first in the marrow, and occasionally *PML-RARA* transcripts do not become detectable in PB until time of hematologic relapse.[90,130] Therefore, in some patients the monitoring of PB alone (even if performed monthly) could reduce the opportunity for successful delivery of preemptive therapy to prevent disease progression. Because the kinetics of disease relapse can be relatively rapid,[130] preemptive therapy has to be started promptly to prevent frank relapse. The lack of specific data about optimal management for patients with documented molecular relapse leads us to assume a similar strategy to that recommended for patients with visible relapse (see section 7.2).

7.2. Hematologic relapse

Before the demonstration of the striking activity of ATO in APL, salvage therapy usually consisted of the readministration of ATRA and chemotherapy for induction, generally containing high-dose cytarabine and an anthracycline, followed by further chemotherapy and/or HSCT.[95,133-135] Given the high antileukemic efficacy of ATO in relapsed patients and its relatively favorable toxicity profile, this agent is presently regarded as the best treatment option in this setting.[10,136] Preliminary studies with ATO as salvage therapy were carried out by the Shanghai group in the early 1990s,[137] and then subsequently replicated in a Western population in whom the disease had either relapsed or not responded after standard treatment with ATRA and/or anthracycline-based chemotherapy.[138,139] Confirmation of the high and sustained efficacy of ATO in patients with relapsed/refractory APL has been provided by more recent studies.[140-144] CR rates in these trials were 80% to 90% and, in those studies that evaluated survival, 50% to 70% of patients were alive at 1 to 3 years. Current evidence suggests that use of at least 2 cycles of ATO results in the achievement of second molecular CR in nearly 80% of cases.[145] The best consolidation strategy after ATO induced second remission is unknown; options include continued treatment with repeated cycles of ATO, the use of standard chemotherapy in combination with ATRA and/or ATO, and HSCT. While there is some evidence to suggest that treatment intensification with HSCT[146] or chemotherapy[141] may improve outcomes of patients achieving second remission with ATO, selection of the most appropriate treatment option, as well as the modality of HSCT, depends on a range of prognostic and logistic variables (eg, molecular status, duration of first remission, age, donor availability). There are no strict guidelines as regards the choice of autologous HSCT versus allogeneic HSCT in second CR. Autologous HSCT is obviously associated with a lower transplantation-related mortality than allogeneic HSCT and is a reasonable option in patients without detectable MRD and prolonged (>1 year) first CR. Allogeneic HSCT involves a greater risk of nonrelapse mortality (transplantation-related) but offers a greater antileukemic activity due to the graft-versus-leukemia effect. Allogeneic HSCT could be recommended in patients failing to achieve a second molecular remission and for those with short first CR duration.[145] For patients unfit to proceed to HSCT, the available options include repeated cycles of ATO with or without ATRA/standard chemotherapy. In addition, the antiCD33 monoclonal antibody conjugated to calicheamicin (gemtuzumab ozogamicin) appears to induce a high rate of molecular responses even as a single agent in advanced disease.[147,148] Therefore, although the precise role of this agent in the management of relapsed APL remains unsettled, it should be explored further in the treatment strategy for relapsed patients.

7.3. CNS and other extramedullary relapses

At least 1 in 10 relapses of APL have a CNS component and therefore involvement of extramedullary sites (particularly CNS) should be considered in patients subject to molecular or hematologic relapse.[96-98] Management of relapse in the CNS and other extramedullary sites in patients with APL is a challenging issue for which there is a notable lack of information. Extramedullary relapse, including in the CNS, can occur either in isolation or associated with BM involvement as a first relapse, but also after one or more hematologic relapses. Optimal management and outcome of APL patients in these different situations have not been critically assessed. Relapse at extramedullary sites occurs in up to 3% to 5% of patients and is emerging as a new therapeutic issue that would need international cooperation to prospectively evaluate treatment strategies in sufficient numbers of cases. In the meantime, it seems pragmatic to pursue an approach derived from experiences of the management of extramedullary relapse in acute lymphoblastic leukemia and other subtypes of acute myeloblastic leukemia. In this regard, induction treatment of CNS relapse would consist of weekly triple intrathecal therapy (ITT) with methotrexate, hydrocortisone, and cytarabine until complete clearance of blasts in the CSF, followed by 6 to 10 more spaced out ITT treatments as consolidation. Because CNS disease is almost invariably accompanied by hematologic or molecular relapse in the marrow, systemic treatment should also be given. The timing of this may be dictated by clinical circumstances. One approach could be to give ATO and ATRA as a nonmyeloablative treatment approach while ITT is being delivered. Chemotherapy regimens with high CNS penetrance (eg, high-dose cytarabine) have been used in this situation and in patients responding to treatment, allogeneic or autologous transplant should be the consolidation treatment of choice including appropriate craniospinal irradiation. In case of granulocytic sarcoma, wherever it is localized, radiation and intensive systemic therapy might be considered.

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Authorship

Contribution: M.A.S. drafted the manuscript; and D.G. and F.L.-C. helped to integrate all changes and suggestions made by the rest of the authors (M.S.T., B.L., P.F., E.H.E., T.N., E.L., T.B., H.D., and A.K.B.), who also reviewed the manuscript and contributed to the final draft.

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Appendix

Classification of evidence levels

These classifications are used in Tables 1 through 4.

Ia. Evidence obtained from meta-analysis of randomized controlled trials.

Ib. Evidence obtained from at least one randomized controlled trial.

IIa. Evidence obtained from at least one well-designed controlled study without randomization.

IIb. Evidence obtained from at least one other type of well-designed quasi-experimental study.

III. Evidence obtained from well-designed nonexperimental descriptive studies, such as comparative studies, correlation studies, and case studies.

IV. Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

Classification of grades of recommendations

A. Requires at least one randomized controlled trial as part of a body of literature of overall good quality and consistency addressing specific recommendation (evidence levels Ia and Ib).

B. Requires the availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation (evidence levels IIa, IIb, and III).

C. Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality (evidence level IV).

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ORIGINAL ARTICLE

Management of infection in patients with acute leukemia during chemotherapy in Japan: questionnaire analysis by the Japan Adult Leukemia Study Group

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Abstract Guidelines for the management of febrile neutropenia (FN), deep fungal infection or use of granulocyte colony-stimulating factor (G-CSF) published in the US and Europe cannot be directly applied in other countries. In this study, we undertook a questionnaire survey of member institutions of the Japan Adult Leukemia Study Group to investigate the status of, and problems with, the management of infectious complications in patients with acute leukemia. The questionnaire consisted of 52 multiple-choice questions covering therapeutic environment, antibacterial, and antifungal prophylaxis, empirical therapy (ET) for FN, and use of G-CSF. The results were compared to a previous survey performed in 2001. Usable responses were received from 134 of 184 (71.7%) institutions. With regard to antibacterial prophylaxis, fluoroquinolones and sulfamethoxazole-trimethoprim were most commonly used. Regarding antifungal prophylaxis, the most frequently used agent was fluconazole, followed by itraconazole. In ET for FN, monotherapy with cephems or carbapenems accounted for almost all of the responses. Most respondents indicated that they used micafungin (MCFG) in ET. Prophylactic use of G-CSF during remission induction therapy in acute myeloid leukemia was reported by only 4% of respondents. Strategies for antibacterial and antifungal prophylaxis or treatment of FN should be reviewed and updated as needed.

Keywords JALSG · Febrile neutropenia · Prophylaxis · G-CSF · Leukemia

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1 Introduction

Recent advances in chemotherapy and transplantation have improved the treatment of adult acute leukemia. The major complication during chemotherapy for acute leukemia is infection, such as sepsis and pneumonia, highlighting the clinical importance of preventing and treating infection in these patients. Guidelines for the management of febrile neutropenia (FN) or deep fungal infection or use of colony-stimulating factors (CSFs) published in the US and Europe cannot necessarily be applied in other countries due to differences in national health systems and in climate, especially humidity. For this reason, a guideline specific to Japanese settings was released in 1998 [1], and subsequently revised in 2004 [2]. A barrier to the development of such guidelines is the lack of domestic information on the actual management of infectious complications. The Japan Adult Leukemia Study Group (JALSG) was established in 1987 and is the largest adult leukemia study group in Japan. Although the identical chemotherapeutic regimen is administered by all JALSG-member institutions, supportive care is decided by each institution. A fact-finding questionnaire on the management of infectious complications in patients with acute leukemia, developed by the Supportive Care Committee of the JALSG, was distributed to all 196 and 187 member institutions in 2001 and 2007, respectively. In this report, we evaluate the results of the follow-up 2007 questionnaire. In particular we investigated

the current status of, and problems with, the management of infectious complications according to members of the JALSG, especially focusing on current antibiotic regimens. The results were compared to the previous analysis performed in 2001 [3, 4].

2 Methods

A questionnaire on infectious complications in patients with acute leukemia was mailed to all members of the JALSG in July 2007, and the results were collected by the end of September 2007 and analyzed. The questionnaire consisted of 52 multiple-choice questions covering the therapeutic environment, antibacterial prophylaxis, antifungal prophylaxis, empirical therapy (ET) for FN and treatment in patients unresponsive to ET, therapy for deep fungal infection, the use of anti-methicillin-resistant *Staphylococcus aureus* (MRSA) drugs, and the use of granulocyte colony-stimulating factor (G-CSF). Responses were calculated as percentage of respondents. For all questions, multiple answers were allowed giving the possibility of scores greater than 100%. Respondents were instructed to complete the questionnaire as follows: in principle, they should assume the development of neutropenia during remission induction therapy for acute myeloid leukemia (AML), as it is a frequent complication of infection; answers should reflect actual practice rather than literature knowledge or goals; each JALSG institution should answer according to its own practice, and whenever possible the questionnaire should be completed by a physician involved in daily practice. Approval for the study was obtained from the JALSG. The results of the current survey were compared with those from the 2001 survey.

