Anti-Cancer Drugs 1999, **10**, pp. 267–273

Clinical study

A phase II study employing combination regimens containing KRN8602 in drug-resistant acute myeloid leukemia and acute lymphoblastic leukemia

Y Kishimoto, K Sampi,[1] Y Kuraishi,[2] Y Takemoto,[3] K Okabe,[4] K Tamura,[5] H Mizoguchi,[6] H Saito,[7] T Masaoka[8] and M Ogawa[9] on behalf of the KRN8602 Leukemia Study Group

Kansai Medical University. [1]Shiraoi Town Hospital. [2]The Jikei University School of Medicine. [3]Hyogo College of Medicine. [4]National Shikoku Cancer Center Hospital. [5]School of Medicine, Fukuoka University. [6]Tokyo Women's Medical College. [7]Nagoya University, School of Medicine. [8]Osaka Medical Center for Cancer and Cardiovascular Diseases. [9]Aichi Cancer Center.

This study was supported by the grant of Kirin Brewery Co., Ltd, which provided the study drugs. It was authorized by the institutional review board of each participating institution.

Institutions (Representative Investigators) in the KRN8602 Leukemia Study Group: Asahikawa Municipal Hospital (I Maekawa), Hokkaido University, School of Medicine (M Asaka, T Miyazaki), National Sapporo Hospital (H Yoshida, C Mikuni), Sapporo Hokuyu Hospital (M Kasai), Sapporo Medical University (Y Niitsu), Aomori Prefectural Central Hospital (Y Sakata), Akita University, School of Medicine (A Miura), Niigata University, School of Medicine (A Shibata), Niigata Cancer Center (N Hayashi), Jichi Medical School, School of Medicine (Y Miura), School of Medicine, Chiba University (N Yoshida), Chiba Cancer Center Hospital (M Oguro, T Takagi), Nihon University, School of Medicine, Itabashi Hospital (T Oshima), Cancer Chemotherapy Center, Japanese Foundation for Cancer Research (N Horikoshi), National Cancer Center Hospital (K Tobinai), The Jikei University School of Medicine (Y Isogai), St Marianna University School of Medicine (T Ishida), School of Medicine, Tokai University (T Nagao, S Yonekura), Toyama Prefectural Central Hospital (T Yoshida), School of Medicine, Kanazawa University (T Matsuda), Hamamatsu University School of Medicine (R Ohno), Faculty of Medicine, Mie University (S Shirakawa, H Shiku), Anjo Kosei Hospital (H Obara, A Matsuoka), Okazaki Municipal Hospital (H Suzuki), Aichi Cancer Center (M Ogura), Japanese Red Cross Nagoya First Hospital (Y Kodera), Aichi Sannomaru Hospital (S Yokomaku), Nagoya University, School of Medicine (H Saito), Nagoya University, Branch Hospital (T Naoe), Kyoto University, Faculty of Medicine (M Okuma), Shiga University of Medical Science (S Hosoda, Y Fujiyama), Shiga Medical Center for Adults (T Suzuki), Kansai Medical University (H Fujitake, S Fukuhara), Osaka City University Medical School (N Tatsumi), Osaka Medical Center for Cancer and Cardiovascular Diseases (T Masaoka, A Hiraoka), Higashi-Osaka City Central Hospital (T Yamazaki, H Kawagoe), Kinki University, School of Medicine (A Horiuchi), Hyogo College of Medicine (E Kakishita, Y Takemoto), Okayama University, Medical School (I Kimura, M Harada), Hiroshima Red Cross and Atomic Bomb Survivors Hospital (H Dohi), School of Medicine, Tokushima University (S Saito, T Matsumoto), National Shikoku Cancer Center Hospital (K Okabe), Ehime Prefectural Hospital (M Hara), Kochi Municipal Central Hospital (I Takahashi), Nagasaki University, School of Medicine (M Tomonaga), Oita Medical University (H Kikuchi, M Nasu), Oita Prefectual Hospital (T Hosokawa, Y Saburi), NTT Kyusyu General Hospital (H Nishimura) and Miyazaki Prefectual Hospital (K Tamura)

