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A Randomized Comparison of Four Courses of Standard-Dose Multiagent Chemotherapy versus Three Courses of High-Dose Cytarabine alone in Post-remission Therapy for Acute Myeloid Leukemia in Adults: the JALSG AML201 Study

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Abstract

We conducted a prospective randomized study to assess the optimal post-remission therapy for adult acute myeloid leukemia of age less than 65 in the first complete remission (CR). Seven hundred eighty-one patients in CR were randomly assigned to receive consolidation chemotherapy of either 3 courses of high-dose cytarabine (HiDAC) (2 g/m^2 twice daily for 5 days) alone or 4 courses of conventional standard-dose multiagent chemotherapy (Multiagent CT) established in the previous JALSG AML97 study. Five-year disease-free survival (DFS) was 43% for HiDAC group and 39% for Multiagent CT group (P = 0.724), and 5-year overall survival (OS) was 58% and 56%, respectively (P = 0.954). Among the favorable cytogenetic risk group (n=218), 5-year DFS was 57% for HiDAC and 39% for Multiagent CT (P = 0.050), and 5-year OS was 75% and 66%, respectively (P = 0.174). In HiDAC group, the nadir of leukocyte counts was lower, and the duration of leukocyte < 1.0 x 10^9/L longer, and the frequency of documented infections higher. The present study demonstrated that Multiagent CT regimen is as effective as our HiDAC regimen for consolidation.

Our HiDAC regimen resulted in a beneficial effect on DFS only in the favorable cytogenetic leukemia group. The study was registered at http://www.umin.ac.jp/ctr/ as C000000157.

Key words; AML, post remission therapy, high-dose Ara-C

Introduction

Approximately 70 to 80% of the newly diagnosed younger adult patients with acute myeloid leukemia (AML) achieve complete remission (CR) when treated with an anthracycline, usually daunorubicin (DNR) or idarubicin (IDR), and cytarabine (Ara-C), however, only about one third of these patients remain free of disease for more than 5 years.[1-5] If CR patients are left untreated, almost all of them will relapse and die.[6] Therefore, post-remission therapy is indispensable. Post-remission therapy is divided into consolidation and maintenance therapy. In the previous studies of Japan Adult Leukemia Study Group (JALSG) for adult AML (AML87, 89, 92 and 95),[1-3,5] we administered 3 courses of consolidation therapy and 6 courses of intensified maintenance therapy. In the AML97 study,[7] we conducted a randomized study to compare the conventional 3-course consolidation and 6-course maintenance therapies with 4 courses of intensive consolidation therapy without maintenance, and demonstrated no difference in overall survival (OS) and disease-free survival (DFS). Therefore, the 4 courses of conventional standard-dose multiagent

chemotherapy (Multiagent CT) became the standard regimen in Japan. On the other hand, multiple cycles of high-dose cytarabine (HiDAC) has been commonly utilized as consolidation therapy in U.S.A. and other countries. However, our national medical insurance system did not allow us to use HiDAC until 2001, and thus we could not employ HiDAC in the previous treatment regimens for leukemia. We therefore conducted this prospective, multicenter cooperative study to compare 4 courses of Multiagent CT with 3 courses of HiDAC therapy after its approval in April 2001.

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 of registered patients were reevaluated by the central

review committee. FAB-M3 was not registered. Eligibility criteria included adequate function of liver (serum bilirubin < 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 or prior chemotherapy for other disorders. Cytogenetic abnormalities were grouped by standard criteria and classified according to the Medical Research Council classification.[8] The study was approved by 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.

Induction therapy consisted of Ara-C 100 mg/m^2 for 7 days and either IDR (12 mg/m^2 for 3 days) or DNR (50 mg/m^2 for 5 days). If patients did not achieve remission after the first course, the same therapy was administered once more. The outcome of induction therapy was reported to the JALSG Statistical Center before the consolidation therapy started. All CR patients were stratified

according to induction regimen, number of courses of induction, age and karyotype, and randomized to receive either 4 courses of Multiagent CT or 3 courses of HiDAC therapy. The first course of Multiagent CT consisted of mitoxantrone (MIT; 7 mg/m^2 by 30-minute infusion for 3 days) and Ara-C (200mg/ m^2 by 24-hour continuous infusion for 5 days). The second consisted of DNR (50 mg/m^2 by 30-minute infusion for 3 days) and Ara-C (200 mg/m^2 by 24-hour continuous infusion for 5 days). The third consisted of aclarubicin (ACR; 20 mg/m^2 by 30-minute infusion for 5 days) and Ara-C (200 mg/m^2 by 24-hour continuous infusion for 5 days). The fourth consisted of Ara-C (200 mg/m^2 by 24-hour continuous infusion for 5 days), etoposide (ETP; 100 mg/m^2 by 1-hour infusion for 5 days), 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 started as soon as possible after neutrophils, white blood cells (WBC) and platelets recovered to over 1.5 x 10^9/L, 3.0 x 10^9/L and 100.0 x 10^9/L, respectively. In the HiDAC group, 3 courses of Ara-C 2.0 g/m^2 by 3-hour infusion every 12 hours for 5 days were given. Each course was started one

week after neutrophils, WBC and platelets recovered to the above counts.

