1083-8791/07/1309-0001$32.00/0
doi:10.1016/j.bbmt.2007.05.014

Deletion of the Short Arm of Chromosome 1 (del 1p) is a Strong Predictor of Poor Outcome in Myeloma Patients Undergoing an Autotransplant

Muzaffar H. Qazilbash,[1] Rima M. Saliba,[1] Bilal Ahmed,[1] Gaurav Parikh,[1] Floralyn Mendoza,[1] Noman Ashraf,[1] Chitra Hosing,[1] Thuy Flosser,[1] Donna M. Weber,[2] Michael Wang,[2] Daniel R. Couriel,[1] Uday Popat,[1] Partow Kebriaei,[1] Amin M. Alousi,[1] Paolo Anderlini,[1] Rizwan C. Naeem,[3] Richard E. Champlin,[1] Sergio A. Giralt[1]

[1]Stem Cell Transplantation and Cellular Therapy, [2]Lymphoma and Myeloma, UT-M.D. Anderson Cancer Center, Houston, Texas; [3]Texas Children's Cancer Center and Baylor College of Medicine, Houston, Texas

Correspondence and reprint requests: Muzaffar H. Qazilbash, MD, Stem Cell Transplantation and Cellular Therapy, M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX, 77030 (e-mail: mqazilba@mdanderson.org).

Received March 14, 2007; accepted May 25, 2007

ABSTRACT

Several chromosomal abnormalities detected by conventional cytogenetic analysis have an adverse impact on the outcome in myeloma patients. A wide spectrum of abnormalities involving chromosomes 1, 13, 14, and 17 has been described. We analyzed the outcome of 83 patients with clonal cytogenetic abnormalities, who underwent high-dose therapy and autologous stem cell transplantation for multiple myeloma at our institution. Clonal abnormalities were detected at diagnosis by conventional cytogenetic analysis in 83 patients. Patients underwent a single autologous transplant between April 2000 and May 2005. Preparative regimen was high-dose melphalan alone (73), or a combination of topotecan, melphalan, and cyclophosphamide (TMC = 10). The most commonly observed chromosomal abnormalities were deletion of chromosome 13 (32%), hyperdiploidy (21%), deletion of chromosome 1p (18%), and t (11; 14) in 7% patients. Median follow-up among surviving patients was 25.5 months. Median interval from diagnosis to autotransplant was 7.7 months (range: 2.5-52). Median progression-free survival (PFS) for the entire group was 19 months and the median overall survival (OS) was 52 months. On univariate analysis, both PFS and OS were significantly shorter in patients with deletion 1p (P = .001 and <.0001, respectively). Thirty-two patients whose cytogenetic abnormalities returned to normal prior to autotransplant had longer PFS and OS than patients with persistent abnormalities (P = .02 and .08, respectively). Deletion 1p is associated with a significantly shorter remission and survival in patients undergoing high-dose therapy and a single autologous transplant for myeloma.

KEY WORDS

Multiple myeloma • Autotransplant • Chromosome abnormalities • Conventional cytogenetics • Deletion 1p • Outcome

INTRODUCTION

Each year approximately 15,000 patients in the United States are diagnosed with multiple myeloma (MM) a clonal disorder of plasma cells [1]. The median survival is about 3.5 years, but it ranges from a few months to more than 10 years [2]. Several randomized trials have shown that autologous HSCT is associated with superior complete remission (CR) rates, prolonged event-free survival (EFS), and overall survival (OS) [3-5]. Two other randomized trials, however, were unable to confirm the benefits of autotransplants [6,7].

The presence or the absence of chromosomal abnormalities has emerged as an important prognostic factor in MM. Clonal chromosomal abnormalities can be detected in approximately 30% of patients with MM by conventional cytogenetic studies [8,9]. This low yield has been attributed to a low percentage of plasma cells in the bone marrow (BM) and low proliferation rate of plasma cells as only a few analyzable

cells can be obtained [10]. However, chromosomal abnormalities are almost universal if more sensitive molecular genetic techniques, such as interphase fluorescent in situ hybridization (FISH) and comparative genomic hybridization (CGH) are used [11,12].

