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ORIGINAL ARTICLE

Different prognostic effects of core-binding factor positive AML with Korean AML registry data

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Abstract

Core-binding factor acute myeloid leukemia (CBF-AML) data in Asian countries has been rarely reported. We analyzed 392 patients with CBF-AML [281 with t(8;21), 111 with inv.(16)/t(16;16)] among data from 3041 patients with AML from the Korean AML Registry. Interestingly, del(9q) was less frequently detected in Korean than in German patients with t(8;21) (7.5% vs. 17%), and del(7q) was more frequently detected in Korean patients with inv(16). Overall survival (OS) was similar between patients in the first complete remission (CR) who received allogeneic (alloSCT) and autologous stem cell transplantation (ASCT) for CBF-AML. OS of t(8;21) patients was poor when undergoing alloSCT in second/third CR, while OS of inv(16) patients in second/third CR was similar to that in first CR. Patients with > 3-log reduction of *RUNX1/RUNX1T1* qPCR had improved 3-year event-free survival (EFS) than those without (73.2% vs. 50.3%). Patients with t(8;21) AML with D816 mutation of the *c-Kit gene* showed inferior EFS and OS. These poor outcomes might be overcome by alloSCT. Multivariate analysis for OS in patients with t(8;21) revealed older age, > 1 course of induction chemotherapy to achieve CR, loss of sex chromosome, del(7q), and second/third CR or not in CR before SCT as independent prognostic variables. Especially, del(7q) is the most powerful prediction factor of poor outcomes, especially in patients with t(8;21) (hazard ratio, 27.23; $P < 0.001$). Further study is needed to clarify the clinical effect of cytogenetics and gene mutation in patients with CBF-AML, between Asian and Western countries.

Keywords Acute myeloid leukemia · Core-binding factor · Stem cell transplantation · Cytogenetics · D816 mutation · RUNX1/RUNX1T1

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Introduction

Core-binding factor acute myeloid leukemia (CBF-AML), defined by the presence of t(8;21)(q22;q22) or inv(16)(p13q22)/t(16;16)(p13;q22), results from the fusion of genes *RUNX1/RUNX1T1* and *CBFβ/MYH11*, respectively [1, 2]. This leads to disruption of the CBF complex. CBF-AML presents in approximately 15% of all AML patients younger than 60 years and 7% in patients older than 60 years [3–5]. This type of leukemia has a relatively favorable prognosis compared with other forms of AML [3, 6–8]. In younger patients, repeated cycles of high-dose cytarabine (HDAC) therapy can prolong survival [7, 8]. Therefore, patients with CBF-AML are typically excluded from allogeneic stem cell transplantation (alloSCT) if they are in the first complete remission (CR1) [9, 10]. However, the major treatment failure is disease recurrence, and approximately 50% of patients with CBF-AML remain incurable [4, 11, 12]. Although the two different cytogenetic presentations of CBF-AML had similar clinical characteristics, patients with t(8;21) seem to have a worse disease-free survival (DFS) and overall survival (OS) than those with inv(16) [4, 5, 7]. In particular, it has been observed that patients with t(8;21) have significantly shorter survival rates after relapse than those with inv(16) [4], suggesting that the difference in OS between them might be related to inferior response to salvage treatment in the former.

Autologous stem cell transplantation (ASCT) is generally associated with lower procedure-related toxicity and mortality than alloSCT, but the relapse rate is a major concern. Although alloSCT is the most effective way to control leukemia relapse in patients with AML, this benefit is partially superseded by the toxicity associated with the procedure. Nonetheless, alloSCT can improve the clinical outcomes in high-risk patients with t(8;21) [13]. Recently, major advances in supportive care practices and management of graft-versus-host disease (GVHD) resulted in significant survival benefits in patients undergoing alloSCT [14], and many centers in Korea have been utilizing alloSCT for AML patients with t(8;21) who achieved CR1 after remission induction chemotherapy [15]. Meanwhile, nationwide data on CBF-AML in Asian countries, comparing them with Western countries, have been rarely reported.

This study aimed to evaluate the clinical characteristics, treatment outcomes including SCT, and prognostic factors for CBF-AML using the Korean AML registry.

Patients and methods

Patients

In this study, we analyzed data from the Korean AML registry, a national AML database operated by the Korean Society of Hematology AML/Myelodysplastic syndrome (MDS) Working Party since 2006. AML was diagnosed according to the World Health Organization definition of ≥ 20% blasts in the bone marrow (BM) or peripheral blood [16]. Demographic, diagnostic, clinical, cytogenetic, induction, and treatment outcome information were collected and were sent to a central registration center. Cytogenetic studies were conducted in each center; however, a central review of cytogenetic analysis was not performed. Several centers do not check polymerase chain reaction (PCR) or fluorescence in situ hybridization using BM samples at diagnosis. From March 2006 to December 2011, 3041 patients with AML were registered. Among them, 392 (12.9%) were diagnosed with core-binding factor AML (CBF-AML). CBF-AML was defined as AML with t(8;21)(q22;q22), *RUNX1-RUNX1T1*, or AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22), *CBFβ-MYH11*. The incidence of CBF-AML in patients aged < 60 years was 15.4% (313 of 2038 patients with AML) and 7.9% in those aged ≥ 60 years (79 of 1003 patients with AML), which was lower than those in younger age and was comparable with the previous studies [3–5, 17]. Among the 392 patients with CBF-AML, with a median age of 45 years (range, 14 to 89 years), 281 (71.7%) had t(8;21) or *RUNX1-RUNX1T1* and 111 (28.3%) had inv(16)/t(16;16) or *CBFβ-MYH11*. The study protocol was approved by the institutional review board of each center. All procedures complied with the Helsinki Declaration standards and approved by the each hospital institutional review board. The requirement for written informed consent was waived off, because this study used retrospective data from the Korean AML registry, and there were no interventions in the patients.

Treatment

Patients received either one or two courses of remission induction chemotherapy: 294 patients (75.1%) were treated with remission induction chemotherapy using "3 + 7" idarubicin or daunorubicin plus intravenous cytarabine, 21 (5.4%) received other combination chemotherapy, and 21 (5.4%) did not receive any induction chemotherapy due to poor performance status or any other causes. A total of 56 (14.3%) patients had missing data.

Molecular study

The recorded molecular data in the CBF-AML registry included *RUNX1/RUNX1T1*, *CBFβ-MYH11*, *c-Kit*, *FLT3/ITD*, *NPM1*, *BAALC*, and *WT1*. However, most of these molecular analyses were performed differently at each center; therefore, we tried to analyze using the molecular data, which used the following method. All molecular studies were performed using the BM samples at the time of initial diagnosis and post-induction periods. *RUNX1/RUNX1T1*, the representative

molecular residual disease (MRD) markers for CBF-AML, was detected by a multiplex RT-PCR screening assay using the HemaVision Kit (DNA Technology, Risskov, Denmark), and quantification of both was performed using qPCR. The qPCR level represented the ratios of *RUNX1/RUNX1T1* expression normalized to the expression of the reference gene, *ABL1* (1.0×10^4) as previously reported. The *c-Kit* mutation was detected by the melting curve analysis using RT-PCR (Real-Q *c-Kit* screening kit and D816 muta-ID kit, Biosewoom Inc.), which can detect the *c-Kit* mutation located at Asp816 (D816) and Asn822 (N822K) in exon 17.

