Treatment of light chain (AL) amyloidosis with the combination of bortezomib and dexamethasone

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ABSTRACT

Background and Objectives

High-dose melphalan and autologous stem cell transplantation is currently the treatment of choice for selected patients with AL amyloidosis; however, new treatments are needed for patients who are ineligible for or relapse after this procedure. Bortezomib is a proteasome inhibitor with proven activity in multiple myeloma, and the addition of dexamethasone results in superior outcome. We evaluated the activity and feasibility of the combination of bortezomib and dexamethasone (BD) in patients with AL amyloidosis.

Design and Methods

Consecutive patients with histologically proven, symptomatic AL amyloidosis were treated with BD.

Results

Eighteen patients, including seven who had relapsed or progressed after previous therapies were treated with BD. Eleven (61%) patients had two or more organs involved; kidneys and heart were affected in 14 and 15 patients, respectively. The majority of patients had impaired performance status and high brain natriuretic peptide values; serum creatinine was elevated in six patients. Among evaluable patients, 94% had a hematologic response and 44% a hematologic complete response, including all five patients who had not responded to prior high dose dexamethasone-based treatment and one patient under dialysis. Five patients (28%) had a response in at least one affected organ. Hematologic responses were rapid (median 0.9 months) and median time to organ response was 4 months. Neurotoxicity, fatigue, peripheral edema, constipation and exacerbation of postural hypotension were manageable although necessitated dose adjustment or treatment discontinuation in 11 patients.

Interpretation and Conclusions

The combination of BD is feasible in patients with AL amyloidosis. Patients achieve a rapid hematologic response and toxicity can be managed with close follow-up and appropriate dose adjustment. This treatment may be a valid option for patients with severe heart or kidney impairment.

Key words: primary amyloidosis, bortezomib, BNP, renal failure

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Primary systemic (AL) amyloidosis is a clonal plasma cell disorder in which the N-terminal fragments of monoclonal light chains form fibrils that accumulate in various organs ultimately leading to organ dysfunction and death.[1] Once the diagnosis of AL amyloidosis has been established, prompt initiation of treatment is required in order to inhibit growth of the malignant clone and to reduce the supply of the amyloidogenic light chains. Treatment choices depend on the patient's age and performance status and on the type and extent of organ damage.[2] Older studies with standard doses of melphalan and prednisone provided modest results but some patients survived for 10 years or more.[3-5] Intravenous administration of high dose melphalan (HDM) supported by autologous stem cell transplantation (ASCT) significantly increased the hematologic and organ responses and improved survival, but at the expense of a treatment-related mortality rate ranging between 14% and 43% depending on the severity of the heart involvement and number of organs affected.[6-15] A risk-adapted approach has been attempted to adjust the dose of melphalan according to the patient's age and organ involvement;[12, 16] with this approach early mortality is reduced but the response rate appears to be lower.[12, 17] Another important advance in the treatment of AL amyloidosis was the observation that a modified schedule of high dose dexamethasone was effective in many patients with this disease.[18] When oral melphalan was added to dexamethasone, hematologic responses were observed in 67% of patients ineligible for HDM.[19] Furthermore, a recently reported randomized trial which compared melphalan-dexamethasone to HDM with ASCT showed that both approaches induced similar response rates and that the survival of patients treated with HDM and ASCT was inferior in centers without significant experience.[20] Despite these advances there is a need to discover new agents with activity in AL amyloidosis, especially for patients who have failed to benefit from the above-mentioned treatments. Novel biological agents that have been used successfully in the treatment of refractory/relapsed multiple myeloma, such as thalidomide and lenalidomide, have been used with encouraging results in the treatment of AL amyloidosis.[21-26] Bortezomib is a selective proteasome inhibitor that has significant activity in patients with refractory/relapsed multiple myeloma including those who have failed to benefit from HDM and/or thalidomide.[27,28] Furthermore there is a significant *in vitro* and *in vivo* synergism between bortezomib and dexamethasone both in pretreated[29] and in newly diagnosed[30,31] patients with multiple myeloma. Based on the significant activity of bortezomib and dexamethasone in multiple myeloma, we administered this combination to consecutive patients with AL amyloidosis in order to assess its tolerability and efficacy.

