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Induction Therapy with Bortezomib and Dexamethasone and Conditioning with High-Dose Melphalan and Bortezomib Followed by Autologous Stem Cell Transplantation for Immunoglobulin Light Chain Amyloidosis: Long-Term Follow-Up Analysis

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A B S T R A C T

In immunoglobulin light-chain (AL) amyloidosis, the depth of hematologic response to treatment is associated with improved survival and organ responses. We conducted a clinical trial using bortezomib in induction and in conditioning with melphalan before stem cell transplantation (SCT) for AL amyloidosis. The results of this clinical trial with a median follow-up of 36 months have been reported previously. Here we report the long-term results of this clinical trial with a median follow-up of 77 months. We describe survival, durability of hematologic and organ responses, and relapse rates. Thirty-five patients were enrolled between 2010 and 2013. Hematologic complete response and very good partial response (VGPR) were noted in 100% (27 of 27) of the evaluable patients at 6 months post-SCT. Four patients (15%) had hematologic relapse at a median of 42 months, and 1 patient (3.7%) had organ progression despite maintaining a VGPR at 37 months. The median overall survival and progression-free survival have not yet been reached at the time of this report. Renal and cardiac responses occurred in 65% and 88%, respectively, at 5 years post-SCT. The median time to renal and cardiac response was 12 months and 6 months, respectively. In conclusion, incorporating bortezomib into induction and conditioning yielded durable hematologic responses of AL amyloidosis, with corresponding organ responses and prolonged survival.

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INTRODUCTION

Immunoglobulin light chain (AL) amyloidosis is a rare disease caused by monoclonal light chains secreted by clonal plasma cells. These light chains misfold and form insoluble fibrils, which can be deposited into the extracellular space of tissues and organs, leading to progressive organ impairment and organ failure if left untreated.

Current treatments for AL amyloidosis target the underlying plasma cell dyscrasia in an effort to stop production and hence the deposition of amyloidogenic proteins, which has been shown to improve survival [1]. Among a highly selected group of patients at a tertiary referral center, high-dose i.v. melphalan followed by autologous stem cell transplantation (HDM/SCT) resulted in a hematologic complete response (CR) rate of 34% and median overall survival (OS) of up to 6.3 years [2]. For intermediate- to high-risk patients who are not candidates for HDM/SCT, melphalan in conjunction with dexamethasone is considered standard therapy and has been shown to result in a high rate of hematologic response (67%) and a median OS of 5.1 years [3]. More recently, the proteasome inhibitor bortezomib, either as a single-agent [4] or as part of a multidrug regimen (ie, cyclophosphamide, bortezomib, and dexamethasone [CyBorD]), has been shown to improve hematologic response rates and OS [5].

In an earlier report in 2015, we published the results of a clinical trial (ClinicalTrials.gov identifier NCT01083316) using bortezomib and dexamethasone followed by HDM/SCT for AL amyloidosis [6]. This prospective single-arm trial aimed to assess the efficacy of induction therapy with bortezomib and dexamethasone for 2 cycles, followed by conditioning with bortezomib in addition to high or modified doses of the melphalan and autologous SCT for 35 patients with AL amyloidosis. We found hematologic responses to be unprecedentedly high, with hematologic very good partial response (VGPR) or CR at 6 months post-SCT of 77% among all enrolled participants

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and 100% for the 27 evaluable patients. Organ-specific responses were also reported, with a renal response of 56% and cardiac response of 87% at 24 months post-SCT.

Here we report on the long-term outcomes of these patients treated on this clinical trial with a median follow-up of 77.3 months (range, 55.4 to 100.1 months). This longer follow-up allows us to address the issues of durability of hematologic and organ response and probabilities of relapse and survival.