Transplantation

A total of 201 patients underwent SCT: 146 of them underwent alloSCT and 55 underwent ASCT. Patients were treated with various conditioning regimens; however, most of those who underwent ASCT received total body irradiation (TBI)-based regimens (72.7%), such as TBI with cytarabine and melphalan, or TBI with fludarabine and busulfan. The most frequently used conditioning regimen for alloSCT was TBI-based (44.5%), followed by busulfan plus cyclophosphamide (22.6%) and busulfan plus fludarabine (24.0%) regimens.

The most common donor stem cell source for alloSCT was peripheral blood ($n = 110$; 75.3%), followed by BM ($n = 34$; 23.2%), and two patients had missing data. A total of 87 (59.6%) patients underwent alloSCT from a related donor, 45 (30.8%) from unrelated donor, and 14 (9.6%) from human leukocyte antigen haploidentical family member donor.

Statistical analysis

The correlation between the two groups was analyzed using the chi-squared test, Fisher's exact test, and Mann-Whitney *U* test.

OS and event-free survival (EFS) were defined according to ELN Recommendations [2]. EFS was defined as the time from AML diagnosis to the date of primary refractory disease, or relapse from CR, CRi, or death from any cause. OS was defined as the time from AML diagnosis to the date of death or last follow-up. OS and EFS were determined using Kaplan-Meier analysis, and differences between survival curves were tested for statistical significance using two-tailed log-rank tests. Univariate and multivariate survival analyses were performed using the Cox proportional hazards model. *P* values of < 0.05 were considered significant. All calculations were performed using the Windows version of IBM SPSS software version 18.0.1 (PASW Statistics for Windows, SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Table 1 summarizes the comparison between baseline characteristics of 281 patients with t(8;21) and 111 patients with inv(16). At diagnosis, patients with inv(16) AML had higher WBC ($P < 0.001$) and hemoglobin ($P = 0.017$) levels, and peripheral blood blast compared with those with t(8;21) AML. Median age, sex, platelet counts, bone marrow blast, and lactate dehydrogenase at diagnosis were not different between patients with t(8;21) and inv(16).

Additional cytogenetic abnormalities were significantly different between patients with t(8;21) and inv(16). The del(9q) and loss of sex chromosome were detected more frequently in patients with t(8;21) than in patients with inv(16). The del(7q), trisomy 8, trisomy 22, and complex karyotypes were detected more frequently in patients with inv(16) than in patients with t(8;21). We compared the frequency of additional cytogenetic abnormalities between the Korean registry ($n = 392$ patients) and the German AML intergroup data and revealed that del(9q) was less frequently detected in Korean than German patients with t(8;21) (7.5% vs. 17%), while the frequency of other cytogenetic abnormalities was similar between Korean and German patients (Fig. 1). The del(7q) was more frequently detected (9.9%) in Korean patients with inv(16).

Survival analysis

The estimated 3-year EFS rates were $46.2\% \pm 3.6\%$ and $47.1\% \pm 6.2\%$, and 3-year OS rates were $54.9\% \pm 3.7\%$ and $59.9\% \pm 5.8\%$ for patients with t(8;21) and inv(16), respectively (Fig. 2a, b). In patients aged < 60 years, the 3-year OS rates were similar in all the population ($60.0\% \pm 4.0\%$ vs. $66.0\% \pm 6.1\%$), but lower in patients with aged ≥ 60 years t(8;21) ($31.9\% \pm 8.2\%$) and inv(16) ($25.0\% \pm 12.2\%$) compared with younger patients (Fig. 2c, d).

Figure 3a and b focus on the OS of t(8;21) and patients with inv(16), stratified according to the type (alloSCT vs. ASCT) and disease status at the time of transplantation (first CR, second or third CR, and no CR). The estimated 3-year OS of patients with t(8;21) in the first CR was similar between alloSCT and ASCT ($72.6\% \pm 5.3\%$ and $74.5\% \pm 7.9\%$, respectively). Similarly, the estimated 3-year OS of patients with inv(16) was also similar between alloSCT and ASCT when they underwent transplantation in the first CR ($75.8\% \pm 8.8\%$ and $77.9\% \pm 11.3\%$, respectively). The estimated 3-year OS of patients with t(8;21) was poor when they underwent transplantation in the second or third CR compared with that in the first CR ($51.6\% \pm 13.6\%$ and $72.6\% \pm 5.3\%$, respectively), while 3-year OS of patients with inv(16) in the second or third

Table 1 Baseline characteristics of CBF-AML patients

Variables	t(8;21) ($n = 281$) No.	%	Inv(16)/t(16;16) ($n = 111$) No.	%	*P*
Median age, years (range)	44 (14–89)		45 (17–85)		0.727
Sex					0.345
Male	162	57.7	56	50.5	
Female	119	42.3	55	49.5	
Median WBC, × 10^9/L (range)	9.45 (0.18–435.53)		38.68 (0.62–374.18)		< 0.001
Median Hgb, g/dL (range)	8.0 (1.2–14.6)		8.6 (4.0–15.2)		0.017
Median PLT, × 10^9/L (range)	38 (3–600)		40.5 (2–307)		0.770
Median PB blast, % (range)	35 (0–100)		49 (0–100)		0.024
Median marrow blast, % (range)	90 (10–100)		70 (0.4–100)		0.194
Median LDH, IL/U (range)	973.5 (208.0–16468.0)		876.0 (156.0–7810.0)		0.434
Additional cytogenetic abnormalities					
del(7q)	6	2.2	11	9.9	0.002
del(9q)	21	7.5	3	2.7	0.040
Loss of sex chromosome	155	55.2	3	2.7	< 0.001
Trisomy 8	9	3.2	14	12.6	< 0.001
Trisomy 22	0	0	20	18.0	< 0.001
Complex karyotype	15	5.3	14	12.6	0.026

CBF-AML, core-binding factor acute myeloid leukemia; *WBC*, white blood cell; *Hgb*, hemoglobin; *PLT*, platelet; *PB*, peripheral blood; *LDH*, lactate dehydrogenase

CR was similar compared with that in the first CR (76.2% ± 14.8% and 75.8% ± 8.8%, respectively).