Correspondence to Y Kishimoto, First Department of Internal Medicine, Kansai Medical University, Fumizono-cho 10-15, Moriguchi-shi, Osaka 570-8507, Japan.
Tel: (+81) 6 6992 1001; Fax: (+81) 6 6992 1293;
E-mail: kishimoy@takii.kmu.ac.jp

We conducted a phase II multicenter study in order to evaluate the efficacy and toxicity of two combination regimens containing KRN8602 (MX2) for drug-resistant acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL). AML was treated with KRN8602, 15 mg/m^2 i.v. push for 5 days, and cytarabine (AraC), 100 mg/m^2 by 24 h coutinuous infusion for 7 days. ALL was treated with KRN8602, 15 mg/m^2 i.v. push for 5 days, vincristine (VCR), 1.4 mg/m^2 i.v. push, once weekly, and prednisolone (PSL), 40 mg/m^2, 3 h infusion for 5 days. In AML and ALL, the complete remission (CR) rate was 36.4% (16 of 44) and 24.1% (seven of 29), and the overall response rate (CR+PR) was 52.3% (23 of 44) and 51.7% (15 of 29), respectively. Among the 29 relapsed cases of AML, a higher CR rate, 51.7% (15 of 29), was obtained. A high incidence of nausea/vomiting and anorexia was observed, and some patients experienced central nervous system disorders and peripheral neuropathy. There was a low incidence of severe neurotoxicities; all other toxicities were manageable. KRN8602 was found to overcome drug resistance clinically, confirming results based on the preclinical studies. We conclude that KRN8602 is an effective novel anthracycline for drug-resistant acute leukemias. [© **1999 Lippincott Williams & Wilkins.**]

Key words: Acute leukemia, combination chemotherapy, drug-resistant, KRN8602, P-glycoprotein.

Introduction

High complete remission rates have been reported for the initial treatment of acute leukemia.[1-8] However, about 20-30% of patients fail to show a complete remission and even if they achieve a complete remission, more than half experience a recurrence. Drug resistance is considered one of the reasons for the recurrence and it is necessary to use new anticancer agents that overcome resistance as a means of inducing a remission in patients with relapsed or refractory acute leukemia.

KRN8602 (3'-deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin hydrochloride, MX2) is a novel anthracycline compound developed by the Institute of Microbial Chemistry and Kirin Brewery Co., Ltd.[9,10] In preclinical studies it showed high antitumor effects against a variety of transplantable tumors in animals, including P388 leukemia. It was also effective against adriamycin (ADM)-resistant P388 leukemic cells,[11] suggesting that KRN8602 might be clinically effective against drug-resistant acute leukemia.

In the phase II study conducted on the basis of these preclinical findings and phase I studies, administration of KRN8602, 15 mg/m^2 for 5 days, to patients with relapsed or refractory acute leukemia yielded an overall remission rate (CR+PR) of 21.4% (three of 11) in acute myeloid leukemia (AML) and 29.4% (five of 12) in acute lymphoblastic leukemia (ALL).[12] In the pilot phase II study carried out to assess the optimal dosage of KRN8602 in the combination therapy with cytarabine (AraC) to patients with relapsed or refractory acute leukemia, KRN8602, 15 mg/m^2 for 5 days, in combination with AraC, 100 mg/m^2 for 7 days, yielded an overall remission rate of 100% (four of four) in AML, and in combination with vincristine (VCR), 1.4 mg/m^2 once weekly, and prednisolone (PSL), 40 mg/m^2 for 5 days, yielded an overall remission rate of 100% (four of four) in ALL.[13] In both studies there was a high incidence of gastrointestinal toxicities, including nausea/vomiting and anorexia, whereas other toxicities were mild. All toxicities appeared to be clinically tolerable. From these results, it seemed that further studies are necessary to assess the efficacy and toxicity of KRN8602 for acute leukemias.

In the present study, we conducted a multi-center phase II study from November 1993 to October 1995 in order to evaluate the efficacy and toxicity of combination therapy with KRN8602 against relapsed or refractory acute leukemias. This study was carried out in accordance with 'Good Clinical Practice' that went into effect on 2 October 1989.

The expression of P-glycoprotein (P-gp),[14,15] which is considered to be one of the multidrug resistance factors, was analyzed in some of the cases, and the possibility of an association between the therapeutic efficacy of KRN8602 combination therapy and P-gp expression was investigated.