Design and Methods

Consecutive patients with biopsy-proven AL amyloidosis were treated with the combination of bortezomib and dexamethasone on a compassionate basis. All AL patients seen in our Center since September 2005 were offered treatment with BD. Although this was not a formal clinical trial, all adverse events were prospectively and systemically recorded. Patients were excluded if they had uncontrolled diabetes, active peptic ulcer disease, had prior malignancy or were pregnant or lactating. All diagnostic material was centrally reviewed by an experienced pathologist (AT). All patients signed informed consent, which was approved by the Institution's review board.

Laboratory and clinical assessments

Baseline evaluation prior to treatment initiation included a complete physical examination, serum and urine immunofixation and electrophoresis, measurement of serum free light chains, β-2 microglobulin levels, assessment of liver and renal function, 12-lead ECG, cardiac and abdominal echocardiography, bone marrow aspirate and biopsy and skeletal survey. Congo red staining was available for all patients but amyloid typing with κ or λ antibodies was available for only 12 (67%) patients due to technical difficulties that are well known with amyloid typing with anti-κ or anti-λ. However in all patients without amyloid typing but only Congo red staining, typical clinical and laboratory features were considered to establish the diagnosis of AL amyloidosis. Brain natriuretic peptide (BNP) in plasma was used for assessment of risk and follow-up of heart disease (Triage B-type Natriuretic Peptide test, Biosite Diagnostics Inc., San Diego, California, USA). It has been shown that BNP assessment can accurately follow heart failure patients with renal insufficiency, even those who undergo dialysis, while it has been validated as a risk marker and has been found to have a strong correlation with NT-pro-BNP levels in heart failure patients as well in AL patients.[32-34] Depending on their clinical presentation patients had a computed tomography of the chest abdomen and pelvis. Complete blood count, biochemical survey and free light chains (FLC) were assessed before each cycle. In the case of cardiac or renal involvement, cardiac biomarkers and 24-hour urinary proteins were also assessed before each cycle. Cardiac echocardiography was conducted at baseline and every 3 months thereafter.

Organ involvement, response and progression were assessed and followed as described in the Consensus Criteria by Gertz *et al*.[35] Hematologic response was assessed as described in the same criteria[35] for patients with measurable disease (i.e. those with immunoglobulin light chain values greater than 100 mg/L) using the FREELITE assay. FLC partial response (PR) was defined as a ≥ 50% fall in the involved monoclonal class; FLC complete response (CR) was defined as normalization of the FLC ratio and both light chain classes. For patients with severely impaired renal function FLC response assessment is difficult due to polyclonal light chain retention. Therefore for patients with renal failure the FLC ratio was used for assessment of response as previously described.[23] When the

95% confidence interval (CI) for the concentration of the affected light chain of the FREELITE assay is used, a value twice or more the upper limit of the 95% range (≥38.8 mg/L for κ light chains and ≥52.6 mg/L for λ chains)[36] was considered assessable for patients without renal failure.[23] Standard EBMT criteria were also used for the assessment of patient with measurable disease. Toxicity was recorded according to the National Cancer Institute Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (Version 3.0). Performance status was assessed as described by the Eastern Cooperative Oncology Group (ECOG) criteria.

On an intention-to-treat basis, patients who died during the study before hematologic response could be assessed were rated as having had hematologic progression. Progression-free survival was defined as the time from initiation of treatment to hematologic or organ relapse or death due to progressive amyloidosis. Overall survival was calculated from the date of initiation of treatment to the last contact with the patient or death.

Treatment schedule

The treatment schedule consisted of bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11 and dexamethasone 40 mg on days 1-4, every 21 days for up to six cycles. All patients received prophylaxis with valacyclovir 500 mg daily and trimethoprim-sulfamethoxazole three times weekly. Omeprazole was given to all patients at least during the administration of dexamethasone. Supportive treatment for edema, congestive heart failure or autonomic neuropathy was administered according to clinical requirements. Amiodarone was given as prophylaxis to patients with abnormal results of a 24-hour Holter monitoring study. Depending on toxicity the dose of bortezomib was reduced stepwise to 1 mg/m^2 or 0.7 mg/m^2 with the same schedule or to 0.7 mg/m^2 on days 1 and 8 as described in the drug's prescribing information.[37] The dexamethasone dose was reduced to 32 mg or 24 mg depending on toxicity.

