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For a complete list of Japan Adult Leukemia Study Group (JALSG) participants, please see the supplemental appendix.

Abstract

We conducted a multi-institutional randomized study to determine whether high-dose daunorubicin (DNR) would be as effective as standard-dose idarubicin (IDR) in remission induction therapy for newly diagnosed adult patients aged younger than 65 with acute myeloid leukemia (AML). Of 1,064 patients registered, 1,057 were evaluable. They were randomly assigned to receive either DNR (50 mg/m^2 daily for 5 days) or IDR (12 mg/m^2 daily for 3 days), in combination with 100 mg/m^2 cytarabine by continuous infusion daily for 7 days, as induction therapy. Complete remission (CR) was achieved in 407 (77.5%) of 525 patients in the DNR group and 416 (78.2%) of 532 in the IDR group (P = 0.79). Patients achieving CR received intensive post-remission therapy consisting of either 3 courses of high-dose cytarabine or 4 courses of standard-dose therapy. Overall survival rates at 5 years were 48% for the DNR group and 48% for the IDR group (P = 0.54), and relapse-free survival rates at 5 years were 41% and 41% (P = 0.97), respectively. Thus, high-dose DNR and standard-dose IDR are equally effective for the treatment of adult AML, achieving a high CR rate and good long-term efficacy. This study is registered at http://www.umin.ac.jp/ctrj/ as C000000157.

Introduction

The combination of anthracycline and cytarabine (Ara-C) with or without other antileukemic drugs is a standard induction therapy for acute myeloid leukemia (AML)[1-3], and a combination of daunorubicin (DNR) at a dose of 45 to50 mg/m^2 given daily for 3 days and Ara-C at a dose of 100 to 200 mg /m^2 given daily for 7 days was generally used. In late 1980s, however, idarubicin (IDR) was introduced into clinics and 3 randomized studies comparing IDR with DNR reported significantly higher complete remission (CR) rates in favor for IDR.[4-6] A meta-analysis also confirmed a superior effect of IDR at a dose of 10 to 12 mg/m^2 for 3 days to DNR at a dose of 45 to 60 mg/m^2 for 3 days in the achievement of CR. Nevertheless, the long-term follow-up of above mentioned 3 randomized studies comparing IDR with DNR revealed that, in only one study, the IDR group resulted in better overall survival (OS) compared with the DNR group.[8]

Japan Adult Leukemia Study Group (JALSG) employed IDR and Ara-C as induction therapy in the AML95 and AML97 studies,[9-11] after IDR was registered and approved for the national health insurance system in 1995. Both studies resulted in satisfactorily high CR rates, 80% and 79%, respectively. However, these CR rates were not superior to those of our earlier AML87, AML89, and AML92 studies, which used DNR in combination with other anti-leukemia drugs.[12-14] In these 3 earlier studies, DNR and other drugs were administered in a response-oriented individualized manner, that is, additional drugs were given for a few days when the bone marrow at day 8 was not hypoplastic, containing a substantial number of blasts. Therefore, the total doses of DNR administered during the first course

of induction therapy were 240 to 280 mg/m^2 given over 5 to 7 days, which were more than the conventional dose of 40 to 60 mg/m^2 for 3 days. Usui et al. also reported that the optimal dose of DNR in their induction therapy for newly diagnosed adult AML was approximately 280 mg/m^2 (40 mg/m^2 for 7 days). [15]

Since there had been no prospective randomized study comparing a higher dose of DNR with the standard dose of IDR (12mg/m^2) in adult AML, in the present multi-institutional randomized study, we prospectively compared IDR (12 mg/m^2 for 3 days) with DNR (50 mg/m^2 for 5 days), in combination with Ara-C (100 mg/m^{2}for 7 days), as induction therapy of previously untreated adult AML. High-dose DNR resulted in the same CR rate and predicted 5-year OS compared with standard-dose IDR.

