HOKKAIDO UNIVERSITY

Title	Successful treatment of acute myelogenous leukemia with favorable cytogenetics by reduced-intensity stem cell transplantation
Author(s)	Kondo, Takeshi; Yasumoto, Atsushi; Arita, Kotaro; Sugita, Jun-ichi; Shigematsu, Akio; Okada, Kohei; Takahata, Mutsumi; Onozawa, Masahiro; Kahata, Kaoru; Takeda, Yukari; Obara, Masato; Yamamoto, Satoshi; Endo, Tomoyuki; Nishio, Mitsufumi; Sato, Norihiro; Tanaka, Junji; Hashino, Satoshi; Koike, Takao; Asaka, Masahiro; Imamura, Masahiro
Citation	International Journal of Hematology, 91(2), 310-321 https://doi.org/10.1007/s12185-009-0487-y
Issue Date	2010-03
Doc URL	http://hdl.handle.net/2115/49669
Rights	The final publication is available at www.springerlink.com
Type	article (author version)
File Information	IJH91-2_310-321.pdf

Successful treatment of acute myelogenous leukemia with favorable cytogenetics by reduced-intensity stem cell transplantation

Takeshi Kondo[1,2], Atsushi Yasumoto[1,3], Kotaro Arita[1,3], Jun-ichi Sugita[1,3], Akio Shigematsu[1,3], Kohei Okada[1,2], Mutsumi Takahata[1,2], Masahiro Onozawa[1,2], Kaoru Kahata[1,2], Yukari Takeda[1,4], Masato Obara[1,4], Satoshi Yamamoto[1,4], Tomoyuki Endo[1,4], Mitsufumi Nishio[1,4], Norihiro Sato[1,4], Junji Tanaka[1,3], Satoshi Hashino[1,2], Takao Koike[4], Masahiro Asaka[2] and Masahiro Imamura[1,3]

Runnning title: RIST for AML with favorable cytogenetics

[1]Stem Cell Transplantation Center, Hokkaido University Hospital

[2]Department of Gastroenterology and Hematology, [3]Department of Hematology and Oncology and [4]Department of Medicine II, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Kita 14 Nishi 5, Kita-ku, Sapporo 060-8648, Japan

Tel +81-11-716-1161   Fax +81-11-706-7867

Corresponding author: Takeshi Kondo, MD, PhD (e-mail: t-kondoh@med.hokudai.ac.jp)

ABSTRACT

Acute myelogenous leukemia (AML) with favorable cytogenetics responds well to chemotherapy. If the leukemia relapses, allogenic hematopoietic stem transplantation (allo-HSCT) is considered as a treatment option. Since the efficacy of reduced-intensity stem cell transplantation (RIST) for AML with favorable cytogenetics has not been established, we retrospectively analyzed the outcomes of allo-HSCT in AML patients according to cytogenetic risks. The outcome of allo-HSCT for AML patients with favorable cytogenetics seemed to be superior to that for AML patients with intermediate cytogenetics. In AML patients with favorable cytogenetics, the 3-year overall survival (OS) and relapse-free survival (RFS) rates were 88% and 76%, respectively, in the RIST group. Both the 3-year OS and RFS rates were 81% in the conventional stem cell transplantation (CST) group. The outcome of RIST for AML patients with favorable cytogenetics was comparable to that for patients who received CST despite the more advanced age and greater organ dysfunction in RIST group than in CST group. None of the patients died within 90 days after RIST. Moreover, there was no relapse in patients with favorable cytogenetics who were in hematological remission prior to RIST. Thus, RIST for AML patients with favorable cytogenetics in remission is safe and effective.

Acute myelogenous leukemia (AML) represents a group of acute leukemias that generally express a myeloid phenotype but clinically have heterogeneous and diverse characteristics. At the onset and during treatment of AML, patients are evaluated by clinical risk factors and are considered for allogenic hematopoietic stem cell transplantation (allo-HSCT) based on the risk factors [1, 2]. Cytogenetic abnormality is one of the most widely recognized risk factors in AML patients. AMLs with karyotype t(8;21), inv(16), t(16;16) and t(15;17) are expected to be controlled by chemotherapy alone, and patients with these AMLs are thus categorized into a favorable cytogenetic risk group [3]. For this reason, indication for allo-HSCT for patients in this group is considered not at the first complete remission (CR1) but at the state of relapse, after the second remission (CR2) or in the case of failure to achieve remission [4, 5, 6, 7].

Although many studies have suggested that cytogenetic risk in AML correlates with the outcome of chemotherapy, the relation between cytogenetic risk and outcome of allo-HSCT is still controversial [8, 9]. Ferrant et al. reported that cytogenetics of AML at diagnosis had the strongest prognostic value for relapse, leukemia-free survival, and survival for first complete remission (CR1) patients who received matched sibling-donor HSCT [8]. On the other hand, Tallman et al. reported that cytogenetics had little influence on the overall outcome for CR1 patients

who received matched unrelated-donor HSCT, though favorable cytogenetics had better, but not significant, outcome for CR2 patients [9]. These two studies were based on analysis of outcomes in patients who received allo-HSCT with a myeloablative conditioning regimen (conventional stem cell transplantation, CST).

A strategy for allo-HSCT using a reduced-intensity conditioning regimen (reduced-intensity stem cell transplantation, RIST) has been developed and has been used for treatment of patients with AML to reduce regimen-related toxicity (RRT) of the conditioning regimen [10-13]. However, the efficacy and feasibility of RIST for treatment of AML according to cytogenetic risk have not been established. We retrospectively analyzed AML patients treated with RIST in our institute and compared the outcome with that for AML patients who underwent CST. We report here that RIST for AML patients with favorable cytogenetics is safe and can be effectively performed and that the outcome for AML patients with favorable cytogenetics who received RIST was comparable to that for patients with favorable cytogenetics who underwent CST.

PATIENTS AND METHODS

Patients and preparative regimens

This study was approved by our institutional review board. We

4

retrospectively reviewed the medical records of patients with *de novo* AML who received allo-HSCT in our hospital. Sixty-nine patients with *de novo* AML have received allo-HSCT since 1988 (Figure 1). Six patients were excluded from analysis because of incomplete information. A RIST regimen was introduced to our hospital in 2002. Twenty patients received allo-HSCT with an RIST regimen and 43 patients were treated with a CST regimen. The reason for selecting an RIST regimen was mainly advanced age of the patients or organ dysfunction.

Among the 20 patients who received an RIST regimen, nine patients had AML with favorable cytogenetics, eight patients had AML with intermediate cytogenetics, and three patients had AML with adverse cytogenetics. Among the 43 patients who were treated with a CST regimen, 11 patients had AML with favorable cytogenetics, 29 patients had AML with intermediate cytogenetics and three patients had AML with adverse cytogenetics. Since the number of AML patients with adverse cytogenetics was too small for analysis, we focused on AML patients with favorable and intermediate cytogenetics.

The conditioning regimens for HSCT are as follows. CY/VP-16/TBI12, CY/TBI or CY/AraC+G-CSF/TBI12 was used for the CST conditioning regimen [14, 15]. CY/VP-16/TBI12 consisted of etoposide (VP-16, 15 mg/kg once daily intravenously [i.v.] for two days,

total dose of 30 mg/kg) + cyclophosphamide (CY, 60 mg/kg once daily i.v. for two days, total dose of 120 mg/kg) + total body irradiation (TBI; 12 Gy in six fractions). The CY/TBI regimen is the same as CY/VP-16/TBI regimen with exclusion of VP-16 [14]. CY/AraC+G-CSF/TBI12 consisted of cytosine arabinoside (AraC, 3 g/m^2 every 12 hours i.v. for two days, total dose of 12 g/m^2) with administration of granulocyte colony-stimulating factor (G-CSF, continuous infusion at a dosage of 5 µg/kg per day, starting 12 hours before the first dose of AraC and stopped at the completion of the last dose) + cyclophosphamide (60 mg/kg once daily i.v. for two days, total dose of 120 mg/kg) + total body irradiation (12 Gy in six fractions) [15]. FLU/BU/TBI2, FLU/BU/TBI4 or FLU/L-PAM was used for the RIST conditioning regimen. FLU/BU/TBI2 or FLU/BU/TBI4 consisted of fludarabine (FLU, 30 mg/m^2 once daily i.v. for six days, total dose of 180 mg/m^2) + oral busulfan (BU, 4 mg/kg orally in divided doses daily for two days, total dose of 8 mg/kg) or intravenous busulfan (3.2 mg/kg i.v. in divided doses daily for two days, total dose of 6.4 mg/kg) + low-dose (2 or 4 Gy) TBI [16]. FLU/L-PAM consisted of fludarabine (30 mg/m^2 once daily i.v. for five days, total dose of 150 mg/m^2) and melphalan (L-PAM, 70 mg/m^2 once daily i.v. for two days, total dose of 140 mg/m^2) [17]. As GVHD prophylaxis, either cyclosporine A (3 mg/kg) or tacrolimus (0.03 mg/kg) combined with

