Phase I and Pharmacokinetic Study of KRN5500, a Spicamycin Derivative, for Patients with Advanced Solid Tumors

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Background: KRN5500, a novel spicamycin derivative, shows an inhibitory effect on protein synthesis. This phase I study was aimed at investigating the toxicity, maximum tolerated dose (MTD) and pharmacokinetics of this compound.

Patients and methods: Patients with solid tumors not amenable to standard forms of treatment were eligible. KRN5500 was administered as a 2 h intravenous infusion every 4 weeks at doses of 3, 6, 10, 15 and 21 mg/m². Pharmacokinetic evaluation was performed at the first cycle.

Results: Eighteen patients with advanced solid tumors were enrolled. A total of 26 cycles of KRN5500 were administered. The major toxicities were nausea, vomiting, diarrhea, fatigue and a mild reversible prolongation of prothrombin time. Grade 4 pulmonary toxicity (interstitial pneumonitis) was observed in one patient at a dose level of 15 mg/m². Severe fatigue was observed in one patient at a dose level of 21 mg/m² and the duration of fatigue tended to increase with the dose of KRN5500. Nausea and vomiting were frequently observed and became prolonged with increasing dose of KRN5500. These toxicity profiles were identified as unacceptable and further dose escalation above 21 mg/m² was withheld. The MTD was therefore determined as 21 mg/m².

Conclusion: KRN5500, a structurally novel protein synthesis inhibitor, warrants further investigation to overcome these toxicity profiles and improve its efficacy.

Key words: fatigue – KRN5500 – phase I study – protein synthesis inhibitor – pulmonary toxicity

INTRODUCTION

Spicamycin, originally described as a mixture of a unique nucleotide-like component derived from Streptomyces alanosinicus 879-MT3, reportedly induces cell differentiation in human promyelocytic leukemia cells (HL60) and M1 myeloid leukemia cells (1,2). This compound is composed of a long-chain fatty acid, glycine, aminohexose and adenine and appears to be from a family of unusual nucleotides with a variety of fatty acids. The derivatives show potent antitumor activity against MX-1 human breast cancer and SC-9 human stomach cancer in human tumor xenograft models (3).

Subsequent studies were conducted to increase the therapeutic effects of spicamycin analogues, during which time KRN5500, 6-[4-deoxy-4-(2E,4E)-tetradecadienoylglycyl]-L-glycero-L-mannoheptopyranosylamino-9H-purine, was semi-synthetized. The structure of KRN5500 is different from those of any other existing anticancer drugs in that it consists of spicamycin amino nucleotide (L-mannoheptopyranosylamine 9H-purine; Fig. 1, SAN), glycine and 2,4-tetradecadienoyl acid moieties.

KRN5500 itself is incorporated into tumor cells where it is converted to an active metabolite, ‘SAN-Gly’, by an unknown intracellular enzyme which is presumed to be an acyl amide hydrolase. The active metabolite exhibits an inhibitory effect on protein synthesis (4). In several in vitro studies, KRN5500 showed inhibitory activities against P388 leukemia, U937 lymphoma, HT29 colon, LS-174T colon, LS-180 colon, COLO205...
colon, WiDr colon and SC-6 stomach cancer cells, with a 50% inhibitory concentration (IC\textsubscript{50}) ranging from 0.31 to 61 nM (4). Furthermore, KRN5500 showed marked effects against gastrointestinal (10 stomach, 14 colon and two esophagus) and lung (six) cancers in human tumor xenograft models, which were superior to mitomycin C (MMC) and cisplatin (4). In P388 leukemia cells, the IC\textsubscript{50} decreased with increasing exposure time to KRN5500, suggesting that the antitumor effect of KRN5500 is exerted in an area under the concentration–time curve (AUC)-dependent manner.

