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Autologous

Clinical Implications of t(11;14) in Patients with Multiple Myeloma Undergoing Autologous Stem Cell Transplantation

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Conventional cytogenetic analyses and fluorescent in situ hybridization (FISH) are helpful for stratifying patients with multiple myeloma (MM) into high-risk [t(4;14), t(14;16), and/or del 17p] and standard-risk [t(11;14)] categories. However, the prognosis of patients with MM treated with autologous stem cell transplantation (ASCT) stratified according to these categories remains unclear. This retrospective observational study analyzed 97 patients with MM who received a single, planned ASCT after treatment with 200 mg/m^2 melphalan between 2001 and 2011. The patients were grouped according to chromosomal abnormality, including t(11;14) (n = 45), t(4;14) (n = 31), del 17p (n = 10), t(11;14) with del 17p (n = 7), and t(4;14) with del 17p (n = 4). Median overall survival (OS) of the t(11;14) group (64.1 months) was not significantly different from that of the t(4;14) group (not reached), but it was significantly longer than that of the del 17p group (23.0 months; $P = .002$). G-banding revealed that the median OS of the t(11;14) group with additional chromosomal abnormalities (ACAs) (46.2 months) was significantly shorter than that of the t(11;14) group without ACAs (not reached; $P = .005$) and the t(4;14) group (not reached; $P = .010$). These findings highlight the importance of G-banding in patients with t(11;14) MM.

INTRODUCTION

Multiple myeloma (MM) with t(11;14) is classified into the standard risk category according to the International Myeloma Working Group (IMWG) and Mayo Clinic criteria [1,2]. However, recent reports have shown that the prognosis for MM with t(11;14) falls between that for MM without t(11;14)/t(4;14)/t(14;16)/del 17p and that for MM with t(4;14)/t(14;16)/del 17p [3,4]. Furthermore, additional chromosomal abnormalities (ACAs) detected by G-banding, except for nonhypodiploid and del(13) [5], are excluded from the IMWG and Mayo Clinic criteria, and many US hospitals no longer perform cytogenetic analyses to evaluate the metaphase (Dr Shaji Kumar, Mayo Clinic, e-mail, 12 July 2018; with written permission) despite

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their recommendation by the National Comprehensive Cancer Network Guidelines in Oncology version 1.2019, and to date no studies have determined the prognosis of patients with MM harboring t(11;14) with or without ACAs, as identified on G-banding. Therefore, we conducted a retrospective study using the registry data of the Japan Society for Hematopoietic Cell Transplantation (JSHCT) to evaluate the prognosis of patients with t(11;14) MM who underwent autologous stem cell transplantation (ASCT), as evaluated by fluorescence in situ hybridization (FISH) and G-banding.

METHODS

Study Design and Participants

In this retrospective observational study, data were collected and analyzed using the Transplant Registry Unified Management Program (TRUMP) of the JSHCT. Because the registry data comprised anonymized clinical information, patient consent was not required for registration with the JSHCT TRUMP. This study was approved by the Data Management Committee of the JSHCT and the Institutional Review Board of Kanazawa University.

Conventional Cytogenetic Analysis by G-Banding and Interphase FISH

t(11;14), t(4;14), and del 17p detected by G-banding and/or interphase FISH (iFISH) in bone marrow aspirates before treatment were defined as abnormal patterns, and complex cytogenetic anomalies were defined as the presence of more than 2 chromosomal abnormalities detected by G-banding. The cutoff values for t(11;14), t(4;14), and del 17p by iFISH were based on the upper limit of the 95% confidence interval (CI) for the expected false-positive rate [6].

Response and Outcome Measures

Patient responses to therapy were assessed on the basis of the IMWG criteria [7,8]. Primary outcomes were progression-free survival (PFS) and overall survival (OS) [7]. PFS was defined as the time from the date of ASCT to the first disease progression or death, whichever was earlier. OS was defined as the interval from the date of ASCT to the date of death or the date of last contact. Patients who could not be followed up were censored at the date of last contact.