When analyzing the OS based on the conditioning regimen of alloSCT (myeloablative vs. reduced intensity conditioning regimen) as well as ASCT in the second or third CR, OS of reduced intensity hematopoietic stem cell transplantation (RIST), SCT with myeloablative conditioning regimen, and ASCT were similar, while RIST had marginally improved estimated 3-year OS compared with the SCT with myeloablative conditioning regimen or ASCT in patients who achieved the first CR (93.8% ± 6.1% vs. 67.0% ± 6.4% vs. 74.5% ± 7.9%), but the difference was statistically insignificant (Fig. 4a, b). OS in patients aged < 45 years was similar between patients who underwent alloSCT with myeloablative conditioning regimen and RIST; however, the estimated 3-year OS of RIST in patients aged ≥ 45 years was marginally improved than that of alloSCT with myeloablative conditioning regimen (57.3% ± 15.2% and 37.4% ± 10.8%, respectively), but the difference was statistically insignificant.

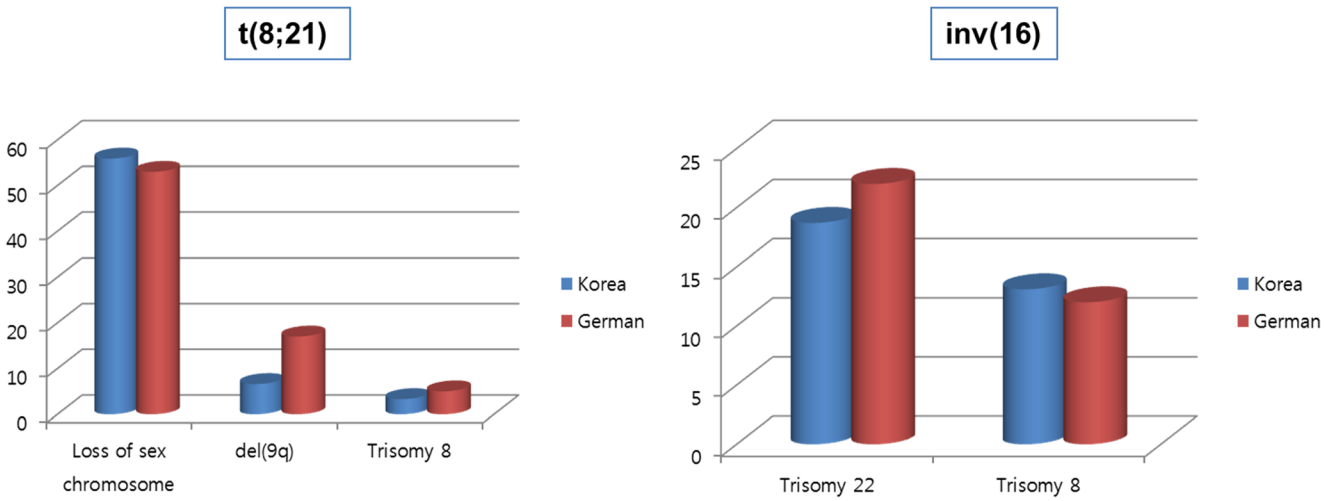

Fig. 1 Difference in the frequency of additional cytogenetic abnormalities between Korean registry data and the German acute myeloid leukemia intergroup data

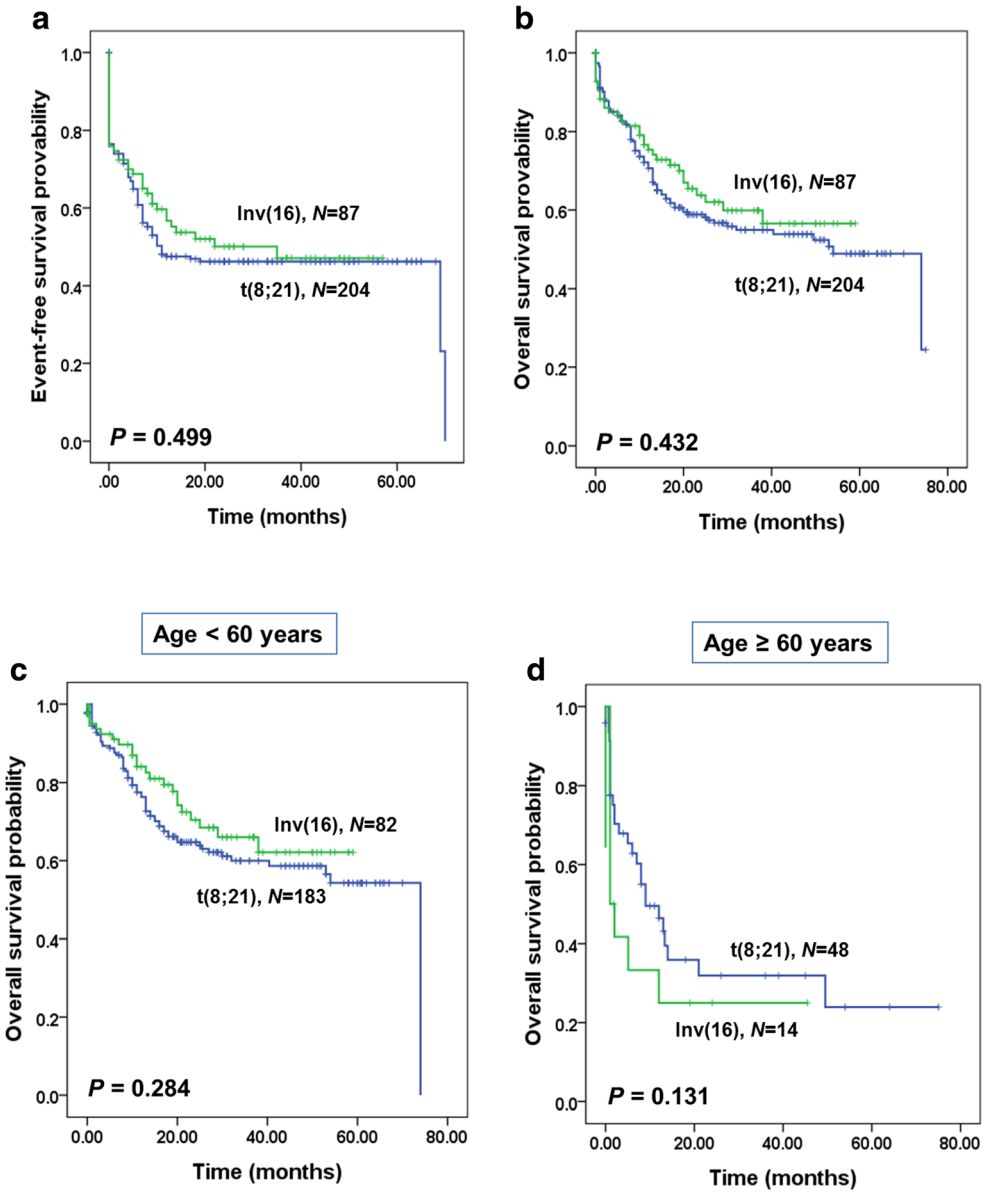

Fig. 2 **a**, **b** The event-free survival or overall survival by CBF-AML type. **c**, **d** The overall survival by CBF-AML based on patients aged < 60 or ≥ 60 years

