Table 1 Patient characteristics

Males/females	6/14
Age, median (range)	75 (25–87)
IPSS	
Low	2
Intermediate-1	18
WHO classification (2008)	
RCUD (RA)	6
RARS	2
RCMD	11
RAEB-1	1
Transfusion dependency[a]	8
Severe anemia[b]	14
WPSS	
Very low	1
Low	9
Intermediate	6
High	4
Very high	0
IPSS-RA	
Very low	1
Low	7
Intermediate	10
High	2
Very high	0
Hemoglobin level median (range) (g/L)	78 (57–89)
WBC median (range) ($\times 10^9$/L)	2.35 (1.50–6.80)
Platelet count median (range) ($\times 10^9$/L)	109 (9–357)
Ferritin median (range) (mg/L)	367 (12–2647)
Time since diagnosis median (range) (months)	24 (1–276)

Hemoglobin level was less than 90 and 80 g/L for males and females, respectively

IPSS the international prognostic scoring system, *WPSS* the 2008 WHO classification prognostic scoring system, *IPSS-RA* age-adjusted calculation of revised IPSS, *WBC* white blood cells

[a] Transfusion dependency was defined as requirement of two units of red blood cells transfusions or more per month

[b] Severe anemia was based on the definition of WPSS

Results

Of the twenty cases (6 males and 14 females, median age of 75 years), eight were transfusion-dependent (defined as requirement of two units of red blood cells transfusions or more per month) (Table 1). Median level of hemoglobin was 78 g/L (range 57–89 g/L). EPO levels were measured by radioimmunoassay, and ranged between 26.4 and 11300 IU/L (median 645 IU/L), including 10 cases (50 %) with more than 500 IU/L. Serum creatinine levels exceeded 2.0 mg/dL in two cases with concomitant chronic renal failure and transfusion dependence. Both of them were not given ESAs.

The rate of the cases with EPO levels below 500 IU/L was significantly higher in the group without transfusion support than the others (75 versus 13 %, $p = 0.020$, Fisher's exact test). EPO levels were significantly higher in the transfusion-dependent group than the others ($p = 0.046$). Age, sex, WPSS and age-adjusted calculation of revised IPSS (IPSS-RA) had no significant impact on EPO levels [9, 10]. Logarithmic values of EPO levels were inversely correlated to hemoglobin levels by correlation analysis especially in patients with no support of red cells transfusions. Correlation coefficient was 0.65 in transfusion-dependent patients ($p = 0.086$), and 0.92 in non-transfusion-dependent patients ($p < 0.001$), respectively (Fig. 1a, b). In the latter group, 76 g/L of hemoglobin level corresponded to serum erythropoietin value of 500 IU/L according to the regression line. All the three cases with hemoglobin levels below 76 g/L revealed EPO levels over 500 IU/L, which was the upper limit of good application of ESAs to MDS-derived anemia according to the international guidelines [1–4]. The EPO values of the rest nine cases did not reach 500 IU/L. In the former group, almost all the cases in need of transfusion showed more than 500 IU/L of EPO levels excluding only one patient suffering from concomitant chronic renal failure (Fig. 1a).

Discussion

The previous studies demonstrated the effectiveness of ESAs including epoetin alfa/beta and darbepoetin alfa for MDS with anemia [11–19]. They also revealed that low serum EPO levels or transfusion independency predicted higher probability of response to ESAs [11–18]. The inclusion criteria regarding anemia in these studies were hemoglobin level between 90 and 100 g/L or dependence on transfusions [11–19]. On the other hand, indication of transfusion is around 70 g/L of hemoglobin concentration for chronic diseases in this study, which is much lower than the hemoglobin level of the criteria described above [20]. EPO values of all seven cases with hemoglobin levels below 70 g/L exceeded 500 IU/L in this study, and EPO levels were significantly higher in the transfusion-dependent cases than the others. These findings revealed that the two traits represent the same aspect of ESAs-effective patients. International guidelines proposed symptomatic anemia as one of the requirements of application of ESAs [1, 2, 4], however, EPO levels possibly surpass 500 IU/L before development of symptoms in the cases similar to those in this study.

Unfortunately, treatment by ESAs is yet to be approved for MDS with anemia by public health insurance in Japan. Moreover, this study is a single center study, so a multicenter study is required to survey serum EPO levels in

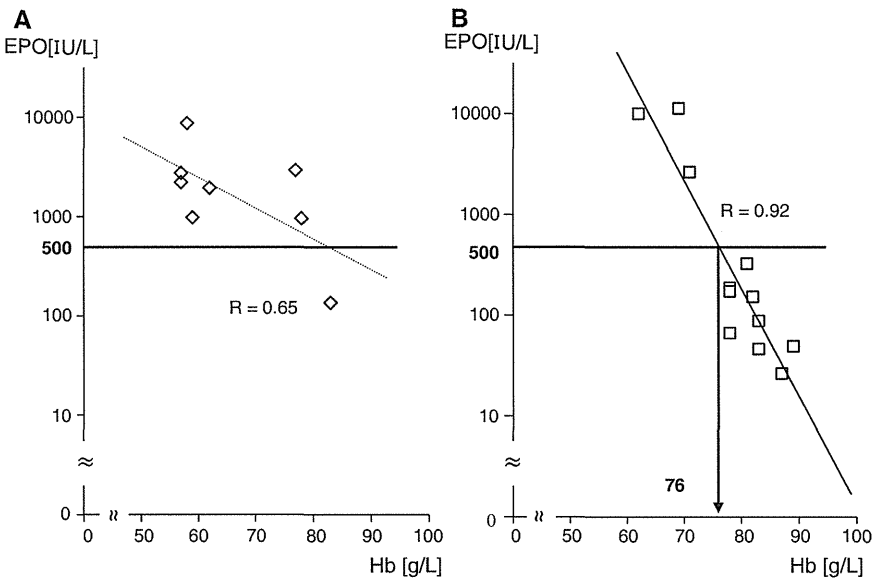

Fig. 1 Hemoglobin levels and serum erythropoietin levels in **a** eight cases with transfusion dependency and **b** twelve cases without transfusion dependency. Regression lines are shown. In panel (**b**), 76 g/L of hemoglobin level corresponds to serum erythropoietin value of 500 IU/L according to the regression line. *EPO* serum erythropoietin, *Hb* hemoglobin, *R* correlation coefficient

lower risk MDS in the Japanese population. Most of the patients have anemic symptoms before the hemoglobin levels decline to 70 g/L. In addition, early introduction of ESAs before 6 months from diagnosis was reported to be one of the predictive factors of better response in lower risk MDS group with low serum EPO levels [12]. So taking into account of the gap between the recommended hemoglobin values for application of ESAs by the international guidelines and for transfusions in this study [20], some of the MDS patients have a chance to avoid future transfusion if they undergo administration of ESAs before progression to symptomatic anemia. Moreover, ESAs would improve quality of lives for moderately anemic patients with hemoglobin levels around 70–80 g/L, which correspond to serum EPO value of 500 IU/L in non-transfusion-dependent cases. Of course, it should be examined in clinical trials whether early administration of EPO really diminishes total amount of transfusions.

In conclusion, we demonstrated distribution of serum EPO levels in lower risk MDS cases with anemia, increasing levels of EPO levels according to progression of anemia especially in the cases with no support of transfusions, and possibility of prevention of future transfusions by ESAs.

Conflict of interest Expenses for EPO evaluation were supported by Kyowa Hakko Kirin Co., Ltd. We have no other conflicts of interests regarding the content of the manuscript.

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Short Communication

The Effect of Decreased-dose Idarubicin for Elderly Patients with Acute Myeloid Leukemia

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We evaluated whether reduced-dose chemotherapy with 2 days of idarubicin (12 mg/m^2) and 5 days of cytarabine (100 mg/m^2) (2 + 5) is effective for patients aged 65–74 by retrospectively comparing the results with those aged 55–64 treated with 3 + 7. In 1999–2009, we treated 20 patients aged 65–74 with 2 + 5, and 23 patients aged 55–64 with 3 + 7. The complete remission rates by the first induction were 50.0 and 69.6% for older and younger groups ($P = 0.203$). Two-year overall survival rates were 55.9 and 32.3% for older and younger groups; 2-year rates of relapse-free survival for all these patients were 15.7 and 36.5%. The differences in overall and relapse-free survival were statistically insignificant ($P = 0.726$ and 0.413, respectively). The treatment results of 2 + 5 for the older group were not significantly worse compared with those of 3 + 7 for the younger. Therefore, elderly patients who do not tolerate 3 + 7 should still benefit from 2 + 5.

