making such a decision. In addition, the present protocol states that, if the decision is difficult due to equivocal findings, additional drugs should be given.

It was considered that the higher CR rates of previous JALSG studies for adult AML: AML87 [4], AML89 [5] and AML92 [6], were due to response-oriented individualized therapy, giving highly intensive but not too toxic doses of anti-leukemia drugs, especially IDR, to make the bone marrow severely hypoplastic, reduce the percentage of blasts to less than 5% within 10 days, and aim to obtain CR by the first course of induction therapy. For example, in the AML89 study, the primary objective of which was to compare Ara-C with BHAC in remission induction therapy, 130 (82%) of 159 patients in the DNR + Ara-C + 6MP + PSL group achieved CR by this individualized induction therapy [5]. It is clear that without a prospective randomized study, one cannot argue whether the individual therapy is superior to a standard fixed-schedule remission induction therapy. However, it is noteworthy, that in the 3 randomized studies in the USA mentioned in Sect. 1, which compared IDR plus Ara-C with DNR plus Ara-C, the fixed-schedule therapy with DNR plus Ara-C resulted in merely 57–58% CR rates, while IDA plus Ara-C regimens produced 70–80% CR rates [8–10].

Disappointingly, the present study could not demonstrate that response-oriented individualized therapy was superior to the fixed-schedule therapy. Both regimens resulted in almost the same CR rates: 79 and 82%, respectively. Actually, both therapies produced very good CR rates. The results were interpreted as follows: IDR is a good but very powerful drug, therefore, additional IDR and Ara-C on day 8 or later may not be necessary and gave too much myelosuppression. In fact, in the individualized group, leukocytopenia was significantly more severe and its duration was significantly longer, and early death within 30 days tended to occur more frequently. From the present study it is suggested that response-oriented individualized therapy could be successful in cases where DNR is used as a key drug. Usui et al. [12] reported that the optimal dose of DNR in the induction therapy for newly diagnosed adult AML was approximately 280 mg/m^2 (40 mg/m^2 for 7 days), which was more than its conventional dose of 40–60 mg/m^2 for 3 days.

It is very interesting that among patients of age 50 years or older, the individualized group had significantly lower RFS than the fixed group, but there was no such difference in younger patients. However, we cannot clearly explain the real reason of this observation. There may be potential sources of bias in our subset analysis of clinical data that have many confounding factors. Therefore, we must be cautious in drawing a conclusion from this observation.

So far, CR rates around 80% for newly diagnosed adults of age less than 65 years with non-M3 AML seems to be the upper limit by currently available anti-leukemia drugs in multi-institutional studies [7]. To increase the CR rates and improve treatment outcomes, novel drugs other than cytotoxic ones such as all-*trans* retinoic acid (ATRA) for acute promyelocytic leukemia (APL) are needed. With ATRA in combination with conventional cytotoxic drugs such as IDR and Ara-C, CR rates around 95% and more than 80% overall survival for APL with PML/RARα can be obtained [13, 14]. The remarkable success of molecule targeting therapy with ATRA against APL as well as imatinib mesylate against chronic myeloid leukemia [15] and Philadelphia chromosome-positive ALL [16] with BCR/ABL is a good example. Specific molecule targeting therapy should be developed against pathogenic molecules responsible for leukemogenesis. Meanwhile, it is necessary to explore separate treatment regimens for prognostically different subtypes of AML with conventionally available modalities in order to increase the cure rate of adult leukemia.

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ORIGINAL ARTICLE

Comparative analysis of remission induction therapy for high-risk MDS and AML progressed from MDS in the MDS200 study of Japan Adult Leukemia Study Group

Yasuyoshi Morita · Akihisa Kanamaru · Yasushi Miyazaki · Daisuke Imanishi · Fumiharu Yagasaki · Mitsune Tanimoto · Kazutaka Kuriyama · Toru Kobayashi · Shion Imoto · Kazunori Ohnishi · Tomoki Naoe · Ryuzo Ohno

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Abstract A total of 120 patients with high-risk myelodysplastic syndrome (MDS) and AML progressed from MDS (MDS–AML) were registered in a randomized controlled study of the Japan Adult Leukemia Study Group (JALSG). Untreated adult patients with high-risk MDS and MDS–AML were randomly assigned to receive either idarubicin and cytosine arabinoside (IDR/Ara-C) (Group A) or low-dose cytosine arabinoside and aclarubicin (CA) (Group B). The remission rates were 64.7% for Group A (33 of 51 evaluable cases) and 43.9% for Group B (29 out of 66 evaluable cases). The 2-year overall survival rates and disease-free survival rates were 28.1 and 26.0% for Group A, and 32.1 and 24.8% for Group B, respectively. The duration of CR was 320.6 days for Group A and 378.7 days for Group B. There were 15 patients who lived longer than 1,000 days after diagnosis: 6 and 9 patients in Groups A and B, respectively. However, among patients enrolled in this trial, intensive chemotherapy did not produce better survival than low-dose chemotherapy. In conclusion, it is necessary to introduce the first line therapy excluding the chemotherapy that can prolong survival in patients with high-risk MDS and MDS–AML.

For the Japan Adult Leukemia Study Group.

Y. Morita (✉) · A. Kanamaru
Department of Hematology,
Kinki University School of Medicine,
377-2 Ohno-Higashi,
Osaka-Sayama, Osaka 589-8511, Japan
e-mail: morita@int3.med.kindai.ac.jp

Y. Miyazaki · D. Imanishi
Department of Hematology, Molecular Medicine Unit,
Atomic Bomb Disease Institute, Nagasaki University
Graduate School of Biomedical Sciences, Nagasaki, Japan

F. Yagasaki
Department of Hematology,
Saitama Medical University Hospital, Saitama, Japan

M. Tanimoto
Blood Transfusion Division, Department of Internal
Medicine II, Okayama University Graduate School
of Medicine and Dentistry, Okayama, Japan

K. Kuriyama
Blood Immunology Laboratory, School of Health Sciences,
Faculty of Medicine and University Hospital,
University of the Ryukyus, Okinawa, Japan

T. Kobayashi
Department of Hematopoietic Pathobiology
and Medical Oncology,
Mie University Graduate School of Medicine,
Tsu, Japan

S. Imoto
Hyogo Prefectural Red Cross Blood Center,
Hyogo, Japan

K. Ohnishi
Third Department of Internal Medicine,
Hamamatsu University School of Medicine,
Hamamatsu, Japan

T. Naoe
Department of Hematology and Oncology,
Nagoya University Graduate School of Medicine,
Nagoya, Japan

R. Ohno
Aichi Cancer Center, Aichi, Japan

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1 Introduction

Myelodysplastic syndrome (MDS) is a group of disorders in which abnormalities occur at the level of hematopoietic stem cells [1], leading to disturbance in the production of blood cells characterized by ineffective hematopoiesis [2], decrease in the number of peripheral blood cells and morphological/functional abnormalities in blood cells [3]. Allogeneic hematopoietic cell transplantation (allo-HCT) is the most effective curative therapy for acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) [4]. However, for patients with high-risk MDS (those with refractory anemia with excess of blasts in transformation (RAEB)-t and some patients with RAEB) and patients with acute myeloid leukemia progressed from MDS (MDS–AML), chemotherapy aimed at remission is being used. The reasons for this are that MDS often affects elderly people [5], suitable donors are not always available at the time of disease onset, the necessity of pretransplant conditioning chemotherapy is controversial [6, 7] with a lack of sufficient evidence, and the optimal timing for transplantation varies widely depending on disease type [8].

On the other hand, reduced-intensity conditioning has extended the use of allo-HSCT to patients otherwise not eligible for this treatment due to older age or frailty [9]. However, allo-HSCT using traditional myeloablative preparative regimens is not easily tolerated by the elderly or frailer patient, and may lead to prohibitive treatment-related mortality rates. Most patients treated in the past were younger and devoid of comorbid clinical conditions. Novel reduced-intensity regimens have recently made allogeneic transplants applicable to the elderly, providing the benefit of the graft-versus-leukemia effect to a larger number of patients in need [10].