Chromosomal abnormalities include loss or gain of chromosomes, or chromosomal translocations [13,14]. Hypodiploidy (10%-15% of chromosomal abnormalities) is associated with a shorter survival [15], and, conversely, hyperdiploidy (30% of chromosomal abnormalities) tends to have a better prognosis [16,17]. Among other common abnormalities chromosome 13 deletions (50% of conventional cytogenetic abnormalities) are associated with a lower response rate and shorter survival [18-21]. Translocations involving IgH locus (14q32) have also been reported in a significant number of patients (10% of conventional cytogenetic abnormalities). Of these, t (11; 14) is associated with improved or neutral survival [22,23], whereas t(4; 14) and t(14; 16) are associated with a shorter survival [24-26]. Deletion of short arm of chromosome 17 (17p13) is seen in 10% of myeloma patients and involves the p53 tumor suppressor gene. This is associated with disease progression and advanced disease stage [26].

Loss of chromosome 1p (del 1p) and gain of chromosome 1q have been described in many cancers [27]. These chromosomal abnormalities are frequently observed in MM [28,29]. In a recent report by Shaughnessy et al. [28] altered transcriptional regulation of genes mapping to chromosome 1 contributed to disease progression and early death.

We retrospectively analyzed the frequency of various chromosomal abnormalities and their impact on the outcome of high-dose therapy and a single autotransplant in patients treated at our institution between January 2000 and November 2005.

METHODS

Patients

Between January 2000 and November 2005, 625 patients with MM underwent an autotransplant at our institution. We identified 162 patients (26%) who had cytogenetic abnormalities detected by conventional chromosomal analysis at the time of diagnosis. When we narrowed down our search to patients with symptomatic myeloma according to International Myeloma Working Group's classification [30], who underwent a single autotransplant, and who had at least 2 abnormal metaphases by conventional cytogenetic analysis, the number was reduced to 83. We excluded isolated deletion of the Y chromosome that is considered an age-related phenomenon [31].

Treatment

Seventy-three patients received an autotransplant after a preparative regimen of high-dose melphalan (200 mg/m^2 i.v.). Ten patients were treated with TMC regimen: topotecan 3 mg/m^2 i.v. $\times$ 5 days + melphalan 70 mg/m^2 i.v. $\times$ 2 days + cyclophosphamide 1 g/m^2 i.v. $\times$ 3 days [32]. All patients provided signed institutional review board-approved informed consent for an autotransplant. Unmanipulated autografts were infused 48 hours later. All patients received granulocyte colony-stimulating factor (G-CSF), 5 μg/kg/day from day +1 until the absolute neutrophil count (ANC) was 0.5 $\times$ 10^9/L for 2 consecutive days, in accordance with our departmental guidelines. Oral levofloxacin, acyclovir, and fluconazole were given for the duration of neutropenia. Blood products were given for hemoglobin $\leq$8 g/dL and platelets $<$20 $\times$ 10^9/L.

Response Criteria

The European Group for Blood and Marrow Transplantation (EBMT) response criteria was used to define complete response (CR), partial response (PR), and relapse [33]. CR was defined as the absence of original monoclonal protein in urine and serum by immunofixation, $<$5% plasma cells in marrow aspirate, and no circulating plasma cells, no increase in size or number of lytic bony lesions, and disappearance of soft tissue plasmacytomas. Progressive disease was defined as 1 of the following: (1) $>$25% increase in serum or urine monoclonal protein, or plasma cells in the bone marrow, or (2) increase in the size or number of lytic bony lesions.