3 Results

Usable responses were received from 134 out of 184 institutions (Appendix 1), giving a response rate of 71.7% for the 2007 survey (compared with a response rate of 63.8% for the 2001 survey). Answers to the main questions are summarized below.

3.1 Therapeutic environment

Overall, 98% of respondents indicated that their institution had a single- or multi-patient rooms with high efficiency particulate air filtration and laminar airflow (HEPA/LAF) units, and 76% said that a HEPA/LAF unit room was often used during AML remission therapy (vs. 37% in the survey of 2001). Given the fact that the same facility may use a variety of different ward settings for the management of neutropenia during AML remission induction, the respondents were allowed to select two alternative settings used at their institution, if applicable. On this basis, it was found that 66% used a single-patient room with HEPA/LAF unit, 27% used a multi-patient room with HEPA/LAF unit, 44% used a single-patient conventional isolation room with a portable HEPA/LAF system, and 19% used a multi-patient conventional isolation room with a portable HEPA/LAF system.

3.2 Prophylaxis

Oral drugs commonly used for antibacterial and antifungal prophylaxis are listed in Table 1. With regard to antibacterial prophylaxis, fluoroquinolones (58%), sulfamethoxazole-trimethoprim (ST, 37%) and polymixin-B (26%) were most commonly used, while 13% of respondents indicated that they did not use prophylaxis against bacterial infection. In contrast, in the 2001 survey the three most frequently used prophylactic drugs for bacterial infection

Table 1 Comparison of survey results regarding the drugs used for antibacterial and antifungal prophylaxis in Japanese hospitals in 2007 (134 institutions) and 2001 (125 institutions)

	2007 (%)	2001 (%)
Antibacterial agent		
1. PL-B	26	42
2. ST	37	30
3. Fluoroquinolones	58	52
4. Combinations of 1,2 and/or 3 above	3	5
5. Did not respond	3	2
6. No approved policy[a]	7	4
7. Did not use prophylaxis	13	6
Antibacterial agent		
1. FLCZ 100-200 mg	64	47
2. FLCZ 400 mg	1	3
3. MCFG 50 mg	1	NA
4. MCFG 75 mg	0	NA
5. ITCZ cap/os	25	14[b]
6. AMPH-B syrup	5	50[c]
7. Combination of AMPH-B and FLCZ	2	0
8. Did not respond	1	4
9. Did not use prophylaxis	8	3

Percentages exceed 100% since respondents could tick more than one box if applicable

NA not available in 2001, *PL-B* polymixin-B, *ST* sulfamethoxazole-trimethoprim, *MCFG* micafungin, *FLCZ* fluconazole, *ITCZ* itraconazole, *cap* capsule, *os* oral solution, *AMPH-B* amphotericin B

[a] Treatment policy not finalized by the hospital and thus no approved recommendation available, and decision was on a case by case basis

[b] Only capsules (200 mg/day) were available in 2001

[c] 300–2,400 mg/kg (2001)

were fluoroquinolones (52%), polymixin-B (42%) and ST (30%), and 6% of respondents gave no prophylaxis. Regarding antifungal prophylaxis, the most frequently used agent was fluconazole (FLCZ, alone or in combination) (67%) followed by itraconazole (ITCZ) (oral solution and capsule, 25%), and amphotericin B (AMPH-B, alone or in combination) syrup (7%), compared with FLCZ (50%), AMPH-B syrup (50%), and ITCZ (14%) in 2001. No prophylaxis for fungal infection was given by 8% of respondents (3% in 2001 survey). ST was used in remission induction therapy (32%) and consolidation therapy (32%) in patients with AML, and also in remission induction therapy (63%) and consolidation therapy (59%) in acute lymphoblastic leukemia (ALL).

3.3 Empirical antibiotic therapy

With regard to FN, intravenous treatment with antibiotics in patients with FN was given prophylactically before the onset of fever by 3% of respondents, and after the onset of fever at ≥37, ≥37.5, and ≥38°C by 4, 37, and 53%, respectively. Drugs used in ET for FN are listed in Table 2. Monotherapy with either cephems (77%) or carbapenems (31%) accounted for the majority of responses. Dual therapy which included aminoglycosides was used by 31%, including combinations with cephems (20%) or carbapenems (5%). Results from the 2001 survey showed that cephems plus aminoglycoside were used by 37% of respondents, cephems alone by 29%, and carbapenems alone by 21%.

The timing of anti-MRSA drug administration was investigated, and the results showed that administration was started by 12% of respondents if the first-line antibacterial therapy was ineffective, and by 41% if second-line or subsequent therapy was ineffective. Thirty-four percent of respondents started administration of anti-MRSA drugs if any gram-positive strain was detected in culture, while 7% said it was not used until a definite diagnosis of MRSA infection was made, and 12% said it was used as first-line therapy if the patient was at a high risk according to the US guidelines. Among anti-MRSA drugs, the initial drug prescribed was most frequently vancomycin (80%), followed by teicoplanin (13%), arbekacin (5%), or linezolid (2%).

Table 2 Comparison of survey results regarding empirical antibacterial therapy for febrile neutropenia in Japanese hospitals in 2007 (134 institutions) and 2001 (125 institutions)

Antibacterial agent	2007 (%)	2001 (%)
1. Cephems	77	29
2. Cephems + AG	20	37
3. Carbapenems	31	21
4. Carbapenems + AG	5	16
5. Antipseudomonal penicillins	5	1
6. Antipseudomonal penicillins + AG	5	14
7. Cephems + Antipseudomonal penicillin	0	4
8. Cephems + Antipseudomonal penicillin + AG	0	1
9. AntiMRSA[a] + Cephems	1	1
10. AntiMRSA[a] + Carbapenems	0	2
11. AntiMRSA[a] + Cephems + AG	0	0
12. AntiMRSA[a] + Carbapenems + AG	0	0
13. Others	1	10
14. None	0	0

Percentages exceed 100% since respondents could tick more than one box if applicable

AG aminoglycoside

[a] With regard to anti-MRSA, the 2001 questionnaire only enquired about vancomycin

3.4 Empirical and targeted antifungal therapy

With regard to antifungal therapy, standard ET and a preemptive/presumptive approach using β-glucan/galactomannan or CT-scan was adopted by 54 and 42% of respondents, respectively. The timing of initiation of antifungal therapy was selected empirically by 54% of respondents, while 20% said it was preemptive and 22% said it was done presumptively. Among respondents who used an empirical approach for antifungal treatment, 88% prescribed micafungin (MCFG) either with or without antifungal prophylaxis. The percentage of each antifungal agent is shown in Table 3. In targeted therapy for *Candida albicans*, *Candida glablata*, and *Candida parapsilosis*, the

Table 3 Drugs used for empirical antifungal therapy in respondents of the 2007 survey of Japanese hospitals who used an empirical approach ($n = 73$)

Antifungal agent	Patients with febrile neutropenia	
	Without antifungal prophylaxis 2007 (%)	With antifungal prophylaxis 2007 (%)
1. FLCZ	4	8
2. MCFG	11	77
3. VRCZ	3	12
4. ITCZ	0	4
5. L-AMB	1	3
6. AMPH-B	1	0
7. Others	0	0

Percentages exceed 100% since respondents could tick more than one box if applicable

FLCZ fluconazole, *MCFG* micafungin, *VRCZ* voriconazole, *ITCZ* itraconazole, *L-AMB* liposomal amphotericin B, *AMPH-B* amphotericin B

three most commonly used drugs were FLCZ, MCFG, and voriconazole (VRCZ). The rates of FLCZ use for these organisms were 57, 2, and 7%, respectively; rates for MCFG use were 28, 50, and 26%, and for VRCZ were 7, 27, and 36%, respectively. In the treatment of invasive pulmonary aspergillosis (IPA), VRCZ and L-AMB were used by 69 and 21% of respondents, respectively. This was markedly different from the 2001 survey, in which the main treatments used for IPA were AMPH-B (80%) and combination treatment (18%) (Table 4).

In fungemia, susceptibility to antimycotic drugs was tested by only 28% of responders. ß-D-glucan measurement was used for monitoring or early diagnosis of fungemia by 99% of facilities, and most respondents (53%) reported that the frequency of ß-D-glucan testing was once a week. It was performed either by an outside contractor (46%, including Biochemical Seikagaku 45% and Wako 1%) or in-house using a Wako test kit (34%) or using a biochemical method such as Fungitec (9%). With regard to galactomannan antigen, 75% of facilities used this method for the purpose of diagnosis of IPA, compared with 57% in 2001. Most responders (71%) did not perform genetic diagnosis.