Low-dose chemotherapy, which has been used in clinical practice for 20 years, reduces the number of myeloblasts, improves pancytopenia and induces remission not only in MDS patients but also in some MDS–AML patients [11]. Common antineoplastic agents used in low-dose chemotherapy include cytosine arabinoside (Ara-C), aclarubicin (ACR), melphalan and etoposide. Nevertheless, despite improved Ara-C and regimens, the prognosis of AML in patients beyond 60 years of age remains dismal [4]. Low-dose antineoplastic drug therapy is still being used in some patients with MDS, which is common in elderly people, especially when the patient is at risk due to poor general condition or organ disorder [12].

The Japan Adult Leukemia Study Group (JALSG) previously conducted a pilot study for the treatment of high-risk MDS and MDS–AML to compare low-dose monotherapy with low-dose Ara-C plus granulocyte colony-stimulating factor (G-CSF) and multiple drug therapy with Ara-C plus Mitoxantrone plus VP-16. Later, JALSG conducted studies using a single protocol (JALSG MDS96) in 1996, in which remission induction and post-remission therapies using Ara-C and IDR in patients with high-risk MDS (RAEB-t) and in those with MDS–AML were performed, after which the efficacy and safety of these therapies were evaluated [13]. Furthermore, a randomized controlled study (JALSG MDS200) of intensive chemotherapy (IDR/Ara-C) or low-dose chemotherapy (CA) for high-risk MDS was also performed by JALSG.

Here, we present and analyze the results of the JALSG MDS200 study to assess and evaluate the validity of the MDS200 protocol for MDS treatment.

2 Patients and methods

2.1 Patient eligibility

A total of 120 patients were initially registered into the JALSG MDS200 study between June 2000 and March 2005. They were assigned into two groups, namely, Groups A and B (Table 1). Patients aged 15 years or more and diagnosed as having high-risk RAEB with high International Prognostic Scoring System score [14], RAEB-t or MDS-AML were eligible for this study. MDS–AML denotes secondary AML transformed from MDS.

Other eligibility criteria were as follows: patients with a performance status (PS) of 0–2 (ECOG); patients whose key organs other than the bone marrow retain intact function; patients who have not undergone any chemotherapy, except for pretreatment that does not affect the outcome of the main therapy; and patients who have given informed consent. Informed consent was obtained after carefully explaining the protocol and before registration.

2.2 Study protocol

The MDS200 protocol (Fig. 1) was designed based on the results of MDS96, and involved a dose-attenuation plan and allowed a wider range of chemotherapy. Patients were randomly assigned to either Group A or B.

In therapy A, the dose was adjusted according to a dose attenuation plan based on the presence of risk factors. The following 3 factors were regarded as risk factors: (1) Age ($\geq$60 years), (2) hypoplastic bone marrow and (3) PS $\geq$ 2. Patients with no risk factor received the standard dose, those with 1 risk factor received 80% of the dose and those with 2 or more risk factors received 60% of the dose (equivalent to the dose of MDS96). In therapy B, the use of

Table 1 Characteristics of patients

Group	A ($n = 53$)	B ($n = 67$)	P value (A vs. B)
Age (range)	63 (23–77)	61 (32–81)	0.505
Gender			
Male	37	52	0.332
Female	16	15	
Disease type			
HR-RAEB	4	11	0.269
RAEB-T	22	29	
MDS–AML	27	27	
Infection			
Presence	10	11	0.726
None	43	56	
Karyotype[a]			
Good	23 (44.2%) $n = 52$	21 (33.9%) $n = 62$	0.524
Int	11 (21.2%)	15 (24.2%)	
Poor	18 (34.6%)	26 (41.9%)	
PB (range)			
WBC (/μL)	2,500 (700–64,240)	2,720 (600–43,700)	0.665
Hb (g/dL)	8 (4.7–12.6)	7.9 (4.4–12.7) $n = 66$	0.562
Plt (/μL)	5.8 (0.2–31.4)	5.9 (0.5–36.7)	0.363
BM (range)			
Blast (%)	30 (4–95) $n = 51$	24.2 (1.9–96) $n = 66$	0.171
Biochemical data (range)			
LDH (IU/L)	296 (132–882)	303.5 (111–906) $n = 66$	0.998
CRP (mg/dL)	0.5 (0–20.2)	0.35 (0–11.7) $n = 66$	0.292

Patients who met all of the inclusion criteria and did not meet any of the stated exclusion criteria were included the study. The disease types were classified by FAB classification

Statistical analysis between Group A and Group B was done using χ^2 test or Mann–Whitney U-test

MDS myelodysplastic syndrome, *HR-RAEB* high risk-refractory anemia excess of blasts with high International Prognostic Scoring System Score, *RAEB-T* refractory anemia excess of blasts in transformation, *MDS–AML* MDS overt leukemia, *WBC* white blood cell, *Hb* hemoglobin, *Plt* platelet, *LDH* lactate dehydrogenase, *CRP* C-reactive protein, *PB* peripheral blood, *BM* bone marrow

[a] Shows IPSS risk

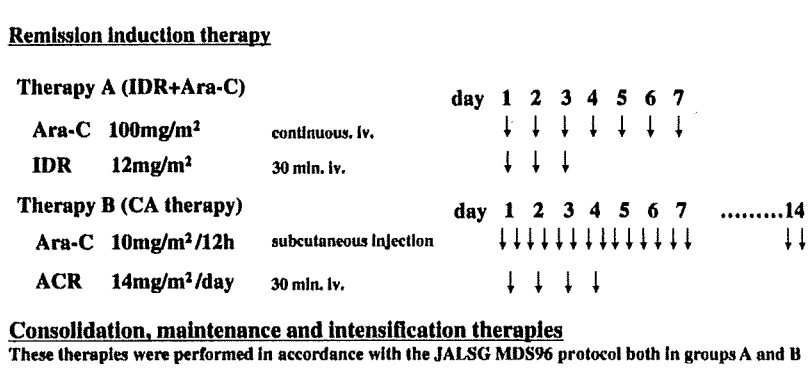

Fig. 1 Japan Adult Leukemia Study Group—myelodysplastic syndrome (JALSG MDS200 Protocol). In therapy A, the dose was adjusted according to a dose attenuation plan based on the presence of risk factors. The following 3 factors were regarded as risk factors: (1) Age (≥60 years), (2) hypoplastic bone marrow and (3) PS ≥ 2. Patients with no risk factor received the standard dose, those with 1 risk factor received 80% of the dose, and those with 2 or more risk factors received 60% of the dose (equivalent to the dose of MDS-96). In therapy B, the use of CAG therapy involving co-administration of G-CSF was allowed. *IDR* idarubicin, *Ara-C* cytosine arabinoside, *ACR* aclarubicin, *G-CSF* granulocyte colony-stimulating factor, *iv* intravenous injection, *min* minutes

CAG therapy involving the co-administration of granulocyte colony-stimulating factor (G-CSF) was allowed.

Untreated adult patients (≥15 years) with MDS (RAEB, RAEB-t or MDS–AML) were randomly assigned to receive either IDR/Ara-C (Group A) or CA (Group B) [15]. Complete remission (CR) rate, CR duration, overall survival (OS) rate and disease-/relapse-free survival (DFS/RFS) rate were compared between the two groups.

Consolidation therapy and maintenance therapy were performed in accordance with JALSG MDS96 [13].

2.3 Evaluation of response

Response to treatment was evaluated in accordance with JALSG criteria [13]. CR was considered achieved when the following conditions remained for at least 4 weeks. For the bone marrow: blasts accounting for ≤5% of all cells; absence of blasts with Auer body; and presence of normal erythroblasts, granulocytes and megakaryocytes. For peripheral blood: absence of blasts; neutrophils ≥ 1,000/ml; platelets ≥ 100,000/μL; and no evidence of extramedullary leukemia. CR duration was defined as the duration from the day when CR is achieved to the day of relapse or death, OS or DFS as the duration from the day of initiation of treatment to the day of death and DFS as the duration in which CR patients survived without relapse. Patients who were treated with HCST were not censored at the date of transplantation. All toxicity was graded using the World Health Organization criteria [16].

2.4 Statistical analysis

The primary endpoint of this study is DFS. Assuming a 1-year DFS rate of 60% in the Group A and 40% in the Group B, this design required the randomization of 200 patients. Eligible patients were randomized according to age, sex and disease type. Differences in background factors (e.g., age, gender and disease type) between Groups A and B were statistically analyzed using the χ^2 test or Mann–Whitney *U*-test. Probability of OS and DFS were estimated according to the method of Kaplan and Meier.

