Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem-cell transplantation

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Long-term survival and outcome were determined for 80 patients with immunoglobulin light chain (AL) amyloidosis treated with high-dose melphalan and stem cell transplantation (HDM/SCT) more than 10 years ago. Seventeen (21%) patients died within the first year of treatment, of treatment-related complications (14%) or progressive disease (8%). Of the 63 surviving evaluable patients at one year, 32 (51%) achieved a complete hematologic response (CR). For all 80 patients, the median survival was 57 months (4.75 yrs). The median survival exceeds 10 years for patients achieving a CR after HDM/SCT, compared with 50 months for those not achieving a CR (P < .001). In conclusion, HDM/SCT leads to durable remissions and prolonged survival, particularly for those patients who achieve a hematologic CR. (Blood. 2007;110:3561-3563)

Introduction

Immunoglobulin light chain (AL) amyloidosis is a plasma cell dyscrasia in which clonal immunoglobulin light chains misfold, forming amyloid fibrils that are deposited in tissues and vital organs, leading to organ dysfunction and failure.1 Median survival of untreated patients is 10 to 14 months from the time of diagnosis and is marginally prolonged to 16 to 18 months with oral cyclic melphalan and prednisone regimen.2,3 Moreover, this form of treatment rarely results in hematologic complete response (CR).

High-dose intravenous melphalan and autologous stem cell transplantation (HDM/SCT) has become a first-line treatment for patients with multiple myeloma because of high hematologic response rates and survival benefits when compared with conventional chemotherapy regimens.4,5 Promising treatment outcomes observed with HDM/SCT in myeloma provided a rationale for evaluating this aggressive treatment approach in AL amyloidosis. HDM/SCT has been shown to induce both hematologic and clinical remissions in AL amyloidosis, and it appears to prolong survival substantially when hematologic remissions are achieved.6,7 At Boston University Medical Center, we began treating patients with AL amyloidosis with high-dose melphalan and autologous stem cell transplantation (HDM/SCT) in 1994.8 The hematologic relapse rate and long-term survival have not been studied in AL amyloidosis, but short-term results of hematologic responses and survival are promising. To address the durability and long-term results of treatment with HDM/SCT, here we report on the outcome for AL amyloidosis patients treated with HDM/SCT more than 10 years ago.

Patients and methods

Patients with AL amyloidosis undergoing HDM/SCT from July 1994 to July 1997 were studied with the approval of the Institutional Review Board of Boston University Medical Center. Informed consent was obtained in accordance with the Declaration of Helsinki. All patients had a histologic diagnosis of amyloidosis with evidence of a plasma cell dyscrasia and met eligibility criteria for HDM/SCT treatment in clinical protocols. Patients received 100 mg/m² to 200 mg/m² intravenous melphalan, followed by stem cell transplant 24 to 72 hours after completion of chemotherapy. The dose of intravenous melphalan was selected as described in our previous report.7 All patients were followed for hematologic and clinical responses at 3 and 6 months, and annually thereafter. At these visits, immunofixation electrophoresis (IFE) of serum and urine was performed, and bone marrow biopsies for immunohistochecmical analysis of plasma cell numbers and κ and λ light chain expression were performed. Hematologic complete responses (CR) following treatment required a normalization of all these studies, as reported previously. Since 2003, we also have used the measurement of serum-free light chains (FreeLite, the Binding Site) to assess plasma cell dyscrasia, but this was not available at the time for these patients. Hematologic relapses were defined as reappearance of monoclonal protein in serum and/or urine by IFE or clonal plasma cell expression in the bone marrow biopsy. All patients were followed for survival and for clinical improvement of the amyloid-related organ dysfunction. Kaplan-Meier estimates were obtained for all patients and for patients with hematologic CR and for patients without hematologic CR. We used the log-rank test to compare the survival distributions in patients who achieved CR and patients without CR. Patients who survived through the end of the study period were considered censored observations. All deaths were classified as either related or unrelated to progressive amyloid disease. Treatment-related mortality was defined as death...
Results and discussion

Eighty patients with AL amyloidosis received HDM/SCT from July 1994 to July 1997. Their median age was 56 years (range, 29-71), performance status was Southwest Oncology Group (SWOG) 1 (range, 0-3), and number of organ involvement was 2 (range, 1-5). Thirty-eight (48%) had cardiac involvement. Forty-three (54%) patients received full high-dose melphalan at 200 mg/m², while 37 (46%) received modified high-dose melphalan at 100 mg/m² to 140 mg/m². All patients underwent stem-cell mobilization with G-CSF (granulocyte colony stimulating factor) alone. The treatment-related mortality in these earlier patients was 14% (n = 11/80). In addition, 5 more patients died during the mobilization and collection phase of treatment, prior to initiating HDM. Furthermore, 6 (8%) patients died of complications related to amyloidosis prior to 1-year follow-up evaluation.

Hematologic responses were assessed in 63 (79%) patients at one year following treatment. Of evaluable patients, 32 (51%) achieved a complete hematologic response, and of these, 19 patients had received high-dose melphalan at 200 mg/m². Hematologic relapses occurred in 34% (n = 11/32) patients at a median time of 2.5 years (range, 2-8). Patients with hematologic relapses were treated with a second line of treatment if there was evidence of clinical disease progression.

The median survival for all 80 patients is 57 months. Kaplan-Meier estimates of survival with 95% confidence bands are shown in Figure 1. Eighteen (23%) of these patients are alive at present, 10 or more years after undergoing HDM/SCT. In Figure 2, Kaplan-Meier survival is plotted separately for those patients who achieved a hematologic CR and for those who did not. The median survival for patients achieving a hematologic CR has not yet been reached; the survival at 10 years is 53%. In contrast, the median survival for patients failing to achieve a hematologic CR is 5.1 years. Thus, efforts should continue to be directed at increasing the hematologic CR rate. Strategies to accomplish this include the use of tandem transplantation and the use of new agents, for example, thalidomide, lenalidomide, or bortezomib. The optimal timing and sequencing of regimens containing these agents, and comparison to or combination with one or 2 cycles of HDM/SCT, will be determined in future trials.

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Authorship

Contribution: V.S. designed and performed research, analyzed data, and wrote the manuscript. M.S. edited the manuscript with critical review. K.Q. designed and performed research, analyzed data, and critically reviewed the manuscript. K.T.F. collected and analyzed data, and designed research. G.D. performed statistical analysis. D.S. designed and performed research, analyzed data, and critically reviewed the manuscript.

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References

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