Biol Blood Marrow Transplant 22 (2016) 1729–1732

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

The Effect of Bone Marrow Plasma Cell Burden on Survival in Patients with Light Chain Amyloidosis Undergoing High-Dose Melphalan and Autologous Stem Cell Transplantation

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Article history:
Received 21 April 2016
Accepted 29 May 2016

Key Words:
Plasma cells
Light chain (AL) amyloidosis
Survival
Melphalan
Stem cell transplantation

A B S T R A C T

The prognosis in light chain (AL) amyloidosis has been linked to several variables, which are primarily related to end-organ damage. Recently, bone marrow plasma cell (BMPC) burden >10% has also been described as an adverse prognostic factor. We reviewed data pertaining to 546 patients with AL amyloidosis who underwent high-dose melphalan (HDM) and stem cell transplantation (SCT) to determine if BMPC > 10% was a negative prognostic factor. Of these patients, 445 had a BMPC burden ≤ 10% and 101 had a BMPC burden > 10%. Patients with BMPC > 30% were excluded from the study. The median overall survival (OS) was 7.86 years (95% confidence interval [CI], 6.69 to 9.83) in patients with BMPC ≤ 10% and 6.8 years (95% CI, 5.75 to 10.17) for those with BMPC >10% (hazard ratio, 1.106; 95% CI, .78 to 1.45; $P = .70$) after HDM/SCT. Of the 101 patients with a BMPC burden > 10%, 25 received induction therapy. The median OS was 7.78 years (95% CI, 5.4 to 13.4) for those without induction therapy and 5.75 years (95% CI, 3.94 to not available; $P = .28$) for those with induction therapy. Furthermore, hematologic response and relapse rates did not differ in these 2 groups after HDM/SCT. We conclude that BMPC > 10% and < 30% is not a poor prognostic factor with respect to survival in patients with AL amyloidosis treated with HDM/SCT and that induction therapy in this group does not impact OS.

INTRODUCTION

Immunoglobulin light chain (AL) amyloidosis results from misfolding of immunoglobulin light chains produced by the plasma cell dyscrasia, leading to formation of oligomers, aggregation, and amyloid fibril deposition in various organs and tissues [1]. High-dose melphalan (HDM) and autologous stem cell transplantation (SCT) have been effective in selected patients with AL amyloidosis and have led to improvement in survival, hematologic responses, and organ function [2]. Overall survival (OS) of patients with AL amyloidosis has improved over the last 2 decades because of improvement in supportive care, availability of novel therapies, and better patient selection for HDM/SCT [3].

Several important prognostic variables that are associated with decreased OS have been identified in AL amyloidosis. These include measures of advanced organ dysfunction, such as poor performance status, advanced cardiac involvement with Mayo clinic stage III disease, severe postural hypotension, > 2 organ system involvement, and excessive weight loss [4,5]. Other prognostic criteria include measures of aggressive plasma cell dyscrasia, such as an elevated difference in involved and uninvolved serum free light chain > 180 mg/L [6], and certain cytogenetics abnormalities [7].

A recent study by Kourelis et al. identified bone marrow plasma cell (BMPC) burden > 10% as a poor prognostic factor in AL amyloidosis [8]. Moreover, this study suggested that patients with AL amyloidosis with > 10% BMPCs have a prognosis similar to that of patients with AL amyloidosis associated with hypercalcemia, renal failure, anemia, and/or bone lesions (CRAB), and should therefore be considered together as AL amyloidosis with myeloma. It has been our practice to classify any patient with AL-CRAB or BMPC burden > 30% as having myeloma-associated AL amyloidosis. Therefore, these patients with AL-CRAB and > 30% BMPC have not been

Financial disclosure: See Acknowledgments on page 1732.
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http://dx.doi.org/10.1016/j.bbmt.2016.05.027
1083-8791/

included in our reports of HDM/SCT in AL amyloidosis. We reviewed our experience of patients undergoing HDM/SCT with AL amyloidosis to assess the impact of BMPC burden on survival and to assess if BMPC burden of > 10% portends a poor prognosis in patients undergoing HDM/SCT. Additionally, we assessed whether induction therapy improved survival in patients with BMPC burdens > 10%.

METHODS

A total of 546 patients with AL amyloidosis who received HDM/SCT (100 mg/m^2 to 200 mg/m^2) at the Amyloidosis Center at Boston University School of Medicine from July 1994 through December 2014 were included in this analysis. Data were collected prospectively during this time period. This study was approved by the institutional review board of Boston Medical Center and all patients signed informed consent per the Declaration of Helsinki. The following variables were queried in the database: day 0 of SCT, date of death, BMPC burden before treatment, induction therapy status, conditioning regimen, hematologic complete response (CR), hematologic relapse, and date of relapse. Kaplan-Meier (KM) survival curves were calculated for OS in patients with BMPC ≤ 10% and for those with > 10%. In patients with a BMPC burden > 10%, we compared KM survival curves for those who received induction therapy versus those who did not. Hematologic CR rates were compared between the ≤ 10% and > 10% BMPC groups as well as between those receiving full HDM (200 mg/m^2) versus those receiving modified HDM (100 mg/m^2 to 140 mg/m^2). Of note, 63 patients with early death (within 6 months of SCT) were excluded from the CR evaluation ("evaluable" group). Hematologic relapse rates were determined for ≤ 10% and > 10% BMPC burden groups, as well as for full and modified HDM doses. Patients with a BMPC burden > 30% and/or CRAB features were excluded from this study. BMPC were counted based on CD138 staining by an experienced hematopathologist on bone marrow biopsy specimen.

