Autologous Stem Cell Transplantation Is an Effective Salvage Therapy for Primary Refractory Multiple Myeloma

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A B S T R A C T

High-dose therapy and autologous stem cell transplantation (ASCT) have proven efficacy in patients with multiple myeloma responding well to induction therapy. For those who fail to achieve a stable partial response (PR), the effect of ASCT is unclear. We report on 126 patients identified from a national database, who underwent ASCT having achieved <PR after induction with modern induction regimens. The overall response rate was 86% (24% complete response). Patients with progressive disease at the time of transplantation had poorer outcomes than those with minimally responsive or stable disease, but clinical benefit was seen in all groups. Day 100 and 1-year nonrelapse mortalities were 2% and 4%, respectively. The 5-year relapse rate and progression-free survival were 84% and 14% (median, 18 months), respectively. The 5-year overall survival was 42% (median, 51 months). Our findings support the use of ASCT in myeloma patients responding suboptimally to modern induction therapies. Patients should not be excluded on the basis of refractoriness to induction, as ASCT is effective in this group conventionally considered to have a poor outcome. Comprehensive multivariate analysis identified no disparate subgroups, meaning ASCT is a reasonable strategy for all fit primary refractory patients.

INTRODUCTION

Since the initial demonstration of high-dose melphalan for multiple myeloma (MM), in excess of 500 reports have been published on its use, with nearly 15,000 patients undergoing autologous stem cell transplantation (ASCT) in Europe. Randomized controlled studies show improved response rates, progression-free survival (PFS), and overall survival (OS) compared with conventional chemotherapy [1]. ASCT has, therefore, become the established front-line therapy for those biologically fit enough for its physiological challenges. The depth of response to induction therapy is correlated with outcome after ASCT; attainment of at least a very good partial response (PR) is associated with superior PFS [2]. However, even with novel agent–containing induction regimens, up to 25% of newly diagnosed patients have poorly responsive disease (<PR), and this proportion rises with sequential relapses.

Studies in other refractory B cell malignancies (eg, non-Hodgkin lymphoma) have yielded disappointing results with ASCT [3]. However, this may not be the case for MM—the few published reports are conflicting and largely predate novel agents. In the early 2000s, Singhal et al. and Kumar et al. reported cohorts with primary refractory MM (PRM) (43 and 50 patients, respectively) who received ASCT after conventional induction therapy [4,5]. They found no difference in long-term outcomes compared with patients undergoing ASCT with chemo-sensitive disease. In contrast, in a post hoc analysis of the IFM 2005-01 trial, Moreau et al. reported failure to achieve ≥very good PR after bortezomib-based induction resulted in inferior PFS after ASCT [2]. Nonetheless, even if outcomes of ASCT for <PR are inferior to those of ASCT for ≥PR, the modality might nevertheless offer clinical benefit.

We sought to delineate the clinical course of patients who underwent ASCT despite failing to achieve a PR after induction with modern therapies. Patients were identified as having achieved minimal response (MR), stable disease (SD), or progressive disease (PD) at the time of ASCT. In this report, we examine the impact of ASCT and discuss the clinical utility of ASCT for aggressive and poorly responding disease.

DESIGN AND METHODS

Patient Selection, Definitions, and Procedures

This retrospective study was approved and registered by the British Society of Blood and Marrow Transplantation Clinical Trials Committee. Eligible patients were identified from the British Society of Blood and Marrow Transplantation Data Registry. Consent was obtained at the time of transplantation, in line with European Bone Marrow Transplant Registry directives with European Bone Marrow Transplant response criteria [6] were used throughout, as the majority of patients underwent transplantation in or before 2006, when the more recent International Myeloma Working Group criteria were published. Patients were eligible if, at the time of ASCT, they had never achieved PR (ie, best response was MR, SD, or PD) and had undergone stem cell collection sufficient to undertake ASCT, by either peripheral apheresis or bone marrow harvesting. Bone marrow aspirate and trephine biopsy was performed at 100 days after transplantation, unless declined.

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Statistical Analysis

Metrics collected for all patients were as follows: age at diagnosis, age at ASCT, gender, Karnofsky status at ASCT, β_2-microglobulin at diagnosis, albumin at diagnosis, serum creatinine at diagnosis, serum creatinine at ASCT, number of lines of prior therapy, disease status at time of ASCT, time from diagnosis to ASCT, time from first therapy to ASCT, and ASCT conditioning regimen. The Kaplan-Meier product-limit estimator was used for median and range of the follow-up time and univariate (UVA) probabilities. Nonrelapse mortality (NRM), relapse, PFS, and survival after ASCT were evaluated in multivariate analyses (MVA) using competing risk analysis to identify patient-, disease-, and transplantation-related variables prognostic of outcomes (relapse and NRM were used as competing risks for each another). The assumption of proportional hazards for each factor in the Cox model was tested using time-dependent covariates. For nonproportional hazards, the post-transplantation time course was broken into 2 periods, using the maximized partial likelihood method to find the most appropriate breakpoint. Interactions between covariates were tested before stepwise modeling. The final MVA model was built using a forward stepwise model. All *P* values were 2-sided.