Patients' characteristics

Between September 2005 and January 2007, 18 consecutive patients were treated with the combination of bortezomib and dexamethasone. Table 1 presents the baseline characteristics of these patients. Fifteen patients (83%) had positive serum or urine immunofixation before treatment initiation: four had IgG(λ), three had IgA(λ), six had λ-light chains and two κ-light chains while in three patients immunofixation was negative in both serum and urine. The median bone marrow plasmacytosis was 20% (range 0 to 80%). Ten patients had >10% plasma cells. However, none of these patients had other features suggestive of myeloma such as lytic bone lesions, hypercalcemia, significant anemia unrelated to renal impairment or predominant Bence Jones proteinuria. Eleven patients (61%) were previously untreated and seven were rated as having relapsed after or been refractory to previous treatments (median number of previous treatments one, range 1-3).

Table 1. Patients' characteristics.

Male/Female	8 / 10
Age (median/range)	60.5 (42-80)
Untreated/Pretreated	11 / 7
Previous treatments*	
p.o Melphalan/high dose dexamethasone	2
VAD	5
IV Melphalan/high dose dexamethasone	1
HDM	1
Thalidomide/cyclophosphamide/dexamethasone	1
Light chain type κ/λ	2/16
Heavy chain (by immunofixation) IgG/IgA/light chain only	4/3/8
Involved FLC, mg/L (median/range)	216 (41-2739)
Bone marrow plasma cells (median/range)	20% (<5-80%)
Organ involvement	
Heart	15
Kidney	14
Liver	0
Peripheral nerve	3
Gastrointestinal tract	3
Number of organs involved	
One	7
Two	6
More than two	5
Ejection fraction (median/range)	70% (47-84%)
EF <55%	1
LV septum mm (median/range)	15 (10-20)
NYHA class >1	12
Baseline biochemical measurements	
BNP pg/mL (median/range)	324/59-4790
BNP >120 pg/mL	14
β2-microglobulin >3.5 mg/dL	8
Creatinine >2 mg/dL	6
Albumin <3.5 g/dL	10
Urine protein (mg/24hrs)	2800 (900-7600)

**Three patients had received more than one prior treatment. EF: ejection fraction; LV: left ventricular.*

The median duration of prior treatments in pretreated patients was 17 months (range, 1 to 42). Five patients (28%) had not responded to previous high dose dexamethasone-based treatments and one had not responded to thalidomide/dexamethasone-based treatment. Eleven (61%) patients had two or more organs involved (median number of involved organs; range, 1-4); kidneys and heart were affected more often (Table 1).

The majority of patients had significant morbidity related to their amyloidosis: peripheral edema (89%), weight loss (50%), syncope (17%), dyspnea (67%), neuropathic pain (22%), and orthostatic hypotension (39%). Twelve (67%) patients had severely affected functional status (ECOG performance status ≥2), 12 (67%) patients were in NYHA class >1 and 14 (78%) patients had pretreatment BNP values >120 pg/mL. The median serum