Materials and methods

Patients

Patients who met the following eligibility criteria were enrolled: (i) patients with treatment-resistant acute leukemia whose bone marrow comprised at least 10% leukemic cells; (ii) patients who had no influence from previous therapy (at least 2 weeks from the prior therapy); (iii) life expectancy of at least 2 months; (iv) performance status (PS) 0-2; (v) no liver and kidney dysfunction (total bilirubin less than 3.0 mg/dl; AST and ALT within twice the upper limit of normal limit; serum creatinine less than 2.0 mg/dl; (vi) no ECG abnormalities; (vii) age between 15 and 59 years; and (viii) patients who gave informed consent.

The following patients were excluded: (i) patients who had been previously treated with KRN8602; (ii) patients who were pregnant, lactating or who expected to become pregnant; (iii) patients with serious complications; (vi) patients with other active cancer; and (v) patients with a history of severe allergy.

'Drug-resistant cases' in this study means those patients who met the following criteria: (i) patients to whom this treatment will be given as the first induction chemotherapy after relapse (relapsed cases) and (ii) patients who showed no response in the previous chemotherapy (refractory cases).

Methods

Administration and dosage was based on the results of the pilot phase II preliminary study.[13] AML patients were treated by administering KRN8602, 15 mg/m^2 bolus i.v. for five consecutive days, and AraC, 100 mg/m^2 by 24 h i.v. continuous infusion for seven consecutive days. ALL patients were treated by administering KRN8602, 15 mg/m^2 bolus i.v. for five consecutive days, VCR, 1.4 mg/m^2 i.v. push, once weekly (4 times/month), and PSL, 40 mg/m^2 3 h infusion on five consecutive days. Each of these schedules was defined as one course and in principle two courses were administered. If bone marrow suppression was less than expected during the first course (day 5-7), the additional administration of KRN8602 was permitted.

Evaluation criteria

The evaluation scores for acute leukemia were based upon Kimura's criteria,[16] with a complete remission (CR) being defined by normocellular bone marrow containing normal erythroid and granuloid series with less than 5% myeloblasts, accompanied by normal levels of peripheral WBC and platelet counts with no circulating blasts. A partial remission (PR) was defined by a myeloblast reduction in bone marrow to less than half the percentage observed at the initiation of therapy and by a blast reduction in the peripheral WBC to less than 5%.

Acute and subacute toxicities were graded according to adverse drug reaction criteria[17] by the Japan Society of Cancer Therapy, which are almost the same as the WHO toxicity criteria.

The final evaluation was made by the evaluation committee.

P-gp analysis

Bone marrow or peripheral blood was collected from patients before the start of the administration and the level of P-gp expression was determined by the MACS method[18] at Kirin Brewery Co., Ltd Pharmaceutical Research Laboratory.

Results

Patients

A total of five out of the 79 patients who were enrolled in the study (AML: 46; ALL: 33) were judged to be ineligible. The reasons for the ineligibility were: no drug administration in one AML case, inadequate interval from the prior therapy in two ALL cases and two early deaths (leukemia death on day 4; AML 1, ALL 1). The evaluations of efficacy and toxicity were conducted on a total of 74 patients, 44 with AML and 30 with ALL.

Efficacy (Tables 1 and 2).

AML. The results in the 44 AML cases were CR in 16 cases and PR in seven cases, and thus the CR rate was 36.4% and the overall response rate (CR+PR rate) was 52.3%. Among the 29 relapsed cases, a CR was obtained in 15 cases (51.7%) and a PR in five cases, with an overall response rate of 68.9%. By contrast, in the 15 refractory cases, there was one CR (6.7%) and two PRs with an overall response rate of 20.0%, and thus higher CR and the overall response rates were obtained in the relapsed cases.

ALL. One case was excluded from the efficacy evaluation because a bone marrow examination was not performed after administration. The results in the 29 ALL cases were CR in seven cases and PR in eight cases, and thus the CR rate was 24.1% and the overall response rate was 51.7%. Among the 16 relapsed cases, a CR was obtained in six cases (37.5%) and a PR in six cases, with an overall response rate of 75.0%. By contrast, in the 13 refractory cases, there was a CR in one case (7.7%) and a PR in two cases, with an overall response rate of 23.1%, and thus higher CR and overall response rates were obtained in the relapsed cases of ALL as well.

