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ORIGINAL REPORT

Relationship Between Depth of Response and Outcome in Multiple Myeloma

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ABSTRACT

Purpose
High-dose therapy with autologous stem-cell transplantation (HDT-ASCT) is now almost standard therapy for many patients with multiple myeloma, partly because of higher complete response (CR) rates. Some studies suggest that tandem transplantation gives superior results. The aim of this study was to determine whether the depth of the response to HDT-ASCT leads to an improvement in time to progression (TTP) and overall survival (OS). We hypothesized that patients with CR before HDT-ASCT (BCR) will have their disease burden reduced further and experience a longer TTP and perhaps OS.

Patients and Methods
All patients who achieved BCR or CR after HDT-ASCT (ACR) were identified. The characteristics and long-term outcome of these patients were evaluated.

Results
We identified 14 patients with BCR and 103 patients with ACR who were treated in similar fashion. The patients have been followed for more than 6 years, and the median for OS has not been reached (60-month survival, 55% for BCR and 63% for ACR; $P = .83$). The median TTP was 43 months for BCR and 34 months for ACR ($P = .39$).

Conclusion
The depth of the response in myeloma does not necessarily lead to an improvement in TTP and OS. Tumor dynamics considerations show that the yield from sequential cycles of chemotherapy decreases. Patients who achieve CR with the first transplant can be safely observed without jeopardizing OS.

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INTRODUCTION

Therapy for multiple myeloma (MM) has been transformed in the last decade with the advent of novel therapeutic agents such as thalidomide and bortezomib as well as high-dose therapy with autologous stem-cell transplantation (HDT-ASCT).[1-3] Despite the introduction of novel agents, complete responses (CRs) are still uncommon.[4-6] In contrast, HDT-ASCT is associated with CR rates of up to 40%,[7-11] leading to an improved event-free survival.[12,13] Thus, most centers offer this therapeutic option to relatively healthy patients, although overall survival (OS) is not always prolonged.[14-16]

The principle of curative cancer therapy is to achieve the lowest tumor burden possible, aiming for a cure. Thus, there is significant interest in dose escalation because higher doses of therapy may give superior results by reducing the disease burden even further.[17,18] There are instances where this strategy works, as in some patients with acute myeloid leukemia [t(8,21)] treated with repeated cycles of high-dose cytarabine.[19] However, evaluation of the response requires measuring the disease burden in vivo, and this is often difficult. In this respect, MM presents a unique opportunity given that in the majority of patients, tumor cells produce a monoclonal protein that can be detected in the blood and/or urine and serves as a convenient marker of response to therapy or relapse. Indeed, Sullivan and Salmon used data for the production and clearance of the monoclonal protein to measure the in vivo tumor burden and follow the response to therapy in a cohort of patients with this disease.[20] They showed that myeloma growth follows a Gompertz function and that, starting from one tumor cell, they could estimate the time for the disease to appear.

Given the importance of the depth of the response, it is understandable that many studies in myeloma aim to lower the disease burden further

and further by escalating therapy, including tandem transplantation and maintenance therapy.[9,10,21] However, additional therapy comes at a cost that must be compensated by an improvement either in survival or quality of life. To evaluate the importance of the depth of the response in MM, we compared outcomes between two cohorts of patients. One cohort achieved CR before proceeding to HDT-ASCT (BCR), and the second cohort achieved CR after HDT-ASCT (ACR). Patients with BCR went for HDT-ASCT with a tumor burden less than 10^9 cells,[22] and one expects that these patients will therefore have their tumor burden reduced to even lower levels compared with patients who achieve CR because of the transplant procedure. Our results show that sequential therapies are not additive in nature and that sequential chemotherapy more likely obeys the law of diminishing returns. We propose explanations for this observation that can have implications for therapy.

PATIENTS AND METHODS

Patients

All patients with MM who undergo HDT-ASCT at the Mayo Clinic (Rochester, MN), are maintained in a database that is continuously updated by the senior author. This database contains all the relevant demographic, clinical, and laboratory characteristics of the patients. All patients are asked and give informed consent for inclusion in the database in compliance with Minnesota state law. Whenever a patient is being considered for HDT-ASCT, he/she undergoes evaluation of disease status before transplantation including measurements of the serum M-protein, bone marrow aspirate, and biopsy with cytogenetic analysis and plasma cell-labeling index (PCLI). We recorded the pretransplant induction regimen as well as the conditioning regimen used for all patients. None of the patients received additional therapy after HDT-ASCT, but were simply observed until relapse, last follow-up, or death. This study was approved by the Mayo Foundation institutional review board on February 20, 2007, in compliance with both federal regulations and the Declaration of Helsinki. For the purpose of this analysis, we identified all the patients undergoing ASCT between January 1, 1990, and December 31, 2004. All patients received transplants within 12 months from the diagnosis of multiple myeloma and had at least a partial response to induction therapy.

