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Idarubicin, Cytarabine, and Topotecan in Patients With Refractory or Relapsed Acute Myelogenous Leukemia and High-Risk Myelodysplastic Syndrome

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In an effort to develop more effective therapy for patients with refractory or relapsed acute myelogenous leukemia (AML) and high-risk myelodysplastic syndrome (MDS), we investigated the efficacy of a combination chemotherapy consisting of idarubicin, cytarabine, and topotecan. Twenty-seven patients were treated: four with primary refractory AML, nine with AML in first relapse, four with AML in second relapse, and 10 with MDS-RAEB/RAEBT. Patients received as salvage therapy a single course of idarubicin 12 mg/m^2 IV bolus on days 1–3, cytarabine 1 g/m^2 over two hours q 12 hr on days 1–5, and topotecan 1.25 mg/m^2 over 24 hr on days 1–5. Median age was 42 years (range 17–65 years). All patients were evaluable for response: 14 (51.9%) achieved complete remission, 10 with AML (59%) and four with MDS (40%), respectively. Thirteen AML patients (excluding four relapsed after autologous stem cell transplantation) were grouped into four categories to stratify the probability of achieving complete remission (CR): group 1, first CR duration > or = 2 years and receiving first salvage treatment (S1); group 2, first CR duration 1–2 years and receiving S1; group 3, first CR duration 0–1 years and receiving S1; and group 4, first CR duration 0–1 years and receiving S2, S3, or S4 after failing S1. The response rate of each group was as follows: group 1, one of two (50%); group 2, one of one (100%); group 3, four of four (100%); group 4, two of six (33.3%). The median remission duration and survival of patients with AML were six and 12 months, respectively. Median duration of survival in 10 MDS patients was 15 months, and all four MDS patients achieving a CR maintained continuous CR with a median follow-up of 11 months. Severe myelosuppression was observed in all patients, resulting in fever or documented infections in 89% of patients. Median time to recovery of neutrophils $\geq 0.5 \times 10^9$/l was 22 days (11–34) and for platelets $> 20 \times 10^9$/l 35 days (11–58). Reversible grade 3–4 toxicities included diarrhea (two patients) and mucositis (seven patients). We conclude that combination chemotherapy with intermediate dose cytarabine, idarubicin, and topotecan has significant antileukemic activity and acceptable toxicity in salvage AML and high-risk MDS. Am. J. Hematol. 68:237–245, 2001. © 2001 Wiley-Liss, Inc.

Key words: acute myelogenous leukemia; myelodysplastic syndrome; salvage chemotherapy; topotecan; cytarabineidarubicin

INTRODUCTION

For adults with acute myelogenous leukemia (AML) who fail to achieve complete remission with frontline therapy, or who relapse, current therapy is inadequate with a true long-term cure rate of less than 10% [1]. Therapy for advanced myelodysplastic syndromes (MDS), including refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia is also poor, with median survivals of less than 12 months [2].

The only form of "salvage" that may offer long-term survival is transplantation of allogeneic progenitor cells following myeloablative preparative conditioning [3]. In contrast to allogeneic bone marrow transplantation (BMT), most standard or high-dose

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chemotherapy used for relapsed or refractory AML is unable to produce prolonged disease-free survival. Response rates to salvage therapy are considerably lower with complete response (CR) attained in only 7 to 40% of patients [4–10]; invariably the duration of leukemia-free survival is three to six months.

High-dose cytarabine is the most effective drug in the AML salvage setting, often producing CR in patients refractory to conventional dose cytarabine [1]. Most salvage regimens are based on variations of the same topoisomerase II reactive agents (i.e., anthracycline or VP-16) and cytarabine combination schedules used in front-line therapy [7]. Such regimens are effective among patients with a long first CR duration (a "long" CR is variably defined as more than six months or one year, depending on the report) who have relapsed off therapy. They are, however, of limited efficacy among patients relapsing on therapy or with a first CR duration of less than one year [7].

