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Induction Therapy with Bortezomib Followed by Bortezomib-High Dose Melphalan and Stem Cell Transplantation for Light Chain Amyloidosis: Results of a Prospective Clinical Trial

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The depth of hematologic response has been shown to correlate with survival and organ responses for patients with light chain (AL) amyloidosis. We conducted a prospective trial of 2 cycles of induction with bortezomib and dexamethasone on a twice a week schedule followed by conditioning with bortezomib and high-dose melphalan (HDM) and autologous stem cell transplantation (SCT). The objectives were hematologic responses, tolerability, and survival. Thirty-five patients were enrolled from 2010 to 2013. Of these, 30 proceeded with SCT, whereas 5 did not because of clinical deterioration during induction (n = 3) or complications after stem cell collection (n = 2). Two patients developed features of an autologous graft-versus-host disease–like syndrome post-SCT, which responded to steroids; no other unusual complications were seen. Treatment-related mortality occurred in 8.5% (3/35). Hematologic responses were achieved by 100% of the 27 assessable patients (63% complete response, 37% very good partial response [VGPR]) who completed the planned treatment. By intention-to-treat, hematologic responses occurred in 77% of patients (49% complete response, 29% VGPR). With a median follow-up of 36 months, the median overall survival and progression-free survival were not reached. In conclusion, incorporating bortezomib into induction and conditioning yielded a high rate of hematologic responses after HDM/SCT in patients with AL amyloidosis.

INTRODUCTION

Immunoglobulin light chain (AL) amyloidosis is the most commonly diagnosed form of systemic amyloidosis. In this potentially lethal disorder, there is widespread deposition of amyloid fibrils, derived from monoclonal Ig light chains associated with an underlying clonal plasma cell dyscrasia [1]. Without effective treatment, amyloid oligomers and fibrillar deposits progressively damage organs and tissues. Chemotherapy that ablates the underlying plasma cell dyscrasia can arrest the deposition process and improve survival. This was suggested in early randomized trials using oral melphalan [2,3] but is much more evident in trials using high-dose i.v. melphalan and autologous peripheral blood stem cell transplantation (HDM/SCT) in which much higher hematologic response rates are seen [4-9]. In our cumulative data of more than 600 patients treated with HDM/SCT, the median overall survival (OS) of patients who achieve a hematologic complete response (CR) is >13.2 years compared with 5.9 years for those who do not, and clinical improvement in affected organ systems occurs in 76% of patients achieving a hematologic CR compared with only 39% of those who do not. There are similar differences with respect to improvements in performance status, quality of life, and organ responses [10-12]. Examination of the correlation of survival with suppression of serum free light chain levels after a variety of treatments also supports the importance of the depth of hematologic response [13,14].

Because hematologic CR is such a critical determinant of treatment outcome, different strategies have been studied that might increase the proportion of patients who ultimately achieve a hematologic CR after HDM/SCT. A randomized study examined the role of induction treatment

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with 2 cycles of oral melphalan and prednisone before HDM/SCT [15]. Following the experience in myeloma, tandem cycles of HDM/SCT have been studied in a phase II fashion [16,17]. Other phase II clinical trials have explored the role of consolidation therapy with novel agents after HDM/SCT [18,19].

Novel agents, including thalidomide [20], lenalidomide [21,22], and bortezomib [23,24], alone or in combination with steroids, are effective in the treatment of AL amyloidosis. Bortezomib, a reversible proteosome inhibitor, is an active and rapidly acting regimen for relapsed patients with AL amyloidosis when used alone as a single agent, in combination with dexamethasone, or in combination with an alkyating agent [25]. Furthermore, bortezomib has been combined with HDM conditioning regimens in a pilot study in AL amyloidosis with promising hematologic responses without additional toxicities [26].

These considerations prompted us to conduct a prospective trial of 2 cycles of bortezomib and dexamethasone as induction therapy followed by incorporation of bortezomib with HDM before SCT for the treatment of AL amyloidosis. The objectives of this prospective clinical trial were to determine the safety profile, hematologic response rate, and survival of 2 cycles of induction therapy with bortezomib and dexamethasone followed by incorporation of bortezomib into the conditioning regimen with HDM.