3 Results

3.1 Recruitment of patients and suspension of the study

The initially registered 120 patients were assigned into two groups, namely, Groups A and B. The clinical characteristics of the registered patients are shown in Table 1. The present protocol was originally planned to recruit 200 patients for Groups A and B within 3 years. However, the recruitment pace was slower than expected and thus the study period was extended from 3 years to 4.5 years. At the end of 2004, that is, after 4.5 years from the start of the study, the number of registered patients was only 113 in Groups A and B, which was 56.5% of the target number. At that point, the committee members discussed the progress of the MDS200 study and decided to suspend it at the end of March 2005. Since the final total number of patients did not reach the target number, we did not statistically compare DFS between Groups A and B, which was the primary endpoint of this study.

3.2 Characteristics of patients

There were no clear differences in the clinical characteristics of the patients between Groups A and B, such as FAB subtype, initial blood cell count, presence of infection, distribution in the karyotype group and biochemical data, as well as sex distribution (male/female ratio, 37/16 = 2.315 in Group A, and 52/15 = 3.467 in Group B).

3.3 Treatment outcome

The remission rates were 64.7% in Group A (33 out of 51 evaluable cases) and 43.9% in Group B (29 out of 66 evaluable cases). The 2-year overall survival (OS) rates were 28.1% in Group A and 32.1% in Group B, and the 2-year DFS rates were 26.0% in Group A and 24.8% in Group B. The mean duration of CR was 320.6 days (median: 213 days) in Group A and 378.7 days (median: 273 days) in Group B (Table 2). Reflecting the intensity of the remission induction chemotherapy, the period of WBC (<1,000/μL) after the therapy was longer in Group A than in Group B (19 days and 4 days, respectively). There were more grade 3 or 4 adverse events during the remission induction therapy in Group A (19 out of 53 evaluable patients) than in Group B (13 out of 67 evaluable patients). This difference was mostly attributable to infectious episodes (17 patients in Group A and 4 patients in Group B). In terms of bleeding episodes, 1 patient in Group A and 2 in Group B had grade 3/4 adverse events. The numbers of

Table 2 Treatment outcome (Group A vs. B)

	Group A ($n = 53$)	Group B ($n = 67$)
Remission rate (%)	64.7	43.9
Mean duration of remission (days)	320.6 (median: 213)	378.7 (median: 273)
2-Year survival rate (%)	28.1	32.1
2-Year disease-free survival rate (%)	26.0	24.8

The remission rates, 2-year overall survival (OS) rates and 2-year disease-free survival (DFS) rates are shown as percentages

early death in remission induction chemotherapy (death within 30 days) were 1 patient in Group A and 3 patients in Group B (Table 3). The cause of death in each group was infection or tumor progression. The completion rate of consolidation therapies were 37.3% in Group A (12 out of 33 evaluable cases), 37.9% in Group B (11 out of 29 evaluable cases). On the other hand, the maintenance therapies were completed 21.2% in Group A (7 out of 33 evaluable cases), and 15.2% in Group B (5 out of 33 evaluable cases). The numbers of dose attenuation in Group A were 30 patients of 100% dose, 21 patients of 80% or 60% dose and 2 patients of unknown.

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) was performed in 11 out of 50 patients (22%) in Group A and 19 out of 66 patients (28.8%) in Group B. Among those who received allo-HSCT, the transplantation was performed during the first remission in 40%, 21% of patients in Groups A, B, respectively.

There were 15 patients who lived longer than 1,000 days after diagnosis: 6, 9 patients in Groups A, B, respectively. Regarding the transplantation among long-term survivors, 3 out of 6 patients were transplanted in Group A, 6 out of 9 in Group B. Comparing the achievement of CR among these patients in Groups A and B, all 6 patients in Group A achieved CR, but only 4 out of 9 patients in Group B achieved CR.

Table 3 Toxicity of the induction therapy

	A ($n = 53$) (range)	B ($n = 67$) (range)	P value (A vs. B)
Period of WBC <1,000 (day)	19 (0–44) $n = 49$	4 (0–50) $n = 63$	<0.0001
Toxicity (grade 3/4)			
Presence	19	13	0.427
Bleeding	2	1	ND
Infection	17	11	0.04
Others	2	2	ND
Early death (<30 days)	1	3	ND

Statistical analysis between Groups A and B was performed using the χ^2 test or Mann–Whitney U-test

ND not done

4 Discussion

In this MDS200 study, patients with high-risk MDS and AML transformed from MDS (MDS–AML) were treated with either intensive or low-dose remission induction therapy, followed by intensive post-remission therapy that was the same as in the JALSG MDS96 study [13].

Although we did not perform statistical comparison of DFS or OS between these two treatment groups due to the insufficient number of patients enrolled, the results suggest that there was no significant difference, that is, survival curves were superimposable (Figs. 2, 3). Intensive chemotherapy similar to that for AML can produce a CR rate of 64.7% for high-risk MDS and MDS–AML patients, whereas low-dose induction therapy can result in a CR rate of 43.9%. However, among the patients enrolled in this trial, the difference in CR rate did not lead to better survival as described above. In terms of adverse events, patients who received intensive treatment had more grade 3 or 4 adverse events, particularly infectious events with a longer period of leukopenia. There was no increase in the number of patients succumbing to early death (death within 30 days after the

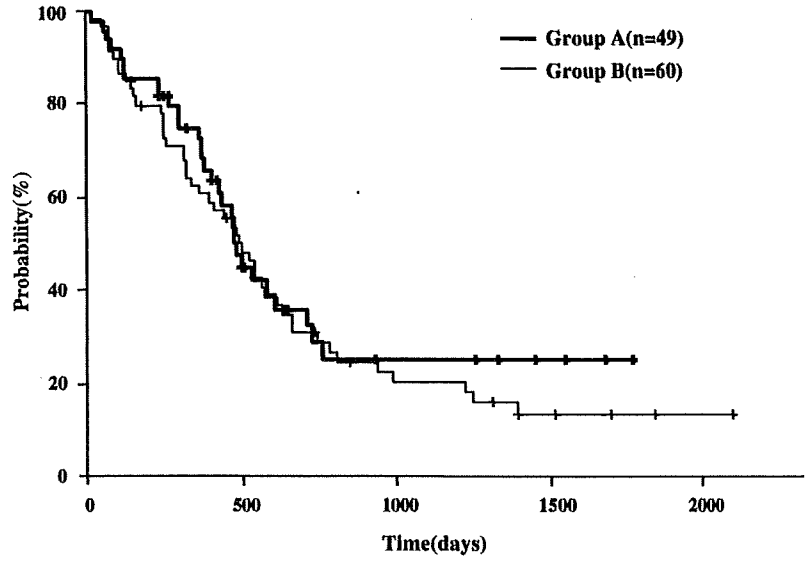

Fig. 2 Overall survival. Survival was calculated from the date of the start of treatment to the date of death due to any cause or to the date of the most recent follow-up. These data were not censored at the time of HSCT. All randomized patients were not included this data in each group. Due to this reason, some patients were not known to be CR or not, but known to be alive or not

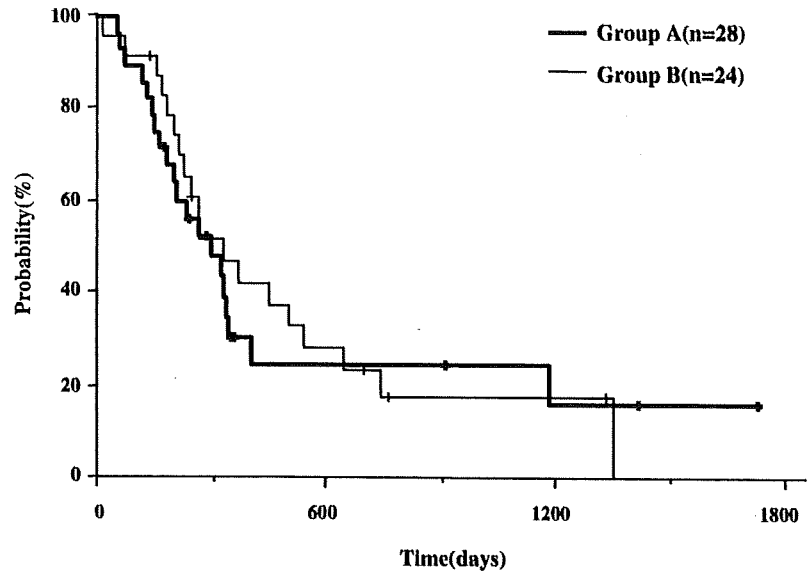

Fig. 3 Disease-/relapse-free survival. RFS was calculated from the date of achieving complete remission to the date of relapse, death or the most recent follow-up. These data were not censored at the time of HSCT. All randomized patients were not included this data in each group. Due to this reason, some patients were not known to be CR state or relapse, but known to be alive or not

start of treatment) in Group A, suggesting that intensive treatment produced higher CR rate, and higher toxicity resulted in a similar survival rate with low-dose induction therapy at least during the early phase of treatment.