Topotecan interacts with the enzyme topoisomerase I (topo I), and stabilization of the topo I-DNA complexes by the drug is thought to lead to cell death [11]. More topo I is present in tumor cells than in normal cell counterparts [12], which makes the enzyme a logical target for drugs such as topotecan. As a single agent, it has antileukemic activity in acute leukemia, MDS, and chronic myelogenous leukemia (CML) in acute phase. In AML, objective antileukemic activity has been observed in two phase I studies of topotecan [13,14]. Previous studies with single-agent topotecan in MDS and chronic myelomonocytic leukemia (CMML) showed encouraging activity with a CR rate of 30% [15,16].

The anthracycline idarubicin has been claimed to be more effective than daunorubicin based on a prolonged half-life in plasma, with conversion to an active metabolite idarubicinol [17], and reduced sensitivity to p-glycoprotein overexpression [18]. Idarubicin is now considered a potent antileukemic agent included in the salvage regimen for AML [19,20] as well as front-line therapy [21–23].

We therefore combined these agents to reduce the incidence of severe complications noted with high-dose cytarabine containing regimens and introducing more potent antileukemic efficacy, using a combination of idarubicin [21–23] plus topotecan at optimal dosage [24] and cytarabine at intermediate dosage. In this study, we report the results obtained using this new regimen as therapy for refractory or relapsed AML and high-risk MDS.

PATIENTS AND METHODS

Selection of Patients

Between January 1998 and June 1999, 17 adult patients with relapsed or primary refractory AML and 10 patients with newly diagnosed high-risk MDS were studied. They were 17 males and 10 females, ranging in age from 17 to 65 years (median: 42 years). We defined primary refractory as the persistence of >30% bone marrow blasts and the absence of clearing of blast cells from the peripheral blood after two courses of induction therapy, and relapse as overt leukemia or >20% BM blast cells. Patients were required to have adequate kidney, liver, and cardiac function and had to be off therapy for at least two weeks, unless they had a life-threatening increase in their leukemic burden before that time. Initial evaluation included a history and physical examination with documentation of measurable disease; a bone marrow aspirate and biopsy; routine blood tests with complete blood counts (CBC), differential, and hepatic and renal function studies; and radiologic studies to document any extramedullary disease if present. The protocol was reviewed and approved by local institutional review boards, and written informed consent was obtained from all patients.

Treatment

Patients received topotecan 1.25 mg/m^2/day continuous IV infusion over 24 hours daily for five days, intermediate dose cytarabine 1.0 g/m^2 IV infusion over two hours every 12 hours for five days, and idarubicin 12 mg/m^2/day IV bolus for the first three days. Follow-up studies included CBC, differential and platelet counts, serum chemistries, and electrolytes two to three times a week until recovery of counts during induction, then every one to four weeks as indicated. Bone marrow examination was performed on days 14 and 21. Patients with complete remission after salvage therapy were given consolidation chemotherapy with one more course of the same regimen, or allogeneic bone marrow transplantation in case of having a HLA-matched sibling. Those who lacked a suitable donor received maintenance chemotherapy by monthly courses of 6-TG plus cytarabine for two years or until relapse occurred after achieving CR [25].

Response and Toxicity Criteria

A complete remission (CR) was defined as disappearance of all evidence of leukemia with a neutrophil count of 1,000/μl or more, a platelet count of 100,000/μl or more, no circulating blasts, and a normal marrow differential with less than 5% blasts in a normocellular marrow, with the response lasting for at least four weeks. Other response patterns were considered as failures and categorized as follows: early death (ED), if death occurred prior to day 14; aplastic death

(AD), if a patient died after day 14 with an aplastic marrow; primary resistance, if the marrow leukemic infiltrate (MLI) (% cellularity × % blast) was never below 20% during therapy; secondary resistance, if the MLI became less than 20% but with subsequent leukemic regrowth. Partial response (PR) was defined as for CR, except for the persistence of more than 5% marrow blasts. Nonhematologic toxicity was graded according to the World Health Organization (WHO) scale.

Patients with AML were grouped into four categories to stratify the probability of achieving CR according to the system devised by Estey et al. [26]: group 1, first CR duration ≥ two years and receiving first salvage treatment (S1); group 2, first CR duration 1–2 years and receiving S1; group 3, first CR duration 0–1 years and receiving S1; and group 4, first CR duration 0–1 years and receiving S2, S3, or S4 after failing S1. Expected CR rates in the four groups are known to be 70, 40, 10–20, and <1%, respectively [26].

