% (1). Thus this combination appears to have no benefit in ORR and some benefit in CR. The phase 1 portion of the combination study had lower ORR (61%) and CR rate (18%). The difference may have been due to lower drug doses, or it may have been due to the patient population. Patients in the phase 1 portion were more heavily pretreated, with a median of 5 prior therapies, compared with patients in the phase 2 portion who had a median of 3 prior therapies. There was also a notable difference in the proportion of patients who had received prior brentuximab vedotin in the phases 1 and 2 portions of the trial (29% and 8%, respectively).

Given that the combination is efficacious and tolerable, it seems that this regimen can be incorporated into the treatment landscape for patients with relapsed/refractory HL. The question is where does it fit in? Should the regimen be used in the first relapse setting as a bridge to autologous stem cell transplantation (ASCT)? Should it be used for patients who relapsed after ASCT as a bridge to alloHCT? Or should it be a palliative measure for patients who have progressed after all available curative options? The author concludes that this strategy can be employed as a bridge to ASCT. A similar study conducted by LaCasce and colleagues using this combination as a bridge to ASCT showed a higher ORR of 92% and CR of 74% (4) in patients who had only 1 prior line of therapy. Thus it seems

that this combination is more effective when given in an earlier line setting. However, this conclusion is tempered by the lack of data on both long-term progression free survival post ASCT, and on the ability to collect stem cells. While O'Connor and colleagues do give some OS and PFS results, there is a lack of detail on how many patients proceeded to ASCT or alloHCT. Given that it is an alkylating agent, there is some concern about the ability to collect stem cells post bendamustine. Both concerns should be alleviated when the full results of Dr. LaCasce's trial are published.

This combination can certainly be used in patients who have progressed after ASCT. The long-term follow-up from the pivotal phase 2 trial of brentuximab vedotin alone showed a 5-year PFS of 22% (5). However, patients who achieved a CR had a better PFS of 52%. A small subset of patients who received brentuximab vedotin in the post ASCT relapse setting can achieve durable remission. Again, that number seems to be higher in patients who achieved a CR. Thus this combination may be able to offer durable remissions for patients who achieve CR post ASCT relapse. However, longer follow up, including data on patients who progress to ASCT or alloHCT, is needed.

Also given the current treatment landscape, with the recent approval of brentuximab vedotin in the frontline setting for patients with advanced HL, it is unclear if this combination will have the same efficacy in patients who have prior exposure to brentuximab vedotin. Judging from the results of the phase 1 portion of the study, it does appear that the combination will have lower efficacy in patients who have had prior brentuximab vedotin or patients who have been more heavily pretreated. Thus the results from this study would need to be applied with these concerns in mind. Overall, this combination is efficacious and tolerable and can be incorporated into the treatment regimen for patients with relapsed/refractory HL.

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Footnote

Conflicts of Interest: RW Chen has served on advisory board and speaker bureau for Seattle Genetics.

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