short-course methotrexate (15 mg/m^2 on day 1, 10 mg/m^2 on days 3 and 6) was used. The disease status of AML was evaluated about one month before HSCT by bone marrow examination. Hematopoietic cell transplantation-specific comorbidity index (HCT-CI) was assessed and determined by the medical record [18]. Differences in age distribution, HCT-CI and occurrence of GVHD in each group were evaluated by Mann-Whitney's U test. OS and RFS were analyzed by the Kaplan-Meier method and compared using the log-rank test. Bone marrow examination was performed regularly after HSCT to evaluate disease status. Minimal residual disease (MRD) in bone marrow was monitored by nested reverse transcription-polymerase chain reaction (nested RT-PCR) to detect disease-specific fusion transcripts (AML1-MTG8, PML-RARA or CBFb-MYH11). Graft-versus-host disease (GVHD) was clinically diagnosed and graded according to the consensus criteria [19, 20].

Analysis of efficacy and safety of the treatment

Since the purpose of this study was to analyze the efficacy and safety of RIST for AML, we evaluated overall survival (OS) and relapse-free survival (RFS) rates for AML patients according to cytogenetic risks. OS was calculated from transplantation to death from any cause, and RFS was defined as the time from transplantation to the first event, either relapse or death in complete remission. OS and RFS were analyzed by the

7

Kaplan-Meier method and compared using the log-rank test. We also analyzed early death and cause of death to evaluate the safety.

RESULTS

Characteristics of AML patients who received allo-HSCT

Initially, we analyzed AML patients with favorable cytogenetics who were treated with allo-HSCT. The characteristics of AML patients with favorable cytogenetics who received RIST or CST are shown in Table 1. Patients 1 to 9 received RIST and Patients 10 to 20 received CST. Four patients in CR1, nine patients in CR2, three patients in CR3 and four patients in a non-CR condition received allo-HSCT. Three patients in CR1, Patients 10, 12 and 14, received CST before establishing the idea of cytogenetic risk. Patient 9 in CR1 had granulocytic sarcoma presenting in conjunction with AML. Since the presence of granulocytic sarcoma is usually related to poor prognosis [21], RIST was performed after achievement of CR1. Among the characteristics of the patients, age distribution and HCT-CI were significantly different between the RIST group and CST group. Median ages of the patients were 48 years (range: 28 − 68 years) in the RIST group and 27 years (range: 21 − 55 years) in the CST group, and the patients who received RIST were significantly older than the patients who received CST (Mann-Whitney U test, p<0.001).

Median HCT-CI was 2 in RIST group, and this was significantly higher than that in the CST group, where HCT-CI of all patients was 0 (Mann-Whitney U test, p<0.001).

Next, we analyzed the AML patients with intermediate cytogenetics who were treated with allo-HSCT (Table 2).   Patients 21 to 28 received RIST and Patients 29 to 57 received CST.   Different from the patients with favorable cytogenetics, a large number of patients, 25 of 37 patients, with intermediate cytogenetics received allo-HSCT in CR1.   Among the characteristics of the patients, only age distribution was significantly different between the RIST group and CST group.   Median ages of the patients were 60 years (range: 52 − 68 years) in the RIST group and 30 years (range: 15 − 55 years) in the CST group, and the patients who received RIST were significantly older than the patients who received CST (Mann-Whitney U test, p<0.001).   HCT-CI was not significantly different between the RIST group and CST group in AML patients with intermediate cytogenetics (Mann-Whitney U test, p=0.42).

Hematological recovery

In nine AML patients with favorable cytogenetics who received RIST (Patients 1 to 9), neutrophil engraftment was observed in eight patients and platelet engraftment was observed in seven patients (Table 1).   Patient 6, who received cord blood transplantation (CBT), showed engraftment

failure and received a second CBT, and then engraftment of both neutrophils and platelets was achieved. Patient 8, who had central nervous system (CNS) involvement before SCT, relapsed in the CNS at day 176 without platelet recovery. After treatment with CNS irradiation and donor lymphocyte infusion (DLI), the hematopoiesis was persistently suppressed. In AML patients with favorable cytogenetics who received CST (Patients 10 to 20), engraftment of both neutrophils and platelets was observed in all patients except Patient 19, who died before engraftment (Table 1).

Engraftment of both neutrophils and platelets was observed in all of the eight AML patients with intermediate cytogenetics who received RIST (Patients 21 to 28) (Table 2). In AML patients with intermediate cytogenetics who received CST (Patients 29 to 57), neutrophil engraftment was observed in 24 patients and platelet engraftment was observed in 22 patients (Table 2). Patients 31, 34, 45 and 57 died of RRT before engraftment. Patient 55, who received cord blood transplantation (CBT), showed engraftment failure and died of RRT during the second CBT. Patients 37 and 47, who received CST in non-remission status, did not show engraftment because of early growth of leukemia cells.

The duration for neutrophil engraftment varied from 9 to 34 days and the duration for platelet engraftment varied from 12 to 106 days.

Neutrophil engraftment in Patients 10 and 29, who received HSCT in 1988, was day 23 and day 34, respectively. This late engraftment was probably caused by no use of G-CSF, which was not available at the time of transplantation. Except for these two cases, the duration for engraftment seemed to be dependent on the stem cell source.

GVHD and monitoring of MRD

Occurrence of acute and chronic GVHD and the status of MRD in AML patients with favorable cytogenetics are summarized in Table 3. Acute GVHD was observed in two of the patients who received RIST. Extensive type of chronic GVHD developed in three patients, and Patient 1 died of pulmonary infection during treatment for chronic GVHD. In the patients who received CST, acute GVHD was observed in six patients, limited type of chronic GVHD developed in two patients, and extensive type of chronic GVHD developed in four patients. Since MRD status of favorable cytogenetics could be monitored by nested RT-PCR, we regularly analyzed MRD of bone marrow before and after HSCT in patients who received HSCT after 2002. In the patients who received RIST, three of eight patients in hematological CR before HSCT, Patients 1, 3 and 5, were PCR-positive. Patients 1 and 5 became PCR-negative after HSCT. Patient 3 was PCR-positive at day 30, PCR-negative at days 51 and 77, and PCR-positive at day 146 but became persistently PCR-negative after day

197.   Patient 8, who was in non-CR and was PCR-positive before HSCT, was PCR-positive until day 117 and became PCR-negative after day 159. However, Patient 8 relapsed in the CNS at day 176, while MRD in bone marrow remained PCR-negative.   After CNS irradiation followed by DLI, remission was re-induced in Patient 8.   In the patients who received CST, MRD status was followed only in three patients.   Patients 18 and 20 were PCR-negative throughout the treatment.   Patient 15 was in non-CR before HSCT and was PCR-positive until day 47 after HSCT, although Patient 15 achieved hematological CR at the time of engraftment.   Patient 15 became PCR-negative at bone marrow examination on day 67 and remained PCR-negative thereafter.

Acute and chronic GVHD and the outcome of AML patients with intermediate cytogenetics are summarized in Table 2.   In the patients who received RIST, acute GVHD was observed in four patients and chronic GVHD developed in four patients.   In the patients who were treated with CST, acute GVHD was observed in 16 patients and chronic GVHD developed in 12 patients.   Patient 39 died from complication of chronic GVHD.

Totally, acute GVHD was observed in six of 17 patients who received RIST and in 22 of 32 patients who received CST.   Chronic GVHD was observed in seven of 17 patients who received RIST and in 18 of 31

patients who received CST. There was a tendency of higher frequencyof occurrence of acute and chronic GVHD in patients who received CST than in patients who received RIST, although the frequencies of both acute GVHD and chronic GVHD were not statistically significant between patients who received RIST and patients who received CST (Mann-Whitney U test, p=0.07 in acute GVHD and p=0.64 in chronic GVHD).