3.5 Use of G-CSF

Because the use of G-CSF in the treatment of AML and ALL may differ, questions were asked separately for AML remission induction therapy (disappearance of blasts in peripheral blood), AML consolidation therapy (with or without high dose cytarabine), ALL remission induction therapy, and ALL consolidation therapy. The results are shown in Tables 5 and 6. While G-CSF was used primarily in the treatment of life-threatening infections in patients with AML (25–37%; versus 28% in the 2001 survey), prophylactic use of G-CSF before the onset of fever was common in patients with ALL (63–65%), compared with the 2001 survey rates of 52–54%. Only 4% of respondents used prophylactic G-CSF during remission induction therapy in AML.

4 Discussion

This survey adds additional information to the previous 2001 survey on the treatment practices of member hospitals of the JALSG with regard to infectious complications in patients with acute leukemia during chemotherapy in Japan. This is useful because guidelines for the management of FN, deep fungal infection, or the use of G-CSF published in the US and Europe cannot necessarily be applied in other countries.

The proportion of institutions using single- or multi-patient rooms with a HEPA/LAF unit for AML remission therapy increased from 37% in 2001 to 76% in 2007. Of the member institutions of JALSG, 98% have a room with HEPA/LAF unit. The National Health Insurance reimbursement for the treatment of leukemia in a room with HEPA/LAF unit is 30,000 yen (about 300 US dollars) per

Table 4 Comparison of survey results regarding targeted antifungal therapy for fungal infection in Japanese hospitals in 2007 (134 institutions) and 2001 (125 institutions)

Antifungal agent	*Candida albicans* 2007 (%)	*Candida glablata* 2007 (%)	*Candida parapsilosis* 2007 (%)	Candidemia 2001 (%)	Invasive pulmonary aspergillosis 2007 (%)	Invasive pulmonary aspergillosis 2001 (%)
1. FLCZ	57	2	7	26	0	0
2. MCFG	28	50	26	NA	4	NA
3. VRCZ	7	27	36	NA	69	NA
4. ITCZ	1	4	9	0	1	2
5. L-AMB	3	13	16	NA	21	NA
6. AMPH-B	2	4	4	58	3	80
7. MCZ	0	0	0	3	0	0
8. FLCZ + AMPH-B	0	0	0	12	0	0
9. 5FC + AMPH-B	0	0	0	1	0	2
10. ITCZ + AMPH-B	0	0	0	1	0	16
11. MCFG + VRCZ	0	0	0	NA	1	NA
12. No approved policy[a]	1	1	2	0	1	0
13. Others	0	0	0	0	0	0

Percentages exceed 100% since respondents could tick more than one box if applicable

NA not available in 2001, *FLCZ* fluconazole, *MCFG* micafungin, *VRCZ* voriconazole, *ITCZ* itraconazole, *L-AMB* liposomal amphotericin B, *AMPH-B* amphotericin B, *MCZ* miconazole, *5FC* flucytosine

[a] Treatment policy not finalized by the hospital and thus no approved recommendation available, and decision was on a case by case basis

Table 5 Comparison of survey results regarding the use of G-CSF in AML in Japanese hospitals in 2007 (134 institutions) and 2001 (125 institutions)

Clinical status	AML remission induction 2007 (%)	AML remission induction 2001 (%)	AML consolidation high dose Ara-C regimen 2007 (%)	AML consolidation no high dose Ara-C regimen 2007 (%)	AML consolidation 2001 (%)
1. Prophylaxis for neutropenia	4	3	13	7	8
2. FN with ET	7	12	13	10	10
3. FN if refractory to ET	16	20	17	19	19
4. Clinically documented infection	26	23	24	31	21
5. Microbiologically documented infection	11	6	9	10	5
6. Life-threatening infection	37	28	25	30	28
7. Not used	10	7	6	7	7
8. No approved policy[a]	1	3	3	2	3
9. Others	1	3	4	2	2

G-CSF granuloyte-colony stimulating factor, *AML* acute myeloid leukemia, *Ara-C* cytarabine, *FN* febrile neutropenia, *ET* empiric antibiotic therapy

[a] Treatment policy not finalized by the hospital and thus no approved recommendation available, and decision was on a case by case basis

Table 6 Comparison of survey results regarding the use of G-CSF in ALL in Japanese hospitals in 2007 (134 institutions) and 2001 (125 institutions)

Clinical status	ALL remission induction 2007 (%)	ALL remission induction 2001 (%)	ALL consolidation 2007 (%)	ALL consolidation 2001 (%)
1. Prophylaxis for neutropenia	65	52	63	54
2. FN with ET	10	20	10	18
3. FN if refractory to ET	13	14	14	13
4. Clinically documented infection	6	2	6	4
5. Microbiologically documented infection	5	2	6	2
6. Life-threatening infection	6	1	5	1
7. Not used	1	0	1	1
8. No approved policy[a]	2	3	3	4
9. Others	2	5	3	4

G-CSF granulocyte-colony stimulating factor, *ALL* acute lymphoblastic leukemia, *FN* febrile neutropenia, *ET* empiric antibiotic therapy

[a] Treatment policy not finalized by the hospital and thus no approved recommendation available, and decision was on a case by case basis

patient per day in Japan. HEPA/LAF units are quite effective in the management of fungal infection, and this administrative policy did much to help increase the number of institutions in which a room with a HEPA/LAF unit is available, not only for patients receiving hematopoietic stem cell transplantation, but also for patients with leukemia.

The prophylactic use of fluoroquinolones during neutropenia after chemotherapy in patients with AML is controversial. In the current survey, 58% of respondents indicated that they used fluoroquinolones. The Infectious Disease Society of America (IDSA) guideline published in 2002 did not recommend the routine use of antibiotic prophylaxis in afebrile neutropenic patients except for ST, which was used to prevent *Pneumocystis jiroveci*. In contrast, a large-scale meta-analysis published in 2005 reported that all-cause mortality, as well as infection-related mortality, fever and the risk of documented infection, were lower in patients receiving fluoroquinolones compared with a placebo group [6]. A prospective randomized study published in the same year by Bucaneve and colleagues also concluded that fluoroquinolones were effective in the prophylactic treatment of bacterial infections, with the risk of fever, microbiologically documented infection, and bacteremia reduced to a greater extent in a levofloxacin group compared with a placebo group [7]. Since fluoroquinolone use has the potential to increase the risk of producing fluoroquinolone resistant gram-negative bacilli, this may raise some epidemiological concerns; nonetheless, fluoroquinolones can be useful for prophylaxis, particularly in patients with neutropenia of long duration, such as during the chemotherapeutic treatment of leukemia.

With regard to antifungal prophylaxis, the most frequently used agent was FLCZ, at 67%, followed by ITCZ (oral solution and capsule), at 25%. In contrast, use of amphotericin (as AMPH-B syrup) was only 7%. Compared to the previous survey, the use of AMPH-B syrup decreased markedly. Recently, a large-scale meta-analysis comparing anti-fungal prophylaxis with placebo, no treatment, or nonsystemic antifungals in cancer patients after chemotherapy was reported [8]. According to this analysis, the use of antifungal prophylaxis in patients with acute leukemia resulted in the reduction of fungal-related mortality rates and documented invasive fungal infections. There was a reduction in all-cause mortality, which did not reach statistical significance. This meta-analysis also found that ITCZ, posaconazole, and amphotericin (i.e. drugs with anti-mold activity), rather than FLCZ, reduced the risk of documented aspergillus infection and possibly had some effect on all-cause mortality [8]. The incidence of invasive fungal infection and the species of offending organisms varied widely between institutions, and the local epidemiology of fungal infections is very important in making therapeutic choices. If IPA is prevalent at institutions, agents with anti-mold activity, such as ITCZ, are more appropriate than FLCZ for antifungal prophylaxis. On the basis of this background, a nationwide epidemiological investigation of IPA is being undertaken in Japan and the results are awaited with keen interest.

Among patients with fever, treatment of those with neutropenia was primarily symptom-based, with 53% initiating treatment in those with a temperature of 38°C. With regard to empirical therapy for FN, monotherapy with cephems or carbapenems was most common, while in patients unresponsive to empirical therapy, the addition of, or change to, cephems, aminoglycosides, or carbapenems was implemented by 49% of respondents. These results might reflect the influence of reports on mono- and dual-therapy randomized controlled trials published overseas [9] or in Japan [10] since the previous survey. The incidence of infections with gram-positive cocci causing FN has increased in recent years. This change can be accounted for by a relative decrease in the incidence of infections with gram-negative bacilli because of prophylaxis with fluoroquinolones, and an increase in the incidence of intravascular catheter-related infections. The timing of initiation of anti-MRSA agents in the treatment of FN has always been debated. The National Health Insurance system of Japan supports the use of anti-MRSA drugs only for patients with documented MRSA infection. Thus, it is difficult to use anti-MRSA drugs as part of initial empirical therapy and in this survey the proportion of institutions withholding use until MRSA infection was confirmed was 7%. Compared to the results of the 2001 survey, in which the proportion was 30%, this percentage has clearly decreased. The US IDSA guideline suggests that the use of intravenous vancomycin should be limited wherever possible, on account of the potential emergence of vancomycin-resistant organisms [5]. The IDSA guideline also notes that initial empirical therapy with vancomycin is allowed only when the following clinical findings are obtained: (1) clinically suspected serious catheter-related infections, (2) known colonization with penicillin- and cephalosporin-resistant pneumococci or MRSA, (3) positive results of blood culture for gram-positive bacteria before final identification and susceptibility testing, and (4) hypotension or other evidence of cardiovascular impairment. The National Health Insurance of Japan does not cover the use of anti-MRSA agents except for the treatment of documented infections with MRSA. While patients would suffer greatly from such infections, the situation would be more serious if resistant organisms were to appear. From an epidemiological viewpoint we think that the use of anti-MRSA agents should continue to be restricted. Similar concerns have been expressed regarding the use of the carbapenems, although they are included in both the IDSA and Japanese guidelines. Interestingly, carbapenem use (with or without an aminoglycoside) remained relatively constant between the 2001 and 2007 surveys, and perhaps somewhat disappointingly the use of antipseudomonal penicillins remained at a relatively low level.