Response Definitions

The response criteria were as defined by Bladé et al.[23] Thus, patients were considered to have a BCR or ACR if the monoclonal protein in the blood and urine resolved and they had a negative immunofixation at the time of response evaluation. As a corollary, the return of immunofixation-positive serum defined relapse for that patient. Patients with nonsecretory myeloma were excluded from this analysis.

Statistical Analysis

All statistical analyses were performed using StatView (SAS Institute, Cary, NC). Comparisons between nominal variables were performed using the χ^2 test, whereas differences between continuous variables were evaluated with the Mann-Whitney *U* test. The time to progression (TTP) was defined as the interval between ASCT and evidence of progression and was estimated using the Kaplan-Meier product limit estimate. Differences in TTP between groups were evaluated with the log-rank test. TTP was chosen as a measure of the effectiveness of therapy in keeping with recent recommendations.[24] Survival was estimated as the time between HDT-ASCT and either death or last contact with the patient. The appropriate censor was used both when calculating the TTP and OS. Univariate and multivariate analyses were performed using the Cox proportional hazards method.

RESULTS

Between January 1, 1990, and December 31, 2004, 543 ASCTs for MM were performed at the Mayo Clinic. Of these, 14 patients (2.6%) had achieved BCR, whereas an additional 103 patients (19%) achieved ACR. The relevant demographic, clinical, and laboratory characteristics of these patients are presented in Table 1. As expected, patients with BCR had a lower disease burden before HDT-ASCT compared with the larger (ACR) cohort, on the basis of percentage of bone marrow plasma cells (BMPC).[25] However, other prognostic markers such as β2-microglobulin, PCLI, lactate dehydrogenase, and frequency of cytogenetic abnormalities did not differ significantly between the two groups. There were no significant differences between the two groups with respect to sex, age at the time of transplant, time between diagnosis and HDT-ASCT, and conditioning regimen. The median number of therapy regimens received was 1 for both cohorts. None of the patients had been treated with lenalidomide or bortezomib before HDT-ASCT.

The median follow-up for the two cohorts since HDT-ASCT exceeded 4 years (range, 6 to 133 months). Within this follow-up

Table 1. Demographic, Clinical, and Laboratory Characteristics of the Two Cohorts of Patients Before ASCT

Characteristic	BCR (n = 14)	ACR (n = 103)	*P*
Male sex, %	35.7	50	.30
Age, years			.91
Median	56.8	57.0	
Range	30-68.9	30-72.6	
Diagnosis to transplant, months			.61
Median	7.4	6.3	
Range	3.4-11.6	3.4-11.6	
B2M, mg/dL			.98
Median	2.15	2.1	
Range	1.28-4.34	1-9.74	
LDH, U/L			.36
Median	178	186	
Range	139-240	92-484	
CRP			.84
Median	0.38	0.40	
Range	0.07-4.94	0.01-10.0	
BMPC, %			.023
Median	1.5	4.0	
Range	0-5	0-41	
PCLI, %	0	0	.1
Median			
Range	0-0.3	0-10.5	
Normal cytogenetics, %	100	89	.21
ISS, %			.19
1	85	59	
2	15	36	
3	0	5	
HD-CTX, %	57	64	.62
Conditioning regimen, mg/m^2			.24
MEL 200	79	85	
MEL 140	0	6	
MEL-TBI	21	9	

Abbreviations: HDT-ASCT, high-dose chemotherapy with autologous stem-cell transplantation; BCR, complete response before HDT-ASCT; ACR complete response after HDT-ASCT; B2M, beta-2 microglobulin; LDH, lactate dehydrogenase; CRP, C-reactive protein; BMPC, bone marrow plasma cells; PCLI, plasma cell labeling index; ISS, international staging system; HD-CTX, high-dose cyclophosphamide; MEL, melphalan; TBI, total-body irradiation.

interval, seven patients (50%) in the BCR have progressed, whereas 64 patients (62%) in the ACR cohort had progressive disease; three (21%) of the 14 patients in the BCR cohort have died, whereas 31 (30%) of the 103 patients in the ACR group have died. When the two cohorts were evaluated for TTP (Table 2; Fig 1A), we found no evidence of statistically significant differences in TTP (BCR, 43 months; ACR, 34 months; log-rank $P = .39$). Similarly, there was no difference in OS between the two cohorts (Table 3; Fig 1B; BCR, 74 months; ACR, 74 months; log-rank $P = .83$).

Multivariate analysis was performed for both TTP and OS. For this highly select group of patients, the BMPC (likelihood ratio = 1.03; 95% CI, 1.001 to 1.059; $P = .04$) was the only parameter that affected TTP. With respect to OS, patients with an International Scoring System (ISS)[26] score of 1 had a better outcome compared with those with a higher score (likelihood ratio = 0.306; 95% CI, 0.126 to 0.746; $P = .01$).