METHODS

Patient Eligibility

This clinical trial was approved by the Institutional Review Board of Boston Medical Center in accordance with federal regulations and the Declaration of Helsinki (ClinicalTrials.gov Identifier: NCT01083316). Eligibility for the study required a tissue diagnosis of amyloidosis with evidence of an underlying clonal plasma cell dyscrasia and absence of evidence of another type of amyloidosis. The plasma cell dyscrasia was assessed by clonal dominance of plasma cells in the bone marrow and/or detection of a monoclonal gammopathy by immunofixation electrophoresis of serum and urine proteins and/or an abnormal elevated serum free light chain concentration and/or ratio. Other eligibility criteria included a Southwest Oncology Group performance status score of $\leq$2, left ventricular ejection fraction >45%, and diffusion capacity of >50%. Patients with uncompensated congestive heart failure, symptomatic cardiac arrhythmias, syncope, pleural effusions refractory to medical management, or supine systolic blood pressure <90 mm Hg were excluded, as were patients with overt myeloma (>30% plasma cells, lytic bone lesions, or hypercalcemia) and grade $\geq$2 peripheral neuropathy. Patients requiring dialysis for end-stage renal disease were not excluded if other eligibility criteria were met. Modified cardiac biomarker staging was defined by the presence of brain natriuretic peptide >100 pg/mL and troponin I >.1 ng/mL, with stage I having no elevated biomarkers, stage II having either elevated, and stage III having both elevated.

Treatment Design

In this prospective study, newly diagnosed patients with AL amyloidosis who met the eligibility criteria for HDM/SCT were enrolled. Patients received 2 cycles of induction therapy with bortezomib 1.3 mg/m^2 i.v. and dexamethasone 20 mg i.v. on days 1, 4, 8, and 11 of the 21-day cycle. All patients received prophylaxis with a proton pump inhibitor and an antiviral medication. Bortezomib was held for grade 3 or 4 nonhematologic toxicities, until the toxicity resolved to grade 1 or better, for up to 2 weeks. Bortezomib was resumed at the next lower dose level. Planned dose reductions were 1.0 mg/m^2 (dose level −1) and .7 mg/m^2 (dose level −2). If the adverse event did not resolve as defined above after holding and delaying bortezomib, the drug was discontinued. Dose escalation was not allowed.

After the 2 induction cycles, stem cell mobilization was begun within 1 to 2 weeks. Stem cells were mobilized with granulocyte colony-stimulating factor (G-CSF) alone at 16 μg/kg/day for 3 to 4 days before stem cell

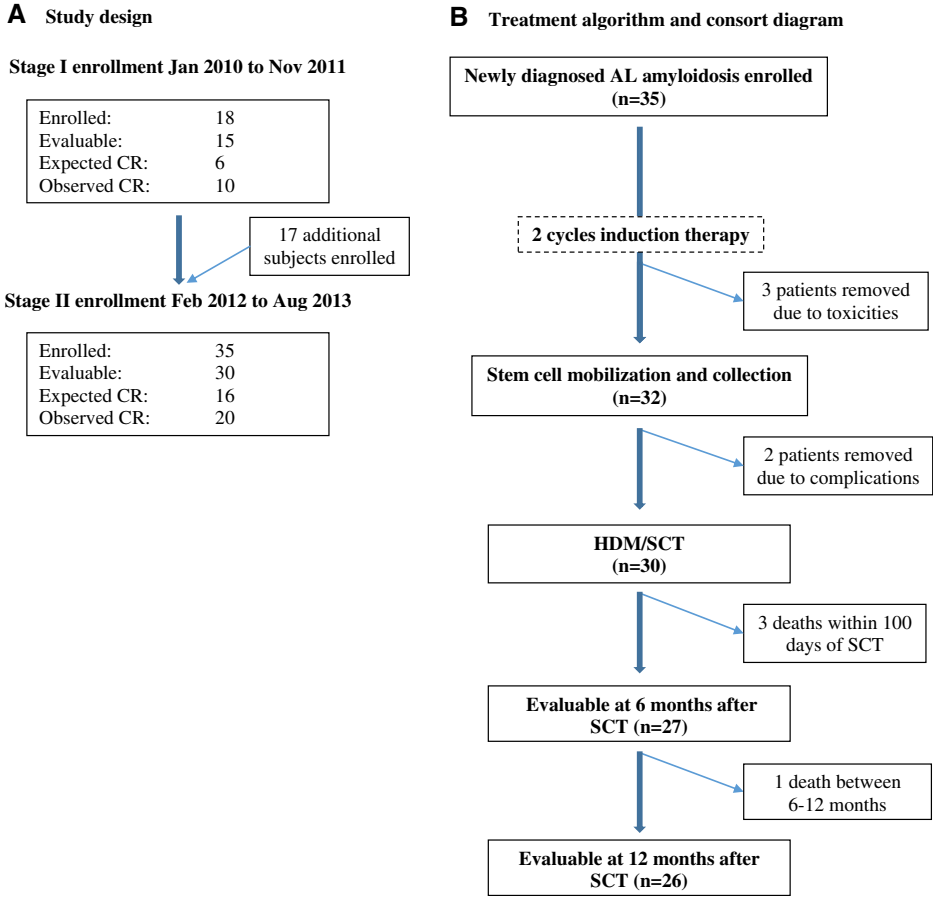

Figure 1. (A) Study design. (B) Treatment algorithm and consort diagram.