Hepatic response after high-dose melphalan and stem cell transplantation in patients with AL amyloidosis associated liver disease

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ABSTRACT

High-dose melphalan chemotherapy and autologous peripheral blood stem cell transplantation has been shown to result in durable hematologic response and prolonged overall survival in systemic AL amyloidosis. In this retrospective study, we evaluated clinical and hematologic responses in 69 patients with predominant liver involvement who were treated with high-dose intravenous melphalan and autologous stem cell transplantation from 1998 to 2006. Nine patients (13%) died from treatment-related mortality, similar to patients without hepatic involvement. The overall survival was 81% at one year and 61% at five years, by Kaplan-Meier estimates. A hematologic complete response was achieved by 53% (31/58) of patients at one year. A hepatic response occurred in 57% (33/58) at one year after high-dose intravenous melphalan and autologous stem cell transplantation and 63% (19/30) at two years after high-dose intravenous melphalan and autologous stem cell transplantation. In conclusion, hepatic disease improves in almost 2/3 patients treated with high-dose intravenous melphalan and autologous stem cell transplantation who have a complete or partial hematologic response to treatment.

Key words: AL amyloidosis, stem cell transplantation, liver disease.

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Introduction

AL (immunoglobulin light chain) 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 death.[1] The kidneys, heart, and the nervous system are most commonly affected. About 30% of patients with AL amyloidosis have clinical evidence of hepatic involvement, although one autopsy series found histological evidence of liver involvement with amyloid in 70% of patients.[2-4] Amyloid deposition commonly involves the central vein, portal vessels, portal stroma, and sinusoidal areas.[2] Liver involvement with AL amyloidosis can manifest with abdominal pain, decreased appetite, hepatomegaly and elevated alkaline phosphatase and transaminases.[5] Hyperbilirubinemia occurs as a late manifestation in the course of liver disease associated with AL amyloidosis.

Untreated AL amyloidosis has an overall poor prognosis, with a median survival of 10-14 months from diagnosis.[6] In patients treated with oral melphalan and prednisone, the median survival is marginally increased to 17 months[6,7] with a 5-year and 10-year survival rate of 16% and 5%, respectively.[8] In patients with hepatic involvement, the median survival seems to be even less, reported as nine months, with 5-year and 10-year survival rates of 13-17% and 1-7%, respectively.[5]

High-dose intravenous melphalan and autologous stem cell transplantation (HDM/SCT) has become a first-line treatment for selected patients with 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.[9-11] Recently, we reported the long-term follow-up of 80 patients treated with HDM/SCT with a median survival of 57 months.[12] In the present study, we have carried out a retrospective analysis of hepatic response after HDM/SCT treatment for patients with AL amyloidosis related liver disease.

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Design and Methods

Patients with AL amyloidosis undergoing HDM/SCT from 1998 to 2006 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. We retrospectively reviewed cases of patients with AL amyloidosis and predominant hepatic involvement who underwent HDM/SCT at this institution. Light chain gene families and subfamilies were determined by cloning the monoclonal light chain gene from bone marrow plasma cells and comparing the sequence to the germ line donors, as reported in previous reports.[13] Inclusion criteria for HDM/SCT included confirmed tissue diagnosis, clear evidence of a clonal plasma cell dyscrasia, age >18 years, performance status of ≤2 using the Southwest Oncology Group criteria, left ventricular ejection fraction >40%, room air oxygen saturation >95%, lung diffusion capacity >50%, and supine systolic BP >90 mmHg, as described in our previous reports.[10] Hepatic involvement was defined as liver enlargement palpated below the costal margin in the absence of heart failure or alkaline phosphatase >1.5 times institutional upper limit of normal, as described by criteria established in the Consensus Opinion from the 10th International Symposium on Amyloid and Amyloidosis.[14] All patients had hepatitis B and hepatitis C serologies checked prior to undergoing HDM/SCT. Hematopoietic stem cells were mobilized with granulocyte colony-stimulating factor (G-CSF) alone, and a minimum yield of at least 2.5×10^6 CD 34^+ cells/kg was required to proceed to HDM. Patients received 100-200 mg/m^2 of intravenous melphalan in two divided doses followed by stem cell transplantation 24-72 h afterwards. All patients were assessed for hematologic and organ responses within 3-6 months, at one year post-transplant, and annually thereafter. Hematologic and hepatic responses were determined as reported previously[10] and by the Consensus Opinion from the 10th International Symposium on Amyloid and Amyloidosis.[10,14] Hepatic response was defined as greater than 30% reduction in hepatomegaly on physical exam or a 50% decrease of an elevated alkaline phosphatase level. Treatment-related mortality was defined as death within 100 days of the SCT.