Statistical Analysis

Categorical and continuous variables were compared using Fisher's exact test and the Kruskal-Wallis test and Mann-Whitney *U* test, respectively. PFS and OS were calculated from the time of ASCT using the Kaplan-Meier method and compared among groups using a log-rank test. A Cox proportional hazard model was used to calculate hazard ratios (HRs) with 95% CIs for all variables

Multivariate analysis was conducted by entering all variables associated with survival at $P < .20$ into the Cox proportional hazard model. The following variables were considered: patient sex, age at transplantation (<65 versus ≥ 65 years), myeloma type (non-light chain myeloma versus light chain myeloma), International Staging System (ISS) stage (I/II versus III), cytogenetic abnormalities [del 17p versus t(11;14) without ACAs or t(11;14) with ACAs or t(4;14)], pre-ASCT response (complete response [CR]/very good partial response [VGPR] versus partial response [PR]/stable disease [SD]/progressive disease [PD]), and any post-ASCT therapy using novel agents until PD versus no post-ASCT therapy until PD). All statistical analyses were performed using the EZR software package (Saitama Medical Center/Jichi Medical University, Saitama, Japan) [9], which is a graphical user interface for R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria). $P < .05$ was considered to indicate statistical significance.

RESULTS

Patient Characteristics

The study cohort included 1432 Japanese patients (811 males and 621 females), with a median age of 58 years (range, 18 to 73 years) who underwent upfront single ASCT in Japan between March 2001 and December 2011 after treatment with 200 mg/m^2 melphalan for newly diagnosed symptomatic MM [8]. After reviewing the registry data, information on 110 patients with MM harboring t(11;14), t(4;14), and/or del 17p detected by G-banding and/or FISH were extracted and investigated using detailed questionnaires. After reviewing the questionnaires and confirming the chromosomal abnormalities, 97 patients were included in the final analysis. Among these 97 patients, 31 patients harbored t(4;14), 10 harbored t(11;14), 45 harbored del 17p, 4 harbored t(4;14) with del 17p, and 7 and harbored t(11;14) with del 17p (Supplemental Figure S1). We performed G-banding in 91 of the 97 patients (94%). The abnormalities in all patients with t(4;14) (n = 35) were identified by FISH alone. Conversely, abnormalities in 34 of the 52 patients with t(11;14) were analyzed using both FISH and G-banding. Specifically, abnormalities in all but 8 of these 34 patients with t(11;14) (n = 34) were identified using FISH alone; in these 8 patients (24%), abnormalities were identified using both FISH and G-banding. Table 1 summarizes the patient characteristics.

Owing to the extremely poor prognosis of patients with del 17p, patients with t(11;14) and del 17p and those with t(4;14) and del 17p were included in the del 17p category (Table 1). As standard-risk controls who have normal karyotype by G-banding and/or FISH, we randomly selected 291 cases from the same cohort (n = 1432) who were matched for sex, age at ASCT, and date of ASCT ($<$2007 or $\geq$2007) as abnormal FISH cases (n = 97) using optimal matching algorithms at a 1:3 ratio (Table 1S). The median duration of follow-up was 2.1 years (range, .02 to 1.1 years).

Response

Table 1 presents the pre-ASCT response and the best response rates among the 3 study groups. Although there were no significant differences in the pre-ASCT response and best response rates among the groups, stringent CR (sCR) + CR in the best response was lower in patients with del 17p (24%) than in those with t(4;14) (32%) and those with t(11;14) (38%). Comparison of response rates according to ACAs detected by G-banding revealed that sCR + CR rate in the best response was lower in patients with t(11;14) with ACAs than in those with t(11;14) without ACAs (23% [5 of 22] versus 52% [11 of 21]; $P = .06$).

