STAT3 expression is associated with poor survival in non-elderly adult patients with newly diagnosed multiple myeloma

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Background
Signal transducer and activator of transcription 3 (STAT3) is not only a key signaling molecule in the regulation of growth but is also involved in malignant transformation. We investigated the prognostic significance of STAT3 expression in 94 non-elderly adult patients (aged 38 to 65 yr) with newly diagnosed multiple myeloma (MM).

Methods
Tumor cell-specific phosphotyrosine-STAT3 (PY-STAT3) expression at the time of diagnosis was evaluated with dual immunohistochemical (IHC) staining for PY-STAT3 and CD138.

Results
PY-STAT3 positivity was detected in 10 patients (10.6%), including three who showed strong expression. PY-STAT3-positive patients had higher serum C-reactive protein and calcium levels at diagnosis than did PY-STAT3-negative patients. PY-STAT3 positivity had predictive value for poor progression-free survival (PFS; $P=0.001$) and overall survival (OS; $P=0.003$). Among the 60 patients who received frontline autologous stem cell transplantation, PY-STAT3-positive patients had poorer PFS than did PY-STAT3-negative patients (4.2 vs. 19.2 mo, respectively; $P=0.013$). Multivariate analysis identified PY-STAT3 expression as an independent prognostic factor for PFS (relative risk [RR]=2.706, $P=0.014$) and OS (RR=3.091, $P=0.044$).

Conclusion
These data show that PY-STAT3 positivity, as determined using dual IHC, is a marker of poor prognosis in non-elderly adult patients with MM.

Key Words   STAT3, Multiple myeloma, Prognosis

INTRODUCTION

Multiple myeloma (MM) is a malignant disorder characterized by the proliferation of clonal plasma cells in the bone marrow (BM) and accompanying secretion of monoclonal immunoglobulin. Patients with MM develop anemia, renal failure, hypercalcemia, and extensive skeletal destruction with osteolytic lesions [1]. Although the introduction of novel highly effective agents such as thalidomide, bortezomib, and lenalidomide has resulted in considerable improvement in outcomes and has extended the overall survival (OS) of patients with MM [2, 3], the course of the disease is highly variable. Some patients may survive for more than 10 years, while the prognosis in others is dismal owing to an aggressive disease course. This difference reflects the clonal, heterogeneous nature of MM, a disease that is accordingly largely resistant to treatment and associated with frequent relapse [4]. The International Staging System (ISS) proposed by Greipp *et al.* [5] in 2005 is the most widely used staging system in patients with newly diagnosed MM, but it does not fully represent the highly heterogeneous nature of the disease. More reliable markers would facilitate improved prediction of treatment outcomes and survival in patients

with newly diagnosed MM.

Activation of signal transducer and activator of transcription (STAT) proteins are strongly associated with carcinogenesis and metastasis [6, 7]. STAT proteins comprise a group of shuttle proteins in the cytoplasm that act as transcriptional activators following translocation to the nucleus, where they regulate cellular growth, differentiation, and survival. Among the various STAT proteins, STAT3 participates in critical cellular functions. STAT3 is phosphorylated in response to the binding of certain cytokines to its receptor, resulting in the dimerization of phosphotyrosine STAT3 (PY-STAT3) and its translocation to the nucleus, where it activates the transcription of target genes. In normal cells, STAT3 activation is a transient and tightly controlled process, whereas in various types of solid cancers, STAT3 signaling is aberrantly activated [8, 9]. Dysregulated STAT3 activation promotes tumor cell growth and survival as well as metastasis. Among the hematologic malignancies, STAT3 activation has been reported to play a pathologic role in MM, Hodgkin's lymphoma, and anaplastic large B-cell lymphoma [10-12]. An association between PY-STAT3 positivity and poor OS was recently demonstrated in patients with diffuse large B-cell lymphoma treated with R-CHOP chemotherapy [13]. However, the prognostic significance of STAT3 expression in the BM of patients with newly diagnosed MM has not been thoroughly investigated.