Key words: acute myeloid leukemia – elderly patients – chemotherapy – anthracycline

INTRODUCTION

Several studies report that the rates of complete remission (CR) for the elderly patients with acute myeloid leukemia (AML) are ~60%, but the remission periods are short with the median survival being 5–10 months, and the probability of remaining in remission for 3 years after diagnosis is <10% (1–3). Recent studies show that intensifying the anthracycline doses for the induction therapy for AML improves the rates of CR and overall survival (OS) (4,5). There exist conflicting reports, however, showing that intensifying the doses of chemotherapy may be too toxic to elderly patients, and therefore, reduced chemotherapy doses may be of benefit in these patients. It still remains to be proven whether the decreased dose of the induction therapy for elderly patients with AML is appropriate or not, in terms of overall and relapse-free survival (RFS).

Compared with daunorubicin (DNR), idarubicin (IDR) at the dose of '3 + 7' is as effective as increased DNR (6), and therefore, even if reduced doses of IDR are used in remission induction, the induction regimen may cause a comparably good response in induction chemotherapy without increasing the life-threatening side effects, including profound neutropenia. In this regard, we employed a reduced dose of IDR in the induction therapy for elderly patients with AML, who are aged ≥65. Here, we retrospectively evaluated the outcomes of the reduced-dose induction therapy for elderly patients with AML by comparing the overall and relapse-free rates of survivals with those of the slightly younger patients who were treated with the standard dose of induction therapy.

PATIENTS AND METHODS

Patients aged 55–74, who presented at the University of Tokyo Hospital and were newly diagnosed as AML from January 1999 to December 2009, were retrospectively analyzed. Patients diagnosed as acute promyelocytic leukemia (APL) were excluded. We stratified those patients into two groups: the younger group, aged 55–64 at diagnosis, who were treated with the standard induction therapy consisting of three daily doses of IDR (12 mg/m^2) and 7 days of continuous infusion of cytarabine (Ara-C, 100 mg/m^2) (3 + 7); and the older group, aged 65–74 at diagnosis, who were treated with

the reduced induction therapy consisting of two daily doses of IDR (12 mg/m^2) and 5 days of continuous injection of Ara-C (100 mg/m^2) (2 + 5), respectively. The age of the patient ($\geq$65 years old) was the only criterion for applying the reduced regimen.

A statistical comparison was performed using two-sided *t*-tests. The karyotypes of the chromosomes were categorized into three groups as defined by an MRC AML10 trial (7). The observation period for each patient is from the day on which the patient was diagnosed as AML. The patients who were transferred to other hospitals and were lost from follow-up were excluded at the time of transfer. We also reviewed the number of chemotherapies required to achieve hematologic CR for each patient.

Adverse events of the patients were evaluated according to the Common Terminology Criteria for Adverse Events version 4.0, in which the laboratory findings of disseminated intravascular coagulation (DIC) were evaluated according to the Japanese Ministry of Health, Labor and Welfare criteria (8).

We estimated the 2-year overall and RFS by the Kaplan–Meier method, using GNU R version 2.10.1. Furthermore, we searched the risk factors that may affect the overall and RFS by analyzing the patients' data with the univariate Cox proportional hazards model, using JMP®8.0.

Retrospective analyses of patients have been approved by the institutional ethics committee and have been performed in accordance with the institutional and national guidelines.

RESULTS

Of the patients aged 55–74, 43 non-treated patients were newly diagnosed with AML (non-APL) from January 1999 to December 2009, and received induction chemotherapy. Twenty of them were at age 65–74 (older group; median age 68) and 23 of them were at age 55–64 (younger group; median age 59), and underwent the decreased-dose therapy (IDR + Ara-C, 2 + 5) and the standard-dose therapy (IDR + Ara-C, 3 + 7), respectively.

Table 1 provides the demographic and clinical characteristics of the patients at their diagnoses. Among patients treated with IDR + Ara-C, younger patients exhibited poorer performance statuses, and older patients had more adverse karyotype risks.

The consolidation therapy for 13 patients (81.3%) in the younger group after achieving the first CR was high-dose Ara-C (2000 mg/m^2 × 2, Days 1–5 for age 55–59, and 1500 mg/m^2 × 2, Days 1–5 for age 60–64), and the consolidation therapy for 4 patients (40.0%) in the older group after achieving the first CR was IDR + Ara-C (2 + 5), the same as the induction therapy. The first consolidation therapy for the other patients varied, such as IDR + Ara-C (1 + 5) (two patients in the older group), intermediate dose Ara-C (1000 mg/m^2 × 2, Days 1, 3 and 5; two patients in the older group), and MA (MIT 7 mg/m^2, Days 1–3; Ara-C 200 mg/m^2, Days 1–5) (three in the younger group and one in the older group), due to the delayed recovery of the blood counts and severe non-hematologic toxicities. When CR was not achieved by the initial induction therapy, the same regimens were repeated for the reinduction therapy.

We evaluated both the chance of achieving CR in the first induction therapy and the chance of death without achieving CR using index variables (Table 1). Sixteen patients (69.6%) in the younger group achieved hematologic CR by the first induction therapy of IDR + Ara-C (3 + 7), and 10 patients (50.0%) in the older group achieved hematologic CR by the first induction therapy of IDR + Ara-C (2 + 5) ($P = 0.203$). Five patients (21.7%) of the younger group and three patients (15.0%) of the older group died without achieving CR ($P = 0.578$).

Only one patient in the older group died of treatment-related mortality after the initial induction therapy, to whom G-CSF was administered for severe neutropenia and sepsis but died of septic shock and multiple-organ failure. The most common adverse events (Grade 2 or more) observed in older and younger groups after the initial induction therapy were febrile neutropenia [100 and 95.7% ($P = 0.357$)], pneumonia [35.0% and 26.1% ($P = 0.537$)], and DIC [25.0% and 4.35% ($P = 0.053$)] (8).

Six patients in the older group and four patients in the younger group either underwent the second regimens or died without reaching the absolute neutrophil count (ANC) over 1000/μl. For other patients, the median durations for recovery of the ANC over 1000/μl were 33 days (range: 21–70) and 32 days (range: 23–46) for older and younger groups, respectively. Likewise, four in the older group and two in the younger group either underwent the second regimens or died without reaching the platelet count over 100 000/μl, and the median durations for recovery of the platelet count over 100 000/μl were 26.5 days (range: 20–51) and 27 days (range: 21–40) for older and younger groups, respectively.

We evaluated the OS and the RFS by the Kaplan–Meier method, and compared the results between these two groups (Fig. 1). The 2-year rates of OS were 32.3% for patients treated with 3 + 7 (younger group), and were 55.9% for patients treated with 2 + 5 (older group). The difference in rates of OS between these two groups was statistically insignificant ($P = 0.726$). The 2-year rates of RFS were 36.5% for patients treated with 3 + 7 (younger group), and were 15.7% for patients treated with 2 + 5 (older group). The difference in RFS between these two groups was also statistically insignificant ($P = 0.413$).

We used the univariate proportional hazards model to figure out which characteristics of the patients serve as the risk factors to affect the rates of survival (Table 2). For OS, none of these characteristics were statistically significant with the data for all, younger and older patients, although the karyotype risks for all patients tend to affect the OS ($P = 0.0949$). For RFS, the karyotype risks for all and younger patients were statistically different and, therefore, we may consider karyotype risks as the risk factors to affect the rates of RFS. The

Table 1. The characteristics of patients

	Younger group (age 55–64)	Older group (age 65–74)	*P* value
Sex			
Male	16 (69.6%)	13 (65.0%)	0.758
Female	7 (30.4%)	7 (35.0%)	
Performance status			
0	5 (21.7%)	11 (55.0%)	0.008[a]
1	14 (60.9%)	9 (45.0%)	
2	2 (8.7%)	0 (0%)	
3	1 (4.3%)	0 (0%)	
4	1 (4.3%)	0 (0%)	
Median	1	0	
Range	0–4	0–1	
Leukocyte			
$<10 \times 10^3/\mu l$	11 (47.8%)	13 (65.0%)	0.205
$\geq 10 \times 10^3/\mu l$	12 (52.2%)	7 (35.0%)	
Range (median) ($\times 10^3/\mu l$)	1.4–262.0 (11.8)	0.1–101.7 (7.3)	
Hemoglobin			
<10 g/dl	16 (69.6%)	17 (85.0%)	0.914
≥10 g/dl	7 (30.4%)	3 (15.0%)	
Platelet			
$<50 \times 10^3/\mu l$	16 (69.6%)	10 (50.0%)	0.813
$\geq 50 \times 10^3/\mu l$	7 (30.4%)	10 (50.0%)	
Range (median) ($\times 10^3/\mu l$)	1.1–22.0 (3.7)	0.9–15.7 (6.1)	
Blast in peripheral blood			
Range (median) (%)	0–97.0 (26.0)	0–87.0 (22.8)	0.166
Blast in bone marrow			
Range (median) (%)	10.9–96.0 (60.0)	20.0–98.0 (53.4)	0.481
Missing data (dry tap)	2	0	
Karyotype risks			
Favorable	8 (34.8%)	3 (15.0%)	0.011[a]
Intermediate	12 (52.2%)	10 (50.0%)	
Adverse	1 (4.3%)	7 (35.0%)	
Missing data (dry tap)	2 (8.7%)	0 (0%)	
Induction therapy			
CR in the first induction	16 (69.6%)	10 (50.0%)	0.203
CR in the second induction	2 (8.7%)	5 (25.0%)	
CR in the third induction or above	0 (0%)	2 (10.0%)	
Death without CR	5 (21.7%)	3 (15.0%)	
Observation period (days)	31–2758 (median: 464.5)	153–2555 (median: 304)	0.947

CR, complete remission.
The characteristics of patients. The karyotypes are categorized into favorable, intermediate and adverse groups according to Grimwade et al. (7). The *P* value for the induction therapy was evaluated for the percentage of CR in the first reduction.
[a]Statistically significant.

