Table 1. Characteristics of patients and response to induction therapy

No.	Age	Sex	PS	FAB	WBC (μl^{-1})	BM blasts (%)	Karyotype	FLT3/ ITD	Induction therapy	Total DNR dose in induction therapy (m^{-2})	During induction therapy		Response
											G-CSF rescue	Infection (>grade 2)	
1	70	M	0	M5	39 000	40.0	46XY	Positive	One cycle	200		FN	CR
2	71	M	0	M2	24 600	94.6	46XY	Negative	Two cycles	320	yes	Sepsis	CR
3	65	F	1	M1	29 400	82.8	Complex, +21, −20		One cycle	200		FN	CR
4	73	M	1	M2	42 800	30.0	46XY	Negative	One cycle	200		FN	CR
5	70	M	1	M4	30 300	30.2	Complex, del(5)		One cycle	200			NR[a]
6	72	M	3	M1	1000	30.4	46XY	Negative	One cycle	200		FN	CR
7	69	M	3	M2	31 000	54.4	46XY	Negative	Two cycles[b]	240	yes	Pneumonia	CR
8	69	M	1	M4	89 700	64.6	46XY	Negative	One cycle	200	yes	Sepsis	CR
9	66	M[c]	1	M1	1900	24.5	Complex, −5, +8		Two cycles[b]	240		FN	CR
10	73	F	1	M2	1200	37.5	46XX	ND	Two cycles	320	yes	Sepsis	CR
11	72	M	0	M2	4000	28.2	t(8;21), −Y		One cycle	200		FN	CR
12	71	M	1	M4	6500	26.2	46XY	ND	Two cycles	320		FN	NR
13	69	F	2	M4	31 400	78.2	46XX	Negative	Two cycles	320		FN	NR
14	69	F[c]	1	M0	600	66.6	49XX, +8 × 3		One cycle	200		Sepsis	CR
15	70	M	0	M5	14 600	63.4	46XY	ND	One cycle	200		FN	CR
16	65	F[c]	1	M1	5700	77.2	Complex, −5		One cycle	200		FN	CR[d]

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.
[a]This patient discontinued therapeutic program after receiving the first cycle of the induction therapy.
[b]In these patients, DNR was administrated for 3 days.
[c]These patients were diagnosed with therapy-related AML.
[d]Chromosomal aberration was retained after hematologic CR.

The dose of DNR per day (40 mg/m^2) was relatively low; however, the total DNR dose per cycle (200 mg/m^2) was higher than the conventional dose per cycle, which is 135 mg/m^2 (45 mg/m^2/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 anthraqinone) 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/m^2/day for 3 days, 270 mg/m^2/cycle) as induction therapy compared with conventional dose DNR (45 mg/m^2/day for 3 days) have been assessed in

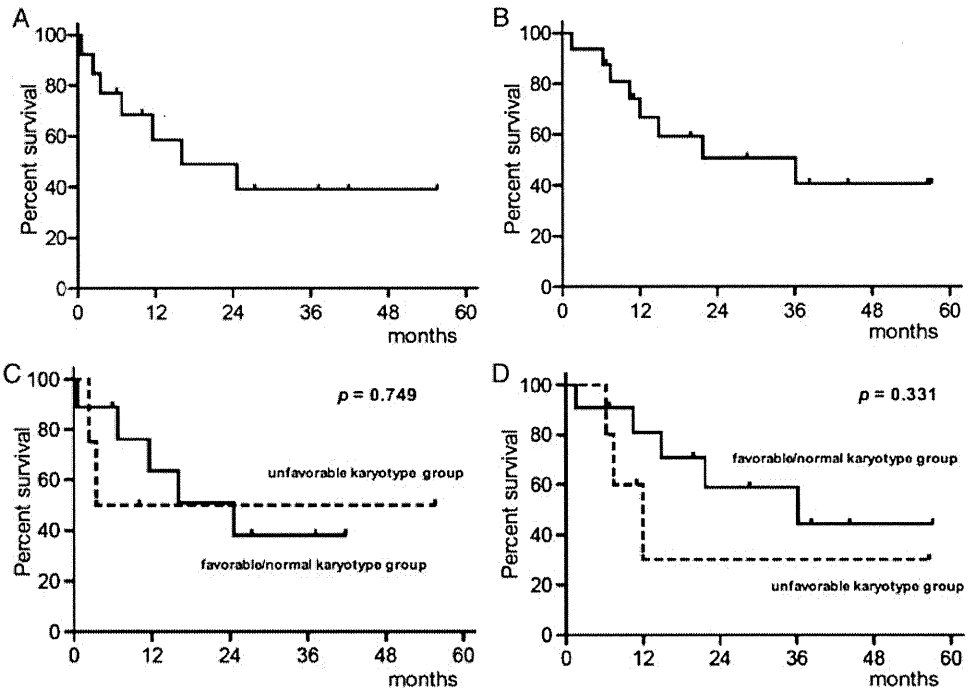

Figure 1. Disease-free survival (DFS) curve (A) and overall survival (OS) curve (B). DFS curves (C) and OS curves (D) according to the favorable/normal karyotype group and the unfavorable karyotype group. The median DFS and OS times were 17.2 and 19.9 months, respectively. There was no significant difference in DFS and OS by comparison between the favorable/normal karyotype group and the unfavorable karyotype group.

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/m^2/day for 3 days). DNR was administrated at a dose of 50 mg/m^2/day for 5 days (250 mg/m^2/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.

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