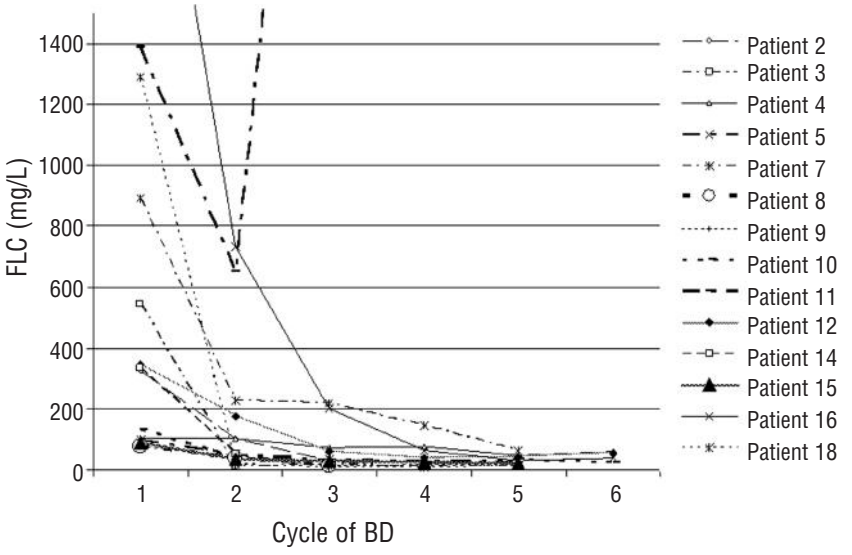

Figure 1. Involved FLC at baseline and after each cycle of BD.

creatinine was 1.65 mg/dL (range, 0.5-8.9), five patients (28%) had a baseline serum creatinine of more than 4 mg/dL and three patients (17%) were on dialysis due to end-stage renal failure.

Treatment outcome

According to EBMT criteria only five patients (29%) had measurable disease and all of them responded: three with immunofixation negative CR and two with a PR. The CR were confirmed by bone marrow aspiration. Among ten patients who were assessable for hematologic response by FLC (i.e. involved FLC >100 mg/L)[35] eight (80%, 95% CI 44-97%) patients responded with a >50% reduction in their involved FLC (Figure 1). Of the three patients with an abnormal FLC ratio but with involved FLC <100 mg/L, two achieved a normal FLC ratio and could be classified as responders. With either EBMT or FLC criteria 14 out of 15 (93%) evaluable patients had a hematologic response. When all assessable patients with an abnormal FLC ratio were considered, 12 out of 15 evaluable patients (80%, 95% CI 52-96%) achieved a normal FLC ratio. Among patients who achieved a normal FLC ratio, ten had negative serum and urine immunofixation after treatment and three had negative immunofixation before treatment while in two patients immunofixation data were not available after treatment. Thus 15 (94%) of 16 evaluable patients had a hematologic response and seven (44%) achieved a hematologic CR.[35] Five patients who had hematologic progression while on or shortly after high dose dexamethasone-based therapy all had a hematologic response, with three of them achieving a normal FLC ratio. The patient refractory to thalidomide-dexamethasone also had a hematologic response to BD. Of the three patients who were under dialysis while on treatment, one achieved a normal FLC ratio, one progressed and died after 4 months and one died before she was assessable for response. Renal responses were seen in two of 14 (14%) patients with renal involvement. There were no cardiac responses according to echocardiographic criteria;[35] however, in three of 15 (20%) patients NYHA class improved by two classes (without an increase in diuretic need or wall thickness) including two patients who before BD treatment had weekly infusions of inotropes and discontinued inotropes after treatment completion. Seven of 15 (47%) patients had a sustained >50% reduction in BNP levels. Thus, overall five patients (two patients with renal and three patients with heart response) (28%, 95% CI 10-53%) had a response in at least one affected organ. The median time to hematologic response was 0.93 months (range, 0.7-1.5) and median time to organ response was 4 months (range, 2-8). Seven patients continue to be in hematologic CR (a median of 8.5 months, range, 2.6-19). On an intention-to-treat basis, eight (44%) patients have had disease progression, including three patients (17%) who died while on treatment (two of whom had a partial hematologic response at the time of their death while the other died before she was assessable for response). Five patients had either hematologic or organ progression at a median of 6.8 (range, 1.3-10.3) months after the initiation of treatment. The median follow-up after initiation of treatment for all patients was 9.5 months (range, 0.7-21) and 11.2 months (range, 3.5-21) for living patients. The median overall survival for all patients has not been reached with 14 (78%) patients alive 3.5 to 21 months after initiation of treatment.

Toxicity

The median number of cycles administered was five (range 1 to 6), Twelve patients received four or more courses and six patients (33%) received six courses. Among the 12 patients who received less than six courses the reasons were: hematologic or organ progression (1 patient), disease-related death (3 patients) and toxicity of BD (8 patients). Bortezomib toxicity was the main reason for discontinuation; dexamethasone toxicity was manageable and transient.

Table 2. Detailed patient outcome.

