Phase I Trial of Dolastatin-10 (NSC 376128) in Patients with Advanced Solid Tumors


ABSTRACT
Dolastatin-10 (dola-10) is a potent antimitotic peptide, isolated from the marine mollusk Dolabela auricularia, that inhibits tubulin polymerization. Preclinical studies of dola-10 have demonstrated activity against a variety of murine and human tumors in cell cultures and mice models. The purpose of this Phase I clinical trial was to characterize the maximum tolerated dose, pharmacokinetics, and biological effects of dola-10 in patients with advanced solid tumors. Escalating doses of dola-10 were administered as an i.v. bolus every 21 days, using a modified Fibonacci dose escalation schema. Pharmacokinetic studies were performed with the first treatment cycle. Neurological testing was performed on each patient prior to treatment with dola-10, at 6 weeks and at study termination. Thirty eligible patients received a total of 94 cycles (median, 2 cycles; maximum, 14 cycles) of dola-10 at doses ranging from 65 to 455 μg/m². Dose-limiting toxicity of granulocytopenia was seen at 455 μg/m² for minimally pretreated patients (two or fewer prior chemotherapy regimens) and 325 μg/m² for heavily pretreated patients (more than two prior chemotherapy regimens). Nonhematological toxicity was generally mild. Local irritation at the drug injection site was mild and not dose dependent. Nine patients developed new or increased symptoms of mild peripheral sensory neuropathy that was not dose limiting. This toxicity was more frequent in patients with preexisting peripheral neuropathies. Pharmacokinetic studies demonstrated a rapid drug distribution with a prolonged plasma elimination phase (t₁/₂a = 320 min). The area under the concentration-time curve increased in proportion to administered dose, whereas the clearance remained constant over the doses studied. Correlation analysis demonstrated a strong relationship between dola-10 area under the concentration-time curve values and decrease from baseline for leukocyte counts. In conclusion, dola-10 administered every 3 weeks as a peripheral i.v. bolus is well tolerated with dose-limiting toxicity of granulocytopenia. The maximum tolerated dose (and recommended Phase II starting dose) is 400 μg/m² for patients with minimal prior treatment (two or fewer prior chemotherapy regimens) and 325 μg/m² for patients who are heavily pretreated (more than two prior chemotherapy regimens).

INTRODUCTION
Dola-10 is a potent antimitotic peptide, isolated from the marine mollusk Dolabela auricularia. In addition to disrupting tubulin polymerization, dola-10 noncompetitively inhibits the binding of Vinca alkaloids to tubulin, inhibits nucleotide exchange and formation of the β cross-link, and stabilizes the colchicine binding activity of tubulin. Preclinical studies of dola-10 in L1210 and CHO cell lines demonstrated IC₅₀ₐ of 0.4 and 0.5 nM, respectively. Studies of several human lymphoma cell lines cultured in the presence of dola-10 revealed an IC₅₀ in the range of 0.13–1.3 pm for the sensitive cell lines. These results demonstrate that dola-10 was 3–4 times (logarithmic scale) more effective than vincristine as an antiproliferative agent against lymphoma cell lines on a molar basis. Dola-10 induced apoptosis in several human lymphoma cell lines and was cytostatic against human leukemia cell lines in vitro. When administered i.p., dola-10 exhibited good activity against i.p. implanted tumors (murine L1210 leukemia, P388 leukemia, B16 melanoma, M5076 sarcoma, human LOX melanoma, and OVCAR-3 ovarian carcinoma) in mice.

Preclinical pharmacology and pharmacokinetics have been investigated in mice following administration of [³H]dola-10 (0.32 mg/kg) to mice by i.p., i.v., and s.c. routes. After i.v. administration, parent dola-10 was eliminated with a t₁/₂ of 2.4 h. By 8 h, <10% of plasma radioactivity was identified as parent drug. Less than 1.25% of administered [³H]dola-10 was recovered in the urine within 24 h of drug administration.