Patients and methods

Patients

From December 2001 to December 2005, 1,064 newly diagnosed adult patients aged 15 to 64 years with "de novo" AML were consecutively registered from 129 participating institutions. AML was first diagnosed by the French-American-British (FAB) classification at each institution. Peripheral blood and bone marrow smears from all registered patients were sent to Nagasaki University, and examined by May-Giemsa, peroxidase, and esterase staining. Then, diagnosis was reevaluated by the central review committee. FAB-M3 was not registered in this study. Eligibility criteria included adequate function of liver (serum bilirubin level < 2.0 mg/dL), kidney (serum creatinine < 2.0 mg/dL), heart, and lung, and an Eastern

Cooperative Oncology Group performance status between 0 and 3. Patients were not eligible if they had prediagnosed myelodysplastic syndrome (MDS), but were eligible if they had no definite diagnosis of MDS confirmed by bone marrow histological analysis even when they had a previous history of hematological abnormality. Cytogenetic abnormalities were grouped by standard criteria and classified according to the Medical Research Council (MRC) classification.[16] The study was approved by the Institutional Review Boards at each participating institution. Written informed consent was obtained from all patients before registration in accordance with the Declaration of Helsinki. The study was registered at http://www.umin.ac.jp/ctr/ as C000000157.

Treatments

Patients were randomly assigned to receive either IDR or DNR using a centralized computer system. Randomization was stratified by age (younger or older than 50 years) and type of AML (FAB classification). All patients received 100 mg/m^2/day Ara-C, by 24-hour continuous infusion from days 1 to 7. In the IDR group, patients received 12 mg/m^2/day IDR for 3 days, and in the DNR group, 50 mg/m^2/day DNR for 5 days. If patients did not achieve CR by the first course, the same induction therapy was repeated after an approximately 3- to 4-week interval. If patients did not achieve CR with two courses, they were judged as failure cases.

All patients who achieved CR were again randomized to receive either 4 courses of conventional consolidation therapy or 3 courses of high-dose Ara-C therapy. In the conventional consolidation group, the first course consisted

of mitoxantrone (MIT; 7 mg/m^2 by 30-minute infusion on days 1 to 3) and Ara-C (200 mg/m^2 by 24-hour continuous infusion on days 1 to 5). The second consisted of DNR (50 mg/m^2 by 30-minute infusion on days 1 to 3) and Ara-C (200 mg/m^2 by 24-hour continuous infusion on days 1 to 5). The third consisted of aclarubicin (ACR; 20 mg/m^2 by 30-minute infusion on days 1 to 5) and Ara-C (200 mg/m^2 by 24-hour continuous infusion on days 1 to 5). The fourth consisted of Ara-C (200 mg/m^2 by 24-hour continuous infusion on days 1 to 5), etoposide (ETP; 100 mg/m^2 by 1-hour infusion on days 1 to 5), vincristine (VCR; 0.8 mg/m^2 by bolus injection on day 8), and vindesine (VDS; 2 mg/m^2 by bolus injection on day 10). Each consolidation was administered as soon as possible after the neutrophils, white blood cells (WBC), and platelets recovered to over 1.5 x 10^9/L, 3.0 x 10^9/L, and 100 x 10^9/L, respectively. In the high-dose Ara-C group, 3 courses of 2.0 g/m^2 Ara-C were given by 3-hour infusion every 12 hours on days 1 to 5. Each course was administered one week after the neutrophils, WBC, and platelets recovered to the above counts.

The best supportive care, including administration of antibiotics and platelet transfusions, was given as indicated. When patients had life-threatening documented infections during neutropenia, the use of granulocyte colony-stimulating factor was permitted.

After completion of consolidation therapy, no patients received further chemotherapy. Allogeneic stem cell transplantation (SCT) was offered during the first CR to patients aged 50 years or less and with a histocompatible donor in the intermediate or adverse cytogenetic risk groups.

Definition and study end points

Responses were evaluated by the recommendations of the International Working Group.[17] CR was defined as the presence of all of the following: less than 5% blasts in bone marrow, no leukemic blasts in peripheral blood, recovery of peripheral neutrophil counts over 1.0 x 10^9/L and platelet counts over 100 x 10^9/L, and no evidence of extramedullary leukemia. Relapse after CR was defined as the presence of at least one of the following: reappearance of leukemic blasts in the peripheral blood, recurrence of more than 5% blasts in the bone marrow not attributable to any other cause (e.g., bone marrow regeneration after consolidation therapy), and appearance of extramedullary leukemia.