Patient/ Gender/ Age	Pre-treated	Status	BD cycles	Mean bortezomib dose per cycle (mg/m^2)	Organs involved	BNP baseline >120 pg	NYHA baseline	ECOG PS	Affected FLC before treatment	Affected FLC after treatment	Hematologic response	Organ response[35]	Follow-up (months)	Hematologic OR organ relapse
1/F/ 47	No	Alive	3	5.2	R	No	0	0	MD	13	YES- CR (EBMT+FLC)	NR	21	
2/M/45	No	Dead	3	5.2	H,R,GI,N	Yes	3	3	326	31	YES (FLC)	NE	1.8	Early death
3/F/60	Yes	Alive	5	4.8	H,R,GI	Yes	2	2	546	5	YES- CR (FLC)	R,H	19	
4/M/61	Yes	Alive	4	5.2	H,R,N,ST	Yes	2	2	105	47	YES (EBMT+FLC)	NR	20	
5/M/79	No	Alive	5	5.2	H,R	Yes	2	2	100	25	YES (EBMT+FLC)	NR	17	Yes
6/M/62	Yes	Alive	4	4.4	R	NO	0	1	41	29	NE	NR	16	Yes
7/F/68	No	Alive	5	5.2	H,R,N,ST,GI	Yes	2	2	894	64	YES (FLC)	H	15.5	Yes
8/F/76	No	Dead	3	3.6	H	Yes	3	2	77	14	YES (FLC)	NR	1.8	
9/F/42	No	Alive	6	5.2	R,H	NO	0	0	78	13	YES – CR (FLC)	R	10	
10/F/46	Yes	Alive	6	4	R,H	Yes	0	1	134	25	YES (FLC)	NR	10.2	
11/F/50	No	Dead	2	4.9	H,R(DIALYSIS),ST	Yes	3	3	1390		PD	NR	3,4	
12/F/47	Yes	Alive	6	5.2	H,R(DIALYSIS)	Yes	4	2	347	38	YES-CR (FLC)	H	12	
13/F/80	No	Dead	1	5.2	H,R(DIALYSIS)	Yes	3	3	216	–	NE	NE	0.7	Early death
14/M/58	Yes	Alive	2	5.2	R	MD	0	2	334	53	YES (FLC)	NR	9	
15/F/61	Yes	Alive	5	4.2	R,H	Yes	3	2	89	22	YES (FLC)	NR	5.8	
16/M/78	No	Alive	6	5	H	Yes	2	1	2780	20	YES-CR (EBMT+FLC)	NR	5	
17/M/56	No	Alive	6	4.6	H	Yes	1	1	52	21	YES-CR (EBMT)	NR	4.5	
18/M/75	No	Alive	6	4	H	Yes	3	2	1290	13	YES-CR (FLC)	H	3.5	

H: heart; R: renal; N: peripheral nerve; ST: soft tissue; GI: gastrointestinal; NE: not evaluable; NR: no response.

There were no treatment-related deaths although three patients died due to complications of their disease while they were on treatment. All three of these patients had multiorgan involvement with severe cardiac dysfunction (Table 2). Grade 3-4 hematologic toxicity occurred in two patients and consisted of short lasting thrombocytopenia. Non-hematologic toxicities were mainly neurotoxicity, fatigue, peripheral edema, constipation and exacerbation of postural hypotension. Grade 3 non-hematologic toxicities necessitating dose reduction or treatment termination were grade 3 fatigue together with grade 3 orthostatic hypotension in two patients who had received four and five cycles, respectively, and neurotoxicity in one patient, after two cycles of treatment. Other grade 3 toxicities were diarrhea, constipation and orthostatic hypotension. Exacerbation of orthostatic hypotension was a considerable problem in the management of our patients, especially in those who had symptoms suggestive of autonomic neuropathy at baseline. Nine (50%) patients were given fluorocortisone for symptomatic treatment of orthostasis. Notably all patients who responded to treatment have fully recovered and are completely asymptomatic from orthostatic symptoms, even these who had such symptoms pre-treatment.

Dose reduction was required in seven (39%) patients, one patient discontinued treatment due to peripheral neuropathy and one due to fatigue, neurotoxicity and orthostatic hypotension. There were no infectious complications during the treatment course or at least 6 months after its termination.

