Effect of hematologic response on outcome of patients undergoing transplantation for primary amyloidosis: importance of achieving a complete response

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ABSTRACT

Our objective was to determine whether the goal of high-dose therapy should be a partial hematologic response or a complete response. We analyzed 282 consecutive stem cell transplant patients. A partial hematologic response was achieved in 108 patients (38%), and 93 (33%) achieved a complete hematologic response. Survival rates of patients with complete, partial, or no response were significantly different ($p<0.001$), even after eliminating bias from early death. The degree of response was affected by the intensity of chemotherapy conditioning, septal thickness, and cardiac biomarkers. Hematologic response translates to longer survival.

Key Words: amyloidosis, chemotherapy, complete response, immunoglobulin free light chain, stem cell transplant, survival.

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Stem cell transplantation has increasingly been used in the initial therapy of patients with newly diagnosed primary systemic amyloidosis (AL).[1] Previously, the high prevalence of small monoclonal (M) proteins in the serum and the high prevalence of Bence-Jones proteinemia in patients with AL made quantification of a 50% reduction in M protein levels difficult to achieve. Because nearly half the patients have nephrotic-range non-specific proteinuria, light chains and M protein in the urine are also frequently obscured. With the recent introduction of the immunoglobulin free light-chain assay, the response of AL patients can be more accurately evaluated.[2-4] The ultimate goals of therapy for patients with multiple myeloma remain undefined after 40 years. The Southwest Oncology Group and others[5,6] have shown that achievement of a plateau phase (stable M protein levels) is considerably more important than the extent of response after conventional dose systemic chemotherapy. For myeloma patients who undergo transplantation, the goal of therapy is a complete response or a very good partial response. The benefit of stem cell transplantation for patients who do not achieve this level of response has been questioned.[7,8] Unlike multiple myeloma, in which outcome is determined exclusively by tumor mass, outcome of AL is based on (i) the deposition of immunoglobulin proteins or protein fragments (fibrils) and (ii) subsequent organ dysfunction. Therefore, when compared with patients with myeloma, patients with AL should have a better correlation between M protein reduction and clinical outcome. The purpose of the current study was to assess whether the therapeutic end point of hematologic response is a useful surrogate marker for the ultimate desired outcome: prolonged survival of patients with AL. Two questions were asked: (i) how much of a reduction in M protein is sufficient to affect outcome? (ii) how valid are clinical trials that use M protein as a therapeutic end point?

Design and Methods

Patients

All patients undergoing high-dose therapy for amyloidosis were included in this study. No patients were excluded, and none were lost to follow-up. All patients gave written research consent in accordance with Minnesota state laws and the Mayo Clinic Institutional Review Board.

Treatment

All patients had AL histologically verified with Congo red tissue stain. Beginning in 2002, immunohistochemical studies were performed on all tissue samples to confirm that amyloidosis was due to deposition of immu-

noglobulin light-chain proteins. Baseline evaluation of all patients being considered for stem cell transplantation included assessment of creatinine clearance and an echocardiographic examination. Echocardiography was used to determine cardiac involvement based on Doppler studies of relaxation, septal thickness, and strain. Patients were conditioned on the basis of their risk for toxicity after high-dose therapy (melphalan was administered over 2 days). The dose was reduced for patients with 3-organ involvement, age over 65 years, creatinine level higher than 1.7 mg/dL, and cardiac involvement (New York Heart Association class III). Patients who underwent transplantation had a minimum of 2×10^6 CD34$^+$ cells/kg, although our target was 4×10^6 cells/kg. Apheresis was performed by processing 11-14 L of blood in 4 hours. Thirty-six patients were mobilized using cyclophosphamide and sargramostim, and 246 patients received filgrastim only.

Response criteria

Response criteria were defined by the Tenth International Symposium on Amyloid and Amyloidosis.[9] Briefly, a complete response is defined as serum and concentrated 24-hour urine specimens that are negative for M protein (measured by an immunofixation assay). The immunoglobulin free light-chain ratio is normal. A partial response is defined as a 50% reduction of serum M protein (when measurable), a 50% reduction of urine M protein (when measurable), and a 50% reduction of the involved immunoglobulin free light-chain protein.

Statistical analysis

Differences among nominal variables were analyzed using χ^2 statistics. Differences among continuous variables were evaluated with the Mann-Whitney U test. Survival analysis was performed using the Kaplan-Meier method. Differences between survival curves were evaluated using log-rank tests. Analysis for factors that affected response was performed using the Cox proportional hazards model. For multivariate analysis, parameters with the most significant results from the univariate χ^2 test were included first. Additional parameters were added in a stepwise fashion. Parameters that remained independent were retained, and parameters that were not independent were discarded in subsequent analyses.

Results and Discussion

Seventy-five percent of patients underwent transplantation within 7 months of diagnosis. Only 10% had a serum creatinine level greater than 1.8 mg/dL; serum creatinine levels were normal for 75% of patients. One-, 2-, and 3-organ involvement was observed for 48%, 38%, and 14% of patients respectively. The day-100 mortality rate was 11%; 28% of the entire cohort had died by the time of this report. Sixty-seven percent of patients had renal involvement, 47% had cardiac involvement, 16% had hepatic involvement, and 11% had peripheral nerve involvement.