DISCUSSION

Over the last few years, much has been said about the importance of achieving CR in patients with myeloma, and this is in part correct because patients who achieve CR with HDT-ASCT generally have a longer TTP.[12,13] In an effort to consolidate these responses even further, tandem transplantation has been advocated, although less than 10% of patients who do not attain CR with the first transplant will achieve this goal after the second procedure.[10] Some also advocate maintenance therapy after transplantation.[9] Patients who achieve CR have disease that is not biologically detectable with less than 10^9 myeloma cells.[22] HDT-ASCT with melphalan can achieve up to a 5 log reduction in tumor burden,[27] and therefore provides significant tumor reduction leading to the higher CR rates observed. In this study, we compared two cohorts of MM patients: one with successful HDT-ASCT because they achieved CR and the other a smaller group who went into transplant already in CR. Yet, despite the fact that one expects the latter cohort to have the tumor burden reduced even further, this did not translate into a longer TTP or OS. How can these observations be explained?

Sullivan and Salmon have shown that myeloma growth can be described by the Gompertz function.[20,28] Starting from a single cell, $N(0) = 1$, the number of tumor cells at any time, $N(t)$, is given by

$$N(t) = N(0)e^{\frac{\alpha}{\beta}(1 - e^{-\beta t})}$$

Defining $n = \ln(N)$, Equation 1 can be rewritten as

$$n(t) = K(1 - e^{-\beta t})$$

where $K = \alpha \div \beta$ defines the carrying capacity of the tumor (the maximum growth that the tumor can theoretically achieve). We refer the readers interested in a more in-depth analysis of the Gompertz function to Dingli et al.[28,29] Let us consider two individuals undergoing HDT-ASCT, one an ACR (A, with a log-burden = n_A) and the other BCR (B, with a log-burden = n_B). By definition, we have $n_B < \ln(10^9) < n_A$.[29] Let us denote the log reduction on HDT-ASCT by L_A and L_B, respectively. We consider the case where both individuals are well described by the same Gompertz function, and the same

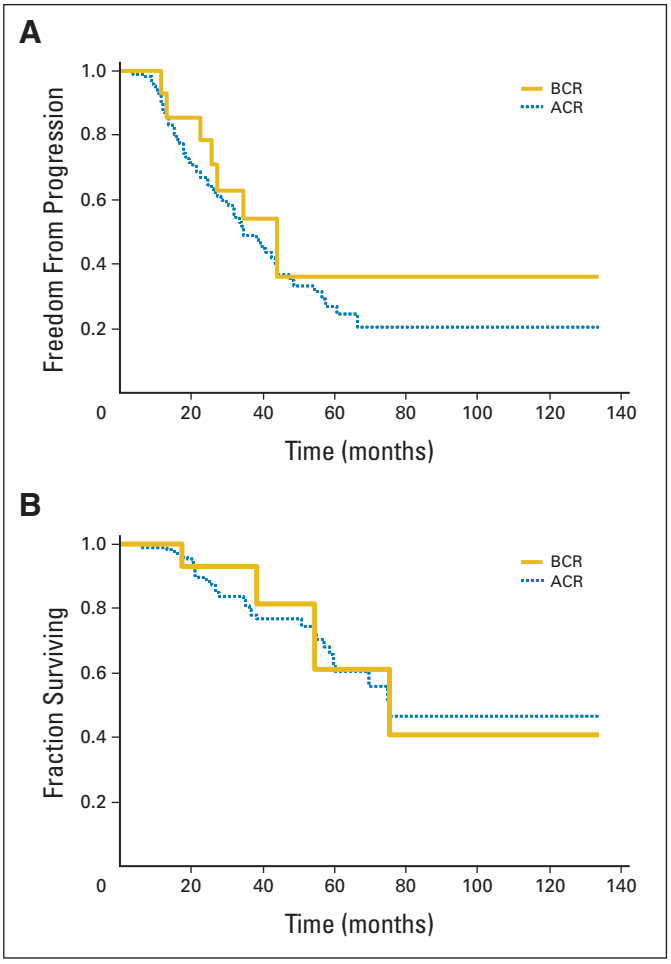

Fig 1. Comparison of the (A) time to progression and (B) overall survival for patients with complete response before (continuous line) and after (dotted line) high-dose therapy with autologous stem-cell transplantation. There was no statistical difference between the two groups for either end point. BCR, complete response before high-dose chemotherapy with autologous stem-cell transplation; ACR, complete response after high-dose chemotherapy with autologous stem-cell transplation.

Table 2. TTP for Patients at Serial Time Points After HDT-ASCT

Cohort	Months (%)				P
	12	24	36	48	
BCR	92.9	78.6	53.9	35.9	.39
ACR	87.3	67.0	49.0	33.1	

Abbreviations: TTP, time to progression; HDT-ASCT, high-dose chemotherapy with autologous stem-cell transplantation; BCR, complete response before HDT-ASCT; ACR, complete response after HDT-ASCT.

