Comment on "Retrospective matched-pairs analysis of bortezomib plus dexamethasone *versus* bortezomib monotherapy in relapsed multiple myeloma"

We read with interest the paper by Dimopoulos *et al*. concerning a comparison of bortezomib plus dexamethasone (BzD) *versus* bortezomib monotherapy in relapsed multiple myeloma (MM).[1] In their manuscript the authors presented a *post hoc* matched-pair analysis of patients treated in three separate clinical studies: MMY-2045 (patients treated with BzD),[2] APEX (patients treated with single-agent bortezomib)[3] and the single-agent bortezomib arm of the DOXIL-MMY-3001 trial.[4] They found that BzD is associated with a significantly higher response rate and time to progression but has no impact on survival.

We recently published the results of the BoMER study,[5] which involved 100 patients and recapitulated the original APEX study design (i.e. patients with relapsed or refractory MM who were bortezomib-naïve, required second- or subsequent therapy and were not dexamethasone-resistant. In our BoMER trial, patients were treated with eight 21-day cycles of intravenous bortezomib (1.3 mg/m^2; days 1, 4, 8, and 11) and three 35-day cycles of bortezomib (1.3 mg/m^2; days 1, 8, 15, and 22) with the incorporation of dexamethasone from cycle 1. Our study also examined subsequent maintenance BzD; patients with stable disease or better continued on BzD therapy every 2 weeks until progression or unacceptable toxicity. The study design included a prospectively planned analysis comparing the BoMER results to those of a matched cohort in the APEX study. While our study agrees with the overall conclusions of Dimopoulos *et al*. - that BzD improves the depth and duration of response in patients with refractory or relapsed MM, with no compromise in the safety profile of the therapy and no impact on overall survival - we have a number of comments on the design and methodology of the study by Dimopoulos *et al*.

The BzD arm in the MMY-2045 study included only two patients who had received more than one prior line of therapy; thus, only patients who had received just one prior therapy were used for the matched analysis from all three studies, which may partially explain the higher response rate (73.2%) and longer time to progression (12.9 months; 95% confidence interval: 9.5-15.7 months) in the study by Dimopoulos *et al*. compared to the more heavily pretreated BoMER study cohort with an overall response rate of 53% and time to progression of 10.1 (95% confidence interval: 7.8-13.3) months. Moreover, only 142 of the 163 patients who started treatment on the MMY-2045 protocol were available for response assessment, as adjudged by the independent data monitoring committee. In addition, after four cycles of therapy in the MMY-2045 study, patients with stable disease (n=19/120 with a locally assessable response) were then randomized to BzD, BzD plus lenalidomide or BzD plus cyclophosphamide. The authors do not comment as to whether these patients were excluded from the matching process given that they had received additional therapy. Given these factors, the BzD cohort could be biased in favor of responders.

The matching used in the study by Dimopoulos *et al*. did not include β_2 microglobulin levels (or International Staging System score), which is highly predictive of response and survival at diagnosis (and remained so in our cohort of patients with relapsed disease). This variable was collected for the APEX cohort, as it was included in the criteria for matching in our study. In addition we showed that prior therapy with thalidomide increases the risk of progressive disease in patients treated with BzD.

Finally, Dimopoulos *et al*. suggest that since we used maintenance BzD in our study, the results cannot be compared with the long-term outcome from the current study. However, we show that while initial therapy with BzD improves the depth and duration of response, maintenance had no impact on survival, although the number of patients who would have been eligible for maintenance in either cohort was small (34 *versus* 14).

We believe that these two studies clearly demonstrate the benefit of the addition of dexamethasone to bortezomib in patients with relapsed MM. The BoMER study in particular, with its more heavily pretreated group of patients, is more representative of real-life expected outcomes.

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