On the basis of this preclinical evidence, we conducted a phase I study of KRN5500 administered as a 2 h intravenous infusion every 4 weeks for patients with advanced solid tumors such as gastric, colorectal and lung cancers. The 2 h intravenous infusion was chosen because of the unexpected and potential safety concerns with the high basicity (pH 10–11) of the drug solution, which was caused by the organic solvents used for the drug formulation. The objectives of this study were as follows: (1) to determine the maximum tolerated dose (MTD), (2) to identify the toxicity profiles including the dose-limiting toxicity (DLT), (3) to characterize the pharmacokinetic (PK) profiles and (4) to observe any antitumor activities.

PATIENTS AND METHODS

ELIGIBILITY

Eligible patients were with histologically or cytologically confirmed gastric, colorectal or lung cancers who were refractory to standard therapy or for whom there was no effective therapy. Eligibility criteria included the following: age between 20 and 74 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, life expectancy of >2 months, adequate organ function (WBC count ≥4000/μl, platelet count ≥100 000/μl, serum total protein (TP) ≥6.3 g/dl, serum total bilirubin (T.bil) ≤1.5 mg/dl, aspartate amino transferase (AST) and alanine amino transferase (ALT) levels less than two times upper standard limits, serum creatinine (Cr.) ≤1.5 mg/dl, creatinine clearance (Cr.c) ≥50 ml/min and arterial oxygen pressure (PaO\textsubscript{2}) ≥70 Torr), normal coagulation tests [i.e. normal prothrombin (PT) and activated partial thromboplastin time (APTT), fibrinogen ≥200 mg/dl] and normal ECG. At least 4 weeks must have elapsed since the completion of previous therapy. Also patients must have recovered from the toxic effects of previous therapy. Exclusion criteria included the following: pregnancy, lactation, hepatitis B or C virus infection, human immunodeficiency virus or human T-cell leukemia virus type I infection, a history of hypersensitivity reactions to any drugs, prior radiotherapy to the pelvis, brain metastasis, pleural effusion and ascites that required drainage, serious pre-existing medical conditions such as uncontrolled infections, severe heart disease, uncontrolled diabetes, gastrointestinal hemorrhage, watery diarrhea, ileus, psychogenic disorders and active concurrent primary malignancies.

Written informed consent was obtained from all patients. This study was approved by the institutional review board at the National Cancer Center and conducted in accordance with the Japanese Good Clinical Practice (GCP) guidelines.

PRETREATMENT ASSESSMENT AND FOLLOW-UP STUDIES

Complete clinical assessments including physical examination, ECOG PS, blood pressure, weight, ECG, chest X-ray and routine laboratory tests were performed for all patients before the study entry and prior to each subsequent treatment cycle. Routine laboratory tests included a complete blood count and differential testing of electrolytes, urea nitrogen, Cr., TP, albumin, glucose, cholesterol, triglycerides, alkaline phosphatase, T.bil, AST, ALT, lactate dehydrogenase, \( \gamma \)-glutamyl transferase, cholinesterase, PaO\textsubscript{2}, tumor markers, PT, APTT, fibrinogen, fibrinogen degradation products, urinalysis and Ccr. Except for the PaO\textsubscript{2}, tumor marker and Ccr testing, these laboratory studies were repeated on the days 2, 4, 7 and 10 and then weekly. Tumor markers were obtained biweekly and PaO\textsubscript{2} and

![Figure 1. Structures of KRN5500, SAN-Gly, SAN and spicamycin.](https://academic.oup.com/jjco/article-abstract/33/6/302/905271)}
Ccr. were measured before each treatment cycle. Toxicities were evaluated by the National Cancer Institute common toxicity criteria (NCI-CTC). Tumor responses were evaluated according to the WHO criteria and through the use of adequate radiological studies (5). A complete response (CR) was defined as the complete disappearance of all disease for at least 4 weeks, with no evidence of new areas of malignant disease. A partial response (PR) was defined as a >50% decrease in the sum of the products of the perpendicular diameters of all measured lesions for at least 4 weeks. Progressive disease (PD) was defined as any increase of >25% in the products of the perpendicular diameters of any measured lesions or the appearance of a new lesion in any imaging studies. Other tumor status was categorized as no change (NC).