Table 1. Therapeutic responses

	n	Response				
		CR	PR	NR	CR(%)	CR+PR(%)
AML	44	16	7	21	36.4	52.3
Relapse	29	15	5	9	51.7	68.9
first relapse	26	14	5	7	53.8	73.1
second relapse	3	1		2	33.3	33.3
Refractory	15	1	2	12	6.7	20.0
ALL[a]	29	7	8	14	24.1	51.7
Relapse	16	6	6	4	37.5	75.0
first relapse	15	6	5	4	40.0	73.3
second relapse	1		1		0	100.0
Refractory	13	1	2	10	7.7	23.1

[a]Except one patient not evaluable.

Table 2. Patient characteristics and therapeutic responses

	AML (*n*=44)				ALL (*n*=29)			
	Total	CR	PR	NR	Total	CR	PR	NR
No. of patients	44	16	7	21	29	7	8	14
Age								
15–29	6	0	3	3	8	3	2	3
30–44	20	7	2	11	9	3	3	3
45–60	18	9	2	7	12	1	3	7
Sex								
male	25	8	4	13	16	2	5	9
female	19	8	3	8	13	5	3	5
PS								
0	21	10	4	7	10	3	3	4
1	16	5	2	9	10	3	3	4
2	7	1	1	5	9	1	2	6
FAB classification								
M0	4	2	0	2				
M1	7	1	2	4				
M2	15	8	1	6				
M3	1	0	0	1				
M4	11	4	3	4				
M5a	5	1	1	3				
M5b	1			1				
L1					7	1	2	4
L2					22	6	6	10
Dose of anthracyclines (DNR conversion[a]) (mg/body)								
1–200	0	0	0	0	3	1	1	1
201–550	11	3	2	6	15	5	3	7
551–1000	27	12	5	10	7	0	2	5
>1001	6	1	0	5	4	1	2	1

[a]DNR 25 mg/kg is equal to adriamycin 500 mg/m^2, acrarubicin 600 mg/body, pirarubicin 500 mg/m^2, epirubicin 900 mg/m^2 and mitxantrone 160 mg/m^2.

Table 3. Non-hematologic toxicity

Symptom	AML							ALL						
	Grade				Total	Incidence (%)		Grade				Total	Incidence (%)	
	1	2	3	4		Grade 1–4	Grade 3, 4	1	2	3	4		Grade 1–4	Grade 3, 4
Nausea/vomiting	6	7	29	–	42/44	95.5	65.9	2	5	17	–	24/30	80.0	56.7
Anorexia	3	11	28	–	42/44	95.5	63.6	2	7	16	–	25/30	83.3	53.3
Diarrhea	6	5	5	1	17/44	38.6	2.3	2	4	3		9/30	30.0	10.0
Stomatitis	8	5	1		14/44	31.8	2.3	2	3			5/30	16.7	
Alopecia	5	10	5		20/44	45.5	11.4	5	4	3	–	12/30	40.0	10.0
Cutaneous	10	3	2		15/44	34.1	4.5	2			–	2/30	6.7	
Pain	3	2			5/44	11.4		2				2/30	6.7	
Fever	2	21	13		36/44	81.8	29.5	3	10	7		20/30	66.7	23.3
Infection	7	8	1	4	29/44	65.9	11.4	6	6	6	2	20/30	66.7	26.7
Abscess surrounding tonsilla					1/44	2.3								
Cardiotoxicity		1			2/33[b]	6.1		1	2			3/22	13.6	
General malaise		1			1/44	2.3			2	1		3/30	10.0	3.3
Central nervous toxicity[a]	2		1	1	4/44	9.1	4.5	2		2	2	9/30	30.0	13.3
Peripheral neuropathy								1	2			3/30	10.0	

[a]Includes depressed state in three cases (two cases in grade 1 and one case in grade 3) for AML and one case (grade 3) for ALL, coma might be caused by brain hemorrhage; (grade 4) on one case for AML, ischuria in one case for ALL (not graded), mesentery numbness (grade 4) in two cases for ALL, cacosima (grade 1) in one case for ALL, dysgeusia (grade 1) in one case for ALL, lethargy–mental disorder–seizure (grade 3) in one case for ALL, disorientation (not graded) in one case for ALL and dyscaluculia (not graded) in one case for ALL.
[b]Not graded in one case.