In this study, we assessed the prognostic significance of PY-STAT3 expression in patients with newly diagnosed MM.

Paraffin-embedded BM tissue obtained from patients with newly diagnosed MM was examined for CD138 (a plasma cell marker) and PY-STAT3 expression using dual immunohistochemical (IHC) staining.

MATERIALS AND METHODS

Patients

A total of 233 patients at Chonnam National University Hwasun Hospital (South Korea) with newly diagnosed MM underwent screening from January 2004 to May 2013. Patients aged <65 years were included in the study. Exclusion criteria were a diagnosis of asymptomatic MM, amyloidosis, or plasma cell leukemia; the absence of BM tissue obtained at diagnosis and paraffin-embedded for IHC processing; and unavailability of medical records. The initial study population therefore comprised 98 patients. Review of the paraffin-embedded BM samples revealed that four were inappropriate for IHC staining and analysis. Thus, 94 patients were included in the IHC analysis for expression of PY-STAT3.

Data regarding patient demographics, induction regimen, treatment response, and survival outcomes were obtained by medical record review. Renal function was assessed using the estimated glomerular filtration rate (eGFR), calculated using the simplified Modification of Diet in Renal Disease formula. The study protocol was reviewed and approved
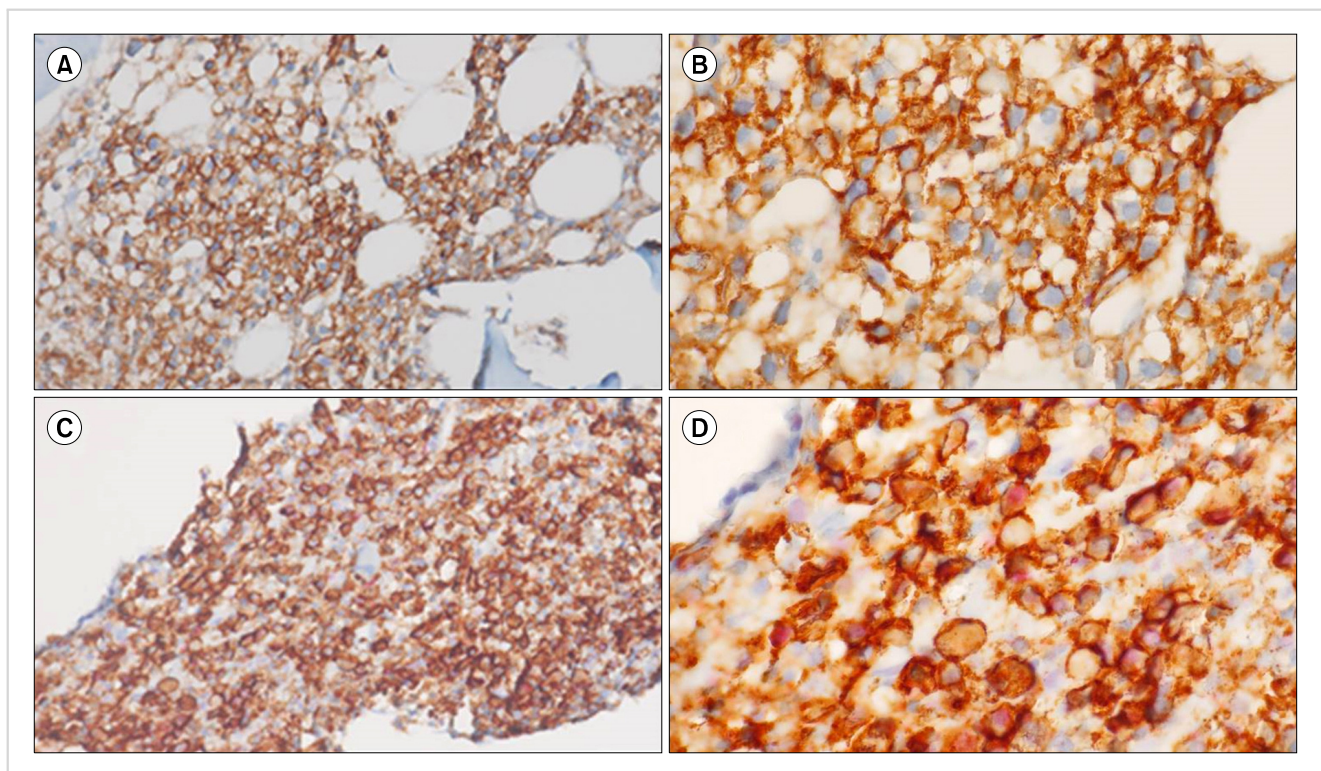
Fig. 1. Dual immunohistochemical staining of bone marrow sections obtained at diagnosis shows **(A, B)** plasma cells positive for CD138 (brown cell membranes) and negative for STAT3 expression and **(C, D)** plasma cells positive for both CD138 and STAT3 (red nuclei, ×400, ×1,000).

