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## Inpatient vs outpatient autologous hematopoietic stem cell transplantation for multiple myeloma

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### Keywords

Multiple myeloma; outpatient; stem cell transplantation

## INTRODUCTION

Multiple myeloma (MM) is the second most common adult hematologic malignancy and is the most common indication for autologous hematopoietic stem cell transplantation (auto-HCT) [1, 2]. In the current era of novel therapeutics, this treatment is still considered beneficial, with improvements in progression free survival (PFS) [3, 4]. The process of high dose chemotherapy and auto-HCT has thus become routine at most transplant centers and has given rise to the paradigm of out-patient auto-HCT [5].

Initial experience with myeloablative chemotherapy suggested the need for a lengthy hospital stay. However, the evolution of supportive care, including antimicrobial prophylaxis and growth factors, has changed the approach to this procedure [6]. Indeed, numerous transplant centers now routinely offer an out-patient treatment option and several studies have demonstrated comparable if not improved clinical outcomes with out-patient management [7–9].

In this manuscript, we compare the characteristics and clinical outcomes of a large cohort of patients who were treated with auto-HCT as in-patients with those who were treated as out-patients. Our findings indicate that the procedure itself is safe in either setting, but the choice for either option is strongly related to baseline risk factors, including the Hematopoietic Stem Cell Comorbidity Index, (HCTCI).

## METHODS

We performed a retrospective chart review of all MM patients undergoing auto-HCT between 2008 and 2012. We divided patients into 2 groups: in-patient versus out-patient, based on their treatment plan. Primary endpoints were incidence of unscheduled admissions, treatment-related mortality (TRM), grade 2–4 adverse events (AEs) and average cost of auto-HCT in each group. Secondary endpoints were overall response (ORR) rates, PFS and overall survival (OS).

We compared clinical characteristics and outcomes between the two groups. Comorbidity was measured by the HCT-CI [10]. Time to neutrophil engraftment was defined as the first day of absolute neutrophil count  $>500/\text{ul}$  for 3 consecutive days. Time to platelet recovery was defined as the first day of platelet count  $>20,000/\text{ul}$  without need for transfusion. TRM was defined as death occurring within the first 100 days, not due to disease progression. AEs were graded per as by the National Cancer Institute's Common Terminology Criteria, version 4.

Differences in baseline characteristics and outcomes between the 2 groups as was determined by a t-test. For patients in the out-patient group, we performed a multivariate analysis to determine which factors were significantly associated with occurrence of unplanned hospital admission. PFS and OS were calculated using the Kaplan Meier method and the long-rank test was used to determine differences in survival between the in-patient and out-patient groups and between those patients with HCT-CI  $>2$  or  $\leq 2$ . Using hospital billing data, we determined the average cost per transplant for both the in-patient and out-patient groups.

## RESULTS

We identified 1046 patients who had undergone auto-HCT for MM between 2008–2012 at our institution. Of these, 669 (64%) were treated in the in-patient setting while 377 (36%) were treated in the out-patient setting. Baseline characteristics are listed in Table 1. Notably, the patients who were treated as out-patients were significantly younger (median age 62 for in-patients versus 58 for out-patients,  $p<0.001$ ). Out-patients were also more likely to have an HCT-CI score of  $<2$  ( $p=0.003$ ) and serum creatinine  $<2$  ( $p<0.001$ ). A greater percentage of patient in the out-patient group were receiving their HCT as a first remission consolidation (73% versus 64%,  $p=0.02$ ) and not in the primary refractory or relapsed setting. Finally, the preparative regimen for the out-patient group tended to be melphalan alone (95% versus 81%,  $p<0.002$ ) rather than combination chemotherapy.

In the out-patient group, 55% of patients required admission to the hospital within the first 30 days. The main cause (42%) of these admissions was neutropenic fever. Other causes included gastrointestinal complications (nausea, vomiting or diarrhea, requiring intravenous hydration), pain (stomatitis or mucositis requiring intravenous analgesics) or treating physician's discretion. The median time from day of transplant to admission for these patients was 8 days (range: 4–25) and median duration of admission was 6 days (range 0–77). On multivariate analysis, a serum creatinine of  $>1.5\text{mg/dL}$  and HCT-CI  $>2$  were

significantly associated with risk of unscheduled admission, (HR=1.6, 95% CI 1.2–2.2,  $p = 0.001$ ).