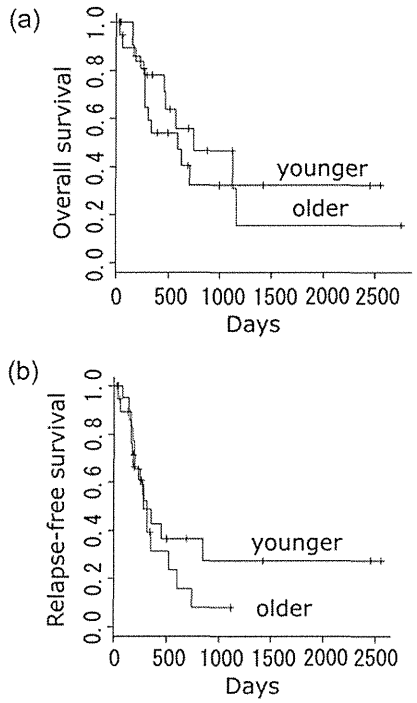

Figure 1. Overall survival (OS) (a) and relapse-free survival (RFS) (b) of the younger and the older groups. The 2-year rates of both OS and RFS were not statistically different between these two groups ($P = 0.726$ and 0.413, respectively).

RFS of older and younger patients did not differ across the post-remission therapies ($P = 0.590$ for the older group, between IDR + Ara-C (2 + 5) and other regimens; $P = 0.084$ for the younger group, between high-dose Ara-C and other regimens).

DISCUSSION

Although intensive anthracycline in elderly patients with AML causes improved survival, toxicity of the treatment is comparably high (4,5). The reported ~20% of treatment-related mortality (TRM), when increased doses of DNR are employed for the remission induction therapy, might be considered too high (5).

In contrast to the reports in favor of intensified chemotherapy for older patients with AML, Kantarjian et al. retrospectively analyzed the clinical courses of 446 older patients with AML, aged ≥70 years, and concluded that although intensified chemotherapy results in an improved CR rate, toxicities of the chemotherapy were excessively high, and the courses remain poor (9). The randomized study for elderly patients with AML by Pautas et al. showed that anthracycline dose intensification is of no clinically relevant benefit (10).

Although Dobashi et al. present favorable outcomes of administering DNR for elderly patients with AML by expanding the total period of infusion instead of increasing the daily dose of DNR (11), IDR gives higher rates of OS and RFS than DNR in most of other studies (12–15), while some other studies present statistically indifferent outcomes (16).

In our present study, the decreased dose of IDR + Ara-C (2 + 5) resulted in statistically insignificant difference in the rates of OS and RFS for patients at age ≥65 when compared with the standard 3 + 7 for patients slightly younger. Furthermore, both the rates of deaths without achieving CR and the chance of achieving CR in the first induction therapy were not statistically different between the two age groups. This observation is of interest, because age is a major risk factor for the AML treatment. This may be because older

Table 2. Univariate Cox proportional hazards model analysis of the risk factors that may affect the rates of survival

	Overall survival			Relapse-free survival	
	Coefficient	*P* value		Coefficient	*P* value
All patients			All patients		
PS	0.1776	0.4086	PS	0.0729	0.7335
Leukocyte	−0.001	0.7448	Leukocyte	−0.0005	0.8492
Hemoglobin	0.0444	0.6125	Hemoglobin	0.0627	0.4882
Platelet	0.0265	0.4017	Platelet	0.0021	0.9479
Blast (PB)	0.0087	0.1919	Blast (PB)	0.0121	0.058
Blast (BM)	0.0011	0.8672	Blast (BM)	0.0089	0.2229
Sex	−0.3025	0.4012	Sex	−0.3087	0.3942
Karyotype	0.4314	0.0949	Karyotype	0.6004	0.036[a]
Older			Older		
PS	0.0006	0.9991	PS	−0.1513	0.7725
Leukocyte	−0.0118	0.2001	Leukocyte	0.001	0.9218
Hemoglobin	−0.0714	0.5793	Hemoglobin	−0.0825	0.5767
Platelet	0.0277	0.5809	Platelet	−0.0125	0.8167
Blast (PB)	−0.0112	0.3864	Blast (PB)	0.0071	0.5118
Blast (BM)	−0.007	0.4653	Blast (BM)	0.0123	0.3013
Sex	0.2314	0.65	Sex	0.1708	0.7443
Karyotype	0.5193	0.1291	Karyotype	0.9863	0.0277[a]
Younger			Younger		
PS	0.2612	0.321	PS	0.2063	0.4275
Leukocyte	0.0003	0.9316	Leukocyte	−0.0003	0.9278
Hemoglobin	0.1467	0.2263	Hemoglobin	0.1135	0.3627
Platelet	0.0336	0.4085	Platelet	0.017	0.6801
Blast (PB)	0.0143	0.0817	Blast (PB)	0.0173	0.0426
Blast (BM)	0.0085	0.4219	Blast (BM)	0.0115	0.2845
Sex	−0.7557	0.1698	Sex	−0.6572	0.232
Karyotype	0.4644	0.3259	Karyotype	0.4822	0.2901

PS, performance status; PB, peripheral blood; BM, bone marrow; OS, overall survival; RFS, relapse-free survival.
[a]Statistically significant ($P < 0.05$).

patients with a poor general status were not given intensive induction therapy including 2 + 5, while slightly younger patients were given 3 + 7 in spite of the poorer condition. Supporting this, older patients who were treated with 2 + 5 showed a better performance status than the slightly younger patients, as shown in Table 1. Therefore, a further prospective study is required to determine whether reduced chemotherapy may benefit the younger patients and improve survival. Although intensified chemotherapy for elderly patients often results in too much toxicity, it remains unclear whether reduced chemotherapy for AML in turn benefits those patients. Our results here provide evidence for this issue, suggesting that reduced chemotherapy with IDR + Ara-C should be a reasonable option for the treatment of patients in this age group. The tendency that DIC is observed more frequently in the older group than in the younger group even with the reduced regimen, as well as the fact that the median durations for recovery of ANC and platelet count were almost identical between the two groups, may also support our proposition that the reduced regimen is suitable for older patients.

In the previously reported articles that emphasize the benefit of dose intensification of anthracycline for elderly patients, DNR is used (5). However, a recently reported meta-analysis revealed that IDR is superior to DNR in improving survival (17) and, furthermore, TRM is observed in ~20% of patients when treated with increased anthracycline (5). Therefore, the decreased dose of IDR may improve survival of the elderly patients without increasing their adverse events, and it is worth comparing the effect of the decreased dose of IDR with the increased/standard dose of DNR in the survival analysis.

Conflict of interest statement

None declared.

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Difference In Erythrocyte Alloantibodies After Blood Transfusion In Patients With Hematological and Non-Hematological Diseases

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Abstract

Introduction The incidence of irregular erythrocyte allo-antibodies (Abs) increases with the amount of previous erythrocyte transfusions. Blood transfusion has been one of the most important supportive cares in patients with hematological diseases. Therefore, patients with hematological diseases, such as leukemia and myelodysplastic syndrome, have often received considerable amounts of blood transfusion, and have a higher risk for alloimmunization against erythrocyte antigens. On the other hand, patients receiving chemotherapy and immunotherapy exhibit less antibody response than do patients with non-hematological diseases. Several authors reported that the frequency of irregular erythrocyte Abs was unexpectedly low in these patients (Schonewille et al., 2009). In this study, we retrospectively analyzed the *frequency and the contents of Abs after blood transfusion in patients with* hematological and non-hematological diseases.

Materials and Methods We selected patients with hematological or non-hematological diseases, who were transfused in our hospital from 2000 to 2011. We analyzed the patients' profiles including gender, age, the number of blood units previously transfused, and category of transfused products. We also studied the frequencies of irregular erythrocyte Abs. If the same patient was tested more than once, it was counted as one case. If more than two antibodies were detected in the same blood sample, they were tallied separately. If a patient had different antibodies at different times, all of them were summarized. We compared antibody frequencies between the patients with hematological or non-hematological diseases. Statistical analysis was performed by chi-square test and F-test followed by Student's t-test.