by the institutional review board of Chonnam National University Hwasun Hospital in accordance with the Declaration of Helsinki.

IHC staining and analysis of STAT3-PY

Paraffin-embedded BM tissue sections were examined for CD138 and PY-STAT3 expression using dual IHC staining as follows. Sections (4-μm thick) were deparaffinized, rehydrated, rinsed with distilled water, and washed with Tris-buffered saline. Automated IHC staining of the BM sections was carried out using a Ventana BenchMark GX instrument (Ventana Medical Systems, Inc., Tucson, AZ, USA) with a dual stain for the simultaneous detection of CD138 (Cell Marque, Rocklin, CA, USA) and STAT3 (pTyr705; Novus Biologicals, Littleton, CO, USA) according to the manufacturers' protocols (Fig. 1).

The stained slides were analyzed and scored by an experienced hematopathologist blinded to all of the study data. Samples were considered positive when immunoreactivity for CD138 and STAT3 (pTyr705) was observed within the same cells, with dual staining present in more than 10% of plasma cells. CD138 positivity was detected as brown-stained membranes and STAT3 (pTyr705) positivity as red-stained nuclei (Fig. 1). The presence of dual staining in at least 30% of plasma cells was used as a cutoff to consider the sample strongly positive.

Statistical analysis

Pearson's χ^2 test for discrete variables and the Mann-Whitney U test for continuous variables were used to compare patient characteristics. Progression-free survival (PFS) was calculated from the start of treatment until disease progression or death from any cause. OS was defined as the period from the date of diagnosis until the date of last follow-up or death from any cause. PFS and OS were evaluated using Kaplan-Meier estimates and compared using the log-rank test. The relative risk (RR) of an event and the 95% confidence interval (95% CI) were estimated using a Cox proportional hazards model. Covariates with a P value of <0.1 in the univariate analyses were included in the Cox proportional hazards regression model. All statistical computations were performed using SPSS v.21 (SPSS Inc., Chicago, IL, USA). A P value of <0.05 was considered to indicate statistical significance.

RESULTS

Patient population

The median age of the patients was 55 years (range, 38–65 yr), and 48 (51.1%) were men. According to the ISS, 32 patients (34.0%) had stage I, 28 (29.8%) had stage II, and 34 (36.2%) had stage III disease. At diagnosis, 22 patients

Table 1. Baseline clinical characteristics of the 94 patients with multiple myeloma according to STAT3 expression.