Among antifungal agents used in empirical therapy for FN, the recent launch of new products has led to marked changes in patterns of administration. MCFG, which was not marketed at the time of the previous survey, was the most frequently prescribed agent, at 88% among respondents who used an empirical approach to antifungal treatment. In contrast, the use of ITCZ and L-AMB was low (each $\leq$4%) in spite of their indication for FN. With regard to strain-specific treatment, FLCZ was most frequently prescribed (57%) for *C. albicans*, followed by MCFG (28%). Among other fungi, MCFG was most frequently prescribed for *C. glablata* (50%), followed by VRCZ (27%), L-AMB (13%), and ITCZ and AMPH-B (4%) while FLCZ was prescribed least often (2%). For *C. parapsilosis*, VRCZ was most frequently prescribed (36%), followed by MCFG (26%), L-AMB (16%), ITCZ (9%), and FLCZ (7%). Invasive aspergillosis was treated with VRCZ in 69% of respondents, probably owing to overseas evidence, particularly the Herbrecht study [11].

With regard to the determination of ß-D-glucan, only 1% failed to perform this test. Determination was contracted out by 46% of institutions, while the Wako kit was most commonly used by those hospitals performing this test in-house (34%). Based on the survey, opinion on the suitability of ß-D-glucan for use as a screening tool for fungi, especially *Candida* or *Aspergillus* appears to vary. In contrast, determination of galactomannan antigen had increased from 57 to 75% in 2007.

The criteria for starting G-CSF therapy differs between the US and Japan. According to the American Society of Clinical Oncology (ASCO) guideline published in 2006, the use of G-CSFs following initial induction therapy for AML is reasonable [12]. The ASCO guideline states that CSFs have no favorable impact on remission rate, remission duration or survival, but have beneficial effects on the incidence of severe infection. However, most Japanese hematologists prefer to use G-CSF for documented infections in patients with AML, because of the possible stimulating activity of G-CSF on AML cells. The results of the 2007 questionnaire showed little change from the 2001 survey with regard to AML induction therapy, AML consolidation therapy, ALL induction therapy, or ALL consolidation therapy.

In conclusion, comparison of the results of the present survey with those from 2001 highlights some significant changes in the use of drugs for the management of infections, including antifungal prophylaxis and empirical therapy. One reason for these changes is the introduction of a number of new antifungal agents since 2001. In addition, anti-MRSA drugs have also been launched, meaning that treatment strategies for FN will change further in the future. Guidelines for FN are currently available, and therapeutic measures should be reviewed and updated as needed, bearing in mind the changing medical environment in Japan, including technical improvements in diagnostic methods and the launch of new antibacterial and antifungal agents. This 2007 questionnaire analysis provides background information which broadens our perspective of current prophylactic practices in the treatment of acute adult leukemia in Japan, and will hopefully help establish guidelines for the management of infections in the fight against FN and leukemia.

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Appendix 1: Institutions responding to the questionnaire

Nihon University School of Medicine, Higashijujo Hospital, Kasukabe Municipal Hospital, Tokyo Metropolitan Komagome Hospital, Nagoya University Graduate School of Medicine, Daido Hospital, Yokkaichi Municipal Hospital, Aichi Cancer Center, Japanese Red Cross Nagoya First Hospital, Fujita Health University School of Medicine, Mie University Graduate School of Medicine, Suzuka Kaisei Hospital, Takeuchi Hospital, Kinki University School of Medicine, Osaka Medical Center for Cancer and Cardiovascular Diseases, Shikoku Cancer Center, Atomic Bomb Disease Institute - Nagasaki University, Graduate School of Biomedical Sciences, Sasebo City General Hospital, National Hospital Organization Nagasaki Medical Center, Kumamoto University School of Medicine, Kumamoto City Hospital, NTT West Kyushu General Hospital, Jichi Medical School, Okayama University Hospital, National Hospital Organization Minami-Okayama Medical Center, Chugoku Central Hospital of the Mutual Aid Association of Public School Teachers, National Hospital Organization Okayama Medical Center, Okayama Rosai Hospital, Kagawa Rosai Hospital, Gunma University Graduate School of Medicine, National Hospital Organization Nishigunma National Hospital, Fukaya Red Cross Hospital, University of Fukui, Kurashiki Central Hospital, Kanazawa Medical Center, Shimada Municipal Hospital, National Cancer Center Hospital, International Medical Center, Saitama Medical University, Hyogo College of Medicine, National Hospital Organization Osaka National Hospital Internal Medicine, Takarazuka Municipal Hospital, Uegahara Hospital, Kawasaki Medical School, Chiba University Hospital, Chiba Aoba Municipal Hospital, Social Insurance Funabashi Central Hospital, Nara Medical University, Jikei University School of Medicine, Dokkyo University School of Medicine, National Hospital Organization Nagoya Medical Center, Kochi Medical School - Kochi University, Shiga University of Medical Science, National Cancer Center East, Anjo Kosei Hospital, St. Marianna University School of Medicine, Yokohama Seibu Hospital, Shinshu University School of Medicine, Nagano Red Cross Hospital, Tokyo Women's Medical University, Tama-Hokubu Medical Center, Hamamatsu University School of Medicine, Fujieda Municipal General Hospital, Kagoshima University Hospital, Tochigi Cancer Center, Kanazawa University Graduate School of Medical Science, Toyama City Hospital, Seirei Numazu Hospital, Hematology, Tokyo Medical, University, Kyorin University School of Medicine, Hokkaido University Graduate School of Medicine, Sapporo Kousei Hospital, Hakodate Central Hospital, Saiseikai Maebashi Hospital, Higashi Municipal Hospital of Nagoya, Tokai University School of Medicine, Yamaguchi University School of Medicine, Yamaguchi Prefecture Central Hospital, Osaka City University, University of Tokyo, Niigata University, Medical and Dental Hospital, Oita University Faculty of Medicine, Oita Prefectural Hospital, Kouseiren Tsurumi Hospital, National Kyushu Cancer Center, National Hospital Organization Kyushu Medical Center, Fukuoka Postal Services Agency Hospital, Aso Iizuka Hospital, Teikyo University School of Medicine, Teikyo University Mizonokuchi Hospital, Sapporo Hokuyu Hospital, Aichi Medical University, Yamagata University Faculty of Medicine, Aomori Prefectural Central Hospital, Hyogo Cancer Center, Kyoto Prefectural University of Medicine, Social Insurance Kyoto Hospital, Social Insurance Kobe Central Hospital, National Hospital Organization Shiga Hospital, National Defense Medical College,

Akita University School of Medicine, NTT Kanto Medical Center, Yokohama City University Hospital, Yokohama City University Medical Center, Kanagawa Cancer Center, Fujisawa City Hospital, Shizuoka Red Cross Hospital, Tohoku University School of Medicine, Osaki Citizen Hospital, Hiroshima University, Kagawa University, Kagawa Prefectural Central Hospital, Sakaide City Hospital, Juntendo University School of Medicine, Kanazawa Medical University, Kobe University Graduate School of Medicine, Jiaikai Imamura Bun-in Hospital, Ehime University Graduate School of Medicine, Metropolitan Bokuto Hospital, Otsu Red Cross Hospital, Yokohama City Minato Red Cross Hospital, Saitama Medical Center Jichi Medical University, Ehime Prefectural Central Hospital, International Medical Center of Japan, National Hospital Organization Kure Medical Center, Nagoya Daini Red Cross Hospital, University of Yamanashi Hospital, Heartlife Hospital, Musashino Red Cross Hospital, Saitama Medical Center, PL Hospital, Toyama Prefectural Central Hospital, Shimane Prefectural Central Hospital, Miyagi Cancer Center.

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Hematopoietic stem cell transplantation for core binding factor acute myeloid leukemia: t(8;21) and inv(16) represent different clinical outcomes

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We analyzed 338 adult patients with acute myeloid leukemia (AML) with t(8;21) and inv(16) undergoing stem cell transplantation (SCT) who were registered in the Japan Society for Hematopoietic Cell Transplantation database. At 3 years, overall survival (OS) of patients with t(8;21) and inv(16) was 50% and 72%, respectively ($P = .002$). Although no difference was observed when restricted to allogeneic SCT in first complete remission (CR; 84% and 74%), OS of patients with t(8;21) and inv(16) undergoing allogeneic SCT in second or third CR (45% and 86% at 3 years; $P = .008$) was different. OS was not different between patients in first CR who received allogeneic SCT and those who received autologous SCT for both t(8;21) AML (84% vs 77%; $P = .49$) and inv(16) AML (74% vs 59%; $P = .86$). Patients with inv(16) not in CR did better after allogeneic SCT than those with t(8;21) (70% and 18%; $P = .03$). Patients with t(8;21) and inv(16) should be managed differently as to the application of SCT. SCT in first CR is not necessarily recommended for inv(16). For t(8;21) patients in first CR, a prospective trial is needed to clarify the significance of autologous SCT and allogeneic SCT over chemotherapy. (Blood. 2009;113:2096-2103)

Introduction

Core binding factor (CBF) acute myeloid leukemia (AML) including t(8;21)(q22;q22) and inv(16)(p13q22)/t(16;16)(p13;q22) [t(8;21) and inv(16)] is considered to be a favorable cytogenetic subgroup in clinical studies.[1-4] Patients with t(8;21) and inv(16) have shown a markedly improved outcome with repetitive use of high-dose cytarabine.[5-13] However, the major treatment failure is disease recurrence.[14-16] These patients frequently become stem cell transplantation (SCT) candidates.