Toxicity

The summary of toxicities is shown in Table 3. Gastrointestinal symptoms were frequently observed in both AML and ALL. Nausea/vomiting occurred in 42 (95.5%) of the 44 AML cases and in 24 (80.0%) of the 30 ALL cases, anorexia occurred in 42 (95.5%) of the AML cases and 25 (83.3%) of the ALL cases, diarrhea in 17 (38.6%) of the AML cases and nine (30.0%) of the ALL cases, and stomatitis in 14 (31.8%) of the AML cases and five (16.7%) of the ALL cases. As for other major toxicities: alopecia was observed in 20 AML patients (45.5%) and 12 ALL patients (40.0%), and cutaneous symptoms including erythema and rash were observed in 15 AML patients (34.1%). In the AML patients, there were two cases (4.5%) of central nervous system disorders and coma in one case (2.3% each). In the ALL patients, there were three cases of peripheral neuropathy (10.0%), and one case each of various central nervous toxicities including depressed state, ischuria, cacosmia, dysgeusia, lethargy/mental disorder/seizure, disorientation and dyscaluculia. Cardiotoxicity was observed in 6.1% (two of 33) of the AML cases and 13.6% (three of 22) of the ALL cases.

Clinical laboratory studies showed a high rate of reversible and transient liver dysfunction in 63.6% for AML and 66.7% for ALL, but none of the abnormal findings were particularly serious. Renal dysfunction was mild; evelation of serum creatinine was 4.5% in AML and 3.3% in ALL. Mild ECG abnormality was observed in only two patients (6.1%) with AML.

Results of P-gp determinations

P-gp was determined in the cases in which it was possible to collect peripheral blood or bone marrow specimens before the start of treatment. The cutoff value was set to 10% on the basis of P-gp expression levels in healthy subjects. Values of 10% or more above the cutoff value were judged to be P-gp-positive and correlations were examined with the results of clinical efficacy (Table 4). There were no differences between the P-gp-positive rate in the relapsed cases and the refractory cases in either AML or ALL. There were no significant differences in CR rates or the overall response rates between the P-gp-positive cases and the P-gp-negative cases in any of the groups.

Discussion

KRN8602 is a novel anthracycline compound developed for the purpose of overcoming the resistance and reducing such adverse reactions as cardiotoxicity that had become a problem in treatment with anthracycline drugs including ADM. In preclinical studies, it was observed that KRN8602 was highly effective against multidrug-resistant P388 or K562 cells *in vitro* and *in vivo*. The lack of cross-resistance to pleiotropic drug-resistant tumor cells may be explained by the fact that drug efflux via P-gp is not rate limiting for KRN8602 as it is for ADM, because of the very rapid accumulation in the cells due to its high lipophilicity.[19] Moreover, in a study in rabbits, KRN8602 showed milder cardiotoxicity than ADM.[20] In addition, KRN8602 has been reported to pass through the blood-brain barrier (BBB) and penetrate into the brain due to its high lipophilicity.[21]

In the present study, we evaluated the efficacy and toxicity of KRN8602 in AML patients in combination with AraC, and in ALL patients in combination with VCR and PSL as induction chemotherapy for relapsed or refractory acute leukemia. In combination therapy with AraC in refractory cases, idarubicin and mitoxantrone yielded a CR rate of 60%[22] and 48%,[23] respectively. The CR rate of 51.7% of KRN8602 obtained in relapsed AML in the present study was compared favorably with those of these pre-existing drugs. KRN8602 is a novel drug and has been expected to overcome the cross-resistance based on

Table 4. Relationship between P-gp and clinical effect

		P-gp	*n*	CR	(%)	PR	(CR+PR%)	NR	Wilcoxon two-sample test
AML	relapse	positive	9	4	(44.4%)	0	(44.4%)	5	$p=0.962$
		negative	9	2	(22.2%)	4	(66.7%)	3	
	refractory	positive	4	1	(25.0%)	0	(25.0%)	3	$p=0.453$
		negative	4	0		0		4	
ALL	relapse	positive	5	2	(40.0%)	1	(60.0%)	2	$p=0.744$
		negative	3	2	(66.7%)	0	(66.7%)	1	
	refractory	positive	3	0		1	(33.3%)	2	$p=0.414$
		negative	4	0		3	(75.0%)	1	

the results of preclinical studies. The results of the present study confirmed this effect clinically, as well.

