Phase I Trial of Docetaxel with Filgrastim Support in Pediatric Patients with Refractory Solid Tumors: A Collaborative Pediatric Oncology Branch, National Cancer Institute and Children’s Cancer Group Trial

Nita L. Seibel, Susan M. Blaney, Michelle O’Brien, Mark Krailo, Ray Hutchinson, Revonda B. Mosher, Frank M. Balis, and Gregory H. Reaman

Department of Hematology Oncology, Children’s National Medical Center and Department of Pediatrics George Washington University School of Medicine, Washington, DC 20010 [N. L. S., R. M. B., G. H. R.]; Texas Children’s Cancer Center, Houston, Texas 77030 [S. M. B.]; Pediatric Oncology Branch, National Cancer Institute, Bethesda, Maryland 20892 [M. O’B., F. M. B.]; Department of Preventive Medicine, University of Southern California, Los Angeles, California 90033 [M. K.]; and Department of Pediatric Hematology/Oncology, University of Michigan, Ann Arbor, Michigan 48109-0914 [R. H.]

ABSTRACT

Neutropenia is the dose-limiting toxicity of docetaxel in children. This Phase I trial was designed to determine the maximum tolerated dose, the dose-limiting toxicities, and the incidence and severity of other toxicities of docetaxel with filgrastim (G-CSF) support in children with refractory solid tumors. Docetaxel was administered as an i.v. infusion for 1 h every 21 days with a starting dose of 150 mg/m² and an escalation to 185 mg/m² and 235 mg/m² in subsequent patient cohorts. G-CSF (5 μg/kg/day) was administered s.c., starting 48 h after docetaxel and continuing until the post-nadir neutrophil count reached 10,000/μl. Seventeen patients received 27 courses of docetaxel with G-CSF support. Generalized erythematous desquamating skin rash and myalgias were dose-limiting at 235 mg/m². Localized and generalized rashes were seen at all of the three dose levels. Neutropenia (median nadir, 95/μl) occurred at all of the dose levels but was brief in duration and not dose-limiting. Thrombocytopenia was minimal (median platelet count nadir, 139,000/μl), and the severity of neutropenia and thrombocytopenia did not seem to be related to the docetaxel dose. Other docetaxel-related toxicities included hemorrhage (associated with mucositis), sepsis, hypersensitivity reaction, transient elevation of liver enzymes, stomatitis, back pain, asthenia, and neuropathy. One minor response was observed in a patient with colon cancer. The maximum tolerated dose of docetaxel with G-CSF support in children is 185 mg/m², which is 50% higher than the maximum tolerated dose of docetaxel alone in children and 85% higher than the recommended adult dose.

INTRODUCTION

Docetaxel (Taxotere) is a semisynthetic taxane that interferes with microtubule function by blocking depolymerization of microtubule bundles (1–3). Docetaxel has a broad spectrum of antitumor activity in preclinical studies and in Phase II clinical trials in adults (4–13). The recommended dose of docetaxel in adults is 100 mg/m² infused over 1 h every 21 days (14, 15). Neutropenia is the DLT, and other common toxicities include nausea and vomiting, stomatitis, diarrhea, alopecia, hypersensitivity reactions, skin rashes, asthenia, peripheral sensory neuropathy, myalgias, arthralgias, and fluid retention, which is a cumulative toxicity that is manifested as peripheral edema, weight gain, pleural effusions, and ascites (1, 16). Hypersensitivity reactions, rashes, and fluid retention seem to be ameliorated by premedication with an antihistamine and corticosteroid.

In our prior Phase I trial of docetaxel in pediatric patients (17), the MTDs in heavily pretreated and less-heavily pretreated patient populations were 65 mg/m² and 125 mg/m², respectively. The toxicity profile in children was similar to that reported in adults. Nonhematological toxicities included stomatitis, asthenia, myalgias, skin rashes, and mild elevations of serum transaminases. Peripheral edema and weight gain were observed in two of five patients who received more than three cycles of docetaxel. The primary DLT was neutropenia, but thrombocytopenia was minimal even in patients who experienced dose-limiting neutropenia (defined as neutrophil count <500/μl for more than 7 days; Ref. 17). The median platelet count nadir at the 125-mg/m² dose level was 142,000/μl.

