Efficacy of bortezomib in systemic AL amyloidosis with relapsed/refractory clonal disease

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ABSTRACT

We report preliminary observations on the efficacy of bortezomib in 20 patients with AL amyloidosis whose clonal disease was active despite treatment with a median of 3 lines of prior chemotherapy, including a thalidomide combination in all cases. Patients received a median of 3 (range 1-6) cycles of bortezomib and 9 (45%) patients received concurrent dexamethasone. Three (15%) patients achieved complete hematologic responses, and a further 13 (65%) achieved partial responses. Fifteen (75%) patients experienced some degree of toxicity, which in 8 (40%) cases resulted in discontinuation of bortezomib. Bortezomib shows promise in the treatment of systemic AL amyloidosis.

Key words: amyloidosis, bortezomib, chemotherapy..

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Introduction

AL amyloidosis is characterized by misfolding of structurally unstable light chains. The objective of treatment in systemic AL amyloidosis is suppression of monoclonal amyloidogenic light chain production. The prognosis is poor for patients whose underlying plasma cell dyscrasia cannot be suppressed or when it relapses after such treatment.

Bortezomib is a small boronic acid derivative that inhibits the 26S proteosome[1] which can produce clinically useful remissions in patients with relapsed myeloma.[2,3] Bortezomib has efficacy in myeloma refractory to thalidomide[4] but has substantial, although often manageable, toxicity.[5] Encouraging data from myeloma suggested that it might also be a useful agent in AL amyloidosis. We report preliminary clinical observations on the efficacy of bortezomib in a cohort of patients with systemic AL amyloidosis and relapsed or refractory clonal disease.

Design and Methods

We performed a retrospective analysis of all patients with AL amyloidosis who were followed up at the UK NAC between April 2004 and November 2006, and who had received off-label treatment with bortezomib. Bortezomib treatment was offered only to patients who: had received at least 1 line of prior treatment (including in every case a thalidomide based combination regimen); had evidence of active clonal disease and progressive amyloidosis; were considered ineligible for stem cell transplantation;[6] and did not have clinically significant neuropathy. Patients were informed that bortezomib had been demonstrated to have activity and was licensed in myeloma, but that it had not been studied in AL amyloidosis and did not have marketing authorization for this particular indication. All patients gave written informed consent to treatment. Approval for retrospective analysis and publication was obtained from the institutional review board, and written consent for publication of anonymous material was obtained from all patients. Diagnosis of AL amyloidosis was made immunohistochemically supported by genetic testing as previously described .[7] All patients were evaluated before receiving bortezomib and 6 monthly thereafter for assessment of involvement and change in amyloidotic organ function and whole body amyloid load by SAP scintigraphy.[8,9] Blood samples were obtained at monthly intervals during and immediately after bortezomib treatment for measurement of serum free light chain (FLC) concentration (*Freelite™, The Binding Site,*

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Birmingham, UK) and two monthly for monoclonal immunoglobulin measurements. Bortezomib was administered as a bolus intravenous injection twice weekly for 2 weeks (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12-21). Since this was not a prospective trial, doses were adapted from standard myeloma treatment at the discretion of individual hematologists. All patients received standard antifungal, antiviral, co-trimoxazole and proton pump inhibitor prophylaxis according to local protocol. Hematologic response, toxicity, overall survival (OS), time to clonal disease relapse, amyloidotic organ response and change in amyloid load by serial SAP scintigraphy were evaluated. Hematologic response to bortezomib was systematically determined by conventional serum and urine electrophoresis and immunofixation as well as by FLC assay, and was conservatively classified as the worst of either the FLC response or conventional serum or urine monoclonal protein response. Conventional response and relapse was defined according to the Bladè criteria.[10] FLC response and relapse were as previously defined.[11] Although FLC concentration was measured after each cycle of bortezomib, the final classification of response was determined ≥3 months after completion/discontinuation of bortezomib therapy or before the next line of treatment began. All monoclonal protein studies and FLC measurements were undertaken centrally at the NAC and were reported by a senior scientist according to standard NAC practice. Progression free survival was defined as the time to clonal relapse or death due to progressive amyloidosis. Toxicity was graded according to the National Cancer Institute Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (Version 3.0). Amyloidotic organ involvement and responses were defined according to the international consensus criteria[12] and performance status was assessed according to Eastern Cooperative Oncology Group (ECOG) criteria.[13] Statistical analysis was undertaken using the SPSS 14 software package (SPSS, Chicago, USA). Survival was assessed by the Kaplan-Meier method. Categorical variables were compared with χ^2 or Fishers tests as appropriate.

