

Disease-free survival following high dose or standard dose therapy in patients with amyloidosis

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Keywords: bortezomib, melphalan, autologous haematopoietic cell rescue, treatment related mortality

Systemic amyloidosis (AL) is the deposition of amyloid fibrils derived from monoclonal light chains that are reproduced by clonal plasma cells. Without treatment, AL is fatal within 2 years, secondary to fibril deposits in vital organs. The disease course depends on halting monoclonal light chain production. Early assessment of haematological response, free light chain (FLC) production and prognostic markers [i.e. N-terminal natriuretic peptide type B (BNP)] every 3 months following induction therapy helps distinguish patients that are likely to have resolution of organ damage (Bird et al, 2004; Palladini et al, 2012).

Historically, treatment consisted of alkylator-based therapy, with data extrapolated from response in multiple myeloma. High dose melphalan with haematopoietic cell rescue (high-dose therapy) is standard induction therapy for eligible patients (Vesole et al, 2006; Santhorawala et al, 2007), resulting in an improved median survival to 4.5 years, a haematological response of 30–70% and treatment-related mortality (TRM) as high as 22%. Standard dose melphalan with dexamethasone in patients ineligible for high dose therapy (HDT) has not shown matched long-term survival outcomes to high-dose therapy studies (Jaccard et al, 2007; Lebovic et al, 2008; Dietrich et al, 2010).

This is the author's manuscript of the article published in final edited form as:

Kiel, P. J., Trueg, A. O., Ferguson, M., Benson, M., & Abonour, R. (2015). Disease-free survival following high dose or standard dose therapy in patients with amyloidosis. *British Journal of Haematology*. <http://doi.org/10.1111/bjh.13656>

The comorbidities of patients ineligible for high-dose therapy in addition to the lack of survival benefit of standard therapy to high-dose therapy, gives rise to the need for alter-native options. Wechalekar et al (2008) assessed bortezomib in the relapsed/refractory setting; 20 patients who progressed after at least one line of prior treatment were consented. Haematological response was seen in 16 patients (80%) (Wechalekar et al, 2008). Four patients died during follow-up, three from progressive disease; median overall survival was not reached. Palladini et al (2014) matched 87 patients ineligible for HDT to receive melphalan, dexamethasone and bortezomib (MBDex) to 87 historic controls of melphalan and dexamethasone (MDex). Primary outcome was haematological response. A complete response was observed in 36 (42%) vs. 16 (19%) of MBDex v MDex group respectively ($P = 0.002$), and overall response was 69% vs. 51%; there was no difference in overall survival.

We conducted a retrospective, single institution evaluation of 68 patients with AL, comparing high dose melphalan with autologous haematopoietic cell rescue to non-intensive therapy. Patients aged over 18 years diagnosed with systemic AL amyloidosis between January 1987 and February 2014 were evaluated. Patients were stratified based on receipt of high dose melphalan with cell rescue. Those that received non-intensive therapy were treated with either alkylator- or bortezomib-based regimens. Patients were not included if they did not receive systemic therapy for AL or had a concomitant malignancy. Approval was obtained through the Indiana University Institutional Review Board.

Initial data collected for each patient consisted of age at diagnosis, gender, the number and type of organs involved. In patients with cardiac involvement, baseline mean BNP and per cent of troponin above normal value (0.035) were evaluated. Baseline involved FLC, time to progression and survival data, which were collected in all patients.

The primary objective of this study was to determine the disease-free survival (DFS) of HDT to non-intensive dose therapy. Nominal data was analysed with a chi-squared or Fishers exact tests; continuous data was evaluated by Stu-dent's t-test and DFS via log rank. All statistics were con-ducted through SPSS version 22 (SPSS, Chicago, IL, USA).

Sixty-eight patients met the inclusion criteria. Forty-three underwent HDT with stem cell rescue and 25 received non-intensive dose therapy. Mean age was 65 (range: 37–73) years for those receiving HDT and 55 (range: 49–82 years) for those who received non-intensive therapy ($P < 0.001$). Renal involvement was the primary organ involved in a majority of patients in both groups (Table I). Most patients in both groups had one involved organ: 83.7% in high-dose and 76% in non-intensive dose. Baseline involved FLC and troponin, and were well matched between the two groups. The baseline mean BNP was elevated in the non-intensive dose group (643 pg/ml) compared to the high-dose group (167 pg/ml) ($P = 0.003$).

The majority of patients in the non-intensive therapy group received intravenous bortezomib without an alkylating agent for induction therapy (76%); median number of cycles was 4 (range 1–16). Other regimens included: cyclophosphamide plus bortezomib (8%), melphalan and prednisone (MP; 8%) and other (8%). Seven per cent of patients received some type of induction therapy prior to HDT.

Median DFS was 53 months for patients receiving high dose melphalan and 59 months for those receiving non-intensive dose therapy ($P = 0.86$) (Fig 1). DFS of HDT compared to bortezomib-only patients was also not statistically significant, 60 months vs. 51 months ($P = 0.477$).