Preclinical toxicology indicated that the MTD for mice was 1350 μg/m². The MTD in dogs (the most sensitive species tested preclinically) could not be determined in preclinical studies but was estimated to be ~20 μg/kg (400 μg/m²). Observed
animal toxicities in preclinical studies included neutropenia, thrombocytopenia, hypoglycemia, hypertension, and liver function abnormalities.

dola-10 has also been evaluated previously in vitro for neurotoxicity using a rat embryo DRG culture system (10, 11). Studies using this culture system demonstrated neurite outgrowth inhibition by dola-10 similar to other chemotherapy agents known to cause peripheral neuropathies in humans (12, 13). Drugs that do not produce neurotoxicity (e.g., fluorodeoxyuridine) do not inhibit neurite outgrowth in this culture system.

We performed a Phase I study of dola-10 given by a brief i.v. injection every 3 weeks to determine the MTD, pharmacokinetic characteristics, and biological effects of this compound. In addition, based on in vitro data predicting that dola-10 had neurotoxic potential, we performed prospective neurological testing in patients to investigate the neurotoxic effects caused by dola-10.

MATERIALS AND METHODS

Patients. All patients participating in this study had histological confirmation of a nonlymphoid malignancy for which there was no known standard therapy that was curative or capable of extending life expectancy. Additional eligibility criteria at study entry consisted of: Eastern Cooperative Oncology Group performance status, ≤2; age, ≥18 years; WBC count, ≥3,500/μl; platelet count, ≥100,000/μl; hemoglobin level, ≥10 g/dl; serum creatinine, ≤1.25 times the upper limit of normal; normal total and direct bilirubin; AST, ≤3 times the upper limit of normal; oral intake, ≤1200 calories per day; and life expectancy, ≥12 weeks. Written informed consent was obtained from all patients prior to study entry. Patient exclusion criteria included: prior therapy with chemotherapy or biological therapy within 4 weeks of entering the study; radiation therapy within 4 weeks of entering the study; nitrosourea or mitomycin C within 6 weeks of entering the study; radiation within 4 weeks of entering the study; nitrosourea or mitomycin C within 6 weeks of entering the study; radiation to 25% of the bone marrow; uncontrolled infection; New York Heart Association class III or IV heart disease; pregnancy or lactation; and men and women of childbearing age, lack of willingness to practice adequate contraception; central nervous system metastases; seizure disorder; or uncontrolled hypertension. This study was approved and monitored by the Institutional Review Board of the Mayo Clinic and Foundation.

Study Design. dola-10 was administered as a single peripheral i.v. bolus every 3 weeks. The study drug was supplied by the National Cancer Institute (Bethesda, MD) in sterile vials containing 1 ml of a solution of 200 μg/ml dola-10 in 0.1% m (pH 7) potassium phosphate buffer and stored refrigerated at 2–8°C. Patients were treated until disease progression or unacceptable toxicity (DLT). The starting dose of dola-10 was 65 μg/cm², with planned dose escalations to 130, 217, 325, and 455 μg/cm², based on a modified Fibonacci escalation schema. An intermediate dose level of 400 μg/cm² was subsequently added to better define the MTD after DLT was observed at the highest dose level. Patients were divided into two groups based on previous chemotherapy. Those patients with two or fewer prior regimens and no prior mitomycin C or nitrosourea were considered to be minimally pretreated. All other patients were defined as heavily pretreated. A minimum of three patients were treated at each dose level, and no intrapatient dose escalation was allowed. All patients at a given dose level were observed for at least 3 weeks before new patients were treated at a higher dose level.

Presubject evaluations included: a complete history and physical examination including height, weight, performance score, and tumor measurement; complete blood count; serum chemistries; an electrocardiogram; chest X-ray; neurological studies; indicator lesion imaging (magnetic resonance imaging, computed tomography, and so on); and a serum pregnancy test in women of childbearing potential. All patients underwent an interim history and physical examination prior to each subsequent cycle of therapy. Blood counts and serum glucose levels were repeated twice weekly in the interval between subsequent treatments. The first cycle of therapy for each patient was administered on an inpatient basis in the Mayo General Clinical Research Center to expedite pharmacokinetic sampling, and subsequent cycles were administered on an outpatient basis.