Variables	PY-STAT3-negative (N=84)	PY-STAT3-positive (N=10)	P
Median age, yr (range)	56 (38–65)	53 (46–61)	0.253
Men, N (%)	44 (52.4%)	4 (40.0%)	0.519
Immunoglobulin (Ig) type, N (%)			
IgG	48 (57.1%)	4 (40.0%)	0.334
IgA	13 (15.5%)	2 (20.0%)	0.659
Light chain only	23 (27.4%)	4 (40.0%)	0.465
International Staging System, N (%)			
I	31 (36.9%)	1 (10.0%)	0.156
II	24 (28.6%)	4 (40.0%)	0.478
III	29 (34.5%)	5 (50.0%)	0.488
ECOG PS ≥2	10 (11.9%)	3 (30.0%)	0.140
Median BM plasma cells, %	28.0 (10–90)	42.6 (21–74)	0.041
Median lactate dehydrogenase, IU/L	351 (117–1492)	411 (218–591)	0.346
Median lymphocyte count (×10^9/L)	1.9 (0.4–7.3)	1.5 (0.9–1.6)	0.062
Median platelet count (×10^9/L)	198 (60–380)	151 (53–286)	0.070
Median C-reactive protein, mg/dL	0.37 (0.0–19.0)	1.16 (0.2–14.0)	0.018
Median serum calcium, mg/dL	8.9 (7.2–16.0)	9.5 (8.8–14.7)	0.013
Median serum hemoglobin, g/dL	9.8 (4.9–15.3)	8.9 (6.5–12.3)	0.086
Serum albumin <3.5 g/dL	38 (45.2%)	6 (60.0%)	0.507
Serum β2-microglobulin ≥3.5 mg/L	33 (39.3%)	7 (70.0%)	0.091
eGFR <30 mL/min/1.73 m^2	19 (22.6%)	3 (30.0%)	0.694
Cytogenetic high risk[a]	3 (3.6%)	0	0.729
Performance of ASCT	63 (75.0%)	8 (80.0%)	1.000

[a]Standard risk: del(17) (−), del(13) (−) as determined by fluorescence in situ hybridization and a normal karyotype; high risk: del(17) (+), 1q/del1p (+), t(4;14).
Abbreviations: ASCT, autologous stem cell transplantation; BM, bone marrow; ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; N, number; PS, performance status; PYSTAT-3, phosphotyrosine-signal transducer and activator of transcription 3.

(23.4%) had an eGFR of <30 mL/min/1.73 m^2. Dual IHC staining of BM samples showed PY-STAT3 positivity in 10 patients (10.6%), including 3 (3.2%) with strongly positive expression. Baseline clinical characteristics of patients according to PY-STAT3 positivity are presented in Table 1. A comparison between PY-STAT3-negative and PY-STAT3-positive patients showed that the latter had a higher median percentage of BM plasma cells (28.0 vs. 42.6%, respectively; *P*=0.041); higher median C-reactive protein (CRP) level (0.37 vs. 1.16 mg/dL, respectively; *P*=0.018); and higher median serum calcium level (8.9 vs. 9.5 mg/dL, respectively; *P*= 0.013). Patients with PY-STAT3 positivity also had lower median lymphocyte counts, platelet counts, and hemoglobin levels than did PY-STAT3-negative patients, but the differences were not statistically significant.

The vast majority of the patients (N=89, 94.7%) received primary therapy with novel agents such as thalidomide, bortezomib, and lenalidomide. Five patients received primary therapy with conventional chemotherapies, including vincristine, doxorubicin, and dexamethasone (VAD), or cyclophosphamide and dexamethasone (CD). Among the PY-STAT3-positive patients, one patient was treated with a CD

regimen and nine with regimens containing novel agents (either CD and thalidomide or CD and bortezomib). Among the 94 patients included in the analysis, 71 underwent high-dose chemotherapy and autologous stem cell transplantation (HDT/ASCT), and 60 received frontline HDT/ASCT, including seven who were PY-STAT3-positive. In eight patients, the yield of collected stem cells was insufficient for HDT/ASCT, and seven patients refused to undergo HDT/ASCT. In addition, eight patients did not undergo HDT/ASCT based on a physician's recommendation owing to their poor general condition, comorbidities, or disease status. The median time to frontline HDT/ASCT was 6.1 months.

PY-STAT3 expression and clinical outcomes

The overall response rate (ORR) after initial therapy was 76.6%, including 24.5% of patients with complete response, 13.8% with very good partial response, and 38.3% with partial response. PY-STAT3-positive patients showed inferior treatment response compared with PY-STAT3-negative patients (ORR 60% vs. 78.6%, respectively, *P*=0.236).