Survival

PFS rates were not significantly different among the t(11;14), t(4;14), and del 17p groups (Figure 1A), whereas PFS in patients with t(11;14) and ACAs was significantly shorter than that in patients with t(11;14) without ACAs (HR, 2.04; 95% CI, 1.06 to 3.92; $P = .029$) and was close to that of patients with del 17p ($P = .940$) (Figure 1B). OS was significantly shorter in the del 17p group compared with the t(11;14) group (HR, 1.18; 95% CI, 1.06 to 1.32; $P = .002$), t(4;14) group (HR, 1.12; 95% CI, 1.05 to 1.19; $P = .0003$), and normal karyotype/FISH group (HR, 2.03: 95% CI, 1.52 to 2.72: $P < .00001$), whereas OS of the t(4;14) group was not significantly different from that of the t(11;14) group ($P = .281$) and normal karyotype/FISH group ($P = .710$), and OS of the t(11;14) group was also not significantly different from that of the normal karyotype/FISH group ($P = .275$) (Figure 1C). Conversely, OS of the t(11;14) group without ACAs was significantly longer than that of the t(11;14) with ACAs group (HR, .27; 95% CI, .10 to .71; $P = .005$) and the del 17p group (HR, .76; 95% CI, .65 to .89; $P = .0002$) (Figure 1D) and was not significantly different from that of normal karyotype/FISH group ($P = .294$). OS of the t(11;14) with ACAs group was significantly shorter than that of the t(4;14) group (HR, 1.14; 95% CI, 1.03 to 1.26; $P = .010$) and the normal karyotype/FISH group (HR, 1.39; 95% CI, 1.14 to 1.69; $P = .0006$), but was not significantly different from that of the del 17p group ($P = .262$) (Figure 1D). Finally, the comparison of the t(4;14) and del 17p groups revealed no significant differences in PFS and OS rates between the ACA$^-$ and ACA$_+$ subgroups (data not shown). Although G-banding was performed in all 45 patients with t(11;14) without del17p (100%), FISH was performed in

Table 1
Patient Characteristics and Responses

Characteristics and Responses	t(4;14) (n = 31)	del 17p (n = 21)*	t(11;14) (n = 45)		*P* Value
			ACA⁻ (n = 23)†	ACA⁺ (n = 22)	
Age at ASCT, yr, median (range)	58 (33-69)	59 (40-68)	58 (40-64)	58 (45-69)	.0498
Female sex, n (%)	16 (52)	9 (43)	6 (26)	7 (32)	.241
PS 0 or 1 at ASCT, n (%)	30 (97)	15 (71)	19 (83)	18 (82)	.065
M-protein isotype, n (%)					.065
IgG	15 (48)	10 (48)	4 (17)	8 (36)	
IgA	12 (39)	4 (19)	3 (13)	2 (9)	
IgD	0	1 (5)	0	1 (5)	
IgM	0	0	1 (4)	1 (5)	
Light chain only	4 (13)	5 (24)	10 (43)	9 (41)	
Nonsecreting	0	1 (5)	5 (22)	1 (5)	
Risk stratification					
ISS at diagnosis, n (%)					.661
I	9 (29)	7 (33)	11 (48)	6 (27)	
II	12 (39)	8 (38)	4 (17)	6 (27)	
III	8 (26)	4 (19)	7 (30)	9 (41)	
Unknown	2 (6)	2 (10)	1 (4)	1 (5)	
Elevated LDH, n/N (%)	2/26 (8)	5/16 (31)	3/20 (15)	5/19 (26)	.180
Cytogenetics based on G-banding, n (%)					.180
Normal	25 (81)	4 (19)	16 (70)	0	
Hypodiploidy (≦44)	0	4 (19)	0	2 (9)	
Pseudodiploidy (45, 46 with abnormalities)	2 (6)	4 (19)	5 (22)	7 (32)	
Hyperdiploidy (47-74)	0	5 (24)	0	9 (41)	
Near-tetraploidy (≥75)	0	0	0	4 (18)	
Not assessable/not done	4 (13)	4 (19)	2 (9)	0	
Complex	0	12 (57)	0	20 (91)	<.00001
13q-/monosomy 13	0	6 (29)	0	8 (36)	<.0001
Treatment					
Novel agents during induction and post-ASCT, n (%)	28 (90)	18 (86)	22 (96)	19 (86)	.665
PI-based	10 (32)	5 (24)	5 (22)	4 (18)	
IMiD-based	1 (3)	5 (24)	2 (9)	2 (9)	
PI + IMiD-based	17 (55)	8 (38)	15 (65)	13 (59)	
Post-ASCT novel agents until PD, n (%)	8 (26)	5 (24)	6 (26)	2 (9)	.429
PI-based	4 (13)	2 (10)	1 (4)	0	
IMiD-based	3 (10)	3 (14)	4 (17)	2 (9)	
PI + IMiD-based	1 (3)	0	1 (4)	0	
Pre-ASCT response, n (%)					.808‡
CR	4 (13)	1 (5)	3 (13)	3 (14)	
VGPR	12 (39)	9 (43)	5 (22)	3 (14)	
PR	11 (35)	8 (38)	11 (48)	11 (50)	
SD	4 (13)	2 (10)	3 (13)	5 (23)	
PD	0	1 (5)	1 (4)	0	
Best response, n (%)					.147‡
sCR	8 (26)	1 (5)	4 (17)	2 (9)	
CR	2 (6)	4 (19)	8 (35)	3 (14)	
VGPR	12 (39)	9 (43)	4 (17)	6 (27)	
PR	9 (29)	5 (24)	7 (30)	8 (36)	
SD	0	2 (10)	0	3 (14)	

