We evaluated the efficacy of daunorubicin (40 mg/m²/day for 5 days, 200 mg/m²/cycle) combined with standard dose of cytarabine (100 mg/m²/day for 7 days) for acute myelogenous leukemia patients aged 65–74 years as induction therapy. Complete remission (81.3%) was achieved in 13 of 16 patients following the therapeutic program. The median duration of recovering absolute neutrophilic counts over 1000/µl and platelet counts over 100 000/µl were 33 days and 27 days, respectively. None of the patients had any adverse cardiac complications or died during administration of the induction therapy. Patients achieving complete remission received post-remission therapy consisting of two regimens other than induction therapy. The 3-year disease-free and overall survival rates were 36.9 and 50.0%, respectively. Extending the total period of the daunorubicin therapy might be an alternative to increasing the daily dose of daunorubicin in the induction therapy for elderly patients who were candidates for receiving intensified chemotherapy.

Key words: elderly patients – AML – intensified DNR – induction therapy

REFERENCES

INTRODUCTION

Advances in the treatment for acute myelogenous leukemia (AML) have been obtained with intensified approaches and development of novel agents. In elderly AML patients who were judged by physicians to be fit for intensive chemotherapy, standard therapy such as ‘3 + 7’ [3 days of daunorubicin (DNR) and 7 days of cytarabine at conventional dose] or intensive investigational therapy are usually employed (1–3). However, the most appropriate chemotherapy for elderly AML patients is still controversial due to both biological disease-related and patient-specific factors (4–6). There is an urgent need to find innovative treatments for elderly AML patients. We previously reported two studies on intensified DNR in induction therapy for adult AML patients younger than 65 years (7,8). To increase the intensity of induction therapy, we administrated DNR (40 mg/m²/day) by expanding the total period of infusion more than 3 days instead of increasing daily dose of DNR in these two studies. On the basis of our institution’s experience, we administrated DNR (40 mg/m²/day for 5 days, 200 mg/m²/cycle) combined with cytarabine (100 mg/m²/day for 7 days) to previously untreated AML patients aged 65–74 years as induction therapy. Here, we conducted retrospective analysis of the clinical outcome of elderly AML patients treated by extending the total period of DNR combined with cytarabine in induction therapy.

PATIENTS AND METHODS

Patients

Between January 2003 and March 2008, 21 untreated AML patients aged 65–74 years, except previously diagnosed myelodysplastic syndrome were admitted to our institution. Of the 21 patients, 4 patients did not undergo the therapeutic program because of their comorbid conditions (cerebral hemorrhage, senile dementia, uncontrolled diabetes mellitus and active double cancer). One patient refused receiving...
intensive chemotherapy. Thus, 16 patients (76.2%) were enrolled in the therapeutic program.

**TREATMENT PROTOCOL**

The dose and schedule of induction therapy were as follows: DNR was administered intravenously (IV) at a dose of 40 mg/m²/day for 5 days, and cytarabine was administered continuous intravenously (CIV) at a dose of 100 mg/m²/day for 7 days. When bone marrow (BM) examination revealed sufficient hypoplastic marrow (cellularity < 10 000 cells/µl) and M1 marrow (<5% blasts) at 4 days after initiating therapy, the administration of DNR was discontinued. If complete remission (CR) was not attained by the first cycle of treatment, 40 mg/m²/day of DNR for 3 days and 100 mg/m²/day of cytarabine for 7 days were administrated as the second cycle. The post-remission therapy was administered as follows: one cycle of DNR (40 mg/m²/day IV for 3 days) combined with cytarabine (100 mg/m²/day CIV for 7 days), two cycles of behenoyl cytarabine (170 mg/m²/day IV for 7 days) combined with aclarubicin (17 mg/m²/day IV for 7 days) and two cycles of mitoxantrone (10 mg/m²/day IV for 1 day) combined with etoposide (200 mg/body/day orally for 5 days) and cytarabine (80 mg/m²/day subcutaneous injected for 5 days).