RESULTS

Patients

One hundred twenty-six eligible patients were identified and underwent transplantation between 2000 and 2008 at 18 centers in the United Kingdom. Patient and transplantation characteristics are shown in Table 1. All patients in this study had primary refractory disease, having failed to achieve at least a PR in response to any and all prior therapies; 67 (53%) patients received ASCT "up front" after 1 line of induction therapy resulting in <PR (including 11 patients with PD during induction); 59 (47%) received ASCT after more than 1 cycle of therapy, again having never achieved a PR or better in response to any therapy. Induction regimens were not standardized but were in keeping with current United Kingdom practice during that time period, and, therefore, some incorporated thalidomide but not lenalidomide or bortezomib. No patients had received prior ASCT. Cytogenetic data were available for too few patients to allow subgroup analysis. Median time to engraftment (defined as peripheral blood neutrophils $> .5 \times 10^9$/L) was 14 days (range, 9 to 117) and platelet engraftment ($>50 \times 10^9$/L unsupported) was 19 days (range, 10 to 132). Median follow-up is 61 months (range, 1 to 112).

NRM

Three of 126 evaluable patients died of treatment-related causes within 100 days. NRM at 100 days, 1 year, and 5 years were 2%, 4%, and 10%, respectively. UVA and MVA are shown in Table 2 (variables listed as collected in the Methods section, and those not included in the table did not reach significance).

Response to ASCT and Relapse Rate

At day 100, the complete response (CR) rate was 21% (95% confidence interval [CI], 13% to 29%) and the PR rate was 74% (95% CI, 65% to 82%) (Table 1). Response rate was not correlated with any demographic or treatment factors. Patients with MR or SD at the time of transplantation demonstrated a CR rate of 24% and PR rate of 70%, compared with those with PD at the time of transplantation, who had 16% and 79%, respectively ($P = .608$). Disease response at day 100 (CR versus PR versus PD) was strongly predictive of OS, PFS, and relapse rate ($P = .02$, $P = .003$, $P = .003$, respectively). Given that administration of high-dose melphalan is the rationale for ASCT, UVA and MVA for response rate, OS, PFS, and relapse rate by melphalan dose were untaken and did not reach significance.

Table 1
Patient Characteristics and Response to ASCT at Day 100

Characteristics	Value
No. of patients, n	126
Sex, n (%)	
Male	77 (61)
Female	49 (39)
Age at diagnosis, median (range), yr	54 (25-69)
Age at transplantation, median (range), yr	56 (33-72)
Time from first treatment to transplantation, median (range), mo	7 (3-73)
>12 months (%)	16
ISS score, n (%)	
I	22 (50)
II	15 (34)
III	7 (16)
Unknown	82
Karnofsky status at transplantation, n (%)	
100	12 (15)
90	39 (48)
80	25 (31)
70	4 (5)
60	1 (1)
Unknown	45
Serum creatinine at diagnosis, median (range), μmoL/L	86 (43-577)
Unknown	69
Serum albumin at diagnosis, median (range), g/L	38 (21-49)
Unknown	80
Serum β2-microglobulin at diagnosis, median (range), mg/L	3.2 (1.1-76)
Unknown	82
Prior lines of therapy, median (range)	1 (1-4)
Unknown (n)	12
Prior exposure to	
Vincristine	79
Idarubicin	21
Cyclophosphamide	49
Melphalan	10
Adriamycin	79
Etoposide	9
Thalidomide	17
Disease status at transplantation, n (%)	
MR	48 (38)
SD	31 (25)
PD	47 (37)
High-dose therapy regimen, n (%)	
Melphalan 200 mg/m^2	62 (52)
Melphalan 140 mg/m^2	16 (13)
Melphalan 100 mg/m^2	8 (6)
Melphalan other dose	34 (27)
Unknown	6
Stem cell source, n (%)	
Peripheral blood	123 (98)
Bone marrow	2 (2)
Combination of both	1 (1)
Response to transplantation at day 100, n (%)	
CR	24 (21)
PR	84 (74)
MR	1 (1)
SD	3 (3)
PD	2 (2)
Death (disease)	0
Death (ASCT-related)	3 (3)
Unknown	6 (6)

ISS indicates International Scoring System.

At the time of analysis, 65 patients had died at a median of 25 months after ASCT (95% CI, 19 to 35): 54 were due to disease progression and 11 unrelated causes. The relapse rates at 1 year and 5 years were 33% and 84%, respectively. PD at the time of transplantation conferred an increase in rate of relapse (47% at 1 year, compared with 18% and 20% for SD and MR, respectively, $P = .022$).