**DOSAGE AND DOSE ESCALATION**

The starting dose of KRN5500 was 3.0 mg/m², based on the preclinical toxicity data indicating that one-third of the toxic dose low (TD1/3) in dogs was 3.4 mg/m².

Owing to the extremely low solubility of KRN5500, the LD₉₀ in mice could not be determined and therefore was not applicable for setting the starting dose above. Subsequent dose escalations were 6, 10, 15 and 21 mg/m², according to the modified Fibonacci scheme (6). At least three patients were entered at each dose level. Three additional patients were entered at the same dose if the dose-limiting toxicity (DLT) was observed in one of the initial three patients. The MTD was defined as the dose level at which two out of three to six patients experienced DLT. The definition of DLT was as follows: (1) grade 4 hematological toxicities except for anemia, (2) grade 3 or 4 non-hematological toxicities except for nausea, vomiting, hyperbilirubinemia and alopecia, (3) grade 4 hyperbilirubinemia. Intrapatient dose escalation was not allowed.

**DRUG ADMINISTRATION**

KRN5500 was supplied by the Kirin Brewery (Tokyo, Japan) in 1.5 ml sterile vials. Each vial contained 5.0 mg of KRN5500, 0.05 g of N,N-dimethylacetamide, 0.4 g of propylene glycol, 0.3 g of polysorbate 80 and an adequate volume of ethanol. The vial was reconstituted with 1.0 ml of sterile water containing 0.1 g of monoethanolamine for infusion. The pH of reconstituted KRN5500 ranged from 9.5 to 11.0. The reconstituted solution was diluted in 500 ml of saline just before administration. The calculated dose was administered by 2 h intravenous infusion through a central venous catheter. No prophylactic premedication to reduce emesis was administered at the beginning of the study. However, from the fourth cohort at the dose level of 15 mg/m², 3 mg of granisetron were administered by 30 min intravenous infusion prophylactically (described in the Results section). Treatment was repeated every 4 weeks. In patients receiving the initial cycle of treatment, a subsequent cycle was started after recovery from the toxic effects of the previous cycle. If more than 6 weeks had passed from the previous cycle before recovery from toxicities, then the patient was withdrawn from the study. Patients were taken off the study in cases of disease progression.

**PHARMACOKINETICS**

Pharmacokinetic (PK) evaluation was performed in all patients during the initial cycle of the treatment. Heparinized venous blood samples (4 ml) were taken before infusion and at 30 min and 1 and 2 h just before the end of infusion, and also 5, 15 and 30 min and 1, 2, 4, 6, 8, 12, 24 and 48 h after the infusion. Blood samples were immediately centrifuged at 3000 r.p.m. for 5 min and plasma was aliquoted and stored at –20°C or lower in polyethylene tubes until analysis. Fractionated urine was collected in glass containers from 0 to 4, 4 to 8 and 8 to 12 h and every 12 h until 72 h after administration of KRN5500. The total volume of each fraction was recorded and a 100 ml aliquot was obtained and frozen at –20°C until analysis.

**Table 1. Patients' characteristics**

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Total No. of patients</th>
<th>Male/female</th>
<th>Age (years)</th>
<th>ECOG* performance status</th>
<th>Prior treatment</th>
<th>No. of prior chemotherapy regimens</th>
<th>Sites of metastasis</th>
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<td></td>
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<td>4</td>
<td>3</td>
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</tr>
</tbody>
</table>

*Eastern Cooperative Oncology Group.

