Outcomes Among High-Risk and Standard-Risk Multiple Myeloma Patients Treated With High-Dose Chemotherapy and Autologous Hematopoietic Stem-Cell Transplantation

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Abstract

We retrospectively compared the outcomes of autologous hematopoietic stem-cell transplantation (auto-HCT) among 670 patients with multiple myeloma (MM) stratified as high risk and standard risk on the basis of cytogenetic and fluorescence in-situ hybridization abnormalities. High-risk MM patients had shorter survival than standard-risk MM patients. Having more than 1 high-risk cytogenetic abnormality and not experiencing very good partial remission after auto-HCT further reduces survival.

Background: Conventional cytogenetics and interphase fluorescence in-situ hybridization (FISH) identify a high-risk multiple myeloma population characterized by poor response and short survival. **Patients and Methods:** We compared outcomes between high-risk and standard-risk myeloma patients who underwent autologous hematopoietic stem-cell transplantation (auto-HCT) at our institution between January 2005 and December 2009. High-risk myeloma was defined as −13/del(13q) or hypodiploidy in at least 2 metaphases of conventional cytogenetics, or −17/del(17p), t(4;14), t(14;16), t(14;20), hypodiploidy (< 45 chromosomes excluding −Y), or chromosome 1 abnormalities (+1q, −1p, t(1;x)) on FISH or conventional cytogenetics. **Results:** Of 670 myeloma patients, 74 (11%) had high-risk myeloma. These high-risk patients had significantly lower overall response rates (74% vs. 85%; $P < .01$), shorter median progression-free survival (10.3 vs. 32.4 months; $P < .001$), and shorter overall survival (28 months vs. not reached; $P < .001$) than the standard-risk patients. Having only 1 high-risk cytogenetic abnormality or experiencing at least very good partial remission after auto-HCT independently predicted improved progression-free survival and overall survival ($P < .05$) in high-risk patients. **Conclusion:** Even in an era of novel therapies, cytogenetically identified high-risk myeloma patients have worse prognoses than standard-risk myeloma patients after auto-HCT, and having more than 1 high-risk cytogenetic abnormality further reduces survival.

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Introduction

Structural chromosomal alterations in clonal myeloma cells, recognized by conventional metaphase cytogenetics and interphase fluorescence in-situ hybridization (FISH), are used to identify a subgroup (15%-25%) of high-risk multiple myeloma (MM) patients with poor prognosis.[1-4]

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A consensus statement from the International Myeloma Working Group recommends classifying MM as high risk if cytogenetic analysis of bone marrow samples reveals monosomy 13 (−13) or del(13q), del(17p), t(4;14), or t(4;16); or if interphase FISH identifies t(4;14), t(14;16), or del(17p) in MM cells. Identification of −13/del(13q) by FISH alone does not confer high-risk status.[5] A classification system proposed by Mayo Clinic group defines high-risk MM as having t(4;14), t(14;16), t(14;20), or del(17p13) on FISH analysis of clonal plasma cells or having −13/del(13q) or aneuploidy on metaphase cytogenetic analysis and a plasma-cell labeling index of > 3.[6] Other high-risk chromosomal abnormalities include: chromosome 1 aberrations, which are complex and may involve deletions in 1p, amplifications in 1q, and unbalanced translocations,[7,8] and the presence of a hypodiploid karyotype, which are independently associated with short survival.[9]

Approaches for treating high-risk MM are evolving. Induction regimens containing novel antimyeloma agents such as bortezomib, thalidomide, and lenalidomide show promise; however, these agents typically cannot completely overcome the resistance of high-risk MM.[10] Bianchi et al[11] reported that the adverse risk of t(4;14) was abated by the use of bortezomib in induction and maintenance therapy in association with tandem auto-HCT. Other evidence suggests that allogeneic hematopoietic stem-cell transplantation (allo-HCT) can overcome the negative prognostic effects of del(17p13) and/or t(4;14) and that the achievement of molecular remission after allo-HCT can result in longer relapse-free survival; however, only a minority of patients are eligible for allo-HCT.[12]

Auto-HCT is available broadly, improves survival in MM patients, and is currently considered a standard of care for transplant-eligible patients.[13] Data about the benefits of auto-HCT in high-risk MM, however, are limited. Thus, to elucidate the benefits and characterize in greater detail the role of auto-HCT in patients with high-risk MM, we compared patient characteristics and outcomes between high-risk and standard-risk myeloma patients who underwent auto-HCT at our institute.