During a median follow-up of 38.9 months, PFS and OS
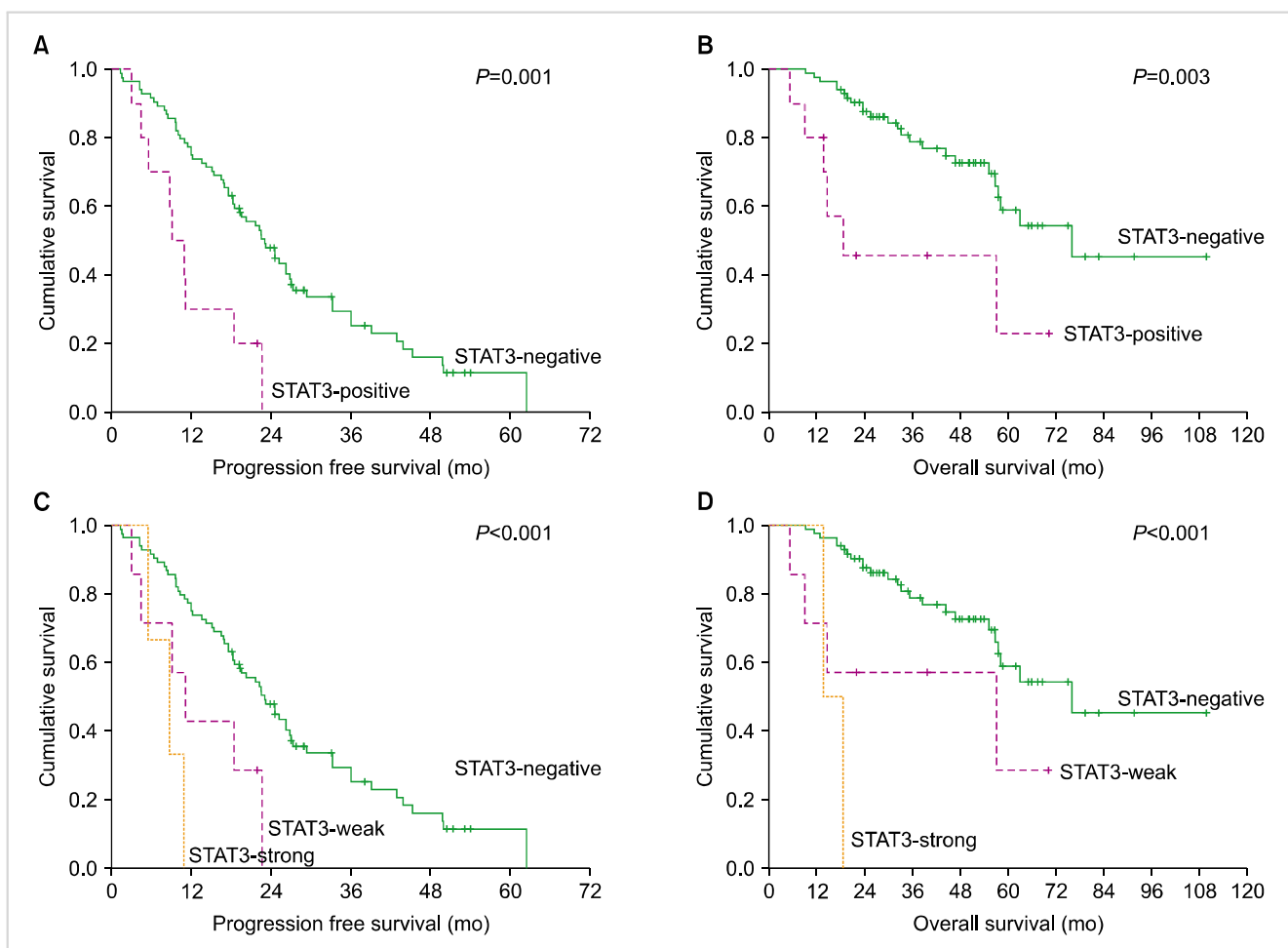
Fig. 2. Kaplan–Meier survival curves for progression-free survival and overall survival according to **(A, B)** PY-STAT3-positivity and **(C, D)** intensity of PY-STAT3 expression.
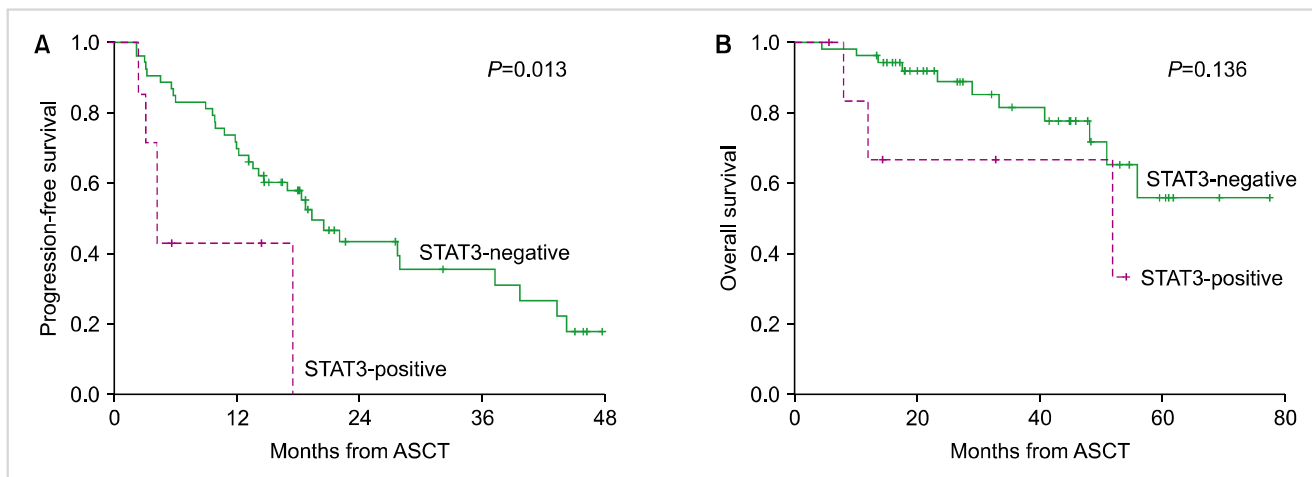
Fig. 3. Kaplan–Meier survival curves for **(A)** progression-free survival and **(B)** overall survival according to PY-STAT3 positivity in patients who underwent frontline autologous stem cell transplantation.