There are several reasons that could explain why no difference in survival rate was observed regardless of the difference in CR rate. One could be the similar post-remission therapy between Groups A and B, as demonstrated by the almost similar DFS curves among the two groups. Another reason could be the disease status at the time of transplantation for patients in the two groups. In Group A, 60% of the transplantation was performed during the period other than that covering the first CR; this was 79% in Group B. Allo-HSCT has been shown to have the strongest antileukemia effect, and this was also found in the current study in which 6 out of 15 long-term survivors received allo-HSCT in Groups A and B. From the viewpoint of transplantation, intensive treatment merely selected cases that were suitable for transplantation, as observed in the case of transplantation for relapsed AML patients [17]. There are arguments against remission induction therapy for MDS patients in that it does not affect post-transplant prognosis [6, 18]. In the results of JSHCT, the chemotherapy before undergoing allo-SCT is not necessary in patients with MDS [6]. A group from the Institute of Medical Science of Tokyo University performed umbilical cord blood stem cell transplantation without remission induction therapy in high-risk MDS patients aged not more than 55 years and obtained favorable results with reduced time from diagnosis to transplantation [19]. It is important to perform clinical studies based on the concept that HCST should be performed immediately after diagnosis without remission induction, and determine the types of patients who would benefit from remission induction therapy prior to transplantation in terms of prognosis. In the present study, although suspended because of the insufficient number of patients enrolled, it appears that remission induction therapy with IDR and Ara-C did not produce better survival than that with low-dose chemotherapy despite higher CR rate. Therefore, it is suggested that CR rate is not a suitable surrogate marker for the evaluation of the outcome of chemotherapy for high-risk MDS and MDS–AML. In the latest reports, induction chemotherapy for patients with high-risk MDS and MDS–AML also provide no survival advantage [20, 21]. Considering the low survival rate of patients in this category, it is clearly necessary to introduce new strategies for the treatment of high-risk MDS and MDS–AML, such as molecular targeting agents and allo-HSCT with reduced-intensity conditioning regimens.

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ORIGINAL ARTICLE

Allogeneic stem cell transplantation versus chemotherapy as post-remission therapy for intermediate or poor risk adult acute myeloid leukemia: results of the JALSG AML97 study

Hisashi Sakamaki · Shuichi Miyawaki · Shigeki Ohtake · Nobuhiko Emi · Fumiharu Yagasaki · Kinuko Mitani · Shin Matsuda · Yuji Kishimoto · Yasushi Miyazaki · Norio Asou · Masatomo Takahashi · Yoshiaki Ogawa · Sumihisa Honda · Ryuzo Ohno

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Abstract We prospectively compared allogeneic hematopoietic stem cell transplantation (allo-HSCT) with chemotherapy as a post-remission therapy in a multicenter trial (JALSG AML97) of adult patients with intermediate or poor risk acute myeloid leukemia (AML). Of 503 patients aged 15–50 years old registered between December 1997 and July 2001, 392 achieved complete remission (CR). CR patients classified in the intermediate or poor risk group using a new scoring system were tissue typed. Seventy-three with and 92 without an HLA-identical sibling were assigned to the donor and no-donor groups. Of 73 patients in the donor group, 38 (52%) received allo-HSCT during CR1 and 17 (23%) after relapse. Intention-to-treat analysis revealed that the relapse incidence was reduced in the donor group (52 vs. 77%; $p = 0.008$), and the disease-free survival (DFS) improved (39 vs. 19%; $p = 0.016$), but overall survival (OS)

For the Japan Adult Leukemia Study Group (JALSG).

H. Sakamaki (✉)
Division of Hematology, Tokyo Metropolitan Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan
e-mail: sakamaki-h@cick.jp

S. Miyawaki
Division of Hematology, Tokyo Metropolitan Ohtsuka Hospital, Tokyo, Japan

S. Ohtake
Department of Clinical Laboratory Science, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan

N. Emi
Department of Hematology, Fujita Health University, Aichi, Japan

F. Yagasaki
Department of Internal Medicine (Hematology), Saitama Medical School, Saitama, Japan

K. Mitani
Department of Hematology, Dokkyo University School of Medicine, Tochigi, Japan

S. Matsuda
Center for Hematopoietic Disorders, Ohtanisinouchi Hospital, Kohriyama, Japan

Y. Kishimoto
The First Department of Internal Medicine, Kansai Medical University, Osaka, Japan

Y. Miyazaki
The Department of Hematology, Atomic Bomb Disease Institute, Nagasaki University School of Medicine, Nagasaki, Japan

N. Asou
Department of Hematology, Kumamoto University School of Medicine, Kumamoto, Japan

M. Takahashi
Division of Hematology and Oncology, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan

Y. Ogawa
Department of Hematology and Oncology, Tokai University School of Medicine, Kanagawa, Japan

S. Honda
Department of Radiation Epidemiology, Atomic Bomb Disease Institute, Nagasaki University School of Medicine, Nagasaki, Japan

R. Ohno
Aichi Cancer Center, Aichi, Japan

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was not significantly different (46 vs. 29%; $p = 0.088$). The OS benefit was seen in the patients aged 36–50 years old (49 vs. 24%; $p = 0.031$), suggesting an advantage of allo-HSCT among older patients with leukemia that is more resistant to chemotherapy than that among younger patients.

Keywords AML · Allogeneic hematopoietic stem cell transplantation · Post-remission chemotherapy

1 Introduction

Around 70–80% of newly diagnosed patients with adult acute myeloid leukemia (AML) achieve complete remission (CR) when treated with cytarabine (AraC) and anthracycline, usually daunorubicin (DNR) or idarubicin (IDR). However, only about one-third of these patients remain disease free for more than 5 years [1–5]. Intensified post-remission chemotherapy has improved the survival rates of patients with AML, especially of younger patients [6]. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is considered to be the most intensive post-remission treatment consisting of high-dose chemoradiotherapy and allo-immune mechanisms. However, the powerful anti-leukemic effects of this treatment are counterbalanced by a high incidence of treatment-related mortality (TRM). Thus, allo-HSCT has not always been considered superior to chemotherapy [7, 8]. Intensified chemotherapy with high-dose Ara-C confers promising results on good risk patients [9] for whom allo-HSCT is currently abstained in the first CR (CR1). The Japan Adult Leukemia Study Group (JALSG) AML97 protocol committee circulated a questionnaire among the institutions participating in JALSG regarding their policy about indications for allo-HSCT among AML patients in CR1. The findings revealed that good risk patients in CR1 did not undergo an allo-HSCT at most of these institutions. Cytogenetic profile has been widely used to classify the patients with AML [7–13]; however, cytogenetic studies are not always foolproof. The JALSG established a scoring system that adopted significant factors including cytogenetic results from previous JALSG AML trials [14]. We applied this scoring system to stratify patients and conducted a prospective, multicenter cooperative study (AML97) to compare allo-HSCT with chemotherapy among intermediate and poor risk patients with AML in CR1.

2 Patients and methods

2.1 Patients and study design

The JALSG AML97 study was implemented between December 1997 and July 2001 at 103 institutions where the ethical committees approved the protocol. Adult patients aged from 15 to 64 years newly diagnosed with de novo AML according to the French–American–British (FAB) classification at each institution were eligible, but those with acute promyelocytic leukemia (APL) were excluded. Peripheral blood and bone marrow smears of the registered patients were stained with May-Giemsa, peroxidase, and esterase at Nagasaki University and subsequently reviewed by a central review committee. All patients provided written informed consent to participate before registration in this study.

