High-dose melphalan and peripheral blood stem cell transplantation for light-chain amyloidosis with cardiac involvement

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High-dose melphalan (HDM) plus stem cell transplantation is an effective treatment for light-chain amyloidosis (AL), but is associated with high treatment-related mortality in patients with cardiac involvement. We studied 187 patients with cardiac involvement with AL who underwent HDM between 1996 and 2008. The median age was 57 years and the median time from diagnosis to HDM was 3.6 months. Half of the patients received reduced-dose melphalan (100-160 mg/m²). The median overall survival (OS) was 66 months, 54 months from diagnosis and HDM, respectively, and 91 patients (49%) were alive at the last follow-up 52 months (median) from HDM. Thirty patients (16%) died within 100 days of transplantation; only low serum albumin predicted early deaths. Overall, hematologic response (HR) and cardiac responses were seen in 66% and 41% of patients, respectively. The median OS for patients with and without HR was not reached and 22 months, respectively (P < .01); and for those with any decrease and no decrease in N-terminal-pro-brain natriuretic peptide was not reached and 26 months, respectively (P < .01). In multivariate analysis of baseline factors, only reduced-dose melphalan predicted shorter OS.

HDM is feasible in patients with cardiac amyloidosis, and achievement of HR and organ response is associated with improved survival. (Blood. 2012;119(5): 1117-1122)

Introduction

Amyloidosis is a group of rare diseases characterized by multiorgan deposition of amyloid fibrils. In light-chain (AL) amyloidosis or primary systemic amyloidosis, the fibrils are derived from the immunoglobulin light chains secreted by clonal plasma cells. AL amyloidosis represents the most common type of systemic amyloidosis and cardiac involvement is seen in more than half of patients at diagnosis. It affects approximately 10 patients per million per year, including 10%-15% of patients with multiple myeloma (MM).1 The treatment approaches used for AL amyloidosis are directed toward the eradication of the abnormal plasma cell clone with the aim of eliminating the supply of the amyloidogenic light chains.2 Compared with myeloma, AL is typically associated with a lower burden of clonal plasma cells.3 High-dose melphalan (HDM) and peripheral blood stem cell transplantation (SCT) have been used since the mid-1990s and remain an effective treatment for AL amyloidosis.4 However, the transplantation-related mortality (TRM) in AL amyloidosis (approximately 10%-15%) is significantly higher than that seen in patients with MM and lymphoma (1%-2%) and is often attributed to the presence of underlying cardiac and/or multiorgan involvement.5 The outcome with HDM among patients with cardiac amyloidosis has not been examined systematically. Therefore, we undertook the present study to examine the outcome of patients with AL amyloidosis receiving HDM, with particular focus on transplantation-related complications, hematologic response (HR) and organ response rates, impact on cardiac function, and factors predicting post-HDM survival.

Methods

We selected the patients for the present study from 382 patients with AL amyloidosis who underwent HDM at our institution between May 1996 and September 2008. We used a cutoff of September 2008 to allow for adequate long-term follow-up given the potentially slow rate of organ improvement in this disease. The follow-up status was updated as of December 31, 2010. Among this group, 193 patients had documented cardiac involvement, which was defined by the presence of echocardiographic findings consistent with an infiltrative cardiomyopathy or cardiac biopsy that confirmed the presence of heart involvement.6 Six patients who underwent orthotopic heart transplantation were excluded from the analysis, and the remaining 187 (49%) patients were included. The histological diagnosis of AL amyloidosis was confirmed using Congo red staining of biopsy specimens in all patients. All patients had either a demonstrable monoclonal protein in the serum and/or urine or a clonal plasma cell population in the BM. Patients with secondary, familial, or localized amyloidosis and those with overt MM were excluded. The organ involvement and responses (hematologic and organ) were assessed using the consensus criteria reported in the 10th International Symposium on Amyloid and Amyloidosis.7 A hematologic partial response (PR) requires a 50% reduction in serum M protein, along with a 90% reduction or a reduction to < 200 mg/24 hours in urine M protein. Complete response (CR) requires the disappearance of the M protein by serum and urine immunofixation along with a BM showing < 5% plasma cells. A cardiac response required either a ≥ 2-mm reduction in the interventricular septal thickness by echocardiogram or improvement of ejection fraction (EF) by ≥ 20% (baseline EF must be ≥ 45%).

