Predictive Factors for Early Relapse in Multiple Myeloma after Autologous Hematopoietic Stem Cell Transplant

Andrew Mayer Pourmoussa, MD[1]; Ricardo Spielberger, MD[2]; Jilian Cai, MD[2]; Odelia Khoshbin, OMS[3]; Leonardo Farol, MD[2]; Thai Cao, MD[2]; Firoozeh Sahebi, MD[2]

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ABSTRACT

Introduction: Despite advances in therapy for multiple myeloma, patients have continued to experience relapse. We sought to better understand this.

Objective: To identify factors that predict early relapse in patients with multiple myeloma who receive autologous hematopoietic peripheral stem cell transplant (HSCT).

Methods: Retrospective analysis of Kaiser Permanente Southern California patients who received HSCTs between 2008 and 2012.

Results: A total of 141 patients were included. Factors found to be associated with inferior progression-free survival were disease status less than complete response at the time of HSCT, no use of maintenance therapy after HSCT, International Staging System stage III, and high Freiburg Comorbidity Index. Disease status less than complete response, stage III, higher Freiburg Comorbidity Index, no use of maintenance therapy, and male sex were the most predictive factors for early relapse (< 18 months).

Discussion: Our results identified a subgroup of high-risk individuals with multiple myeloma who will continue to do poorly after HSCT with the best available treatment using a combination of proteasome inhibitors and immunomodulatory drugs. These results highlight the need for consideration of alternative therapy in such instances.

INTRODUCTION

Multiple myeloma is a neoplastic proliferation of plasma cells accounting for 10% of hematologic malignancies.[1] Rapid advances in the understanding of genetics and biology of the disease have led to the introduction of new targeted therapeutic agents and clinically significant improvements in disease outcome.[2,3] An induction regimen using a combination of immunomodulatory drugs, proteasome inhibitors, and dexamethasone followed by autologous hematopoietic stem cell transplant (HSCT) is considered standard treatment of newly diagnosed multiple myeloma in physically fit patients.[4-8] The superiority of high-dose chemotherapy and autologous HSCT was initially shown in comparison to conventional chemotherapeutic agents.[9,10] More recently, in the era of targeted therapies, several randomized clinical trials have confirmed improved progression-free survival (PFS)[11-13] and overall survival (OS)[11] in favor of a combination of new targeted therapies and early autologous HSCT. The beneficial role of maintenance treatment after autologous HSCT has also been examined in randomized clinical trials, supporting its use in this setting.[14,15] Despite these advances, patients continue to experience relapse. Factors such as lack of response, stage, and high-risk cytogenetics have been linked to poor outcome.[1,16-18] Scoring systems that consider additional factors such as age, comorbidities, and cognitive/physical conditions have been described in helping to predict survival.[19,20]

We examined PFS and OS in patients who received induction therapy using immunomodulatory drugs and/or proteasome inhibitor-based regimens followed by autologous stem cell transplant between 2008 and 2012. The objective of this study was to investigate prognostic factors that correlate with early relapse using the best available treatment in the modern era of new targeted agents, reflecting real-world practice. The electronic medical records were available for all patients, allowing for evaluation of all preexisting comorbidities and all health-related issues outside the transplant center—data that may not always be captured.

METHODS

The study was approved by the institutional review board of Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA. Patients with multiple myeloma who were treated at Kaiser Permanente Southern California medical centers and received autologous HSCT between January 1, 2008, and January 1, 2012, were identified for chart review electronically through International Classification of Diseases, Ninth Revision (ICD-9) codes for multiple myeloma (203.0) and multiple myeloma post HSCT (41.0X). This chart review was carried out via an integrated electronic system (Epic, Epic Systems, Verona, WI), which allows access to patient medical records outside the transplant referral center. Protected health information was used in conducting our research in accordance with the Health Insurance Portability and Accountability Act (HIPAA).