Supportive Care

Supportive care for granulocytopenic patients consisted of reverse isolation and administration of prophylactic antibiotics, usually with fluconazole 200 mg orally per day and ciprofloxacin 500 mg orally twice per day. Febrile granulocytopenic patients received imipenem or cefoperazone/sulbactam, or other broad-spectrum antibiotics. Patients with documented or suspected fungal infections were treated with empiric amphotericin B. Platelet transfusions were given to maintain a platelet count $\geq 30 \times 10^3/\mu l$ and RBC were transfused to maintain an hematocrit ≥30%. Granulocyte-colony stimulating factor (G-CSF) administration was recommended not to be given unless granulocyte recovery was delayed for more than 35 days or overwhelming sepsis was present.

Statistical Analysis

Intergroup comparisons of CR rates, as well as the relationship with different variables studied, were tested for significance using the Fisher's χ^2-test. Disease-free survival (DFS) was measured from the date of CR to the date of last follow-up examination, death, or relapse. Overall survival (OS) was measured from the date of inclusion to the date of last follow-up examination or death. Survival was censored at the time of allogeneic bone marrow transplantation. Time-dependent analysis was performed using the product-limit (Kaplan-Meier). Comparisons between life curves were done using the log-rank (Mantel-Cox) test.

TABLE I. Patients Characteristics in Advanced AML (n = 17)

Parameter	
Age (yr)	42 (17–65)
Sex (M/F)	13/4
Hemogram at diagnosis	
WBC ($\times 10^3/\mu l$)	36.4
Platelet ($\times 10^3/\mu l$)	38
Hemoglobin (g/dl)	10.4
FAB	
AML M1/M2	3/7
M4/M5	3/1
Secondary AML	3
Karyotype subgroups	
Good	1
Intermediate	6
Poor	7
No data	3
Disease status	
Refractory	4
1 relapse (relapse after ASCT[a])	9 (4)
2 relapse	4
Salvage group[b]	
Group 1	2
Group 2	1
Group 3	4
Group 4	6

[a]ASCT: autologous stem cell transplantation.
[b]Excludes four patients relapsed after ASCT.

RESULTS

Patients Characteristics

Patient characteristics of advanced AML are shown in Table I. Four patients were primarily resistant to standard induction therapy with three daily doses of daunorubicin/idarubicin combined with standard dose cytarabine. Nine patients were in first relapse, four in second or third relapse, and four patients in relapse after autologous stem cell transplantation. According to the cytogenetic subgroups proposed by Keating et al. [27], one patient fell in the good prognosis group, six in intermediate group, seven in poor group, and data were not available in the remaining three cases.

Previous treatment of AML patients comprised induction therapy with cytarabine 100 mg/m^2 CIV for seven days plus daunorubicin 45 mg/m^2 IV for three days in all patients; consolidation therapy with intermediate dose cytarabine (1 g/m^2/12 hr for four days) and etoposide (100 mg/m^2/day for three days) plus mitoxantrome (10 mg/m^2/day for two days) in seven patients; four patients had myeloablative therapy supported by autologous stem cell transplantation; and two patients received no postremission therapy. Distribution of salvage group according to the probability of achieving CR among 13 AML patients (excluding four patients relapsed after

TABLE II. Patients Characteristics in MDS (n = 10)

Parameter	Category	No. (%)
Age (yr)	>60	1 (10)
Median (range)	44.5 (28–65)	
WBC ($\times 10^3/\mu l$)	≥20	1 (10)
Median (range)	2.7 (1.8–59.4)	
Platelet ($\times 10^3/\mu l$)	<50	7 (70)
Median (range)	29.5 (8–526)	
Hemoglobin (g/dl)	<10	7 (70)
Median (range)	7 (3.7–12.3)	
FAB subtype	RAEB	3 (30)
	RAEB-T	7 (70)
Karyotype	Diploied	2 (20)
	5 or 7 abnormality	3 (30)
	Trisomy 8/11q23	1 (10)
	Other abnormality	4 (40)
IPSS score		
	Low	–
	Intermediate-1	–
	Intermediate-2	1 (10)
	High	9 (90)
Prior therapy	Yes	4 (40)