Chromosomal Analysis

Bone marrow samples were obtained at the time of diagnosis and before an autotransplant from all the analyzed patients. Conventional chromosomal analysis was performed on the bone marrow cells by using standard cytogenetic techniques. Briefly, after a 3- to 5-day culture with interleukin-3 and interleukin-6, G-banding with Wright stain was done for all karyotypes. The Chromosomal abnormalities were defined according to the International System for Human Cytogenetic Nomenclature (ISCN) 95 [9,34]. At least 20 metaphases, where possible, were analyzed for each patient. A clonal abnormality was defined as 2 metaphases with the same numerical or structural abnormality.

Statistical Analysis

Actuarial rates of OS and progression-free survival (PFS) were estimated by the Kaplan-Meier method. PFS and OS were defined as the time from the day of transplant to progression or death. Prognostic factors

for survival were evaluated using Cox's proportional hazards model for univariate analyses and multivariate analysis. The factors evaluated included in addition to cytogenetic abnormalities, age, disease stage, disease status at transplant, time between diagnosis and transplant, lactate dehydrogenase (LDH) level, β2m, serum albumin level, serum creatinine level, and conditioning regimen. Outcomes according to prognostic factors were compared at 2 years after transplantation. Statistical significance was defined at the .05 level. Analysis was performed using STATA 7.0 (StataCorp, 2001, Stata Statistical Software: Release 7.0. College Station, TX: Stata Corporation). EFS and OS were measured from the day of transplant.

RESULTS

Patients

Table 1 outlines the basic patient characteristics of the 83 patients reported in this retrospective analysis. Median follow-up among surviving patients was 25.5 months (range: 3-69). Median age was 56 (range: 34-75) years, and the median interval from diagnosis to autotransplant was 7.7 months (range: 2.5-53).

According to Durie-Salmon Staging System for MM [35], 44 patients (53%) had stage III disease at diagnosis. Sixty-four patients were transplanted for the consolidation of first remission or for primary refractory disease, whereas 19 patients were transplanted for relapsed disease. Eleven patients (13%) had elevated serum creatinine above the upper limits of normal (1.5 mg/dL).

Response and Survival

CR were seen in 19% of patients, whereas partial responses (PR) were seen in 45%, with an overall response rate (Cr + PR) of 64%. Median PFS for the entire group was 19 months and the median OS was 52 months.

Table 1. *Patient Characteristics*

Parameter	Number (%)
Male	53 (63%)
Median interval diagnosis to transplant (months)	7.7 (2.5-53)
Durie-Salmon Stage III	44 (53%)
ISS Stage >II-III	35 (42%)
Immunoglobulin subtype	46 (55%)
Normalization of cytogenetic abnormalities at transplant	32 (38%)
Albumin ≤ 3.5 g/dL	25 (30%)
Creatinine ≥1.5 mg/dL	11 (13%)
β_2 microglobulin > 3 mg/dL	48 (58%)
LDH > normal	30 (36%)
Relapsed disease at transplant	19 (23%)
Preparative regimen	
Melphalan (200 mg/m^2)	73 (88%)
TMC (topotecan/melphalan/cyclophosphamide)	10 (12%)
Median age (months)	56 (34-75)

Table 2. *Common Chromosomal Abnormalities at Diagnosis*

Abnormality	Frequency (%)
Hyperdiploidy	18 (22%)
Hypodiploidy	6 (7%)
Del 1p	15 (18%)
Del 13	27 (32%)
14q32 abnormalities	12 (14%)
Del 1p + Del 13	10 (12%)
Del 1p + Del 17	5 (6%)
Del 1p + hypodiploidy	2 (2.5%)
Del 1p + hyperdiploidy	3 (3.6%)

Del 13 indicates deletion of chromosome 13; Del 1p, deletion of short arm of chromosome 1; Del 17, deletion of chromosome 17.

Chromosomal Abnormalities

The frequency of common chromosomal abnormalities is shown in Table 2. The most frequently observed abnormality was the deletion of chromosome 13 that was seen in 27 of 83 (32%) patients. Other commonly seen abnormalities were: hyperdiploidy in 18 (22%) patients, del 1p in 15 (18%) patients, del 17p in 12 (14%) patients, and t (11; 14) in 6 (7%) patients.