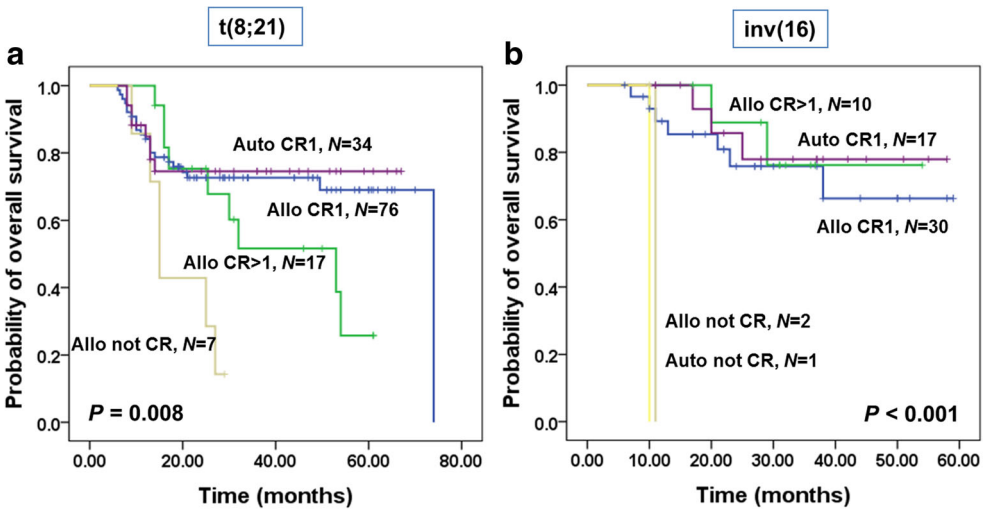

Fig. 3 Overall survival difference in patients with **a** t(8;21) or **b** inv(16) who underwent autologous or allogeneic stem cell transplantation. Both graphs are stratified based on the type of transplantation and disease status at the time of transplantation (CR1 means first CR, CR > 1 means second or third CR, and no CR means not in CR or refractory)

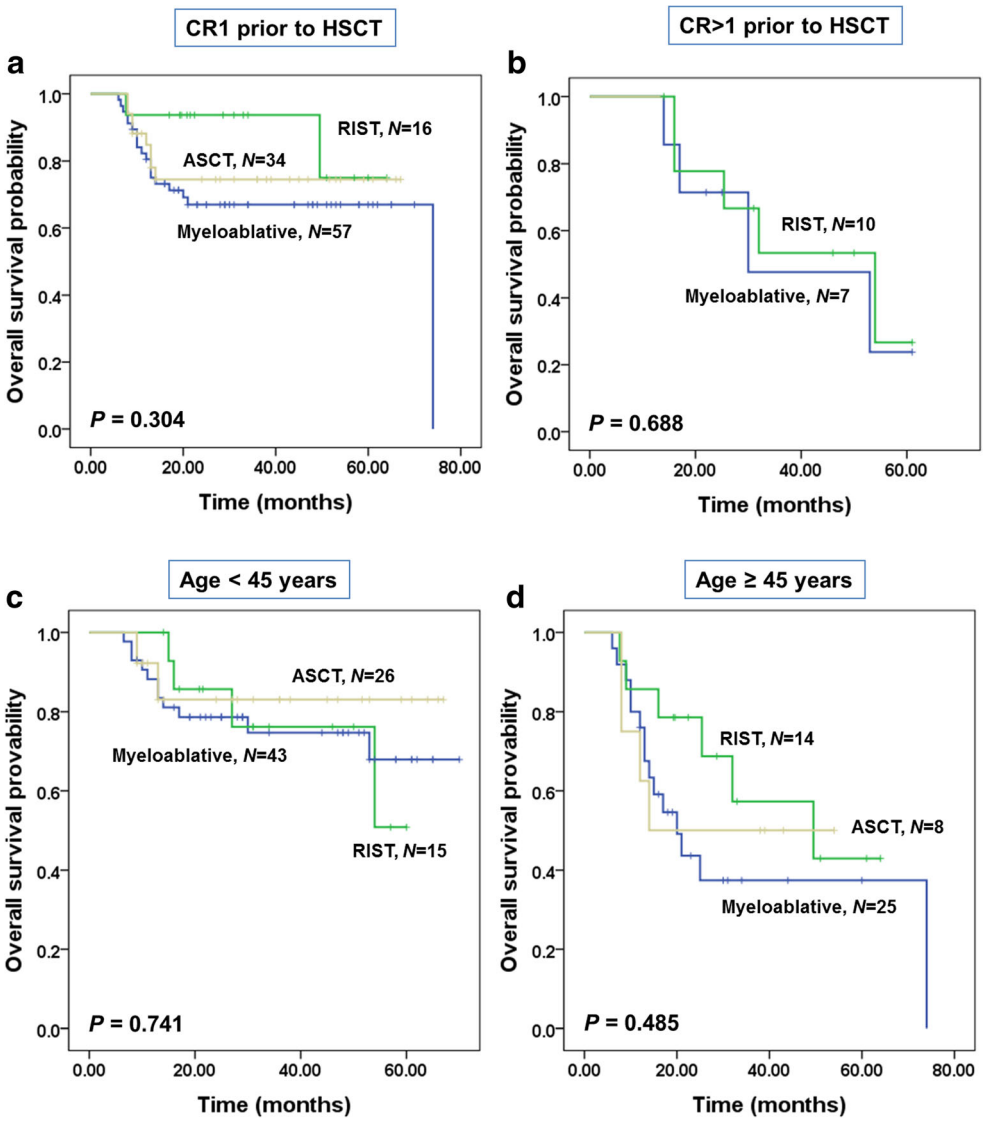

Fig. 4 Overall survival in patients with t(8;21) who underwent autologous or allogeneic stem cell transplantation with myeloablative or reduced intensity conditioning regimen. **a**, **b** Overall survival difference based on the achievement of first CR versus second or third CR at the time of transplantation; **c**, **d** overall survival difference according to patients aged < 45 years versus aged ≥ 45 years

Survival analysis according to 3-log reduction of RUNX1/RUNX1T1 qPCR after one course of induction chemotherapy

After one course of induction therapy, patients with more than 3-log reduction of *RUNX1/RUNX1T1* qPCR compared with the pre-induction chemotherapy baseline had improved estimated 3-year EFS than those without 3-log reduction (73.2% ± 8.7% and 50.3% ± 7.4%, respectively) ($P = 0.030$) (Fig. 5a). However, the OS was not different between patients with ≥ 3-log reduction and < 3-log reduction of *RUNX1/RUNX1T1* qPCR (Fig. 5b).

When focusing on the subgroup analysis with post-remission treatment strategies, EFS between patients with and without 3-log reduction of *RUNX1/RUNX1T1* qPCR was statistically insignificant when alloSCT or ASCT was performed as post-remission therapy, while the estimated 3-year EFS of patients with ≥ 3-log reduction of *RUNX1/RUNX1T1* qPCR was higher in patients who received high-dose cytarabine chemotherapy alone as post-remission treatment (100% vs. 50% ± 25.0%), but only two cases in each could be analyzed for EFS in the chemotherapy alone group.