Table 2. Univariate analysis of progression-free survival (PFS) and overall survival (OS) in 94 patients with multiple myeloma.

	PFS		OS	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Men	0.932 (0.584–1.486)	0.767	1.558 (0.749–3.242)	0.235
ECOG PS ≥2	1.725 (0.868–3.426)	0.120	1.724 (0.654–4.549)	0.271
ISS III	1.580 (0.965–2.585)	0.069	1.811 (0.870–3.767)	0.112
LDH >1×ULN	1.167 (0.657–2.070)	0.599	2.440 (1.103–5.400)	0.028
ALC ≤1.1×10^9/L	1.642 (0.875–3.079)	0.122	1.231 (0.467–3.244)	0.674
Hemoglobin <10 g/dL	1.511 (0.939–2.433)	0.089	1.965 (0.918–4.206)	0.082
Platelet <130×10^9/L	7.371 (3.665–14.823)	<0.001	4.589 (1.982–10.624)	<0.001
BM plasma cells ≥40%	1.023 (0.626–1.672)	0.923	0.965 (0.451–2.064)	0.927
Calcium ≥11.5 mg/dL	0.865 (0.374–2.002)	0.735	1.681 (0.573–4.925)	0.344
STAT3-positive	3.270 (1.575–6.789)	0.001	3.665 (1.484–9.053)	0.005
eGFR <30 mL/min/1.73 m^2	1.224 (0.685–2.187)	0.495	3.029 (1.374–6.677)	0.006
Cytogenetic high risk	3.802 (1.172–12.335)	0.026	7.482 (2.161–25.912)	0.001