METHODS

Patient Eligibility and Treatment Design

This clinical trial was approved by the Institutional Review Board at Boston Medical Center in accordance with federal regulations and the Declaration of Helsinki (ClinicalTrials.gov identifier NCT01083316). Criteria for undergoing HDM/SCT with bortezomib induction and patient eligibility have been reported previously [6]. The treatment design consisted of 2 cycles of induction chemotherapy with bortezomib 1.3 mg/m^2 i.v. and dexamethasone 20 mg i.v. on days 1, 4, 8, and 11 in a 21-day cycle. This was followed by stem cell mobilization using granulocyte colony-stimulating factor at 16 μg/kg/day. Patients then underwent conditioning with bortezomib at 1.0 mg/m^2 i.v. on days -6, -3, +1, and +4, and high-dose melphalan at 200 mg/m^2 or at a modified dose of 140 mg/m^2, administered in divided doses on days -2 and -1, followed by reinfusion of collected stem cells.

Hematologic and Organ Response Criteria

Hematologic responses were evaluated according to the consensus criteria of the International Society of Amyloidosis published in 2010 [7]. Cardiac response was measured as a 30% reduction in brain natriuretic peptide (BNP) from baseline [7]. Renal response was measured as a 30% decrease in proteinuria (or <.5 g/24 hours) compared with baseline, in the absence of a >25% reduction in estimated GFR [8].

Outcomes

The primary outcome was the hematologic CR rate at 2, 3, 4, and 5 years following HDM/SCT. Secondary outcomes included OS as measured from the time of enrollment, progression-free survival (PFS) as measured from time of enrollment to initiation of second-line treatment, and organ response rate. All patients were censored at the time of last contact (May 8, 2018).

Statistical Analysis

This follow-up analysis was conducted using MATLAB (MathWorks, Cambridge, MA). OS and PFS were calculated using the Kaplan-Meier method, with a start date of the time of enrollment and a data cutoff date of May 8, 2018.

RESULTS

Patient Characteristics

A total of 35 patients with newly diagnosed AL amyloidosis were enrolled between January 2010 and August 2013. Demographic and baseline disease characteristics of the study cohort have been reported previously [6]. In summary, the median patient age at time of enrollment was 56 years (range, 36 to 70 years), and 22 patients (63%) were women. As expected, 30 patients (86%) had a lambda light chain isotype, 20 (57%) had multiorgan involvement, 30 (86%) had renal involvement, and 18 (51%) had cardiac involvement. Of the 35 enrolled patients, 32 proceeded to stem cell mobilization and collection, and 30 proceeded to SCT. Of the 5 patients who did not undergo SCT, 3 (8.6%) did not proceed to stem cell mobilization because of worsening performance status and organ function during induction, and 2 (5.7%) did not proceed after stem cell collection owing to the development of heparin-induced thrombocytopenia in 1 patient and worsening of performance status due to lumbar radiculopathy in the other, which made them ineligible for SCT. Five patients (14%) required dosage modification and/or discontinuation of bortezomib during induction owing to grade 3 or 4 adverse events: skin rash in 1, syncope due to orthostatic hypotension in 2, and worsening renal function progressing to end-stage renal disease (ESRD) in 2. One patient (3%) required discontinuation of dexamethasone because of grade 3 peripheral edema.

Hematologic Responses

Hematologic CR and VGPR were achieved by 100% (27 of 27) of evaluable patients at 6 months and 12 months post-SCT, respectively. Hematologic CR was achieved by 20 patients (77%) and hematologic VGPR was achieved by 6 patients (23%) at 12 months post-SCT. By intention-to-treat analysis, hematologic CR and VGPR were achieved by 77% (27 of 35) and 74% (26 of 35) at 6 months and 12 months post-SCT, respectively. Two patients converted from VGPR at 1 year post-SCT to CR at 2 years post-SCT without receiving additional therapy.

Hematologic Relapse and Progression

Of the 27 patients who achieved a hematologic CR or VGPR, 4 (14.8%) had a hematologic relapse at a median of 42.3 months (range, 34.5 to 63.0 months), and 1 (3.7%) required second-line treatment owing to worsening proteinuria and renal function despite maintaining a hematologic VGPR. Of the 4 patients who experienced hematologic relapse, 2 had achieved a VGPR and 2 had achieved a CR at 6 months. Immunomodulatory agents were used for treatment in 2 patients (lenalidomide in 1 and pomalidomide in 1), and ixazomib was used in 2 other patients. The patient with organ progression and maintenance of VGPR received treatment with bortezomib followed by daratumumab.