This was a multi-institutional randomized phase 3 study with a 2 x 2 factorial design. The primary end point of the first randomization was CR rate. The result of the second randomization is partially reported here but will be presented fully in a separate paper. OS was calculated from the date of entry to the study until death from any cause and censored at the last follow-up. Relapse-free survival (RFS) for patients who achieved CR was measured from the date of CR until the date of AML relapse or death from any cause and censored at the last follow-up. Patients who underwent allogeneic SCT were not censored at the date of SCT.

Statistical methods

This study was prospectively powered to demonstrate non-inferiority of DNR compared with IDR. With a sample size of 420 patients per group (840 in total), the study had a power of 90% at a 1% level of significance to

demonstrate non-inferiority (assuming 80% CR rate for both groups). Statistical testing for the non-inferior trial was performed according to the method of Blackwelder.[18] The Kaplan-Meier method was used to estimate probabilities of OS and RFS.[19] To test factors to predict CR, the χ^2 test and the Wilcoxon rank-sum test were used for univariate analysis and the multiple logistic regression model for multivariate analysis. For comparison of OS and RFS, the log-rank test was used for univariate analysis and the proportional hazard model of Cox for multivariate analysis.[20, 21] Cumulative rates of CR, neutrophil recovery and platelet recovery were estimated according to the Kaplan–Meier method and were evaluated with the log-rank test. JMP program (SAS Institute Inc., Cary, NC) was used for these analyses. All analyses were performed according to the intent-to-treat principle. All statistical tests except the method of Blackwelder were 2-sided, and the significance level was set at 0.05.

Results

Patient characteristics

Among 1,064 registered patients, 7 did not meet the inclusion criteria (misdiagnosis: one, infectious complication: one, without therapy: one, and withdrawal of consent: 4). The study population thus comprised 1,057 patients (Fig. 1). Patient characteristics are presented in Table 1. Median age was 47 years (range, 15 to 64). Cytogenetics data were available for 1,021 (96.6%) patients. Among these, 247 (24.2%) were classified in the favorable-risk group, 681 (66.7%) in the intermediate-risk group, and 93 (9.1%) in the high-risk group. Five hundred and thirty-two patients were assigned to the

IDR group, and 525 to the DNR group. The two groups were well balanced for pretreatment characteristics such as age, initial WBC counts, FAB classification, and cytogenetic prognostic grouping.

Response to Induction Therapy

Overall, of 1,057 evaluable patients, 823 (77.9%) achieved CR. Of 532 patients in the IDR group, 416 (78.2%) achieved CR, and of 525 in the DNR group, 407 (77.5%) obtained it (P = 0.79). Non-inferiority for the primary end point was assessed by determining whether the lower bound of the 95% confidence interval (CI) of the difference between the CR rates for DNR and IDR groups was less than - 10%. The CR rate of the DNR group was non-inferior to that of the IDR group (Table 2). In the IDR group, 341 (64.1%) patients achieved CR after the first course, and in the DNR group, 321 (61.1%) did so (P = 0.39). The average period to achieve CR was 33.8 days (95% CI, 32.9 to 34.6) in the IDR group and 32.4 days (95% CI, 31.6 to 33.2) in the DNR group (P = 0.038). CR rates related to FAB classification, age, and cytogenetics are shown in Table 3. Although they were few in number, patients with FAB M6 responded better to IDR: 78% of 17 patients in the IDR group and 38% of 16 in the DNR group achieved CR (P = 0.037). There were no differences in CR rate between the two groups in other FAB subtypes, cytogenetic risk groups, age, myeloperoxidase (MPO) positivity of blasts, initial WBC count, and performance status (Table 3). Overall, logistic regression analysis revealed that induction regimen was not an independent prognostic factor but that cytogenetic group and percentage of MPO-positive

blasts were significant independent factors for achieving CR (Table 4). Cut-off value of WBC at 20 or 50 x 10^9/L did not change the result.