The chemotherapeutic design of AML97 has been described elsewhere in detail [15]. In short, all the patients were treated with the same induction therapy consisted of AraC (100 mg/m^2, continuous infusion, days 1–7) and IDR (12 mg/m^2 days 1–3). If the patients did not achieve remission after the first induction therapy, then the same therapy was given again. For patients who did not achieve a CR even after second induction therapy, no further treatment was defined in this study. In the comparison between allo-HSCT and chemotherapy as post-remission therapy, these patients were not included in the analysis. All patients who achieved CR were randomized to receive either 4 courses of consolidation therapy without maintenance therapy (group A) or the conventional JALSG post-remission regimen with maintenance therapy (group B) [3]. The results of the two post-remission chemotherapeutic strategies (group A vs. group B) were comparable [15]. The CR patients were classified into good, intermediate or poor risk groups according to the scoring system described below. Intermediate or poor risk patients younger than 50 years old with living siblings were tissue typed. Patients with an HLA-identical sibling were assigned to undergo allo-HSCT soon after three courses of consolidation therapy (donor group), and those without living or HLA-identical siblings were assigned to the no-donor group that continued receiving chemotherapy.

Patients in the donor group with AST or ALT values fourfold higher than the normal range, serum bilirubin and creatinine more than 2 mg/dl, ejection fraction based on an echocardiogram of less than 50% or oxygen saturation according to pulse oximetry of less than 90% were ineligible for allo-HSCT, but were analyzed as a donor group one in an intention-to-treat fashion. Conditioning before transplantation and prophylaxis for graft-versus-host disease was performed according to each institutional standard. Either allogeneic peripheral blood or bone marrow was allowed to be the stem cell source.

2.2 Scoring system

We collected clinical and laboratory data (except for APL) from previous JALSG AML trials (AML87, $n = 234$

Table 1 JALSG scoring system

Scoring system		
System 1		
MPO positive blasts	>50%	+2
Age	≤50 years	+2
WBC	≤2 × 10^9/l	+2
FAB subtypes	non-M0, M6, M7	+1
Performance status	0, 1, 2	+1
No. of induction	1	+1
t(8;21) or inv(16)	+	+1
Total score		
Good risk group		8–10
Intermediate risk group		5–7
Poor risk group		0–4
System 2		
MPO positive blasts	>50%	+2
Age	≤50 years	+2
WBC	≤2 × 10^9/l	+2
FAB subtypes	non-M0, M6, M7	+1
Performance status	0, 1, 2	+1
Total score		
Good risk group		7–8
Intermediate risk group		4–6
Poor risk group		0–3

MPO myeloperoxidase, *WBC* white blood cell

patients; AML89, $n = 311$; AML92, $n = 986$), and then selected significant factors for achieving CR, disease-free survival (DFS) and overall survival (OS) using multivariate analysis [14]. According to the weight of significance, myeloperoxidase positivity of blasts, patient age, and WBC count at diagnosis were valued at 2 points, and FAB subtypes, performance status, numbers of inductions required to achieve CR, and favorable karyotypes of t(8;21) or inv(16) were valued at 1 point (Table 1, system 1). When we originally planned to use this system, cytogenetic data were not always available at diagnosis. Thus, we designed the system 2 that could be applied even without a cytogenetic data.

2.3 Statistical analysis

The aim of this study was to compare the efficacy of allo-HSCT and chemotherapy as a post-remission treatment, by evaluating DFS and OS rate. Forty-two patients were estimated for an evaluation of the primary endpoint of this study. The JALSG data management committee collected the clinical data from all participating institutions, then fixed them and analyzed the OS of each risk group in July 2004 and the relapse rate (RR), DFS, OS and TRM of the donor and no-donor groups in January 2009. The OS, DFS, RR and TRM were measured from the date of CR. The event for OS was death due to all causes, and patients were censored at the last observation date if alive. The events of DFS were death during CR or relapse. The RR was defined as the cumulative probability of relapse, censoring at death in CR. The events of TRM comprised death before relapse. We estimated OS, DFS, RR and TRM with their respective standard errors using the Kaplan–Meier method [16]. We compared the OS, DFS, RR and TRM between the patients with and without a donor using the log-rank test. Furthermore, the hazard ratio and the 95% confidence interval (CI) of the OS, DFS, RR and TRM were calculated using Cox regression analysis. The Wilcoxon rank-sum test was used for the continuous data, such as age and WBC count, while the Chi-square test was used for the ordinal data, such as the risk group and the frequency of allo-HSCT. All analyses were performed on the intention-to-treat principal with all patients in their allocated arms. Adding to the prospective comparison of the efficacy between allo-HSCT and chemotherapy, we also retrospectively performed subgroup analysis by age. Statistical analyses were conducted using the SAS software package (SAS Institute, Inc, Cary, NC).

3 Results

3.1 Study patients and genetical allocation

Five hundred and three de novo AML patients aged from 15 to 50 years participated in the AML97 comparison of allo-HSCT with chemotherapy as a post-remission therapy. Of 392 patients achieved CR, 62 patients were excluded from the analysis because of insufficient data mainly deficient clinical data at diagnosis which were essential to verify their classification. Three hundred and thirty evaluable patients were classified into the good ($n = 149$), intermediate ($n = 162$) or poor risk ($n = 19$) groups using the scoring system described above (Fig. 1). The 5-year OS

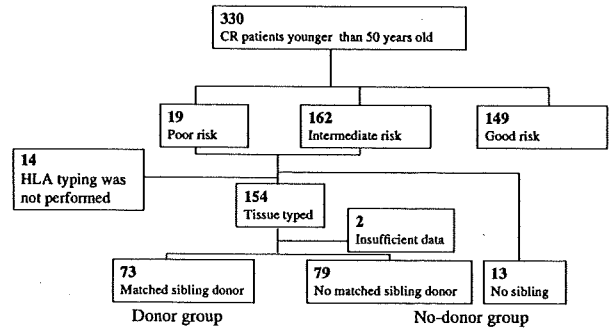

Fig. 1 Overview of patients included in analysis by risk classification, HLA typing, and donor availability

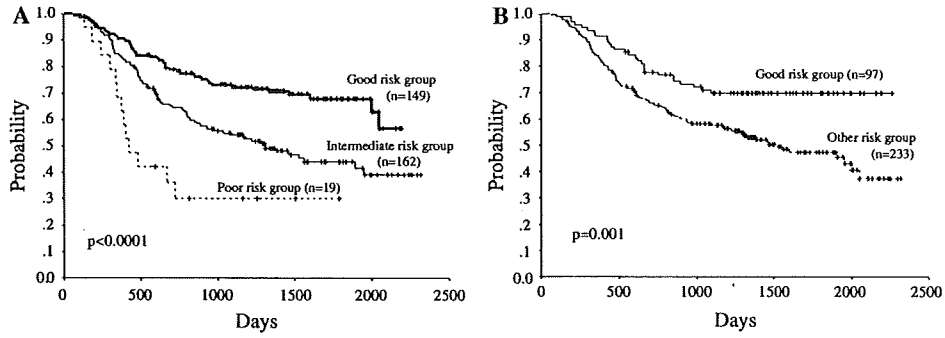

Fig. 2 Overall survival of patients in CR according to JALSG scoring system (**a**) and by cytogenetic studies (**b**)

rates of the CR patients with good, intermediate and poor risk were 68, 44 and 30%, respectively [hazard ratio (HR), 0.51 (good vs. intermediate) and 0.25 (good vs. poor), respectively; 95% confidential interval (CI), 0.35–0.73 (good vs. intermediate) and 0.14–0.48 (good vs. poor); $p < 0.0001$; Fig. 2a]. Among the intermediate and poor risk patients with living siblings, 154 patients and their siblings were examined for their HLA types. Seventy-three of these patients had an HLA-identical sibling and were assigned to the donor group. Thirteen patients with no siblings and 79 patients without an HLA-identical sibling were assigned to the no-donor group (92 patients). Finally, one patient in donor group and one patient in no-donor group were excluded from the analysis because of their insufficient data of survival (Fig. 1). The follow-up durations of the donor and no-donor groups were 1854 days (range 163–3176 days) and 1010 days (range 93–3008 days), respectively.