Transplant outcomes are detailed in Table 2. 100-day TRM did not differ between the groups. However there were significantly more grade 2–4 ( $p=0.003$ ) and grade 3–4 ( $p=0.003$ ) AE's in the in-patient group versus the out-patient group. For each cohort and the entire patient population, those with a HCT-CI of  $>2$  had a greater incidence of grade 3–4 AEs ( $p = 0.03$  for the out-patients,  $p=0.001$  for the in patients and  $p<0.001$  for all pts). With regard to disease outcomes, more patients in the out-patient group achieved a CR (96.5%) than those in the in-patient group (89.5%,  $p<0.001$ ). Two-year PFS was significantly longer in the out-patient versus in-patient group (60% versus 50%, HR =HR 0.7, 95% CI 0.6–0.9,  $p =0.005$ , Figure 1A). Two-year OS was also longer in the out-patient versus in-patient group (83% vs. 77%, HR 0.6, 95% CI 0.4–0.9,  $p=0.01$  Figure 1B). Finally, with regard to resource utilization, the average cost of the transplant procedure was \$416,154 (range----) versus \$292,572 (range----)

## DISCUSSION

In this analysis of a large cohort of MM patients undergoing auto-HCT, we were able to corroborate previous reports [9, 11, 12] suggesting that this procedure can be done safely in the out-patient setting. Though over half of the out-patients eventually required in-patient admission, the overall incidence of AEs was far less in this group and there was no difference in 100-day TRM.

The differences discovered between groups in clinical outcome is likely due to the differences that existed before the transplant. As would be predicted, patients treated in the in-patient setting tended to be older, with more advanced disease and with more co-morbidities (a finding also previously reported in the literature [9]). Therefore, it is not surprising that the in-patient group had greater AEs and inferior PFS and OS. Another factor in our analysis that likely impacted admission decision was the choice of chemotherapy preparative regimen; for patients treated with combination chemotherapy (for example, busulfan and melphalan) the logistics of treatment necessitated in-patient management and may have impacted AEs.

Though there are some guiding resources [5], at our institution there is no defined algorithm for determining in-patient versus out-patient treatment. However, it appears that those patients chosen for out-patient management were done so appropriately, as their toxicities were not worse than their in-patient counterparts. This suggests that the treating physician is likely able to gauge properly the patients who are best suited to be out-patients. However, it also does not answer the next question: are there patients who are being admitted for this procedure who should actually be treated as an out-patient?

There are a variety of reasons why a patient who is physiologically suitable for out-patient treatment will instead be treated as an in-patient. Housing, caregiver availability and anxiety are likely common factors [13]. However, our rough but informative cost analysis suggests that the out-patient option could save 30% of the entire transplant cost, a finding similar