All patients provided written informed consent for the use of their medical records. Approval from the Mayo Clinic Institutional Review Board was obtained in accordance with federal regulations and the Declaration of Helsinki.


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the majority of patients (n = 105, 56%) had heart and 1 other organ involved. The remaining 50 (27%) patients had involvement of heart along with 2 or more affected organs. Among the patients with > 1 organ involvement, the kidney was the most commonly affected in 115 (61%) patients. Approximately half of the patients had received at least one treatment before the HDM. Cardiac involvement was confirmed on endomyocardial biopsy in 38 patients. The median septal thickness was 14 mm (range, 9-25) and the median EF was 63% (range, 28%-84%). The baseline cardiac features are included in Table 1.

Early (day-100) mortality

Overall, 30 (16%) patients died within 100 days of transplantation. Of these, 29 deaths were considered to be directly related to treatment. The causes of death were considered to be due to cardiac-related causes in 15 (52%) patients, multiorgan failure in 7 (24%), bleeding in 4 (14%), and infection in 3 (10%), whereas 1 patient died because of rapidly evolving plasma cell leukemia before day 100. The cardiac stage was known for 15 of these patients; 7 each were stage 2 and 1 patient was stage 1. Among the various pre-HDM factors examined (age, time from diagnosis to transplantation, serum albumin, serum creatinine, plasma cell percentage, reduced-dose melphalan conditioning, number of organs involved, septal thickness, left ventricular mass index, EF, serum troponin, serum NT-ProBNP, and serum free light chain levels), only serum albumin was found to be significantly related to the risk of death by day 100. Among the 65 patients with a serum albumin < 2.5 gm/dL at the time of transplantation, 17 patients (26%) died by day 100, compared with 11% of the remaining patients (P < .01). In comparison, among the 189 patients with no cardiac involvement receiving transplantations during the same time period, there were only 9 (5%) deaths within 100 days of transplantation (P < .001). We also compared the day-100 mortality rate among the patients with cardiac involvement receiving transplantations between 1996 and 2002 and those receiving transplantations between 2003 and 2008; day-100 mortality was 17% for the initial half of the patients and 15% for the latter half (P = nonsignificant).

Response and survival

We first examined the hematologic response (HR) after transplantation using an intention-to-treat approach. Overall, an HR (≥ PR) was seen in 124 (66%) patients, including a CR in 56 (30%) patients. We then examined the response rate using a landmark analysis at 100 days, because patients dying early after transplantation are typically not evaluable for response. The median estimated time (Kaplan-Meier estimate, patients censored at last follow-up or initiation of new therapy) to an HR was 3.2 months from HDM (95% CI, 2.9-3.4). Considering only the 157 (84%) patients surviving beyond 100 days, the HR rate (≥ PR) was 79%, including a 36% CR rate. A conventional cardiac response (decrease in septal thickness ≥ 2 mm and/or EF increase ≥ 20%) was observed in 60 (41%) of the 148 patients evaluable for cardiac response. The cardiac response was based on a decrease in septal thickness in 57 of these patients, whereas an increase in EF was the basis of response in only 3 of the patients. The median estimated time (Kaplan-Meier estimate, patients censored at last follow-up or initiation of new therapy) to cardiac response was 51 months from HDM (95% CI, 37-75). At the last follow-up, 65 patients (41%) had