3.2 Patient characteristics of donor versus no-donor groups

Table 2 shows the characteristics of patients in the donor and no-donor groups. The distributions of these features were comparable in both groups with respect to age, gender, initial WBC count, MPO positivity of blasts, FAB subtype, performance status, prognostic risk according to JALSG score, presence of favorable cytogenetic abnormalities, and the groups of post-remission chemotherapy.

3.3 Donor group

Fifty-six patients (76%) in the donor group actually underwent allo-HSCT (Table 2). Thirty-eight patients (52%) received an allo-HSCT during CR1 at a median of 159 days (range 43–314 days) from CR1. Eighteen patients underwent allo-HSCT after relapse. The median times between CR1 and relapse and between CR1 and a transplantation were 183 days (range 39–757 days) and 248 days (range 157–973 days), respectively. Thirty and 24 patients were transplanted after undergoing a conditioning regimen with or without total body irradiation (TBI), respectively, and conditioning information was not available for 2 patients. The sources of transplanted stem cells were bone marrow cells ($n = 26$), peripheral blood cells ($n = 27$) and bone marrow cells together with peripheral blood cells ($n = 2$). Twenty-nine of the 56 patients in the donor group who underwent allo-HSCT remain alive. Twenty patients died of recurrent leukemia and 7 of transplant-related causes. Seventeen patients allocated to the donor group did not receive a transplantation for the following reasons; patients' refusal ($n = 6$), donors' refusal to donate ($n = 2$), physician's decision ($n = 1$), disease progression before transplantation ($n = 2$), donor health problems ($n = 2$) and unknown reasons ($n = 4$).

3.4 No-donor group

Of the 92 patients in the no-donor group, 42 eventually underwent HSCT (Table 2): autotransplantation ($n = 3$), allo-HSCT from HLA mismatched-related donors ($n = 4$), allo-HSCT from an HLA matched-unrelated donor ($n = 28$), and allo-HSCT from an HLA-mismatched unrelated donor ($n = 7$). Eleven patients underwent a transplantation during CR1 from an unrelated donor or mismatched-related donor at a median of 281 days (range 170–1700 days) from CR1, significantly later than those transplanted during CR1 in the donor group ($p < 0.001$). Thirty-one patients received a transplantation after relapse. The median times between CR1 and relapse and between CR1 and a transplantation were 329 days (range 92–876 days) and 519 days (range 167–1373 days), respectively.

3.5 Comparison of donor versus no-donor groups

The actual risk of relapse at 8 years was significantly lower in the donor group than in the no-donor group (52 vs. 77%, respectively, HR, 0.58; 95% CI, 0.39–0.88; $p = 0.008$; Table 3). The TRM did not significantly differ between the donor and the no-donor groups (16 vs. 17%, respectively, HR, 0.97; 95% CI, 0.34–2.80; $P = 0.959$; Table 3). Seven

Table 2 Patients' characteristics

	Donor	No-donor	*p*
Total number	73	92	
Age			
Median (range)	37 (16–50)	36 (15–50)	0.60[a]
15–35 years	33	46	
36–50 years	40	46	0.54[b]
Sex			
M/F	44/29	45/47	0.15[b]
WBC at diagnosis (10^9/l) (range)	3.8 (0.05–36.8)	5.1 (0.14–45.0)	0.16[a]
MPO positivity of blasts (range)	30 (0–100)	50 (0–100)	0.18[a]
FAB classification			
M0	4	6	
M1	18	25	
M2	22	24	
M4	20	23	
M5	7	14	
M6	1	0	
M7	1	0	0.67[b]
Performance status			
0–1	66	84	
2–3	7	8	0.70[b]
Risk classification by JALSG scoring system			
Intermediate	64	84	
Poor	9	8	0.45[b]
Cytogenetics			
t(8;21) or inv(16)	4	4	0.74[b]
Chemotherapy group			
Group A	38	42	
Group B	30	47	0.28[c]
Not randomized	5	3	
Allogeneic transplant			
During CR1	38	11	
		9 from UD	
		1 from MUD	
		1 from MRD	
After relapse	18	31	
No transplant	17	50	

UD HLA-matched unrelated donor, *MUD* HLA-mismatched unrelated donor, *MRD* HLA-mismatched related donor, *WBC* white blood count, *MPO* myeloperoxidase

[a] Mann–Whitney test

[b] Chi-square test

[c] Chi-square test excluding non-randomized

patients in the donor group and four in the no-donor group died of transplant-related causes during CR1. The lower RR in the donor group resulted in a significantly better DFS compared with the no-donor group (39 vs. 19%, respectively, HR, 0.63; 95% CI, 0.44–0.92; $P = 0.016$; Table 3; Fig. 3). The significant superiority of DFS in the donor group translated into a higher OS rate, but the difference in OS between the two groups did not reach statistical significance (46 vs. 29%, HR, 0.70; 95% CI, 0.47–1.06; $p = 0.088$; Table 3; Fig. 4).

The donor/no-donor analysis was performed on the intention-to-treat principal, which may underestimate the beneficial effect of allo-HSCT probably because of low compliance of transplantation. The 8-year DFS and OS of the recipients actually transplanted during CR1 ($n = 38$) in the donor group were significantly better than those of the patients not transplanted in the no-donor group ($n = 50$); 58 versus 27%, HR, 0.36; 95% CI, 0.20–0.66; $p < 0.001$, and 61 versus 24%, HR, 0.36; 95% CI, 0.19–0.68; $p = 0.001$, respectively.

Table 3 Effects of donor availability on outcome in donor and no-donor groups

Outcome	Donor			No-donor			*p*	HR (95% CI)
	n	No. of events	Probability of outcome at 8 years ±SE (%)	*n*	No. of events	Probability of outcome at 8 years ±SE (%)		
All patients	73			92				
RR		36	52 ± 6		67	77 ± 5	0.008	0.58 (0.39–0.88)
TRM		7	16 ± 6		7	17 ± 7	0.959	0.97 (0.34–2.80)
DFS		44	39 ± 6		74	19 ± 4	0.016	0.63 (0.44–0.92)
OS		37	46 ± 7		61	29 ± 6	0.088	0.70 (0.47–1.06)
Age ≤35	33			46				
RR		17	52 ± 9		31	70 ± 7	0.309	0.74 (0.41–1.33)
TRM		2	12 ± 8		3	15 ± 8	0.785	0.78 (0.13–4.71)
DFS		20	39 ± 9		34	26 ± 7	0.366	0.78 (0.45–1.35)
OS		18	42 ± 10		27	35 ± 9	0.860	0.95 (0.52–1.72)
Age >35	40			46				
RR		19	52 ± 9		36	85 ± 6	0.006	0.46 (0.26–0.81)
TRM		5	19 ± 8		4	19 ± 11	0.962	1.03 (0.27–3.92)
DFS		24	39 ± 8		40	12 ± 5	0.012	0.52 (0.31–0.87)
OS		19	49 ± 9		34	24 ± 7	0.031	0.54 (0.31–0.95)

RR relapse rate, *DFS* disease-free survival, *TRM* treatment-related mortality, *OS* overall survival