Results and Discussion

Twenty patients who were treated with bortezomib (alone or with additional dexamethasone) were identified from the NAC database. They had received a median of 3 (range 1-6) lines of previous chemotherapy, including an autologous stem cell transplant in 5 (25%) cases, and were refractory to the last line of treatment. Median age was 59 years (range 42-73), median ECOG performance status was 2, and median number of organs involved by amyloid was 2 (range 1-4). Twelve patients had cardiac amyloidosis and 4 were dialysis dependent. Patients received a median of 3 (1-6) cycles of bortezomib, at a median dose of 1.3 mg/m^2/dose (range 1-1.3). One mg/m^2/dose was administered to patients receiving renal replacement therapy. Nine (45%) patients received concurrent dexamethasone, 6 the days of bortezomib infusions (i.e. days 1, 4, 8, 11) and 3 others on days 1-4 of each cycle. The median daily dexamethasone dose was 20mg (10-40mg).

Median follow-up from end of treatment was 11 (3-30) months, and from diagnosis of amyloidosis 33 (range 6-92) months. A complete hematologic response (CR) occurred in 3 (15%) patients, and a partial response (PR) in 13 (65%) further cases. A median of 3 (range 1-6) cycles of bortezomib was administered before a free light chain response was recorded. Seven out of 9 (77%) patients who were given bortezomib with dexamethasone responded compared to 9 out of 11 (81%) patients given bortezomib alone. Four responders subsequently relapsed, after a median remission of 9 (range 4-22) months.

Amyloidotic organ function improved in 6 out of 16 (38%) responders and remained stable in the remaining 10. Three showed improvement in renal function with a decrease in 24 hour proteinuria of 55%, 60% and 80% respectively, in the presence of stable or improving renal excretory function. Two patients had hepatic improvement but no patient had cardiac improvement. Serial SAP scintigraphy revealed amyloid regression in 2 out of the 16 (13%) (Figure 1) responders and stable deposits in the remainder. The median survival was not reached by Kaplan-Meier estimation at 24 months from the end of treatment. Four patients died during the follow-up period, 3 from progressive cardiac amyloidosis (at 4, 5 and 23 months from completion of bortezomib) and 1, who had received dexamethasone, from gastrointestinal blood loss after development of renal failure (at 1 month).

Toxicity is detailed in Table 1. Fifteen (75%) patients reported toxicity and 8 (40%) had toxicity which required interruption of therapy, including 5 (25%) after just one cycle. Three cases had a dose reduction after the first cycle due to adverse effects. The reasons for discontinuation due to toxicity included in 1 case each: fatigue, hypotension and diarrhoea, dizziness and postural hypotension, renal impairment, disseminated zoster, fluid overload (two cases) and hemiballism. Peripheral neuropathy was uniquely sensory and recovered completely after interruption of bortezomib treatment in 3 out of 4 patients.

There is an urgent need to identify new treatments for patients with AL amyloidosis who do not respond adequately to currently used chemotherapy regimens or stem cell transplantation. Thalidomide is poorly tolerated as a single agent at therapeutic doses in AL amyloidosis,[14] although lower doses in combination regimens show promise.[11, 15] Early data suggest some efficacy of lenalidomide in AL amyloidosis, mainly in association with dexamethasone.[16] A commercially sponsored study of bortezomib in AL is in progress and the results are

eagerly awaited.

The preliminary observations we report in the present small cohort suggest that bortezomib can have efficacy in patients with AL amyloidosis whose clonal disease has relapsed. A hematologic response rate of 80% observed among these 20 patients with relapsed AL amyloidosis was encouraging and appears to be superior to that reported in patients with relapsed myeloma,[2] probably in keeping with the frequently low grade nature of the clone in AL amyloidosis. Suppression of monoclonal light chains was remarkably rapid in some patients, as demonstrated in Figure 2. Improvement in amyloidotic organ function became evident in over one quarter of the patients, all of whom had progressive amyloid disease before bortezomib had been administered. These encouraging preliminary findings were countered by toxicity leading to discontinuation of treatment in 40% of cases, and by relapse of the clonal plasma cell disease in one quarter of hematologic responders after a median

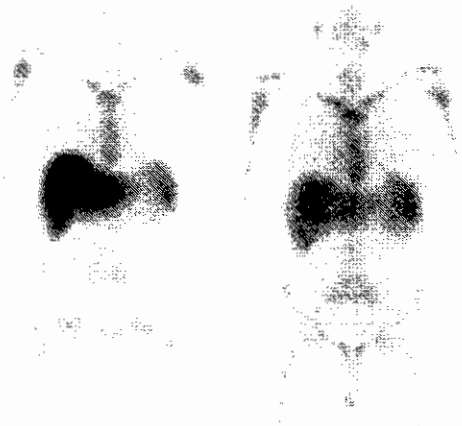

Figure 1. Serial ^{123}I labeled whole body SAP scintigraphy (pre- and post-treatment scans - left and right panels respectively) showing amyloid regression from the liver six months post-bortezomib treatment. The pre-treatment scan (left) shows markedly greater tracer uptake in the liver compared to the spleen while the post treatment scan (right) shows a much reduced liver uptake (which is now similar in intensity to the splenic uptake) compared to the earlier scan. Both scans show bony uptake, which appears unchanged.