Survival rate in AML patients according to cytogenetic risk and conditioning regimen

We next calculated OS and RFS to evaluate the efficacy of allo-HSCT for AML according to cytogenetic risk and conditioning regimen. Median follow-up durations were 916 days (range: 305-2486 days) in AML patients with favorable cytogenetics who received RIST, 3115 days (range: 23-6800 days) in AML patients with favorable cytogenetics who received CST, 865 days (range: 257-1449 days) in AML patients with intermediate cytogenetics who received RIST, and 932 days (range: 6-6438 days) in AML patients with intermediate cytogenetics who received CST. Three-year OS rates were 88% in AML patients with favorable cytogenetics who received RIST, 81% in AML patients with favorable cytogenetics who received CST, 74% in AML patients with intermediate cytogenetics who received RIST, and 58% in AML patients with

13

intermediate cytogenetics who received CST (Figure 2a).   Three-year RFS

rates were 76% in AML patients with favorable cytogenetics who received

RIST, 81% in AML patients with favorable cytogenetics who received

CST, 61% in AML patients with intermediate cytogenetics who received

RIST, and 48% in AML patients with intermediate cytogenetics who

received CST (Figure 2b).   Survival of AML patients with favorable

cytogenetics tended to be better than that of AML patients with

intermediate cytogenetics, but these results were not statistically significant

because of the small sample size.

Since the disease status of AML is one of the most critical factors that

affect outcome of allo-HSCT, we also analyzed the patients in

hematological remission prior to allo-HSCT.   Here we just categorized the

patients in hematological remission, because the remission status was

variable among the patients.   AML patients with favorable cytogenetics

tended to receive allo-HSCT in CR2 or CR3, but most of the AML patients

with intermediate cytogenetics underwent allo-HSCT in CR1.   As shown

in Figure 3a, three-year OS rates were 87% in AML patients with favorable

cytogenetics who received RIST, 100% in AML patients with favorable

cytogenetics who received CST, 74% in AML patients with intermediate

cytogenetics who received RIST, and 60% in AML patients with

intermediate cytogenetics who received CST.   Three-year RFS rates were

87% in AML patients with favorable cytogenetics who received RIST, 100% in AML patients with favorable cytogenetics who received CST, 61% in AML patients with intermediate cytogenetics who received RIST, and 50% in AML patients with intermediate cytogenetics who received CST (Figure 3b). In this analysis also, AML patients with favorable cytogenetics seem to have a better outcome than that in AML patients with intermediate cytogenetics. These results are still statistically not significant due to the small sample size, except for the differences in OS and RFS rates between patients with favorable cytogenetics and patients with intermediate cytogenetics who received CST (log-rank test, $p<0.05$ in OS and $p<0.01$ in RFS). In AML patients with favorable cytogenetics, it is noteworthy that the outcome of the patients who received RIST was comparable to that of the patients who underwent CST.

To evaluate the safety and efficacy of each conditioning regimen in AML patients with favorable and intermediate cytogenetics, we analyzed the timing of death and the causes of death. The results are summarized in Table 4a. Three of the patients who received RIST died after 90 days; one patient died of pulmonary infection and two patients died of relapse. None of the patients who received RIST died of RRT within 90 days. In contrast, five of the patients who received CST died within 30 days and eight patients died within 90 days. Among the eight patients who died in

the early period after transplantation, two patients died of AML, one died of a graft failure and five patients died from conditions related to RRT.

To exclude the effect of disease status prior to HSCT, we also analyzed patients in hematological remission prior to HSCT (Table 4b). Two of the patients who received CST died within 30 days and four patients died within 90 days. The deaths in these four patients were not related to relapse; one death was due to graft failure and three deaths were associated with RRT. As expected, non-relapse mortality rate was lower in the patients who received RIST than in the patients who received CST. There were relapse-related deaths in two of the 16 patients who received RIST and in one of the 28 patients who received CST, and these three patients were associated with intermediate cytogenetics. There was no relapse-related mortality, regardless of the conditioning regimen, in the patients with favorable cytogenetics who were in hematological remission prior to HSCT.

DISCUSSION

RIST is generally considered for patients for whom CST is not feasible because of advanced age or organ dysfunction. Although a graft-versus-leukemia (GVL) effect is expected by RIST, the anti-leukemic effect of the conditioning regimen is reduced. Thus, it is necessary to

16

identify specific prognostic factors that affect outcome of AML patients who undergo RIST.   There have been several studies on the outcomes of RIST for treatment of myeloid malignancies [10-13].   Hegenbart et al. reported outcomes of RIST for AML patients, including patients with *de novo* AML and secondary AML, 2-year OS rates being 51% in CR1, 61% in CR2 and 28% beyond CR2 [13].   Hamaki et al. analyzed AML and MDS patients and classified then into two groups according to disease status, with AML in CR1 and MDS RA being defined as low risk and others being defined as high risk.   They showed that the outcome in the low-risk group was better than that in the high-risk group [10].

In our study, we analyzed the safety and efficacy of RIST in AML patients according to cytogenetic risks.   For the safety, most of the patients achieved hematological recovery, the time to engraftment varying depending on the stem cell source, and this result was comparable to previously reported results (Tables 1 and 2) [22, 23].   In addition, none of the patients who received RIST died within 90 days after HSCT (Tables 4a and 4b).   On the other hand, eight of the 40 patients who received CST and four of the 28 patients who received CST at hematological remission died within 90 days after HSCT.   A possible explanation for the high incidence of RRT in the patients who received CST is that most of the patients in CST group received a higher intensity of the conditioning

regimen, CY/VP-16/TBI, than the standard conditioning regimen of CY/TBI, although CY/VP-16/TBI is effective for treatment of acute lymphoblastic leukemia [14].   The low incidence of early death in the patients who received RIST might reflect the low incidence of RRT, and this result is also similar to results of previous studies [24, 25].   In addition to RRT, the high frequency of GVHD in the patients who received CST could affect the outcome (for example, Patients 11 and 39).

In investigation of the efficacy of treatment, it was found that the OS and RFS rates for AML patients with favorable cytogenetics were similar to those for patients who received RIST and patients who received CST (Figures 2a and 2b).   Although age of the patients and HCT-CI were different between the RIST group and CST group, the results suggest that RIST is not inferior to CST for treatment of AML patients with favorable cytogenetics.   We also analyzed the effect of cytogenetics on the outcome of allo-HSCT.   OS and RFS rates in patients with favorable cytogenetics tended to be better than those in patients with intermediate cytogenetics (Figures 2a and 2b).   Among the patients with favorable cytogenetics, no patients in hematological remission prior to HSCT, regardless of molecular status, relapsed after HSCT, irrespective of the conditioning regimen, RIST or CST.   MRD-positive status before HSCT in four patients became MRD-negative after RIST.   This means that eradication of MRD may be

achieved possibly by an RIST regimen and/or graft-versus-leukemia (GVL) effect [26]. In contrast to this result, among the patients with intermediate cytogenetics, three of eight patients in hematological remission prior to HSCT relapsed after RIST. These results suggest that the cytogenetic risk in AML could reflect the outcome of RIST. Schmid et al. analyzed the effect of DLI on AML with first relapse after allo-HSCT and reported that DLI was effective for AML with favorable cytogenetics [27]. This may mean that AML with favorable cytogenetics is more responsive to the GVL effect than are other types of AML.

We also analyzed the results of HSCT for patients with intermediate cytogenetics. The outcome appeared to be better in patients who received RIST than in patients who received CST, and this result was caused by the high incidence of RRT-related death in the patients who received CST. In spite of the better outcome in RIST, we cannot conclude that RIST is superior to CST for the treatment of AML patients with intermediate cytogenetics. In the patients who received HSCT in hematological remission, three of eight patients relapsed after RIST, while only one of the 20 patients relapsed after CST (Table 3). In addition, five of the nine patients who were non-CR at HSCT achieved long-term remission after CST (Patients 30, 33, 42, 50 and 54). These facts indicate that CST is still valuable for the treatment of AML with intermediate cytogenetics. AML

patients with intermediate cytogenetics comprise a heterogeneous population, and AML with a normal karyotype is one of the representative AMLs with intermediate cytogenetics. There has been an accumulation of data recently for clarifying the genetic risks for stratification of AML with a normal karyotype, i.e., genetic alteration of FLT3, NPM1 or CEBPA [28, 29]. These molecular signatures can affect not only the efficacy of chemotherapy but also the outcome of HSCT [30]. It would be ideal to isolate the subgroup of AML patients with intermediate cytogenetics who would be cured by RIST.

Taken together, the results suggest that RIST for AML patients with favorable cytogenetics, especially those in hematological remission, is safe and effective. Since our study is a retrospective analysis, patients with favorable cytogenetics received RIST due to advanced age or organ dysfunction. The modality of ideal HSCT is to minimize RRT and to obtain maximal curability. Based on the good outcome of RIST for AML patients with favorable cytogenetics in our study, a prospective study should be carried out to confirm the safety and efficacy of RIST for all AML patients with favorable cytogenetics who have indication for allo-HSCT.