Bone marrow examination was performed to confirm CR in both groups before each consolidation therapy and at the end of all consolidation therapy.

Best supportive care, including administration of antibiotics and platelet transfusions, was given if indicated. When patients had life-threatening documented infections during neutropenia, the use of granulocyte colony-stimulating factor (G-CSF) was permitted.

After the completion of consolidation therapy, patients received no further chemotherapy. Allogeneic stem cell transplantation (allo-SCT) was offered during the first CR to patients of age 50 years or less with a histocompatible donor in the intermediate or adverse cytogenetic risk groups. Stem cell source was related donor or unrelated donor. Cord blood was not used. Conditioning before transplantation and prophylaxis for graft-versus-host disease were performed according to each institutional standard.

Responses were evaluated by the recommendations of the International Working Group.[9] CR was defined as the presence of all of the following: less

than 5% of 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 100.0 x 10^9/L, and no evidence of extramedullary leukemia. Relapse was defined as the presence of at least one of the following: reappearance of leukemic blasts in peripheral blood, recurrence of more than 5% blasts in bone marrow, and appearance of extramedullary leukemia.

Statistical Analysis

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, and a sample size of 420 patients per group was estimated to have a power of 90% at a 1% level of significance to demonstrate non-inferiority (assuming 80% CR rate for both groups). For the second randomization, i.e. this study, the primary end point was DFS, and the secondary endpoints were OS and adverse events of Grade 3 or more by NCI Common Toxicity Criteria. A sample size of 280 patients per group was estimated to have a power of 80% at a 5% level of significance to

demonstrate 10% superiority in 5-year DFS for the HiDAC arm (40% vs 30%). OS was defined as the time interval from the date of diagnosis to the date of death. DFS for patients who had achieved CR was defined as the time interval from the date of CR to the date of the first event (either relapse or death). Patients who underwent allo-SCT were not censored. The Kaplan-Meier method was used to estimate probabilities of DFS and OS. For comparison of DFS and OS, the log-rank test was used for univariate analysis and the proportional hazard model of Cox for multivariate analysis. Cumulative incidence of relapse and treatment related mortality were estimated according to the competing risk method and were evaluated with Gray's test. The Wilcoxon rank-sum test was used for continuous data such as age and WBC count, while the chi-square test was used for ordinal data such as risk group and frequency of allo-SCT. Statistical analyses were conducted using the JMP program (SAS Institute Inc., Cary, NC) and R software (www.r-project.org).

Results

Response to Induction Therapy

Of 1,064 patients registered, 1,057 patients were evaluable. Seven patients (misdiagnosis: one, infectious complication: one, without therapy: one, and withdrawal of consent: 4) were excluded. Median age was 47 years (range, 15 to 64). Cytogenetic studies were performed in 99.2% of registered patients and the results were available in 97%. Of 1,057 evaluable patients, 823 (78%) achieved CR (662 of them after the first induction course). CR rate in the IDR and DNR arms was similar (78.2% versus 77.5%). Percentage of patients who reached CR after the first induction course was also similar (64.1% versus 61.1%, $P = 0.321$). Day to achieve CR was longer in the IDR arm than the DNR arm (33.8 versus 32.4 days, $P = 0.038$). The detailed result of induction phase of this study is reported in a separate paper.[10]

Post-remission Randomization

Of 823 patients who achieved CR, 42 did not undergo the second

randomization for a variety of reasons, which included residual toxicity from induction therapy (12), allo-SCT (8), death (1), refusal (1) and unknown (20). Remaining 781 patients were randomly assigned to receive either the HiDAC regimen (389) or the Multiagent CT regimen (392) (Fig. 1). Clinical characteristics of two treatment groups were well balanced in age, initial WBC count, cytogenetic risk, induction arm, and induction cycle (Table 1).

Disease-free Survival and Overall Survival

The median follow-up period of living patients was 48 months (range, 5-78 months). Five-year DFS was 43% for the HiDAC group and 39% for the Multiagent CT group (P = 0.724) (Fig. 2-a). Five-year OS was 58% for the HiDAC group and 56% for the Multiagent CT group (P = 0.954) (Fig. 2-b). After censoring the observation on the date of SCT in transplanted patients, 5-year DFS was 41% for the HiDAC group and 36% for the Multiagent CT group (P = 0.608) (Fig. 3).

The cumulative incidence of relapse and treatment-related mortality during CR

were 49% and 8% for the HiDAC group and 56% and 5% for the Multiagent CT group (P = 0.294, P = 0.172), respectively (Fig. 4-a). After censoring the observation in transplanted patients, those were 55% and 4% for the HiDAC group and 61% and 3% for the Multiagent CT group (P = 0.402, P = 0.409), respectively (Fig. 4-b).

In patients with the favorable cytogenetics, i.e. core-binding factor (CBF) leukemia with t(8;21) or inv(16), 5-year DFS was 57% in the HiDAC group and 39% in the Multiagent CT group (P = 0.050) (Fig. 5-a), and 5-year OS was 75% and 66%, respectively (P = 0.174) (Fig. 5-b).