Prognostic Factors

Del 1p emerged as the strongest negative predictor of outcome. In 15 patients with del 1p, the median PFS and OS were 12 and 22 months, respectively. As shown in Figure 1A and B, these were significantly lower than all the other patients, who had a PFS of 26 months and an OS that has not been reached yet (P = .001 and <.0001, respectively).

In our analysis del 13 (P = .2 and .3), del 17 (P = .2 and .6), and abnormalities of chromosome 14q32 (P = .5 and .5) did not emerge as significant predictors of PFS or OS. Ten of the 15 patients with del 1p had concurrent del 13. There was no significant difference between the PFS of these 10 patients compared to the 5 patients with del 1p alone (2-year PFS = 20% versus 17%, P = .77). Similarly, there was no impact for conditioning regimen, age, disease stage, β2m, or serum creatinine.

Resolution of Chromosomal Abnormalities before Autotransplant

Thirty-two of the 83 patients had converted to normal karyotype after induction treatment and prior to autotransplant. Only 3 of the 15 patients with del 1p had achieved a normal diploid cytogenetics prior to autotransplant. When compared to patients with persistent chromosomal abnormalities at autotransplant, these 32 patients had a significantly better PFS (P =

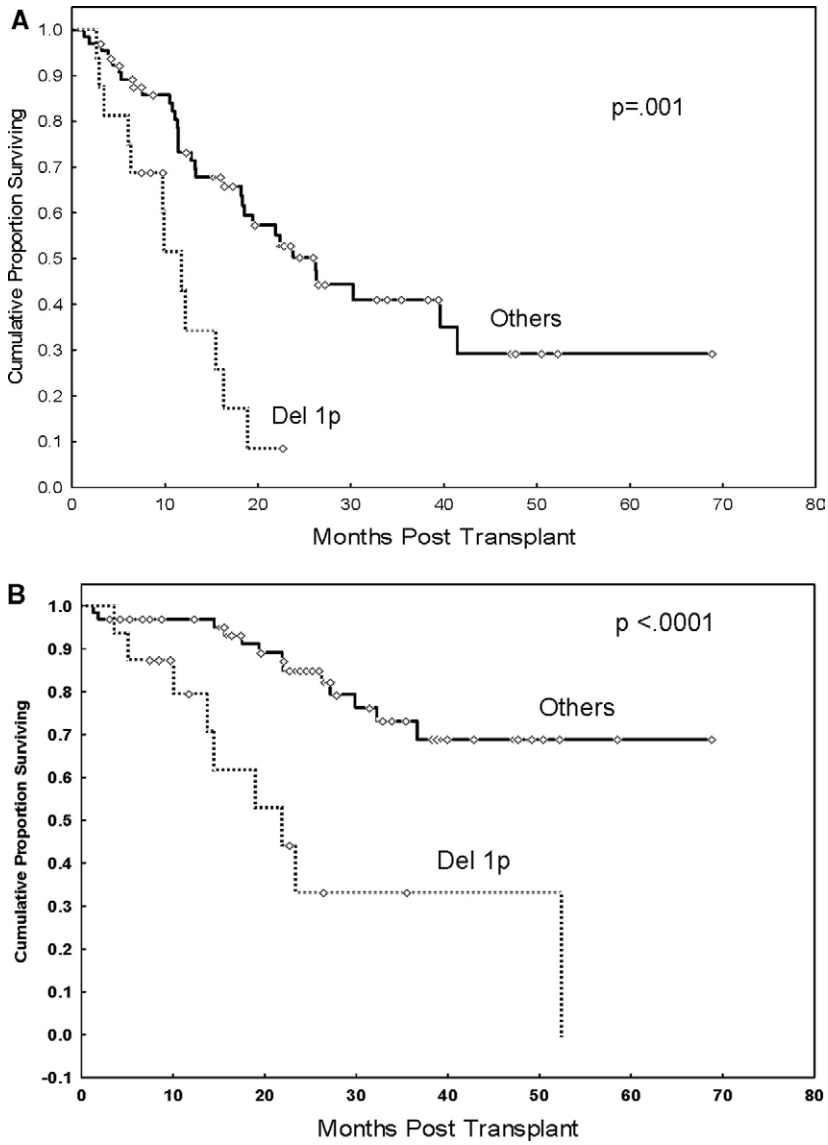

Figure 1. A, Kaplan-Meier estimate of progression-free survival in patients with del 1p versus others. B, Kaplan-Meier estimate of overall survival in patients with del 1p versus others.

.02) and a trend towards superior OS ($P = .08$) (Figure 2A and B).

DISCUSSION

The adverse prognostic role of chromosomal abnormalities has recently been established in MM [8]. In this analysis, we observed that del 1p was associated with a short PFS and OS after a single autologous transplant. The response rate of 64% in this analysis was lower than our historic control (approximately 80%), perhaps because of the inclusion of a greater number of high-risk patients, and a significant number of patients (25%) with relapsed or refractory disease [36]. The PFS and OS of 12 and 22 months, respectively, in these patients were significantly lower than our historic control, which includes comparable patients without chromosomal abnormalities. In this control group of patients, we observed PFS of 24-36 months, and a OS of >5 years [36,37].

Abnormalities of chromosome 1 are commonly seen in MM [28,29,38]. In a recent report by Shaughnessy et al. [28], altered transcriptional regulation of genes mapping to chromosome 1 contributed to disease progression and early death. Short-arm abnormalities were usually deletional and long-arm abnormalities were generally associated with amplification. Majority of upregulated genes were mapped to 1q and downregulated genes mapped to 1p. In another report by Wu et al. [39], abnormalities of chromosome 1 p and q were strongly associated with chromosome 13 deletion and a shorter OS. In our analysis, del 13 did not emerge as an independent predictor of PFS or OS, although it assumed statistical significance when com-