REFERENCES

1. Wheatley K, Burnett AK, Goldstone AH, Gray RG, Hann IM, Harrison CJ, et al. A simple, robust, validated and highly predictive index for the determination of risk-directed therapy in acute myeloid leukaemia derived from the MRC AML 10 trial. United Kingdom Medical Research Council's Adult and Childhood Leukaemia Working Parties. Br J Haematol. 1999;107(1):69-79.

2. Lodewyck T, Cornelissen JJ. Allogeneic stem cell transplantation in acute myeloid leukemia: a risk-adapted approach. Blood Rev. 2008;22(6):293-302.

3. Grimwade D, Walker H, Oliver F, Wheatley K, Harrison C, Harrison G, et al. The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. The Medical Research Council Adult and Children's Leukaemia Working Parties. Blood. 1998;92(7):2322-33.

4. Slovak ML, Kopecky KJ, Cassileth PA, Harrington DH, Theil KS, Mohamed A, et al. Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group Study. Blood. 2000;96(13):4075-83.

5. Kanamaru A, Takemoto Y, Tanimoto M, Murakami H, Asou N,

Kobayashi T, et al.   All-trans retinoic acid for the treatment of newly diagnosed acute promyelocytic leukemia. Japan Adult Leukemia Study Group.   Blood. 1995;85(5):1202-6.

6. Jourdan E, Boiron JM, Dastugue N, Vey N, Marit G, Rigal-Huguet F, et al.   Early allogenic stem-cell transplantation with acute myeloblastic leukemia in first complete remission: An intent-to-treat long-term analysis of the BGMT experience.   J Clin Oncol. 2005;23(30):7676-84.

7. Yanada M, Matsuo K, Emi N, Naoe T.   Efficacy of allogenic hematopoietic stem cell transplantation depends on cytogenetic risk for acute myeloid leukemia in first disease remission.   Cancer 2005;103(8):1652-8

8. Ferrant A, Labopin M, Frassoni F, Prentice HG, Cahn JY, Blaise D, et al. Karyotype in acute myeloblastic leukemia: prognostic significance for bone marrow transplantation in first remission: a European Group for Blood and Marrow Transplantation study. Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT).   Blood. 1997;90(8):2931-8.

9. Tallman MS, Dewald GW, Gandham S, Logan BR, Keating A, Lazarus HM, et al.   Impact of cytogenetics on outcome of matched unrelated donor hematopoietic stem cell transplantation for acute myeloid leukemia in first or second complete remission.   Blood.

2007;110(1):409-17.

10. Hamaki T, Kami M, Kim SW, Onishi Y, Kishi Y, Murashige N, et al. Reduced-intensity stem cell transplantation from an HLA-identical sibling donor in patients with myeloid malignancies. Bone Marrow Transplant. 2004;33(9):891-900.

11. Taussig DC, Davies AJ, Cavenagh JD, Oakervee H, Syndercombe-Court D, Kelsey S, et al. Durable remissions of myelodysplastic syndrome and acute myeloid leukemia after reduced-intensity allografting. J Clin Oncol. 2003;21(16):3060-5.

12. Bertz H, Potthoff K, Finke J. Allogeneic stem-cell transplantation from related and unrelated donors in older patients with myeloid leukemia. J Clin Oncol. 2003;21(8):1480-4.

13. Hegenbart U, Niederwieser D, Sandmaier BM, Maris MB, Shizuru JA, Greinix H, et al. Treatment for acute myelogenous leukemia by low-dose, total-body, irradiation-based conditioning and hematopoietic cell transplantation from related and unrelated donors. J Clin Oncol. 2006;24(3):444-53.

14. Shigematsu A, Kondo T, Yamamoto S, Sugita J, Onozawa M, Kahata K, et al. Excellent outcome of allogeneic hematopoietic stem cell transplantation using a conditioning regimen with medium-dose VP-16, cyclophosphamide and total-body irradiation for adult patients with

acute lymphoblastic leukemia.　Biol Blood Marrow Transplant. 2008;14(5):568-75.

15. Ooi J, Iseki T, Takahashi S, Tomonari A, Takasugi K, Uchiyama M, et al.　Unrelated cord blood transplantation after myeloablative conditioning for adult patients with refractory anemia.　Int J Hematol. 2005;81(5):424-7.

16. Sugita J, Tanaka J, Hashimoto A, Shiratori S, Yasumoto A, Wakasa K, et al.　Influence of conditioning regimens and stem cell sources on donor-type chimerism early after stem cell transplantation.　Ann Hematol. 2008;87(12):1003-8.

17. Devine SM, Hoffman R, Verma A, Shah R, Bradlow BA, Stock W, et al. Allogeneic blood cell transplantation following reduced-intensity conditioning is effective therapy for older patients with myelofibrosis with myeloid metaplasia.　Blood. 2002;99(6):2255-8.

18. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, et al.　Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT.　Blood. 2005;106(8):2912-9.

19. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, et al.　1994 Consensus Conference on Acute GVHD Grading.　Bone Marrow Transplant. 1995;15(6):825-8.

20. Sullivan KM, Agura E, Anasetti C, Appelbaum F, Badger C, Bearman S, et al. Chronic graft-versus-host disease and other late complications of bone marrow transplantation. Semin Hematol. 1991;28(3):250-9.

21. Chevallier P, Mohty M, Lioure B, Michel G, Contentin N, Deconinck E, et al. Allogeneic hematopoietic stem-cell transplantation for myeloid sarcoma: a retrospective study from the SFGM-TC. J Clin Oncol. 2008;26(30):4940-3.

22. Kasai M, Kiyama Y, Kawamura A. Application of peripheral blood stem cells (PBSC) mobilized by recombinant human granulocyte colony stimulating factor for allogeneic PBSC transplantation and the comparison of allogeneic PBSC transplantation and bone marrow transplantation. Transfus Apher Sci. 2002;26(2):121-7.

23. Grewal SS, Barker JN, Davies SM, Wagner JE. Unrelated donor hematopoietic cell transplantation: marrow or umbilical cord blood? Blood. 2003;101(11):4233-44.

24. Giralt S, Estey E, Albitar M, van Besien K, Rondón G, Anderlini P, et al. Engraftment of allogeneic hematopoietic progenitor cells with purine analog-containing chemotherapy: harnessing graft-versus-leukemia without myeloablative therapy. Blood. 1997;89(12):4531-6.

25. Slavin S, Nagler A, Naparstek E, Kapelushnik Y, Aker M, Cividalli G, et al. Nonmyeloablative stem cell transplantation and cell therapy as

an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases.   Blood. 1998;91(3):756-63.

26. McSweeney PA, Niederwieser D, Shizuru JA, Sandmaier BM, Molina AJ, Maloney DG, et al.   Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects.   Blood. 2001;97(11):3390-400.

27. Schmid C, Labopin M, Nagler A, Bornhäuser M, Finke J, Fassas A, et al.   Donor lymphocyte infusion in the treatment of first hematological relapse after allogeneic stem-cell transplantation in adults with acute myeloid leukemia: a retrospective risk factors analysis and comparison with other strategies by the EBMT Acute Leukemia Working Party.   J Clin Oncol. 2007;25(31):4938-45.

28. Bienz M, Ludwig M, Leibundgut EO, Mueller BU, Ratschiller D, Solenthaler M, et al.   Risk assessment in patients with acute myeloid leukemia and a normal karyotype.   Clin Cancer Res. 2005;11(4):1416-24.

29. Schlenk RF, Döhner K, Krauter J, Fröhling S, Corbacioglu A, Bullinger L, et al.   Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia.   N Engl J Med. 2008;358(18):1909-18.

30. Bornhäuser M, Illmer T, Schaich M, Soucek S, Ehninger G, Thiede C;

AML SHG 96 study group. Improved outcome after stem-cell transplantation in FLT3/ITD-positive AML. Blood. 2007;109(5):2264-5.

Figure Legends

Figure 1.   Sixty-nine patients with de novo AML received allogenic stem cell transplantation.   Sixty-three patients were analyzed in this study.   Twenty patients received RIST and 43 patients received CST. Patients were subcategorized according to cytogenetic risk [3].

Figure 2.   Kaplan-Meier survival estimates according to cytogenetic risk and conditioning regimen in AML patients who received allo-HSCT.   Data are shown for three-year OS (Figure 2a) and three-year RFS (Figure 2b).   P-value for group comparison of OS or RFS was determined by the log-rank test.

