The t(11;14)(q13;q32) Translocation as a Poor Prognostic Parameter for Autologous Stem Cell Transplantation in Myeloma Patients With Extramedullary Plasmacytoma

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Abstract

Among a total of 290 multiple myeloma (MM) patients undergoing autologous stem cell transplantation between April 2004 and December 2012, the data of 58 patients with extramedullary plasmacytoma (EMP) who had available fluorescence in-situ hybridization information for bone marrow samples obtained at diagnosis were analyzed. The t(11;14), t(4;14), del(13q), and 1q gain were associated with worse survival in MM patients with EMP. In particular, t(11;14) showed important prognostic factor for progression-free survival and overall survival in multivariate analysis.

Introduction: Fluorescence in-situ hybridization (FISH)-detected abnormalities, including del(17p), del(13q), and t(4;14), have been associated with inferior prognosis. However, there are few data about the prognostic significance of cytogenetic abnormalities for autologous stem cell transplantation (ASCT) in multiple myeloma (MM) patients with extramedullary plasmacytoma (EMP). **Patients and Methods:** Between April 2004 and December 2012, 290 MM patients underwent ASCT at 3 centers. FISH data for bone marrow samples obtained at diagnosis were available for 58 patients who had EMP at diagnosis or during treatment. **Results:** The t(11;14), t(4;14), del(13q), and 1q gain abnormalities were seen in 14.9%, 6.3%, 25.6%, and 42.9%, respectively. No t(14;16) or del(17p) cytogenetic abnormality was detected in the examined patients. Patients with t(11;14) had a lower response rate compared to patients with other cytogenetic abnormalities. EMP-specific relapse was higher in patients with t(11;14) than in patients with other cytogenetic abnormalities (42.9% vs. 10%-33.3%). Each of the 4 cytogenetic abnormalities predicted shorter median progression-free survival (6-12 months vs. 27-37 months) and shorter overall survival (16-22 months vs. 68 months or not reached) compared to no cytogenetic abnormality. The t(11;14) translocation was an important prognostic factor for both progression-free survival (hazard ratio, 25.154; $P < .001$) and overall survival (hazard ratio, 7.484; $P = .024$) in the multivariate analysis. **Conclusion:** In the current study, t(11;14), t(4;14), del(13q), and 1q gain were associated with worse survival in MM patients with EMP. The role of t(11;14) as a prognostic parameter for ASCT in MM patients with EMP should be confirmed with a large, well-designed study.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 15, No. 4, 227-35
Keywords: Autologous stem cell transplantation, Cytogenetic abnormality, Fluorescence in-situ hybridization, Multiple myeloma, Plasmacytoma

Introduction

Multiple myeloma (MM) is a clonal disorder of malignant plasma cells. In patients with MM, extramedullary plasmacytoma (EMP) may develop as a result of bone marrow (BM) escape of an MM subclone, with either extension through the bone cortex or hematogenous spread to other organs. EMP that accompanies MM is

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Submitted: Sep 9, 2014; Revised: Nov 23, 2014; Accepted: Dec 6, 2014; Epub: Dec 12, 2014

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2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2014.12.007

associated with poor outcome in patients treated with conventional chemotherapy.[1,2] The incidence of EMP in newly diagnosed MM ranges from 7% to 18%.[1-4] In addition, 6% to 20% of patients develop EMP later in the course of the disease.[3,4]

Because cytogenetic abnormalities help identify high-risk patients, they have important prognostic value in MM. With the use of fluorescence in-situ hybridization (FISH), cytogenetic abnormalities in BM plasma cells have been observed in approximately 90% of MM patients at initial diagnosis.[5] A number of cytogenetic abnormalities in the malignant plasma cell clone have been described, including deletions of chromosome 13 or chromosome 17 and translocations involving the immunoglobulin heavy chain.[6] The del(17p) and t(4;14)(p16;q32) abnormalities have been identified as independent poor prognostic factors for survival in MM patients.[5] In other studies, del(17p) and del(13q) were suggested as markers for progression to extramedullary disease.[7-9] Translocation of t(11;14)(q13;q32) may predict better survival and response to treatment, particularly high-dose therapy and stem cell support.[10]

In a recent autologous stem cell transplantation (ASCT) study from Spain, 18% of patients had extramedullary involvement, and the incidence of high-risk cytogenetics was similar in patients with and without extramedullary involvement (24% vs. 21%, respectively).[11] Thus, the authors concluded that genetic abnormalities in BM myeloma cells detected by FISH were not associated with extramedullary spread. However, few cytogenetic abnormality studies using FISH have investigated prognostic factors after ASCT in MM patients with EMP. Here, we carried out a retrospective study in MM patients with EMP who underwent ASCT. We detected several genetic abnormalities, including del(13q), t(4;14), del(17p), t(11;14), t(14;16), and 1q gain, by FISH and evaluated their prognostic impact.