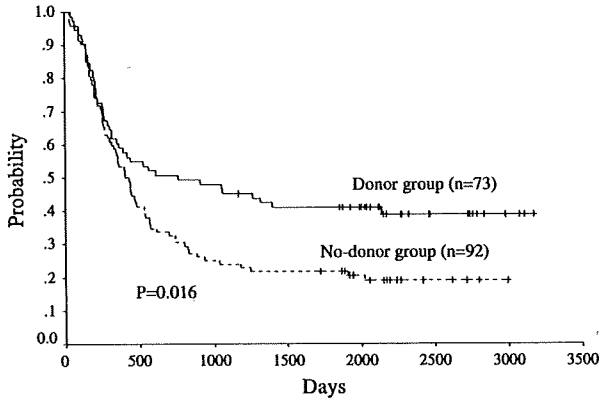

Fig. 3 Disease-free survival in donor and no-donor groups

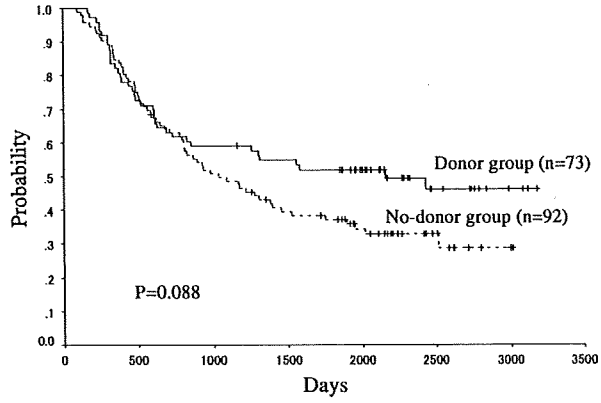

Fig. 4 Overall survival in donor and no-donor groups

3.6 Subset analysis according to patient age

The OS of the patients younger than 35 years of age were comparable between the donor and the no-donor groups (Fig. 5a). However, the OS of the patients aged >35 in the donor group was significantly better compared with the no-donor group (49 vs. 24%, respectively, HR, 0.54; 95% CI, 0.31–0.95; $p = 0.031$; Table 3; Fig. 5b). The RR, TRM, DFS and OS in the donor group were comparable between the two age categories (Table 3; Fig. 5c). In contrast, OS and DFS were marginally worse in the no-donor group of patients aged >35 than ≤35 years (Table 3; Fig. 5d). The distribution of the cytogenetic profile, risk by the JALSG scoring system, myeloperoxidase positivity of blasts, WBC count, FAB classification and performance status at diagnosis did not significantly differ between the two age categories in the no-donor group (data not shown).

4 Discussion

Many clinical trials have compared allo-HSCT with chemotherapy as a post-remission therapy for the patients with AML during CR1. Most of these targeted all patients in CR1 as a single population without prospective stratification by the prognostic factors. Thus, patients were simply assigned into the allo-HSCT or the chemotherapy groups according to donor availability [7, 10, 17, 18]. Here, we

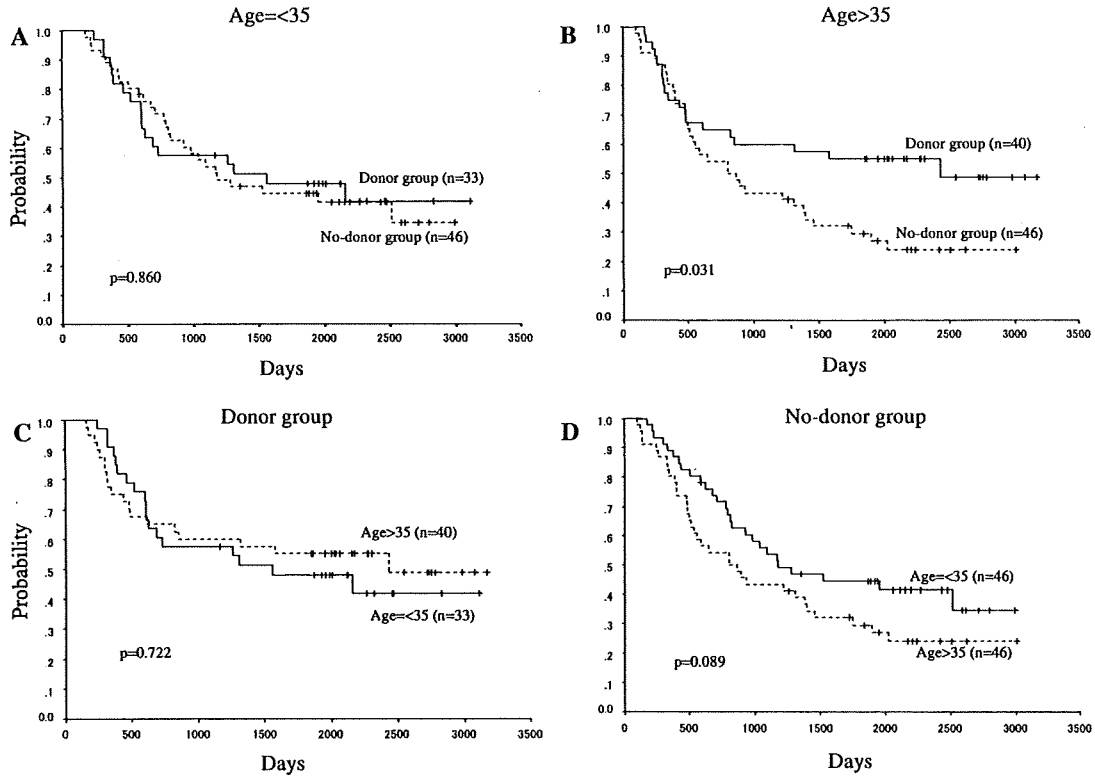

Fig. 5 Overall survival of patients according to age (**a** and **b** ≤35 and >35 years, respectively) and donor availability (**c** and **d**, donor and no-donor groups, respectively)

prospectively compared the effectiveness of allo-HSCT with chemotherapy among patients who were stratified into intermediate or poor risk groups according to JALSG scoring, which constitutes a new means of predicting the prognosis of AML. When this study was planned, as the availability of the cytogenetic study was expected to be variable, and the JALSG scoring system was revealed to be useful to stratify the patients, we adopted a scoring system to select the intermediate and poor risk patients. In contrary to our expectation, cytogenetic studies were performed in 99.2% of the registered patients and the results were available in 97% of the patients. Of 330 CR patients younger than 50 years old, cytogenetic studies disclosed that 97 had good prognostic chromosomal abnormalities, i.e., t(8;21) or inv(16). The OS was significantly better among patients with than without good prognostic cytogenetic profiles (70 vs. 47% at 5 years, with HR, 0.51; 95% CI, 0.34–0.77; $p = 0.001$; Fig. 2b). According to JALSG scoring, 87, 10 and 0 patients with good prognostic cytogenetic abnormalities corresponded to the good, intermediate and poor risk groups, respectively. More good risk patients were selected using this scoring system than by that using karyotype of AML cells alone and about 10% of patients who might be classified into the good risk group by cytogenetic profiles entered the comparison groups by the JALSG scoring system. The JALSG scoring system, which resembles the index used in the Bordeaux Grenoble Marseille Toulouse (BGMT) intergroup study [18], obviously separated patients with a good prognosis who should be excluded from the transplantation trials.

Allo-HSCT prevents AML relapse through intensive cytoreduction using high-dose chemoradiotherapy and graft-versus-leukemia effects. However, previous trials have not always shown advantages of this strategy on the survival of AML patients in CR1. Some studies have not found a benefit of allo-HSCT either on DFS or OS [7, 8], and some showed an advantage only on DFS [10, 17] compared with chemotherapy/auto-transplantation. Retrospective subgroup analysis and meta-analysis have shown a better OS in the donor group [10, 13, 19, 20], demonstrating the importance of limiting the indication of allo-HSCT for only the patients with an intermediate or poor risk.

The following issues should be considered regarding the prospective comparison of allo-HSCT with chemotherapy: assignment of patients according to sibling donor availability [21], low compliance of allo-HSCT for patients in the donor group, and allo-HSCT performed in the no-donor

group from unrelated donors. We could compare the effectiveness of treatment strategies using the intention-to-treat analysis. However, the intrinsic issues of this type of trial and recent advances in alternative stem cell sources will cause difficulties with future prospective comparison of allo-HSCT and chemotherapy using a similar study design.

Although the comparison was performed among patients in the intermediate and poor risk groups, the benefit of allo-HSCT was not significant in OS. Low compliance of allo-HSCT during CR1 in the donor group (52% in the current trial) and allo-HSCT in the no-donor group (total 45%; 11% during CR1) appeared to make the efficacy of allo-HSCT underestimated, especially with regard to OS. However, survival was significantly better among older patients in the donor group (Table 3; Fig. 5b), which seemed to contradict previous findings [19]. Age usually adversely affects allo-HSCT outcome, but it was not associated with the decrease of OS in the donor group in the present study (Table 3; Fig. 5c). Low incidence of TRM probably allowed the powerful anti-leukemic effect of allo-HSCT to function properly, indicating the advantage of allo-HSCT especially among older patients with leukemia that was more resistant to chemotherapy than that among younger patients [1] shown in the no-donor group (Fig. 5d), and caused a contrary result from HOVON/SAKK study. The recent reduction in TRM seemed to contribute much to these results as suggested by others [22, 23]. Different population of the cohorts selected by JALSG scoring and by cytogenetic profiles might also have influenced the present findings.