Figure 3.   Kaplan-Meier survival estimates of AML patients who were in hematological remission at allo-HSCT.   Data are shown for three-year OS (Figure 3a) and three-year RFS (Figure 3b) of the patients in hematological remission.   P-value for group comparison of OS or RFS was determined by the log-rank test.
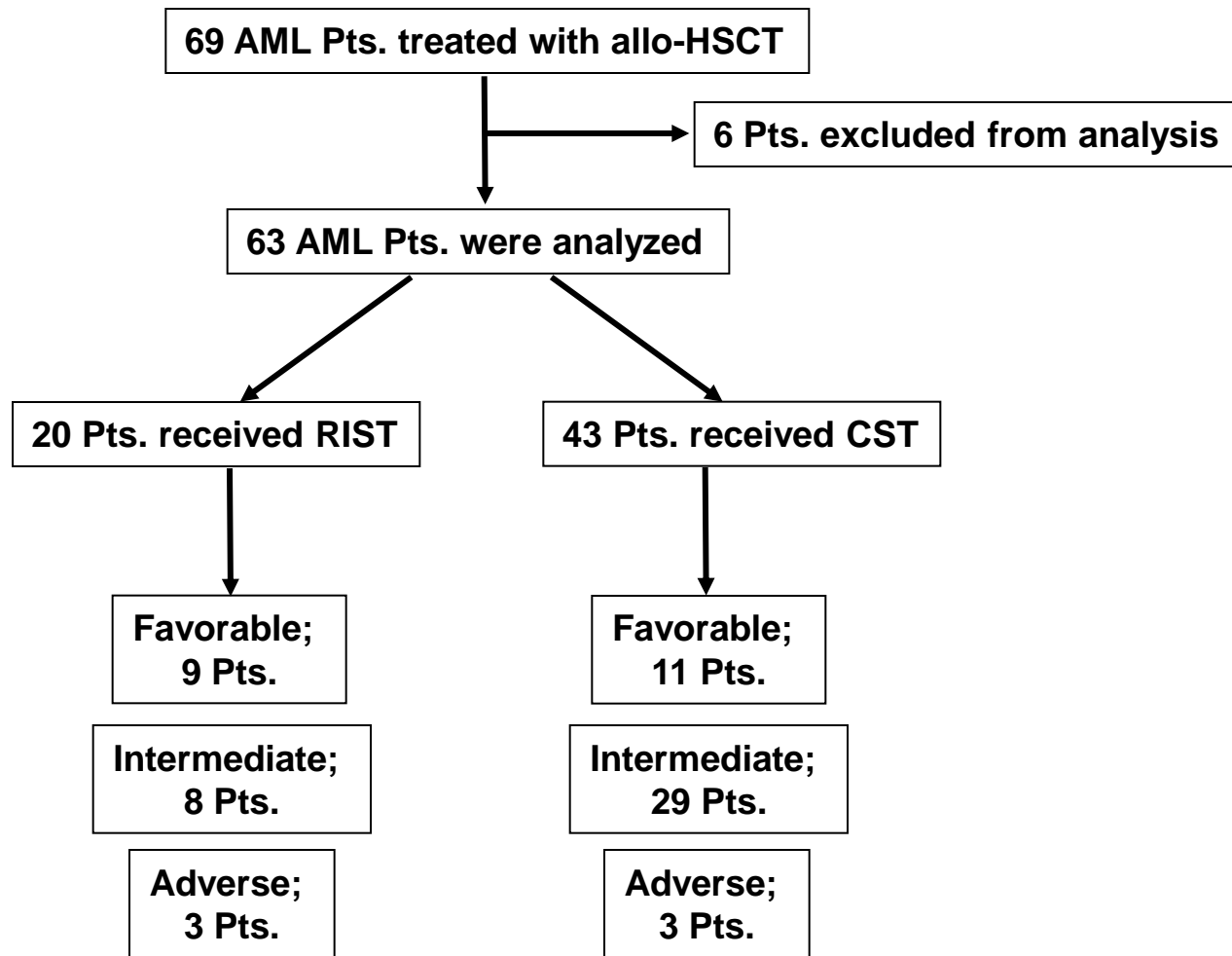
Figure 1

Table 1. Characteristics of AML patients with favorable cytogenetics receiving RIST or CST

Pt.	Age/Sex	Cytogenetics	Year of SCT	Disease Status	HCT-CI	Conditioning	Stem Cell Source	WBC recovery (day)	PLT recovery (day)
1	68/F	t(8;21)	2005	CR2	2	FLU/BU/TBI4	rPBSCT	13	15
2	52/M	t(8;21)	2006	CR3	3	FLU/BU/TBI4	uBMT	17	39
3	28/M	t(8;21)	2007	CR2	3	FLU/BU/TBI4	uBMT	21	37
4	56/M	t(15;17)	2002	CR2	1	FLU/L-PAM	rPBSCT	9	12
5	45/F	t(15;17)	2003	CR2	0	FLU/BU/TBI2	rPBSCT	12	18
6	28/F	t(15;17)	2003	CR3	1	FLU/BU/TBI2	uCBT	Graft Failure(22)	Graft Failure(67)
7	48/M	inv(16)	2003	CR2	2	FLU/BU/TBI2	uCBT	27	51
8	52/M	inv(16)	2007	non-CR	1	FLU/BU/TBI4	uBMT	18	N.D.
9	46/M	inv(16)	2008	CR1	3	FLU/BU/TBI4	rBMT	15	24
10	40/M	t(8;21)	1988	CR1	0	CY/TBI12	rBMT	23	36
11	33/M	t(8;21)	1992	non-CR	0	CY/VP-16/TBI12	rBMT	19	22
12	21/F	t(8;21)	1992	CR1	0	CY/VP-16/TBI12	rBMT	13	33
13	27/M	t(8;21)	1994	CR2	0	CY/VP-16/TBI12	uBMT	14	18
14	24/F	t(8;21)	1995	CR1	0	CY/VP-16/TBI12	uBMT	18	25
15	34/F	t(8;21)	2004	non-CR	0	CY/AraC＋G-CSF/TBI12	uCBT	23	56
16	25/M	t(15;17)	1990	CR3	0	CY/VP-16/TBI12	rBMT	19	26
17	25/F	t(15;17)	1998	CR2	0	CY/VP-16/TBI12	uBMT	18	22
18	24/M	t(15;17)	2002	CR2	0	CY/VP-16/TBI12	uBMT	15	24
19	55/F	inv(16)	2003	non-CR	0	CY/VP-16/TBI12	uCBT	N.D.	N.D.
20	29/F	inv(16)	2006	CR2	0	CY/AraC＋G-CSF/TBI12	uCBT	26	41

Pt. 1 to 9 received RIST and Pt 10 to 20 received CST.

＊Parenthesis indicates the duration of WBC and platelet recovery after second HSCT in Pt. 4. N.D. ; not determined

Table 2. Characteristics of AML patients with intermediate cytogenetics receiving HSCT