All patients underwent induction therapy using combinations of immunomodulatory drugs, proteasome inhibitors, and dexamethasone followed by autologous HSCT. Data on age, sex, International Staging System (ISS) stage, type of induction therapy, bone marrow cytogenetics and/or fluorescence in situ hybridization (FISH) abnormalities, disease status at the time of HSCT, and use of maintenance therapy were collected (Tables 1 and 2). High-risk cytogenetic abnormalities were defined by the presence of at least 1 of the following: del(17p), t(4;14), t(14;16), t(14;20), del(1p), and hypoploidy. The Freiberg Comorbidity Index (FCI) was evaluated as well. The FCI is a simple assessment that is used

Author Affiliations

[1] Department of Internal Medicine, Los Angeles Medical Center, CA

[2] Bone Marrow Transplant Department, Los Angeles Medical Center, CA

[3] College of Osteopathic Medicine, Western University of Health Sciences, Pomona, CA

Corresponding Author

Andrew Mayer Pourmoussa, MD (andrew.pourmoussa@kp.org)

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to determine risk relating to comorbidities in multiple myeloma. This index takes into account performance status, renal impairment, and lung disease. In this 0- to 3-point total scale, individual points are assigned for Karnofsky Performance Status less than or equal to 70% vs greater than 70%, a glomerular filtration rate less than 30 mL/min/1.73 m^2 vs greater than 30 mL/min/1.73 m^2, and the presence of moderate to severe lung disease vs absence of or mild disease.[21] Compared with other comorbidity indexes, such as the Charlson Comorbidity Index, Hematopoietic Cell Transplantation-specific Comorbidity Index, Kaplan-Feinstein Index, and Satariano Index, the FCI has been reported to better stratify risk in patients with multiple myeloma.[22]

Statistical Analysis

We performed statistical analysis to study the following variables at the time of transplant: Age, sex, ISS classification, FCI, Karnofsky Performance Status, disease status, along with cytogenetics/FISH results, use of posttransplant maintenance therapy, best response after transplant, time to progression, time to last contact, and cause of death related to multiple myeloma. We also computed censoring variables for use in the Cox proportional hazards models in studying our main outcomes of interest: Time to progression in PFS, OS, and relapse in less than 18 months (early relapse). Each of these variables was included in a single-variable proportional hazards model of each outcome. A Kaplan-Meier survival analysis was also done with each corresponding proportional hazards regression for each single variable and the 3 outcomes. Confidence intervals (CIs) for the survival probabilities were calculated using the log transformation. Although the results were similar between these 2 analyses, the software-displayed output (SAS version 9.3, SAS Institute, Cary, NC) was different, which allowed checking different assumptions about the variables. These variables were collected together in main effects, multivariate Cox proportional hazards regression models, 1 for each of the outcomes. The multivariate models were run with hierarchical stepwise selection and also backward elimination with terms being retained at the 0.10 level. In addition, we ran a multivariate logistic regression of PFS less than 18 months vs at least 18 months using main effects with stepwise selection and backward elimination, retaining variables significant at the 0.10 level. Main effects were focused because of an inability to credibly examine interactions stemming from a relatively low sample size.

Table 1. Summary of variables for all patients in study (N = 141)

Variable	No. (%) of patients[a]
Median age at diagnosis, y (range)	58 (30-70)
Sex	
Men	75 (53.19)
Women	66 (46.81)
International Staging System stage	
I	45 (31.91)
II	52 (36.88)
III	44 (31.21)
Disease status at time of transplant	
Complete remission	24 (17.02)
Partial remission	116 (82.27)
Less than partial remission	1 (0.71)
Karnofsky Performance Status	
60	1 (0.71)
70	5 (3.55)
80	29 (20.57)
90	80 (56.74)
100	26 (18.44)
Freiburg Comorbidity Index	
0	127 (90.07)
1	12 (8.51)
2	2 (1.42)
Cytogenetics/FISH results	
Standard	93 (65.96)
High risk	48 (34.04)
Maintenance therapy after transplant	
Yes	102 (72.34)
No	39 (27.66)

[a] Data are number (percent) except for age at diagnosis.
FISH = fluorescence in situ hybridization.

Table 2. Frequency of maintenance therapy after HSCT (n = 102)

Maintenance therapy	Number (%) of patients
Lenalidomide	74 (72.55)
Bortezomib	15 (14.70)
Thalidomide	13 (12.75)

HSCT = hematopoietic stem cell transplant.