Results The numbers of patients with hematological or non-hematological diseases were 517 and 4,311 cases, respectively (Table 1). Gender was similar (male / female: 1.35 *vs.* 1.38, NS). Median age was 64 years (range: 15-93) *vs.* 75 years (2-82) ($p < 0.001$). The median amount of transfused erythrocytes was 18 units (2-358) and 8 units (1-182), respectively. Abs were detected in 24 (4.6%) and 129 cases (2.9%), respectively ($p < 0.05$). Frequently determined Abs were as follows: anti-E (63% *vs.* 34%), anti-Le^a (13% *vs.* 23%), anti-C (4% *vs.* 5%), anti-Di^a (4% *vs.* 5%), anti-Jk^a (4% *vs.* 6%), and anti-E+c Ab(4% *vs.* 8%, respectively) (Fig. 1). The amount of erythrocyte transfusions until determination of Abs was 19 units (10-100) and 14 units (2-84), respectively.

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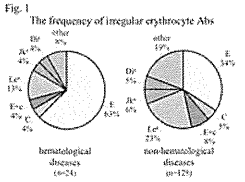

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Discussion The frequency of irregular erythrocyte Abs was significantly greater in patients with hematological diseases than in those with non-hematological diseases. The amount of erythrocyte transfusions was greater and age was

younger in those with hematological diseases. Anti-E Ab, whose frequency is reportedly less in Japanese, was more frequently detected in those with hematological diseases, while non-Rh Abs were more frequently detected in those with non-hematological diseases. Analyses after the exclusion of perioperative transfusion showed that the amount of erythrocyte transfusion until determination of Abs was greater in those with hematological diseases. These results showed that irregular Abs were more frequently detected in patients with hematological diseases, but the Abs are poorly productive in these patients after the same amount of transfusion. Further studies will solve the detailed mechanisms.

Disclosures: No relevant conflicts of interest to declare.

* Asterisk with author names denotes non-ASH members.

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Long-Term Outcome Of Acute Promyelocytic Leukemia (APL) With Lower Initial Leukocyte Counts By Using All-*Trans* Retinoic Acid (ATRA) Alone For Remission Induction Therapy: Japan Adult Leukemia Study Group (JALSG) APL97 Study

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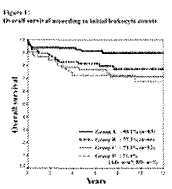
Abstract

Background ATRA and anthracycline-based chemotherapy is a standard remission induction therapy for APL, leading to complete remission (CR) rate of 90% or more. (Asou *et al*, 2007; Ades *et al*, 2010; Avvisati *et al*, 2011). As reported in many APL studies including the JALSG study, risk adopted strategy according to initial leukocyte counts has demonstrated successful results. However, the long-term outcome of the patients with initial leukocyte counts < 3,000/μl received ATRA alone in the induction therapy and followed by post remission chemotherapies, remains to be elucidated. Furthermore, it is controversial whether concomitant chemotherapy is needed for such a very low risk group. In the JALSG-APL97 study, patients with initial leukocyte counts < 3,000/μl received ATRA alone until remission (Group AA), except for patients with leukocytosis during the ATRA therapy who received additional chemotherapy (Group AD). Here, we reported the long-term outcome of this study based on risk adopted therapy, particularly, focusing on the outcome of the very low risk group.

Methods The treatment schedule of JALSG-APL97 study was initially reported by Asou *et al.* in 2007. In brief, patient groups were defined as: leukocytes < 3000/μl (Group A: ATRA alone), 3000/μl ≤ leukocytes < 10,000/μl (Group B: ATRA plus IDA/Ara-C: 2+5), and leukocytes ≥ 10,000/μl (Group C: ATRA plus IDA/Ara-C: 3+5). Patients who experienced leukocytosis received additional chemotherapy (Group D). After 3 courses of consolidation chemotherapy, patients achieved molecular CR were allocated to an intensive chemotherapy group or observation. The CR rate, overall survival (OS), event-free survival (EFS), and cumulative incidence of relapse (CIR) were analyzed for each group.

Results Two hundred and seventy-one newly diagnosed APL patients, ranging from 15 to 70 years of age, were evaluable. The number of patients in each group was 150 (A), 69 (B), 52 (C) and 70 (D), respectively. Of 150 patients in Group A, 83 achieved CR with ATRA alone (AA), and 67 were added chemotherapy due to leukocytosis during ATRA therapy (AD). In Group A, B, C and D, CR rates were 95.2%, 97.0%, 90.4% and 97.1%, respectively (P = 0.30); OS (Figure 1) 90.1%, 77.3%, 73.1% and 71.4%, respectively (P = 0.02); EFS (Figure 2) 71.1%, 63.6%, 55.7% and 64.3%, respectively (P = 0.26); CIR 23.5%, 27.6%, 34.5% and 20.4% (P = 0.51), respectively. Initial leukocyte counts in Group AA were significantly lower compared to those in Group AD (median leukocyte counts; 900/μl vs. 1,100/μl, P = 0.03). The median administration period of ATRA was similar between Group AA and AD (46 days vs. 43 days, P = 0.57). Differentiation syndrome was more frequent in Group AA (28.0% vs. 14.9%, P = 0.04). The CR rate and early death rate were not different between two groups (95.2% vs. 95.5%, P = 0.92 and 3.6% vs. 4.5%, P = 0.79, respectively). OS was significantly inferior (90.1% vs. 73.1%, P = 0.005) and non-relapse mortality after post-remission therapy was significantly higher in Group AD (5% vs. 16%, P = 0.04), compared to Group AA, while EFS was not different between two groups (71.1% vs. 65.7%, P = 0.33). The cumulative incidence of late relapse occurred more than 2 years after CR was significantly higher in Group AA compared to Group AD (17.5% vs. 3.9%, P = 0.04).



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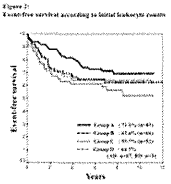

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Conclusions Risk adopted therapy according to initial leukocyte counts is totally useful in this study as well as previous reports including us. OS was favorable in APL patients with initial leukocyte counts < 3,000/μl, achieved CR by using ATRA alone for remission induction therapy, whereas EFS in this group was still unsatisfactory in the long-term follow up. It could be explained by the high frequency of late relapse. Ades *et al* reported better long-term outcomes in patients concomitantly treated with ATRA and chemotherapy rather than in those treated with ATRA followed by chemotherapy in their APL patients with initial leukocyte counts < 5000/μL. However, very low risk patients (Group AA) could be put into the separate category, and therapeutic approaches to reduce the late relapse in this group should be discussed. Additionally, the genetic profile studies will provide us informative data in relation to initial leukocyte counts and leukocytosis during ATRA therapy.

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↵* Asterisk with author names denotes non-ASH members.

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Efficacy and resistance of gemtuzumab ozogamicin for acute myeloid leukemia

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Abstract Seventy to 80 % of patients with acute myeloid leukemia (AML) achieve complete remission following intensive chemotherapy, but more than 50 % of patients in remission subsequently relapse, which is often associated with clinical drug resistance. Therapy based on monoclonal antibodies (mAbs) has been developed to increase the selectivity of cytotoxic agents by conjugating them with a mAb. Gemtuzumab ozogamicin (GO) is a conjugate of a cytotoxic agent, a calicheamicin derivative, linked to a recombinant humanized mAb directed against the CD33 antigen, which is expressed on leukemia cells from more than 90 % of patients with AML. This conjugated mAb was introduced following promising results from phase I and II studies. However, the initial phase III study did not confirm the efficacy of GO in combination with conventional chemotherapies. Several subsequent phase III studies have shown the efficacy of GO in favorable and intermediate risk AML. Several resistance mechanisms against GO have been reported. Multidrug resistant (MDR) P-glycoprotein (P-gp), a trans-membrane glycoprotein that pumps out many anti-leukemic agents from cells, also affects GO. For this reasons, GO has been used in combination with MDR modifiers, such as cyclosporine, and in cases without P-gp. Several investigators have reported successful results of the use of GO in acute promyelocytic leukemia (APL). GO has also been described as effective in cases relapsed after treatment with all-*trans* retinoic acid (ATRA), arsenic acid and conventional chemotherapeutic agents. The efficacy of GO will be studied mainly in a favorable risk of AML, such as core binding factor leukemia and APL. In addition, suitable combinations with other chemotherapies and administration schedules should be discussed.

Keywords Gemtuzumab ozogamicin (GO) · Acute myeloid leukemia (AML) · CD33 · Drug resistance · Acute promyelocytic leukemia (APL)

Introduction

Acute myeloid leukemia (AML) is one of the most prevalent hematological malignancies [1]. It is characterized by the proliferation of clonal hematopoietic precursor cells and impairment of normal hematopoiesis. Many agents have been introduced in the treatment of AML, and 60–80 % of AML cases achieve remission [2, 3]. However, a considerable number of patients relapse, and as a result, disease-free survival (DFS) remains at around 20 % [2]. Recent progress in the molecular analysis of AML has led to molecular-targeted therapies [4, 5]. Monoclonal antibody therapy against CD33 also emerged from advances in molecular biology.