The lack of thrombocytopenia (in both pediatric and adult trials) suggests that further escalation of the docetaxel dose could be accomplished with G-CSF support. The objectives of this Phase I trial of docetaxel plus G-CSF were to determine the MTD, the DLT, and the incidence and severity of other toxicities associated with this combination in pediatric patients with...
limited prior radiation of marrow-producing bones. Pharmacokinetics of docetaxel in children were performed and will be reported separately.

PATIENTS AND METHODS

**Patient Selection.** Patients ≥1 year of age and ≤21 years of age with a histologically confirmed solid tumor refractory to standard therapy were eligible for this trial. Other eligibility criteria included: (a) an Eastern Oncology Group performance status of ≤2; (b) a life expectancy > 8 weeks; (c) adequate bone marrow function (an absolute neutrophil count > 1500/µL, hemoglobin level > 9 g/dL, and platelet count > 100,000/µL); (d) adequate liver function (serum bilirubin level < 1.5 mg/dL, alanine aminotransferase < 2 × the upper limit of normal); (e) adequate renal function (creatinine level < 1.5 mg % or creatinine clearance > 60 ml/min/1.73 m²); (f) recovery from the toxicity of prior therapy; (g) no other chemotherapy within 2 weeks (6 weeks for prior nitrosourea therapy) of entry into this protocol; (h) no prior central axis (skull, spine, ribs, or pelvis) radiotherapy; and (i) no prior bone marrow or cell transplants. Informed consent was obtained from the patient or his/her legal guardian before entry onto the study in accordance with individual institutional policies.

**Trial Design.** Docetaxel in polysorbate 80 was supplied by the Cancer Therapy Evaluation Program of the National Cancer Institute (Bethesda, MD) in 80-mg vials (concentration, 40 mg/ml). The docetaxel was initially diluted to a concentration of 10 mg/ml with 95% ethanol and then to a 1 mg/ml concentration with D₂O. The drug was administered i.v. at a constant infusion rate over 1 h through either a peripheral venous or a central venous catheter. All of the patients were premedicated with diphenhydramine (1 mg/kg four times daily) and dexamethasone (1 mg/ml) for 4 days before docetaxel administration. Dexamethasone administration was continued for 4 days after docetaxel administration. The starting dose of docetaxel in this pediatric Phase I trial was 150 mg/m², the dose at which neutropenia was dose-limiting in less-heavily pretreated patients on our previous pediatric Phase I trial using the same dosing schedule without G-CSF (17). Subsequent planned dose escalations were to 185 mg/m² and 235 mg/m².

G-CSF was supplied by Amgen (Thousand Oaks, CA) and was administered at a dose of 5 µg/kg/day s.c., starting 48 h after docetaxel and continuing until the nadir neutrophil count reached 10,000/µL. A minimum of three patients evaluable for toxicity were treated at each dose level. If one of the first three patients entered at any level experienced a dose-limiting toxicity during the first course of therapy, an additional three patients were entered at that dose level.

Toxicities were graded according to the National Cancer Institute common toxicity criteria (18). Dose-limiting nonhematological toxicity was defined as any grade 3 or 4 nonhematological toxicity, with the specific exclusion of grade 3 nausea and vomiting, grade 3 fever, and grade 3 hepatic toxicity that returned to grade 1 before the scheduled time for the next treatment. Dose-limiting hematological toxicity was defined as grade 4 neutropenia (< 500/µL), or thrombocytopenia (< 25,000/µL) for > 7 days duration. Each course was evaluated for hematological and nonhematological toxicity. The MTD of do-

---

**Table 1** Characteristics of the 17 patients entered onto the trial

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>14</td>
</tr>
<tr>
<td>Median</td>
<td>14</td>
</tr>
<tr>
<td>Range</td>
<td>14</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>7/10</td>
</tr>
<tr>
<td>Prior Therapy</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy only</td>
<td>13</td>
</tr>
<tr>
<td>Chemotherapy plus radiation therapy</td>
<td>4</td>
</tr>
<tr>
<td>Median (range) number of prior regimens</td>
<td>2.5 (1–6)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>9</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>2</td>
</tr>
<tr>
<td>Wilms’ tumor</td>
<td>1</td>
</tr>
<tr>
<td>Hepatoblastoma</td>
<td>1</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>1</td>
</tr>
<tr>
<td>Small round cell sarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Undifferentiated sarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Desmoplastic small round cell tumor</td>
<td>1</td>
</tr>
</tbody>
</table>

---

Results

Seventeen patients were entered onto the trial and received a total of 27 courses of docetaxel. Patient characteristics are listed in Table 1. Sixteen patients were evaluable for response; 15 patients (21 courses) were evaluable for hematological toxicity; and 14 patients (20 courses) were evaluable for nonhematological toxicity. One patient experienced a hypersensitivity reaction and had the docetaxel infusion stopped after only 3% of the prescribed dose had been administered. The hypersensitivity
As in the previous pediatric Phase I trial, platelet toxicity was 235 mg/m². The dermatitis was observed in 42% of the patients in 2 patients were the dose-limiting toxicities observed at a higher dose levels of docetaxel. A generalized erythematous periorbital rash, and on the third course (reduced dose of 150 mg/m²) formed. One of the patients at the 235-mg/m² dose level experienced a rash, which is reported here.