Dose-limiting myelotoxicity was defined as a nadir granulocyte count of <500/mm³ and a platelet count of <25,000/mm³. Dose-limiting renal toxicity was defined as a creatinine elevation of >2 times the upper limit of institutional normal for the patient. Other dose-limiting toxicities were defined as per National Cancer Institute CTC, with those of grade ≥3 considered dose limiting (except for nausea and vomiting, for which grade 4 toxicity was dose limiting). DLTs were evaluated for the first cycle only. The MTD was defined as the dose level at which, at most, one of six patients experienced DLT and the next higher dose level produced DLT in at least two of six patients. Once the MTD was defined for the minimally pretreated patient group, additional heavily pretreated patients were enrolled to better characterize the MTD in this patient group.

Pharmacokinetics. On day 1 of the first cycle of treatment, blood (5 ml) was collected in heparinized tubes prior to and at the following times after i.v. dola-10 administration: 2, 5, 10, 20, 30, 60, 90, 120, 150, 180, 240, 360, 480, 720, 960, and 1440 min. Following centrifugation to separate plasma, specimens were stored at −70°C until analysis. Urine was collected in separate plastic containers during the intervals of 0–4 h, 4–8 h, and 8–24 h following drug administration.

Growth Inhibition Assay. Because initial preclinical studies of dola-10 predicted patient plasma concentrations well below levels detectable by standard analytical methods, an L1210 bioassay was used to determine plasma concentrations. Exponentially growing (2 × 10⁵–3 × 10⁶ cells/ml) L1210 mouse leukemia cells were maintained in RPMI 1640 cell culture medium supplemented with 10% FCS at 37°C under a humidified atmosphere (100% relative humidity) of 5% CO₂–95% air. On the day prior to drug analysis, culture medium was aspirated from the flask, and fresh medium was added to reduce the cell numbers to 5 × 10⁵–8 × 10⁵ cells/ml. Standard curve samples were prepared by diluting stock solutions of drug (0.8 nM in DMSO) to concentrations of 8–40 nM in DMSO, followed by dilution to 0.4–2 nM in a 1:1 cell culture medium: normal human or mouse plasma mixture. Aliquots of these standards (0.158 ml per 3.0 ml incubation) were added to flasks containing medium and 1.2 × 10⁵ L1210 cells. The final con-
centration of drug in the flasks was 20–100 pm. All standard curve flasks contained 0.25% DMSO and 2.4% plasma.

Samples of patient plasma were diluted with cell culture medium or 1:1 cell culture medium: normal human plasma to minimize the growth-inhibitory effect of plasma on L1210 cells and maintain 2.5–3.0% plasma per flask. Two or three dilutions of each plasma sample were made over the range of 1.2–1:200 as needed to achieve cell growth inhibition in the linear range of the standard curve. Aliquots (0.158 ml) of these dilutions were added to flasks containing 3.0 ml medium and 1.2 × 10^5 L1210 cells. Patient urine samples were analyzed in a similar manner, except that standard curve samples and patient sample dilutions were made in 1:1 cell culture medium: normal human urine. All flasks were incubated for 48 h. After incubation, culture aliquots (1 ml) were diluted with Isoton II (19 ml), and cell numbers were determined with a Coulter counter.

The L1210 bioassay was linear in the plasma concentration range of 1.2–3.2 nm (30–80 pm dola-10 in the culture flasks due to the 40-fold sample dilution). The limit of quantitation was 1.0 nm. The value of the coefficient of variation of the slopes of standard curves was 11.3%. Plasma quality assurance samples (1.2, 2.4, and 80 nm) had coefficient of variation values of 6.8–15.2%, and mean calculated values were within ±6% of expected values during the course of the trial. The linear ranges, limit of quantitation, and standard curve slopes for the urinary assays were similar to those for the plasma assays. It should be emphasized that the bioassay lacks specificity and does not distinguish between parent drug and cytotoxic degradation products and/or metabolites that may contribute to growth-inhibitory activity. This is important because dola-10 has been reported to undergo extensive metabolism (9).

**Pharmacokinetic Data Analysis.** Growth inhibition was expressed as a percentage of cells in drug-treated flasks relative to the number of cells in control flasks. The linear portion of the graph of percent growth inhibition versus log(drug concentration) was used to determine IC_{50}s and to calculate nanomolar concentrations of drug equivalents in patient plasma and urine samples. Plasma drug concentrations were fitted by nonlinear least squares regression or noncompartmental analysis using PCNONLIN (Version 4.2).