PS indicates performance status; LDH, lactate dehydrogenase; PI, proteasome inhibitor, IMiD, immunomodulatory drug.
* del17p and t(4;14) (n = 4) and del17p and t(11;14) (n = 7) cases were included.
† Not assessable cases (n = 2) were included.
‡ sCR + CR versus non-CR.

20 of 23 patients with t(11;14) ACA⁻ (87%) and in 12 of 22 patients with t(11;14) ACA⁺ (55%). To analyze the bias for performing FISH, we performed propensity score matching analyses using the following factors: patient sex, age at ASCT, performance status (0/1 versus 2/3), ISS stage (I/II versus III), non-light chain versus light chain myeloma, pre-ASCT response (CR/VGPR versus PR/SD/PD), any post-ASCT therapy using new agents until PD versus no therapy until PD, and date of ASCT (<2007 or ≥2007). There were no significant differences in the foregoing factors, PFS, and OS between FISH plus G-banding and G-banding only cases (data not shown).

Multivariate analyses of PFS and OS performed using established prognostic factors identified non-light chain myeloma (HR, .46; 95% CI, .27 to .78; $P = .004$), t(11;14) without ACAs versus del 17p (HR, .49; 95% CI, .25 to .98; $P = .044$), and pre-ASCT response CR/VGPR (HR, .77; 95% CI, .64 to .92; $P = .004$) (Table 2) as the factors independently associated with superior PFS. Moreover, pre-ASCT response CR/VGPR (HR, .73; 95% CI, .58 to .91; $P = .006$), t(4;14) versus del 17p (HR, .16; 95% CI, .07 to .39; $P < .0001$), and t(11;14) without ACAs versus del 17p (HR, .15; 95% CI, .06 to .40; $P = .0002$) were the factors independently associated with superior OS; however, t(11;14) with ACAs versus del 17p was not an independent factor associated with superior OS ($P = .077$) (Table 2).

DISCUSSION

The IMWG defines patients with MM harboring t(11;14) as a standard-risk group and those harboring t(4;14) and/or del 17p and/or t(14;16) as a high-risk group [2]. Conversely, results regarding patients with t(11;14) MM are conflicting [3,4,10–16]. In a study of 336 evaluable patients who did not receive any novel agents or ASCT, Fonseca et al [11] reported