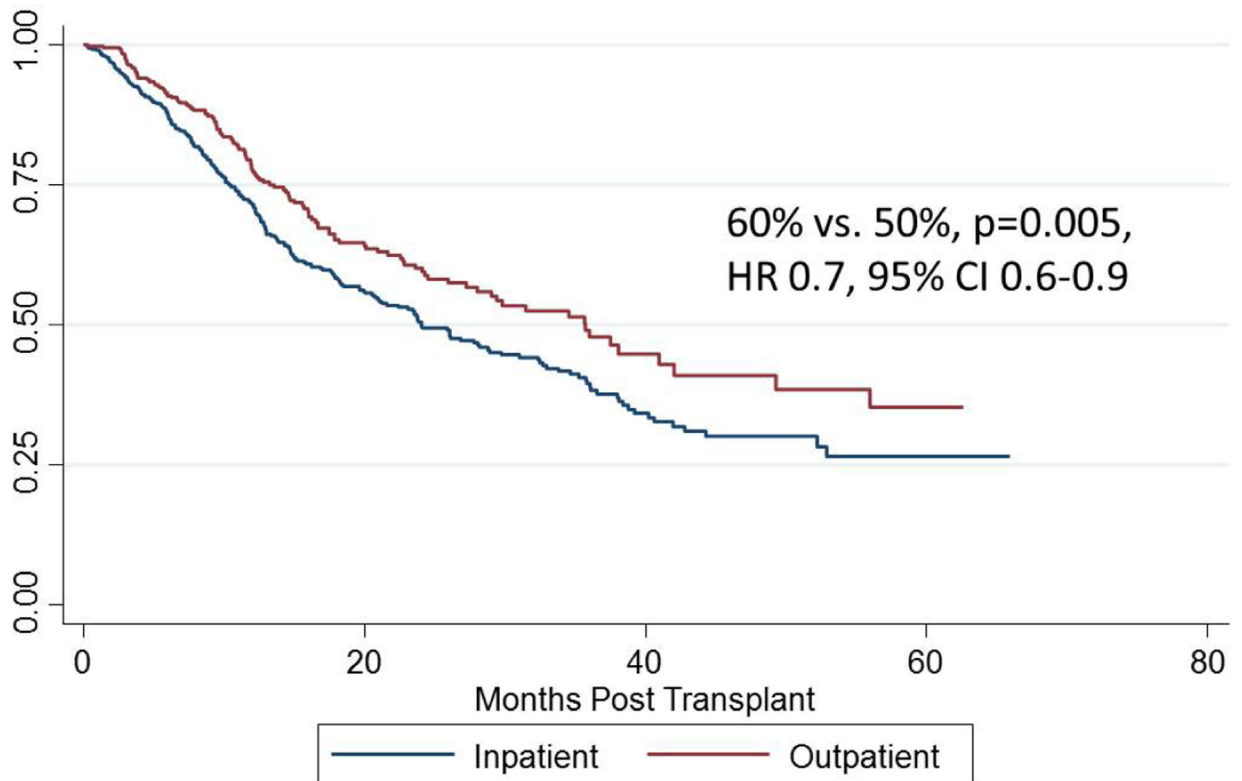
to previously reported analyses [14]. Our data provide the seeds of rationale for third-party payers to consider covering costs of housing or providing a monetary incentive for caregiving. This could maximize the utilization of an out-patient transplant program or even support a mixed out-patient/in-patient program, as has been suggested by others [13, 15].

There are many limitations to our study, with provider bias being the most important. A more rigorous approach, in the absence of randomization, would be to prospectively analyze transplant outcomes between those who were physically capable of out-patient management but admitted for social reasons versus those who were managed as out-patients. This study would be strengthened by accompanying patient-reported outcome data on symptoms and quality of life, which has previously been reported to be favorable in an out-patient cohort [11]. If the outcome data were similar, this would provide stronger rationale for promoting the out-patient transplant approach. Ultimately, patient co-morbidities, provider assessment and, most importantly, patient autonomy must be combined to make the final treatment decision.