Results and Discussion

Patients' characteristics

From 1998 and 2006, 69 patients with AL Amyloidosis and hepatic involvement underwent HDM/SCT at Boston University Medical Center. The median age was 56 years (range, 37-75). There were 47 men and 22 women. All patients had predominant hepatic involvement, although there was multi-organ involvement to a lesser degree: 62 patients (90%) had renal involvement, 45 patients (65%) had cardiac involvement, 30 patients (44%) had neurological involvement, 4 patients (6%) had endocrine involvement, and 8 patients (12%) had soft tissue involvement. The median liver size was 3 cm (range, 0-20) below the costal margin. The median alkaline phosphatase was 193 U/L (range, 59-1243, normal 25-100). The median serum bilirubin level was 0.5 mg/dL (range, 0.1-1.9). There were 28 patients (41%) with k and 41 patients (59%) with λ clonal plasma cell dyscrasia. Light chain sequence information was available for 33 patients. For these 33 patients, the light chain subfamily distribution was κ1 (33%); κ4 (3%); λ1 (24%), λ2 (18%); λ3 (6%); and λ6 (15%). By χ^2 analysis, this distribution of light chain subfamilies is similar to that of the entire group of AL amyloidosis patients that we have sequenced.[15] No patient had serological evidence of chronic hepatitis B or C infection.

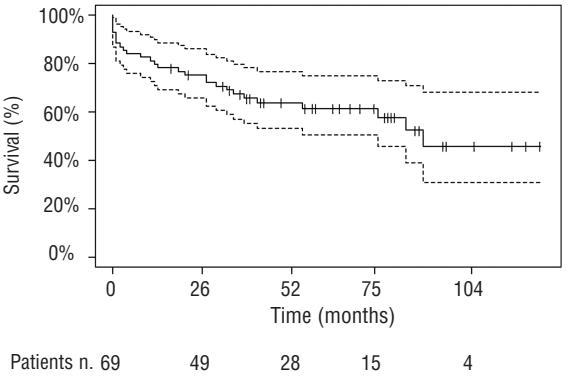

Figure 1. Overall survival of patients with hepatic involvement after high-dose intravenous melphalan and autologous stem cell transplantation.

Treatment characteristics

Of 69 patients with hepatic involvement and AL amyloidosis, 42 (61%) patients received full high-dose melphalan at 200 mg/m^2, while 27 (39%) received modified high-dose melphalan at 100-140 mg/m^2. The median number of stem cells collected was 8.2×10^6 CD34^+ cells/kg (range 1.2-26). The median number of stem cells infused after HDM was 5.62×10^6 CD34^+ cells/kg (range, 1.2-13).

Assessment of treatment results

The treatment-related mortality in these patients was 13% (9/69). The most common cause for treatment-related mortality was sepsis (n=5); and other causes included cardiac arrhythmia (n=1), pulmonary embolism (n=1), respiratory failure (n=1), and spontaneous hepatic rupture (n=1). In addition, 2 more patients (3%) died of complications related to amyloidosis prior to the one year follow-up evaluation.

Using intent-to-treat analysis, the overall survival at one, two and five years was 81%, 75% and 61%, respectively, by Kaplan-Meier estimates. The median survival of these 69 patients was 90 months (7.5 years), with a mean follow-up of 47 months (Figure 1). Hematologic responses were assessed in 58 (84%) sur-

viving patients at one year following treatment with HDM/SCT. A complete hematologic response was achieved by 53% (31/58) of patients, and of these 19 patients had received full high-dose melphalan at 200 mg/m^2. In addition, 40% (23/58) achieved a partial hematologic response at one year following HDM/SCT. Hepatic responses were also assessed in the 58 (84%) patients at one year following treatment with HDM/SCT. Hepatic responses were observed in 57% (33/58) at one year and 63% (19/30) at two years.

Hepatic responses corresponded with achievement of hematologic responses. Hepatic response occurred in 61% of patients with hematologic complete response and in 60% of patients with hematologic partial response. Of 4 patients who did not achieve a hematologic response, one patient had progression of hepatic disease, 2 patients had stable hepatic disease and one patient had hepatic response.