Survival analysis according to c-Kit mutation

The *c-Kit* mutation analysis was only performed in 94 patients in a single center. Patients with D816 mutation had worse EFS ($P = 0.022$) and OS ($P = 0.091$) than those without (Fig. 6a, b). When analyzing according to each cytogenetic or molecular abnormality, t(8;21) patients with AML with D816 mutation showed lower 3-year EFS (31.4% ± 10.4% and 59.0% ± 8.0%, respectively) and OS (33.1% ± 11.9% and 58.8% ± 8.1%, respectively) compared with those of patients without; however, the EFS and OS were statistically insignificant in patients with inv(16) with and without D816 mutation (Fig. 6c–f). The EFS and OS were similar in patients with CBF-AML with and without D816 mutation who underwent alloSCT (Fig. 6g, h).

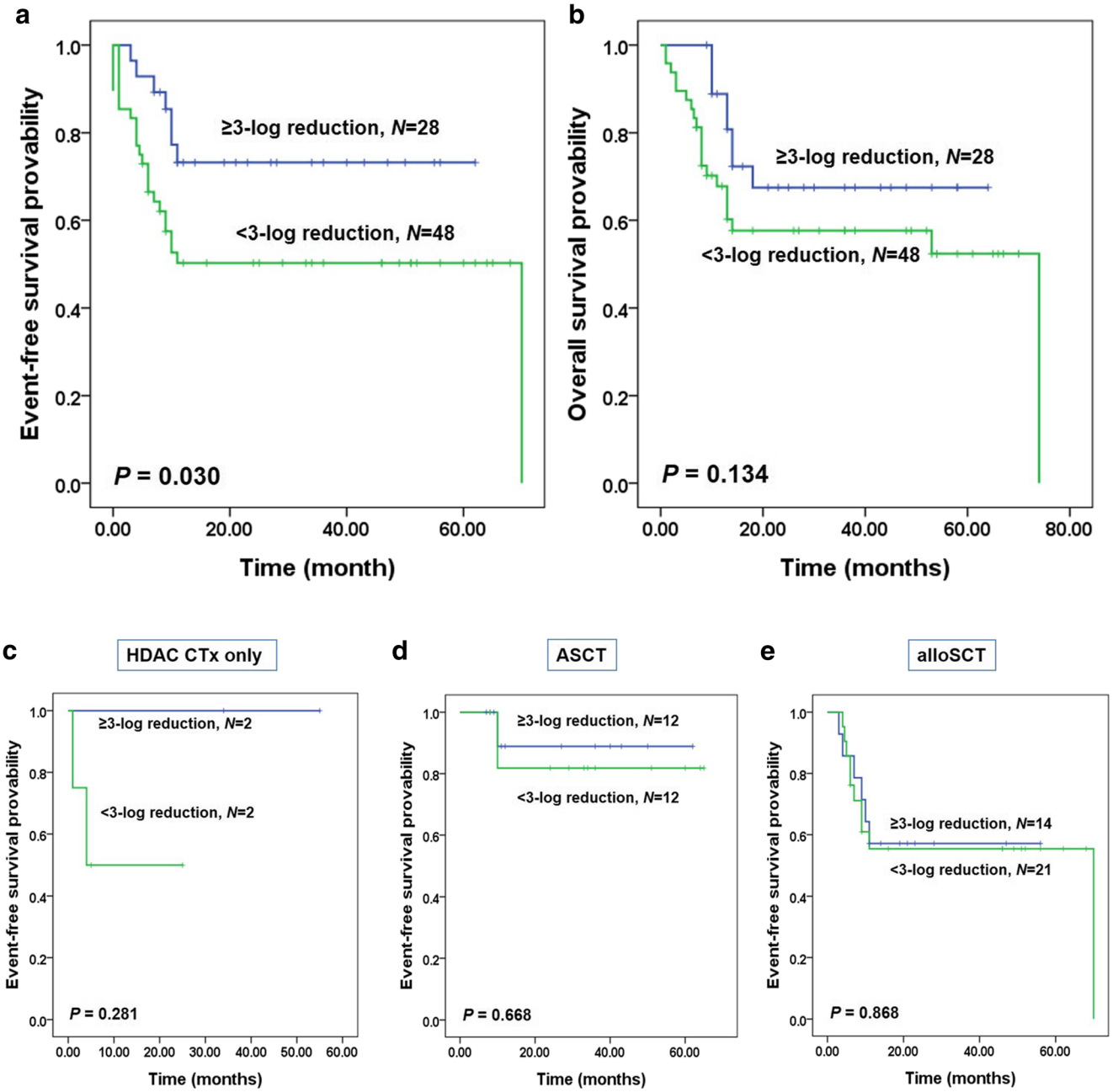

Fig. 5 Survival difference according to the minimal residual disease at the time of first consolidation chemotherapy in patients with t(8;21). **a**, **b** Event-free survival and overall survival by *RUNX1/RUNX1T1* qPCR 3-log reduction, and **c**–**e** event-free survival by *RUNX1/RUNX1T1* qPCR 3-log reduction according to post-remission treatment (high-dose cytarabine only, autologous and allogeneic stem cell transplantation)

Prognostic factors

Univariate analyses for patients with t(8;21) showed that age ($P < 0.001$), number of induction chemotherapy ($P < 0.001$), sex ($P = 0.027$), BM blast percentage ($P = 0.037$), loss of sex chromosome ($P = 0.045$), del(7q) ($P < 0.001$), response after first induction chemotherapy ($P < 0.001$), and disease status at the time of transplantation ($P = 0.003$) were significant prognostic factors indicating poor OS. Multivariate analysis for OS revealed that older age ($P = 0.001$), > 1 course of induction chemotherapy to achieve CR ($P = 0.033$), loss of sex chromosome ($P = 0.012$), del(7q) ($P < 0.001$), and second/third CR or no CR before SCT ($P = 0.043$ or $P = 0.001$) were independent prognostic variables. Univariate analyses for patients with inv(16) showed that age ($P < 0.001$), number of induction chemotherapy ($P = 0.043$), response after first induction chemotherapy ($P = 0.043$), and disease status at the time of transplantation ($P < 0.001$) were significant prognostic factors indicating poor OS. Multivariate analyses for OS revealed no CR at the time of transplantation was the only independent

