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Phase II study of KRN8602, 3′-deamino-3′-morpholino-13-deoxo-10-hydroxycarminomycin hydrochloride, MX2 · HCl in patients with metastatic breast cancer

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Abstract *Purpose*: KRN8602 (3′-deamino-3′-morpholino-13-deoxo-10-hydroxycarminomycin hydrochloride, MX2 · HCl) is a newly developed anthracycline that has been found to be effective against multidrug-resistant tumor cells in vitro and in vivo. In order to clinically confirm these promising preclinical observations, we performed a phase II trial of KRN8602 in patients with anthracycline-resistant metastatic breast cancer. *Methods*: Of 41 patients registered with metastatic breast cancer, 37 were eligible and were given at least two cycles of KRN8602 15 mg/m^2 per day at 3–4 week intervals by intravenous bolus injection on days 1, 2, and 3. *Results*: Of the 37 patients, 6 (16.2%, with a 95% confidence interval of 4.3–28.1%) had a partial response (PR). No complete responses (CRs) were observed. The difference between response rates according to prior history of anthracycline administration was not significant. Myelosuppression was moderately severe, with grade 3 or 4 leukopenia occurring in 65%. Severe nausea/vomiting was observed in 44% of the patients. *Conclusions*: The results indicate that KRN8602 has modest activity in refractory metastatic breast cancer and is associated with relatively severe toxicity. Furthermore, the preclinical finding that KRN8602 overcomes anthracycline resistance was not reliably reproduced in this clinical phase II trial.

Key words Metastatic breast cancer · Chemotherapy · Anthracyclines · KRN8602 (MX2) · Phase II trial

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Introduction

KRN8602 (3′-deamino-3′-morpholino-13-deoxo-10-hydroxycarminomycin hydrochloride, MX2 · HCl) is a new morpholino-anthracycline that has been shown to have a marked effect on pleiotropic drug-resistant tumor cells [4, 8, 17, 19]. In preclinical studies, KRN8602 has been shown to be almost equally effective against murine P388 leukemia and sublines resistant to doxorubicin (P388/ADM) in vitro, and to show higher antitumor activity against P388/ADM in vivo than doxorubicin [10, 19]. The intracellular concentration of KRN8602 increases more rapidly than that of doxorubicin, and this phenomenon may be one of the reasons why KRN8602 circumvents pleiotropic drug resistance [6, 7].

Phase I clinical trials have been performed using two different schedules: a single-dose schedule and a 3-day administration schedule [15, 18]. The dose-limiting toxicities of KRN8602 are leukopenia and nausea/vomiting. The maximum tolerated dose was determined to be 40 mg/m^2 on the 1-day schedule and 18 mg/m^2 on the 3-day schedule. The side effects were reported to be tolerable; however, severe nausea and vomiting were frequently observed. According to a preliminary phase II trial in patients with refractory metastatic breast cancer [20], the response rate with the 3-day schedule is

higher (25%, two of eight patients) than with the 1-day schedule (17%, 2 of 12 patients). Therefore, we adopted the 3-day treatment schedule for this phase II trial.

We report here the results of a multi-institutional phase II trial of KRN8602 administered by the 3-day schedule to 37 women with metastatic breast cancer. All but one patients had a prior history of treatment with at least one chemotherapeutic regimen.

Patients and methods

In August 1992, we initiated this phase II study for the treatment of metastatic breast cancer at the participating institutions listed in Appendix A. All patients had been histologically confirmed to have metastatic breast cancer with measurable or assessable disease. Previous adjuvant chemotherapy or hormonal therapy was also acceptable. Patients who had received previous anthracyclines were eligible, as long as the total anthracycline dose was less than 300 mg/m^2. A 4-week interval was required between prior systemic therapy and the start of the first course of KRN8602. Additional eligibility criteria included: age 15 to 74 years, Eastern Cooperative Oncology Group (ECOG) performance status 0 to 3, life expectancy of at least 8 weeks, WBC count $\geqslant$4000/μl, platelet count $\geqslant$100 000/μl, hemoglobin $\geqslant$10 g/dl, serum bilirubin level $\leqslant$1.5 mg/dl, serum creatinine concentration $\leqslant$1.5 mg/dl, serum aminotransferases not more than twice the upper limit of normal, and normal ECG. Women who were pregnant or lactating were ineligible.