Table 1. Patient characteristics stratified by response (n=282).

Characteristic	*CR*	*PR*	*NR*	*p value*
Full-dose therapy, % (n=189)	43	37	20	<0.001
Reduced-dose therapy, % (n=92*)	14	41	45	<0.001
Brain natriuretic peptide, pg/mL† (n=126)	87	172	286	0.01
Serum troponin T, ng/mL† (n=165)	0.01	0.01	0.02	0.01
Cardiac amyloidosis, %‡	44	51	63	0.05
Men, %	54	60	63	NS
Age, y†	55	58	59	NS
Ejection fraction†‡	0.66	0.65	0.66	NS
Septal thickness, mm†‡	12	12	13	0.02
Marrow plasma cells, %†	8	6	7	NS
Alkaline phosphatase, U/L†	90	92	101	NS
CD34$^+$ count, cells/kg†	7.7×10^6	6.3×10^6	5.9×10^6	0.02
Creatinine, mg/dL†	1.1	1.1	1.1	NS
Urine total protein, g/d	3.24	2.21	4.96	0.01

*CR: complete response; NR: no response; NS: not significant; PR: partial response. *One patient was not evaluable for response. †Median values are reported. ‡Measured by echocardiography.*

When patients were stratified according to response (complete, partial, or no response), the groups did not differ by age, sex, serum creatinine level, ejection fraction, alkaline phosphatase level, or percentage of plasma cells in the bone marrow at diagnosis (Table 1). However, a larger fraction of non-responding patients had echocardiographic evidence of amyloidosis, received lower-intensity therapy, had higher brain natriuretic peptide (BNP) and serum troponin T levels, and had greater septal thickness when compared with patients who achieved a response. The yield of CD34$^+$ cells was greater for patients who subsequently achieved a complete response. Chemotherapy conditioning was risk adapted. Thirty-three percent of the entire cohort (93 patients) received reduced-intensity melphalan conditioning, usually 140 or 100 mg/m^2, and 67% (189 patients) received 200 mg/m^2 (the full dosage). Figure 1 shows the survival of all patients, stratified according to response; 93 patients achieved a complete response, 108 achieved a partial response, and 81 did not respond (p=0.001). Median survival was reached only by patients who had no response. Because response is a time-dependent variable and patients must survive to be evaluated for response, these results are potentially misleading. Therefore, a landmark analysis was performed to study the 213 patients who survived 6 months after stem cell transplantation; 86 achieved a complete response, 91 achieved a partial response, and 36 did not respond. The survival differences remained significant in the landmark analysis (p=0.001). The median survival (40.1 months) was reached only in the non-responder group. Management of patients with cardiac amyloidosis is particularly challenging. Because we recognized that the patients who underwent stem cell transplantation were not representative of all patients with cardiac amyloidosis, a second analysis was performed that was limited to patients with echocardiographic evidence of amyloidosis. Of those 151 patients, 42 achieved a complete response, 56 achieved a partial

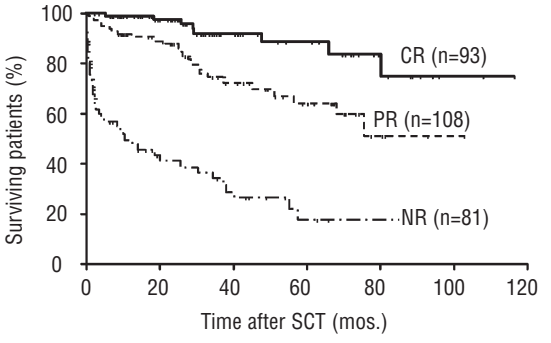

Figure 1. Overall survival after transplantation for primary systemic amyloidosis (n=282). Patients were stratified according to hematologic response (p=0.001). Ticks indicate censored data. CR, complete response; NR: no response; PR: partial response; SCT: stem cell transplantation.

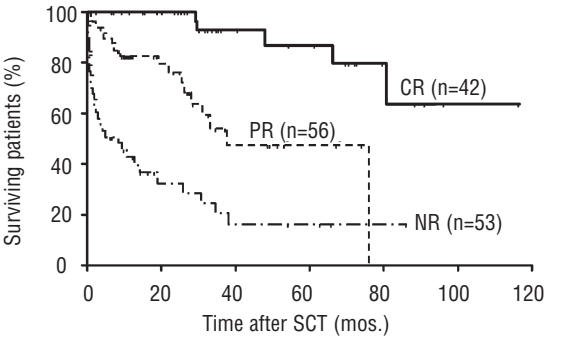

Figure 2. Overall survival after transplantation of patients with cardiac amyloidosis (n=151). Patients were stratified according to hematologic response (p<0.001). Ticks indicate censored data. CR, complete response; NR: no response; PR: partial response; SCT: stem cell transplantation.