Both t(8;21) and inv(16) AMLs are associated with disruption of genes encoding subunits of the CBF, a heterodimeric transcriptional factor involved in the regulation of hematopoiesis.[17,18] Although these 2 different cytogenetics also share common clinical characteristics, they are associated with different clinical features such as morphologic presentation and immunophenotypic marker expression.[19]

Several reports demonstrated inferior outcome of t(8;21) compared with inv(16), but the number of patients who underwent transplantation was limited.[14,15,20] A recent study from the Dana-Farber Cancer Institute reported that both patients with t(8;21) and inv(16) de novo AML who underwent allogeneic transplantation performed favorably compared with other karyotypes.[21] To identify the survival data and prognostic factors among the CBF leukemia population who received SCT, we conducted a retrospective analysis using a Japanese multi-institution database with a large number of patients.

Methods

Study population

A total of 2802 adult patients who underwent autologous or allogeneic SCT from 1996 and 2004 for AML were registered in the Japan Society for Hematopoietic Cell Transplantation (JSHCT) database. Patients who underwent SCT from unrelated donors were registered in the different registry in the study period, but not all of the patients undergoing unrelated SCT were registered in the JSHCT database. Demographic, diagnostic, clinical, cytogenetics, induction, and outcome information were collected for each patient, and were sent to a central registration center. Cytogenetic studies were performed in each center, but a central review of cytogenetic analysis was not performed.

Patients with de novo AML aged 16 to 70 years who received hematopoietic SCT as the first transplant were included in the study. No patients with prior history of autologous or allogeneic SCT were included in the study. Of the remaining 2164 patients, 178 patients with t(15;17) or PML/RARα were excluded from the analysis below (Table 1). Finally, of the 1986 patients included in the analysis, 255 were reported to have t(8;21) abnormality, and 83 to have inv(16). A total of 194 patients had no available cytogenetic data. The remaining 1454 patients with normal karyotype and other cytogenetic abnormalities were further coded and analyzed according to published Southwest Oncology Group (SWOG) criteria.[3] The intermediate risk category included patients characterized by +8, −Y, +6, del(12p), or normal karyotype. The unfavorable risk category was defined by the presence of one or more of −5/del(5q), −7/del(7q), abn 3q, 11q, 20q, or

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Table 1. Cytogenetic risk groups of patients with AML who received autologous SCT and allogeneic SCT

Cytogenetic risk groups	No. patients		
	Auto-SCT	Allo-SCT	Total
t(8;21)	61	194	255
inv(16)	17	66	83
t(15;17)*	65	113	178
Intermediate	140	749	889
Unfavorable	35	325	360
Unknown			
Unknown cytogenetic risk	27	178	205
No available cytogenetic data	44	150	194
Total	389	1775	2164

Auto-SCT indicates autologous stem cell transplantation; Allo-SCT, allogeneic stem cell transplantation.

*Patients with t(15;17) were excluded from the analysis.

21q, del(9q), t(6;9), t(9;22), abn 17p, and complex karyotypes defined as 3 or more abnormalities. Patients with other cytogenetic aberrations were considered an unknown risk group, and were analyzed together with 194 patients with no cytogenetic data.

This study was approved by the Committee for Nationwide Survey Data Management of the JSHCT. Informed consent was obtained in accordance with the Declaration of Helsinki.

Transplantation

A total of 1662 patients underwent allogeneic SCT, and 324 underwent autologous SCT. Patients were treated with various conditioning regimens, but most of those who underwent autologous transplantation received non–total body irradiation (TBI) regimens (97%), including busulfan (BU), cytarabine (CA), and etoposide. The most frequently used conditioning regimens before allogeneic SCT were cyclophosphamide (Cy) plus TBI (n = 327 patients), and BU plus Cy (n = 267). Conditioning regimens before allogeneic SCT also included more intensified regimens such as CA plus Cy plus TBI (n = 262) and BU plus Cy plus TBI (n = 146), or reduced-intensity conditioning regimens with fludarabine (n = 241) or cladribine (n = 19).

Stem cell sources for allogeneic SCT were bone marrow in 871 patients, peripheral blood stem cell in 570 patients, bone marrow plus peripheral blood stem cell in 23 patients, and cord blood in 190 patients. A total of 1242 patients underwent allogeneic SCT from a related donor, and 404 patients underwent SCT from an unrelated donor.

Of the 1637 patients who had available data, 74% received transplants from human leukocyte antigen (HLA)–matched donors. Among patients who received unrelated bone marrow transplants, 156 patients were HLA genotypically matched and 51 were HLA mismatched. HLA data for 39 mismatched unrelated bone marrow transplantation patients were available. A total of 32 patients were one locus mismatched, and 7 patients were 2 loci mismatched. Among patients receiving unrelated cord blood transplants, 19 patients were serologically HLA matched and 170 patients were mismatched. HLA incompatibility was 5 of 6 HLA matched in 57 patients, 4 of 6 HLA matched in 99 patients, 3 of 6 HLA matched in 7 patients, and 1 of 6 HLA matched in 1 patient.

Graft-versus-host disease (GVHD) prophylaxis mostly consisted of methotrexate and a calcineurin inhibitor, either cyclosporin A or tacrolimus. Several other prophylaxes include mycophenolate mofetil, antithymocyte globulin, and $CD34^+$ selection. The incidence of acute GVHD was evaluated in 1488 patients who survived more than 28 days, and chronic GVHD was evaluated in 1302 patients who survived more than 100 days after allogeneic SCT. GVHD was evaluated in each center.

Statistical analysis

Correlation between the 2 groups was examined with the chi-square test, Fisher exact test, and the Mann-Whitney *U* test. Disease-free survival (DFS) was calculated from the date of transplantation until the date of relapse or the date of death in CR. Patient survival data were analyzed with the method of Kaplan and Meier and compared by the log-rank test.

Univariate and multivariate analyses for OS were performed with the aid of the Cox proportional hazard regression model, and variables were selected with the stepwise method. The following variables were evaluated: age, sex, and disease status at transplantation; CR versus not in CR; the number of induction courses to achieve CR; one course versus more than one course and failure; type of transplantation (allogeneic SCT vs autologous SCT); conditioning regimen (reduced intensity vs myeloablative); TBI regimen or not; and the existence of additional karyotype abnormalities or not. For those who received allogeneic SCT, in addition to these variables, the following were also evaluated: type of GVHD prophylaxis; short-course methotrexate plus cyclosporin A or short methotrexate plus FK506; acute GVHD, grade II to IV or grade III to IV; chronic GVHD; HLA mismatch; donor; and donor source. The doses of methotrexate were not surveyed. Each factor was considered to be prognostic if the *P* value was less than .05. Data were analyzed with the Stata 9.2 statistical software (College Station, TX).

Results

Initial characteristics of patients

The median age of all patients with AML in total was 41 years old (range, 16-70 years old). Median follow-up period of living patients was 37.3 months (range, 0.4-108 months). Patients were categorized into 5 cytogenetic subgroups: with t(8;21), with inv(16), intermediate risk cytogenetics, unfavorable cytogenetics, and an unknown risk group. Table 1 shows the number of patients in each cytogenetic subgroup and patients with t(15;17), who were excluded from the analysis.

Characteristics of the patients with CBF who underwent allogeneic SCT or autologous SCT are shown in Table 2. No significant difference was observed between characteristic of 2 groups of patients with CBF who received autologous SCT, except for the initial white blood cell count.

Of the 259 patients with CBF who received allogeneic SCT, significantly more patients with t(8;21) had failed to achieve CR with a single course of induction chemotherapy at diagnosis ($P = .002$), and were not in CR at the time of transplantation ($P < .001$). Among patients in CR at transplantation, the ratio of those in first, second, or third CR was not different between t(8;21) and inv(16) subgroups. Significantly more patients with inv(16) received transplants from an unrelated donor ($P = .004$). Table 3 and Table S1 (available on the *Blood* website; see the Supplemental Materials link at the top of the online article) summarize the transplantation data of those undergoing allogeneic SCT. More patients with inv(16) received unrelated transplants compared with t(8;21) patients ($P = .004$).