All patients gave their informed consent before participating in this study, which was approved by the institutional review boards of the participating institutions. All patients received KRN8602 15 mg/m^2 as an intravenous bolus on days 1, 2, and 3 every 3–4 weeks until disease progression occurred. Subsequent courses were started if the WBC count exceeded 3000/μl. Patients, who developed grade 4 leukocytopenia or neutropenia, were given 80% doses (12 mg/m^2) during the subsequent courses.

Patients were evaluated for response following two courses of therapy. Tumor response criteria were as follows. Complete response (CR) was defined as the complete disappearance of all known disease for a minimum of 4 weeks, with no development of new disease. Partial response (PR) was defined as a $\geqslant$50% reduction in the sum of the products of measurable lesions. Progressive disease (PD) was defined as a $\geqslant$25% increase in the sum of the products of all indicator lesions, or reappearance of any lesion that had disappeared, or appearance of any new lesion. No change (NC) was defined as any situation that did not qualify as response or progression. All responses were strictly judged by extramural review. The Japan Society for Cancer Therapy (JSCT) criteria, which are similar to the WHO criteria, were used to evaluate toxicities.

Results

Between August 1992 and August 1994, 41 patients with metastatic breast cancer were registered at 19 institutions. Of these 41 patients, 37 were eligible, and 4 were excluded. The reasons for ineligibility were: no evaluable or measurable lesions ($n = 1$), an unacceptably brief interval since prior therapy ($n = 2$), and unconfirmed pathologic findings of breast cancer ($n = 1$). Patient characteristics are listed in Table 1. The median age was 54 years; two-thirds of the patients were postmenopausal. Of the 37 patients, 18 (49%) had metastases at one or more visceral sites, 36 (97%) had received prior chemotherapy, and 26 (72%) had received anthracyclines.

Table 1 Patient characteristics ($n = 37$)

Characteristic		No. of patients	%
Age (years)			
Median	54		
Range	36–71		
Performance status			
0		24	65
1		8	22
2		4	11
3		1	3
Menopausal status			
Pre-		13	35
Post-		24	65
Estrogen receptor			
Positive		14	38
Negative		18	49
Unknown		5	14
Progesterone receptor			
Positive		8	22
Negative		15	41
Unknown		14	38
Site of metastasis			
Visceral		18	49
Nonvisceral		19	51
Adjuvant chemotherapy			
No		28	76
Yes		9	24
Prior chemotherapy			
No		14	38
Yes		22	59
Prior anthracyclines			
No		10	27
Yes		26	70

All 37 patients were evaluated for response and toxicity. Six of the 37 patients (16.2%, with a 95% confidence interval of 4.3–28.1%) had an objective response to therapy (CR, $n = 0$; PR, $n = 6$). The response rates in various subgroups of patients are listed in Table 2. There were no significant differences in response rates according to prior anthracycline treatment.

Myelosuppression was the most common toxicity with this regimen (Table 3). Grade 3 or 4 leukopenia occurred in 24 patients (65%). Grade 3 or 4 thrombocytopenia and anemia were observed in 24% and 19% of patients, respectively. Major nonhematologic toxicity was nausea/vomiting (grade 3/4, 43%). Alopecia was very rare. Grade 3 stomatitis was observed in one patient. No cardiac toxicity or ECG abnormalities were observed.

Discussion

The anthracyclines have been considered to be the most active agents for the treatment of metastatic breast cancer [5]. When doxorubicin is used as a single agent in

Table 2 Response to treatment (*CR* complete response, *PR* partial response, *NC* no change, *PD* progressive disease, *NE* not evaluable)

Patient group	CR	PR	NC	PD	NE	Overall (CR + PR) response rate (%)
Entire group (n = 37)	0	6	10	18	3	16.2
Prior chemotherapy (n = 36)	0	6	10	18	2	16.7
Prior anthracyclines (n = 26)	0	4	6	14	2	15.4
No prior anthracyclines (n = 10)	0	2	4	4	0	20

untreated patients with metastatic breast cancer, the response rate range is 40–50% [2, 16]. Although combination regimens with doxorubicin increase response rate and survival compared with non-doxorubicin-containing regimens [1], adverse reactions, including cardiotoxicity, mucositis, alopecia, and bone marrow suppression occur frequently.