No. of patients: 18; Male/female: 10/8; Age (years): Median 53, Range 34–73; ECOG* performance status: 0 5, 1 13; Prior treatment: Surgery 18, Chemotherapy 15, Immunotherapy 1; No. of prior chemotherapy regimens: 0 3, 1 5, 2 5, 3 4, 4 1; Sites of metastasis: Lung 8, Liver 9, Peritoneum 4, Lymph node 9.
The concentrations of KRN5500 in plasma and urine were measured by solid-phase extraction and high-performance liquid chromatography (HPLC) using ultraviolet (UV) absorbance detection according to the previously published method (7). All measurements were performed at Mitsubishi Kagaku Bio-Clinical Laboratories (Tokyo, Japan).

PK parameters were estimated using a non-linear mixed effect model program, NONMEM (version IV, level 2.1; NONMEM Project Group, University of California, San Francisco, CA), with a proportional intra-individual error model. Individual plasma concentration–time data were fitted to a two-compartment PK model with a zero-order infusion input and parameterized in terms of clearance, volume of the central compartment, inter-compartment clearance and volume of distribution at steady-state ($V_{ss}$) using the NONMEM program and PREDPP package (ADVAN3 TRANS3). Fitted parameters permitted the computation of the following PK parameters: half-life ($t_{1/2}$), area under the concentration–time curve (AUC) and systemic clearance (CL).

### RESULTS

#### PATIENTS’ CHARACTERISTICS

Eighteen patients were enrolled in the study. Their characteristics are listed in Table 1. There were 10 males and eight females with good performance status and the median age was 53 years (range, 34–73 years). The predominant type of tumor was colon cancer. All patients had received surgical resection for primary tumors, 15 had received prior chemotherapy and 10 had had more than two modes of prior regimens. A total of 26 cycles (one cycle for 10 patients and two cycles for eight patients) of KRN5500 were administered. One patient, who was diagnosed as non-small cell lung cancer at the time of study entry, was proven to have bladder cancer after the treatment. All patients were included in the toxicity evaluation.

#### TOXICITY

The major toxicities after the first cycle are listed in Table 2. Although only two patients experienced grade 1 and 2 anemia at a dose level of 6 mg/m², hematological toxicities were not observed in the remaining 16 patients.

Non-hematological toxicities consisted of gastrointestinal symptoms (nausea, vomiting and diarrhea), fatigue, hepatotoxicity (hyperbilirubinemia, AST and ALT elevations), PT prolongation and pulmonary toxicity. Nausea and vomiting occurred in 100% and 89% of the patients, respectively. The onset of nausea was within 24 h after KRN5500 treatment and the median duration was 5 days (ranging from 2 to 9 days). The onset of vomiting was within 24 h after KRN5500 treatment and the median duration was 3 days (ranging from 2 to 5 days). Since the supportive treatment consisting of metoclopramide and haloperidol was not effective, 3 mg of granisetron were administered prophylactically from the fourth cohort at a dose level of 15 mg/m². However, the antiemetic effect of granisetron was insufficient. The duration of nausea and vomiting increased significantly with the dose of KRN5500 ($r = 0.678$, $P = 0.002$ for nausea; $r = 0.515$, $P = 0.04$ for vomiting). Diarrhea was generally mild and not dose-related.

Fatigue, the major toxicity related to KRN5500, occurred in 13 (72%) patients. All 13 patients showed some signs of fatigue within 48 h after KRN5500 treatment and the median duration was 6 days (ranging from 2 to 28 days). At a dose level of 21 mg/m², two patients experienced grade 2 fatigue. In one of these two patients, the fatigue lasted for 7 days and was so different in severity from that which other patients experienced at lower dose levels that even parenteral fluid therapy was required for anorexia. This toxicity was considered unacceptable. In the remaining 12 patients, the duration of fatigue increased with the dose of KRN5500. Hyperbilirubinemia and elevations of AST and/or ALT were mild and reversible. PT prolongation occurred on the second day of treatment and recovered within 2–5 days, although the duration seemed to increase with the dose of KRN5500.