RESULTS

A total of 141 patients were identified for our study. Patient characteristics are shown in Table 1. The median follow-up for the study group was 63.9 months (range = 6.2-103.3 months). Patients' median age was 58 years (range = 30-70 years). Seventy-five patients were men and 66 were women. The median Karnofsky Performance Status was 90% (range = 60%-100%), and the median FCI was 0 (range = 0-2). The median time from diagnosis to HSCT was 7.4 months (range = 3.7- 93.2 months). Forty-five patients (31.9%) had ISS stage I disease, 52 (36.9%) had ISS stage II, and 44 (31.2%) had ISS stage III. Twenty-four (17%) patients were in complete response at the time of the transplant, 116 patients (82.3%) had a partial response, and 1 patient (0.7%) had no response. Ninety-three (66%) had standard-risk cytogenetics/FISH findings and 48 (34%) had high-risk findings. One hundred two patients (72.3%) received maintenance therapy after transplant. The practice for posttransplant maintenance therapy changed over the study period from primarily thalidomide (13 patients, 12.8%) to lenalidomide (74 patients, 72.6%). Fifteen patients received bortezomib alone or in combination with immunomodulatory drugs (14.7%) as maintenance therapy (Table 2).

Thirty-eight patients (27%) experienced early time to disease progression less than 18 months from the time of transplant. Variable summaries for early vs late time to progression groups are shown in Table 3. The patient characteristics were balanced between the 2 groups except for lower proportion of ISS stage

III, lower FCI, higher likelihood of receiving complete response, and receiving maintenance therapy in those with late relapse. Four-year PFS for the whole group was 41.8% (95% CI = 34.4% to 50.8%), and the OS was 81.5% (95% CI = 75.4% to 88.2%; Figures 1 and 2). The OS for the early relapse/progression group during the 4-year study period was 44.7% (95% CI = 31.4% to 63.7%; Figure 3). The median PFS for the whole group was 37 months (95% CI = 29-47 months), with a median PFS of 8.6 months (95% CI = 6.9 to 10.7 months) for those with early relapse/progression vs 62 months (95% CI = 47 months to absence of relapse) for those who did not experience relapse. The median PFS for patients receiving maintenance therapy was 47 months (95% CI = 34-67 months) vs 24 months (95% CI = 14-30 months) for those without maintenance therapy.

Table 3. Summary of variables for patients divided into early and late relapse groups

Variable	Late relapse (≥ 18 mo PFS) (n = 103)[a]	Early relapse (< 18 mo PFS) (n = 38)[a]	p value[b]
Median age at diagnosis, y (range)	57 (30-70)	60 (33-68)	0.4156
Sex			
Men	51 (49.5)	24 (63.2)	0.1512
Women	52 (50.50)	14 (36.84)	
International Staging System stage			
I	38 (36.89)	7 (18.42)	0.0145
II	38 (36.89)	14 (36.84)	
III	27 (26.21)	17 (44.74)	
Disease status			
Complete remission	21(20.39)	3 (7.89)	0.0451
Partial remission	82 (79.61)	34 (89.47)	
Less than partial remission	0 (0)	1 (2.63)	
Karnofsky Performance Status			
60	0 (0)	1 (2.63)	0.2592
70	3 (2.91)	2 (5.26)	
80	21 (20.39)	8 (21.05)	
90	58 (56.31)	22 (57.89)	
100	21 (20.39)	5 (13.16)	
Freiburg Comorbidity Index			
0	97 (94.17)	30 (78.95)	0.0078
1	5 (4.85)	7 (18.42)	
2	1 (0.97)	1 (2.63)	
Cytogenetics/FISH results			
Standard	94 (91.26)	35 (92.11)	0.874
High risk	9 (8.7)	3 (7.9)	
Maintenance therapy after transplant			
Yes	79 (76.7)	23 (60.5)	0.0577
No	24 (23.3)	15 (39.5)	

[a] Values are number (percent) of patients except for age at diagnosis. Some percentages do not total to 100% because of rounding.
[b] The p values were calculated with the Kruskal-Wallis test.
FISH = fluorescence in situ hybridization; PFS = progression-free survival.