Gemtuzumab ozogamicin (GO), development code CMA676, is a conjugate of a calicheamicin derivative and a recombinant humanized antibody (IgG_4) directed against the CD33 antigen [6]. Calicheamicin is a highly potent anti-tumor antibiotic [7–10], which binds to DNA, breaks double-stranded DNA, and induces cell death. Extensive basic and clinical results relating to this agent have been reported, and its characteristics and efficacy have been demonstrated over time.

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CD33

The CD33 antigen, a 67-kDa trans-membrane glycoprotein, belongs to the immunoglobulin gene superfamily of sialic acid-binding immunoglobulin (Ig)-like lectins (siglecs) [6, 11, 12]. It consists of two Ig-like extracellular domains and two cytoplasmic domains [13]. Although the precise function of CD33 has not been elucidated, it is thought to be related to cell adhesion and interaction. CD33 suppresses cell proliferation and function, and induces apoptosis in vitro [14], but it remains unclear whether CD33 also exerts these inhibitory functions in vivo.

In normal hematopoiesis, CD33 is expressed on myelocyte and myelomonocytic precursor cells, as well as mature myeloid lineage cells, macrophages, monocytes, and dendritic cells [15–17]. The amount of CD33 peaks in promyelocytes and myelocytes, and is downregulated with maturation of the myeloid lineage. CD33 is also expressed on erythroblasts, megakaryoblasts, and Kupffer cells [11, 12], but not on normal hematopoietic stem cells [18, 19]. Therefore, CD33 is considered to be a useful target for the development of therapeutic agents against AML.

Previous reports have suggested that 65–90 % of AML is CD33-positive. The variation may derive from methodological differences or definitions of what constitutes CD33-positive [17, 20–23]. The amount of CD33 on AML cells is estimated at 10,000–20,000 copies/cell [24]. CD33 is sometimes determined on acute lymphoblastic leukemia (ALL), but the amount is relatively small [25]. The molecular differences of CD33 between AML and ALL cells remain unclear [26].

Since CD33 is rapidly internalized after antibody binding, antibody-cytotoxic agent complexes can effectively be taken up by leukemia cells. Radio- and toxin-labeled anti-CD33 antibodies have been developed, including conjugates of radioisotopes, calicheamicin, gelonin, and ricin [27–30]. Of these, GO has shown the most encouraging results [31].

The effect of GO on leukemia cells in bone marrows is reportedly influenced by the amount of CD33 antigen in the peripheral blood [32]. GO may thus be lost to some extent in the circulation before it reaches the bone marrow. This suggests that GO might be made more effective by the reduction of CD33 in peripheral blood by chemotherapy [33].

CD34 is often co-expressed on CD33-positive AML cells [24]. In our study, GO was less effective on CD34-positive leukemia cells, even when they expressed a sufficient amount of CD33; this effect was independent of the amount of CD34 [34]. Sievers et al. [35] reported that expression of CD34 was associated with shorter survival after treatment with GO. It remains to be determined why GO is less effective on CD34-positive cells. One reason may be that CD34-positive cells express more P-glycoprotein (P-gp) than do CD34-negative cells.

Pharmacology

GO is a humanized IgG4 anti-CD33 monoclonal antibody (hP67.6) conjugated to NAc-gamma calicheamicin DMH, a hydrazide derivative of calicheamicin [36]. Approximately, half of antibodies are linked to calicheamicin, with an average load of several molecules of calicheamicin per antibody, while others are not. After GO binds to CD33 on the cells, CD33-antibody complexes are internalized and transferred into lysosomes [37]. The calicheamicin derivative is released via hydrolysis in the acid environment of the lysosome, and binds to the minor groove of DNA in a sequence-specific manner. This mechanism is central to the efficacy of GO. It explains that cells expressing higher levels of CD33 are more susceptible to GO [38]. However, several patients with CD33-negative leukemia have also responded to GO [39]. Several studies have sought to explain the efficacy of GO on CD33-negative leukemia. One proposed explanation is that GO is partially moved into cell by CD33-independent endocytosis [39]. In their study, anti-CD33 blocking antibodies prevented the death of CD33-positive cells at low concentrations of GO, but not at higher concentrations. Another possible explanation is that CD33-negative leukemia cells may have a subthreshold low amount of CD33, which reacts substantially with GO [33]. These ideas may also explain the mechanism of liver dysfunction, which has been observed in the GO treatment.

Calicheamicin

Calicheamicin, a hydrophobic enediyne antibiotic agent, was first isolated from the actinomycete *Micromonospora echinospora* ssp. *Calichensis* [7, 8]. It binds in a sequence-specific manner to the minor groove of DNA, and cleaves single and double-stranded DNAs by the removal of specific hydrogen atoms from the deoxyribose rings of DNAs [9]. DNA damage leads to apoptotic or non-apoptotic cell death due to mitochondrial damage [40–42]. We observed cell morphology after the incubation of GO by video-microscopy. Some cells exhibited apoptotic changes, while the remaining cells showed non-apoptotic features [43]. The cytotoxic mechanism of GO is the same as that of calicheamicin, except for the internalization via CD33. Cells incubated with calicheamicin undergo either temporary or permanent cell cycle arrest [43, 44]. In our study, transient G_2/M arrest was observed prior to the increase of the hypodiploid portion in cell lines incubated with GO.

Several molecular pathways, such as Chk1 and Chk2 phosphorylation and caspase 3, have been reported as playing roles in this process [45].

Drug resistance

Multidrug resistant (MDR) is a phenomenon in which malignant cells develop cross-resistance to a variety of unrelated cytotoxic drugs. P-gp, a key player in MDR, is a membrane glycoprotein that actively pumps cytotoxic agents out from cells, and decreases intracellular drug accumulation [46, 47]. Calicheamicin derivatives, which are detached from GO in lysosomes, are also effluxed (Fig. 1) [48, 49]. GO showed less effect on sublines that expressed P-gp in vitro, even when they expressed sufficient levels of CD33 [43]. This phenomenon was confirmed by the combined use of GO and MDR modifiers, such as PSC833 and MS209, in the resistant sublines [43, 50, 51]. Cells that were persistently exposed to low-dose GO acquired resistance to GO and expressed P-gp [52]. These in vitro results were confirmed in phase I studies of GO. Good responders were more frequently observed in leukemia cases characterized by low dye efflux in vitro [33, 35]. In GO, MDR modifiers theoretically work only on intracellularly incorporated calicheamicin in CD33-positive cells. Our in vitro study suggested that the combination use of GO and MDR modifiers may be an ideal therapeutic approach for P-gp-expressing leukemia cells, assuming that the hematologic and non-hematologic toxicities are not worsened. Interestingly, similar results were obtained in studies using inotuzumab ozogamicin, a calicheamicin-conjugated anti-CD22 antibody, for lymphoid malignancies [53, 54].

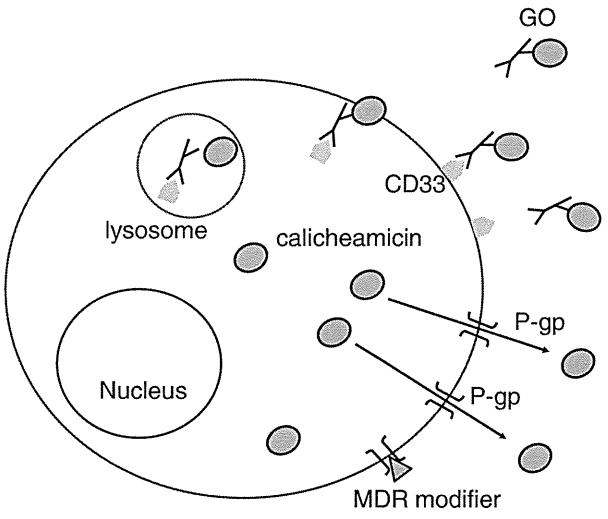

Fig. 1 GO, transported by internalization, is moved to lysosome, in which calicheamicin is detached. Intracellularly released calicheamicin is pumped out via P-gp in multidrug-resistant cells. MDR modifiers recover the effect of GO

Cyclosporin A (CyA), one of the well-known MDR modifiers, has in fact been administered as an adjunct to GO-containing chemotherapy in the treatment of AML [55–57]. CyA did not improve response rate or survival, although veno-occlusive disease (VOD) was observed in some patients [55]. The discrepancy between in vitro and in vivo effects may be explained by the possibility that CyA ablates the function of P-gp, which is widely distributed across critical organ systems, thus increasing adverse effects, and that the clinical outcome from the P-gp negative cases may thereby contribute to the non-significance of the results.