Table 3. Overall Survival for Patients at Serial Time Points After HDT-ASCT

Cohort	Months (%)						P
	12	24	36	48	60	72	
BCR	100	93.0	90.0	81.0	60.0	42.2	.83
ACR	98.1	88.3	81.0	76.5	63.0	53.0	

Abbreviations: HDT-ASCT, high-dose chemotherapy with autologous stem-cell transplantation; BCR, complete response before HDT-ASCT; ACR, complete response after HDT-ASCT.

function describes disease progression before and after HDT-ASCT. According to the definition in the methods section, the two TTP, T_A and T_B, correspond to the time it takes for each patient to relapse back to an overall disease burden of 10^9 (detectable disease).

There are three possible scenarios that we will consider in turn. If $L_A = L_B$, then it follows immediately that $T_A > T_B$, which is contradicted by our observations. A second possibility is the Norton Simon hypothesis,[30-32] where $L_A < L_B$, which also gives $T_A < T_B$, again incompatible with our observations. The remaining option is that, as the disease burden decreases, the mass action principle determines the response, and smaller tumors respond less because of lower productive interactions between tumor cells and chemotherapy; in other words, $L_A > L_B$. In such a scenario, the outcome depends on the relative values of L_A and L_B. If $L_A \approx L_B$, then $T_A < T_B$, but whenever $L_A > L_B$, then it is possible that $T_A > T_B$. Indeed, this is the only condition that can lead to $T_A \approx T_B$, as observed clinically. Our observations suggest that the law of mass action may play an important role on the response of cancer to chemotherapy, and as the disease burden decreases, the yield of therapy decreases further. These results provide an explanation for the apparent disproportionate increase in TTP after tandem transplantation despite the small improvement in CR rates.[10] However, our observations, together with results of randomized studies,[10,33] question the wisdom of repeating HDT-ASCT to patients who achieve CR with the first transplant because chemotherapy obeys a law of diminishing returns; in other words, the absolute yield from sequential therapies decreases. Extrapolating from our results, one could speculate that patients who achieve CR with induction therapy could be spared the morbidity of HDT-ASCT. With the advent of novel agents yielding improved CR rates, this question becomes clinically important. Relevant issues to be considered are the duration of the response compared with the morbidity and mortality associated with either form of therapy. We are currently trying to shed some light on this question based on a retrospective analysis of patients seen at the Mayo Clinic, but ultimately a randomized control trial will be necessary to address the question conclusively.

It is possible that our results are caused by potential problems with the current definition of CR.[23] A CR requires that, after therapy, the bone marrow has less than 5% plasma cells and the serum and/or urine must be negative on immunofixation. However, bone marrow involvement in myeloma may be patchy, and therefore the biopsy specimen may not always be representative of the burden of the disease. The enhanced sensitivity of flow cytometry for clonal myeloma cells together with the ability to analyze thousands of cells could improve the definition of response. Immunofixation detects the monoclonal protein with higher sensitivity, but requires considerable technical skill and can be more subjective.[34] In this respect, we await studies that evaluate the depth of the response based on the immunoglobulin-free light chain assay that has even higher sensitivity. Perhaps the response definitions will be revised based on the availability of studies that incorporate these sensitive techniques.

Given that this is a nonrandomized study, one may have concerns regarding the inclusion of patients who could bias the results. In this respect, we note that the TTP we observed is virtually identical to that reported in various studies.[10,33,35,36] Despite the fact that none of our patients received maintenance therapy after HDT-ASCT, the TTP and OS were very similar to those from randomized studies,[10,33] and therefore further question the benefit of maintenance therapy in patients who had an optimal response to HDT-ASCT. Moreover, our results are similar to what Nadal et al[13] and Qazilbash et al[36] have observed, namely that the only pretransplant predictors of TTP were markers of tumor burden such as the size of the M-spike and BMPC.

Optimal tumor therapy requires an understanding of the target and how it reacts to a perturbation, be it chemotherapy or radiation. Tumors are dynamic processes composed of a population of cells that are replicating, quiescent, or dying. The difference between replication and death rates gives the net tumor growth rate. It is clear that as the tumor burden is decreased, the growth rate increases such that it effectively eliminates any benefit of additional therapy. These observations further support our prior studies demonstrating the lack of benefit of high-dose cyclophosphamide in the pretransplant setting.[37] The same considerations imply that, for patients who achieve CR after the first cycle of HDT-ASCT, a watch-and-wait approach may be adequate[10,33,29] until early relapse rather than proceeding to a second transplant with its higher morbidity and mortality. Sequential therapies do not add up, but are associated with diminishing return.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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