Overall survival

The OS of 1986 patients with AML at 3 years was 48%, and those with t(8;21), inv(16), intermediate, unfavorable, and unknown cytogenetic risks showed OS of 50%, 72%, 52%, 35%, and 45%, respectively ($P < .001$). Figure 1 shows survival curves of patients with AML patients who underwent allogeneic SCT in first CR (Figure 1A), in second or third CR (Figure 1B), or not in CR (Figure 1C), categorized by the cytogenetic abnormalities. Survival data are listed in Table 4. The OS of patients with t(8;21), inv(16), and intermediate, unfavorable, and unknown risk undergoing allogeneic SCT in first CR was 84%, 74%, 69%, 53%, and 52%, respectively ($P < .001$), and that of patients undergoing allogeneic-SCT

Table 2. Characteristics of patients with CBF AML

	Auto-SCT			Allo-SCT		
	t(8;21) (n = 61), no.	inv(16) (n = 17), no.	P	t(8;21) (n = 194), no.	inv(16) (n = 66), no.	P
Median age, y (range)	44 (17-68)	37 (19-61)	.59	39 (16-70)	34 (16-64)	.054
Median WBC, g/L (range)	8.8 (0.2-94)	33 (2.1-199)	.02	11 (.6-366)	53 (1.8-284)	< .001
Sex						
Male	41	12	.79	117	40	.93
Female	20	5		74	26	
No. of induction chemotherapy at diagnosis of AML						
1 course	48	15	.72	125	55	.002
> 1 or failure*	11	2		56	7	
Additional cytogenetic abnormalities						
None	53	15	> .999	153	54	.61
Positive	8	2		41	12	
Disease status at SCT						
CR	55	16	> .999	108	52	< .001
Not in CR	6	1		85	11	
CR1	43	13	.98	49	21	.29
CR2	7	1		45	26	
CR3	0	1		5	4	
Conditioning regimen						
TBI	0	1	.22	118	47	.078
Not TBI	61	16		71	16	

Correlation between the two groups was examined.
WBC indicates white blood cell count; g/L, 10^9/L; CR1, first complete remission; and CR2 or 3, second or third CR.
*More than 1 or failure includes patients who did not achieve complete remission after first course of induction chemotherapy, and those who were resistant to induction chemotherapy.

in second or third CR was 45%, 86%, 57%, 44%, and 64%, respectively ($P = .09$). OS of patients undergoing allogeneic SCT not in CR was 18%, 70%, 25%, 15%, and 18%, respectively ($P = .003$).

Table 3. Summary of allogeneic SCT

	t(8;21) (n = 194), no.	inv(16), (n = 66), no.	P
Conditioning regimen			
RIST	31	9	.66
Myeloablative	161	56	
GVHD prophylaxis*			
sMTX+CyA	136	48	.78
sMTX+FK	20	8	
HLA			
Match	146	47	.5
Mismatch	45	18	
Donor			
Related	161	44	.004
Unrelated	32	22	
Stem cell source			
BM	101	40	.27
PB	72	17	
CB	18	7	
aGVHD grade			
0-I	117	37	.54
II-IV	60	22	
cGVHD type			
None	64	28	.28
Lmt/Ext	67	20	

Correlation between the two groups was examined. Some of the missing data was not available, and total numbers do not add up to the number of the patients in each group.

RIST indicates reduced intensity stem cell transplantation; sMTX, short-course methotrexate; CyA, cyclosporin A; FK, tacrolimus; BM, bone marrow; PB, peripheral blood; CB, cord blood; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; Lmt, limited; and Ext, extensive.

*Dose of methotrexate was not surveyed in the study. Detail of other GVHD prophylaxis regimens are in Table S1.

When patients undergoing allogeneic SCT in first CR were analyzed, 3-year OS was not significantly different between patients with t(8;21) and inv(16) (84% and 74%, respectively; $P = .28$), between inv(16) and intermediate risk groups (74% and 69%, respectively; $P = .84$), or between t(8;21) and intermediate risk groups (84% and 69%, respectively; $P = .06$). However, when patients undergoing allogeneic SCT in second or third CR were analyzed, the 3-year OS of patients with inv(16) was significantly better than patients with t(8;21) (86% and 45%, respectively; $P = .008$), and better than intermediate risk patients (86% and 57%, respectively; $P = .03$). Difference was not significant between patients in the intermediate risk group and t(8;21) undergoing allogeneic SCT in second or third CR ($P = .36$). The OS of inv(16) patients undergoing allogeneic SCT not in CR was 70% at 3 years, which was also significantly better than that of t(8;21) (18%; $P = .03$) and the intermediate risk group (25%; $P = .045$).

In addition, the OS of t(8;21) undergoing allogeneic SCT in first CR was significantly better than that of the unfavorable risk group (84% and 53%, respectively; $P < .001$), but the difference between the 2 groups was not significant among patients undergoing allogeneic SCT in second or third CR. In contrast, OS was not different between inv(16) and unfavorable groups undergoing allogeneic SCT in first CR, but it was significantly different when they underwent allogeneic SCT in second or third CR (86% and 44%, for inv(16) and unfavorable groups, respectively; $P = .01$) or allogeneic SCT in non-CR (70% and 15%, respectively; $P = .006$).

Survival curves of patients who underwent autologous SCT in first CR, second or third CR, and not in CR are shown in Figure 2A, 2B, and 2C, respectively. The overall survival of patients with t(8;21), inv(16), and intermediate, unfavorable, and unknown cytogenetic risks in first CR was 77%, 59%, 74%, 38%, and 71%, respectively ($P = .049$), while that of patients undergoing autologous SCT in second or third CR was 43%, 50%, 59%, 44%, and 42%, respectively ($P = .8$). The OS of patients undergoing autologous SCT not in CR with t(8;21), inv(16), intermediate, and

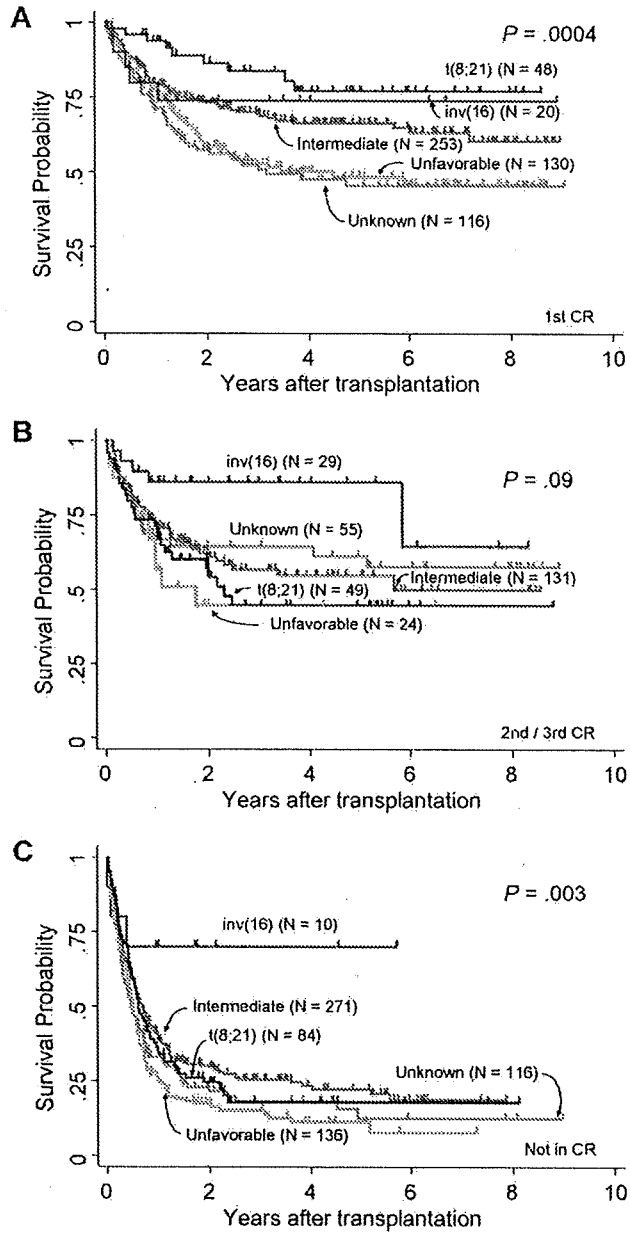

Figure 1. OS difference of patients undergoing allogeneic SCT between cytogenetic subgroups. (A) Survival curves of patients undergoing allogeneic SCT in first CR. (B) Survival curve of patients undergoing allogeneic SCT in second or third CR. (C) Survival curves of patients undergoing allogeneic SCT not in CR. Each are categorized by cytogenetic risk groups, respectively.

unknown risks was 17%, 100%, 25%, and 13%, respectively, and the survival curve of patients in the unfavorable risk group did not reach 3 years ($P = .35$).

Figure 3A and B focus on t(8;21) and inv(16) patients, stratified according to the type of (allogeneic or autologous) and disease status at the time of transplantation (first CR, second or third CR, and not in CR). The 3-year overall survival of t(8;21) patients in first CR was not different between allogeneic and autologous transplantation (84% and 77%, respectively), as well as that of patients in second or third CR (45% and 43%, respectively) and patients not in CR (18% and 17%, respectively). Similarly, the 3-year OS of inv(16) patients was not different between allogeneic and autologous transplantation when they underwent transplantation in first CR (74% and 59%). A significant difference was observed among the 3 disease status groups of t(8;21) patients ($P < .001$; Figure 3A), but not inv(16) patients ($P = .75$; Figure 3B).

The OS of allogeneic SCT, excluding cord blood transplantation, was not different from the analysis presented here, including bone marrow, peripheral blood, and cord blood transplantation (Table S2; Figures S1,S2).