In patients with the intermediate cytogenetics, 5-year DFS was 38% in the HiDAC group and 39% in the Multiagent CT group (P = 0.403) (Fig. 6-a), and 5-year OS was 53% and 54%, respectively (P = 0.482) (Fig. 6-b). In patients with the adverse cytogenetics, 5-year DFS was 33% in the HiDAC group and 14% in the Multiagent CT group (P = 0.364) (Fig. 7-a), and 5-year OS was 39% and 21%, respectively (P = 0.379) (Fig. 7-b). Among younger patients of age 50 years or less, 5-year DFS was 45% in the HiDAC group and 46% in the

Multiagent CT group ($P = 0.590$), and 5-year OS was 62% and 66%, respectively ($P = 0.228$). Among the older patients (> 50 years), 5-year DFS was 40% in the HiDAC group and 28% in the Multiagent CT group ($P = 0.230$), and 5-year OS was 51% and 40%, respectively ($P = 0.159$). In patients treated with the IDR regimen at induction, 5-year DFS was 42% in the HiDAC group and 41% in the Multiagent CT group ($P = 0.641$), and 5-year OS was 58% and 57%, respectively ($P = 0.790$). In patients treated with the DNR regimen at induction, 5-year DFS was 44% in the HiDAC group and 37% in the Multiagent CT group ($P = 0.339$), and 5-year OS was 58% and 56%, respectively ($P = 0.713$). There was no relationship between the duration of myelosuppression and DFS or OS.

Significant unfavorable prognostic features for DFS by the Cox proportional hazard model were WBC more than 20 x 10^9/L, the number of induction therapies and age of more than 50 years, and for OS, age of more than 50 years, the number of induction therapies, WBC more than 20 x 10^9/L and MPO-positive blast less than 50%. Induction therapy, consolidation therapy and cytogenetic risk group, were not an independent prognostic factor for DFS or

OS by this multivariate analysis (Table 2).

Tolerance and Toxicity of Post-remission therapy

All courses of consolidation were administered to 72.5% of patients in the HiDAC group and 70.2 % in the Multiagent CT group (Table 3). In the HiDAC group, 110 patients (28%) did not receive all 3 courses. The reasons included relapse (18), death in CR (10), allo-SCT (34), adverse events (27), patient's refusal (11) and unknown (10). In the Multiagent CT group, 118 patients (30%) did not receive all 4 courses. The reasons included relapse (31), death in CR (8), allo-SCT (42), adverse events (13), patient's refusal (5) and unknown (19). The most common reason was allo-SCT in both groups. Of 125 patients received SCT in 1^{st} CR, 49 (25 in HiDAC and 24 in Multiagent CT) received SCT after completion of full courses of consolidation therapy. The second common reason was adverse events in the HiDAC group, and relapse in the Multiagent CT group. The patients older than 50 years could tolerate both regimens. Table 4 shows a comparison of both groups regarding the nadir of WBC count, and the number of days of WBC $< 1.0 \times 10^9$/L. After each course of

consolidation, the nadir of WBC count was significantly lower ($P < 0.0001$) and the day of WBC < 1.0 x 10^9/L was significantly longer in the HiDAC group ($P < 0.001$). During each course of consolidation, the frequency and the number of days of G-CSF administration were significantly higher in the HiDAC group. Table 5 shows toxic adverse events excluding hematological side effects. The frequency of documented infections was significantly higher in the HiDAC group ($P < 0.001$). The subset analysis showed the high incidence of documented infection in HiDAC regimen only in intermediate cytogenetic risk group ($P < 0.001$).

Discussion

To determine the best post remission therapy, there have been several prospective randomized studies comparing chemotherapy with SCT. Although there is some limitation in SCT such as patient's age and availability of HLA-identical donors, most randomized studies demonstrate that SCT, the most intensive post-remission modality, provides superior or at least

non-inferior prognosis in high or intermediate risk adult AML. [11-13]

As for post-remission chemotherapy, HiDAC therapy is generally used in U.S.A and other countries after the landmark CALGB-8525 study. [14] In Japan, however, since HiDAC therapy was not approved by our national medical insurance system until 2001, combination chemotherapy using non-cross resistant agents was commonly used in previous studies for adult AML. Therefore, in the current study, we compared conventional Multiagent CT with HiDAC therapy.

Our study demonstrated that there is no difference in DFS and OS between the Multiagent CT regimen and the HiDAC regimen. The HiDAC regimen, however, was accompanied with more frequent infectious events due to severer and longer-lasting neutropenia. In the CALGB-8525 study,[14] patients randomized to 4 cycle of HiDAC regimen were administered 3 g/m^2 of Ara-C by 3-hour infusion, twice daily on days 1, 3 and 5, and our patients randomized to 3 cycle of HiDAC regimen were given 2 g/m^2 of Ara-C by 3-hour infusion, twice daily for 5 days. Although there were some differences in schedule and dose