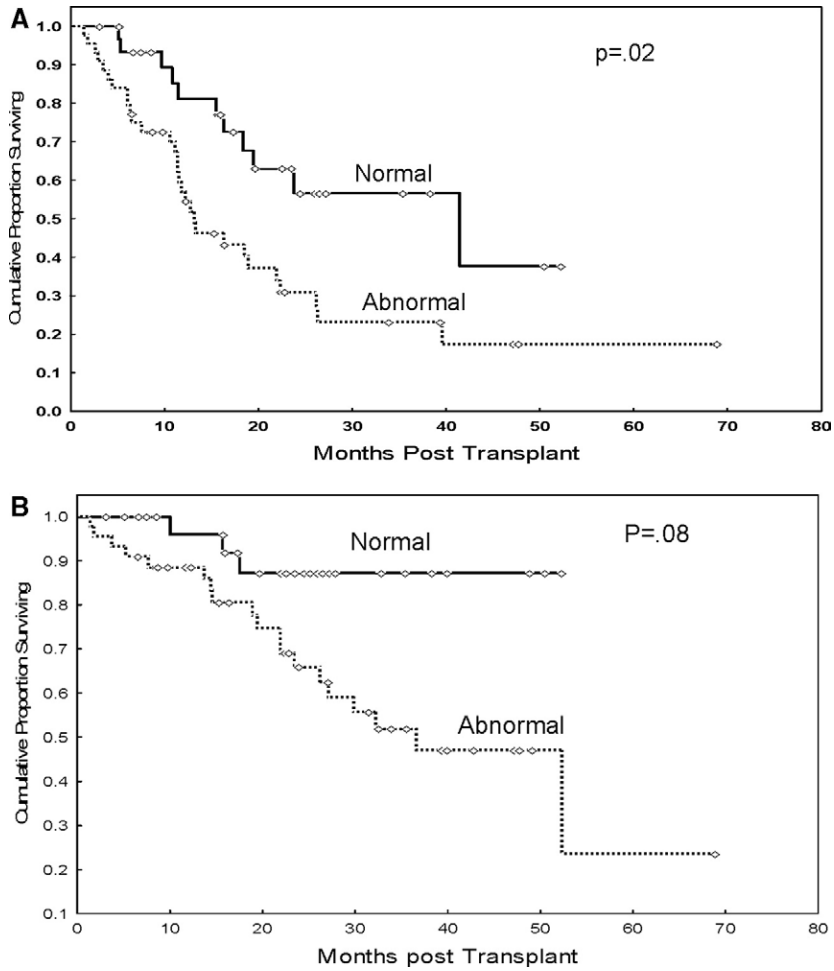

Figure 2. A, Kaplan-Meier estimate of progression-free survival in patients with normal cytogenetics versus persistent chromosomal abnormalities. B, Kaplan-Meier estimate of overall survival in patients with normal cytogenetics vs. persistent chromosomal abnormalities.

bined with del 1p. This discrepancy can be explained by a small number of patients and lack of FISH data; hence, many patients with chromosome 13 abnormalities might not have been detected, retrospective nature of the analysis and heterogeneous patient population.

In this report we identified the del 1p to be associated with poor outcome. Twelve of the 15 (80%) 1p deletions were seen in the 1p13-1p22 region. No unique gene expression consequences of deletions at 1p have been identified. Previous studies have demonstrated that deletion of a particular locus within the chromosome harboring a tumor suppressor gene is crucial in the pathogenesis of cancer. Identification of the specific tumor suppressor genes on chromosome 1 has been an area of growing interest and a few candidate genes have emerged. Tumor suppressor gene p73, with close homology to p53, has been identified on chromosome band 1p36.33 [40]. Del 1 p, resulting in a loss of tumor suppressor genes seems to be the most probable reason for poor outcome in our patients. It will be important to delineate the minimal area of deletion, which could harbor possible tumor suppressor genes. This area will be a focus of research in the future to map the missing gene or genes by more sensitive studies like FISH or array CGH.

In our report 32 patients with baseline chromosomal abnormalities achieved a normal karyotype after induction therapy. These 32 patients had longer PFS and OS after an autotransplant than patients with persistent abnormalities. Rajkumar et al. [41] and Tricot et al. [42] have also reported on the impact of pretransplant cytogenetic abnormalities on the outcome. Their reports, however, did not specifically address the impact of resolution of cytogenetic abnormalities prior to transplant on the outcome. The conversion to normal karyotype may also be a reflection of lower tumor burden and fewer malignant cells with clonal abnormalities. We feel that it is an interesting observation that needs to be validated in larger studies.

Our study for the first time established the prognostic significance of del 1p in patients undergoing high-dose therapy and a single autologous transplant. This abnormality was associated with a significantly shorter remission and survival in patients undergoing

high-dose therapy and a single autologous transplant. We recommend that these high-risk patients should be treated on clinical trials that include more intense induction, tandem autotransplants, and posttransplant maintenance with novel agents.