DFS after SCT was also different among cytogenetic risk groups ($P < .001$). DFS of patients with inv(16) (69% at 3 years) was better compared with t(8;21) (49%), intermediate (46%), unfavorable (31%), and unknown (41%) risk groups. Among patients undergoing allogeneic SCT in first CR, DFS was also different among cytogenetic subgroups ($P < .001$). When t(8;21), inv(16), and intermediate cytogenetic subgroups undergoing allogeneic SCT in first CR were compared, the difference was not statistically significant between t(8;21) and inv(16) (78% and 73% at 3 years; $P = .58$), between t(8;21) and intermediate risk group (78% and 63%; $P = .1$), nor between inv(16) and intermediate risk group (73% and 63%; $P = .65$). DFS of patients with t(8;21) undergoing allogeneic SCT in first CR was better than that of the unfavorable risk group (78% and 47%, respectively; $P < .001$), but the difference was not significant between inv(16) and unfavorable risk groups (73% and 47%, respectively; $P = .16$).

DFS was not significantly different when 5 cytogenetic subgroups among patients undergoing allogeneic SCT in second or third CR were compared ($P = .32$). The DFS of patients undergoing allogeneic SCT in second or third CR was not significantly different between t(8;21) and inv(16) (43% and 71% at 3 years; $P = .053$), t(8;21) and the intermediate group (43% and 47%; $P = .76$), or inv(16) and the intermediate group (71% and 47%; $P = .06$). The difference was also not significant between t(8;21) and unfavorable risk groups (43% and 42%; $P = .7$), nor between inv(16) and unfavorable risk groups (71% and 42%; $P = .06$). The DFS of patients undergoing allogeneic SCT who were not in CR was significantly different among the 5 cytogenetic subgroups ($P = .005$), and that of inv(16) (75% at 3 years) was significantly better than t(8;21) (18%; $P = .02$), the intermediate risk group (22%; $P = .03$) and the unfavorable risk group (10%; $P = .003$).

Relapse and TRM

The relapse rate (RR) after SCT also differed among cytogenetic subgroups ($P < .001$). The RR of patients with inv(16) (18% at 3 years) was lower than t(8;21) (38%), intermediate (38%), and unfavorable (56%) risk groups. The RR of t(8;21) and inv(16) after allogeneic SCT was not statistically different in either first CR (16% and 6%; $P = .45$) or second or third CR (34% and 16%, respectively; $P = .09$).

Transplantation-related mortality (TRM) of all patients with AML was 22% at 3 years. The TRM of t(8;21) (18%), inv(16) (11%), and intermediate (21%), unfavorable (24%), and unknown risk groups (27%) was significantly different among cytogenetic risk groups ($P = .02$).

Evaluation of prognostic variables in CBF

Univariate analyses of t(8;21) showed that age ($P = .004$), not in CR at transplantation ($P < .001$), allogeneic SCT ($P = .01$), and TBI regimen ($P = .006$) were significant prognostic factors indicating poor OS (Table 5). Multivariate analysis for OS revealed older age ($P = .01$) and not in CR at transplantation ($P < .001$) as the independent prognostic variables. Univariate analyses of t(8;21) patients who received allogeneic SCT in CR showed that age ($P = .02$), TBI regimen ($P = .01$), and second and third CR at

Table 4. Outcome of the AML patient population by cytogenetic risk groups

	t(8;21)		inv(16)		Intermediate		Unfavorable		Unknown		
	%	N	%	N	%	N	%	N	%	N	*P*
OS											
Allogeneic SCT											
CR1	84	48	74	20	69	253	53	130	52	116	< .001
CR2/CR3	45	49	86	29	57	131	44	24	64	55	.09
Non-CR	18	84	70	10	25	271	15	136	18	116	.003
Autologous SCT											
CR1	77	42	59	13	74	89	38	15	71	39	.05
CR2/CR3	43	7	50	2	59	15	44	6	42	18	.8
Non-CR	17	6	100	1	25	16	0	10	13	8	.35
DFS											
Allogeneic SCT											
CR1	78	48	73	19	63	249	47	129	48	113	< .001
CR2/CR3	43	48	71	27	47	129	42	22	57	54	.32
Non-CR	18	81	75	8	22	255	10	128	16	107	.005
Autologous SCT											
CR1	73	41	62	13	64	81	33	15	61	36	.09
CR2/CR3	43	7	50	2	36	14	50	6	39	18	.89
Non-CR	17	6	100	1	25	16	0	10	17	6	.45

transplantation ($P < .001$) were also significantly prognostic for poor OS. These variables remained significant after multivariate analysis. Univariate analyses for inv(16) patients showed only age ($P = .009$) to be a significant prognostic factor (Table 5). The univariate analysis of inv(16) patients who underwent allogeneic SCT in CR showed only additional karyotype abnormalities to be an unfavorable prognostic variable ($P = .009$).

Additional cytogenetic abnormalities to CBF

A total of 49 patients with t(8;21) and 14 with inv(16) had additional cytogenetic abnormalities. Data for additional cytogenetic abnormalities were obtained in 42 patients with t(8;21) and 13 patients with inv(16) (Table 6). Additional abnormalities were selected that have been reported to be prognostic by others, including loss of sex chromosome (X or Y), trisomy 8, trisomy 4, del(7q), and del(9q) for the t(8;21) group, and trisomy 22, trisomy 8, trisomy 21, del(7q), and del(9q) for the inv(16) group.[14,15,20,22,23] There were no patients with trisomy 21 in the data of patients with CBF. Patients with t(8;21) and patients with inv(16) were analyzed separately. Among t(8;21) patients undergoing allogeneic SCT, survival was not different between patients with and without additional karyotype abnormalities. When patients with inv(16) were analyzed, the survival was not different between patients with (n = 13) and without (n = 67) additional abnormalities (61% and 74%, respectively; $P = .07$). The survival of patients undergoing allogeneic SCT without additional abnormality (n = 52) was significantly better than that with additional abnormality (n = 11), (85% and 53%, respectively; $P = .004$). When analysis was restricted to patients in CR with inv(16) undergoing allogeneic SCT, a similar difference was observed (86% without additional abnormality [n = 42], and 60% with additional abnormality [n = 8], respectively; $P = .03$). Difference in OS was observed among non-CR patients with (n = 9) and without (n = 1) additional abnormality, but this difference may not be relevant with too few patients in the analysis. We further analyzed subgroups of additional abnormalities of the patients with inv(16). Although the number of patients were limited, significant difference was found among 3 groups of patients; trisomy 8 or trisomy 22 as a sole abnormality (n = 4), without additional abnormality (n = 69), and other additional abnormality to inv(16) (n = 10). The OS at 3 years were 100%, 74%, and 42%, respectively ($P = .002$). The OS of patients undergoing allogeneic SCT was also different among these 3 groups (100%, n = 3; 85%, n = 52; and 33%, respectively; $P < .001$).

Discussion

We analyzed the outcome of a large group of patients with adult CBF AML in Japan who were treated with SCT. The current study focused on the different outcome of the 2 different cytogenetic subgroups of patients with CBF AML undergoing SCT. Our study demonstrated a comparable outcome between patients with t(8;21) and inv(16) undergoing SCT in first CR, but the prognosis between these 2 cytogenetic subgroups was different beyond first CR.

In the literature, there have been several reports showing inferior survival of patients with t(8;21) compared with inv(16) patients undergoing induction chemotherapy and SCT.[14,15,20] Other studies categorized both patients with t(8;21) and inv(16) undergoing allogeneic SCT together as good-risk CBF AML,[1,21] with a relatively comparable prognosis. In our study, OS of patients with t(8;21) undergoing allogeneic SCT in first CR was not statistically different from intermediate cytogenetic subgroup (84% and 79% at 3 years, respectively; $P = .058$). Moreover, the survival of inv(16) (74% at 3 years) and intermediate cytogenetic subgroups showed no statistically significant difference.

In contrast, we have here demonstrated that the prognosis of patients with t(8;21) undergoing allogeneic SCT with second or third CR disease was significantly poor compared with those with inv(16). This finding is consistent with those of other studies reporting differences between the 2 types of CBF AML.[14,15] In the present study, non-CR disease with t(8;21) was also significantly poor compared with patients with inv(16). The Acute Leukemia French Association reported that allogeneic donor availability among patients with CBF AML who were in second CR was a prognostic factor for better survival.[16] We believe that different treatment strategies should be applied for patients with t(8;21) and those with inv(16) other than first CR.