TABLE III. Response According to Patient Characteristics

	Patients	(%)	CR	(%)
All patients	27	100	14	51.9
Age				
<30 years	5	18.5	2	50
≥30 years	22	81.5	12	61.5
Sex				
Male	17	63	10	76.9
Female	10	37	4	40
AML FAB type				
M1	3	11.1	1	33.3
M2	7	25.9	5	71.4
M4	2	7.4	1	50
M5	1	3.7	1	100
Secondary AML	3	11.1	2	66.7
MDS	10	37	4	40
RAEB	3	11.1	2	66.6
RAEBT	7	25.9	2	28.6
AML Status (n = 17)				
Refractory	4	23.5	1	25
Relapsed	13	76.5	9	69.2
1st relapse	9	52.9	6	66.7
2nd relapse	4	23.5	3	75
Type of CR1 therapy in AML (n = 13)				
Chemotherapy	7	53.8	5	71.4
Auto-SCT	4	30.8	2	50
No therapy	2	15.4	2	100
Prior therapy in MDS (n = 10)				
Yes	4	40	1	25
No	6	60	3	50

autologous stem cell transplantation) was as follows: two (15.4%) in group 1, one (7.7%) in group 2, four (30.8%) in group 3, and the remaining six (46.2%) in group 4.

Ten patients with a diagnosis of MDS, three with refractory anemia with excess of blast (RAEB) and seven with refractory anemia with excess of blast in transformation (RAEB-T), were included in this study. One patient was more than 60 years of age (10%). Three patients (30%) had an abnormality in chromosome 5 or 7, which has been established as a poor prognostic variable; one additional patient (10%) had either trisomy 8 or 11q23; other karyotypic abnormalities were noted in four (40%) patients, whereas diploid karyotype was observed in the remaining patients. Four patients (40%) had received prior therapies, two with low dose cytarabine, and two with AML-type induction chemotherapy. Patient characteristics of MDS are depicted in Table II.

Response to Therapy

Response rates according to patient characteristics are depicted in Table III. Of the 27 patients entered in the study, all were assessable for response and toxicity. Overall, 14 (51.9%) achieved a CR based on the response criteria. Ten of the 17 patients with relapsed/refractory AML had a CR (58.8%). Among 10 patients with MDS, four achieved a CR (40%). In addition, we observed hematologic improvement in four patients, including no further requirement of transfusion support. Only one (25%) of four primary refractory AML patients achieved a CR, whereas nine (69.2%) of relapsed AML patients achieved a CR ($P = 0.125$). The response rates of patients with first relapsed AML and patients with second or more relapsed AML were 66.7 and 75%, respectively, which was not different. Among four AML patients relapsed after autologous stem cell transplantation, two achieved a CR (50%), one in PR, and the remaining one patient succumbed to death due to infection during prolonged hypoplasia.

Response rates of 13 AML patients according to the salvage group were as follows: one of two patients in group 1 achieved a CR (50%), and another one showed secondary resistance; one patient in group 2 achieved a CR (100%); all four patients in group 3 achieved a CR (100%); two of six patients in group 4 achieved a CR (33.3%), four nonresponders comprised of one with primary resistance, two with secondary resistance, and the remaining patient died of overwhelming sepsis during the early period (Table IV).

Response rates of MDS patients varied by the extent of prior treatment. Three of six (50%) untreated MDS patients achieved a CR. Only one of four (25%) MDS patient previously treated with chemotherapy achieved a CR (Table III).

TABLE IV. Therapeutic Outcomes in AML According to the Salvage Group*

	Group 1 (n = 2)	Group 2 (n = 1)	Group 3 (n = 4)	Group 4 (n = 6)	Total (n = 13)
CR (%)	1(50)	1(100)	4(100)	2(33.3)	8(61.5)
PR	–	–	–	–	–
ED	–	–	–	1	1
AD	–	–	–	–	–
1°R[a]	–	–	–	1	1
2°R[a]	1	–		2	3
DFS (months)	5	7	6	6	6
OS (months)	7	10	10	8	8

*CR: complete remission; PR: partial remission; ED: early death; AD: aplastic death; DFS: disease-free survival; OS: overall survivial.
[a]1°R: primary resistance; 2°R: secondary resistance.

