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Brief Article

Autologous Stem Cell Transplant for IgM-Associated Amyloid Light-Chain Amyloidosis

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IgM-related amyloid light-chain (AL) amyloidosis is a rare disease, with patients presenting with more renal and neurologic involvement and less cardiac involvement compared with those with non–IgM-related disease. We retrospectively reviewed 38 patients receiving autologous stem cell transplant (ASCT) for IgM-related AL amyloidosis at the Mayo Clinic between May 1999 and June 2018. Median age was 61 years, and 71% were men. The most common organs involved were renal (63%), neurologic (32%), and cardiac (26%). The median difference between involved and uninvolved free light chains was 6.2 mg/dL, and most patients had early Mayo stage disease (87% Mayo stage I 2004 and 74% Mayo stage I 2012). The overall response rate was 92%, with 76% of patients achieving at least a very good partial response. Renal response was seen in 65% of patients (15/23; median time, 18 months post-ASCT; range 3 to 52) and cardiac response in 60% of patients (6/10; median time, 12 months post-ASCT; range 10 to 35). Median progression-free survival (PFS) and overall survival (OS) was 48 and 106 months, respectively. Organ response predicted better PFS and OS (median PFS, 93 months for organ response versus 16 months for no organ response [$P = .0006$]; and median OS, 123 months for organ response versus 41 months for no organ response [$P = .02$]). Two patients died within 100 days of transplant, representing a 5% 100-day mortality. ASCT is an effective therapy that can be safely delivered to carefully selected patients with IgM-related AL amyloidosis.

INTRODUCTION

Amyloidosis related to an IgM monoclonal protein is a rare entity accounting for approximately 5% of patients with immunoglobulin amyloid light-chain (AL) amyloidosis [1,2]. Patients with IgM-related AL amyloidosis tend to present with lower levels of serum free light chains and have less cardiac involvement and more neurologic involvement compared with those with non–IgM-related AL amyloidosis [1-3]. Therapy is generally extrapolated form regimens used for non–IgM-related AL amyloidosis. However, given the lymphoplasmacytic nature of the clonal disorder in these patients, regimens used to treat lymphoplasmacytic lymphoma have also been used.

In general, the response rate to these therapies has been lower than those reported for non-IgM amyloidosis, and this, coupled with the paucity of data, causes difficulties in making treatment decisions. We have previously reported survival outcomes in 22 patients with IgM-related AL amyloidosis treated with autologous stem cell transplantation (ASCT) showing similar survival to patients with non-IgM amyloidosis [2]. Herein we describe 38 patients with IgM-related AL amyloidosis treated with ASCT at the Mayo Clinic, presenting updated data on hematologic response, organ response, and survival.

METHODS

Between May of 1999 and June of 2018, 38 patients with biopsy-proven IgM-associated AL amyloidosis received an ASCT at the Mayo Clinic Rochester. We conducted a retrospective review of patient and disease characteristics and transplant-related outcomes in this cohort. Risk stratification was according to the 2004 and 2012 Mayo staging systems [4]. Organ involvement was defined according to consensus criteria [5]. Response was assessed at approximately 100 days post-ASCT according to updated consensus criteria [6]. One hundred–day mortality was defined as death from any cause within 100 days of ASCT.

Statistical analysis was performed on JMP software (SAS Institute, Cary, NC). Survival analysis was performed using the Kaplan-Meier method. Overall survival (OS) was calculated from day 0 of bone marrow transplant to death from any cause. Progression-free survival (PFS) was defined as time to hematologic progression, assessed by consensus criteria, or time to reinitiation of therapy or death. The study was approved by the Mayo Clinic Institutional Review Board.

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RESULTS

Baseline characteristics for the 38 patients comprising the study cohort are listed in Table 1. Median age and the proportion of men were consistent with a population of patients with AL amyloidosis. The most common organs involved were renal (63%), neurologic (32%), and cardiac (26%). Very few patients had >2 organs involved (n = 5). The monoclonal protein was IgM lambda (n = 18), IgM kappa (n = 13), IgM lambda plus IgM kappa (n = 3), IgM kappa plus IgG lambda (n = 2), IgM lambda plus IgG lambda (n = 1), and IgM lambda plus IgA lambda (n = 1). The median difference between involved and uninvolved free light chains was 6.2 mg/dL.

Most patients had early Mayo stage disease (87% Mayo stage I 2004 and 74% Mayo stage I 2012). Of 5 patients tested for the *MYD88 L265P* mutation, 2 were positive for the mutation. Over half of the patients (58%, n = 22) received therapy before transplantation, and this varied over time, ranging from corticosteroid therapy only in the earlier years to combination chemoimmunotherapy and proteasome inhibitors more recently. Conditioning was high–dose melphalan in 84% of patients (n = 32; melphalan 200 mg/m^2 in 63% [24] and melphalan 140 mg/m^2 in 21% [8]). Six patients received conditioning with a combination of carmustine, etoposide, cytarabine, and melphalan (BEAM). Maintenance therapy was not routinely given to patients. Two patients received consolidation therapy post–transplant, 1 received 4 doses of rituximab over a month, and another patient was started on the combination of velcade revlimid and dexamethasone.