Methods

The charts of 670 patients with MM who underwent auto-HCT and had follow-up at the University of Texas MD Anderson Cancer Center between January 2005 and December 2009 were identified and retrospectively reviewed. Results of metaphase cytogenetic and FISH studies of bone marrow aspiration samples were obtained for all the patients from the clinical chart. Patients who lacked metaphase cytogenetic analysis and FISH analysis results, who had received tandem auto-HCT, or who had undergone allo-HCT were excluded from the study.

Patients were defined as having high-risk MM if conventional cytogenetics in at least 2 metaphases performed at diagnosis or any time before auto-HCT revealed −13/del(13q), −17/del(17p), t(4;14), t(14;16), t(14;20), hypodiploidy (< 45 chromosomes excluding −Y), or a chromosome 1 aberration (+1, −1, t(1;x)), or if FISH or conventional cytogenetics showed del(17p13), t(4;14), t(14;16), t(14;20), or chromosome 1 abnormalities at any time before auto-HCT. CD138 enrichment was done if the plasma-cell percentages in bone marrow aspirate differential revealed 3% to 15% plasma cells. Enrichment was not done if plasma-cell percentage was < 3% (percentage too low) or > 15% (no enrichment needed). Patients were included if data were available for conventional cytogenetics, FISH, or both. Patients who showed no high-risk cytogenetic features were defined as having standard-risk MM; this group included patients in whom −13/del(13q) was identified only through FISH.

Descriptive statistics such as mean, standard deviation, median, and range were used for continuous variables, and frequency counts and percentages were used for categorical variables. Fisher exact tests or chi-square tests were used to compare variables between the groups. Wilcoxon rank sum tests or Kruskal-Wallis tests were used to compare continuous variables between the groups. The primary end points were overall survival (OS) and progression-free survival (PFS) in the high-risk MM and standard-risk MM groups. The secondary end points were overall response rate and treatment-related mortality in each group. Response and progression were defined according to International Myeloma Working Group criteria.[14] The overall response rate was assessed at 3 months after auto-HCT and included patients who had experienced partial remission (PR), very good PR (VGPR), complete remission (CR), or stringent CR. The Kaplan-Meier method was used to calculate PFS from the date of transplantation to the date of progression or death from any cause and OS from the date of transplantation to the date of death. Log-rank tests were used to compare PFS and OS between the high-risk and standard-risk groups. Cox proportional hazard models were fitted for multivariate analysis to assess the effects of significant prognostic factors on survival in the high-risk MM patients. SPSS 20 (IBM, Armonk, NY) was used for all the analyses. The institutional review board at The MD Ander Cancer Center approved the study.

Results

Patient and Disease Characteristics

During the study period, 670 MM patients with a median age of 58 years (standard deviation, 31-80 years), of whom 388 (58%) were male, underwent auto-HCT at the MD Anderson Cancer Center. Seventy-four patients (11%) were classified as having high-risk MM, and 596 patients (89%) had standard-risk MM. Chromosome 1 aberrations, −13/del(13q), hypodiploid cytogenetics, del(17p13), t(4;14), and t(14;16) were observed in 53 (72%), 48 (65%), 27 (36%), 16 (22%), 5 (7%), and none of the high-risk MM patients, respectively. Of the 74 high-risk MM patients, 31 patients had only 1 high-risk abnormality, and 43 (58%) had multiple, concurrent high-risk abnormalities. Of the 31 patients with only 1 high-risk abnormality, 15 had chromosome 1 aberrations, 7 had −13/del(13q), 6 had hypodiploidy, 2 had del(17p), and 1 had t(4;14).

The baseline characteristics of the high-risk and standard-risk MM patients are summarized in Table 1. Compared with the standard-risk MM patients, the high-risk MM patients were more frequently male (72% vs. 56%; $P = .003$), had higher Durie-Salmon stage ($P = .03$), more frequently showed IgA isotype on bone marrow specimen ($P = .03$), had a lower median hemoglobin level at presentation (10.0 vs. 11.4 g/dL; $P < .003$), and had a higher median percentage of clonal plasma cells in bone marrow aspirates at diagnosis (52% vs. 29%; $P < .001$). In the high-risk group, all except 2 patients received induction chemotherapy containing at least 1 novel antimyeloma agent (bortezomib,