Grade 4 pulmonary toxicity was observed in one patient at a dose level of 15 mg/m². This was a case of a 62-year-old male with a PS of 1, who was diagnosed as recurrent non-small cell lung cancer with left malignant pleural effusion. He had received pleural sclerotherapy with talc spray for pleural effusion 6 weeks before the study entry. On the eighth day of KRN5500 treatment, chest X-ray and CT scan showed a

### Table 2. Major toxicities in the first cycle

<table>
<thead>
<tr>
<th>Dose level (mg/m²)</th>
<th>No. of patients</th>
<th>No. of cycles</th>
<th>CTC grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>5</td>
<td>0 3 0 0 3</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>4</td>
<td>0 2 1 0 3</td>
</tr>
<tr>
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<td>3</td>
<td>5</td>
<td>1 1 1 1 2</td>
</tr>
<tr>
<td>15</td>
<td>6</td>
<td>8</td>
<td>2 3 1 1 4</td>
</tr>
<tr>
<td>21</td>
<td>3</td>
<td>4</td>
<td>0 2 1 0 2</td>
</tr>
</tbody>
</table>

*Dose-limiting toxicity.

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ground-glass appearance in the right inferior lobe of the lung suggestive of interstitial pneumonitis. Fever was not observed and the bronchoalveolar lavage fluid did not suggest the presence of any infections such as fungus, Pneumocystis carinii or cytomegalovirus. His respiratory condition was improved transiently by supportive treatment including oxygen inhalation and steroid hormone administration (60 mg/day of prednisone tapered gradually to 20 mg/day). On the 36th day of treatment when he was administered 20 mg/day of prednisone, the ground-glass appearance had almost disappeared and his pulmonary condition had improved so much that oxygen inhalation was stopped. However, on the 43rd day (under 20 mg/day of prednisone administration), he had dyspnea and the ground-glass appearance diffusely recurred in the bilateral lung fields. Although the dose of prednisone was increased to 60 mg/day immediately, his pulmonary condition did not improve. On the 47th day pulse steroid therapy (1000 mg/day of methylpredonisolone sodium succinate for 3 days) was performed for all 18 patients after the first cycle of treatment. An autopsy was performed and the pathological findings suggested there was diffuse alveolar damage (DAD) of the lung, which suggested drug-induced interstitial pneumonitis.

Up to a dose level of 21 mg/m², one DLT (grade 4 pulmonary toxicity at a dose level of 15 mg/m²) and one unacceptable toxicity (grade 2 fatigue at a dose level of 21 mg/m²) were observed. Although no fatigue met the criteria of DLT in this study, the duration of fatigue tended to increase with the dose of KRN5500. Also, nausea and vomiting were prolonged significantly with increasing dose of KRN5500. These toxicity profiles made further dose escalation unacceptable. Furthermore, pulmonary toxicity had also been reported by another group where a phase I study of KRN5500 was being implemented with a different administration schedule (8). Taking these toxicity profiles into consideration, further dose escalation above 21 mg/m² was withheld. Consequently, the MTD of KRN5500 administered as a 2 h infusion every 4 weeks was determined as 21 mg/m².

