Original Study

Long-Term Results in Multiple Myeloma After High-Dose Melphalan and Autologous Transplantation According to Response Categories in the Era of Old Drugs

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Abstract

We investigate the prognosis of multiple myeloma in 173 patients treated with high-dose melphalan and autologous transplantation in the era of old drugs. The relapse rate is low for patients in complete remission after 10 years of follow-up with a PFS and OS values of 58% and 70%. The achievement of depth response represents the most important prognostic factor.

Background: The aim of this study was to investigate the correlation between the long-term prognosis of multiple myeloma (MM) and the quality of response to therapy in a cohort of 173 patients treated with high-dose melphalan (HDM) and autologous transplantation in the era of old drugs. **Patients and Methods:** A total of 173 patients with de novo MM who received a transplant between 1994 and 2010 were analyzed. VAD (vincristine, doxorubicin [Adriamycin], dexamethasone) was used as front-line regimen before auto-HPCT. The conditioning was HDM 200 mg/m^2. Patients were evaluated for clinical response using the criteria from the European Group for Blood and Marrow Transplantation, modified to include near complete remission (nCR) and very good partial remission (VGPR). **Results:** The response distribution after transplantation in our series was complete remission (CR) in 33 cases (19%), nearly complete remission (nCR) in 38 cases (22%), VGPR in 30 cases (17%), partial remission (PR) in 65 cases (38%), and stable disease (SD) in 7 cases (4%). Patients were followed for 48 ± 36 months. Median overall survival (OS) was not reached for the CR group. Progression-free survival (PFS) was 122 months for CR, 55 months for nCR, 56 months for VGPR, 32 months for PR, and 22 months for SD. Significant differences in PFS and OS were found between the CR and nCR groups ($P = .003$ and $P = .001$, respectively), between the CR and VGPR groups ($P = .002$ and $P = .001$, respectively), and between the CR and PR groups ($P = .000$ and $P = .001$, respectively). Responses were clustered in 3 main categories, ie, CR, nCR + VGPR + PR, and SD. The respective 10-year PFS and OS values were 58% and 70% for CR, 15% and 18% for nCR + VGPR + PR, and 0% and 0% for SD. **Conclusion:** The achievement of depth and prolonged response represents the most important prognostic factor. The relapse rate is low for patients in CR after 10 years of follow-up, possibly signifying a cure.

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Introduction

The treatment of multiple myeloma (MM) is in continuous and rapid evolution. Drugs currently used for the treatment of this disease include alkylating agents, corticosteroids, proteasome inhibitors, immunomodulatory drugs, and anthracyclines.[1] Patients who are considered potential candidates for autologous hematopoietic progenitor cell transplantation (AHPCT) receive 2 to 4 cycles of a nonmelphalan-containing regimen and then proceed to stem cell harvest.[2] For many years, VAD or pulsed high-dose dexamethasone (HDD)[3] were used as frontline induction therapy, but now the strategy has changed with new agents such as immunomodulatory drugs and proteasome inhibitors, bortezomib in particular. Before the advent of new drugs, the complete remission (CR) rate after induction therapy was < 10%, and several trials have shown an association between depth of response to therapy and long-term outcome.[4] New induction regimens offer high overall response rates, approaching levels previously noted only with AHPCT.[5] Combined treatment based on novel-agent induction regimens and high-dose chemotherapy (HDC) provide further improvement in the depth of response,[6,7] and for this reason, MM remains the leading indication for AHPCT worldwide,[8,9] and the International Myeloma Working Group recommends that AHPCT be offered at some point during the course of treatment to a medically fit patient.[10]

As a contribution to the field of HDC and AHPCT in MM, we report the results of this therapeutic approach in patients coming from a regional network and treated during the era of the old drugs. We analyzed correlations between prognosis and different response categories after long-term follow-up.

Patients and Methods

A total of 173 patients with de novo MM who received AHPCT between 1994 and 2010 were analyzed. Main patient characteristics at diagnosis are summarized in Table 1. The induction chemotherapy was performed in 6 different institutions in southern Italy. One hundred forty-six patients underwent a single transplantation and 46 patients had a tandem transplantation.

Table 1 Main Patient Characteristics at Diagnosis

No. of patients	173
Age, years, mean ± SD	57 ± 7
Sex, %	
Male/female	60/40
M-protein, %	
IgG/IgA/light chain	52/27/23
Durie-Salmon Stage, %	
I/II/III	1/20/79
PS ≥2 (ECOG), %	53
Serum Creatinine Level, μmol/L, mean ± SD	132 ± 100
Hemoglobin Level, g/dL, mean ± SD	10.7 ± 3.5
Beta-2 Microglobulin ≥2.5 mg/L, %	70
No. Patients Who Received 2 Transplants	46

Abbreviations: ECOG = Eastern Cooperative Oncology Group; PS = performance status.

VAD was used as a frontline regimen before AHPCT. The source of stem cells was peripheral blood stem cells in all cases. Stem cells were collected after cyclophosphamide mobilization at doses ranging from 3 to 4 g/m^2 in association with granulocyte colony-stimulating factor 5 μg/kg. The conditioning HDC was high-dose melphalan (HDM) 200 mg/m^2.

Information about response status after transplantation, evaluated simultaneously by electrophoresis (EP) and immunofixation (IF) for serum and urinary M-protein, was available for all cases. Patients were evaluated for clinical response using the criteria from the European Group for Blood and Marrow Transplantation,[11] which was modified to include nearly complete remission (nCR) and very good partial remission (VGPR). Patients were divided into different groups: CR, defined as absence of a detectable M-component in serum and urine by IF in 2 measurements over 6 weeks and < 5% plasma cells in the bone marrow; nCR, defined by a negative EP result but positive detection of an M-component by IF; VGPR, defined by detection of an M-component at EP e/o IF and reduction in M-component levels between 90% and 99%; partial remission (PR), defined by an M-component reduced to between 50% and 90%. The remaining patients were considered nonresponders, both with progressive disease (PD) or stable disease (SD). Patients with progressive disease were excluded from analysis.

Patients were followed until death or the end of the study, and all participants were monitored by both EP and IF in serum and urine throughout follow-up. In this period, a relapse was considered a major event and it was defined as follows: in patients with CR, by recurrence of a detectable M-component on IF, even with negative EP results; in those with nCR, by a positive EP; in those with VGPR, PR, or SD by an increase of > 25% compared with the lowest M-component level previously achieved.

The evaluation of response was performed after a median time of 3.6 months (range, 3.0-6.7 months) from transplantation, and the follow-up was started at the time of response assessment and included all patients.[12] Progression-free survival (PFS) was measured from the start of follow-up to the date of progression, relapse, or death; patients alive and event free were censored at the date of the last clinical control. OS was calculated from the start of follow-up to date of death or last follow-up visit.

The statistical analysis according to the different response categories was performed using SPSS software (SPSS Inc, Chicago, IL). Data are expressed as mean ± SD, survival curves were calculated according to the Kaplan-Meier method, and differences between curves were evaluated with the log-rank test. *P* values < .05 were considered to reflect statistical significance. Death and event rate were calculated as number of deaths (or events) per 100 patients per year.

Results

The response distribution after AHPCT in the series was 33 cases of CR (19%), 38 cases of nCR (22%), 30 cases of VGPR (17%), 65 cases of PR (38%), and 7 cases of SD (4%) (Table 2).

Patients were followed for 48 ± 36 months. Median survival was not reached for the CR group; PFS and OS curves are reported in Figures 1 and 2, respectively. The median PFS was 122 months for patients who achieved CR, 55 months for patients who achieved