Several resistance mechanisms other than P-gp have also been suggested. Multidrug resistant-related protein 1 (MRP1), another transporter protein, is sometimes expressed in AML [58]. However, the clinical importance of MRP1 is relatively limited among the mechanisms of resistance to GO [59]. Other transporter proteins may have further limited effects.

The roles of bcl-2 and bcl-x, anti-apoptotic proteins, in the resistance to GO have been reported [60, 61]. The effect of GO was enhanced by bcl-2 antisense oligonucleotide, but reduced by overexpression of bcl-2 and bcl-x. Bax, Bak and stress-activated protein kinase may play a role in resistance to GO [62]. GO induced proapoptotic activation of Bak and Bax and stress-activated protein kinase in sensitive AML cells, but not in resistant ones. Peripheral benzodiazepine receptor ligand, PK11195, increased the sensitivity of AML cells to standard chemotherapeutics both by inhibiting P-gp and by promoting mitochondrial apoptosis. [61] It also increased sensitivity to GO in AML cells.

The activation of survival signaling pathways, such as PI3K/AKT, MEK/ERK and JAK/STAT, is reportedly associated with GO resistance in vitro in AML cells [63]. An AKT inhibitor, MK-2206, restored the resistance of GO and calicheamicin in resistant AML cells.

Delivery of GO to bone marrow may be important for enhancing the effect of GO [28, 38]. An excess of circulating CD33-positive cells decreased the effect of GO, and resulted in worse outcomes [27, 64]. However, high blast cell count is an adverse prognostic factor in leukemias treated with other anti-leukemic agents as well.

Several agents other than MDR modifiers reportedly increase the sensitivity of GO in vitro. G-CSF enhanced the effect of GO, and induced AML cells to enter G_2/M and hypodiploid phase [65]. Valproic acid, a histone deacetylase inhibitor, can also strengthen the effect of GO [66]. However, the synergistic effect of GO with these agents has not been well elucidated in clinical studies.

Other resistance mechanisms have been suggested by several groups, including the alternative GO pharmacokinetics, and the reduction of CD33 on leukemia cells [36, 39, 43, 44]. In fact, multiple mechanisms may be at work in the development of resistance to GO.

GO monotherapy

In a phase I study conducted in the US, 40 patients with relapsed or refractory (relapsed/refractory) AML were treated by GO (0.25–9 mg/m^2) [67]. Leukemia cells were eliminated from the blood and bone marrow of eight (20 %) of the 40 patients. Neutrophil counts recovered in five of these eight patients, but platelets recovered in only three. Patients who achieved complete remission (CR) without recovering platelet count more than 100 $\times$ 10^9/L were entered to the concept of CR with thrombocytopenia (CRp), which has been subsequently used in the evaluation of GO.

Phase II trials with GO were started at a dose of 9 mg/m^2 (2-week intervals for two doses) [35]. A total of 142 patients with AML in first relapse were enrolled in the study. Of these patients, 30 % achieved overall response (OR), including CR and CRp. The median relapse-free survival (RFS) was 5.3 months. Grade 3 or 4 bilirubinemia was observed in 23 %, and hepatic transaminitis in 17 %. Veno-occlusive disease (VOD) was observed in seven patients (3 %), and three of these were fatal. Five patients, who received hematopoietic stem cell transplantation (HSCT) before the treatment of GO, did not have evident VOD. However, three of 27 patients who received HSCT after the treatment of GO died of VOD.

Based on these results, the Food and Drug Administration of US approved GO for relapsed CD33-positive AML in patients 60 years of age or older [68].

Larson et al. [69] treated 101 elderly patients with relapsed AML. The OR rate was 28 %, including CR 13 % and CRp 15 %. The OS was 5.4 months. Grade 3 or 4 bilirubinemia and transaminitis were observed in 24 and 15 %, respectively. Most of the liver dysfunctions were reversible.

Results for 128 patients with relapsed AML treated GO were compared with those for 128 patients treated with the combination chemotherapy with high-dose cytarabine (HiDAC) [70]. The OR rates in GO and HiDAC therapy were 38 and 41 %, respectively. GO treatment had a higher response rate if the previous remission duration was 3–10.5 months, whereas HiDAC treatment had a higher response rate if the duration of the previous remission was >19 months.

Twenty-four cases with relapsed/refractory AML were treated with GO (9 mg/m^2 at 2-week intervals for two doses) [71]. The CR and the CRp rates were 13 and 8 %, respectively, and the median duration of second CR was 6 months. VOD was observed in one case.

Larson et al. [72] summarized three open-label, single-arm, phase II trials for AML in first recurrence. Patients received GO monotherapy (9 mg/m^2 two doses separated by 2 weeks). CR or CRp was achieved in 13 % of cases in each study. The OR rates were not different between younger (28 %) and elderly (24 %) patients. The median OS and the RFS were 4.9 and 5.2 months, respectively. The median OS was >18.3, 16.5, 12.2, and 11.2 months for patients who received allogeneic HSCT, autologous HSCT, additional chemotherapy, or no additional therapy, respectively. Eight patients (17 %) developed VOD after HSCT. Five (19 %) of the 27 patients who underwent HSCT prior to GO developed VOD after treatment.

Fifty-seven patients with AML in first relapse received GO monotherapy (3 mg/m^2 on days 1, 4, and 7) [73]. Fifteen patients (26 %) achieved CR and four (7 %) CRp. The median RFS was 11 months. Grade 3 or 4 liver toxicity and VOD were not observed.

The Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA)–the European Organization for Research on the Treatment of Cancer (EORTC) study assessed the efficacy of GO monotherapy (9 mg/m^2 on days 1 and 15) in 40 elderly patients with AML, who were not considered eligible for conventional chemotherapy due to advanced age or poor performance status [74]. The OR rate was 17 %, which was poorer in elderly patients. The median OS was 4.3 months, and the 1-year OS rates were 34 %. Grade 3 or 4 liver toxicity was observed in 10 %.

In Japan, 20 patients with relapsed/refractory AML received GO (9 mg/m^2 for two doses at 2-week intervals) [75]. CR and CRp were achieved in 5 (25 %) and 1 (5 %) patients, respectively. The median OS was 420 days. Grade 3 or 4 transaminitis was observed in 1 patient, but VOD was not.

The results from the study containing a relatively large number of patients are summarized in Table 1. These results encouraged the initiation of trials of combination chemotherapy including GO.

Post-marketing study of GO monotherapy

The efficacy of GO on relapsed/refractory AML, including acute promyelocytic leukemia (APL), in a post-marketing surveillance study of GO was reported in Japan (http://pfizerpro.jp/). A total of 760 patients with relapsed/refractory AML were enrolled, of which 503 were evaluable. In AML, CR and CRp were achieved in 10 and 8 %, respectively; while in APL 48 and 9 %, respectively (Table 5). In AML, the OS and the RFS at 2 years were 14

Table 1 GO monotherapy for relapsed/refractory AML

No. of cases	Median age	Stage of disease	CR (%)	CRp (%)	OS (months)	LFS (months)	VOD (%)	References
142	61 (22–84)	First relapse	16	13	5.9	6.8	1.4	Sievers et al. [67]
101	69 (60–87)	First relapse	13	15	5.4	14.5	5.0	Larson et al. [69]
24	63 (20–75)	Relapse/refractory	13	8	2	6	4.2	Piccaluga et al. [71]
40	76 (61–89)	Untreated	10	7	4.3	6.1	2.5	Amadori et al. [74]
277	61 (20–87)	First relapse	13	13	4.9	5.2	5.3	Larson et al. [72]
57	64 (22–80)	First relapse	26	7	8.4	11.0	0	Taksin et al. [73]
20	58 (28–68)	Relapse/refractory	25	5	14	47	0	Kobayashi et al. [75]

The results from the study containing a relatively large number of patients were summarized

and 20 %, respectively; while these were 63 and 71 %, respectively, in APL. Treatment-related adverse events of GO (grade 3 or 4) in AML patients were infusion reaction (22 %), infection (27 %), bleeding (9 %), lung damage (3 %) and reversible VOD (4 %) [76]. The incidence of VOD in patients administered GO after HSCT was 5.9 %, which showed no change compared to those without HSCT.

Combination chemotherapy with GO for relapsed or/and refractory AML

Based on the data of GO monotherapy for relapsed/refractory AML, many combination chemotherapies with GO have been conducted.

A pilot study of GO combined with topotecan and Ara-C (MTA) was assessed in patients with refractory AML [77]. MTA consisted of GO (9 mg/m^2 on day 1), AraC (1 g/m^2 on days 1–5) and topotecan (1.25 mg/m^2 on days 1–5). A group of 17 patients with relapsed/resistant AML or advanced MDS received 20 courses of MTA. CR was achieved in 12 %. The median OR was 8.2 weeks. Five patients (29 %) developed grade 3 or 4 hepatic transaminitis; one of them died due to VOD.