In addition to the 5 patients requiring second-line treatment, 4 patients (14.8%) also had a biochemical relapse, defined as the reappearance of monoclonal light chains in serum or urine immunofixation electrophoresis without associated difference between involved and uninvolved free light chain (dFLC) progression or organ progression, and did not need second-line treatment. The median time to biochemical relapse was 52.7 months (range, 49 to 78.6 months). The median time since biochemical relapse without the need for additional treatment was 12.5 months (range, 7 to 44 months). All 4 of these patients had initially achieved a hematologic CR at 1 year post-SCT.

OS and PFS

The median duration of follow-up for surviving patients was 77.3 months from enrollment (range, 55.4 to 100.1 months). The Kaplan-Meier survival curves for OS and PFS are shown in Figure 1. The median OS and PFS have not yet been reached.

Eight deaths have occurred in the follow-up period. Three deaths occurred within 100 days of SCT, for an overall early mortality of 8.5%. The causes of death were multiorgan failure due to sepsis, invasive aspergillosis, and influenza A infection complicated by multilobar bronchopneumonia and respiratory failure. Another 5 deaths occurred from fluid overload due to ESRD, including 2 from congestive heart failure, bacterial pneumonia, and *Klebsiella pneumoniae* bacteremia with multiorgan failure.

Organ Response

Renal response was achieved by 65% of patients at 5 years, and cardiac response was achieved by 88% at 5 years. The median time for renal response was 12 months (range, 6 to 24 months) post-SCT. The median time for cardiac response was 6 months (range, 6 to 24 months) post-SCT. The rate of renal response deepened from 40% at 1 year to 50% at 2, 3, and 4 years (Figure 2), and, similarly, cardiac responses deepened from 75% at 1 year to 92% in the years after SCT (Table 1). Of the 6 patients who did not achieve a renal response at 5 years, 3 needed renal replacement therapy for ESRD at a median of 26.3 months (range, 2.5 to 44.8 months). One patient who did not achieve a cardiac response at 5 years is doing well,