Patients with t(8;21) undergoing allogeneic SCT and autologous SCT had a similar survival rate when they underwent transplantation in first CR, and in further CR. No survival difference between allogeneic SCT and autologous SCT was also

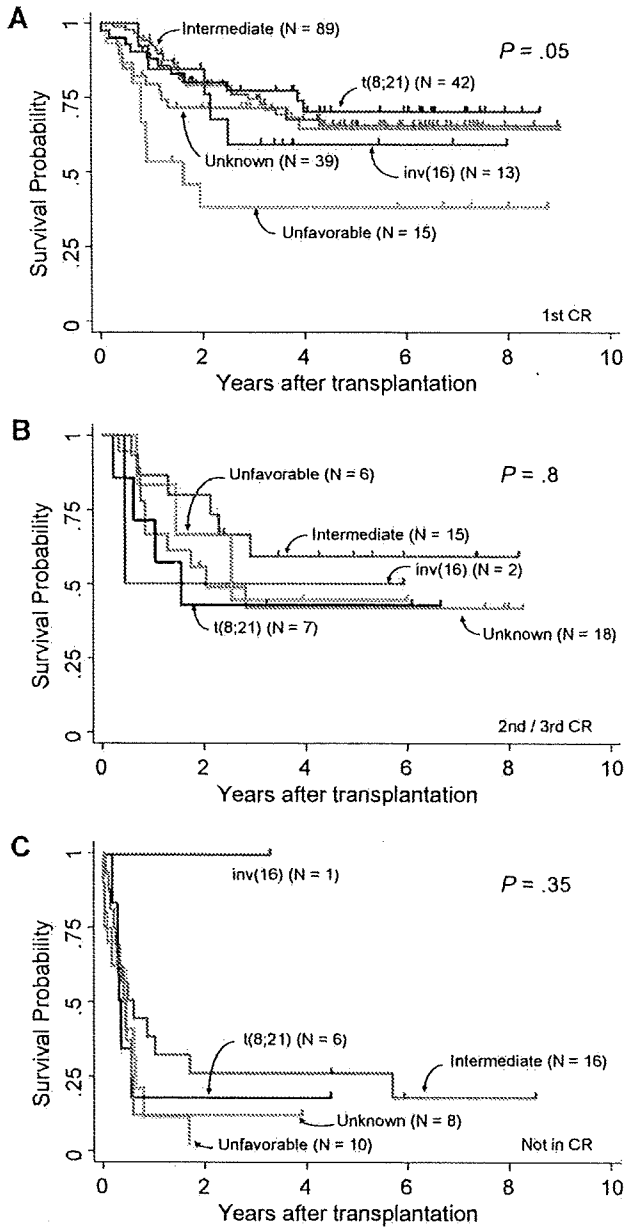

Figure 2. OS difference of patients undergoing autologous SCT between cytogenetic subgroups. (A) Survival curves of patients undergoing autologous SCT in first CR. (B) Survival curves of patients undergoing autologous SCT in second or third CR. (C) Survival curves of patients undergoing autologous SCT not in CR. Each are categorized by cytogenetic risk groups, respectively.

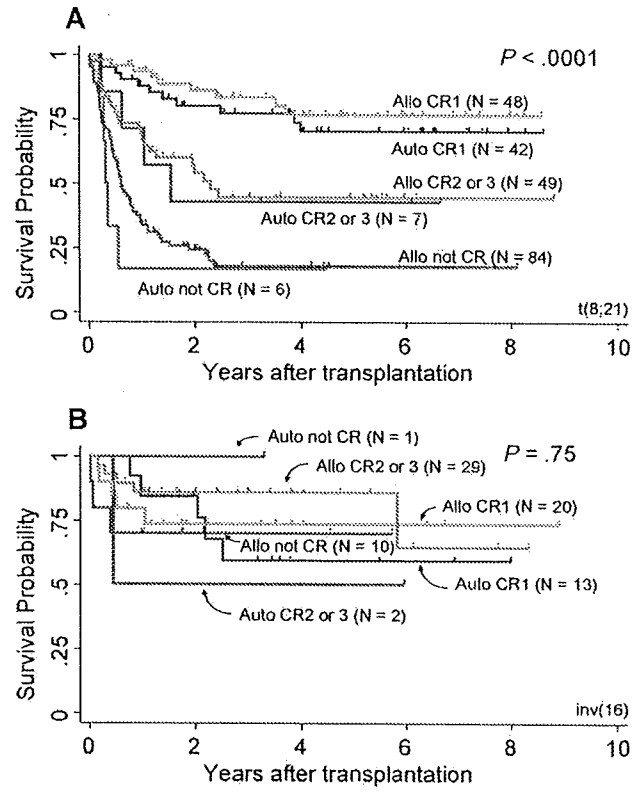

Figure 3. OS of patients with CBF. Survival curves of patients with t(8;21) (A) and with inv(16) (B). Both are stratified according to the type of transplantation (allogeneic or autologous) and disease status at the time of transplantation (first CR, second or third CR, and not in CR).

observed among inv(16) patients receiving SCT in first CR (74% and 59%, respectively). The University of California, San Francisco (UCSF) group described the good results of patients with advanced AML undergoing autologous SCT in second or third remission, including patients with CBF.[24] As in our study, the European Group for Blood and Marrow Transplantation (EBMT) reported that the survival rate of t(8;21) patients who received allogeneic bone marrow transplantation was not significantly different from that of patients who received autologous SCT.[1] Results by others showed that allogeneic SCT in first CR did not benefit good-risk cytogenetic subgroups.[3,25,26] Schlenk et al also demonstrated that t(8;21) patients receiving allogeneic SCT or chemotherapy showed no difference in outcome.[23] These results suggest that autologous SCT can be considered as postremission therapy for patients with CBF AML, but it remains unclear whether SCT is more beneficial for patients with CBF than high-dose cytarabine. Survival of patients with inv(16) was favorable beyond first CR. Patients with inv(16) in second or third CR, or even non-CR patients, are good candidates for allogeneic SCT. There are long-term survivors after allogeneic SCT in non-CR disease, so t(8;21) patients with no other choice of treatment, such as those in further CR or non-CR, can proceed to allogeneic SCT. In order to confirm the appropriate treatment for t(8;21) patients in first CR, a prospective trial is needed to compare the results of autologous SCT for t(8;21) in first CR with standard chemotherapy. t(8,21) patients with suitable related or well-matched donors should be recommended to participate in a risk-adopted prospective trial when they receive allogeneic SCT in first CR.

There were differences between the 2 types of CBF AML with respect to prognostic valuables. Age was a significant and independent prognostic variable in both t(8;21) and inv(16) patients, a finding in agreement with reports from some,[14,27] but not all,

Table 5. Prognostic factors affecting overall survival of patients with t(8;21)

Variables	Unfavorable factors	Hazard ratio	95% CI	P
t(8;21)				
Age		1.02	1.01-1.04	.004
Disease status at SCT	Not in CR	4.4	3.1-6.5	< .001
Transplantation	Allo-SCT	1.9	1.2-3.0	.01
Conditioning regimen	TBI	1.7	1.2-2.5	.005
inv(16)				
Age		1.1	1.0-1.1	.009

CI indicates confidence interval.

Table 6. Additional cytogenetic abnormalities among patients with CBF

Additional cytogenetic abnormalities	t(8;21), no.	inv(16), no.
None	206	69
With additional abnormalities	49	14*
Y	10	0
−X	5	0
Trisomy 22	0	3†
Trisomy 8	0	2†
Trisomy 4	2*	0
Complex	7	4
del(7q)	1†	2
del(9q)	6	0
Other abnormalities	27	9‡
Unknown	7	1

*Patients with additional change to inv(16) and trisomy 4 with t(8;21) tended to show poor survival tendency, with $P < .1$.

†All patients with trisomy 22, trisomy 8 with inv(16), and del(7q) with t(8;21) were alive and censored at survival analysis.

‡Other abnormalities with inv(16) was poorly prognostic, with $P < .001$.

investigators.[28] Transplantation in CR was a significant and independent prognostic factor for patients with t(8;21), but not for those with inv(16). The Cancer and Leukemia Group B (CALGB) also reported differences between t(8;21) and inv(16) in prognostic factors, in terms of race, sex, and secondary cytogenetic abnormalities.[14] Among patients with CBF AML, t(8;21) and inv(16) patients undergoing SCT should be considered 2 separate clinical entities in future clinical studies.

Several specific additional karyotype abnormalities have been reported to be prognostic in patients with CBF AML. Among t(8;21) patients, no specific additional karyotype abnormality was prognostic for overall survival. The poor prognosis of t(8;21) patients with trisomy 4 has been reported by others,[22] but the survival difference was not statistically significant ($P = .085$) in our case series. Since there were limited numbers of patients with additional abnormalities, the real significance of each additional abnormality should be investigated in large numbers of patients.

The reason for the different survival results between patients with t(8;21) and inv(16) undergoing allogeneic SCT in our study remains unclear. The impact of additional mutational events such as c-Kit, FLT3, RAS, and gene-expression profiles was reported to be associated with the clinical outcome of patients with CBF AML.[29-34] The effects of these additional mutational events and gene-expression profiles on the clinical outcome of autologous and allogeneic SCT have not yet been studied. Which proportion of the patients with CBF AML benefited from earlier SCT remains to be identified in future clinical studies. Recent studies by others also suggested that prognosis of CBF AML could differ among different ethnic groups or races.[14,35-37] The background molecular basis among the Japanese population must also be taken into account in future studies.

In conclusion, the survival outcome of patients with CBF AML was similar when they received allogeneic or autologous SCT in first CR. However, the outcomes were significantly different between t(8;21) and inv(16) when they received allogeneic SCT beyond first CR. Therefore, these 2 kinds of CBF AML should be managed differently when applying SCT.

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Authorship

Contribution: Y. Kuwatsuka, K.M., and R.S. contributed to data collection, designed and performed the study, analyzed the data, and wrote the manuscript; M.K., A.M., H.O., R.T., S.T., K.K., K.Y., Y.A., T.Y., and H.S. contributed to data collection and analysis and writing of the paper; and Y. Kodera contributed to data collection and writing of the paper, conceived the study, and provided intellectual input.

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