The overall response rate was 92%, with 76% of patients achieving at least a very good partial response (VGPR). Of patients receiving melphalan conditioning, 22% (n = 7) achieved a complete response (CR) and 50% (n = 16) achieved a VGPR. All 6 patients receiving BEAM conditioning achieved a VGPR. We assessed organ response in patients with renal or cardiac involvement. Of 29 patients with renal and/or cardiac involvement, 28 (97%) had data available for organ response assessment. Renal response was seen in 65% of patients (15/23) at a median time of 18 months post-transplant (range, 3 to 52). Cardiac response was seen in 60% of patients (6/10) at a median time of 12 months post–transplant (range, 10 to 35).

Median PFS and OS was 48 and 106 months respectively (Figure 1). Organ response predicted better PFS and OS (median PFS, 93 months for organ response versus 16 months for no organ response [P = .0006]; and median OS, 123 months for organ response versus 41 months for no organ response [P = .02]) (Figure 2). Two patients died within 100 days of transplant, representing a 5% 100–day mortality. The first patient died due to multiorgan failure in the setting of major gastrointestinal bleeding 40 days post–ASCT, and the second had a sudden cardiac arrest in the setting of a respiratory tract infection 15 days post–ASCT.

Table 1
Patient Characteristics and Hematologic Response (N = 38)

Variable	Value
Median age, yr (range)	61 (40-70)
Male, n(%)	27 (71)
Organ involved, n(%)	
Cardiac	10 (26)
Renal	24 (63)
>2	5 (13)
Light chain type, n(%)	
Lambda	20 (53)
Kappa	13 (34)
Biclonal	5 (13)
Bone marrow findings	
Median involvement, % (range)	8 (1-50)
Lymphoplasmacytic features, n(%)	17 (45)
Median dFLC, mg/dL (IQR)	6.2 (2.3-16.1)
Median serum M protein, g/dL (IQR)	.9 (.5-1.4)
Median creatinine (IQR)	1 (.9-1.3)
Median urine protein,* g/24 hr (range)	5.1 (1.7-34.9)
Median NT-proBNP,† pg/mL (range)	1567 (576-12983)
Mayo stage 2004, %	
Stages I/II/III	87/6/6
Missing, n	7
Mayo stage 2012, n (%)	
Stages I/II/III/IV	74/11/7/7
Missing, n	11
Prior therapy, n(%)	22 (58)
Median no. prior therapies (range)	1 (1-5)
Corticosteroid only	4 (11)
Chemotherapy	5 (13)
Proteasome inhibitor	7 (18)
Chemoimmunotherapy	8 (21)
Single-agent rituximab	3 (8)
Conditioning, n(%)	
Melphalan 200	24 (63)
Melphalan 140	8 (21)
BEAM	6 (16)
Hematologic response, n(%)	
CR	7 (18)
VGPR	22 (58)
PR	6 (16)
NR	3 (8)

Values are n (%) unless otherwise defined. IQR indicates interquartile range; dFLC, difference between involved and uninvolved light chains; PR, partial response; NR, no response.

* Among patients with renal involvement.

† Among patients with cardiac involvement.

DISCUSSION

Our study shows that ASCT is an effective therapy for patients with IgM–related AL amyloidosis. The OS and mortality rate at 100 days compares favorably with recently published data on outcomes in the overall cohort of patients with AL amyloidosis [7,8]. Our data are consistent with previous reports, showing patients with IgM–related AL amyloidosis have more renal involvement, less cardiac involvement, and lower levels of involved serum free light chains. The median difference between involved and uninvolved free light chains seen in this cohort (6.2 mg/dL) is far lower than normally seen in patients with AL amyloidosis [9]. In addition, the rate of cardiac involvement (26%) in our cohort is lower than previous reports of patients with IgM–related AL amyloidosis, and this is likely a reflection of our exclusion of patients with advanced cardiac disease from receiving ASCT.

Response to therapy in patients with IgM–related AL amyloidosis has been less impressive than in those with non–IgM–related

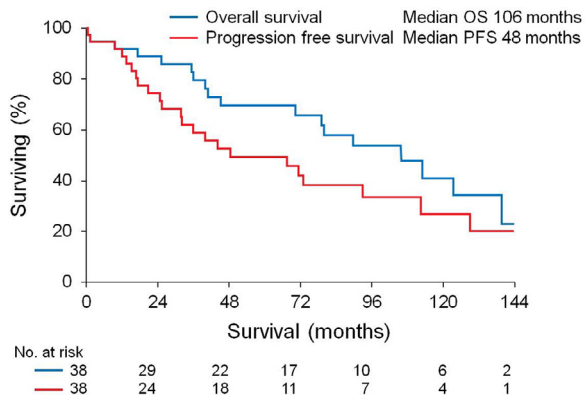

Figure 1. PFS and OS for the entire cohort.