Abbreviations: ALC, absolute lymphocyte count; BM, bone marrow; ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; ISS, International Staging System; LDH, lactate dehydrogenase; PS, performance status; STAT3, signal transducer and activator of transcription 3; ULN, upper limit of normal value.

were found to be significantly shorter in PY-STAT3-positive than in PY-STAT3-negative patients (9.0 vs. 23.0 mo, *P*=0.001 and 18.7 vs. 76.0 mo, *P*=0.003, respectively) (Fig. 2A, B). Median PFS and OS were significantly different when assessed based on the degree of PY-STAT3 staining of BM tissue sections. The median PFS was 8.7 months in patients with strongly positive BM staining, 11.1 months in those with weakly positive BM staining, and 23.0 months in those with PY-STAT3-negative BM (*P*<0.001) (Fig. 2C). The corresponding values for the median OS were 13.7, 57.1, and 76.0 months, respectively (*P*<0.001) (Fig. 2D). In a subgroup analysis of the 60 patients who received frontline HDT/ASCT, PFS was shorter in PY-STAT3-positive than in PY-STAT3-negative patients (4.2 vs. 19.2 mo, respectively; *P*=0.013) (Fig. 3A). However, there was no significant difference in the median OS times (51.9 vs. not reached, respectively; *P*=0.136) (Fig. 3B).

The results of univariate analyses for PFS and OS are summarized in Table 2. Cox multivariate analysis showed that PY-STAT3 positivity (hazard ratio [HR], 2.706; 95% CI, 1.227–5.965; *P*=0.014) and thrombocytopenia (HR, 5.839; 95% CI, 2.810–12.129; *P*<0.001) were significantly associated with poor PFS and that PY-STAT3 positivity (HR, 3.091; 95% CI, 1.029–9.287; *P*=0.044), thrombocytopenia (HR, 5.694; 95% CI, 2.127–15.242; *P*=0.001), and cytogenetic high risk (HR, 6.578; 95% CI, 1.404–30.089; *P*=0.017) were significantly associated with poor OS (Table 3).

DISCUSSION

The Janus kinase (JAK)/STAT signaling pathway is an active focus of MM research. In mononuclear cells from the BM of patients with MM, constitutively activated STAT3

Table 3. Multivariate analysis of progression-free survival (PFS) and overall survival (OS) in 94 patients with multiple myeloma.

	Progression-free survival	
	Hazard ratio (95% CI)	P
Hemoglobin <10 g/dL	1.209 (0.727–2.009)	0.465
ISS III	1.335 (0.780–2.285)	0.292
Cytogenetic high risk	2.626 (0.739–9.335)	0.136
STAT3-positive	2.706 (1.227–5.965)	0.014
Platelets <130×10^9/L	5.839 (2.810–12.129)	<0.001
	Overall survival	
	Hazard ratio (95% CI)	P
Hemoglobin <10 g/dL	0.847 (0.351–2.047)	0.713
eGFR <30 mL/min/1.73 m^2	1.388 (0.524–3.680)	0.510
LDH > (1×ULN)	2.366 (0.929–6.028)	0.071
STAT3–positive	3.091 (1.029–9.287)	0.044
Platelets <130×10^9/L	5.694 (2.127–15.242)	0.001
Cytogenetic high risk	6.578 (1.404–30.809)	0.017

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; ISS, International Staging System; LDH, lactate dehydrogenase; STAT3, signal transducer and activator of transcription 3; ULN, upper limit of normal value.