**Neurological Studies.** Neurological studies were performed prior to treatment, at 6 weeks and at the time of tumor progression, when possible. These studies consisted of three components: the Neuropathy Symptoms and Change Score, a structured symptom score that quantitates the change in a patient’s neurological symptoms; the NIS, a scored neurological examination, emphasizing the peripheral nervous system; and Quantitative Sensory Testing, a threshold test in which graded stimuli are applied to the left great toe. Each of these tests has been described and extensively validated for monitoring the presence and progression of peripheral neuropathy, primarily in the diabetic population (14, 15). Each test is controlled by sex and age for a normal population.

**Statistical Analysis.** Toxicity and pharmacology data were analyzed primarily in a descriptive fashion. The number and severity of toxic incidents indicated the level of tolerance for dola-10 in the treatment of advanced cancer. Hematological toxicity measures of thrombocytopenia, neutropenia, and leukopenia were assessed using the continuous variables as the outcome measures (primarily nadir and percentage change from baseline values) as well as categorization via CTC standard toxicity grading. Nonhematological toxicities were evaluated via the ordinal CTC standard toxicity grading only. Frequency distributions and other descriptive measures formed the basis of the analysis of these variables.

Normality testing was carried out via standard Shapiro-Wilk testing (16). Correlation among the pharmacodynamic outcome measures and other hematological values (neutrophil nadir and percentage change in neutrophil counts from baseline) was carried out via simple graphics and Spearman’s ρ coefficient. Paired t tests and Wilcoxon procedures were used to assess average intrapatient changes in these and other variables. Exploratory analysis was also carried out on time-related variables including time until any treatment-related toxicity, time until treatment-related grade ≥3 toxicity, and time until hematological nadirs (leukocyte, granulocyte, and platelet). Summary statistics were supplemented by Kaplan-Meier survival estimates and related confidence intervals (17, 18).

**RESULTS**

**Hematological Toxicity.** A total of 30 patients were entered and treated in this study. Patient characteristics are shown in Table 1. The dose escalation scheme for dola-10 is shown in Table 2. Doses ranged from 65 to 455 μg/m². A total of 94 courses of dola-10 were administered, and all were assessable (median, 2 courses; range, 1–14 courses). No responses were observed among the 30 patients treated. The DLT of

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**Table 1** Patient characteristics (n = 30)

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Median age, yr (range)</th>
<th>Sex (no. of males/no. of females)</th>
<th>ECOG PS (^a) 0/1/2</th>
<th>Tumor type</th>
<th>Prior therapy</th>
<th>Chemotherapy</th>
<th>Radiation therapy (prior pelvic radiotherapy)</th>
<th>Immunotherapy</th>
<th>Hormonal therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>59 (28–75)</td>
<td>17/13</td>
<td></td>
<td>14/11/5</td>
<td></td>
<td></td>
<td>25</td>
<td>18 (9)</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

\(^a\) ECOG PS, Eastern Cooperative Oncology Group performance score.

**Table 2** dola-10 dose levels

<table>
<thead>
<tr>
<th>Dose level (μg/m²)</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>3</td>
</tr>
<tr>
<td>130</td>
<td>3</td>
</tr>
<tr>
<td>217</td>
<td>3</td>
</tr>
<tr>
<td>≥2 prior regimens</td>
<td>6</td>
</tr>
<tr>
<td>&gt;2 prior regimens</td>
<td>0</td>
</tr>
</tbody>
</table>

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granulocytopenia was observed at 455 μg/m² in patients with minimal prior treatment (Table 3). At this dose level, two of five patients experienced grade 4 neutropenia. The cycle 1 neutrophil nadir for all patients are presented in Fig. 1. Another patient at 455 μg/m², who was heavily pretreated, also experienced a grade 4 neutropenia. The median time to granulocyte nadir for a patient experiencing neutropenia during the first cycle (n = 14) was 19.5 days, with the median time to granulocyte recovery being 6 days. Other hematological toxicities were mild, with one episode of grade 3 anemia at 325 μg/m² and two episodes of grade 1 thrombocytopenia at the 217 μg/m² dose level.