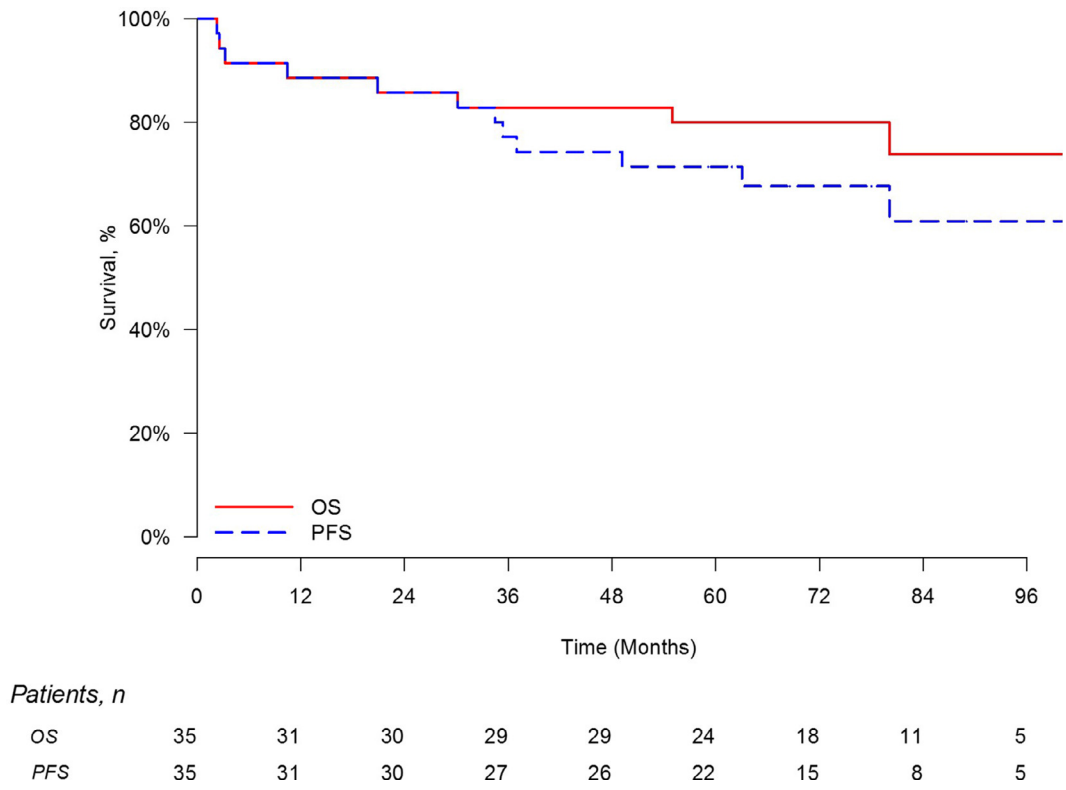

Figure 1. OS and PFS.

although cardiac response assessment by biomarkers has been difficult to access owing to the development of ESRD.

Toxicity

Treatment-related morbidity was described in the previous report and was notable for 2 cases of autologous graft-versus-host disease (GVHD). Both of these patients with possible autologous GVHD are alive at 6.1 and 8 years after SCT and remain in hematologic CR without signs of GVHD at this time. One patient developed spontaneous splenic rupture on day +16 that was successfully treated with splenic artery embolization [9]. She is alive without any associated complications or recurrence at 58 months after enrollment.

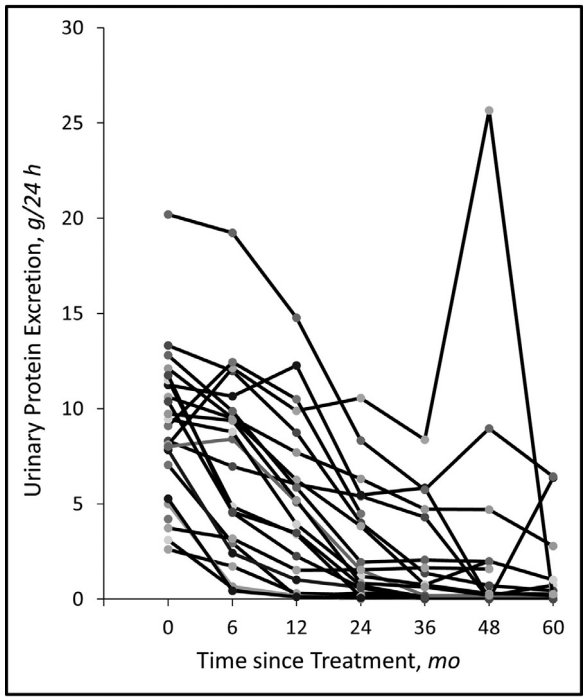

Figure 2. Changes in 24-hour urinary protein excretion in 23 patients with renal involvement after enrollment.

DISCUSSION

The results of long-term follow-up of this clinical trial provide support for the use of novel agents for induction and conditioning before SCT to treat AL amyloidosis to achieve deep and durable hematologic and organ responses, low hematologic relapse, and prolonged OS and PFS.

The present study is among the first to show a benefit of bortezomib in the induction and conditioning regimen in patients undergoing SCT for AL amyloidosis. AL amyloidosis is characterized by a small tumor mass, and thus induction chemotherapy before HDM/SCT is not necessary in many cases. Increasingly, however, induction therapy with novel agents (eg, proteasome inhibitors, immunomodulatory drugs) has been more widely studied and has shown higher hematologic response rates (87% partial response or better) and OS (87% 2-year OS) compared with induction with conventional chemotherapy or no induction [10]. Induction therapy can produce rapid hematologic response and prevent any further decline in organ damage while SCT is being arranged.