GO (6 mg/m^2 on days 1 and 15) was administered with idarubicin (IDA) (12 mg/m^2 on days 2–4) and Ara-C (1.5 g/m^2 on days 2–5) (MIA) [78]. Fourteen patients with relapsed/refractory AML were treated with MIA. CR and CRp were achieved in 21 % of each group. The median OS was 8 weeks, and the median failure-free survival of CR patients was 27 weeks. Grade 3 or 4 hepatic transaminitis was observed in 57 %, and VOD was in 14 %.

The MDAC regimen, consisted of GO (6 mg/m^2 on day 6), Ara-C (1 g/m^2 on days 1–5), liposome-encapsulated DNR (75 mg/m^2 on days 6–8) and CyA (on day 6) (MDAC), was conducted in 11 patients with relapsed/refractory AML [55]. CR and CRp were achieved in one case each, respectively. Grade 3 or 4 bilirubinemia was observed in 54 %, and transaminitis in 9 %.

The MFAC regimen, consisted of GO (4.5 mg/m^2 on day 1), CyA (6 mg/kg on day 1), fludarabine (15 mg/m^2 every 12 h on days 2–4) and Ara-C (0.5 g/m^2 every 12 h on days 2–4), was conducted in 32 patients with relapsed/refractory AML [56]. CR and CRp were achieved in 28 and 6 %, respectively. The median OS was 5.3 months, and the 1-year OS rate was 19 %. Grade 3 or 4 hyperbilirubinemia was observed in 44 %, transaminitis in 18 %, and VOD in 9 %.

Twenty-two patients in CR commenced IDA and AraC (IA) alternating with MFAC or vice versa for 9 months from the date of CR [57]. The failure-free and the 1-year OS rates were 32 and 55 %, respectively. Grade 3 or 4 toxicities were not different between the MFAC and IA regimen.

Nine elderly patients with AML (five untreated and four relapsed/refractory) were treated with GO (6 mg/m^2 on day 1, 4 mg/m^2 on day 8) in combination with AraC (100 mg/m^2 as continuous infusion on days 1–7) [79]. CR was achieved in five patients. The median CR duration was 10 months, and the median OS was 6 months. Grade 3 or 4 bleeding was observed in 44 %. VOD was not observed.

MIDAM regimen, consist of GO (9 mg/m^2 on day 1), AraC (1 g/m^2 every 12 h on days 1–5), mitoxantrone (MIT, 12 mg/m^2 on days 1–3), was conducted in 17 patients with refractory/relapsed AML [80]. CR and CRp were achieved in 70 and 6 %, respectively. The median OS and RFS were 11 months each. Probability of the 1-year OS and RFS was 48 and 36 %, respectively. VOD was observed in one patient (6 %).

The Cancer and Leukemia Group B (CALGB) treated patients with relapsed/refractory AML with HiDAC (3 g/m^2 for 5 days) associated with GO (9 mg/m^2) [81]. HiDAC plus GO 9 mg/m^2 on day 7 and 4.5 mg/m^2 on day 14 was not tolerated, but HiDAC followed by GO 9 mg/m^2 on day 7 was safe. CR was achieved in 32 %. The median OS was 8.9 months. Serious VOD was not observed. They concluded that the regimen merits further study for use both in remission induction and consolidation therapies.

Oblimersen, Bcl-2 antisense, has been shown to enhance the apoptotic activity of various antileukemic agents. Oblimersen (7 mg/kg, days 1–7 and 15–21) was administered with GO (9 mg/m^2 on days 4 and 18) in 48 elderly patients with relapsed AML [60]. Twelve patients (25 %) achieved OR. The median OS for all patients enrolled was 2.3 months. Grade 3 and grade 4 toxicities were sepsis (12 %) urinary tract infection (8 %), pneumonia (6 %) and respiratory events (31 %).

In these studies, GO was used in the dosage from 4.5 to 9 mg/m^2 with other chemotherapeutic agents. (Table 2) Although the outcomes of these studies were not sufficient to demonstrate efficacy overall, usefulness was expected in de novo AML.

Phase II trials of combination chemotherapy with GO for de novo AML and MDS

Based on the results from relapsed/refractory AML, many trials of combination chemotherapy with GO for de novo AML have been conducted. Results from several relatively large groups of patients are shown in Table 3.

Fifty-one patients aged 65 years or older with de novo AML, refectory anemia (RA) with excess of blasts in transformation (RAEBT) or RA with excess blasts were treated with GO (RAEB) [82]. GO was given in doses of 9 mg/m^2 on days 1 and 8, or on days 1 and 15, with or without IL-11 (15 μg/kg on days 3–28). CR was achieved in 8 % in the GO without IL-11 group, and 36 % in the GO with IL-11 group. However, the CR rate and OS were inferior in patients treated with GO compared to historical data from those treated with IDA plus AraC.

Fifty-nine newly diagnosed patients (39 patients with AML, and 20 patients with RAEB/RAEBT) were treated with the MFAC regimen including GO (6 mg/m^2 on day 1); fludarabine (15 mg/m^2 on days 2–6), AraC (0.5 g/m^2 on days 2–6) and cyclosporine A (6 mg/kg on days 1 and 2) [56]. CR and CRp were achieved in 46 and 2 %, respectively. The median OS was 8 months. The 1-year OS and EFS were 38 and 27 %, respectively. Grade 3 or 4 toxicity was observed, including bilirubinemia in 31 % and transaminitis in 7 % of the patients. Four patients (7 %) developed VOD.

The preliminary efficacy of GO with intensive chemotherapy was analyzed in 72 patients with younger de novo AML, aged 17–59 years [Medical Research Council (MRC) AML15 trial] [65]. Sixty-four patients received induction chemotherapy, such as DAT (DNR, AraC, thioguanine), DA (DNR and AraC) or FLAG-Ida (fludarabine,

Table 2 Treatment with GO for the relapsed/refractory AML

Regimen	Combination therapy	GO (/m^2)	No. of cases	Median age	CR (CRp) %	Refractory case (%)	VOD (%)	References
MTA	Tpo, AraC	9 mg × 1	17	55 (20–70)	12 (0)	53	6	Cortes et al. [77]
MIA	IDA, AraC	6 mg × 2	14	61 (34–74)	21 (21)	61	14	Alvarado et al. [78]
MDAC	DNA, AraC, CyA	6 mg × 1	11	37 (16–67)	9 (9)	37	0	Apostlidou et al. [55]
MFAC	F, AraC, CyA	4.5 mg × 1	32	53 (18–78)	28 (6)	34	9	Tsimberidou et al. [56]
MIDAM	MIT, AraC	9 mg × 1	17	54 (21–68)	71 (6)	54	6	Chevallier et al. [80]
Anti-bcl2	Oblimersen	9 mg × 1	48	67 (>60)	10 (15)	0	0	Moore et al. [60]
CALGB	HiDAC	9 mg (±4.5 mg)	37	64 (53–69)	32 (3)	14	0	Stone et al. [81]

F fludarabine, *AraC* cytarabine, *CyA* cyclosporine A, *IDA* idarubicin, *DNR* daunorubicin, *MIT* mitoxantrone, *HiDAC* high-dose AraC

Table 3 Treatment with GO for de novo AML

Target disease	Combination therapy	GO (/m^2)	No. of cases	Median age	CR (CRp) %	VOD (%)	References
AML + MDS	IL-11	9 mg × 2	51 (37 + 14)	71 (65–89)	22 (–)	16	Estey et al. [82]
AML + MDS	F, AraC, CyA	6 mg × 1	59 (39 + 20)	57 (27–76)	46 (2)	7	Tsimberidou et al. [57]
AML	DNR, AraC	3 mg × 1	22	39 (19–56)	91[a]	0	Kell et al. [65]
	FLAG, IDA	3 mg × 1	15		78[a]	0	
AML	DNR, AraC	6 mg × 2	53	47 (18–59)	83	20	de Angelo et al. [83]
	AraC	6 mg × 2	21	69 (62–78)	43	0	
AML	MIT, IDA, AraC, ETP	9 mg × 2	57	68 (61–73)	35 (19)	9	Amadori et al. [84]
AML[b]	G-CSF, AraC	6 mg × 2	53	69 (65–78)	55 (2)	2	Fianchi et al. [85]

F fludarabine, *AraC* cytarabine, *CyA* cyclosporine A, *IDA* idarubicin, *DNR* daunorubicin, *MIT*: mitoxantrone, *ETP* etoposide

[a] Overall survival

[b] Including relapse/refractory AML

AraC, G-CSF, IDA) with GO (3 mg or 6 mg/m^2 on day 1). GO 3 mg/m^2 in the first course was feasible. However, neither GO 6 mg/m^2 in the first course nor GO 3 mg/m^2 in consecutive courses was feasible. VOD was frequently observed in the treatment including thioguanine. OR was achieved in 86 %. These results provided useful data for the phase III trial conducted by the same group.