**RESPONSE CRITERIA AND STATISTICAL ANALYSIS**

CR was defined as the normalization of peripheral blood count and <5% blasts in the BM with normal cellularity. Relapse was defined as the reappearance of leukemic cells in the BM (>5% blasts) and/or reappearance of clinical evidence of the disease. Non-hematologic toxicity was graded according to the National Cancer Institute’s Common Toxicity Criteria (version 3.0). The duration of disease-free survival (DFS) of a patient was measured from the first documentation of achievement of CR to the date of either the first incidence of relapse or death, and overall survival (OS) of a patient was measured from the time of initiation of the induction therapy to the death of the patient from any cause. DFS and OS distributions were computed with the Kaplan–Meier product limit estimator. The difference in DFS and OS between subgroups was evaluated by means of the log-rank test.

**RESULTS**

**PATIENT CHARACTERISTICS**

The characteristics of the patients and their response to induction therapy are outlined in Table 1. All patients provided their written informed consent. Their median age was 70 years. Of the 10 patients with a normal karyotype, 7 patients were tested for FMS-like tyrosine kinase 3 (FLT3)-internal tandem duplication (ITD) by a semiquantitative polymerase chain reaction assay; the FLT3-ITD mutation was detected in only one patient. Nucleophosmin (NPM1) gene status was not tested in those patients. The median follow-up period for seven patients who were still alive at the date of last contact was 54.9 months.

**RESPONSE TO INDUCTION THERAPY AND SURVIVAL**

CR (81.3%; 95% confidence interval: 54.4–96.0%) was achieved in 13 patients; 4 of the 13 patients received a second cycle of the induction therapy. One patient, who did not achieve CR after the first cycle of the induction therapy, refused further treatment. The median percentage of BM blasts at day 4 of the therapy was 30.4% (range: 2–84.2). Only two patients were administered DNR for 3 days because their BM examination showed sufficient degree of hypoplasia at day 4 of the treatment. With regard to the hematologic changes resulting from the induction therapy, the median durations for recovery of the absolute neutrophil count to over 1000/µl and the platelet count to over 100 000/µl were 33 days (range: 19–37+) and 27 days (range: 21–39+), respectively. The major non-hematologic toxicities (grade: >2) were infection (92%), diarrhea (25%), mucositis (19%) and hepatotoxicity (13%). Granulocyte colony-stimulating factor was administered to four patients, because of complication of the documented infection. None of the patients had any adverse cardiac complications (grade: >2), and the median percentages of the left ventricular ejection fraction, measured by echocardiography, were 68% (range: 61–79) after receiving the induction therapy and 67% (range: 59–80) before initiatation of the treatment.

The 13 patients who had achieved CR underwent the post-remission therapy. During this post-remission therapy, three patients relapsed and one patient died of pneumonia. After the post-remission therapy, four patients relapsed. Five patients maintained first CR at the date of this analysis. The 3-year DFS and OS rates were 36.9% (95% CI: 12.5–62.0%) and 50.0% (95% CI, 24.5–71.1%), respectively (Fig. 1A and B). Comparison of the outcomes between the favorable/normal karyotype group and the unfavorable karyotype group was made with regard to DFS and OS rates. There was no significant difference in those groups ($P = 0.749$ in DFS rate, $P = 0.331$ in OS rate) (Fig. 1C and D).

On the other hand, the clinical outcome of five patients who did not undergo the therapeutic program was as follows: three patients were treated with less intensive chemotherapy (DNR, 40 mg/m²/day IV for 1 day, combined with cytarabine); however, they died of leukemia at 2, 6, 24 months after initiating the treatments, respectively. Two patients moved to other hospitals, and we lost their follow-up data.