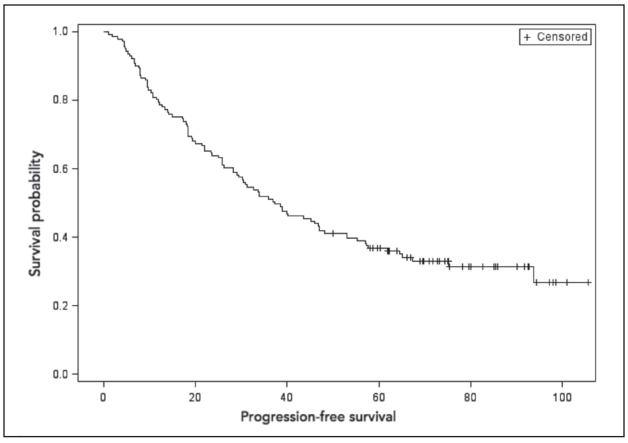

Figure 1. Progression-free survival in months (x axis) vs survival probability expressed as fraction of 1 (y axis) on the basis of data of entire group of patients studied.

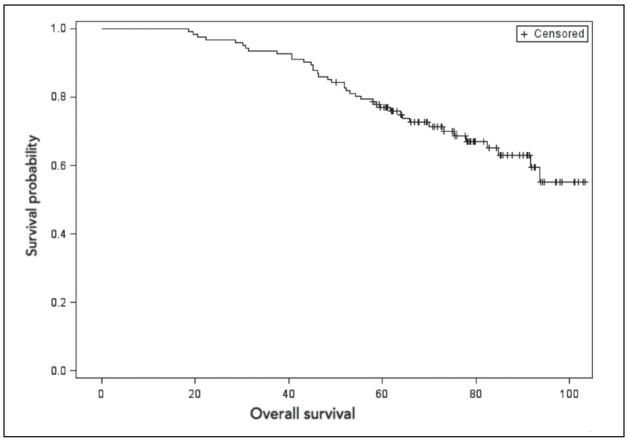

Figure 2. Overall survival in months (x axis) vs survival probability expressed as fraction of 1 (y axis) on the basis of data of entire group of patients studied.

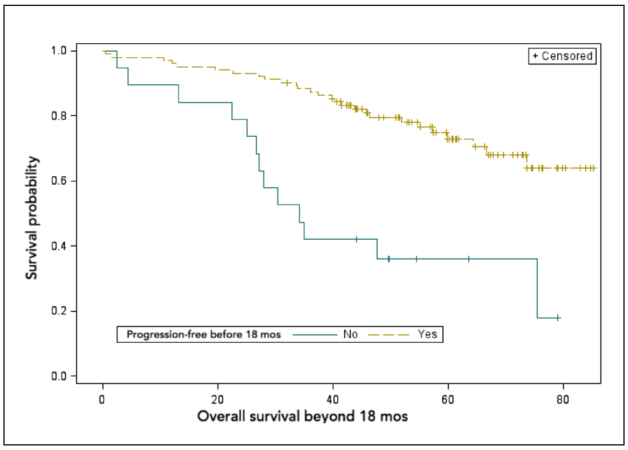

Figure 3. Overall survival beyond 18 months (x axis; expressed in months) vs survival probability expressed as fraction of 1 (y axis) comparing early-relapse and late-relapse groups.

The median OS for the whole group was 109 months (95% CI = 94-151 months), with a median OS of 31.4 months for those with early relapse/progression (95% CI = 22.2-56 months) vs 115 months (95% CI = 109-151 months) for those who did not progress before 18 months.

In the Cox proportional hazards model, built using backward elimination for PFS using continuous age at diagnosis, the factors associated with increased PFS were maintenance therapy ($p < 0.0001$), complete response at the time of HSCT ($p = 0.004$), lower ISS ($p = 0.005$), and lower FCI ($p = 0.024$). Using age at diagnosis dichotomized younger than age 65 years at the time of HSCT, the factors associated with increased PFS were maintenance therapy ($p < 0.0001$), complete response at the time of HSCT ($p = 0.003$), lower ISS stage ($p = 0.010$), lower FCI ($p = 0.014$), and younger age ($p = 0.043$).

