ASBMT
American Society for Blood and Marrow Transplantation

Multiple Myeloma in Serologic Complete Remission after Autologous Stem Cell Transplantation: Impact of Bone Marrow Plasma Cell Assessment by Conventional Morphology on Disease Progression

Carlos Fernández de Larrea,[1] Natalia Tovar,[1] María Rozman,[2] Laura Rosiñol,[1] Juan Ignacio Aróstegui,[3] María Teresa Cibeira,[1] Montserrat Rovira,[1] Jordi Yagüe,[3] Joan Bladé[1]

The current definition of complete remission (CR) in multiple myeloma (MM) requires a negative serum and urine immunofixation (IFE) and <5% bone marrow plasma cells (BMPCs). The aim of this study was to determine the value of BMPCs count by standard microscopic evaluation in patients with MM in serologic CR after autologous stem cell transplantation (ASCT). Thirty-five patients with a median follow-up after ASCT of 7.3 years were studied. The percentage of BMPCs was an independent predictor of progression in multivariate model (hazard ratio 2.02, $P = .009$). Patients with >1.5% BMPCs (median: 0.8%) after ASCT had an increased risk of progression ($P = .016$) and a trend toward a shorter survival ($P = .195$). In conclusion, conventional morphology of bone marrow is a useful and rapid tool as a first step to assess the residual tumor mass in patients with MM in CR after ASCT, and it constitutes a strong predictor for disease progression.

Biol Blood Marrow Transplant 17: 1084-1087 (2011) © 2011 American Society for Blood and Marrow Transplantation

KEY WORDS: Myeloma, Complete remission, Plasma cell, Bone marrow aspirate, Prognosis, Stem cell transplantation

INTRODUCTION

The achievement of complete remission (CR) is the crucial step for a long-lasting response and prolonged survival after autologous stem cell transplantation (ASCT) in patients with multiple myeloma (MM) [1-3]. The European Group for Blood and Marrow Transplantation (EBMT) criteria for CR include the negativity of serum and urine immunofixation (IFE) and <5% of bone marrow plasma cells (BMPCs) [4]. Additionally, the International Myeloma Working Group (IMWG) has even proposed a stringent CR category, which also requires ruling out the clonal nature of the BMPCs [5]. However, few studies have addressed this issue in patients with MM and negative IFE [6]. Despite the EBMT and IMWG recommendations, there have been suggestions to eliminate the bone marrow examination from the clinical practice in patients with negative IFE, arguing that the 5% limit is arbitrary, there is uncertainty in its prognostic value, and that the procedure is uncomfortable for patients [6]. The aim of the present study was to determine the impact of plasma cell count in the bone marrow aspirate estimated by conventional morphology on the long-term outcome of patients with MM with negative IFE after ASCT.

MATERIALS AND METHODS

Thirty-five patients (16 M/19 F; median age at ASCT 55 years, range: 26-68) with symptomatic MM who underwent ASCT from March 31, 1994, to August 29, 2008, with available bone marrow aspirates and adequate cellularity were included in the study. All patients had achieved a negative serum and urine IFE after high-dose therapy with melphalan-based regimens (melphalan 200 mg/m^2, melphalan 140 mg/m^2 plus total-body irridiation [TBI], or melphalan 140 mg/m^2 plus busulfan 12 mg/kg) (Table 1).

Bone marrow aspiration was performed when negative serum and urine IFE was achieved and at least 3

From the [1]Department of Hematology; [2]Hematopathology Unit; and [3]Department of Immunology, Hospital Clínic, Barcelona. Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain.

Financial disclosure: See Acknowledgments on page 1086.

Correspondence and reprint requests: Joan Bladé, MD, Servei d'Hematologia, Hospital Clínic de Barcelona, Villarroel 170, 08036 Barcelona, Spain (e-mail: jblade@clinic.ub.es).

Received August 12, 2010; accepted December 22, 2010

1083-8791/$36.00
doi:10.1016/j.bbmt.2010.12.707

Table 1. Patient Characteristics

	Value
Median age, years. (range)	55 (26-68)
Male/female, no.	16/19
M-protein type (%)	
IgG	42.9
IgA	22.9
Light chain only	25.7
IgD	5.7
IgM	2.9
Light-chain type (%)	
κ	57.1
λ	42.9
Durie-Salmon stage at diagnostic (%)*	
I	11.8
II	38.2
III	50.0
Initial chemotherapy (%)†	
VMCP/VBAP or VBMCP/VBAD	60.0
Other	40.0
HDT regimen	
Mel-200	71.4
BU/MEL	17.2
Mel-140/TBI	11.4

TBI indicates total-body irridiation; V(B)MCP, vincristine; (BCNU), melphalan, cyclophosphamide, prednisone; VBAD(P), vincristine, BCNU doxorubicin, dexamethasone (prednisone); HDT, high-dose therapy; Mel-200, melphalan 200 mg/m^2; BU/MEL, melphalan 140 mg/m^2 plus busulfan 12 mg/kg; Mel-140/TBI, melphalan 140 mg/m^2 plus total-body irradiation.