**Nonhematological Toxicity.** Nonhematological toxicity was generally mild. One episode of grade 3 diarrhea, that was felt to be treatment related, occurred in a patient with extensive prior chemotherapy at the 325 μg/m² dose level. All other gastrointestinal toxicity was mild (grade ≤1), except for one patient who experienced grade 2 nausea. Irritation at the injection site was manageable, did not increase with dose level, and did not preclude further treatment with dola-10. One episode of severe local reaction occurred at 217 μg/m² in a patient who received only one cycle. Another patient who received six cycles of treatment at 400 μg/m² noted improvement of the local reaction if the catheter was flushed with normal saline after drug administration. Elevated blood pressure was very uncommon (one episode of grade 1 toxicity) in this study despite preclinical investigations suggesting the potential for cardiovascular toxicity in dogs. Several episodes of hyperglycemia and one episode of grade 1 hypoglycemia were noted but were felt to be unrelated to treatment and most often related to underlying diabetes mellitus.

**Neurological Toxicity.** All 30 patients had initial neurological symptom assessment. Twenty-five patients were studied at 6 weeks. Nine patients (36% of evaluable patients) had new or increased symptoms at six weeks. The symptoms (grade 1 neurosensory) consisted mainly of mild tingling or electric shock-like sensation in the toes and feet. No hand involvement was described. Three of these patients had an underlying neuropathy at baseline (two with diabetic peripheral neuropathy and one with platinum-induced peripheral neuropathy). Neither of the two patients who had three sequential evaluations developed neuropathy. When baseline measurements were compared with subsequent neurological evaluations, we identified several parameters that changed significantly. The symptom score for the whole group increased significantly (P = 0.04; paired t test or Wilcoxon, two-tailed) between baseline and 6 weeks. This change occurred in seven patients who had developed predominantly positive sensory symptoms. The scored NIS also changed significantly (P = 0.003; paired t test) from 3.2 to 4.9 for the whole group. This was accounted for by changes in nine patients whose NIS increased from 8.9 ± 3.7 (mean ± SE) to 12.4 ± 3.6. Changes in threshold of sensation for vibration, thermal cooling, and heat pain perception for the 25 patients who had evaluation at baseline and 6 weeks did not change significantly. However, if Quantitative Sensory Testing for the nine patients who developed symptomatic neuropathy were compared with the 16 who did not, there were significant differences between baseline and 6 weeks; P = 0.005 for vibration detection threshold and P = 0.003 for thermal cooling detection threshold. The median numbers of cycles of dola-10 given for patients who did and did not experience neurotoxicity were 13 and 12 cycles, respectively (P = 0.96; Wilcoxon rank sum). Neither new nor worsening neurological symptoms were considered to be dose limiting.

**dola-10 Pharmacokinetics.** Patient plasma concentrations of dola-10 equivalents were measured with an L1210 bioassay, which was validated in a preliminary study of pharmacokinetics in mice administered 720 μg/m² dola-10 i.v. The elimination half-life and plasma clearance values of dola-10 were 19 h and 99 ml/min/m², respectively.

The pharmacokinetics of dola-10 were characterized for 15 patients who received doses of 65–455 μg/m². At the lowest dose, 65 μg/m², drug equivalents were detectable for ~120 min following dola-10 administration. At the 325–455 μg/m² dose range, cytotoxic activity was present in patient plasma samples for 24 h following dola-10 administration (Fig. 2). Plasma elimination was best described by a two-compartment open model for two patients treated at the 65 μg/m² level and by a three-compartment open model for the remaining 13 patients (Table 4). Distribution of dola-10 after i.v. infusion was rapid and plasma elimination was extremely slow. Noncompartmental analysis was performed to compare the pharmacokinetic parameters among all patients (Table 4). dola-10 pharmacokinetics were linear over the five dose levels studied. The AUC increased in proportion to dose, and clearance values were similar regardless of the amount of drug administered. The half-life of the drug increased with increasing dosage, consistent with a shift from a two- to a three-compartment model of drug distribution. Urinary recovery was determined in 10 patients who received 130–455 μg/m² dola-10. Excretion of dola-10 drug equivalents over 24 h as a percentage of administered dose was 3.6 ± 0.92%. Most of the drug that was excreted occurred within 8 h of administration (>67%). However, in 8 of 10 patients, drug was detected in the 8–24 h urine sample.