As a means of assessing the effect of KRN8602 on multidrug resistance, P-gp was determined in some of the cases in this study. An association between P-gp expression and clinical effect was investigated. There are reports that the P-gp-positive rate is higher in the relapsed and refractory cases,[24] and that the response rate is lower for P-gp-positive patients than P-gp-negative patients.[25] However, there is also a report denying any association between P-gp expression and therapeutic effects.[26] The results of P-gp in the present study confirmed the latter results, i.e. that the clinical effect is not associated with P-gp expression. However, it was noteworthy that against some P-gp-positive cases, KRN8602-containing regimens were clinically effective and could induce CRs.

In this study, there was one AML patient and one ALL patient with serious adverse reactions, i.e. an AML patient with coma and an ALL patient with serious psychoneurological symptoms, including lethargy, mental disorder and seizure. Since the AML patient had a cerebral hemorrhage due to the infection, the relationship between the coma and KRN8602 was unclear. The ALL patient had received high-dose prior chemotherapy, including methotrexate. The influence of this prior chemotherapy could not be ruled out, and although the relationship between KRN8602 and the neurotoxicity was also unclear, it might be related to the fact that KRN8602 can cross the BBB. The incidence of peripheral neurophathy tended to be higher in ALL. Since similar toxicity has been reported for VCR which was the combination drug for ALL, this peripheral neuropathy seems to have a strong relationship with VCR.

In conclusion, KRN8602 was found to overcome drug resistance clinically, as suspected based on the preclinical studies. Since response rates comparable to those reported with idarubicin and mitoxantrone were obtained, KRN8602 is expected to be an effective novel anthracycline for the treatment of relapsed and refractory acute leukemia.

References

1. Wiernik PH, Banks PL, Case DC, *et al.* Cytarabine plus idarubicin or daunorubicin as induction and consolidation therapy for prerviously untreated adult patients with acute myeloid leukemia. *Blood* 1992; **79**: 313-9.
2. Vogler WR, Velez-Garcia E, Weiner RS, *et al.* A phase III trial comparing idarubicin and daunorubicin in combination with cytarabine in myelogenous leukemia: a Southeastern Cancer Study Group. *J Clin Oncol* 1992; **10**: 1103-11.
3. Berman E, Heller G, Santorsa J, *et al.* Results of a randomized trial comparing idarubicin and cytosine arabinoside with daunorubicin and cytosine arabinoside in adult patients with newly diagnosed acute myelogenous leukemia. *Blood* 1991; **77**: 1666-74.
4. Mandelli F, Petti MC, Ardia A, *et al.* A randomized clinical trial comparing idarubicin and cytarabine to daunorubicin and cytarabine in the treatment of acute non-lymphoid leukemia. *Eur J Cancer* 1991; **27**: 750-5.
5. Arlin Z, Case DC, Moore J, *et al.* Randomized multicenter trial of cytosine arabinoside with mitoxantrone or daunorubicin in previously untreated adult patients with acute nonlymphocytic leukemia (ANLL): Lederle Cooperative Group. *Leukemia* 1990; **4**: 177-83.
6. Hoelzer D, Thiel E, Loffler H, *et al.* Prognostic factors in a muticenter study for treatment of acute lymphoblastic leukemia in adults. *Blood* 1988; **71**: 123-31.
7. Linker CA, Levitt LJ, O'Donnell M, *et al.* Treatment of adult acute lymphoblastic leukemia with intensive cyclical chemotherapy: a follow-up report. *Blood* 1991; **78**: 2814-22.
8. Larson RA, Dodge RK, Burns CP, *et al.* A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: Cancer and Leukemia Group B study 8811. *Blood* 1995; **85**: 2025-37.
9. Komeshima N, Nakajima S, Kawai H, *et al.* New morpholino anthracyclines, MX, MX2, and MY5. *J Antibiot* 1987; **40**: 1058-61.
10. Komeshima N, Tsuruo T and Umezawa H. Antitumor activity of new morpholino anthracyclines. *J Antibiot* 1988; **41**: 548-53.
11. Watanabe M, Komeshima N, Nakajima S, *et al.* MX2, a morpholino anthracycline, as a new antitumor agent against drug-sensitive and mutidrug-registant human and murine tumor cells. *Cancer Res* 1988; **48**: 6653-7.
12. Takemoto Y, Ogawa M, *et al.* Early phase II study of KRN8602(MX2), a novel anthracycline derivative, for acute leukemia. *Jpn J Cancer Chemother* 1998; **25**: in press.
13. Hiraoka A, Ogawa M, *et al.* Pilot late phase II study of KRN8602 (MX2), a novel anthracycline derivative, for acute leukemia—a dose finding study in combination therapy. *Jpn J Cancer Chemother* 1998; **25**: in press.
14. Campos L, Guyotat D, Archimbaud E, *et al.* Clinical significance of multidrug resistance P-glycoprotein expression on acute nonlymphoblastic leukemia cells at diagnosis. *Blood* 1992; **79**: 473-6.
15. Pirker R, Wallner J, Geissler K, *et al.* MDR1 gene expression and treatment outcome in acute myeloid leukemia. *J Natl Cancer Inst* 1991; **83**: 708-12.
16. Kimura K. Chemotherapy of acute leukemia with special reference to criteria for evaluation of therapeutic effect. In: *Proc Advances in Chemotherapy of Acute Leukemia.* A seminar on chemotherapy of acute leukemia under the US-Japan Cooperative Science Program, Bethesda, MD 1965: 21.
17. The response criteria for solid tumor with chemotherapy by Japan Society of Cancer Chemotherapy (in Japanese). *J Jpn Soc Cancer Ther* 1986; **21**: 929-53.