**Table 3. Pharmacokinetic parameters of KRN5500**

<table>
<thead>
<tr>
<th>Dose level (mg/m²)</th>
<th>No. of patients</th>
<th>C_{max} (ng/ml)</th>
<th>t_{(a)}*</th>
<th>t_{(b)}*</th>
<th>V_{dss} (l)</th>
<th>CL (l/h)</th>
<th>AUC (ng h/ml)</th>
<th>Urinary excretion (% of dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>3</td>
<td>183.44 ± 32.42</td>
<td>0.33 ± 0.05</td>
<td>1.34 ± 0.11</td>
<td>11.38 ± 0.81</td>
<td>11.87 ± 3.13</td>
<td>439.3 ± 92.7</td>
<td>ND</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>450.49 ± 81.06</td>
<td>0.36 ± 0.08</td>
<td>1.74 ± 0.13</td>
<td>8.76 ± 0.84</td>
<td>7.81 ± 0.30</td>
<td>1164.7 ± 233.8</td>
<td>ND</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>874.61 ± 285.72</td>
<td>0.42 ± 0.12</td>
<td>1.75 ± 0.34</td>
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<tr>
<td>15</td>
<td>6</td>
<td>1241.45 ± 350.99</td>
<td>0.44 ± 0.08</td>
<td>2.11 ± 0.29</td>
<td>10.34 ± 4.50</td>
<td>7.99 ± 1.75</td>
<td>2997.6 ± 729.2</td>
<td>0.008</td>
</tr>
<tr>
<td>21</td>
<td>3</td>
<td>1719.80 ± 346.90</td>
<td>0.47 ± 0.04</td>
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<td>8.24 ± 2.68</td>
<td>4370.7 ± 1649.3</td>
<td>0.034</td>
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Mean ± SD. *half-life. ND: not detected.

PHARMACOKINETICS

Pharmacokinetic studies using plasma and urine samples were performed for all 18 patients after the first cycle of treatment. Pharmacokinetic parameters are summarized in Table 3 and the mean plasma concentration–time profiles are illustrated in Fig. 2. Plasma disappearance was biphasic with mean α and β phase half-lives of 0.41 and 1.86 h, respectively. V_dss and CL showed moderate inter-individual variability and the mean ± SD values [CV %] for V_dss and CL were 9.81 ± 2.73 [27.82%] (l) and 8.68 ± 2.50 [28.77%] (l/h), respectively. Urinary excretion of KRN5500 was low. The peak plasma concentration (C_{max}) and the AUC increased proportionally to the dose of KRN5500 (r = 0.905 and 0.876, respectively; Fig. 3), suggesting linear pharmacokinetics in this dose range.

**DISCUSSION**

We have reported an initial phase I study of the new protein synthesis inhibitor KRN5500 administered as a 2 h infusion every 4 weeks. Although this study was a phase I study, the objective responses were seen and five NC and 12 PD were observed. Tumor markers including CEA and CA19-9 were evaluated for these patients, and tended to increase after treatment with KRN5500 in 12 patients with PD. In five patients with NC, they did not change significantly.

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</tr>
</tbody>
</table>

Mean ± SD. *half-life. ND: not detected.

**Figure 2. Mean plasma concentration–time curve for KRN5500.**
target disease was restricted to gastrointestinal (stomach and colorectal cancer) and lung cancers, based on the results from the preclinical study (4). Dose escalation above the level of 21 mg/m$^2$ was withheld because of fatigue, prolonged nausea and vomiting and pulmonary toxicity. Consequently, the MTD was determined as 21 mg/m$^2$.

A predominant side effect observed in this study was fatigue. Fatigue is a difficult side effect to assess, because the criteria used to describe it are subjective and not definitely graded in NCC-CTC version 1, which was used for toxicity evaluation in this study. One patient experienced grade 2 fatigue at the dose level of 21 mg/m$^2$. Although his fatigue was graded 2 and was not defined as DLT in this protocol, its severity was different from that which other patients experienced at lower dose levels. The fatigue lasted for 7 days and parenteral fluid therapy was required for anorexia. Hence the fatigue observed in this study was graded 1 or 2, and its duration increased with both the dose and AUC of KRN5500. Taking these profiles into consideration, fatigue for this patient was considered unacceptable. The mechanism of fatigue induced by KRN5500 has not been elucidated. Information about several inflammatory cytokines such as tumor necrosis factor-$
\gamma$ and interleukins may help, but these markers were not evaluated in this study.