**Toxicity.** Grade 4 neutropenia (<500/µL) was seen at all of the dose levels but was <7 days in duration (Table 2). The median nadir neutrophil count was 95/µL (range, 0–8,690/µL) and occurred at a median of day 7 (range, 7–10) after docetaxel administration. The median day of recovery to ANC of 1500 for those patients with grade 4 neutropenia was day 10 (mean, day 10). Dose-limiting neutropenia did not occur as the dose was increased. Five patients required hospitalization for fever and neutropenia (2 of 6 patients at the 150 mg/m² dose level, 1 of 6 patients at 185 mg/m² dose and 2 of 3 patients at 235 mg/m²).

Table 2  Hematologic toxicity from docetaxel + G-CSF in children

<table>
<thead>
<tr>
<th>Dose level (mg/m²)</th>
<th>Neutropenia (&lt;500/µL)</th>
<th>Thrombocytopenia (&lt;50,000/µL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>3/6</td>
<td>0/6</td>
</tr>
<tr>
<td>185</td>
<td>3/6</td>
<td>0/6</td>
</tr>
<tr>
<td>235</td>
<td>3/3</td>
<td>0/3</td>
</tr>
</tbody>
</table>

*The duration of grade 4 neutropenia was <7 days (non-dose-limiting) in all of the patients.

Nonhematological toxicities became dose-limiting at these higher dose levels of docetaxel. A generalized erythematous desquamating skin rash in 3 of 4 evaluable patients and myalgias in 2 patients were the dose-limiting toxicities observed at 235 mg/m². The dermatitis was observed in 42% of the patients and at all of the three dose levels. The incidence and severity of the dermatitis increased with increasing dose. Two of six patients at 150 mg/m² developed rash (grade 1 and grade 2). In one patient, the rash began on day 5 of therapy and resembled a steroid-induced acne that was distributed on the face, back, shoulder, and upper arm. The second patient developed papules on both arms and legs and areas of erythema on the feet that started 10 days after docetaxel and resolved in two weeks. At the 185-mg/m² dose level, two of six patients developed rash that was dose-limiting in one. One patient developed a migrating erythematous rash (grade 3) in the perineal area and at tape sites on the chest and abdomen (Fig. 1). On the second course, the patient experienced recrudescence of perineal rash as well as a periorbital rash, and on the third course (reduced dose of 150 mg/m²²), the erythematous perineal rash was present but also involved the buttocks, scalp, face (along jaw line), soles of feet, popliteal region, and forearm. The rash developed within 1 week of docetaxel administration, resolved within 17 days, and was accompanied by desquamation. The second patient at 185 mg/m²² developed an erythematous rash (grade 2) during the second course with docetaxel. This rash was distributed over the cheeks, periorbital area, and intertriginous areas of the fingers and was accompanied by fever and later desquamation. It developed approximately 10 days after docetaxel and had resolved within 14 days. At 235 mg/m²², 3 of 4 patients developed rash. The rash in all of the three patients was erythematous, accompanied by desquamation, and involved the hands (palms), face, neck, and elbows. One patient’s rash extended over the entire body and was considered grade 3. Another patient developed a rash after each course (2-grade 2, 1-grade 3). In addition to the above mentioned areas, the rash in this patient also involved the nose, eyelids, and back of neck.

Other dose-limiting toxicities included myalgia in two patients at 235 mg/m²², grade 4 hemorrhage associated with severe (grade 4) mucositis in one patient at 150 mg/m²², sepsis in the one patient at 185 mg/m²² who developed a grade 3 rash, and a hypersensitivity reaction in one patient at 235 mg/m²². Peripheral edema and weight gain were not observed; however, only three patients received more than three courses.