18. Okochi E, Iwahashi T, Ariyoshi K, Watabe H, Tsuruo T, Ono K.. Establishment and evaluation of MRK16-magnetic cell sorting assays for detectiong low expression of multidrug resistance P-glycoprotein using human leukemia cell lines and peripheral blood cells from healthy donors. *J Immunol Methods* 1995; **187**: 127–37.
19. Watanabe M, Komeshima N, Naito M, *et al.* Celllular pharmacology of MX2, a new morpholino anthracycline, in human pleiotropic drug-resistant cells. *Cancer Res* 1991; **51**: 157–61.
20. Sato Y, Eddy L, Hochstein P. Comparative cardiotoxicity of doxorubicin and a morpholino anthracycline derivative (KRN8602). *Biochem Pharmacol* 1991; **42**: 2283–7.
21. Yamamoto H, Arita N, Ohnishi T, *et al.* Pharmacokinetics of MX2, a new morpholino anthracycline, in CSF following intravenous injection. *Jpn J Cancer Chemother* 1993; **20**: 1227–30.
22. Harousseau JL, Reiffers J, Hurteloup P, *et al.* Treatment of relapsed acute myeloid leukemia with idarubicin and intermediate-dose cytarabine. *J Clin Oncol* 1989; **7**: 45–9.
23. Hiddemann W, Aul C, Maschmeyer G, *et al.* High-dose versus intermediate dose cytosine arabinoside combined with mitoxantrone for the treatment of relapsed and refractory acute myeloid leukemia: results of an age adjusted randomized comparison. *Leuk Lymph* 1993; **10**: 133–7.
24. Michieli M, Damiani D, Geromin A, *et al.* Overexpression of mutidrug resitance-associated p170-glycoprotein in acute non-lymphocytic leukemia. *Eur J Haematol* 1992; **48**: 87–92.
25. Campos D, Guyotat E, Archimboud E, *et al.* Clinical significance of multidrug resistance P-glycoprotein expression on acute nonlymphoblastic leukemia cells at diagnosis. *Blood* 1992; **79**: 473–6.
26. Ino H, Miyazaki M, Isogai M, *et al.* Expression resistance (*mdr1*) gene expression in adult acute leukemias: correlations with treatment outcome and *in vitro* drug sensitivity. *Leukemia* 1994; **8**: 1492–7.

(Received 13 October 1998; revised form accepted 19 November 1998)