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**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Total (N = 187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at transplant, y (range)</td>
<td>57 (31-71)</td>
</tr>
<tr>
<td>Sex: male</td>
<td>122 (64%)</td>
</tr>
<tr>
<td>Median time from diagnosis to transplant, mo (range)</td>
<td>3.6 (1-75)</td>
</tr>
<tr>
<td>Number of organs involved</td>
<td></td>
</tr>
<tr>
<td>Cardiac only, n (%)</td>
<td>32 (17%)</td>
</tr>
<tr>
<td>Cardiac + 1 other organ, n (%)</td>
<td>105 (56%)</td>
</tr>
<tr>
<td>Cardiac + ≥ 2 other organs, n (%)</td>
<td>50 (27%)</td>
</tr>
<tr>
<td><strong>Baseline cardiac measurements, median (range)</strong></td>
<td></td>
</tr>
<tr>
<td>Septal thickness, mm (n = 185)</td>
<td>14 (9-25)</td>
</tr>
<tr>
<td>Posterior wall thickness, mm (n = 159)</td>
<td>14 (9-26)</td>
</tr>
<tr>
<td>Ejection fraction, % (n = 187)</td>
<td>63 (28-84)</td>
</tr>
<tr>
<td>Cardiac output, l/min (n = 164)</td>
<td>5.8 (2.7-12.8)</td>
</tr>
<tr>
<td>LV mass index, g/m² (n = 181)</td>
<td>124 (60-270)</td>
</tr>
<tr>
<td>Troponin, ng/ml (n = 169)</td>
<td>0.02 (&lt; 0.01-0.9)</td>
</tr>
<tr>
<td>NT-Pro BNP, pg/ml (n = 100)</td>
<td>2686 (22-35 000)</td>
</tr>
<tr>
<td>BNP, pg/ml (n = 116)</td>
<td>330 (18-3050)</td>
</tr>
<tr>
<td><strong>Other laboratory characteristics, median (range)</strong></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine, mg/dl</td>
<td>1.1 (0.7-12)</td>
</tr>
<tr>
<td>Serum albumin, gm/dl</td>
<td>2.9 (0.8-4.4)</td>
</tr>
<tr>
<td>Bone marrow plasma cell, %</td>
<td>7% (1-79)</td>
</tr>
</tbody>
</table>

LV indicates left ventricle; NT-Pro, N-terminal-pro; and BNP, brain natriuretic peptide.

The baseline evaluation included BM examination with confirmation of plasma cell clonality and Congo red staining for amyloid, echocardiogram, electrocardiogram, 24-hour urine protein measurement, serum and urine protein electrophoresis with immunofixation, and an abdominal fat pad aspirate. Although the inclusion criteria for HDM in patients with AL amyloidosis have changed over the years, patients with an Eastern Cooperative Oncology Group performance status ≤ 2 and a New York Heart Association classification of < III were considered eligible to undergo the procedure. A total of 164 patients (88%) had G-CSF alone for stem cell mobilization, and the remaining required cyclophosphamide in addition to G-CSF. Melphalan 200 mg/m² (n = 84 patients) or melphalan/total body irradiation (n = 10) was used for conditioning in 50% of the patients and the other 50% (n = 93) were conditioned with reduced-dose melphalan (100-160 mg/m²). Patients did not routinely receive growth factor support after SCT.

Overall survival (OS) from diagnosis was defined as the time between diagnosis and death or last follow-up; OS for HDM was defined as the time between the stem cell infusion and death or last follow-up estimated by the Kaplan-Meier method. Survival curves were compared using the log-rank test. Groups were compared using the Fisher exact test or the t test. Logistic regression was used to identify the best cutoffs for prognostic variables affecting early mortality within 100 days (day-100 mortality). Cox-proportional hazards analysis was done to examine the effect of various baseline characteristics on OS after HDM.
received another therapy after HDM because of disease progression or lack of response to HDM with median time to next therapy (TTNT) of 58 months (95% CI, 44, not reached [NR]).

The median estimated OS for the entire cohort (N = 187) was 66 months (95% CI, 42-83) from diagnosis and 54 months (95% CI, 35-76) from HDM. In contrast, the median estimated OS for the 157 patients surviving beyond 100 days from transplantation was 76 months (95% CI, 58-121) from HDM. Among the 66 patients dying after day 100 after transplantation, more than half of the deaths were from cardiac causes and considered to be related to progression of cardiac amyloidosis.

We then examined the impact of hematologic and organ response on survival and TTNT using a landmark analysis based on survival at 100 days after HDM (N = 157; Figure 1A). The median OS for patients with (n = 124) and without (n = 33) an HR was 98 months (95% CI, 70 [NR]) and 28 months (95% CI, 14-42), respectively (P < .001; Figure 1B). The median TTNT was 62 months for the responders compared with 24 months (95% CI, 15 [NR]) for those with no hematologic PR (P < .001). (C) Kaplan-Meier curves comparing TTNT between patients with HR and those with no HR. The median TTNT was 62 months for the responders compared with 24 months (95% CI, 15 [NR]) for those with no hematologic PR (P < .001). (D) Kaplan-Meier curves comparing OS between patients with CR and those with no CR. The median OS for patients with (n = 56) and without (n = 101) a CR was NR (95% CI, 98 [NR]) and 45 months (95% CI, 33-69), respectively (P < .001).