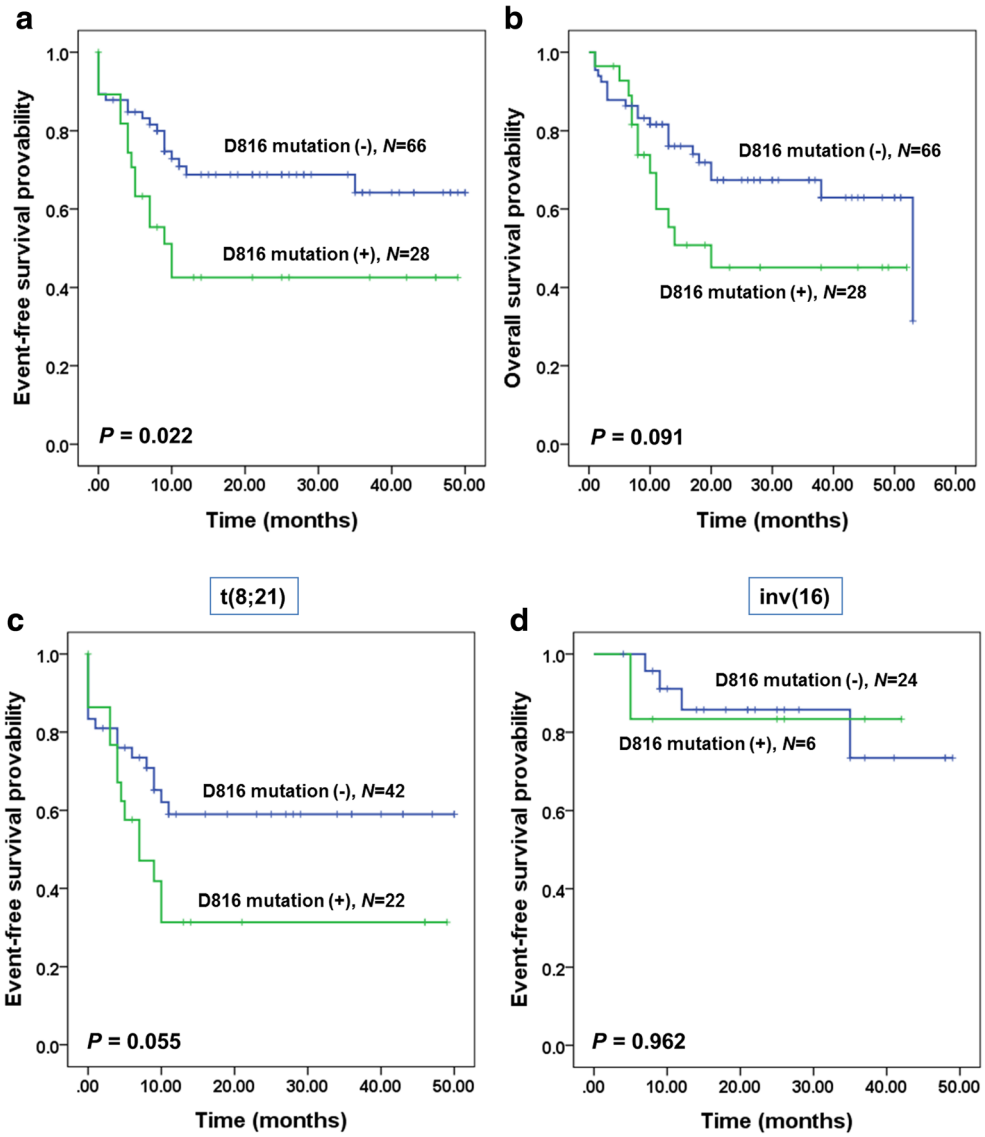

Fig. 6 Comparison of event-free survival and overall survival in patients with CBF-AML between cases with and without D816 mutation. **a**, **b** Event-free survival and overall survival in patients with CBF-AML. **c**, **d** Event-free survival in patients with CBF-AML according to cytogenetic abnormalities. **e**, **f** Overall survival in patients with CBF-AML according to cytogenetic abnormalities. **g**, **h** Event-free survival and overall survival in patients with CBF-AML who underwent allogeneic stem cell transplantation

prognostic variable in patients with inv(16) (Table 2). Patients with t(8;21) with del(7q) showed significantly poor OS than those without del(7q); therefore, all patients with del(7q) died < 2 years after diagnosis ($P < 0.001$). However, patients with inv(16) with del(7q) had better OS than those without (80.0% ± 12.6% and 57.4% ± 6.2%, respectively), but the difference was statistically insignificant. Monosomal karyotype, complex karyotype, del(9q), trisomy 8, and trisomy 22 did not have any statistically significant prognostic power in patients with t(8;21) and inv(16).

Discussion

The clinical characteristics and outcomes in patients with CBF-AML were analyzed using the Korean nationwide AML registry. Integrative data analysis of CBF-AML in Asian countries has been rarely reported, and the frequency of additional CBF-AML cytogenetic abnormalities between Western and Asian countries has not yet been compared. Korean AML registry data revealed that the frequency of del(9q) in patients with t(8;21) was lower than that in the German database (6.6% vs. 17%) (Fig. 1) [11], but similar to that in the Italian database (7.5%) [18]. The frequency of del(7q) in our data was higher than that in Italian data, especially in patients with inv(16) (9.3% vs. 1.8%) [18] and t(8;21) (2.2%), which was similar to data from India (2.4%) [19].

When analyzing patients who underwent SCT, the survival outcome between patients with t(8;21) and inv(16) undergoing SCT in the first CR was comparable, but the OS was different after the first CR. Our study revealed that survival of patients with t(8;21) undergoing alloSCT with second or third CR was significantly poorer than that of patients with inv(16) (Fig. 3). This result is consistent with that of the previous Japanese study that compared the two types of patients with CBF-AML who underwent SCT [20]. Therefore,