OS and RFS

At a median follow-up of 48 months, 5-year predicted OS rates were 48% for the IDR group (95% CI, 43% to 53%) and 48% for the DNR group (95% CI, 43% to 53%; P = 0.54) (Fig. 2a), and 5-year predicted RFS rates of CR patients were 41% (95% CI, 36% to 46%) and 41% (95% CI, 35% to 45%), respectively (P = 0.97) (Fig. 2b). Significant unfavorable prognostic features for OS by the Cox proportional hazard model were adverse cytogenetic risk group, age of more than 50 years, WBC more than 20 x 10^9/L, MPO-positive blasts less than 50%, and FAB classification of either M0, M6, or M7, and for RFS, adverse cytogenetic risk group, WBC more than 20 x 10^9/L, MPO-positive blasts less than 50%, LDH of 500 IU/L or more, and age of more than 50 years. Induction regimen was not an independent prognostic factor for either OS or RFS by this multivariate analysis.

Adverse Events

Patients receiving IDR required a slightly but significantly longer time to recover from neutropenia and thrombocytopenia. Median duration with a neutrophil count less than 1.0 x 10^9/L was 28 days for the IDR group and 27 days for the DNR group (P = 0.0011) (Fig. 3a). Median duration with a platelet count less than 100 x 10^9/L was 25 days for the IDR group and 24 days for the DNR group (P = 0.0034) (Fig. 3b). Sepsis occurred more frequently in the IDR group than in the DNR group (8.7% and 4.9%,

respectively, $P = 0.02$). Early death within 60 days occurred more frequently in the IDR group than in the DNR group (4.7% and 2.1%, respectively, $P = 0.03$, Table 5).

Post-remission Therapy

Of the 823 CR patients, 781 patients were randomly assigned to receive either 4 courses of conventional standard-dose consolidation therapy (392 patients) or 3 courses of high-dose Ara-C therapy (389 patients), and 136 patients (16% of CR patients) underwent allogeneic SCT in the first CR. There was no significant difference in OS and RFS by post-remission therapy between IDR and DNR groups (Table 6). In IDR group predicted 5-year OS rates were 57% for the conventional standard-dose consolidation arm (95% CI, 49% to 65%) and 58% for the high-dose Ara-C arm (95% CI, 51% to 66%; P = 0.79, Fig. 4a). In DNR group predicted 5-year OS rates were 56% (95% CI, 48% to 63%) and 58% (95% CI, 50% to 65%; P = 0.71, Fig. 4b), respectively. If two groups were evaluated together, predicted 5-year OS rates were 56% (95% CI, 51% to 62%) and 58% (95% CI, 53% to 62%; P = 0.95), and predicted 5-year RFS rates were 39% (95% CI, 34% to 44%) and 43% (95% CI, 38% to 48%), respectively (P = 0.72). The detailed results of this consolidation phase will be reported in a separate paper (S.M., S.O. and R.O., manuscript submitted to *Blood*).

Discussion

The present randomized study demonstrates that if the dose intensity is appropriately increased, DNR is as effective as a standard dose of IDR for

newly diagnosed adult patients aged less than 65 with AML. Remission induction therapy using 50 mg/m^2 DNR for 5 days resulted in almost the same CR rate and long-term outcome as those using 12 mg/m^2 IDR for 3 days, in combination with 100 mg/m^2 Ara-C for 7 days. Generally, DNR is used at a dose of 45 to 50 mg/m^2 for 3 days in combination with 100 to 200 mg/m^2 Ara-C for 7 days, and 50 to 70% of newly diagnosed adult patients with AML achieve CR. As stated in the introduction section, JALSG used a response-oriented individualized induction therapy in the AML87, AML89, and AML92 studies for AML, which permitted an additional DNR and other anti-leukemia drugs to be administered according to the bone marrow status on day 8 or later.[12-14] The CR rates in these 3 studies ranged from 77 to 80% and the median total dose of DNR was 240 mg/m^2.