Pt.	Age/Sex	karyotype	Year of SCT	Disease Status	HCT-CI	Conditioning	Stem Cell Source	WBC recovery (day)	PLT recovery (day)	aGVHD	cGVHD	OUTCOME
21	52/F	46, XX	2003	CR1	2	FLU/L-PAM	rPBSCT	13	14	II	0	Dead at day 587/Relapse at day 148
22	58/F	46, XX	2005	CR1	0	FLU/L-PAM	rPBSCT	15	22	0	0	Alive at day 1449
23	61/F	46, XX	2005	CR3	2	FLU/BU/TBI4	uBMT	12	15	0	extensive	Alive at day 1315
24	64/M	46, XY	2006	CR1	3	FLU/BU/TBI4	uBMT	16	27	II	extensive	Alive at day 975 in remission/Relapse at day 563
25	68/F	46, XX	2006	CR2	0	FLU/BU/TBI4	uCBT	20	52	0	extensive	Alive at day 883
26	55/F	46, XX	2006	CR1	0	FLU/BU/TBI4	uBMT	15	21	II	extensive	Alive at day 846
27	63/F	47, XX, +21	2007	CR1	1	FLU/BU/TBI4	rBMT	11	20	0	0	Dead at day 257/Relapse at day 35
28	56/F	46, XX, t(11;19)(q23;p13)	2007	CR1	2	FLU/BU/TBI4	uBMT	14	19	II	0	Alive at day 404
29	34/M	46, XY	1988	CR1	0	CY/ TBI	rBMT	34	30	I	limited	Dead at day 6438 by cerebral hemorrhage
30	24/M	47, XY, +8	1990	non-CR	1	CY/ VP-16/ TBI	rBMT	19	24	II	0	Alive at day 5444
31	22/M	47, XY, +8	1993	non-CR	2	CY/ VP-16/ TBI	uBMT	17	ND	ND	ND	Dead at day 24 by RRT (cardiac failure)
32	29/F	46, XX	1994	CR1	0	CY/ VP-16/ TBI	rBMT	19	31	0	0	Alive at day 2626
33	42/M	t(11;19)(q23;p13.1)	1998	non-CR	0	CY/AraC+G-CSF/TBI	rBMT	17	?	I	0	Alive at day 1493
34	17/M	46, XY	2000	CR1	0	CY/VP-16/TBI	rPBSCT	ND	ND	ND	ND	Dead at day 6 by RRT (sepsis)
35	15/M	46, XY	2000	CR1	0	CY/VP-16/TBI	uBMT	16	19	III	0	Alive at day 2818
36	19/F	46, XX	2000	CR1	1	CY/VP-16/TBI	rBMT	9	14	0	0	Alive at day 2835
37	55/M	46, XY	2001	non-CR	1	CY/VP-16/TBI	uBMT	ND	ND	0	0	Dead at day 78 by leukemia
38	32/M	46, XY, del(7q)	2001	CR1	1	CY/VP-16/TBI	rBMT	17	34	II	extensive	Alive at day 2511
39	19/M	46, XY	2001	CR1	1	CY/VP-16/TBI	uBMT	15	24	I	extensive	Dead at day 607 by cGVHD
40	25/M	46, XY	2002	non-CR	3	CY/AraC+G-CSF/TBI	rBMT	19	28	III	extensive	Dead at day 379/Relapse at day 175
41	40/F	46, XX	2002	CR1	3	CY/VP-16/TBI	uBMT	14	22	0	0	Dead at day 250/Relapse at day 196
42	37/M	46, XY	2002	non-CR	3	CY/VP-16/TBI	rBMT	17	25	I	0	Alive at day 2139
43	28/M	46, XY	2002	CR1	0	CY/VP-16/TBI	rBMT	16	19	II	extensive	Alive at day 1794
44	16/M	46, XY	2003	CR1	0	CY/TBI	rPBSCT	14	20	0	0	Alive at day 1534
45	27/M	46, XY, t(8;22)(p11;q13)	2003	CR1	1	CY/AraC+G-CSF/TBI	uCBT	ND	ND	ND	ND	Dead at day 22 by RRT (sepsis)
46	30/M	46, XY	2003	CR1	0	CY/VP-16/TBI	rBMT	17	27	II	limited	Alive at day 1795
47	35/F	46, XX	2003	non-CR	1	CY/VP-16/TBI	uCBT	ND	ND	ND	ND	Dead at day 29 by leukemia
48	52/M	46, XY	2004	CR1	0	CY/AraC+G-CSF/TBI	uCBT	25	47	0	limited	Alive at day 1404
49	22/F	46, XX,t(11;19)(q23;p13)	2005	CR1	1	CY/AraC+G-CSF/TBI	uCBT	28	42	ND	ND	Dead at day 118 by RRT (thrombotic microangiopathy)
50	50/M	46, XY	2005	non-CR	1	CY/AraC+G-CSF/TBI	uBMT	16	24	I	limited	Alive at day 1283
51	19/M	46, XY, del(9q)	2005	CR1	2	CY/VP-16/TBI	rBMT	15	22	II	extensive	Alive at day 1257
52	34/M	46, XY	2005	CR1	0	CY/TBI	rPBSCT	16	24	II	extensive	Alive at day 932
53	21/M	46, XY	2005	CR1	0	CY/TBI	rPBSCT	15	23	I	limited	Alive at day 813
54	45/M	46, XY, t(11;17)(q23;q25)	2006	non-CR	2	CY/AraC+G-CSF/TBI	uCBT	25	106	III	extensive	Alive at day 504
55	46/M	46, XY	2006	CR2	0	CY/VP-16/TBI	uCBT	ND	ND	ND	ND	Dead at day 58 by graft failure
56	48/M	46, XY	2006	CR1	0	CY/VP-16/TBI	uBMT	15	26	II	ND	Dead at day 500 by pancreatitis
57	46/M	46, XY	2007	CR1	2	CY/VP-16/TBI	rBMT	20	ND	ND	ND	Dead at day 38 by RRT (pulmonary hemorrhage)

Pt. 21 to 28 received RIST and Pt 29 to 57 received CST.

Table 3. Status of GVHD, MRD and outcome of AML patients with favorable cytogenetics

Pt.	aGVHD	cGVHD	MRD marker	pre-SCT	~ day 50	~ day 100	~ day 200	~ day 360	day 360 ~	Outcome
1	0	extensive	AML1–MTG8	(+)	(−)	(−)	(−)	(−)	N.D.	Dead at day 335 by pneumonia
2	0	0	AML1–MTG8	(−)	(−)	(−)	(−)	(−)	(−)	Alive at day 916 in remission
3	0	extensive	AML1–MTG8	(+)	(+)	(−)	(+) → (−)	(−)	(−)	Alive at day 421 in remission
4	0	extensive	PML–RARA	(−)	(−)	(−)	(−)	(−)	(−)	Alive at day 2486 in remission
5	0	0	PML–RARA	(+)	(−)	(−)	(−)	(−)	(−)	Alive at day 1816 in remission
6	I	0	PML–RARA	(−)	(−)	(−)	(−)	(−)	(−)	Alive at day 1931 in remission
7	III	0	CBFb–MYH11	(−)	(−)	N.D.	(−)	(−)	(−)	Alive at day 1903 in remission
8	0	0	CBFb–MYH11	(+)	(+)	(+)	(−)	(−)	(−)	Alive at day 393 in remission/Relapse at day 176
9	0	0	CBFb–MYH11	(−)	(−)	(−)	(−)	(−)	N.D.	Alive at day 305 in remission
10	II	extensive	AML1–MTG8	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	Alive at day 6800 in remission
11	II	extensive	AML1–MTG8	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	Dead at day 919 by cGVHD
12	III	limited	AML1–MTG8	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	Alive at day 5397 in remission
13	I	0	AML1–MTG8	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	Alive at day 4466 in remission
14	0	extensive	AML1–MTG8	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	Alive at day 3115 in remission
15	0	extensive	AML1–MTG8	(+)	(+)	(−)	(−)	(−)	(−)	Alive at day 1156 in remission
16	II	0	PML–RARA	(−)	N.D.	N.D.	N.D.	N.D.	N.D.	Alive at day 3679 in remission
17	0	0	PML–RARA	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	Alive at day 6479 in remission
18	0	limited	PML–RARA	(−)	N.D.	(−)	(−)	(−)	(−)	Alive at day 1261 in remission
19	N.D.	N.D.	CBFb–MYH11	(+)	N.D.	N.D.	N.D.	N.D.	N.D.	Dead at day 23 by RRT (sepsis)
20	I	0	CBFb–MYH11	(−)	N.D.	(−)	(−)	(−)	(−)	Alive at day 712 in remission

Pt. 1 to 9 received RIST and Pt 10 to 20 received CST.