Previous studies evaluating non-intensive dose therapy in patients ineligible for HDT and haematopoietic cell rescue have not matched outcomes seen with HDT, leaving uncertainty as to the optimal induction regimen. Success with bortezomib has been reported in the relapsed setting and those failing to achieve a complete response following HDT. Bortezomib as an induction agent for patients ineligible for HDT is previously unknown.

This study evaluated DFS of high-dose compared to non-intensive dose therapy in patients with AL. The majority of patients who received non-intensive dose therapy were ineligible for high-dose therapy. Unlike previously published experience (Wechalekar et al, 2008; Palladini et al, 2014), the majority of our non-intensive therapy patients received a short course of bortezomib-based therapy due to

the rapid achievement of haematological remission. DFS was not different despite an increased number of patients with cardiac AL in the non-intensive group. The results of this study suggest that bortezomib-based therapy may provide an alternative induction therapy for patients ineligible for HDT, specifically those with underlying cardiac involvement. However, this is a retrospective study spanning many decades; only a prospective randomized controlled trial comparing high-dose and bortezomib induction regimens can accurately assess DFS.

In conclusion, patients with amyloidosis who are unable to pursue high dose melphalan and autologous haematopoietic cell transplant due to organ impairment, induction with a bortezomib-based regimen can lead to a sustained haematological remission and may provide sustained DFS.

Acknowledgements

Drs Abonour and Benson contributed to the design of the study. Drs Kiel and Trueg performed the research. Dr Kiel analysed the data and Drs Trueg and Ferguson wrote the paper.

Declaration of interest

The authors have the following financial interests pertinent to this topic to disclose: co-author Dr Kiel has received honoraria from Takeda Pharmaceuticals and Dr Abonour has received honoraria from Celgene, Takeda and Onyx Pharmaceuticals. No other declarations of interest exist.

References

Bird, J., Cavenagh, J., Hawkins, P., Lachmann, H., Mehta, A. & Samson, D. (2004) Guidelines on the diagnosis and management of AL amyloidosis. *British Journal of Haematology*, 125, 681–700.

Dietrich, S., Schonland, S.O., Benner, A., Bochtler, T., Kristen, A.V., Beimler, J., Zorn, M., Goldschmidt, H., Ho, Ad & Hegenbart, U. (2010) Treatment with intravenous melphalan and dexamethasone is not able to overcome the poor prognosis of patients with newly diagnosed systemic light chain amyloidosis and severe cardiac involvement. *Blood*, 116, 522–528.

Jaccard, A., Moreau, P., Leblond, V., Leleu, X., Benboubker, L., Hermine, O., Recher, C., Asli, B., Lioure, B., Royer, B., Jardin, F., Bridoux, F., Grosbois, B., Jaubert, J., Pietter, J.C., Ronco, P., Quet, F., Cogne, M. & Fermand, J.P. (2007) High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. *N Eng J Med*, 357, 1083–1093.

Lebovic, D., Hoffman, J., Levine, B.M., Hassoun, H., Landau, H., Goldsmith, Y., Maurer, M.S., Steingart, R.M., Cohen, A.D. & Comenzo, R.L. (2008) Predictors of survival in patients with systemic lightchain amyloidosis and cardiac involvement initially ineligible for stem cell transplantation and treated with oral melphalan and dexamethasone. *British Journal of Haematology*, 143, 369–373.

Palladini, G., Dispenzieri, A., Gertz, M.A., Kumar, S., Wechalekar, A., Hawkins, P.N., Schonland, S., Hegenbart, U., Comenzo, R., Kastiris, E., Dimopoulos, M.A., Jaccard, A., Klersy, C. & Merlini, G. (2012) New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. *Journal of Clinical Oncology*, 30, 4541–4549.

Palladini, G., Milani, P., Foli, A., Vidus Rosin, M., Basset, M., Lavatelli, F., Nuvolone, M., Obici, L., Perlini, S. & Merlini, G. (2014) Melphalan and dexamethasone with or without bortezomib in newly-diagnosed AL amyloidosis: a matched case control study on 174 patients. *Leukemia*, 28, 2311–2316.

Santhorawala, V., Skinner, M., Quillen, K., Finn, K.T., Doros, G. & Seldin, D.C. (2007) Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem-cell transplantation. *Blood*, 110, 3561–3563.

Vesole, D.H., Perez, W.S., Akasheh, M., Boudreau, C., Reece, D.E. & Bredeson, C.N. (2006) High-dose therapy and autologous hematopoietic stem cell transplantation for patients with primary systemic amyloidosis: a center for international blood and marrow transplant research. *Mayo Clinic Proceedings*, 84, 880–888.

Wechalekar, A.D., Lachmann, H.J., Offer, M., Hawkins, P.N. & Gillmore, J.D. (2008) Efficacy of bortezomib in systemic AL amyloidosis with relapsed/refractory clonal disease. *Haematologica*, 93, 295–298.

Table 1. Amyloid according to the organ involved

Organ	High-dose, <i>n</i> (%) (<i>N</i> = 43)	Standard dose, <i>n</i> (%) (<i>N</i> = 25)
Renal	32 (76.7)	12 (48)
Gastrointestinal	2 (4.7)	(0)
Hepatic	3 (7)	1 (4)
Cardiac	3 (7)	10 (40)
Other	3 (7)	2 (8)

Figure 1. Disease-free survival.