TABLE V. Cytopenia and Transfusion Requirement in Patients Achieving Cr (n = 14)

Cytopenia (days)	
AGC $< 0.5 \times 10^3/\mu l$	22 (11–34)
Platelet $< 20 \times 10^3/\mu l$	35 (11–58)
Transfusion requirement	
RBC (units)	7 (0–20)
Platelet (times[a])	13.5 (7–36)

[a]Frequency of platelet transfusion given during chemoterapy, usually 8 units of platelet concentrates or 1 unit of platelet apheresis product at a time.

TABLE VI. Toxicity (n = 27)

Toxicity	No. of patients	%
Febrile episode	24	88.9
Documented infection	16	59.3
Mild to moderate (grade I/II)	7	25.9
Severe (grade III/IV)	9	33.3
Hemorrhage	5	18.5
Mild to moderate (grade I/II)	4	14.8
Severe (grade III/IV)	1	3.7
Nausea and vomiting	22	81.5
Mild to moderate (grade I/II)	14	51.9
Severe (grade III/IV)	8	29.6
Mucositis	25	92.6
Mild to moderate (grade I/II)	18	66.7
Severe (grade III/IV)	7	25.9
Diarrhea	19	70.4
Mild to moderate (Grade I/II)	17	63
Severe (grade III/IV)	2	7.4
Hepatotoxicity	4	14.8
Mild to moderate (grade I/II)	4	14.8
Severe (grade III/IV)	–	–
Cardiac toxicity	2	7.4
Mild to moderate (grade I/II)	1	3.7
Severe (Grade III/IV)	1	3.7
TRM[a]	3	11.1

[a]TRM: treatment-related mortality.

Toxicity

This regimen was severely myelosuppressive, with all patients developing profound granulocytopenia (<100/μl) and thrombocytopenia (<20,000/μl) by day 10 from start of chemotherapy. The median duration of granulocytopenia and thrombocytopenia in responding patients was 22 days (range 11–34) and 35 days (range 11–58), respectively (Table V). The most common adverse effects were related to myelosuppression. Granulocytopenic fever was recorded in 24 of 27 patients (88.9%). Clinical or microbiologically documented infection was demonstrated in 16 patients (59.3%), primarily septicemia, pneumonia, or other focal infections. Infection was severe (WHO grade >2) in nine patients (33.3%). Bleeding episodes due to severe thrombocytopenia was found in four of 27 patients, one of whom had severe pulmonary hemorrhage. Nonhematologic toxicity is detailed in Table VI. Mucosits was dose-limiting toxicity; seven (25.9%) of 27 patients were found to have grade 3 or more severe mucositis, and all of them required parenteral nutrition. Nausea and vomiting were frequent (81.5%) but not severe due to the systemic use of prophylactic antiemetics. We did not observe cytarabine induced central nervous system toxicity, even in patients more than 50 years of age. Long-lasting cytopenias attributed to the intensity of the regimen were observed in three patients, one with MDS-RAEB, another with secondary AML, and the third with heavily pretreated relapsed AML. All these patients had adequate clearance of blasts (<5% BM blasts). Three of 27 patients (11.1%) died during the first four weeks of therapy, two of overwhelming infection and one of cardiac failure.

Survival

At the time of analysis (December 1999), seven patients were in continuous CR with a median follow-up of 10 months, two after allogeneic BMT, three after consolidation chemotherapy, and remaining two patients with no further therapy. With a median follow-up duration of 10 months (range: 1–32 months), the 12-month survival rate and disease-free survival rate of 27 patients were 33 and 49%, respectively (Fig. 1). The median remission duration and survival of patients with AML were six and 12 months, respectively. Median duration of survival in 10 MDS patients was 15 months and all four MDS patients achieving a CR maintained continuous CR with a median follow-up of 11 months. There were no differences in survival time for any pretreatment characteristics.