Figure 2a

3-year OS of AML patients treated with allo-HSCT
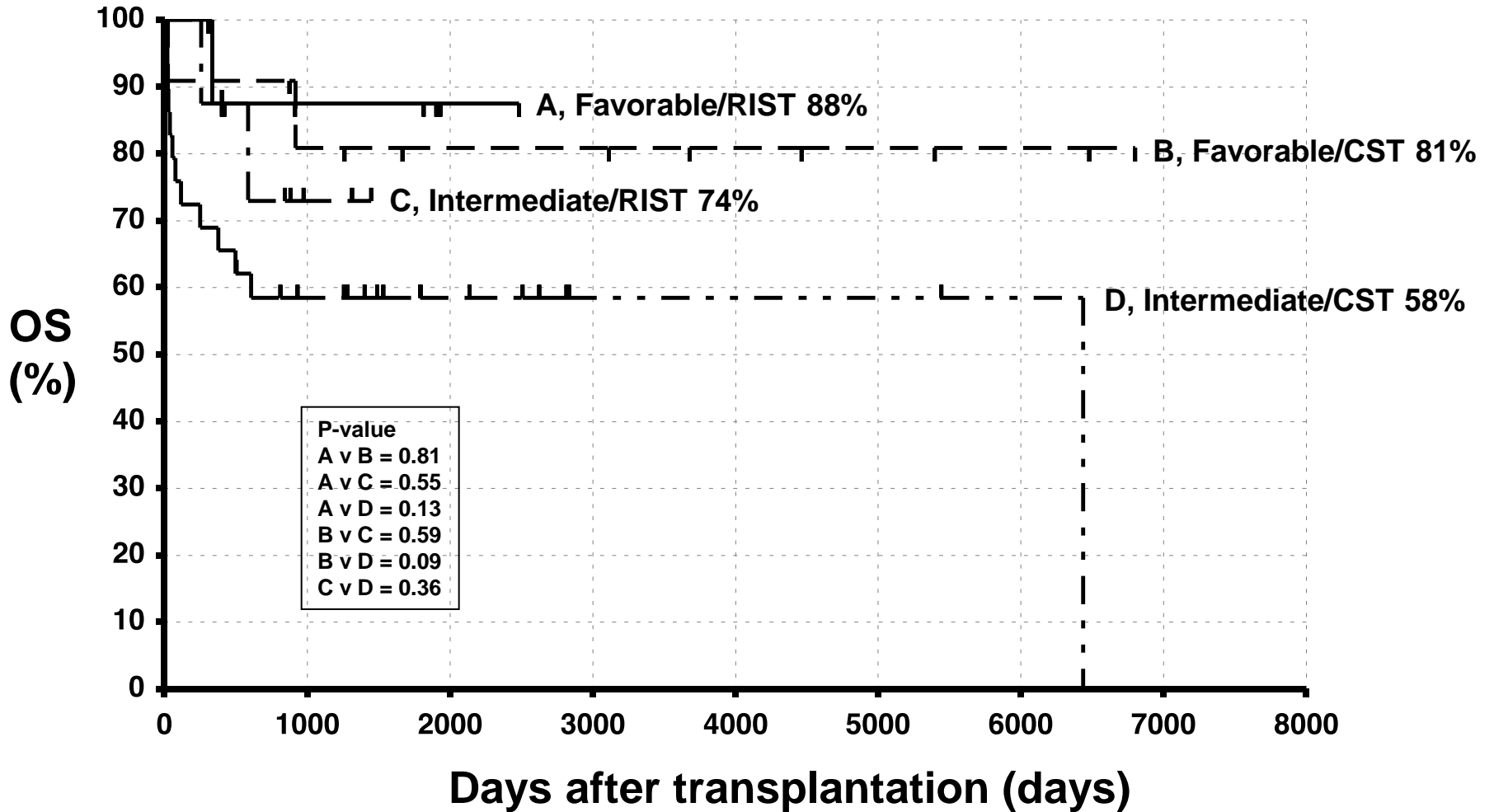
A, Favorable/RIST 88%

B, Favorable/CST 81%

C, Intermediate/RIST 74%

D, Intermediate/CST 58%

OS (%)

Days after transplantation (days)

P-value
A v B = 0.81
A v C = 0.55
A v D = 0.13
B v C = 0.59
B v D = 0.09
C v D = 0.36

Figure 2b

3-year RFS of AML patients treated with allo-HSCT

RFS (%) vs Days after transplantation (days)

B, Favorable/CST 81%
A, Favorable/RIST 76%
C, Intermediate/RIST 61%
D, Intermediate/CST 48%

P-value
A v B = 0.71
A v C = 0.51
A v D = 0.16
B v C = 0.25
B v D = 0.06
C v D = 0.53
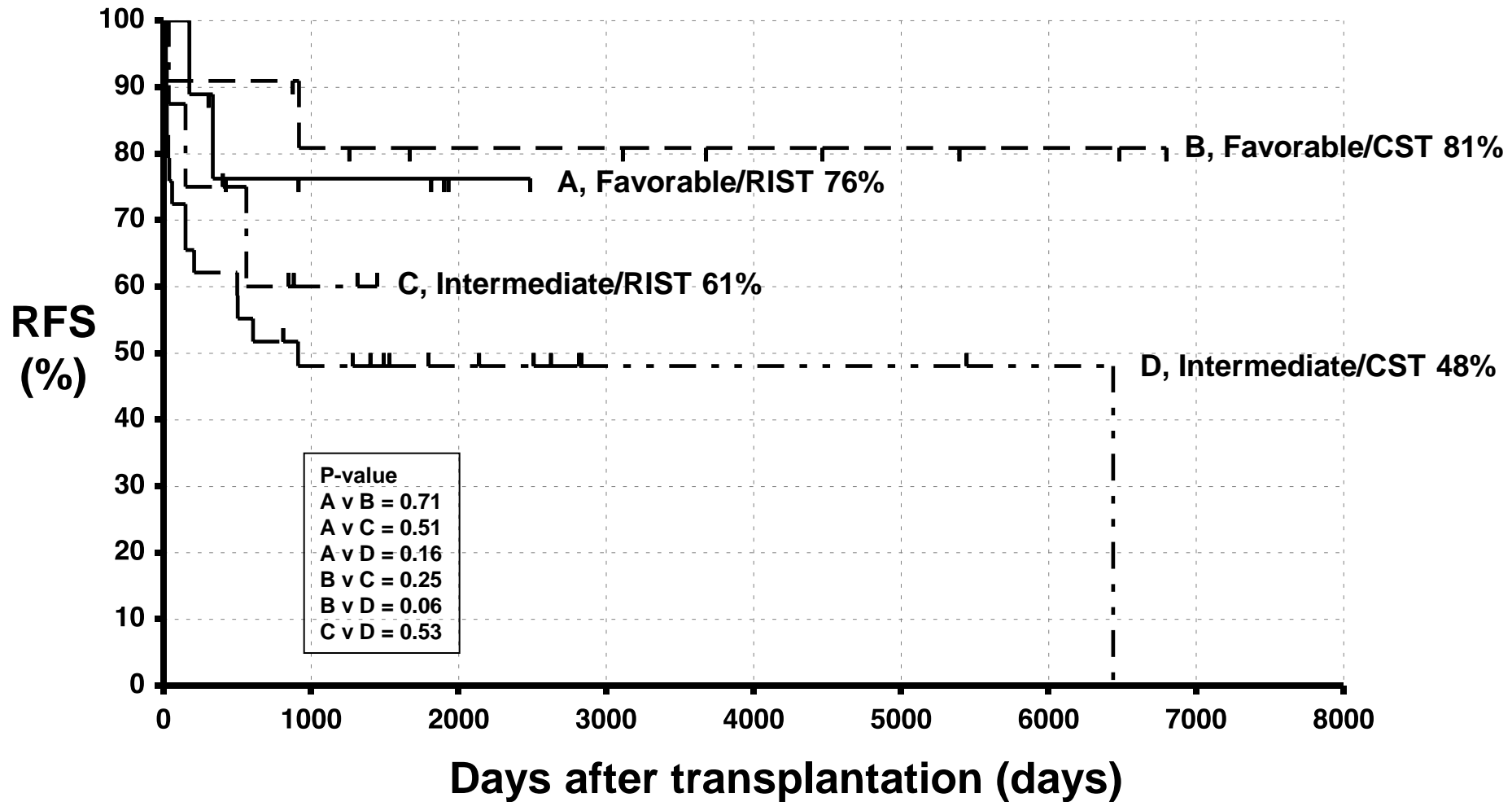
Figure 3a

3-year OS of AML patients in remission treated with allo-HSCT

B, Favorable/CST 100%

A, Favorable/RIST 87%

C, Intermediate/RIST 74%

D, Intermediate/CST 60%

P-value
A v B = 0.28
A v C = 0.60
A v D = 0.20
B v C = 0.13
B v D < 0.05
C v D = 0.43

OS (%)