Discussion

An effective treatment for patients with AL amyloidosis should induce hematologic responses in a high percentage of patients, should lead to a rapid reduction of amyloidogenic free light chains, should be associated with the least possible treatment-related mortality and show activity in patients whom standard regimens fail. These properties are crucial for patients with severe impairment of performance status, with high NYHA class and significantly elevated levels of cardiobiomarkers and with impaired renal function. We provide preliminary evidence that the combination of bortezomib with dexamethasone (BD) fulfills these requirements. We treated 18 consecutive patients with poor risk features who were essentially ineligible for HDM with ASCT and we observed hematologic responses in 94% including CR in 44%. We observed that the BD combination was also active in patients in whom high-dose dexamethasone-based or thalidomide based regimens had failed. Furthermore, the median time to response was rapid, being 0.9 months. In contrast, the median time to response to high dose dexamethasone based regimens ranges from 3.5 to 6 months.[18,19,21,38] The kinetics of FLC after BD showed that at least a 50% reduction occurred in all patients within two courses of treatment. These data suggest that BD may be discontinued after two courses if there is no FLC response and that an alternative treatment could be used. Another report presented in an abstract

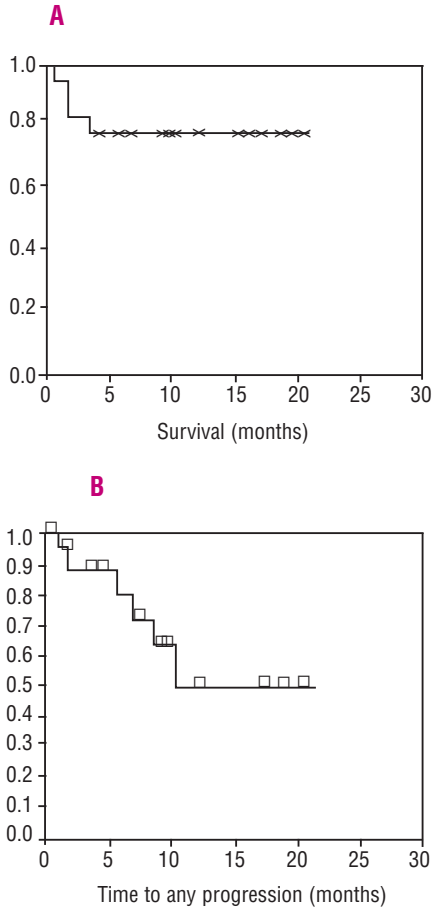

Figure 2. A. Survival (X^2 censored). B. Time to any type of progressived disease (hematologic or organ progression or death) (□ censored).

form indicated that bortezomib as a single agent induced hematologic responses in a significant number of patients.[39] Thus bortezomib may become a valuable treatment option for AL patients, especially those ineligible for HDM or those who relapse after other treatments.

There are considerable difficulties in assessing organ and hematologic responses in amyloidosis patients. Hematologic response is often difficult to measure since most patients with AL do not have measurable disease by classic EBMT criteria or even do not have paraprotein levels detectable by classical methods.[40] Indeed in many reports only a minority of patients have measurable paraprotein levels[3,23,25,35,38,41] and this was also the case in our study. Although the introduction of FLC measurement by the FREELITE assay has become a standard for the quantification of hematologic responses of patients with AL[35] there are still difficulties in the interpretation of the results, especially in patients with renal impairment or those with *non-measurable* absolute FLC values. We assessed hematologic responses using both consensus criteria[35] and criteria outside the consensus statement but that have been reported or published in larger scale studies.[23,42] Although different numbers of patients are assessable by these different criteria, the overall high response rate remains practically unaltered. Although follow-up is relatively limited, seven patients remain in hematologic CR and five patients maintain their organ responses for a median of 8.5 and 7 months, respectively. However longer follow-up is needed to fully evaluate the durability of both hematologic and organ responses.

Table 3. Major toxicities of bortezomib-dexamethasone in AL patients.