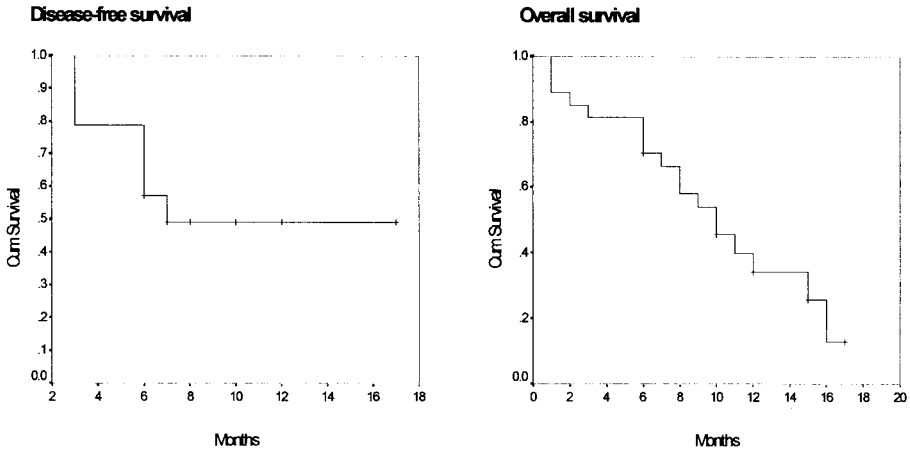

Fig. 1. Disease-free survival and overall survival of the patients.

DISCUSSION

Our study has shown significant activity of topotecan, cytarabine, and idarubicin combination chemotherapy in relapsed/refractory AML, and high-risk MDS with generally manageable toxicities. Overall complete remission rate after a single course was 51.9% with only one case of primary resistance, and the early death rate was only 11.1%. In patients with relapsed AML, the response rate was 69.2%, more than average response rate compared with the previous reports [4–10]. Among four patients with primary refractory AML in this study, only one patient achieved a CR.

Notably, among different salvage groups, group 3 comprising four patients with less than one year of first CR duration and receiving first salvage therapy with the probability of achieving a CR of only 20%, showed 100% (four of four) of response rate. Moreover, this regimen showed significant antileukemic activity even in patients with far-advanced AML; two of six (33.3%) from salvage group 4, with a CR probability of less than 1%, attained a CR (including two third CR out of three second relapsed AML). Among four AML relapsed after autologous stem cell transplantation, another high-risk of refractory AML, two attained a CR (50%). One of two remitters maintained a second CR for only three months, but another remitter who underwent autologous stem cell transplantation in his second CR fared relatively well, showing continuous remission with a follow-up duration of 12 months at the time of analysis.

These results compare favorably with other salvage programs for relapsed/refractory AML including high-dose cytarabine alone [28] or combined with other agents [28–31]. In comparison with other similar triple agent salvage regimens such as idarubicin, intermediate-dose cytarabine and VP-16 (ICE) [32], mitoxantrone, VP-16 and intermediate dose cytarabine (MEC) [33], or recently fludarabine, cytarabine, G-csf and idarubicin (Ida-FLAG) [34,35], the response rate of this regimen is comparable or somewhat better with less toxic death. The recent phase II trial of the Ida-FLAG salvage regimen showed an overall 52% CR rate in refractory/relapsed and secondary AML; 80% of especially excellent response rate in first relapsed AML, but only 7% of response in primary refractory AML. These data are similar to our results, and suggest that to overcome primary drug resistance in this subset of patients, more active and innovative therapeutic strategy is needed.

In patients with MDS, four of 10 (40%) patients achieved a CR, and three achieved a PR with significant hematologic improvement. All four patients entering CR maintained continuous CR with a median follow-up of 11 months; one of them underwent allogeneic bone marrow transplantation from HLA-matched sibling donor.

The apparently better antileukemic activity of our new regimen may be explained partly by the substitution of daunorubicin or mitoxantrone with idarubicin and the addition of novel topoisomerase I inhibitor, topotecan. Idarubicin is known to have a longer half-life with more rapid cellular uptake, and more DNA single-strand breaks in tumor cells. A randomized trial in previously untreated AML comparing idarubicin with daunorubicin in combination with standard dose cytarabine resulted in a significantly higher CR rate (80 vs. 58%) [21], and two similar studies also showed better results with idarubicin [22,23]. The antileukemic activity of topotecan has been verified by previous clinical trials for refractory/relapsed leukemia, and high-risk MDS. In vitro experiments in which a topoisomerase I inhibitor and cytarabine were combined have demonstrated

significant additive cytotoxic effects [36], and following combination chemotherapy with topotecan plus cytarabine showed more encouraging activity in MDS with a response rate of more than 60%, with a median survival of 60 weeks [37].