We have demonstrated improvement in AL amyloidosis associated liver disease following high-dose intravenous melphalan and autologous stem cell transplantation (HDM/SCT). A hepatic response, defined as a greater than 30% reduction in hepatomegaly on physical exam or a 50% decrease of alkaline phosphatase levels, occurred at one year in 57% of surviving patients and was sustained during subsequent follow-up in the vast majority. This outcome compares favorably to renal responses, defined as a 50% reduction in 24 h urinary protein excretion, which occurs in 36% of patients at one year and 52% of patients at two years.[16] The greater rate of hepatic responses may reflect the regenerative capacity of the liver. In addition, it has been proposed that amyloidogenic light chains may have direct, reversible toxic effects on hepatic sinusoidal cells.[17]

Untreated systemic AL amyloidosis with hepatic involvement has a very poor prognosis, with a median survival of 8-9 months. The five-year survival rate is 13-17%.[5,18] In a multi-center trial of the IBMTR registry data, hepatic involvement in AL amyloidosis showed a trend towards worse one year survival following HDM/SCT, as compared to no hepatic involvement (71% *vs.* 59%, p=0.07) Recently, we reported the long-term follow-up on 80 patients treated with HDM/SCT with a median survival of 57 months and a one year survival of 78%.[12] The present retrospective study suggests hepatic involvement in AL amyloidosis does not predict worse outcome, with a median survival of 90 months (7.5 years) after HDM/SCT and 5-year survival of 61%. Hepatic involvement does not lead to an increase in treatment-related mortality. Treatment-related mortality in this retrospective study was 13%, which is comparable to reports from our own center and others.[9,10] One patient with liver involvement died from spontaneous hepatic rupture following HDM/SCT with sepsis; this case is described in a separate report.[19] There were no other deaths from hepatic failure.

Hepatic involvement also appears to not predict a poorer hematologic response. In systemic amyloidosis treated with HDM/SCT at larger, single-center trials, hematologic complete response was achieved in 33-51%.[11] In this study, hematologic complete response was achieved in 53% of evaluable patients. It is important to note that patients with hyperbilirubinemia (serum bilirubin > 2.0 mg/dL) due to hepatic involvement should receive HDM/SCT with great caution. In this present study, no patient had serum bilirubin of >2.0 mg/dL. There was no patient who had worsening of liver function tests after HDM/SCT.

The Consensus Opinion from the 10th International Symposium on Amyloid and Amyloidosis defines hepatic response[14] in part as reduction of hepatomegaly using radiographic imaging. This study had patients enrolled from 1998 to 2006, making it difficult to adapt to these criteria, published in 2005, for all patients. In our study hepatic response was assessed by physical exam as well as by reduction in alkaline phosphatase levels.

Effective treatment regimens, besides HDM/SCT, exist and should be offered to patients who are ineligible for this aggressive treatment. In a study of patients ineligible for HDM/SCT, 46 patients were treated with melphalan and high-dose dexamethasone.[20] Six patients had hepatic involvement and one patient had hepatic response with normalization of alkaline phosphatase after treatment. Similarly, in patients treated with thalidomide and dexamethasone, one of 7 patients showed hepatic response, although this regimen was poorly tolerated.[21] A prospective randomized clinical trial published by the French group suggested similar overall survival for patients treated with oral melphalan and dexamethasone compared to HDM/SCT.[22] In this study, 3 out of 10 patients had hepatic response in the oral melphalan and dexamethasone arm compared to 5 out of 16 patients in the HDM/SCT arm.

In summary, hepatic involvement in patients with AL amyloidosis does not increase treatment-related mortality from HDM/SCT or reduce the hematologic response rate, and hepatic responses follow the hematologic responses over 1-2 years after HDM/SCT.

Authorship and Disclosures

SG designed research, performed research, analyzed data and wrote the manuscript. DCS designed research, performed research, analyzed data and critically reviewed the manuscript. MS edited manuscript with critical review. KTF collected and analyzed data, designed research. KQ edited manuscript with critical review. GD performed statistical analysis. VS designed research, performed research, analyzed data, wrote the manuscript.

The authors reported no potential conflicts of interest.