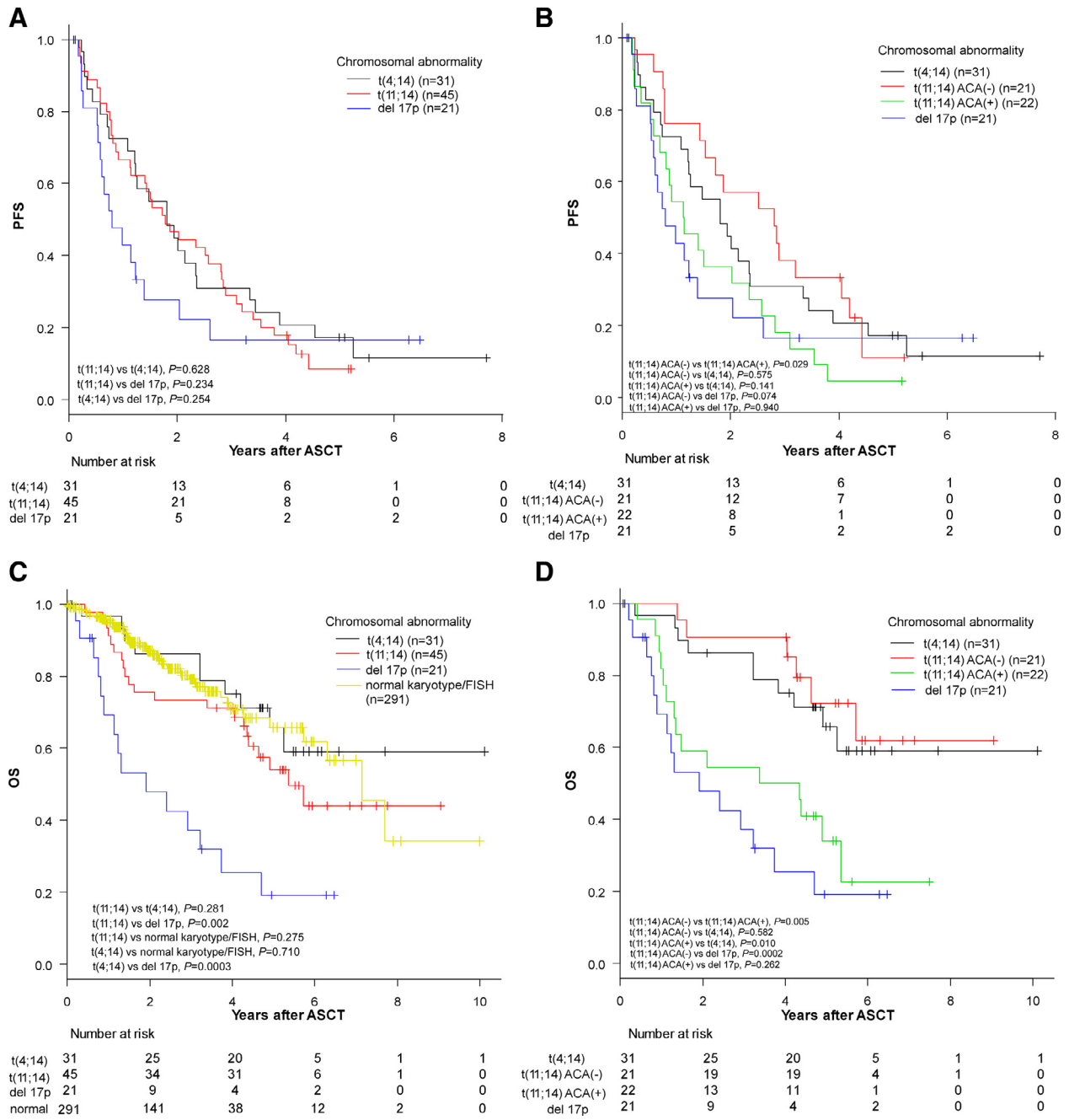

Figure 1. Comparison of PFS and OS in patients with chromosomal abnormalities. (A) PFS in the t(4;14), t(11;14), and del 17p groups. (B) PFS in the t(4;14), t(11;14) without additional chromosomal abnormalities (ACAs), t(11;14) with ACAs, and del 17p groups. (C) OS in the t(4;14), t(11;14), del 17p, and normal karyotype by G-banding and/or FISH groups. (D) OS in the t(4;14), t(11;14) without ACAs, t(11;14) with ACAs, and del 17p groups. Two patients with t(11;14) were excluded from ACA analysis due to the lack of cytogenetics based on G-banding.