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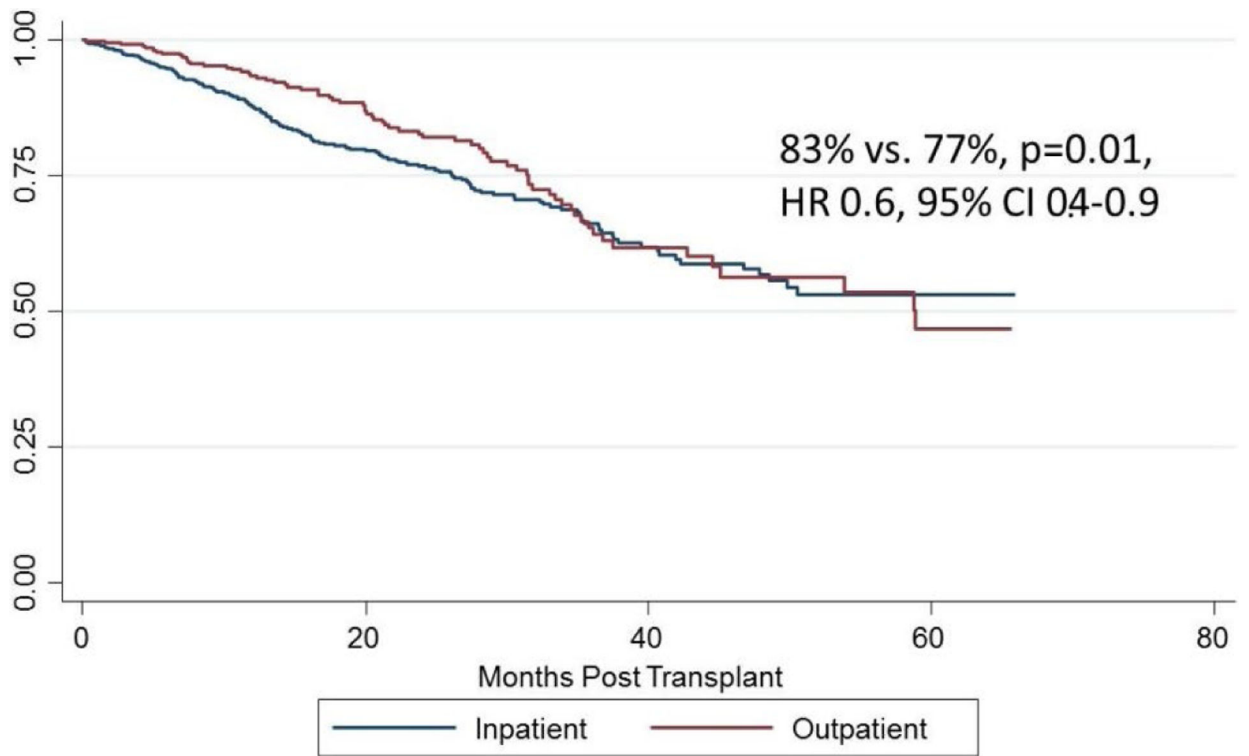
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**Figure 1A.**

Survival outcomes after in-patient or out-patient auto-HCT. Two-year PFS [A] and OS [B] was significantly longer in the out-patient versus in-patient group.



**Figure 1B.** Survival outcomes after in-patient or out-patient auto-HCT. Two-year PFS [A] and OS [B] was significantly longer in the out-patient versus in-patient group.

**Table 1.**

## Patient characteristics

	<b>Inpatient (%) n=669</b>	<b>Outpatient (%) n=377</b>	<b>P</b>
Male	369 (53)	234 (62)	
Median Age	62 [31–82]	58 [34–78]	<0.001
HCT-CI score <3	301 (45)	207 (55)	0.003
HCT-CI score ≥ 3	368 (55)	170 (45)	
Median Karnofsky PS	90 [40–100]	90 [70–100]	
ISS			
ISS I	178 (27)	130 (34)	
ISS II/III	307 (46)	156 (41)	
Unknown	184 (27)	91 (24)	
Cytogenetics at Auto-HCT			
Good	527 (79)	304 (81)	
Bad	114 (17)	62 (16)	
Unknown	28 (4)	11 (3)	
Disease Status Prior to HSCT			
1st Remission Consolidation	427 (64)	275 (73)	0.02
Primary Refractory	38 (6)	9 (2)	
Relapsed	131 (20)	56 (15)	
2nd Auto-HCT	62 (9)	24 (6)	



**Table 2.**

## Transplant outcomes

	<b>Inpatient (%) n=669</b>	<b>Outpatient (%) n=377</b>	<b>P</b>
Time to Engraftment, days			
Platelets, 20,000	11 [5–42]	11 [7–70]	<b>0.05</b>
Neutrophils, ANC 500	11 [7–16]	11 [9–15]	
Treatment Related Deaths: Total	22 (3)	4 (1)	0.04
Infection	8 (1.2)	1 (0.3)	
Cardiac Failure	3 (0.4)	1 (0.3)	
Other	11 (1.6)	2 (0.6)	
Treatment Related Deaths: Day 100	10 (1.5)	1 (0.3)	0.10
Adverse Events			
Grade II–IV	552 (83)	277 (73)	<b>0.003</b>
Grade III/IV	359 (54)	163 (44)	<b>0.003</b>
Grade IV	19 (3)	6 (2)	0.2
Final Response Post Auto HSCT			
CR/VGPR/PR	599 (89.5)	364 (96.5)	<0.0001
<PR	42 (6.3)	7 (1.9)	
PD	21 (3.2)	5 (1.3)	
NE	7 (1)	1 (0.3)	

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