REFERENCES

1. Hari P, Pasquini MC, Vesole DH. Cure of multiple myeloma—more hype, less reality. *Bone Marrow Transplant*. 2006;37:1-18.
2. Kyle RA, Rajkumar SV. Multiple myeloma. *N Engl J Med*. 2004;28;351:1860-1873.
3. Attal M, Harousseau JL, Stoppa AM, et al. Autologous bone marrow transplantation versus conventional chemotherapy in multiple myeloma. *N Engl J Med*. 1996;335:9197.
4. Child JA, Morgan GJ, Davies FE, et al., Medical Research Council Adult Leukaemia Working Party. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med*. 2003;348:1875-1883.
5. Fermand JP, Katsahian S, Divine M, et al. High-dose therapy and autologous blood stem-cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: long-term results of a randomized control trial from the Group Myelome-Autogreffe. *J Clin Oncol*. 2005;23:9227-9233.
6. Blade J, Rosinol L, Sureda A, et al. Programa para el Estudio de la Terapeutica en Hemopatia Maligna (PETHEMA). High-dose therapy intensification compared with continued standard chemotherapy in multiple myeloma patients responding to the initial chemotherapy: long-term results from a prospective randomized trial from the Spanish cooperative group PETHEMA. *Blood*. 2005;106:3755-3759.
7. Barlogie B, Kyle RA, Anderson KC, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. *J Clin Oncol*. 2006;24:929-936.
8. Fonseca R, Barlogie B, Bataille R, et al. Genetics and cytogenetics of multiple myeloma: a workshop report. *Cancer Res*. 2004;64:1546-1558.
9. Stewart AK, Fonseca R. Prognostic and therapeutic significance of myeloma genetics and gene expression profiling. *J Clin Oncol*. 2005;23:6339-6344.
10. Schilling G, Dierlamm J, Hossfeld DK. Prognostic impact of cytogenetic aberrations in patients with multiple myeloma or monoclonal gammopathy of unknown significance. *Hematol Oncol*. 2005;23:102-107.
11. Dewald GW, Therneau T, Larson D, et al. Relationship of patient survival and chromosome anomalies detected in metaphase and/or interphase cells at diagnosis of myeloma. *Blood*. 2005;106:3553-3558.
12. Zandecki M, Lai JL, Facon T. Multiple myeloma: almost all patients are cytogenetically abnormal. *Br J Haematol*. 1996;94: 217-227.
13. Bergsagel PL, Kuehl WM. Chromosome translocations in multiple myeloma. *Oncogene*. 2001;20:5611-5622.
14. Liebisch P, Dohner H. Cytogenetics and molecular cytogenetics in multiple myeloma. *Eur J Cancer*. 2006;42:1520-1529.
15. Smadja NV, Bastard C, Brigaudeau C, Leroux D, Fruchart C, Groupe Francais de Cytogenetique Hematologique. Hypodiploidy is a major prognostic factor in multiple myeloma. *Blood*. 2001;98:2229-2238.
16. Perez-Simon JA, Garcia-Sanz R, Tabernero MD, et al. Prognostic value of numerical chromosome aberrations in multiple myeloma: a FISH analysis of 15 different chromosomes. *Blood*. 1998;91:3366-3371.