Table 1. Toxicity of Bortezomib.

	Number of patients	
Toxicity	*Grade 1-2*	*Grade 3 or more*
Peripheral neuropathy	4 (20%)	–
Fluid retention	1 (5%)	2 (5%)
Diarrhea	2 (10%)	1 (5%)
Fatigue	2 (10%)	1 (5%)
Postural hypotension	1 (10%)	1 (5%)
Herpes Zoster	1 (5%)	1 (5%)
Thrombocytopenia	2 (10%)	–
Myoclonus	–	1 (5%)
Gastrointestinal bleeding	–	1 (5%)
Chest infection	1 (5%)	–
Acute renal failure	–	1 (5%)
No toxicity	5 (25%) patients	

Numbers in columns may not add up as some patients had more than one side effect

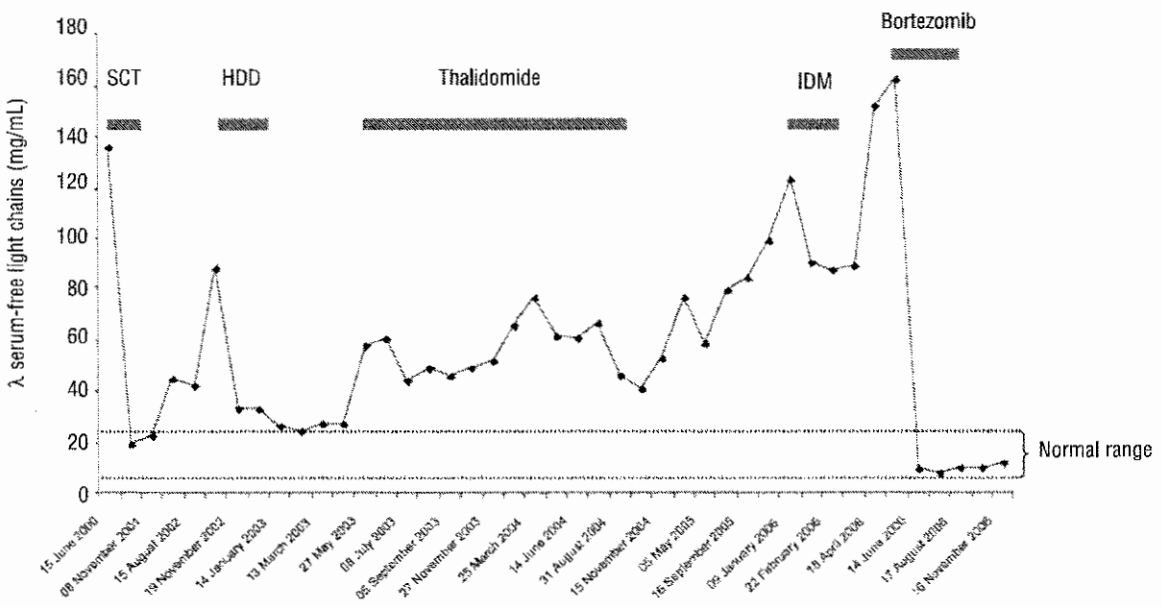

Figure 2. Serial measurement over a six year period of serum lambda free light chain concentration by sensitive nephelometric assay in a patient with AL amyloidosis. Monoclonal light chain production was substantially but briefly suppressed by high dose melphalan and autologous stem cell transplantation (SCT) and by high dose dexamethasone (HDD), but the response to subsequent therapies including thalidomide (with and without dexamethasone) and intermediate dose intravenous melphalan (IDM) was poor. A rapid and complete serum free light chain response was observed after a single cycle of bortezomib.

remission of 9 months. Consistent with experience in AL amyloidosis generally, a substantially higher proportion of patients in this series discontinued bortezomib due to toxicity than has been reported in myeloma.[2] Particular limitations inherent in this retrospective study included lack of prospective collection of details on toxicity (the reasons for interruption of therapy were, however, available for each patient) and limited follow-up.

Therapy with bortezomib is feasible and shows promise in the treatment of relapsed AL amyloidosis and, used alone or in combination with dexamethasone, merits further prospective study.

Authorship and Disclosures

ADW performed research, analyzed data, wrote paper and approved the final version; HJL, MO, PNH and JDG performed research, wrote paper and approved the final version to be published. The authors reported no potential conflicts of interest.

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