On the basis of these experiences and also owing to the regulation of our national medical insurance system, we employed a dose and schedule of DNR of 50 mg/m^2 for 5 days, that is, a total dose of 250 mg/m^2. Additionally we avoided higher daily doses such as 80 mg/m^2 for 3 days, because higher plasma concentration might cause more cardiotoxicity in older patients.[22]

Three randomized studies in the early 1990s[4-6] as well as subsequent studies[23, 24] and meta-analyses[7] reported a superior effect of IDR (12 to 13 mg/m^2 x 3 days) over that of DNR (45 to 50 mg/m^2 x 3 days), in combination with Ara-C, and AML patients receiving IDR obtained 70 to 80% CR without a significant increase in toxic mortality, while those receiving DNR achieved 58 to 65% CR.[4-6] However, because the duration of neutropenia and thrombocytopenia was longer in the IDR groups, it was questioned whether the doses used in these comparisons were equivalent in terms of levels of

toxicity and whether any observed advantage represented an inherent biologic advantage of IDR rather than biologic dose equivalence.[1, 2]

In these randomized studies, Wiernik et al. reported that patients with more than 50 x 10^9/L initial WBC counts obtained only 32% CR by the DNR regimen compared with 68% CR by the IDR regimen, while patients with less than 50 x 10^9/L WBC obtained 65% and 69% CR, respectively[5]. Berman et al. also reported that patients in the IDR group did well regardless of their initial WBC, whereas patients in the DNR group had a decreased response rate as the WBC increased[4]. In the present study, however, a total of 250 mg/m^2 of DNR resulted in almost the same CR rate as a total of 36 mg/m^2 of IDR regardless of initial WBC counts and other prognostic factors such as cytogenetics, age, and FAB classification except M6. Although, among patients with FAB M6, 16 patients in the DNR group had significantly lower CR rate than 17 patients in the IDR group, we have no clear explanation for this observation, because the small number of patients made the further analysis difficult. Thus, the increased total dose of DNR administered in 5 days would be responsible for almost the same satisfactory CR rate and long-term outcome as IDR in 3 days in the present study. As for adverse events, the recovery from neutropenia and thrombocytopenia was slightly but significantly delayed in the IDR group, and sepsis and early mortality occurred more frequently in the IDR group, as shown in Fig. 3 and Table 5.

Before we initiated this AML201 study, there was no evidence that a higher dose of DNR is more effective than its standard dose owing to the lack of a prospective randomized study. In the sequential studies reported by Southwest Oncology Group, however, the CR rate with DNR at a dose of 70

mg/m^2 was better than that with 45 mg/m^2.[25, 26] Very recently, two groups reported that a higher dose of DNR improved the CR rate and OS in prospective randomized studies.[27, 28] The Dutch-Belgian Cooperative Trial Group for Hemato-Oncology (HOVON), German AML Study Group (AMLSG) and Swiss Group for Clinical Cancer Research (SAKK) Collaborative Group compared 3-day DNR at 90 mg/m^2 with 3-day DNR at 45 mg/m^2, in combination with 7-day Ara-C, in elderly patients aged 60 to 83 years with AML or high-risk refractory anemia, and reported a higher CR rate for the escalated-treatment group (52% versus 35%, P = 0.002).[27] Although survival end points did not differ significantly overall, among patients aged 60 to 65 years CR rate (73% versus 51%) and OS (38% versus 23%) were significantly higher for the 90 mg/m^2 group. Eastern Cooperative Oncology Group also compared 3-day DNR at 90 mg/m^2 with 3-day DNR at 45 mg/m^2, in combination with 7-day Ara-C, in patients aged 17 to 60 years with AML, and reported higher CR rate (70.6% versus 57.3%, $P < 0.001$) and longer OS (median, 23.7 months versus 15.7 months, P = 0.003) for the high-dose group.[28] With these reports and ours taken together, the optimal total dose of DNR is still to be explored but may rest somewhere between 250 to 270 mg/m^2. Since we used the FAB classification in this study, we did neither include patients with 20 to 30% of blasts in the bone marrow nor those with refractory anemia with excess blasts. Therefore, it is unclear whether our result is applicable to these patients.