Toxicity	*Any grade (%)*	*> Grade 2 (%)*
Neurotoxicity	67	7
Orthostatic hypotension	56	13
Constipation	39	6
Diarrhea	11	0
Thrombocytopenia	22	11
Hyponatremia/hypokalemia	28/6	6/6
Fatigue	61	11
Edema	50	0
Nausea/vomiting	6	0

It has been postulated that amyloidogenic light chains may have a direct toxic effect on myocardial cells.[43,44] This is in concordance with the observation that NT-proBNP levels in patients achieving a hematologic response decrease along with clinical improvement, although echocardiographic findings are not significantly altered.[45,46] This is an observation that is also applicable to our patients: they did not fulfill echocardiografic criteria of response but had a substantial improvement in NYHA class status along with a decrease in BNP levels, reduction of diuretic needs and discontinuation of inotropes, reflecting the benefit from BD treatment.

The management of patients with severely impaired renal function or those undergoing dialysis is also particularly challenging. HDM is a very high risk procedure for these patients and oral melphalan dosing needs to be adjusted, with unpredictable results.[47,48] Furthermore such patients are not eligible for lenalidomide-based regimens.[25,26] Bortezomib has been used successfully in patients with multiple myeloma and renal dysfunction.[49,50] Two of five patients with a creatinine level of more than 4 mg/dL had a hematologic response and one patient undergoing dialysis achieved a normal FLC ratio. The toxicity profile of BD in patients with or without renal impairment appeared similar. Thus BD is a valid option for patients with severe renal impairment.

Toxicity is a major concern in patients with AL amyloidosis due to multisystemic organ involvement. Thalidomide[22-24] as well as lenalidomide[25,26] were not tolerated well in patients with AL reflecting the difficulties in the management of these frail patients. The toxicity of the BD combination was manageable provided that the patients were followed closely and dose adjustments were made. Neurotoxicity is a major concern with bortezomib treatment and this poses a considerable problem since AL patients very often have peripheral or autonom-

ic neuropathy due to amyloid nerve disease. AL patients treated with bortezomib need close monitoring and dose modifications for the assessment and management of neuropathy. Of particular consideration was the high incidence of postural hypotension, especially in patients with pre-existing symptoms of autonomic neuropathy. However, we observed that symptoms were significantly improved after treatment completion, probably reflecting an overall improvement of these patients' disease. The high incidence of early deaths in our series was not due to treatment but rather reflects the high risk features of the disease in these patients since they all had severely affected general functional status (assessed by ECOG performance status) and cardiac function (as assessed by their NYHA class and high BNP levels). Selection of patients with better prognostic features would probably give significantly better results and this should be evaluated in a larger, prospective study.

Given the small number of patients included in our study it is difficult to identify prognostic factors either for response or survival. However all patients who died had severe cardiac involvement, high BNP values, severely affected ECOG performance status and high NYHA class. Thus we can assume that established prognostic factors[51] can be applied in our patients too. The inclusion of high risk patients makes our series representative of the general AL population and further supports the feasibility of bortezomib use in this population. Myocardial involvement is a common cause of death in AL amyloidosis and a poor predictor of survival[52] while elevated serum cardiac troponins are related to poor prognosis in patients treated with either HDM or conventional treatment.[51,53] This high risk group is the one most difficult to manage and a rapid reduction in light chain production is urgent.

In conclusion, the combination of bortezomib and dexamethasone is a promising treatment option for patients with AL amyloidosis who are not eligible for or relapse after HDM. Patients with severe cardiac dysfunction or renal impairment can be managed with BD with a high probability of rapid response. Toxicity is manageable and predictable although close monitoring of both peripheral and autonomic neuropathy is warranted. Further studies in a larger population are needed in order to establish the role of BD in the treatment of patients with AL amyloidosis.

Authors' Contributions

EK wrote the manuscript, analyzed the data and treated the patients, AA critically reviewed the manuscript, collected data and treated the patients; MR, ST and CP critically reviewed the manuscript; AT reviewed the pathologic specimens of all patients and critically reviewed the manuscript; IX, SD, EP, SM, ET and JN critically reviewed the manuscript and treated the patients; MAD analyzed the data, co-wrote the manuscript and treated the patients.

Conflict of Interest

The authors reported no potential conflicts of interest.

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