The additive effect of topotecan to idarubicin and intermediate dose cytarabine (ida-IDAraC) in refractory and relapsed acute leukemia could be deduced by the apparently superior response rate of this study compared with previous a ida-IDAraC result [38]. Excluding four patients who failed the first salvage therapy given immediately before entering into this study, CR rate of relapsed AML patients was 77% (10 of 13, data not shown), superior to the 54% rate of CR of ida-IDAraC dual combination therapy for similar characteristics of AML patients. In addition, recent results of clinical study about refractory/relapsed acute leukemia with cyclophosphamide, cytarabine, and topotecan combination chemotherapy showed a 20% response rate [39], a less favorable result compared with our data. These results suggest that addition of idarubicin to topotecan and cytarabine might offer more potent antileukemic effect compared with the cyclophosphamide combination.

Unfortunately, like other successful salvage programs reported, remission durations were also brief in this study. High-dose cytarabine, one of the most widely studied and effective drugs in the AML salvage setting, often produces a CR rate of more than 50%, but the median duration of survival is only about three months [1]. Not only to extend the duration of remission but for long-term survival in resistant AML, effective postremission therapy should be required. But the role of postremission therapy except allogeneic stem cell transplantation in poor-prognosis patients remains to be clarified. Of 14 patients with a CR, only three patients received subsequent consolidation chemotherapy with the same regimen, and four patients (three AML and one MDS-RAEBT) proceeded to allogeneic stem cell transplantation, with a median interval of 2.5 months after achieving a CR. Of them, one patient with AML died of fungal pneumonia on day 68 of transplantation, and one succumbed to relapse on day 135 of transplantation. The remaining two patients, one AML and one MDS-RAEBT, maintained a continuous CR with follow-up durations of 11 months and 13 months after BMT, respectively. Overall, the median duration of disease-free survival in patients with AML was only six months. Eight of 10 remitters subsequently relapsed, and only one patient who received allogeneic stem cell transplantation could maintain a continuous CR. Moreover, one patient with MDS-RAEBT who failed to enter CR and subsequently received allogeneic stem cell transplantation survived in CR with a follow-up duration of 15 months, demonstrating that allogeneic stem cell transplantation represents the only available therapeutic modality that may hold out the promise of long-term benefit in these poor-risk categories of patients. It is clear that alternative and more widely applicable treatment strategies in these poor-risk categories are desperately needed.

A major concern of this regimen was the myelotoxicity, because two previous studies reported increased myelotoxicity of idarubicin over daunorubicin [22,23], and the dose-limiting toxicity of topotecan is also known to be myelosuppression. In this study, myelotoxicity was severe but marrow recovery was timely in all but three patients (11.1%). Infection was the major toxicity of the regimen and the main cause of treatment-related morbidity. Overall, 88.9% of the patients experienced at least one episode of granulocytopenic fever requiring IV antibiotics, and 59.3% had documented infections. However, only two patients died of overwhelming infection; one of them with hypoplastic marrow without residual leukemia, and the other in the state of primary resistant disease. This compares favorably with the Ida-FLAG regimen, for which the toxic death rate is 22.8% [35], or more myelosuppressive programs, such as those using megadoses of cytarabine. Nonhematologic toxicities were acceptable and were comparable to those of other induction therapies. One heavily pretreated patient with AML succumbed to severe cardiac failure three days after completion of chemotherapy.

Taken together, the results of this study demonstrate that this regimen can be safely administered to relapsed/refractory AML and high-risk MDS patients, and the efficacy for AML patients with low probability of attaining a CR is excellent with a high rate of CR.

Although the number of patients in our analysis was too small for definitive conclusions, combination chemotherapy with intermediate dose cytarabine, idarubicin, and topotecan has significant antileukemic activity and acceptable toxicity in salvage AML and high-risk MDS. This regimen, or a more dose intense variant, is worthy of a larger clinical trial in salvage groups with a higher likelihood of response.

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