Fifty-three patients with younger de novo AML were treated with DNR (45 mg/m^2 on days 1–3), AraC (100 mg/m^2 on days 1–7) and GO (6 mg/m^2 on day 4) [83]. OR was achieved in 83 % of the patients. Four of eight patients who underwent HSCT < 115 days from the first day of induction developed VOD; while none of 12 patients who underwent HSCT > 115 days developed VOD. These data have been included in the product information. HSCT before and after the administration of GO should thus be conducted with vigilance toward symptoms of VOD. In the study reported by the same group, 21 elder patients with de novo AML were treated with AraC (100 mg/m^2 on days 1–7) and GO (6 mg/m^2 on day 1 and 8). OR was achieved in 43 %. Grade 3 or 4 bilirubinemia was observed in 6 %, but VOD was not.

In the GIMEMA-EORTC study, GO (9 mg/m^2 on days 1 and 15) followed by conventional chemotherapy consisting of MIT, AraC, and ETP (MICE) was administered in 57 elderly patients with de novo AML [84]. OR was achieved in 54 %, with CR in 35 % and CRp in 19 %. One-year OS was 34 %. VOD developed in 9 %.

Combination therapy including G-CSF, AraC, and GO (G-AraMy) was administered in 53 elderly patients with untreated or primary refractory/relapsed AML [85]. Of these, 27 received G-AraMy1 and 26 G-AraMy2 protocols. G-AraMy included G-CSF (5 μg/kg on days 1–8), AraC (100 mg/m^2 continuously on days 4–8 in G-AraMy1 or days 2–8 in G-AraMy2) and GO (6 mg/m^2 on day 9). The outcomes were not different between the two groups. VOD was observed in 2 %. The response rate and toxicity profile were not different between untreated and primary resistant/relapsed AML, or between de novo and secondary AML.

The studies, reported by Kell et al. and De Angelo et al., [65, 83] focused on younger patients with AML. Considerably positive outcomes were obtained in these two studies and encouraged the group to plan open label phase III trials. Outcomes from elderly patients with AML or MDS in contrast were unsatisfactory.

Phase III study with GO

Based on the result of phase I and II trials, the efficacy of GO has been studied in an open label phase III trial (Table 4).

Table 4 PhaseIII trial of chemotherapy with or without GO for de novo AML

Group	No. of cases	Age (years)	Chemotherapy (mg/m^2)	CR (%)	Mortality (%) (without/with GO)	Prognosis (%)	References
SWOG (S0106)	627	18–60	DNR (45 × 3) + AraC (100 × 2 × 7) + GO (6 × 1) vs DNR (60 × 3) + AraC (100 × 2 × 7)	69/66	1/6*	NS (DFS)	Petersdorf et al. [86]
MRC (AML15)	1,113	0–60	DNR (50 × 3) + AraC (100 × 2 × 10) + ETP (100 × 5) vs DNR (50 × 3) + AraC (100 × 2 × 10) ± GO (3 × 1) *vs* F (30 × 5) + AraC (2000 × 5) + G-CSF ± GO (3 × 1)	83/82	6/7	NS (OS) 51 vs 79* (favorable, OS)	Burnett et al. [88]
GOELAMS (AML2006IR)	238	18–60	DNR (60 × 3) + AraC (200 × 7) ± GO (6 × 1)	87/92	3/4	NS (OS, EFS) 54/27* (non-HSCT, EFS)	Delaunay et al. [87]
UK & Denmark	1,115	51–84	DNR (50 × 3) + AraC (100 × 2 × 10) + C (20 × 5) ± GO (3 × 1)	58/62	11/12	25/20* (OS)	Burnett et al. [89]
France (ALFA-0701)	278	50–70	DNR (60 × 3) + AraC (200 × 7) ± GO (3 × 3)	75/81	4/7	42/53* (OS) 17/41* (EFS)	Castaigne et al. [90]
LRF & NCRI	495	54–90	AraC (20 × 2 × 10) ± GO (5 × 1)	11/21*	16/18	NS (OS)	Burnett et al. [91]

F fludarabine, *C* clofarabine, *AraC* cytarabine, *DNR* daunorubicin, *ETP* etoposide, *NS* not significant

* Significant

Table 5 Patients with APL treated by GO

Stage	Dose of GO (mg/m^2)	Concomitant drug	Number of case	Result	References
1st molecular relapse	9	ATRA, ATO	8	88 % MCR	LoCoco et al. [107]
3rd relapse	9	–	2	100 % MCR	Takeshita et al [108]
1st molecular relapse	3	ATRA, ATO	3	100 % MCR	Breccia et al. [109]
de novo	9	ATRA (+IDA)	19	84 % CR	Estey et al. [106]
de novo (high risk)	9	ATRA	19	78.9 % CR	Estey et al. [111]
de novo	9[a]	ATRA + ATO	82	95 % CR (low risk) 81 % CR (high risk)	Ravandi et al. [112]
Relapse/refractory (post-marketing)	9	–	27	48 % CR, 9 % CRp	Takeshita et al. [76]

Report from a case does not appear in the table

CR complete remission, *MCR* molecular remission, *ATRA* all-*trans* retinoic acid, *ATO* arsenic trioxide, *IDA* idarubicin

[a] GO was added if high risk or WBC count increased to >30 × 10^9/l during induction

The Southwest Oncology Group (SWOG) study-S0106 reported the benefit and toxicity of adding GO to standard therapy in 627 patients with de novo AML [86]. Patients were randomized to receive induction therapy with DNR (45 mg/m^2 on days 1–3) and AraC (100 mg/m^2 on days 1–7) and GO (6 mg/m^2 on day 4) (AD + GO) or standard induction therapy with DNR (60 mg/m^2 on days 1–3) and AraC (100 mg/m^2 on days 1–7) (AD). Patients achieving CR received consolidation therapy with three courses of HiDAC. Patients in remission were re-randomized to the treatment of GO (5 mg/m^2 every 28 days, three doses) or observation. The OR rate was 74 % in both induction arms. The RFS was not significantly different between two arms. Fatal adverse events were significantly increased in the AD + GO arm. Clinical outcomes were not improved by GO, and a higher fatality rate was observed on addition of GO.

The results of SWOG-S0106 triggered Pfizer Corp. to voluntarily withdraw GO from the market in 2010. However, several problems in the study have been raised. The doses of DNR were different between the two arms, making it difficult to precisely determine any additional efficacy of GO. Additionally, the induction mortality in the control arm was extremely low compared to other studies. The mortality rate (5.8 %) in GO arm may be within the acceptable range in other studies. Other studies have sought to address these problems and resolve the additional efficacy of GO.

In a subsequent study, 238 patients with de novo AML and intermediate karyotype were treated with standard chemotherapy with or without GO [87]. GO (6 mg/m^2) was added to standard 3 + 7 induction, and to a consolidation of MIT and AraC. The CR rate and early death rate were unchanged in both groups. Grade 3 or 4 hepatic toxicities were increased in GO arm. The EFS and the OS were not changed in both treatment arms. In patients who did not receive HSCT, EFS was significantly higher in the GO arm (54 % vs 27 %) while OS did not improve.

In the MRC-AML15 trial, 1,113 patients with de novo AML, excluding APL, were randomly assigned to receive either of the following three induction treatments: DNR and AraC; DNR, ETP and AraC; or fludarabine, IDA, AraC and G-CSF; with or without GO (3 mg/m^2) [88]. In remission, 948 patients were randomly assigned to GO (3 mg/m^2) in combination with amsacrine, AraC and ETP or HiDAC (1.5 g or 3 g/m^2). The CR rate or the OS was not significantly different. Survival benefit of GO was observed in patients with favorable cytogenetics, but not in patients with high-risk disease. GO did not increase toxicity. This study showed that GO can improve survival for patients with favorable risk AML.

In other results from UK and Denmark, 1,115 patients with AML or high-risk MDS were randomly assigned to receive induction chemotherapy with either DNR (50 mg/m^2 on days 1, 3, 5) and Ara-C (100 mg/m^2 twice a day on days 1–10) or DNR and clofarabine (20 mg/m^2 on days 1–5), with or without GO (3 mg/m^2) [89]. No difference in OR rate was observed between the two arms. GO did not increase toxicity and mortality. Three-year cumulative incidence of relapse was significantly lower, and 3-year OS was significantly better in the patients treated with GO.

Two hundred seventy-eight elderly patients with de novo AML were received DNR (60 mg/m^2 on days 1–3) and AraC (200 mg/m^2 for 7 days) without (control group) or with GO (3 mg/m^2 on days 1, 4, and 7) [90]. The OR rate was not different between the two groups. The 2-year EFS, OS, and RFS were significantly improved by the addition of GO. GO did not increase the risk of death from toxicity. They concluded that the fractionated lower doses of GO were safe and improved outcomes.