Severe pulmonary toxicity characterized as interstitial pneumonitis was observed in one patient at a dose level of 15 mg/m$^2$. In preclinical studies, no particular findings suggestive of pulmonary toxicities were reported. The pathological findings from the autopsy samples revealed DAD. DAD is usually observed bilaterally in the lungs and it may be caused by infectious agents (particularly viruses), inhalants (such as oxygen), drugs (especially anticancer agents and amiodarone), ingesta (such as kerosene or paraquat), shock, sepsis, radiation or other agents. The morphological changes are of a non-specific nature and the etiological agent cannot be determined from microscopic observations alone. In our case, DAD was similar to that caused by other anticancer agents such as busulfan and MMC, suggesting that KRN5500 could have induced interstitial pneumonitis (9–11).

The frequency of nausea and vomiting was high in this study and, notably, the duration of nausea was increased significantly with both the dose and the AUC of KRN5500 (data not shown). KRN5500 itself is barely soluble in water, which necessitates an organic solvent for reconstitution as described earlier. This organic solvent might have caused the nausea and vomiting. Since neither supportive treatment with metoclopramide and haloperidol nor premedication of granisetron was effective, other antiemetic approaches such as premedication with a steroid hormone (e.g. dexamethasone) should be investigated.

The prolongation of PT suggested that KRN5500 inhibited protein synthesis. Furthermore, the decreases in the serum total protein and total cholesterol levels, which were observed for 4–8 and 4–12 days (median), respectively, after the start of KRN5500 administration, also suggested a similar effect (data not shown). None of these changes correlated with the dose or pharmacokinetic parameters. PT prolongation was also observed with another protein synthesis inhibitor, Giroline (RP 49532A) (12). Effects on several coagulation factors should be investigated to elucidate the mechanism of PT prolongation for further development of KRN5500.

Generally, protein synthesis inhibitors are considered to have various non-hematological toxicities, some of which were considered DLTs in previous phase I studies. Catimel et al. (12) reported delayed hypotension and severe asthenia as DLTs in a phase I study of Giroline (RP 49532), while Murphy et al. (13) reported central nervous system symptoms including somnolence, confusion and ataxia as DLTs in a phase I study of Anguidine. In addition to these two agents, several protein synthesis inhibitors reportedly had various non-hematological adverse effects including nausea, vomiting, fever, headache, asthenia, hypotension and hepatic toxicities.

The AUC values obtained at higher dosages have already reached the equivalent level of AUC which preclinical studies suggested as effective exposure against human tumor cell lines tested (14). Since antitumor activities of KRN5500 were considered AUC-dependent in preclinical studies, it was not
considered impossible to observe any tumor responses at these higher doses of drug administration (4). However, severe or unacceptable toxicities made it difficult to repeat the treatment cycle and evaluate its efficacy. We suggest that improvement of the toxicity profile is essential before evaluating any potentially efficacious aspects of this compound for patients.

In this study, pulmonary toxicity, fatigue and prolonged nausea and vomiting were identified as unacceptable. To overcome these toxicities, several approaches could be taken. First, other treatment schedules such as weekly, biweekly and daily administration should be investigated. Second, the use of a steroid hormone (e.g. dexamethasone) as a premedication should be considered. This could contribute to reducing fatigue, nausea and vomiting. Third, the modification of the drug component could improve the selectivity for tumor cells and reduce toxic effects for normal cells. Matsumura et al. (15) reported that KRN5500 incorporated into polymeric micelles exhibited antitumor activity similar to KRN5500 and reduced the toxic effects including vascular damage and focal necrosis of the liver which were observed in intravenous injection studies of this drug.

In conclusion, the MTD of KRN5500 was 21 mg/m² when administered as a 2 h infusion every 4 weeks and pulmonary toxicity, fatigue and prolonged nausea and vomiting were dose-limiting. Further investigations are warranted concerning different treatment schedules, steroid premedication, modification of the drug component, etc., to overcome these toxicity profiles and to evaluate the clinical antitumor activity further.

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