An exploratory analysis was undertaken to evaluate the relationship between several pharmacokinetic parameters and toxicity (hematological and nonhematological). There was a strong relationship between AUC and decrease from baseline for leukocytes (Spearman correlation coefficient = 0.73; range, 0.32–0.97; P = 0.002). There was a moderate correlation between dola-10 AUC and the decrease in neutrophil count (percentage change from baseline; Spearman correlation coefficient = 0.56; range, 0.16–0.80; P = 0.03). The neurological

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**Table 3: DLTs**

<table>
<thead>
<tr>
<th>Dose level (μg/m²)</th>
<th>No. of patients</th>
<th>Leukocyte¹</th>
<th>Granulocyte¹</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>65</td>
<td>3</td>
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<td>0</td>
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<tr>
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<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>217</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>325</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Heavy</td>
<td>6</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>400</td>
<td>6</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>455</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Heavy</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

¹ National Cancer Institute CTC grades.
symptoms observed in this patient population did not correlate with the AUC of dola-10. We could demonstrate no other correlation between standard pharmacokinetic parameters and toxicity.

DISCUSSION

Over the past decade, a number of potent cytotoxic compounds have been isolated from the sea hare, Dolabella auricularia. Two of these compounds, dola-10 and dola-15, have been extensively evaluated in preclinical models. A water-soluble analogue of dola-15, LU-103793, was chemically designed to possibly enhance efficacy. Three Phase I trials have been performed using this analogue. Schedules that have been evaluated include an i.v. bolus (5 min) every 3 weeks, a daily bolus every 3 weeks, and a 24-h infusion weekly × 4 every 5 weeks (19-21). Cardiovascular toxicity (arterial hypertension and myocardial infarction) was dose limiting on the i.v. bolus every 3 weeks schedule. The mechanism for the cardiovascular toxicity remains unclear, and preclinical testing demonstrated reduced cardiovascular side effects with more prolonged infusions. The two prolonged schedules of LU-103793 encountered myelosuppression (primarily neutropenia) as the DLT with few cardiovascular events. The MTD for the three schedules ranged between 12.5 and 40 mg/m² per cycle. Further Phase II investigations with the analogue, LU-102793, are ongoing.

Dola-10 is a unique linear pentapeptide that was isolated from the sea hare Dolabella auricularia by Pettitt et al. (1). Preclinical studies showed that dogs were the most sensitive species, with an MTD estimated to be in the 400 µg/m² dose range. We performed a Phase I study in humans with advanced cancer to determine the MTD of dola-10 administered by a peripheral i.v. bolus on a 21-day schedule. The DLT of granulocytopenia was encountered at 455 µg/m² on a 21-day schedule. The DLT of granulocytopenia was also a DLT for LU-103793 when administered on a more protracted schedule every 3 weeks. We did not encounter any significant cardiovascular toxicity, although one patient had mild blood pressure elevation following repeated cycles of dola-10. Although hypoglycemic reactions occurred in dogs, we only documented one episode of hypoglycemia that was felt to be unrelated to treatment. Several episodes of local irritation were encountered with no relationship to the administered dose of drug. This did not require central line placement. If i.v. site irritation is observed, flushing of the peripheral catheter after the dola-10 i.v. bolus may diminish the local reaction for subsequent cycles.

Neurological complications of chemotherapeutic agents have been reviewed in the past (22, 23). Drugs that inhibit microtubule polymerization are known to be associated with neurotoxicity. Dola-10 was evaluated preclinically in a rat embryo DRG culture system. When exposed to varying concentrations of dola-10, neurite outgrowth was inhibited by 50% at a dola-10 concentration of 1 nM. On the basis of the mouse pharmacokinetic studies, we expected to see patient plasma concentrations of >1 nM. The actual peak plasma concentrations observed ranged from 1 to 297 nM. On the basis of these preliminary studies, we predicted that dola-10 may produce peripheral neuropathy as a side effect (24). In this study, we prospectively evaluated patients using three different validated neurological examinations. Of 25 evaluable patients, 9 patients had progressive neurological symptoms, consistent with an early peripheral neuropathy. This raises the possibility of increased incidence or severity of peripheral neuropathy if the drug is administered over repeated cycles. Future studies should include further assessment of neurotoxicity in patients receiving dola-10. Our results also suggest that the DRG is a useful system for assessing the potential of new chemotherapeutic agents.