References

1. Falk RH, Comenzo RL, Skinner M. The systemic amyloidoses. N Engl J Med 1997;337:898-909.
2. Buck FS, Koss MN. Hepatic amyloidosis: morphologic differences between systemic AL and AA types. Hum Pathol 1991;22:904-7.
3. Kyle RA GM. Primary systemic amylodiosis: clinical and laboratory features in 474 cases. Semin Hematol 1995;32:45-9.
4. Kyle RA, Greipp PR. Amyloidosis (AL). Clinical and laboratory features in 229 cases. Mayo Clin Proc 1983;58:665-83.
5. Park MA, Mueller PS, Kyle RA, Larson DR, Plevak MF, Gertz MA. Primary (AL) hepatic amyloidosis: clinical features and natural history in 98 patients. Medicine (Baltimore). 2003;82:291-8.
6. Skinner M, Anderson J, Simms R, Falk R, Wang M, Libbey C, et al. Treatment of 100 patients with primary amyloidosis: a randomized trial of melphalan, prednisone, and colchicine versus colchicine only. Am J Med 1996;100:290-8.
7. Kyle RA, Gertz MA, Greipp PR, Witzig TE, Lust JA, Lacy MQ, et al. A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. N Engl J Med 1997;336:1202-7.
8. Kyle RA, Gertz MA, Greipp PR, Witzig TE, Lust JA, Lacy MQ, et al. Long-term survival (10 years or more) in 30 patients with primary amyloidosis. Blood 1999;93:1062-6.
9. Gertz MA, Lacy MQ, Dispenzieri A, Hayman SR, Kumar S. Transplantation for amyloidosis. Curr Opin Oncol 2007;19:136-41.
10. Skinner M, Sanchorawala V, Seldin DC, Dember LM, Falk RH, Berk JL, et al. High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: an 8-year study. Ann Intern Med 2004; 140:85-93.
11. Sanchorawala V, Seldin DC. An overview of high-dose melphalan and stem cell transplantation in the treatment of AL amyloidosis. Amyloid 2007;14:261-9.
12. Sanchorawala V, Skinner M, Quillen K, Finn KT, Doros G, Seldin DC. Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem-cell transplantation. Blood 2007;110:3561-3.
13. Weichman K, Dember LM, Prokaeva T, Wright DG, Quillen K, Rosenzweig M, et al. Clinical and molecular characteristics of patients with non-amyloid light chain deposition disorders, and outcome following treatment with high-dose melphalan and autologous stem cell transplantation. Bone Marrow Transplant 2006;38:339-43.
14. Gertz MA, Comenzo R, Falk RH, Fermand JP, Hazenberg BP, Hawkins PN, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18-22 April 2004. Am J Hematol 2005; 79:319-28.
15. Prokaeva T, Spencer B, Kaut M, Ozonoff A, Doros G, Connors LH, et al. Soft tissue, joint, and bone manifestations of AL amyloidosis: clinical presentation, molecular features, and survival. Arthritis Rheum 2007;56:3858-68.
16. Dember LM, Sanchorawala V, Seldin DC, Wright DG, LaValley M, Berk JL, et al. Effect of dose-intensive intravenous melphalan and autologous blood stem-cell transplantation on AL amyloidosis-associated renal disease. Ann Intern Med 2001;134:746-53.
17. Brenner DA, Jain M, Pimentel DR, Wang B, Connors LH, Skinner M, et al. Human amyloidogenic light chains directly impair cardiomyocyte function through an increase in cellular oxidant stress. Circ Res 2004;94:1008-10.
18. Gertz MA, Kyle RA. Hepatic amyloidosis (primary [AL], immunoglobulin light chain): the natural history in 80 patients. Am J Med 1988; 85:73-80.
19. Tam M, Seldin DC, Forbes BM, Connors LH, Skinner M, Oran B, et al. Spontaneous rupture of the liver in a patient with systemic AL amyloidosis undergoing treatment with high-dose melphalan and autologous stem cell transplantation: a case report with literature. Amyloid 2009;16:2.
20. Palladini G, Perfetti V, Obici L, Caccialanza R, Semino A, Adami F, et al. Association of melphalan and high-dose dexamethasone is effective and well tolerated in patients with AL (primary) amyloidosis who are ineligible for stem cell transplantation. Blood 2004;103:2936-8.
21. Palladini G, Perfetti V, Perlini S, Obici L, Lavatelli F, Caccialanza R, et al. The combination of thalidomide and intermediate-dose dexamethasone is an effective but toxic treatment for patients with primary amyloidosis (AL). Blood 2005;105: 2949-51.
22. Jaccard A, Moreau P, Leblond V, Leleu X, Benboubker L, Hermine O, et al. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. N Engl J Med 2007; 357:1083-93.