Molecular markers can be very useful for selecting patients who will most likely benefit from allo-HSCT during CR1 among those with a normal karyotype, which comprises the largest group of patients with AML [24]. The overall safety of allo-HSCT obviously needs improvement, and also patients with chemotherapy-resistant AML who could benefit from allo-HSCT should be identified. Thus, stratification of patients with AML should be improved using a combination of leukemic cell karyotype and, genetic markers and also other clinical findings.

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ORIGINAL ARTICLE

Phase 1/2 clinical study of dasatinib in Japanese patients with chronic myeloid leukemia or Philadelphia chromosome-positive acute lymphoblastic leukemia

Hisashi Sakamaki · Ken-ichi Ishizawa · Masafumi Taniwaki · Shin Fujisawa · Yasuo Morishima · Kensei Tobinai · Masaya Okada · Kiyoshi Ando · Noriko Usui · Shuichi Miyawaki · Atae Utsunomiya · Nobuhiko Uoshima · Tadashi Nagai · Tomoki Naoe · Toshiko Motoji · Itsuro Jinnai · Mitsune Tanimoto · Yasushi Miyazaki · Kazunori Ohnishi · Shinsuke Iida · Shinichiro Okamoto · Taku Seriu · Ryuzo Ohno

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Abstract A phase 1/2 study was conducted to assess the safety and efficacy of dasatinib in Japanese patients with chronic myelogenous leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph^+ ALL) resistant or intolerant to imatinib. In phase 1, 18 patients with chronic phase (CP) CML were treated with dasatinib 50, 70, or 90 mg twice daily to evaluate safety. Dasatinib $\leq$ 90 mg twice daily was well tolerated. In phase 2, dasatinib 70 mg was given twice daily to CP-CML patients for 24 weeks and to CML patients in accelerated phase (AP)/blast crisis (BC) or Ph^+ ALL for 12 weeks. In the CP-CML group ($n = 30$) complete hematologic response was 90% and major cytogenetic response (MCyR) 53%. In the AP/BC-CML group ($n = 11$) major hematologic response (MaHR) was 64% and MCyR 27%, whereas in the Ph^+ ALL group ($n = 13$) MaHR was 38% and MCyR 54%. Dasatinib was well tolerated and most of the nonhematologic toxicities were mild or moderate. Dasatinib therapy resulted in high rates of hematologic and cytogenetic response, suggesting that dasatinib is promising as a

H. Sakamaki (✉)
Department of Hematology,
Metropolitan Komagome Hospital,
3-18-22 Honkomagome,
Bunkyo-ku, Tokyo 113-8677, Japan
e-mail: sakamaki@cick.jp

K. Ishizawa
Tohoku University, Sendai, Japan

M. Taniwaki
Kyoto Prefectural University of Medicine,
Kyoto, Japan

S. Fujisawa
Yokohama City University Medical Center,
Yokohama, Japan

Y. Morishima
Aichi Cancer Center, Nagoya, Japan

K. Tobinai
National Cancer Center, Tokyo, Japan

M. Okada
Hyogo Medical University, Nishinomiya, Japan

K. Ando
Tokai University, Isehara, Japan

N. Usui
Jikei University School of Medicine, Tokyo, Japan

S. Miyawaki
Saiseikai Maebashi Hospital, Maebashi, Japan

A. Utsunomiya
Jiaikai Imamura Hospital Branch Hospital, Kagoshima, Japan

N. Uoshima
Matsushita Memorial Hospital, Moriguchi, Japan

T. Nagai
Jichi Medical School, Shimotsuke, Japan

T. Naoe
Nagoya University, Nagoya, Japan

T. Motoji
Tokyo Women's Medical University, Tokyo, Japan

I. Jinnai
Saitama Medical University, Iruma, Japan

M. Tanimoto
Okayama University, Okayama, Japan

new treatment for Japanese CML and Ph+ ALL patients resistant or intolerant to imatinib.

Keywords CML · Ph+ ALL · Dasatinib · Imatinib resistant · Imatinib intolerant

1 Introduction

Chronic myeloid leukemia (CML) is a disease attributable to abnormalities of hematopoietic stem cells involving uncontrolled proliferation of cells originating from the bone marrow. The Philadelphia (Ph) chromosome is formed by translocation between chromosomes 9 and 22. The *BCR-ABL* fusion gene on this chromosome produces BCR-ABL, which constitutively activates ABL tyrosine kinase and is thus responsible for CML and 20–30% of adult patients with acute lymphoblastic leukemia (ALL) [1]. Imatinib (Glivec®) is a selective BCR-ABL inhibitor effective against CML and Ph-positive (Ph+) ALL. Currently, imatinib is the only tyrosine kinase inhibitor indicated in newly diagnosed CML and Ph+ ALL [2–4]. However, resistance to imatinib gradually develops in many patients with CML and Ph+ ALL, particularly those with advanced disease. Among CML patients treated with imatinib, 31% discontinue the drug within 5 years because of insufficient responses or unacceptable toxicity [5]. As a major factor responsible for development of resistance to imatinib, numerous point mutations in BCR-ABL have been reported [6–8]. Additional factors including *BCR-ABL* gene amplification [6, 9], excretion of the drug through a P-glycoprotein efflux pump [10, 11], and activation of the signal transduction pathway for SRC family kinase and other signals [12, 13] have also been implicated. Therefore the development of new treatments is desirable for patients with insufficient response to imatinib and in whom imatinib cannot be continued at effective doses due to toxicity.

Y. Miyazaki
Nagasaki University, Nagasaki, Japan

K. Ohnishi
Hamamatsu University School of Medicine, Hamamatsu, Japan

S. Iida
Nagoya City University, Nagoya, Japan

S. Okamoto
Keio University, Tokyo, Japan

T. Seriu
Bristol-Myers K.K., Tokyo, Japan

R. Ohno
Aichi Shukutoku University, Nagoya, Japan

Dasatinib (BMS-354825) is a novel oral tyrosine kinase inhibitor that exerts inhibitory activity against BCR-ABL and SRC family kinase. In vitro, dasatinib binds to both active and inactive BCR-ABL and is 325 times more potent than imatinib and 16 times more potent than nilotinib against wild-type BCR-ABL-expressing cells [14]. Dasatinib has demonstrated activity against all reported types of imatinib-resistant mutant BCR-ABL, except for T315I [14–18]. Five phase 2 studies collectively known as START (SRC/ABL Tyrosine kinase inhibition Activity Research Trials of dasatinib) studies demonstrated that dasatinib is safe and elicits hematologic and cytogenetic response at all stages of CML and Ph+ ALL resistant or intolerant to imatinib [18–22]. Against chronic phase (CP)-CML, dasatinib was highly effective with 91% of patients showing complete hematologic responses (CHR) and 62% major cytogenetic responses (MCyR). Efficacy for CP-CML was durable and duration of MCyR was 88%, progression-free survival was 80% and overall survival was 94% at 2-year follow-up [23]. Dasatinib (Sprycel®) was initially approved in the United States in June 2006 and has received marketing approvals in numerous other countries world-wide.

We conducted an open-label phase 1/2 study of dasatinib in Japanese patients with CP-CML, accelerated phase (AP)/blast crisis (BC)-CML or Ph+ ALL resistant or intolerant to imatinib. This study comprised two parts. Phase 1 evaluated the safety of dasatinib at escalating doses in patients with CP-CML. Phase 2 evaluated the efficacy and safety of dasatinib in patients with all-stage CML or Ph+ ALL.

2 Methods

2.1 Patients

Adult CML or Ph+ ALL patients aged 20–75 years who were resistant or intolerant to imatinib were conducted from 2005 to 2007. Because imatinib had no registered indication for Ph+ ALL in Japan at the start of this study, patients with Ph+ ALL resistant to or intolerant of prior therapies were eligible. Treatment and analysis were conducted in three cohorts with CP-CML, AP/BC-CML and Ph+ ALL (Table 1).

CP-CML was considered to be resistant to imatinib when given at a dose level ≥ 400 mg/day if the following occurred: (1) white blood cell count (WBC) showed a ≥2-fold increase from nadir to >20000/mm^3 or rose from nadir to ≥50000/mm^3; (2) CHR was not achieved despite ≥3-month treatment with imatinib; (3) cytogenetic response was not achieved despite ≥6-month treatment with imatinib; (4) MCyR was not achieved despite ≥12-month