Materials and Methods

Patients

To be included in the current study, MM patients with EMP, detected at diagnosis or during the course of the disease, had to have received ASCT and a FISH cytogenetic test for at least 1 of the 6 abnormalities, ie, del(13q), t(4;14), t(11;14), del(17p), t(14;16), and 1q gain. Of 290 MM patients who received ASCT between April 2004 and December 2012 at 3 centers in Korea, 86 patients had EMP at diagnosis or during the course of the disease before ASCT. For 58 of these patients, FISH results for 1 or more chromosomal abnormalities in BM samples obtained at diagnosis were available. Baseline clinical data were derived from questionnaires that were distributed to each hospital. The presence of EMP was diagnosed by magnetic resonance imaging, computed tomography, or pathologic confirmation.

Probes for Interphase FISH

All samples were analyzed with the interphase FISH method. The t(4;14), t(14;16), t(11;14), del(17p), del(13q), and 1q gain abnormalities were assessed simultaneously in BM samples obtained from patients newly diagnosed with MM. Not all abnormalities were analyzed in each patient because of the small quantities of purified plasma cells. The following commercial probes were used: locus-specific identifier IGH/CCND1, IGH/FGFR3, IGH/MAF dual color, dual fusion translocation probe, and locus-specific identifier 13 (D13S319) 13q14.3 probe (Vysis Inc, Abbott Laboratories, Abbott Park, IL, USA).

To improve the sensitivity of laboratory diagnosis, Fluorescence Immunophenotyping and Interphase Cytogenetics as a Tool for the Investigation of Neoplasm (FICTION) was introduced. FITC-conjugated antibodies directed against the human κ and λ light chain were used to stain and identify plasma cells.

As reference values for the respective probes, the normal cutoff for an analysis of 200 cells was calculated using the BETAINV function in Microsoft Excel. This formula calculated a 1-sided upper confidence limit for a specified percentage proportion based on an exact computation for the binomial distribution on the specimens obtained from 20 normal controls.

Statistical Analysis

Response to treatment was defined by the international response criteria for MM.[12] Complete remission (CR) was defined as the absence of a detectable monoclonal component in serum and urine by immunofixation and fewer than 5% BM plasma cells. Very good partial response (VGPR) was defined as a 90% decrease in the blood monoclonal component level and a urine monoclonal component lower than 100 mg per 24 hours. Partial response was defined as a 50% decrease in the serum monoclonal component or a 90% decrease in the urine monoclonal component. Progression-free survival (PFS) was defined as the time from transplantation to relapse. Overall survival (OS) was defined as the time from transplantation to the date of death or last follow-up. OS and PFS were determined by the Kaplan-Meier analysis, and differences between survival curves were tested for statistical significance using 2-tailed log-rank tests. Univariate and multivariate survival analyses were carried out by the Cox proportional hazards model. P values of $< .05$ were considered significant. All calculations were performed using the Windows version of IBM SPSS software, version 18.0.1 (PASW Statistics for Windows; IBM, Armonk, NY, USA).

Results

Patient Characteristics

The current study included 34 men and 24 women with a median age of 53 years (range, 34-66 years) at the time of diagnosis. The median age of the patients was younger than that of classical MM patients, which was consistent with previous reports.[13,14] It is possible that the younger age reflected the fact that we analyzed patients undergoing ASCT. The median time from diagnosis to ASCT was 7 months (range, 4-36 months). The initial patient characteristics are summarized in Table 1.

The immunoglobulin G monoclonal component was the most frequent heavy chain type. Light chain disease was 29.3%, and nonsecretory type was 8.6%. Of the light chain components, λ light chain expression was more frequent than κ light chain expression (56.9% vs. 32.8%). Frequency of light chain disease and nonsecretary type in our patients was higher than that of classical myeloma patients. Extramedullary plasmacytoma at the time of MM diagnosis occurs more frequently in patients who are male, those with IgD plasma cell myeloma, those with λ light chain myeloma, those with nonsecretary myeloma, and those younger than 40 years of age without prior monoclonal