In the final Cox proportional hazards model, built using backward elimination for OS using continuous age at diagnosis, the factors associated with increased OS were lower FCI ($p = 0.019$) and lower ISS stage ($p = 0.066$). With use of age at diagnosis dichotomized at less than 65 years vs 65 years or more, the factors associated with increases OS were lower FCI ($p = 0.016$), younger age ($p = 0.093$), and lower ISS stage ($p = 0.099$).

Factors associated with early relapse (< 18 months) were examined with logistic regression built using backward elimination. Using continuous age at diagnosis, the factors associated with early relapse/progression were higher FCI ($p = 0.024$), no use of maintenance therapy ($p = 0.032$), less than complete response at the time of HSCT ($p = 0.063$), and male sex ($p = 0.064$). The model was unchanged when we used age at diagnosis dichotomized at younger than age 65 years vs older than age 65 years.

DISCUSSION

Despite significant improvement in the outcomes of patients with multiple myeloma, relapse remains the main cause of treatment failure. Determination of patients destined for early progression is of particular importance in selecting those who are expected to have a poor outcome with best available treatment using a combination of proteasome inhibitors, immunomodulatory drugs, and autologous stem cell transplant.

Traditionally, patients receive a few cycles of induction therapy followed by stem cell transplant. The results of our study suggest that the achievement of complete response before transplant may help to prevent early relapse or progression of the disease. This is in accordance with prior observations where achievement of complete response or very good partial response before autologous stem cell transplant translated to better long-term outcomes.[23,24] Therefore, efforts to achieve a deep cytoreduction and preferably complete response, which may be attainable with newer, more effective targeted agents and monoclonal antibodies, should be explored as a means to improve outcomes in future prospective trials. Indeed, achievement of a negative minimal residual state is the subject of ongoing studies.[25]

Limitations of our study included broader categorization of pretransplant disease status as complete response vs less than complete response because of difficult extraction of very good partial response vs partial response status from medical records during the chart review process. We did not find any association between high-risk cytogenetics/FISH findings and early relapse. This may be related to the small number of patients with poor cytogenetics results. We did observe a statistically significant correlation between higher FCI and early relapse and progression. The FCI has shown a strong clinical relevance for OS and PFS in patients with multiple myeloma. To our knowledge, this is the first report that has shown a high FCI to predict early relapse/progression. This requires further examination to determine if the presence of other comorbidities promotes a permissive microenvironment for tumor growth.

In a study by the Mayo Clinic consisting of 511 patients, the authors reported serum albumin level below 3.5 g/dL and high-risk FISH results to be predictive of early relapse.[26] A recent report by the Center for International Blood and Marrow Transplant Research group reported that the proportion of patients with early relapse was stable over time, at 35% to 38%.[27] Similarly, this group reported a higher cancer stage, unresponsiveness to chemotherapy, and no use of post-HSCT maintenance therapy associated with early relapse.[27] Novel monoclonal antibodies daratumumab, isatuximab, and elotuzumab alone or in combination with other new targeted agents have been shown to have significant activity in relapsed refractory multiple myeloma.[28-34] Our results, however, have identified a subgroup of high-risk patients who will continue to do poorly with the best available treatment and should be included in clinical trials investigating new therapeutic strategies such as novel monoclonal antibodies daratumumab, isatuximab, and elotuzumab. Indeed, ongoing clinical trials are examining the addition of these monoclonal antibodies as induction or consolidation therapy before and after HSCT.[35] Other immune-modulating approaches such as vaccination and T-cell therapy (CAR T-cell, bispecific T-cell engagers, also called BiTE monoclonal antibodies)[36] are also under investigation and hold promise for a better cytoreduction and long-term disease control for high-risk patients.

CONCLUSION

We conducted this retrospective analysis to identify the risk factors predictive of early relapse despite best available treatment. In our study, the risk factors identified were disease status of less than complete response at the time of HSCT, no use of maintenance therapy after HSCT, ISS stage III, and high FCI. We also examined factors predictive of early relapse within 18 months of transplant. Disease status less than complete response, ISS stage III, no use of maintenance therapy, and male sex were the most predictive for early relapse, supporting the need for better disease control prior to transplant. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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