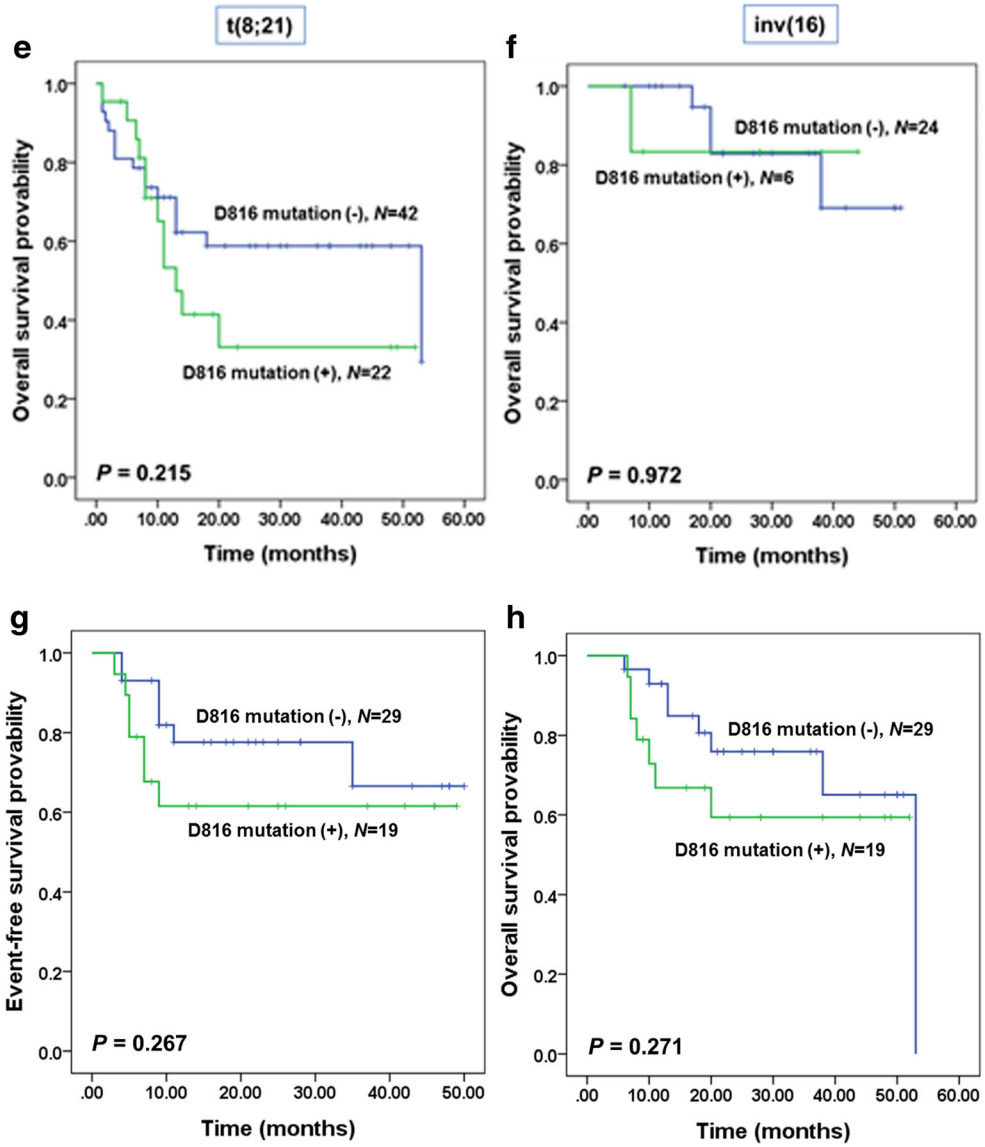

Fig. 6 (continued)

Table 2 Multivariate analyses for OS in CBF-AML patients

Variables	t(8;21)		Inv(16)	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Age (≥ 60 years vs. < 60 years)	4.79 (1.91–12.01)	0.001		
No. of induction chemotherapy (> 1 vs. 1 course)	2.88 (1.09–12.01)	0.033		
Loss of sex chromosome (yes vs. no)	2.51 (1.23–5.15)	0.012		
del(7q) (yes vs. no)	27.73 (5.35–143.71)	< 0.001		
Disease status prior to HSCT				
CR2/3 vs. CR1	2.36 (1.03–5.42)	0.043	0.76 (0.16–3.48)	0.718
Not CR vs. CR1	4.94 (1.95–12.52)	0.001	16.77 (2.62–107.36)	0.003

OS, overall survival; *CBF-AML*, core-binding factor acute myeloid leukemia; *CR*, complete remission

different treatment strategies such as more intensive or new agents for consolidated treatment should be used in patients with t(8;21) who have poor prognostic factors for early relapse. Furthermore, clinical trials are needed to improve the outcomes in relapsed patients with t(8;21).

Patients with t(8;21) and inv(16) undergoing ASCT and alloSCT had a similar survival rate when they underwent SCT during the first CR. Consistent with our results, the European Group for Blood and Marrow Transplantation (EBMT) reported that the survival rate of patients with t(8;21) who underwent alloSCT was not significantly different from those who underwent ASCT [21]. This finding is similar to that of the previous Japanese study group comparing SCT results in CBF-AML [20], suggesting that ASCT can be considered as the post-remission therapy for selected patients with CBF-AML; however, whether the use of ASCT is more beneficial for patients with CBF-AML than high-dose cytarabine, consolidation chemotherapy alone as post-remission treatment remains unclear. Nakasone et al. showed that ASCT based on the infusion of peripheral blood stem cells with undetectable minimal residual disease (MRD) using *RUNX1-RUNX1T1* or *CBFβ-MYH11* PCR (PCR-negative graft) was associated with excellent EFS [22]. This ASCT strategy using PCR-negative graft can be beneficial in patients with CBF-AML, especially with adverse factors or remnant MRD in the BM.

Recently, RIST has been increasingly used in patients with myeloid malignancies and is associated with lower non-relapse mortality (NRM) than myeloablative conditioning SCT while preserving the graft-versus-leukemia (GVL) effect. A previous study evaluating the role of alloSCT in the CR1 of patients with CBF-AML showed no improvement in the OS after SCT, because the relapse reduction was offset by a high NRM rate [23]. This might have resulted from the fact that the majority of the patients received myeloablative conditioning regimen, and the NRM was considerably high. RIST has been known to reduce NRM while preserving the antileukemic efficacy and is therefore expected to improve the transplant outcome. In the current study, patients with t(8;21) who underwent RIST had marginally improved OS compared to those who underwent myeloablative conditioning SCT, especially in patients who achieved first CR (3-year OS, 93.8% vs. 67.0%) or relatively older aged patients (3-year OS, 57.33% vs. 37.4%). Because patients with t(8;21) had relatively poor prognosis after relapse, but not those with inv(16), patients with unfavorable factors may be considered to undergo alloSCT in the first CR. In this situation, RIST may be the appropriate option for alloSCT to reduce NRM while conserving the GVL effect in patients with high-risk factors or in relatively older patients who are vulnerable to undergo myeloablative conditioning SCT.

Molecular analysis, including *RUNX1-RUNX1T1* qPCR monitoring after induction treatments, showed good prognostic values comparable to previous reports [13, 15, 24, 25]. Most of them used more log reduction or lower qPCR levels after a consolidation therapy to predict decreased relapse and superior survival outcome. The role of *RUNX1-RUNX1T1* qPCR in predicting the survival outcome was also considered. This poor prognostic outcome can be overcome using ASCT or alloSCT as post-remission treatment but cannot be overcome with high-dose cytarabine chemotherapy alone (Fig. 5). *c-Kit* gene mutation could also be considered in predicting poor survival outcome, which is consistent in patients with t(8;21), but did not affect those with inv(16). AlloSCT also can beneficially overcome the poor prognosis in patients with *c-Kit* mutation (Fig. 6). Yoon et al. showed a higher NRM than relapse rate after SCT in patients with *c-Kit* mutation [15], which might be caused by a higher proportion of myeloablative conditioning alloSCT producing higher therapy-related mortality. Based on these findings, RIST may be the appropriate post-remission treatment strategy in *c-Kit* positive or no 3-log reduction of *RUNX1-RUNX1T1* qPCR patients with t(8;21) after the induction chemotherapy. The poor outcome of *c-Kit* mutation in patients with t(8;21) can be overcome by new tyrosine kinase inhibitors, which are selectively active against specific *Kit* mutations. Imatinib is active against various exon 8 and exon 17 mutations involving codon N822, but not with codon D816, which can be successfully treated with dasatinib and midostaurin [26, 27]. Recently, the German-Austrian AML Study Group conducted phase Ib/IIa dasatinib study in first-line treatment of patients with CBF-AML, in which dasatinib was added to intensive induction and consolidation chemotherapy, and administered as single agent for one-year maintenance [28]. In this study, dasatinib, in combination with chemotherapy as well as single agent during the maintenance treatment, showed acceptable toxicity profile and favorable outcomes. AlloSCT is also another option to overcome the poor outcome of D816 mutation in patients as shown in our study (Fig. 6g, h). Interestingly, D816 mutation did not affect the survival prognosis in patients with inv(16), but significantly decreased the survival in patients with t(8;21) (Fig. 6c–f). In t(8;21) AML, *c-Kit* mutations occur mostly in exon 17 and confer adverse prognosis, whereas the prognostic significance of *c-Kit* mutations in inv(16) is not well established. To confirm whether the prognostic significance of D816 mutation was observed in patients with inv(16), further studies with larger number of patients should be conducted.