Days after transplantation (days)
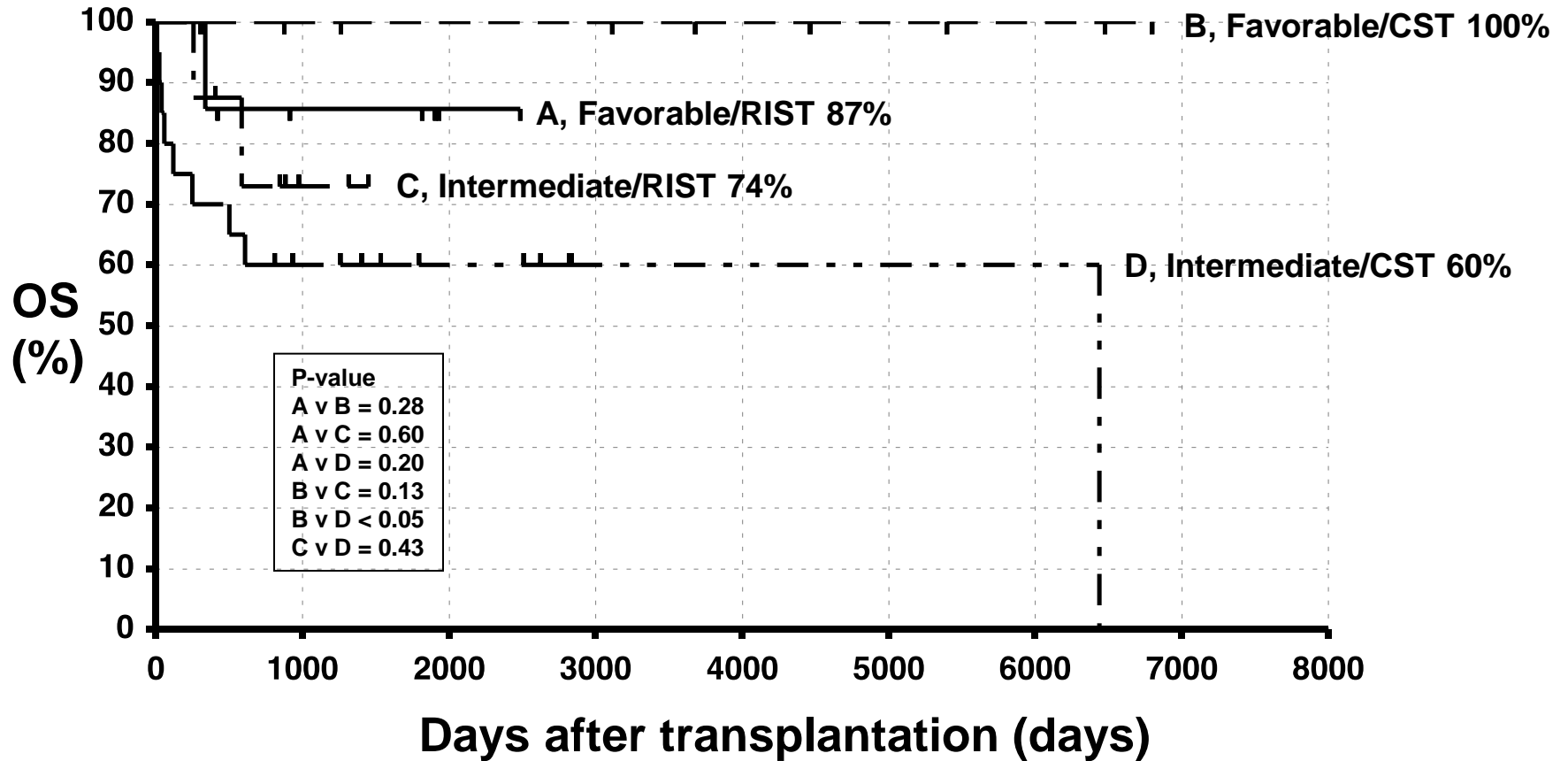
Figure 3b

3-year RFS of AML patients in remission treated with allo-HSCT
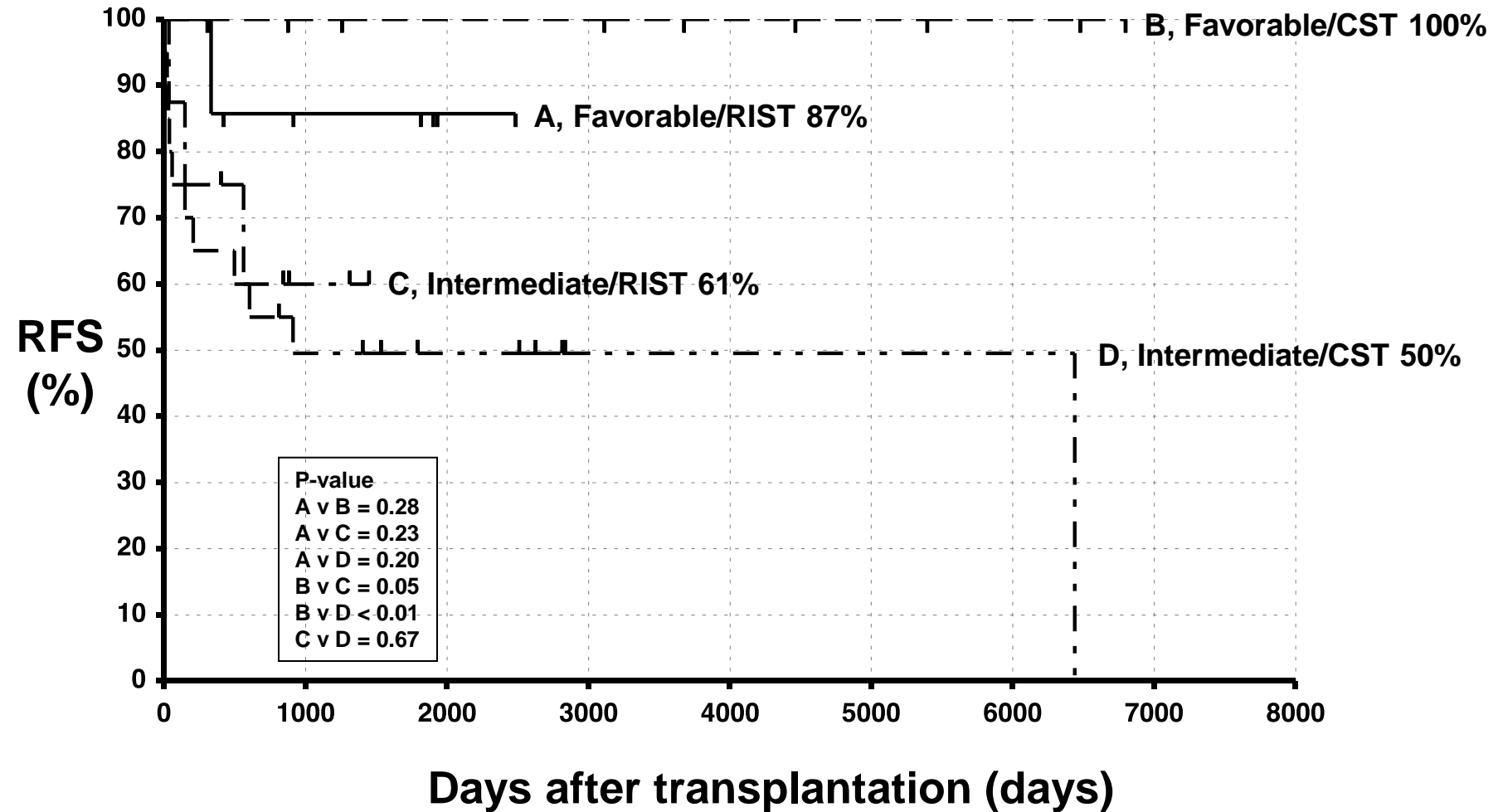
Figure shows four Kaplan-Meier survival curves:
- B, Favorable/CST 100%
- A, Favorable/RIST 87%
- C, Intermediate/RIST 61%
- D, Intermediate/CST 50%

Y-axis: RFS (%), ranging 0 to 100
X-axis: Days after transplantation (days), ranging 0 to 8000

P-value
A v B = 0.28
A v C = 0.23
A v D = 0.20
B v C = 0.05
B v D < 0.01
C v D = 0.67

	N	Mortality after SCT			Cause of mortality	
		~ 30 days	31 ~ 90 days	91 days ~	Relapse-related mortality	Other death
RIST with Favorable Cytogenetics	9	0(0%)	0(0%)	1(11%)	0(0%)	1(11%)
RIST with Intermediate Cytogenetics	8	0(0%)	0(0%)	2(25%)	2(25%)	0(0%)
CST with Favorable Cytogenetics	11	1(9%)	0(0%)	1(9%)	0(0%)	2(18%)
CST with Intermediate Cytogenetics	29	4(14%)	3(10%)	6(21%)	4(14%)	9(31%)

Table 4 The timing and cause of mortality after allo-HSCT in AML patients with favorable and intermediate cytogenetics

	N	Mortality after SCT			Cause of mortality	
		~ 30 days	31 ~ 90 days	91 days ~	Relapse-related mortality	Other death
RIST with Favorable Cytogenetics	8	0(0%)	0(0%)	1(13%)	0(0%)	1(13%)
RIST with Intermediate Cytogenetics	8	0(0%)	0(0%)	2(25%)	2(25%)	0(0%)
CST with Favorable Cytogenetics	8	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
CST with Intermediate Cytogenetics	20	2(10%)	2(10%)	5(25%)	1(5%)	8(40%)

Table 5 The timing and cause of mortality after allo-HSCT in AML patients with favorable and intermediate cytogenetics in hematological remission prior to HSCT