IDR is a derivative of DNR and differs from its parent compound by the deletion of a methoxy group at position 4 of the chromophore ring. *In vitro* and preclinical data have shown that IDR is more lipophilic, faster in cellular

uptake, exhibits increased cellular retention, lower in susceptibility to p-glycoprotein-dependent resistance, and less cardiotoxic than DNR. Both IDR and DNR undergo conversion to their respective alcohol metabolites, idarubicinol and daunorubicinol. Unlike the latter, idarubicinol has a prolonged plasma half-life and is thought to have a pharmacological advantage.[29-32]

The pediatric Berlin-Frankfurt-Münster (BFM) group previously compared 12 mg/m^2 IDR for 3 days with 30 mg/m^2 DNR twice daily for 3 days, in combination with Ara-C and etoposide, and reported almost the same CR rates (85% versus 86%, respectively) and predicted 5-year event-free survival (55% versus 49%, respectively, P = 0.29) in newly diagnosed childhood AML.[33] Furthermore, DNR at a dose of 60 mg/m^2 for 3 days as well as IDR at a dose of 12 mg/m^2 for 3 days achieved similar CR rates in the studies by Eastern Cooperative Oncology Group that consisted of a large number of adult patients.[34, 35]

Recently, French Acute Leukemia Association reported a randomized study comparing standard doses of IDA (12 mg/m^2 for 3 days) with high doses of DNR (80 mg/m^2 for 3 days) or IDA (12 mg/m^2 for 4 days) for remission induction in newly diagnosed elderly patients aged 50 to 70 years (median, 60) with AML.[36] CR rates were significantly higher for the standard-dose IDA group (83%) compared with the high-dose DNR group (70%, P = 0.007) but not compared with the high-dose IDR group (78%, P = 0.12). Although OS, relapse incidence, and event-free survival were not different among the 3 arms, DNR (80 mg/m^2 for 3 days) did not improve the CR rate of elderly AML up to the level of the standard-dose IDR.

As for adverse events, recovery from myelosuppression was faster and sepsis was less frequent in the DNR group. Both acute and late-onset cardiotoxicity was only reported in a small number of patients in both groups. Knowing that there was no increase in severe cardiac toxicities in patients receiving high-dose DNR (90 mg/m^2 for 3 days) compared with standard-dose DNR (45 mg/m^2 for 3 days) in the ECOG study (7.9% and 7.2%, respectively) [28], DNR may not necessarily be administered for 5 days as in the present study (50 mg/m^2 for 5 days), although further follow-up observation is needed for late-onset cardiotoxicity.

After the landmark study of Cancer and Leukemia Group B[37], it has been believed that high-dose Ara-C was superior to consolidation therapy that contained intermediate (400 mg/m2 for 5 days) or conventional (100mg/m2 for 5 days) dose of Ara-C. In this study we prospectively compared high-dose Ara-C with consolidation therapy that contained conventional dose of Ara-C and non-cross resistant agents. Our results clearly demonstrated that there was no difference in RFS and OS between the two consolidation arms, even if we used either IDR or DNR as induction chemotherapy.

In conclusion, the intensified dose of DNR in the present setting, that is, 50 mg/m^2 for 5 days, proved to be biologically equivalent in terms of efficacy and not more toxic in terms of myelosuppression compared with the standard dose and schedule of IDR, that is, 12 mg/m^2 for 3 days, for remission induction therapy in newly diagnosed younger patients aged 15 to 64 years (median, 47) with AML.

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Authorship

Contribution: S.O. designed and performed research, collected and interpreted data, and wrote the manuscript; S.M. designed and performed research, analyzed data, and participated in writing the manuscript; H.F., H.K., K.S., N.U., H.O., K.M., C.N., Y.M., A.F., T.N., T.Y., M.T., M.T., F.Y., Y.K., N.A., H.S., and H.H. performed research; S.H. analyzed data; K.O. and T.N. conducted and performed research; and R.O. conducted research, interpreted data, and participated in writing the manuscript.

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