Multivariate analysis on the prognostic factors of OS in patients with CBF-AML was performed and revealed that del(7q) is the most powerful prediction factor of poor outcomes, especially in patients with t(8;21) (hazard ratio, 27.23; $P < 0.001$). All patients with t(8;21) who had del(7q)

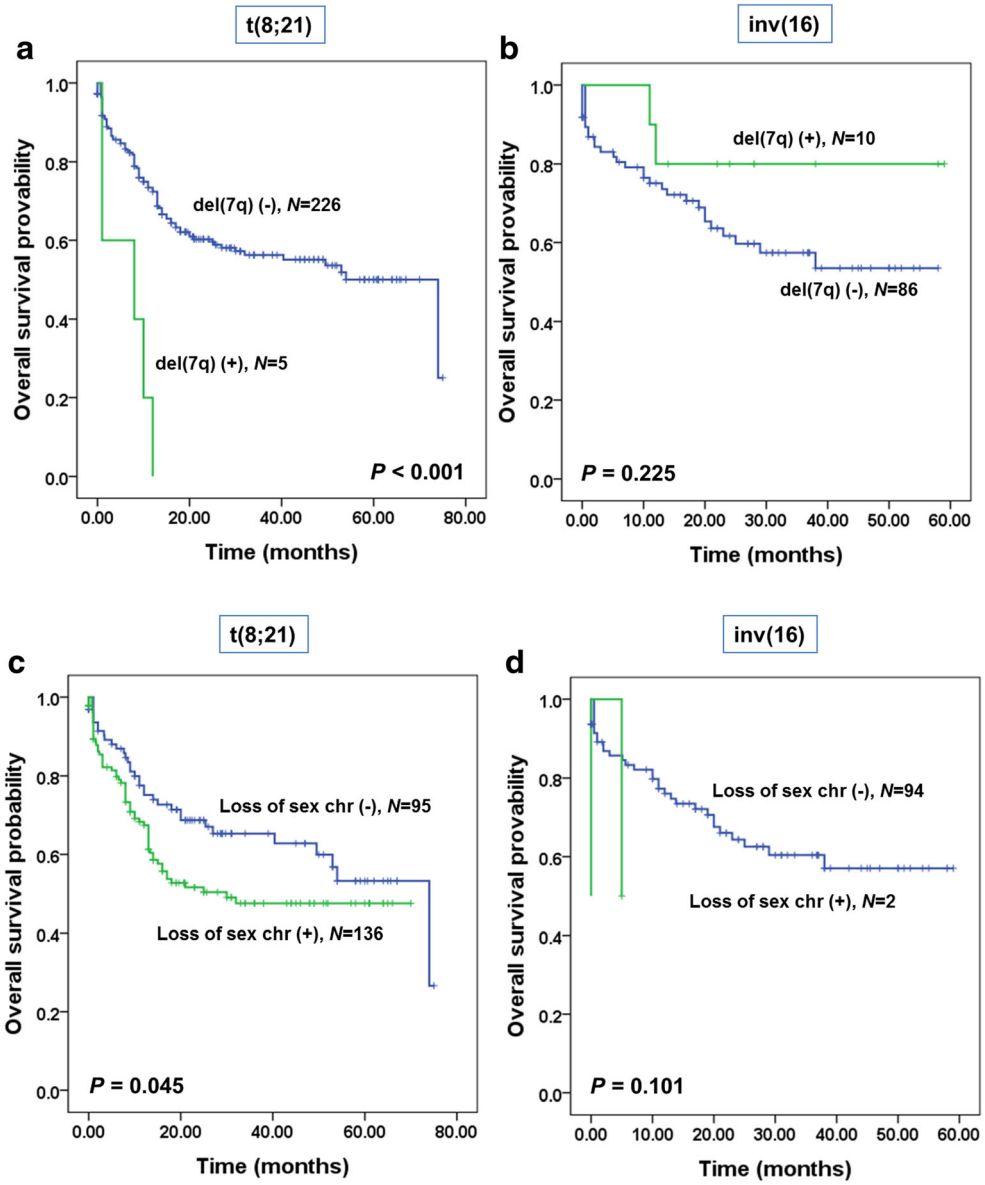

Fig. 7 Comparison of overall survival in patients with CBF-AML according to cytogenetic abnormalities between cases with or without del(7q) [(**a**) and (**b**), respectively], and with or without loss of sex chromosome [(**c**) and (**d**), respectively]

at the time of diagnosis died in < 20 months (Fig. 7a). However, in patients with inv(16), the presence of del(7q) showed a different survival outcome compared to those with t(8;21). The del(7q) is consistently found in malignant myeloid disorders, such as myelodysplastic syndrome and AML, and is particularly associated with therapy-related diseases. In adults, del(7q) patients are generally > 50 years and have a poor prognosis with short survival time [29, 30]. The prognostic significance of del(7q) is still unknown in patients with CBF-AML, which is an interesting factor in these patients. Therefore, further studies in patients with CBF-AML, especially different survival outcomes of del(7q) among patients with t(8;21) and inv(16), should be conducted in the future.

In conclusion, we evaluated the nationwide CBF-AML registry data of an Asian country, and showed the different frequencies of del(9q) and del(7q) cytogenetic abnormalities in patients of a Western and an Asian country with t(8;21) and inv(16). The survival outcome in patients with CBF-AML was similar in those who underwent alloSCT or ASCT in the first CR. However, the outcomes were significantly different between t(8;21) and inv(16) when they underwent alloSCT beyond the first CR. Therefore, these two types of CBF-AML should be treated differently when applying SCT, especially based on important prognostic factors, including *c-Kit* (D816) mutation or 3-log *RUNX1-RUNX1T1* qPCR reduction after induction chemotherapy. When undergoing alloSCT in

CBF-AML, RIST can be applied in a specific subgroup of these patients. The prognostic significance of del(7q) in different subtypes of CBF-AML greatly varies and should be focused on future studies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was waived off, because this study used retrospective data from the Korean AML registry, and there were no interventions in the patients.

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