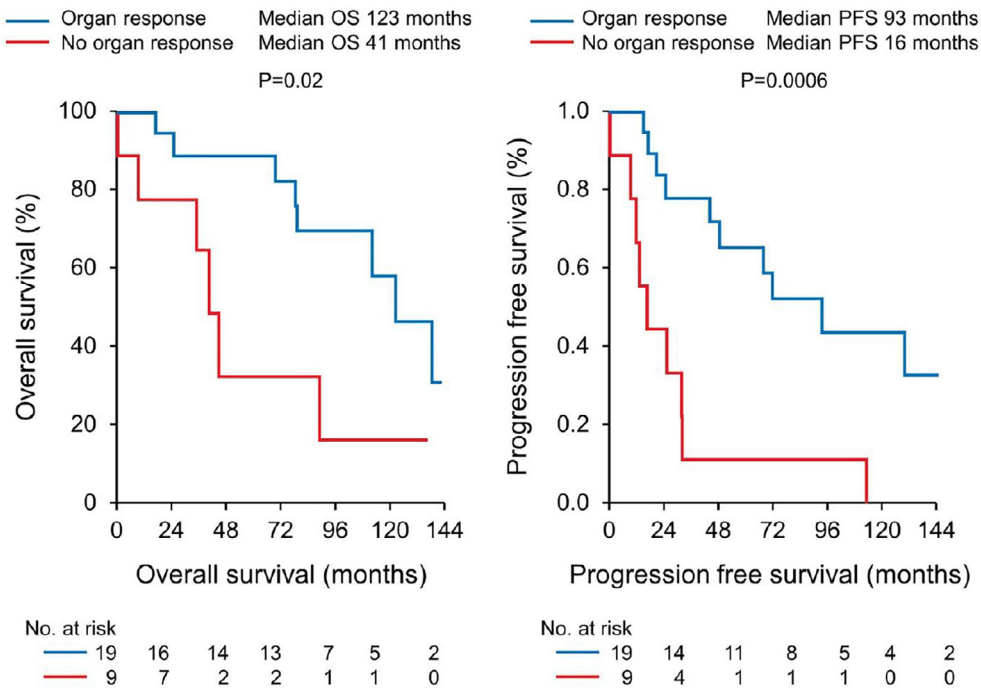

Figure 2. PFS and OS by organ response.

disease. The behavior of the underlying neoplastic clone in patients with IgM–related AL amyloidosis varies between a low–grade non–Hodgkin lymphoma and multiple myeloma, and this may explain the heterogeneity in the therapeutic approach reported in the literature as well as the lower response depth. In a large European collaborative study of 250 patients with IgM–related AL amyloidosis, 212 received treatment (various regimens), of whom 172 had available data on hematologic response [1]. The hematologic response rate was 57%, with most having partial responses (43% partial response, 9% VGPR, and 5% complete response). Organ response rates were poor, with renal and cardiac response rates of 18% and 5%, respectively. A smaller study of 10 patients treated with a combination of rituximab, bortezomib, and dexamethasone reported responses in 7 of 9 assessable patients (78%), suggesting that plasma cell directed therapy in conjunction with B cell therapy may be a more effective approach [10].

Given the effectiveness of the combination of bendamustine and rituximab in patients with low–grade lymphoma, this regimen has also been used in the setting of IgM–related AL amyloidosis. Recently, Manwani et al. [11] reported outcomes in 27 patients treated with bendamustine and rituximab and showed a hematologic response rate of 59% (11% CR, 37% VGPR, and 11% partial response) and renal and cardiac response rates of 18%. These results are encouraging and suggest this combination should be further studied in patients with IgM–related AL amyloidosis. Compared with the regimens described above, our cohort of patients treated with ASCT with a hematologic response rate of 92% (18% CR) and organ responses in approximately two–thirds of patients suggests that ASCT should be considered in all eligible patients with this disease. We recognize, however, that this population is selected, and only 20% to 25% of patients with AL amyloidosis are eligible for ASCT at presentation.

One of the concerns with ASCT in AL amyloidosis traditionally has been the high treatment–related mortality. We have recently shown a marked reduction in early mortality (<5%) is possible with careful patient selection for ASCT in AL amyloidosis [7]. Our preference for the conditioning regimen has evolved over time. High–dose melphalan was the preferred conditioning regimen in earlier years; however, in recent years we have moved toward BEAM conditioning in patients with lymphoplasmacytic disease identified on bone marrow or lymph node biopsy.

Our study is limited by its retrospective nature and long time period over which it was conducted. Furthermore, therapy before transplantation was not uniform; because we are a tertiary referral center many patients present to us having already commenced therapy locally. We also included 4 patients who had an additional non-IgM monoclonal protein detected, and determining which protein is amyloidogenic in these cases is difficult. Despite these limitations, we report the largest single–center experience on a rare disease, showing that ASCT is an effective therapy for patients with IgM–related AL amyloidosis.

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