that 53 patients (16%) exhibited abnormal FISH patterns compatible with t(11;14)(q13;q32) and appeared to show better survival and response to treatment compared with patients not harboring t(11;14)(q13;q32), although the difference was not statistically significant. Similarly, Avet-Loiseau et al [14] reported that the presence of t(11;14) did not affect prognosis in their analysis of a large series of patients with newly diagnosed MM enrolled in the IFM99 trials who were treated with VAD (vincristine + doxorubicin + dexamethasone) induction and tandem ASCT. In contrast, Sasaki et al [3] showed that 27 patients with MM carrying t(11;14)(q13;q32), which was detected by conventional cytogenetic analysis or FISH, who underwent high-dose melphalan treatment and ASCT showed intermediate PFS (27% at 3 years) and OS (63% at 3 years) compared with those with high-risk disease [del(13q)/−13 or hypoploidy detected by conventional cytogenetic analysis only or t(4;14)(p16.3;q32), t(14;16)(q32;q23), t(14;20)(q32;q11.2), or del(17p13) detected by conventional cytogenetic analysis or FISH (n = 97)] or those with normal conventional cytogenetics and FISH (n = 869) before ASCT. In their cohort, 78% of the patients with t(11;14) received novel agents, such as thalidomide, lenalidomide, and bortezomib. Shin et al [13] identified t(11;14) translocation as a poor prognostic factor for ASCT in patients with MM and extramedullary plasmacytoma (n = 7).

Table 2
Effect of Patient Characteristics on Survival (n = 97)

Independent variables	PFS			OS		
	P value for univariate analysis	HR (95% CI) for PFS from multivariate analysis	*P* value for multivariate analysis	*P* value for univariate analysis	HR (95% CI) for OS from multivariate analysis	*P* value for multivariate analysis
Sex, male versus female	.051	.76 (.47-1.21)	.246	.070	.55 (.30-1.01)	.055
Age at ASCT, <65 yr versus ≥65 yr	.132	.44 (.15-1.25)	.124	.997	NI	-
Non-light chain myeloma versus light chain myeloma	.037	.46 (.27-.78)	.004	.174	.57 (.28-1.16)	.120
ISS I/II versus III	.386	NI	-	.207	NI	-
t(4;14) versus del 17p abnormality	.257	.64 (.33-1.23)	.179	.001	.16 (.07-.39)	< .0001
t(11;14) without ACA versus del 17p abnormality	.078	.49 (.25-.98)	.044	.001	.15 (.06-.40)	.0002
t(11;14) with ACA versus del 17p abnormality	.940	1.01 (.51-1.99)	.982	.266	.49 (.23-1.08)	.077
Pre-ASCT response CR/VGPR versus PR/SD/PD	<.001	.77 (.64-.92)	.004	.015	.73 (.58-.91)	.006
Any post-ASCT therapy using new agents until PD versus no therapy until PD	.041	.63 (.34-1.15)	.129	.138	.81 (.35-1.87)	.621

NI indicates not included in the analysis.

In a recent retrospective analysis from the Mayo Clinic, Lakshman et al [4] reported that outcomes of patients with t(11;14) MM were inferior to those of other standard-risk patients. In their recent analysis of the Connect MM registry, Gasparetto et al [15] identified t(11;14) as an independent negative prognostic factor for OS ($P = .009$) and PFS ($P = .073$) in African American patients (n = 53); however, they found no such association between t(11;14) and PFS or OS in non-African American patients (n = 310). In their cohort, approximately 50% of the patients (27 [51%] African American and 164 [53%] non-African American patients] underwent stem cell transplantation. Our retrospective analyses also showed that the OS of MM with t(11;14) was between that for MM with normal karyotype/FISH and MM with del 17p. Overall, these results suggest that patients with MM harboring t(11;14) who undergo ASCT might not be considered standard risk.

