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A cautionary tale of the use of lenalidomide and dexamethasone for relapsed/refractory AL amyloidosis.

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In this edition of the *Journal*, Basset *et al*. describe the largest retrospective study to date of the use of lenalidomide and dexamethasone (RD) for the treatment of relapsed/refractory AL amyloidosis (1). There are a number of key messages that are of substantial clinical value; there is information on predictors of efficacy and also a forensic-like approach to the data that highlight the toxicities of this combination in AL amyloidosis – toxicities that are not prominent in the existing *myeloma* literature.

The authors examined a variety of outcome measures including overall survival (OS), hematologic response rate (HRR), very good haematological response (VGHR), hematologic event-free survival (hemEFS) and organ response, in particular, renal survival (RS). The three-month HRR was 31% with an 18% VGHR and a hemEFS of 9 months. Given, the median duration of RD treatment was short at only 4 cycles, it is imperative to ask – why such a short time on drug? The answer probably lies in the fact that these patients had difficult to treat disease (seemingly a worse patient population than some other previously published studies) along with the observation that the RD combination is associated with substantial toxicity. The authors go to pains to demonstrate that their study population and outcomes do reflect what is observed in the real world and it is reassuring to see that their data is similar to that of a recent meta-analysis of IMiDs for AL amyloid (2).

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So how does one predict who are likely to respond to the RD combination? The authors chose to investigate their predictors of outcome by examining 'clonal' and 'organ' biomarkers; clonal biomarkers included chromosomal/iFISH abnormalities, light chain (LC) isotype and level of difference in free light chains (dFLC) while organ biomarkers were NT-proBNP and renal parameters. The major predictors of haematological response were dFLC and light chain isotype and not surprisingly, poor OS was predicted by elevated NT-proBNP and dialysis at initiation of RD, as well as dFLC and light chain isotype. With respect to gain of 1q21, it predicted for a shorted hemEFS with a *trend* for poorer OS. Taken together, at baseline, those patients that are predicted to have the best survival are those with low dFLC, low NT-proBNP and absence of clonal risk factors. After 3 and 6 months of RD treatment, those that are predicted to be longer survivors are those with a VGHR with cardiac and renal stability.

Cardiac toxicity was a concern, with 21% of patients developing cardiac toxicity with 12% being grade 3-4. Indeed, we have previously been alerted to the fact that NT-proBNP frequently increases in patients with AL amyloid receiving lenalidomide (3,4) and in this study 83% of patients had substantial increases in NT-proBNP while cardiac progression at 3 and 6 months was a major predictor of poor survival. Thus, it seems that the NT-proBNP increases are not just a biochemical aberration but seem to predict direct cardiac toxicity of lenalidomide. The authors correctly caution: *"signs of early cardiac progression should be evaluated carefully and are clinically meaningful"*. Indeed, further research into potential mechanisms of any direct cardiac toxicity of lenalidomide in the setting or AL amyloid is warranted.

In the same way, renal toxicity is also a concern and this study provides further evidence that renal toxicity of RD can be problematic particularly in those with pre-existing renal dysfunction (5,6). Moreover, renal toxicity was also observed in some patients with even minimal renal disease. The authors again provide words of caution: *"lenalidomide should be avoided in cases of intermediate-advanced renal amyloidosis and careful monitoring of creatinine should be performed during RD treatment"*.

How does this study help us design better treatments for AL amyloidosis into the future? It is clear that proteasome inhibitors are our most important weapon against AL amyloid. Furthermore, recent data would indicate that anti-CD38 antibodies are also highly effective in AL amyloid. Thus, combining these two agents, seems obvious and indeed the preliminary results of the ANDROMEDA study of bortezomib, dexamethasone, cyclophosphamide and subcutaneous daratumumab for first line treatment of AL amyloid has recently been published; the overall HRR was 96% and the regimen well tolerated. (7) Therefore, we must ask, is there a benefit of adding an IMiD such as lenalidomide

to such a triplet? The data form Basset *et al*. indicates that we need to be cautious. With that in mind, I recommend the reader of this editorial seek out Wikipedia's definition of a 'cautionary tale'!

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