dola-10 levels were evaluated in the present trial using an L1210 bioassay. Other investigators have used RIA as well as high-performance liquid chromatography/electrospray ionization mass spectrometry in measuring dola-10 levels (25, 26). There are advantages and disadvantages to performing each of these techniques. Although we cannot rule out the possibility that there are specific cytotoxic metabolites, the comparable AUCs, clearance, and \( t_{1/2}\) that we obtained and Tran et al. (26) reported suggest that there are no metabolites, that they constitute an insignificant component of the dola-10 drug equivalent, or that any metabolites are nontoxic in our assay system.

We have demonstrated that dola-10 can be readily and...
safely administered by peripheral i.v. bolus on a 21-day schedule. The DLT on this administration schedule is granulocytopenia. Preliminary results from a similar trial at The M. D. Anderson Cancer Center also indicate that neutropenia will likely be the DLT (26). The MTD is lower for patients with extensive prior chemotherapy. For those with minimal prior treatment, the MTD is 75 mg/m².

For patients who have received extensive prior chemotherapy, a starting dose of 325 mg/m² is recommended. Phase II studies are under way to investigate dola-10 activity against several tumor types. On the basis of the preclinical data regarding lymphoid malignancies, future trials of dola-10 in this cohort of patients should also be considered. Further evaluation of possible neurotoxic side effects of this agent is warranted, given the preliminary Phase I findings.

ACKNOWLEDGMENTS
The technical assistance of Delores A. Gillen in the Mayo Sensory Lab is gratefully acknowledged. We thank Pamela Atherton Skaff for data analysis, Michelle Daiss for protocol development, and Debra Sprau for data entry/management.

REFERENCES

Table 4
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<thead>
<tr>
<th>Dose (µg/m²)</th>
<th>65</th>
<th>130</th>
<th>217</th>
<th>325</th>
<th>455</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noncompartmental analysis</td>
<td>747 (161)</td>
<td>2,222 (793)</td>
<td>2,728 (569)</td>
<td>6,888 (4,388)</td>
<td>9,685 (6,388)</td>
</tr>
<tr>
<td><em>t</em>₂/₂β (min)</td>
<td>62 (37)</td>
<td>247 (61)</td>
<td>301 (162)</td>
<td>472 (230)</td>
<td>520 (106)</td>
</tr>
<tr>
<td>CI (ml/min/m²)</td>
<td>114 (25)</td>
<td>81 (28)</td>
<td>105 (24)</td>
<td>83 (57)</td>
<td>76 (36)</td>
</tr>
<tr>
<td><em>V</em>₅₀ (liters/m²)</td>
<td>6.57 (2.79)</td>
<td>20.1 (6.77)</td>
<td>38.2 (36)</td>
<td>34.9 (7.57)</td>
<td>43.6 (23.4)</td>
</tr>
</tbody>
</table>

Three-compartment open model

| AUC (nm · min) | 1,050 | 2,528 (1,075) | 3,081 (545) | 13,248 (13,756) | 12,234 (5,033) |
| *t*₁/₂α (min) | 4 | 4 (1) | 4 (2) | 4 (3) | 4 (1) |
| *t*₁/₂β (min) | 14 | 38 (27) | 34 (23) | 86 (71) | 1,295 (2,124) |
| *t*₁/₂γ (min) | 121 | 345 (133) | 414 (331) | 2,262 (2,716) | 681 (507) |
| CI (ml/min/m²) | 78 | 73 (29) | 92 (15) | 68 (63) | 54 (24) |
| *V*₅₀ (liters/m²) | 9 | 21 (4) | 43 (48) | 59 (34) | 94 (72) |

*Mean values (SD) for data from three patients.*

4 J. L. Abbruzzese, personal communication.


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