Using a similar landmark analysis at 100 days, we assessed the impact of cardiac response on survival. Among the 148 patients evaluable for a cardiac response, the median OS for patients with (n = 60) and without (n = 88) a cardiac response was NR and 58 months (95% CI, 38-75), respectively (P < .001; Figure 2A). The likelihood of a cardiac response was significantly higher for
Discussion

We have reviewed our experience with HDM in a large group of patients with cardiac involvement from AL amyloidosis. Cardiac involvement, seen in nearly half of patients with AL amyloidosis, manifests as syncope or sudden cardiac death because of conduction disturbances and arrhythmias, heart failure, or asymptomatic abnormalities noted only on echocardiogram or electrocardiogram. Nearly half of the patients undergoing HDM at our institution had heart involvement documented by biopsy or echocardiographic abnormalities. However, an isolated involvement of the heart because of AL amyloidosis is uncommon, and the majority (83%) of patients in our study had involvement of at least one other organ. The results of the current study highlight several important aspects of this disease.

It is feasible to perform HDM in a selected group of patients with cardiac disease. Whereas in the earlier period of the study, exclusion was mostly based on the presence of cardiac failure and multiorgan involvement and poor performance status, more recently we have relied on cardiac biomarkers for excluding patients at high risk of early mortality. The troponin T value did not predict for day 100 mortality, as reported in a previous study from our...
involvement and 0.75 years from the onset of heart failure. The amyloidosis is approximately 1.1 year from diagnosis of heart involvement of 2 or more organs, BM plasmacytosis greater than 1%, or plasma cell labeling index, increased severity has been shown to be an independent predictor of response and survival in prior studies. It is likely that the decision to reduce dose reflects multiple factors directly related to the number of organs involved and the severity of the organ involvement, as well as other factors such as overall performance status.

Consistent with previous observations, the most important predictor of organ response was the ability to obtain an HR. This group of patients with cardiac involvement, those achieving an HR also had a better OS compared with nonresponders. What is striking in the current analysis is the slow rate of cardiac response as assessed by conventional criteria that depend on echocardiographic findings. Whereas patients with a cardiac response had better survival, the slow onset of response makes it difficult to make treatment decisions regarding additional therapy. In this retrospective analysis, no prespecified criteria for additional therapy were initiated for hematologic progression, lack of organ improvement, or worsening of organ function based on treating physician preference, so no definite recommendations can be made. The subjectivity of the measurements and the inability to accurately assess improvement in those with a relatively normal septal thickness or EF underscores the importance of alternate parameters for the assessment of cardiac improvement. The serum level of NT-ProBNP has been suggested as a better marker of cardiac response than echocardiographic changes, which is supported by the finding of a more rapid onset of change seen in the present study. Given that the majority of patients with cardiac involvement have elevated levels of NT-ProBNP, and that data from this and other studies suggest improved survival with improvements in NT-ProBNP, this should be incorporated into future revisions of the response criteria. The use of NT-ProBNP also allows for earlier assessment of response given the shorter time required compared with echocardiographic parameters.

In conclusion, HDM is a feasible approach in selected patients with cardiac AL amyloidosis and is associated with a high rate of hematologic and organ responses that lead to prolonged survival. In the present study, improvement in survival was associated with hematologic and organ responses and with NT Pro-BNP reduction after transplantation. Conventional measures of cardiac response are often slow in onset and assessments using cardiac biomarkers may allow earlier determination of therapeutic benefit.

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<table>
<thead>
<tr>
<th>Parameter, N (%)</th>
<th>Patients with a hematologic complete response (N = 56)</th>
<th>Patients with a hematologic response (≥ PR) (N = 124)</th>
<th>Patients with no hematologic response (N = 33) P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional cardiac response</td>
<td>55 (60)</td>
<td>122 (47)</td>
<td>32 (16)</td>
</tr>
<tr>
<td>NT-Pro BNP decrease ≥ 30%</td>
<td>25 (84)</td>
<td>65 (78)</td>
<td>19 (37)</td>
</tr>
</tbody>
</table>

NT-Pro BNP indicates N-terminal-pro-brain natriuretic peptide; and LV, left ventricle.

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Authorship


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References

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