**DISCUSSION**

The current report describes the response of 16 elderly patients to the induction therapy with a combination of DNR (administered for 5 days) and standard dose of cytarabine.
The dose of DNR per day (40 mg/m²) was relatively low; however, the total DNR dose per cycle (200 mg/m²) was higher than the conventional dose per cycle, which is 135 mg/m² (45 mg/m²/day for 3 days). Even though we administered a relatively high dose of DNR in the induction therapy, the toxicity of this therapy was mostly manageable, with no increase in early mortality. Elderly AML patients have a poor prognosis, attributable to having poorer performance status, unfavorable AML karyotype, comorbid disease, antecedent hematologic disorder, and relatively poor tolerance of cytotoxic agents (9–11). Therefore, the ratio of patients diagnosed to patients included in a therapeutic program is insufficient compared with young adult patients (12). In our study, four patients (19%) did not undergo the therapeutic program due to their comorbid disease and poor PS. Genetic alterations also affect clinical outcome in elderly AML patients. The multidrug resistance gene (MDR1) is frequently expressed in leukemic blasts derived from elderly AML patients and associated with lower CR and DFS rates due to resistance to chemotherapeutic agents such as vinca alkaloids and anthracyclines (13). FLT3-ITD is frequently found in elderly AML patients. While FLT3-ITD and NPM1 gene status were associated with normal karyotype in younger AML patients, one study reported the clinical impact of the two genes in elderly AML patients regardless of normal karyotype (14). Further molecular investigation might relieve finding innovative treatments for elderly AML patients.

Intensified chemotherapeutic approach is expected of possibility benefits for patients who were candidates for receiving intensified chemotherapy. To improve prognosis of elderly AML patients, anthracyclines other than DNR in induction therapy and high-dose cytarabine in post-remission therapy have been examined. Unfortunately, anthracyclines (or anthraquinone) other than DNR have not demonstrated an improvement in OS rates and high-dose cytarabine has been too toxic for those patients (15–17). Recently, the benefits of intensified DNR (90 mg/m²/day for 3 days, 270 mg/m²/cycle) as induction therapy compared with conventional dose DNR (45 mg/m²/day for 3 days) have been assessed in

<table>
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<th>Karyotype</th>
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PS, performance status; FAB, French-American-British classification; WBC, white blood cell counts; BM, bone marrow; ND, not determined; FLT3/ITD, FMS-like tyrosine kinase 3-internal tandem duplication; DNR, daunorubicin; G-CSF, granulocyte colony-stimulating factor; FN, febrile neutropenia; CR, complete remission; NR, no response.
²This patient discontinued therapeutic program after receiving the first cycle of the induction therapy.
²In these patients, DNR was administrated for 3 days.
²These patients were diagnosed with therapy-related AML.
²Chromosomal aberration was retained after hematologic CR.
young adult and elderly patients with AML. High-dose DNR resulted in a higher CR rate and improved OS in AML patients younger than 65 years; however, the benefits of such an intensified chemotherapeutic approach were reduced in patients older than 65 years (18,19). The Japan Adult Leukemia Study Group (JALSG) conducted a randomized phase 3 study of AML patients younger than 65 years, which compared intensified DNR with conventional dose idarubicin (IDR) (12 mg/m²/day for 3 days). DNR was administered at a dose of 50 mg/m²/day for 5 days (250 mg/m²/cycle) in the study by JALSG, and intensified DNR proved to be equivalent efficacy without much more adverse events compared with conventional dose IDR (20). Further prospective studies might be needed to establish the optimal dose and schedule of DNR in induction therapy for elderly AML patients who are candidates for receiving intensified chemotherapy.

The number of patients was small, more than half of patients were normal karyotype and MDR1 gene status was not tested; therefore, the results of our study should be interpreted with caution in comparison with other studies. Nevertheless, the CR rate of 81.3% and the 3-year OS rate of 50.0% with this therapeutic program appear high for a group of elderly patients who were candidates for receiving intensified chemotherapy. Main cellular target of DNR is recognized to be DNA topoisomerase II significantly expressed only in dividing cells during selected mitotic phase of cell cycle (21). Expanding the total period of DNR infusion may have an advantage of gain in exposure times for sensitive phase of cell cycle and lead to more anti-tumor activity compared with increasing daily dose of DNR. In addition, extending the total period of the DNR therapy might be an alternative to increasing the daily dose of DNR in induction therapy for selective elderly AML patients.

Conflict of interest statement
None declared.

References