response, and 53 had no response (Figure 2). Again, survival differences were statistically significant for all 3 groups (p<0.001), and when the landmark analysis was performed to exclude patients who did not survive 6 months, a significant difference (p<0.001) was still observed (38 achieved a complete response, 39 achieved a partial response, and 18 did not respond). We note that the percentage of patients with cardiac amyloidosis who achieved a response was not significantly different from that of the total patient cohort (28% vs. 33% for complete response, 37% vs. 38% for partial response). A univariate analysis was performed to identify factors that influenced overall survival. Survival was affected by hematologic response, BNP and serum troponin T levels (the cardiac biomarkers used to measure response), the number of organs involved, therapy intensity, serum creatinine level, and interventricular septal thickness. However, a multivariate analysis showed that the only significant predictors of survival were response (p<0.001) and serum troponin T levels (p=0.02). The data presented in this study suggest that achievement of a hematologic response is an important predictor of prolonged survival after stem cell transplantation for patients with AL. The degree of response also appears to be important because patients who achieved a complete response survived longer than those who achieved a partial response. Furthermore, both groups had an improved outcome when compared with patients who did not achieve a 50% reduction in immunoglobulin light-chain levels. Hematologic response should, therefore, be considered a valid end point in clinical trials because it functions as a surrogate marker for survival. The landmark analysis showed that after correcting for bias from early death, partial responders still survived substantially longer than nonresponders, and this was true even for patients with echocardiographic evidence of amyloidosis. These results confirm those of other published series of high-dose therapy for AL.[10,11] An *Intergroupe Francophone du Myélome* study suggested that no survival advantage or response difference existed for patients who received high-dose therapy.[12] In addition, responses after treatment with melphalan and dexamethasone,[13] or cyclophosphamide, thalidomide, and dexamethasone[14] are quite similar to the response rates reported in this study. Patients selected for stem cell transplantation inherently have superior health characteristics when compared with an unselected cohort of patients with amyloidosis. These patients tend to be younger, have better renal and cardiac function, and have a lower frequency of multiple-organ involvement. Amyloidosis patients selected for transplantation are inherently likely to survive longer than an unselected group of AL patients. Nonetheless, within the group selected for transplantation, response was an important determinant of outcome. In a study of 66 AL patients undergoing transplantation,[15] the complete response rate was 41%. If the free light-chain concentration decreased by more than 90%, the likelihood of clinical improvement was greater and longer survival periods were noted, regardless of whether patients fulfilled strict complete response criteria. In a previous publication,[16] we reviewed 93 patients with serial free light-chain measurements. Interestingly, high pre-transplantation levels of free light-chain protein predicted a higher risk of early death, and elevated light-chain levels were associated with more advanced disease. The absolute level of free light-chain proteins after therapy was highly predictive of survival, and normalization of free light-chain protein levels after stem cell transplantation was a prognostic factor for organ response and complete response. Achievement of a free light-chain response was a better predictor than normalization of the free light-chain ratio. A decrease in free light-chain levels after therapy was correlated with a decrease in the cardiac biomarker N-terminal pro-BNP and with improved survival. When the free light-chain level decreased, cardiac function improved, even though echocardiographic tests showed that cardiac amyloid deposits were unaltered.[17] A recent review of autologous stem cell transplantation from the United Kingdom[18] described a reduction in serum free light-chain proteins (>50% decrease) for 83% of evaluable patients. The over-

all median survival was 8.5 years for patients who survived over 100 days.

Our current study was not a prospective randomized trial, and the groups differed on the basis of conditioning intensity (Table 1). We previously reported[19] that patients who received higher doses of chemotherapy had higher response rates. However, patients who are older, have multiple-organ involvement, and have advanced cardiac involvement receive reduced-intensity conditioning which confounds interpretation of the results. It is possible that the difference attributed to dosage is simply caused by selection and the patient's overall performance status. Other differences between the groups included higher levels of biomarkers and greater septal thickness for patients who did not achieve a response. Because patients who achieved a complete response had a higher yield of stem cells during apheresis, these patients were probably biologically fitter and the *post hoc* finding of response may not reflect the effect of therapy clearly. Response may be a surrogate marker of an inherent and unknown biologic variable that causes the more robust patients to survive longer after intensive therapy. Nevertheless, despite the differences between groups, multivariate analysis suggested that the hematologic response of patients after transplantation is a valid study end point because it was associated directly with improved survival. The only other variable that was predictive of long-term survival was serum troponin T level, as previously reported.[20] In conclusion, the hematologic response criteria (defined at the Tenth International Symposium on Amyloid and Amyloidosis) may be used as an appropriate end point in studies that assess amyloidosis therapies. The key therapeutic outcome for patients with this rare and devastating disease is improved survival.

Author's Contributions

MAG, MQL, AD, SRH, SKK, NL, DAG: contributed in conception and design, acquisition of data, and analysis and interpretation of data.

Conflict of Interest

The authors reported no potential conflicts of interest.

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