RESULTS

Of the 546 patients undergoing HDM/SCT, 445 (81.5%) had a BMPC burden ≤ 10% and 101 (18.5%) had a BMPC burden > 10%. KM analysis for patients with a BMPC ≤ 10% revealed a median survival of 7.86 years (95% confidence interval [CI], 6.69 to 9.83) and for patients with a BMPC >10%, the median survival was 6.8 years (95% CI, 5.75 to 10.17) (Figure 1).

There was no statistically significant difference between the 2 groups (hazard ratio, 1.06; CI, .78 to 1.45; $P = .70$). Five-year OS was comparable between the 2 groups: 63% for those with BMPC ≤ 10% and 65% for those with BMPC > 10%. Of the 101 patients with a BMPC burden > 10%, 25 received induction therapy. Induction regimens included oral melphalan with prednisone (n = 6); bortezomib with dexamethasone (n = 16); and cyclophosphamide, bortezomib, and dexamethasone (n = 3). Patients who did not receive induction therapy had a median survival of 7.78 years (95% CI, 5.4 to 13.4) and those who did receive induction therapy had a median survival of 5.75 years (95% CI, 3.94 to not available). This difference was not significant ($P = .28$); therefore, the use of induction therapy did not have an effect on OS (Figure 2).

Hematologic CR rates and hematologic relapses after HDM/SCT based on dose of HDM for BMPC ≤ 10% and > 10% groups are shown in Table 1.

DISCUSSION

In 1994, the first HDM/SCT for AL amyloidosis was performed at the Amyloidosis Center at Boston Medical Center [9]. Multiple studies conducted at our center have shown impressive median OS with this approach [2,5,10]. Over time, most studies have shown improving median OS and decreasing treatment-related mortality. Most recently, a review looking at the 20-year experience at our center found a median OS of 7.63 years and treatment-related mortality of 7.4% [11]. Additionally, a recent multi-institutional study found that early mortality in HDM/SCT patients has decreased and 5-year OS has improved over time when patient cohorts from 1995 to 2000, 2001 to 2006, and 2007 to 2012 were compared [12].

Despite the improving success of HDM/SCT for AL amyloidosis over the past 20 years, certain subgroups of patients still do poorly. Kourelis et al. found that patients with a BMPC

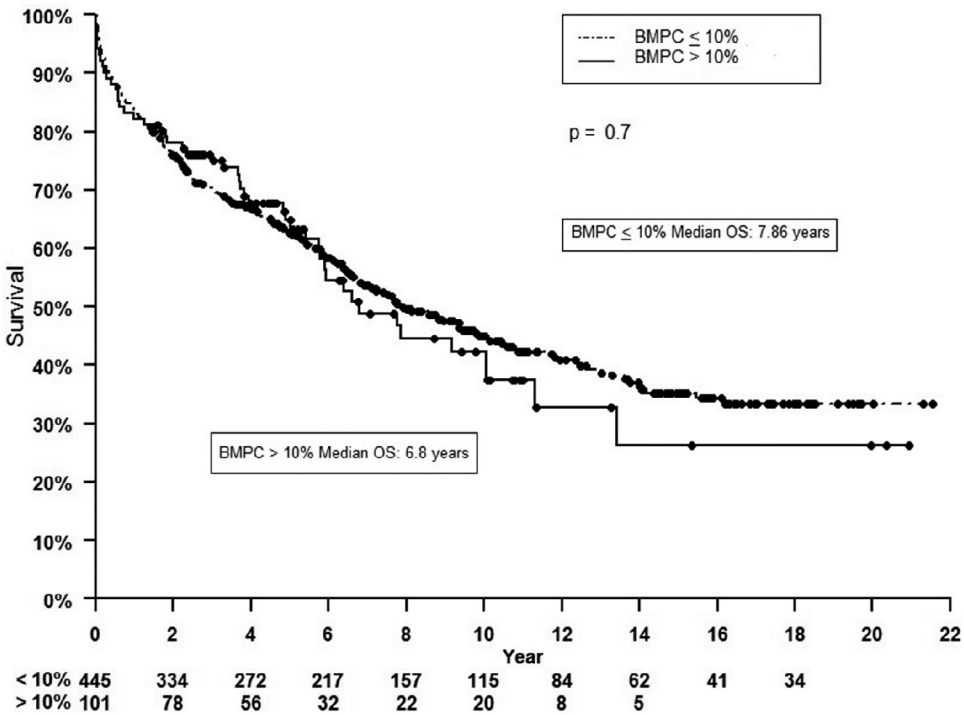

Figure 1. Overall survival after HDM/SCT by bone marrow plasma cell burden.