*Durie-Salmon stage was available in 34 patients.

†One patient did not receive induction chemotherapy because of associated primary amyloidosis (AL).

months from ASCT (median 3.24 months, range: 2-11). The analysis was based on microscopic revision of May-Grünwald–Giemsa–stained bone marrow smears performed according to standard procedures. BMPC percentage was calculated independently by 2 observers (C.F.d.L. or N.T., and the senior cytologist M.Rozman.) counting 500 bone marrow total nucleated cells in random areas from 2 different slides (1000 cells from each patient). The evaluation was repeated in 7 patients (20%) because of a discordance ≥0.5% BMPCs between the 2 observers. In all cases, a new independent revision of 500 cells by each observer resulted in a concordance with <0.5% difference. Baseline demographics, clinical and laboratory data, as well as induction treatment were collected from all patients. Progression-free survival (PFS) was defined as survival from ASCT until relapse or dead from any cause. Overall survival (OS) was calculated from the time of ASCT. IFE was performed every 6 months in patients in CR after ASCT. The median follow-up of the series was 7.3 years, and no patient was lost to follow-up.

RESULTS AND DISCUSSION

The initial clinical and laboratory findings as well as the induction chemotherapy and the high-dose regimen are shown in Table 1. All 35 patients had available bone marrow aspirates with adequate cellularity. Median BMPCs percentage was 0.8 (range: 0.1-5.8). Only 2 patients had >3% BPMCs. These results are in contrast with a recent report from the Mayo Clinic group, where 14% of the patients with MM and negative IFE had 5% or more BMPCs [6]. The discrepancy between our results and those reported by the Mayo group could be explained by several reasons. First, the study population in the Mayo report was heterogeneous. Thus, 55% of the patients had achieved negative IFE after ASCT whereas the remaining 45% were in CR after conventional chemotherapy. Additionally, the BMPCs percentages were not analyzed separately according to the treatment administered. In contrast, all our patients were in CR after ASCT. In fact, the extremely low percentage of BMPCs in our patients in CR is surprising, and it is likely related to the myeloablative high-dose treatment with its possible effect on the myeloma stem cell. Second, the estimation of BMPCs in the Mayo study was not based on a systematic count by independent observers on a large number of cells. Third, the estimation of BMPCs was made on bone marrow aspirate and biopsy in the Mayo report versus the assessment only in bone marrow aspiration in the present study, which could have resulted in underestimation of the proportion of BMPCs in our series.

In univariate Cox model regression analysis, the number of BMPCs showed a significant correlation with PFS (P = .021) with no significant impact on OS (P = .92). This statistical significance on PFS was retained in the multivariate analysis, when baseline prognostic factors such as age, hemoglobin level, serum creatinine, β2-microglobulin, Durie-Salmon stage, or conditioning regimen were added to the model (hazard ratio [HR] 2.02, P = .009). For Kaplan-Meier survival analysis [7], patients were divided according to BMPC percentage into 3 groups (group 1: <1%, group 2: between 1% and 2%, and group 3: >2%). The PFS was significantly longer in the 2 first groups compared with group 3 (log-rank test, P = .01), with no significant difference in OS. To establish the best predictive cutoff for progression and survival, a receiver-operator curve (ROC) analysis was developed [8,9]. It showed the value of 1.5% BMPCs, with a sensitivity of 53%, specificity of 90%, and area under the curve (AUC) of 0.66 for predicting progression. Ten patients had >1.5% BMPC, and 25 ≤1.5% BMPC. Median PFS was 8.5 years (confidence interval [CI] 95% 2.6-14.3) and was not reached in patients with ≤1.5% BMPCs versus 3.1 years in patients with >1.5% BMPCs, with a hazard ratio probability to progression of 3.02 (CI 95% 1.18-9.71) (P = .016) in the group with >1.5% of BMPCs (Figure 1). Of interest, the median BMPC count was similar in patients who received