In addition to achieving unprecedentedly high hematologic response rates at 1 year (63% hematologic CR with a 74% overall hematologic response rate on intention-to-treat analysis), bortezomib induction and bortezomib-melphalan conditioned SCT resulted in durable hematologic responses, with 57% of patients with continued hematologic CR and 64% with an overall hematologic response at 5 years post-SCT. These

Table 1
Renal and Cardiac Responses after SCT

Response	6 Months	1 Year	2 Years	3 Years	4 Years	5 Years
Renal, % (n/N)	26 (6/23)	40 (9/22)	50 (11/22)	50 (11/22)	50 (11/22)	65 (11/17)
Cardiac, % (n/N)	46 (6/13)	75 (9/12)	92 (11/12)	92 (11/12)	83 (10/12)	88 (7/8)

hematologic response rates compare favorably to response rates with HDM/SCT without the incorporation of novel agents into induction and conditioning. Our previous study of 647 patients with AL amyloidosis treated with HDM/SCT found a hematologic CR rate of 32.9% by intention-to-treat analysis [11]. The results of the present clinical trial are favorable, with a hematologic CR rate of 63% by intention-to-treat analysis, which is attributed in part to the incorporation of bortezomib into induction and conditioning regimens. The hematologic relapse rate after initial achievement of CR was quite low, 15% at a median of 3.8 years. This again compares favorably to our previous report of hematologic relapse of 32.3% in a cohort of 647 patients [11]. Biochemical relapse, defined as reappearance of monoclonal light chain in serum or urine immunofixation electrophoresis without associated dFLC progression or organ progression and no need for second-line treatment, was noted in 15% of our present cohort. In these patients, careful and comprehensive evaluation is important to determine the need for further anti-plasma cell therapy versus ongoing active surveillance. It is important to note that early treatment might not be warranted in this group of patients.

Organ responses were also evident in a high proportion of patients, with renal response in 65% and cardiac response in 88% at 5 years on this trial. The median time to organ response was 12 months for renal response and 6 months for cardiac response. Organ responses were higher than reported in previous series from our center (cardiac response, 21%; renal response, 32%), [12] as well as from the Mayo Clinic (cardiac response, 5%; renal response, 23%) [13]. We attribute this to the higher hematologic response rates in our trial leading to higher organ responses.

Notably, the organ responses occurred within 1 year after SCT. Early organ response, defined as any organ response within 1 year after normalization of dFLC, has been associated with improved OS in patients who achieve a hematologic response from treatment [14]. Even though some of our patients did not demonstrate organ response until 2 years after HDM/SCT, 86% (18 of 21) of those who ultimately achieved an organ response met the criteria for early organ response. Organ responses were similar to those reported by Huang et al [15] from a randomized controlled trial of 56 patients with AL amyloidosis comparing bortezomib induction with HDM/SCT and HDM/SCT alone. Organ responses deepened from 12 months to 24 months.

Even with a longer median follow-up of 77 months, OS and PFS were significantly better in this trial compared with previous reports from our center and others. In studies using HDM/SCT, Landau et al [16] reported a median OS of 10.4 years in a cohort of 143 patients, Cibeira et al [2] reported a median OS of 6.3 years in 421 patients, and Warsame et al [14] reported a median OS of 7.4 years. The better OS in the present trial may be attributable to better patient selection and incorporation of novel agents.

This study has several limitations. First, this was a highly selected group of patients with AL amyloidosis, as only 25% of presenting patients are eligible for SCT because of age, comorbidities, or extent of cardiac damage [17]. Second, the small sample size precludes accurate and direct comparison with many larger studies that used HDM/SCT alone; however, we believe that our report may function as a proof of concept to be replicated on a larger scale, given the number and durability of responses. Third, cardiac response was evaluated based on modified biomarker response criteria with the use of BNP rather than NT-proBNP, which is the gold standard and validated biomarker [18]. Fourth, our small sample size did not allow for analysis of subgroups or predictive value of risk factors. Further research is needed to better evaluate these conditions.

In conclusion, the addition of bortezomib to induction and conditioning with HDM before SCT results in deep and durable hematologic and organ responses, with median OS and PFS exceeding 6 years. More research is needed to evaluate the role of incorporating other novel therapies into induction or conditioning before SCT and to assess for a role for novel agents in reducing amyloidogenic light chains such that patients who were previously ineligible for SCT may become candidates. Of note, 5 patients (14%) who were eligible for SCT at enrollment did not proceed to SCT owing to clinical deterioration during induction treatment, suggesting that careful selection of patients and type of induction therapy are crucial before SCT.

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