signaling contributes to disease pathogenesis by preventing apoptosis [14]. MM cells express constitutively active forms of nuclear factor-κB and STAT3, and the suppression of these transcription factors inhibits the survival of these malignant cells [15]. Apoptosis has been shown to be induced in diverse MM cells treated with agents that inhibit the STAT3 signaling pathway [16, 17]. However, few studies have examined the clinical characteristics and prognosis of patients with BM tissue expression of PY-STAT3. Brown *et al.* [18] used phospho-flow cytometry to evaluate the constitutive expression of phosphorylated STAT3 (pSTAT3), pSTAT5, pERK, pAKT, and IL-6 receptor epitope in cryopreserved BM samples with respect to the clinical significance of positivity. In contrast to our results, the authors found no significant difference in OS between patients with high and low pSTAT3 expression (72 vs. 47 mo, respectively). In our study, PY-STAT3 expression by BM plasma cells was assessed by dual IHC in non-elderly adult patients with newly diagnosed MM. Patients with PY-STAT3-positive BM tissue had significantly poorer survival outcomes than those with PY-STAT3-negative BM. Moreover, both the median PFS and median OS were significantly different depending on the intensity of PY-STAT3 staining. Our results also show that the prognostic significance of STAT3 expression is independent of ISS and cytogenetic risk, as reported in studies of other cancers that suggested an association between high-level PY-STAT3 expression and more aggressive disease [19, 20]. Nonetheless, the reasons for the discrepancies regarding the clinical significance of PY-STAT3 expression remain unknown. Further studies of the prognostic significance of PY-STAT3 expression in prospective cohorts are required.

Both the local inflammatory state and the microenvironment are important determinants of malignant transformation and tumorigenesis. Inflammatory conditions can promote oncogenic transformation, while the genetic and epigenetic changes characteristic of malignant cells can lead to an inflammatory microenvironment that further supports tumor progression [21]. Because STAT family proteins, especially STAT3, play a crucial role in inducing and maintaining a procarcinogenic inflammatory microenvironment [8, 21-23], we evaluated several clinical parameters of inflammation and their potential relationship with PY-STAT3 expression. Significantly higher median CRP levels and a trend toward lower lymphocyte and platelet counts were detected in PY-STAT3-positive but not in PY-STAT3- negative patients. These clinical parameters were previously shown to be prognostic in patients with MM [24-26]. Therefore, our results suggest that clinical parameters such as the CRP level and lymphocyte count can provide indirect evidence of STAT3-associated cancer-related inflammation.

HDT/ASCT is an important therapeutic strategy in the management of MM in non-elderly adults. The Intergroupe Francophone du Myelome study was the first randomized trial to show the superiority of high-dose melphalan and total body irradiation followed by ASCT over conventional chemotherapy [27]. Subsequent randomized trials demonstrated improved response rates and survival among patients treated with HDT/ASCT in comparison to those treated with conventional chemotherapy [28, 29]. HDT/ASCT remains an important treatment approach even in the current era of novel biological agents [30]. The role of consolidation therapy using upfront ASCT in patients with PY-STAT3 positivity is unclear. Our evaluation of upfront ASCT as consolidation therapy for patients with PY-STAT3 expression showed no improvement in outcomes. However, the potential benefits of upfront ASCT with respect to outcome may be affected by clinical factors, the conditioning regimen used, and the type of maintenance therapy. Therefore, any conclusions regarding the role of upfront ASCT in patients with PY-STAT3-positive BM would be premature.

There are some limitations to our study. The study data are restricted a heterogeneous population of patients in regard to initial treatment regimens. In addition, the criteria to determine positivity or strong positivity of PY-STAT3 were arbitrary because of the relatively small number of patients.

In conclusion, the present study showed that survival is poor in patients with newly diagnosed MM and PY-STAT3-positive BM tissue, confirmed with the use of dual IHC. Median PFS and OS also differed significantly depending on the intensity of PY-STAT3 staining. The prognosis of patients with PY-STAT3 expression was not improved by upfront ASCT. Inhibition of STAT3 signaling may be an important therapeutic target to improve outcomes in patients with PY-STAT3-positive MM.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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