Furthermore, our analyses revealed that among patients with t(11;14), the survival rate of those without ACAs was higher than that of those with ACAs. Therefore, patients with t(11;14) should be divided into 2 groups—with and without ACAs—as determined by G-banding for the accurate prediction of prognosis. The IMWG and Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) define t(11;14) cases as those at a standard risk and do not take ACAs detected by G-banding into account. Although the prognosis of patients with hypodiploidy is considered high risk, cytogenetic analysis by G-banding is currently not included in the major risk criteria. Patients with t(11;14) and ACAs showed extremely poor prognosis similar to that of patients with del 17p; however, patients with t(11;14) without ACAs showed a better prognosis than that of patients with t(4;14), highlighting the importance of G-banding in patients with t(11;14) and reflecting the rapid growth rate of myeloma cells with abnormalities that could be detected by G-banding. Notably, Leiba et al [16] have shown that compared with t(11;14) alone, the presence of certain ACAs led to worse outcomes; they concluded that patients with coexisting adverse lesions and t(11;14) might be considered as high risk and should be managed accordingly.

In the present study, multivariate analysis revealed that the presence of del 17p and t(11;14) with ACAs had a significantly negative effect on OS, but the presence of t(11;14) without ACAs did not have a similar effect. These results further confirm that patients with MM harboring t(11;14) and ACAs are not standard risk.

Some patients with MM harboring t(11;14) are extremely refractory to novel agents, and Fonseca [17] has suggested that the prognosis of MM with t(11;14) does not improve with the use of novel agents, because the scan cytoplasm observed in t(11;14) clones precluded endoplasmic reticulum stress-induced apoptosis; therefore, innovative therapies are required to treat such patients. Recently, Touzeau et al [18] showed that the orally bioavailable novel BCL-2 inhibitor venetoclax could kill myeloma cells harboring t(11;14), leading to successful treatment of a patient with t(11;14) MM who was heavily treated with novel agents and was refractory to them. Furthermore, Kumar et al [19] have demonstrated that venetoclax monotherapy has an acceptable safety profile with single-agent antimyeloma activity in patients with relapsed/refractory MM, particularly in those with t(11;14). Therefore, reanalyzing the resistance of patients with t(11;14) to novel agents based on the presence of ACAs is imperative.

The present study has several limitations. First, this was a retrospective study, and FISH analyses were not performed routinely. Second, t(11;14) was detected using FISH and/or G-banding , although it can be detected using FISH in patients with MM as well (personal communication (SRL Inc., September 2018)). Finally, regarding the standard-risk patients exhibiting normal FISH and/or G-banding patterns in our database, we did not obtain data for PFS in our study cohort using questionnaires. The OS of the standard-risk group in this study (4-year OS, 70.6%; 95% CI, 61.1 to 78.2) is almost the same as that of the standard-risk cases (n = 43) [normal karyotype using G-banding and negative for t(4;14), t(14;16) and del 17p using FISH] who were administered high-dose melphalan followed by ASCT during novel agents era in our another research group data (4-year OS, 77.4%; 95% CI, 57.6 to 88.7 at a median follow-up of 3.6 years) (Drs Yoshiaki Abe and Kosei Matsue, Kameda Medical Center, e-mail, 7 October 2018; with written permission). Interestingly, the data of the research group (Kameda Medical Center, National Hospital Organization Okayama Medical Center and Keiju Kanazawa Hospital) showed that the OS in t(4;14) cases (n = 17) is also not significantly different from that of the standard-risk group (n = 43) (4-year OS, 86.5% ; 95% CI, 55.8 to 96.5 versus 77.4%; 95% CI, 57.6 to 88.7; $P = .72$). These results are consistent with the results of this study. Recently, Byun et al [20] also showed no significant differences in PFS and OS between t(4;14) and non-t(4;14) groups in Asian patients with MM who underwent ASCT. Based on these results, t(4;14) Asian patients with MM undergoing ASCT might not be high risk.

In conclusion, patients with MM harboring t(11;14) and ACAs are at high risk in the ASCT setting; however, OS of patients with t(11;14) alone was not significantly different from that of patients with normal karyotype/FISH, who are considered standard risk. Our results suggest that the prognostic risk level of patients with t(11;14) can be

classified according to ACAs, as detected by G-banding. Nonetheless, our findings remain to be confirmed in prospective studies.

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A complete list of the investigators in this study is provided in Supplementary Data.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2018.11.003.

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