KRN8602 is a newly developed anthracycline that has been found to be effective against doxorubicin-resistant tumor cell lines in vitro [8, 17] and in vivo [9, 19]. The cardiotoxicity of KRN8602 has been found not to be cumulative and to be lower than that of doxorubicin in a preclinical study [12]. In this phase II study, 6 of the 37 eligible patients (16.2%) had an objective response to therapy. The objective response was 15.4% in the patients treated with anthracyclines previously and 20.0% in the patients not treated with anthracyclines previously. The difference according to prior history of anthracycline treatment was not significant. These results suggest that the outcomes observed in vitro and in vivo in the preclinical study were not reliably reproduced in this clinical situation.

Response rates ranging from 17% to 22% have been reported for mitoxantrone, one of the anthracyclines/anthraquinones, when used as a single agent in previously treated metastatic breast cancer patients [13, 14]. Epirubicin's single agent response rate is comparable to that of doxorubicin, ranging from 25% in previously treated patients to 62% in untreated patients [11]. The response rate to KRN8602 is somewhat lower than obtained with these anthracyclines in similar cases of metastatic breast cancer. In the present study, we consider that reasonable doses were given to the patients, because most patients had grade 3 or 4 leukopenia. Therefore, the results of our study indicate that KRN8602 had only limited activity. In the phase I studies, two different administration schedules, a 1-day schedule [18] and a 3-day schedule [15], were adopted. We assessed only 3-day administration schedule in this phase II study. It might be necessary to assess the 1-day schedule in a further phase II study.

The major objective of clinical trials of KRN8602 is to assess its potential to overcome multidrug resistance, that had been demonstrated in the preclinical studies. However, the present clinical phase II study showed only modest activity in doxorubicin-resistant patients. Therefore, there may be partial cross-resistance between doxorubicin and KRN8602 in clinical situations. Many new active agents are available for the treatment of metastatic breast cancer. Recently, paclitaxel and docetaxel have become widely used as effective agents in anthracycline-resistant patients [3]. Promising newer drugs include the camptothecins and vinorelbine. Therefore, at the present time it is not recommended that KRN8602 be included in the strategy of treatment for metastatic breast cancer.

Table 3 Treatment-related toxicity (n = 37)

Toxicity	Toxicity grade				Grade 3–4 (%)
	1	2	3	4	
Hematologic					
Leukopenia	3	8	12	12	65
Thrombocytopenia	3	5	3	6	24
Anemia	6	4	6	1	19
Other toxicity					
Nausea/vomiting	4	16	16	–	43
Alopecia	10	3	1	–	3
Mucositis	4	1	1	0	3
Diarrhea	3	0	1	0	3
Elevated AST	12	6	1	0	3
Elevated ALT	15	4	0	0	0
Elevated bilirubin	2	1	0	0	0

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Appendix A

Participating institutions and names of the chief investigators: National Sapporo Hospital, Masami Ogita; Tohoku University, School of Medicine, Syozou Mori; Fukushima Medical College, Rikiya Abe; Gunma University, School of Medicine, Yasuo Morishita; Saitama Cancer Center, Toshio Tabei; Tokyo Women's Medical College Daini Hospital, Syunsuke Haga; Keio University, School of Medicine, Masaki Kitajima; Tokyo Medical College, Kousaburou Kimura; Kitasato Institute Hospital, Eiji Kawamura; St. Marianna University School of Medicine, Kenji Katayama; Hamamatsu Medical Center, Kazuhiro Kanda; National Nagoya Hospital, Hideaki Aoyama; Center for Adult Disease, Osaka, Hiroki Koyama; Research Institute for Nuclear Medicine and Biology, Hiroshima University, Tetsuya Toge; Tokushima University, School of Medicine, Yasumasa Monden; Shikoku Cancer Center Hospital, Shigemitsu Takashima; Miyazaki Prefectural Hospital, Kazuo Tamura.

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