Early Versus Delayed Autologous Stem Cell Transplantation and Interferon Maintenance in Multiple Myeloma: Single-Center Experience of 18 Years

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ABSTRACT

Background. Autologous stem cell transplantation (ASCT) has become the mainstay of 1st-line treatment in younger patients with multiple myeloma (MM), but statistical confirmation of its superiority over other therapies, especially in the era of novel agents, is still lacking.

Methods. We reviewed the results of all 548 myeloma ASCTs performed in our institute over the past 18 years.

Results. More than one-half of the patients had access to novel agents before their transplantations. Although the age of the transplanted patients increased significantly over the years, treatment-related mortality (TRM) was remarkably low, especially in 1st-line transplanted patients (100-day TRM, 0.3%). The median overall survival (OS) of the entire cohort was 98.4 months. Patients transplanted within 12 months from the start of their therapy had significantly better responses than those having delayed ASCT (complete response rate, 58.1% vs 46.8%; $P = .016$) and significant post-ASCT progression-free survival (PFS) benefit (30.2 [26.1–34.3] mo vs 23.3 [16.8–29.8] mo; $P = .036$), but we found no significant overall survival difference. The results were similar in patients treated with or without novel agents before ASCT. During a period of time, interferon maintenance was our standard approach to post-ASCT maintenance. Our analysis showed not only a significant PFS advantage with interferon, but also a highly significant overall survival benefit (150.4 [105.1–195.8] mo vs 86.1 [72.5–99.7] mo; $P = .003$).

Conclusions. Our findings demonstrate that delayed ASCT can be feasible in selected patients.

FOR THE past 3 decades, autologous stem cell transplantation (ASCT) been the mainstay of 1st-line multiple myeloma (MM) treatment in younger patients. However, with the arrival of novel agents (thalidomide, bortezomib, and lenalidomide), similar results may be achieved without the toxicity of ASCT. Therefore, many experts now propose delaying it and using it later at relapse [1]. Several publications have analyzed this question from various perspectives, including efficacy [2], curability [3], quality of life of the patients [4], and cost-effectiveness [5].

MM is an incurable disease affecting mainly people >60 years old with overall survival (OS) ~5 years depending on various patient- and disease-related factors [6]. A couple of randomized trials compared conventional chemotherapy

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(CCT) and ASCT [7–10]. Results were conflicting whether patients transplanted in 1st remission fared better than the CCT arm if they, too, had access to transplant later. Transplantation may significantly affect the well-being of patients, sometimes resulting in significant morbidity, not to mention the possible psychologic consequences of prolonged hospital stays [4].

Novel agents have vastly improved the quality of disease response, reaching levels previously achievable only with ASCT. This, together with the high tolerability of these drugs, has leveled the advantages observed with early transplantation, reopening the debate about the optimal place of ASCT in the sequence of various myeloma treatment options [11]. Prospective trials looking into this question are currently running and are expected to be published within the coming years. Until then, our strategies should be mainly based on retrospective comparisons.

Our aim was to compare the outcome of all myeloma patients having had autologous transplant in our center in 1st and subsequent remissions from 1996 to 2013.

MATERIALS AND METHODS

We analyzed the outcome of all 548 myeloma patients transplanted by our team. All transplantations were performed after informed consent. Because all data were reported previously to the European Group for Blood and Marrow Transplantation, we used their database as primary source, and then reviewed written and electronic notes and laboratory results. Response criteria (complete response [CR], very good partial response [VGPR], partial response [PR], no response [NR], and progressive disease [PD]) and survival measures (progression-free survival [PFS] and overall survival [OS]) were defined according to published International Myeloma Working Group guidelines [12].

Statistical Methods

In keeping with other published reports, PFS was determined from the day of stem cell (SC) infusion to the day of documented relapse or progression, and ASCTs performed within 12 months from the start of the 1st chemotherapy were counted as early, others as delayed [13,14]. OS was measured from the day of diagnosis to death from any cause, with censoring performed at the date of last contact. Death from any cause other than relapse was classified as treatment-related mortality (TRM). Comparisons of dichotomous variables were performed with the use of Fisher exact test; continuous variables were compared with the use of Mann-Whitney and Kruskal-Wallis tests. Kaplan-Meier log-rank test was performed to compare PFS and OS. After univariate analysis, variables with P values of $<.05$ in the entire cohort were included in a Cox proportional hazards model for PFS and OS. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were computed, CI is given in the text in brackets after the length of survival. The analyses were carried out with the use of the SPSS (version 20.0) software package (SPSS, Chicago, Illinois).

RESULTS

Study Population

Survival data of 548 patients transplanted from 1996 to 2013 by our team were analyzed. Presentation characteristics and prognostic markers are presented in Table 1. Three hundred seventy-seven patients had their ASCT within 12 months from the start of the 1st chemotherapy and 171 later. Within the 2nd group, 81 had additional chemotherapy before transplantation (35 one, 24 two, 16 three, and 6 four further lines) and 90 had the transplantation without further chemotherapy.

There was an equal distribution of the 2 sexes between the early and late transplant groups. The median age at transplantation was 57.0 years, and, probably as a result of the applied age/fitness threshold, it was equal in the early and late ASCT cohorts. As a consequence, patients in the later group had their 1st-line treatment at a significantly younger age.

The distribution of protein types was in keeping with the literature. The Salmon-Durie stage was available for the majority of patients; it was missing in 161. We found an equal distribution of the protein types and stages across the early and late ASCT groups.

Where it was available, International Scoring System (ISS) was calculated in each case at diagnosis. Within the delayed ASCT group there were 10% more ISS 1 compared with the early group, but the difference was not statistically significant.

Three-hundred fifty-seven patients had fluorescence in situ hybridization (FISH) test, and the distribution of translocation (4; 14) and 1q amplification across the early and late cohorts were asymmetric with fewer high-risk patients in the late transplantation cohort, but these differences were marginal ($P = .06$ and $P = .052$). According to our predefined FISH risk stratification, 96 patients were in the high-risk and 261 in the standard-risk groups, with 29.7% of the early and 19.4% of the late transplanted patients categorized as high risk ($P = .061$).

The median time from diagnosis to transplantation was 9.8 months in the whole cohort, 7.3 months in the early, and 16.9 months in the late ASCT subgroups. We started ASCT for MM in 1996, and initially, until 2001, more patients had delayed transplantation than in 1st remission. After that there were a stable number of late transplantations from 10 to 20, and the number of total myeloma ASCTs increased to ~50 per year.

In keeping with the global trend, the median age of the transplanted patients showed a year-by-year increase. Before 2002 it was 52.5 years, after 2007 it was 59 years, and between the 2 periods it was 55.5 years ($P < .001$).

Protocols

The following protocols were applied: vincristin-doxorubicin-dexamethasone (VAD) [15]; melphalan-prednisolon (MP); thalidomide-dexamethasone [16]; bortezomib-dexamethasone (VD) [17]; bortezomib-doxorubicin-dexamethasone (PAD) [18]; bortezomib-thalidomide-dexamethasone (VTD) [19]; etoposide-dexamethasone-cytarabine-cisplatin (EDAP) [20]; and lenalidomide-dexamethasone [21].

SC collections were usually performed with the use of cyclophosphamide priming plus granulocyte-colony stimulating