17. Wuilleme S, Robillard N, Lode L, et al. Ploidy, as detected by fluorescence in situ hybridization, defines different subgroups in multiple myeloma. *Leukemia*. 2005;19:275-278.
18. Sawyer JR, Waldron JA, Jagannath S, et al. Cytogenetic findings in 200 patients with multiple myeloma. *Cancer Genet Cytogenet*. 1995;82:41-49.
19. Sawyer JR, Lukacs JL, Thomas EL, et al. Multicolour spectral karyotyping identifies new translocations and a recurring pathway for chromosome loss in multiple myeloma. *Br J Haematol*. 2001;112:167-174.
20. Tricot G, Barlogie B, Jagannath S, et al. Poor prognosis in multiple myeloma is associated only with partial or complete deletions of chromosome 13 or abnormalities involving 11q and not with other karyotype abnormalities. *Blood*. 1995;86:4250-4256.
21. Desikan R, Barlogie B, Sawyer J, et al. Results of high-dose therapy for 1000 patients with multiple myeloma: durable complete remissions and superior survival in the absence of chromosome 13 abnormalities. *Blood*. 2000;95:4008-4010.
22. Fonseca R, Blood EA, Oken MM, et al. Myeloma and the t(11;14)(q13;q32); evidence for a biologically defined unique subset of patients. *Blood*. 2002;99:3735-3741.
23. Moreau P, Facon T, Leleu X, et al. Recurrent 14q32 translocations determine the prognosis of multiple myeloma, especially in patients receiving intensive chemotherapy. *Blood*. 2002; 100:1579-1583.
24. Chesi M, Nardini E, Brents LA, et al. Frequent translocation t(4;14)(p16.3;q32.3) in multiple myeloma is associated with increased expression and activating mutations of fibroblast growth factor receptor 3. *Nat Genet*. 1997;16:260-264.
25. Chang H, Sloan S, Li D, et al. The t(4;14) is associated with poor prognosis in myeloma patients undergoing autologous stem cell transplant. *Br J Haematol*. 2004;125:64-68.
26. Fonseca R, Blood E, Rue M, et al. Clinical and biologic implications of recurrent genomic aberrations in myeloma. *Blood*. 2003;101:4569-4575.
27. Atkin NB. Chromosome 1 aberrations in cancer. *Cancer Genet Cytogenet*. 1986;21:279-285.
28. Shaughnessy JD Jr, Zhan F, Burington BE, et al. A validated gene expression model of high-risk multiple myeloma is defined by deregulated expression of genes mapping to chromosome 1. *Blood*. 2006 Nov 14; [Epub ahead of print].
29. Marzin Y, Jamet D, Douet-Guilbert N, et al. Chromosome 1 abnormalities in multiple myeloma. *Anticancer Res*. 2006;26: 953-959.
30. International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *Br J Haematol*. 2003;121:749-757.
31. Pierre RV, Hoagland HC. Age-associated aneuploidy: loss of Y chromosome from human bone marrow cells with aging. *Cancer*. 1972;30:889-894.
32. Donato ML, Aleman A, Champlin RE, et al. High-dose topotecan, melphalan and cyclophosphamide (TMC) with stem cell support: a new regimen for the treatment of multiple myeloma. *Leuk Lymphoma*. 2004;45:755-759.
33. Blade J, Samson D, Reece D, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell trans-

plantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. *Br J Haematol*. 1998;102:1115-1123.
34. Dewald GW, Broderick DJ, Tom WW, Hagstrom JE, Pierre RV. The efficacy of direct, 24-hour culture, and mitotic synchronization methods for cytogenetic analysis of bone marrow in neoplastic hematologic disorders. *Cancer Genet Cytogenet*. 1985;18:1-10.
35. Durie BGM, Salmon SE. A clinical staging system for multiple myeloma. *Cancer*. 1975;36:842-854.
36. Qazilbash MH, Saliba RM, Hosing C, et al. Autologous stem cell transplantation is safe and feasible in elderly patients with multiple myeloma. *Bone Marrow Transplant*. 2007;39:279-283.
37. Qazilbash MH, Saliba RM, Aleman A, et al. Risk factors for relapse after complete remission with high-dose therapy for multiple myeloma. *Leuk Lymphoma*. 2006;47:1360-1364.
38. Panani AD, Ferti AD, Papaxoinis C, Raptis SA, Roussos C. Cytogenetic data as a prognostic factor in multiple myeloma patients: involvement of 1p12 region an adverse prognostic factor. *Anticancer Res*. 2004;24:4141-4146.
39. Wu KL, Beverloo B, Lokhorst HM, et al. Abnormalities of chromosome 1p/q are highly associated with chromosome 13/13q deletions and are an adverse prognostic factor for the outcome of high-dose chemotherapy in patients with multiple myeloma. *Br J Haematol*. 2007;136:615-623.
40. Han S, Semba S, Abe T, et al. Infrequent somatic mutations of the p73 gene in various human cancers. *Eur J Surg Oncol*. 1999;25:194-198.
41. Rajkumar SV, Fonseca R, Lacy MQ, et al. Abnormal cytogenetics predict poor survival after high-dose therapy and autologous blood cell transplantation in multiple myeloma. *Bone Marrow Transplant*. 1999;24:497-503.
42. Tricot G, Sawyer JR, Jagannath S, et al. Unique role of cytogenetics in the prognosis of patients with myeloma receiving high-dose therapy and autotransplants. *J Clin Oncol*. 1997;15:2659-2666.