Other non-DLTs included mild nausea and vomiting, constipation (n = 2), conjunctivitis (n = 1), transient grade 1 elevation of hepatic transaminases (n = 2), stomatitis (≤grade 2, n = 6), back pain (n = 1), fatigue (n = 1), fever (n = 6), infection (≤grade 2, n = 5), hypokalemia (n = 1), hypocalcemia (n = 1), and peripheral neuropathy (n = 1).
Phase I Trial of Docetaxel + G-CSF in Children

Response. A MR was observed in 1 patient of the 16 patients who were evaluable for response. This patient was a 15-year-old female with colon cancer who experienced gradual decrease in the size of an axillary lymph node after two courses of docetaxel at 150 mg/m². However, the patient refused further therapy.

DISCUSSION

The administration of G-CSF after docetaxel ameliorated the dose-limiting neutropenia that is associated with docetaxel alone (17) and permitted substantial escalation of the dose in pediatric patients. This approach has not been used in adults with docetaxel. The MTD of docetaxel (185 mg/m²) with G-CSF support is 50% higher than the MTD in a similar population of children treated with docetaxel alone (125 mg/m²) and 85% higher than the recommended adult dose (100 mg/m²). Patients on this trial who developed grade 4 neutropenia recovered by day 10 (median) in contrast to pediatric patients on the previous Phase I study without G-CSF in which recovery occurred between days 14 to 20. The rapid recovery from neutropenia when G-CSF is administered after docetaxel and the lack of thrombocytopenia allow this higher dose to be administered on an every-21-day schedule, which translates into a 50% increase in dose intensity with the docetaxel + G-CSF regimen. Although grade 4 neutropenia occurred with docetaxel doses of 150 mg/m² followed by G-CSF, the duration of neutropenia was short and the severity of neutropenia and thrombocytopenia did not seem to increase as the dose was escalated to 185 and 235 mg/m². The specificity of the myelosuppressive effects of docetaxel for the granulocyte lineage noted in the present trial and in our prior Phase I trial (17) is unusual for a myelosuppressive agent and deserves further laboratory investigation.

A generalized desquamative dermatitis that has been reported previously (18–20) in both pediatric and adult trials was the primary dose-limiting toxicity in this study. The incidence and severity of the rash seemed to be dose-related. The prolonged course of dexamethasone did not prevent the rash, although the onset of the rash in all of the patients was >24 h after completion of the 5-day course of dexamethasone. Skin reactions in adults at lower docetaxel doses have been reported in 50–75% of patients, and the rashes are characterized as erythematous, pruritic maculopapular rashes that affect the forearms and hands. This is similar to the skin toxicity observed in our pediatric patients. Other cutaneous effects reported in adults include desquamation of the hands and feet, palmar-plantar erythrodysesthesia that may respond to pyridoxine or cooling, and onychodystrophy characterized by brown discoloration, ridging, onycholysis, soreness, and brittleness of fingernails (13). Similar reactions, except for onychodystrophy, were observed on our trial. The cutaneous reactions seen in adults are usually mildly symptomatic, localized and self-limited with rare cases described as severe, whereas the reactions in pediatric patients at higher doses were more generalized and severe.

Dose-limiting myalgias were observed only at 235 mg/m² on the present trial, but myalgias were also dose-limiting in our previous Phase I trial of docetaxel in a single patient treated at the 150 mg/m² dose level (17). Therefore, it is unclear whether myalgias are a dose-related toxicity of docetaxel in children.

G-CSF may produce skin rashes and myalgias, but it is unlikely that G-CSF contributed to these dose-limiting toxicities. Skin rashes and myalgias similar to those observed in our patients have been previously reported in patients receiving docetaxel alone.

Fluid retention, weight gain, and edema, which have been described in adult and pediatric patients receiving multiple courses of docetaxel, were not observed in this study despite the substantially higher doses administered, possibly because only three patients received more than three courses of docetaxel. This toxicity may be more problematic in children in the Phase II setting because more patients receive multiple courses of docetaxel.

The minimal antitumor activity observed in this trial, despite the higher doses administered, probably reflects the small number of patients treated and the somewhat skewed patient population (9 of 17 patients had osteosarcoma). In our prior pediatric Phase I trial of docetaxel, responses were observed in rhabdomyosarcomas, peripheral primitive neuroectodermal tumors, and colon cancer. In this study, one MR was seen in a patient with colon cancer, but the other previously responsive tumor types were not represented in the present trial.

Myelosuppressive drugs are often tested in separate Phase I trials in relapsed leukemia patients to identify an MTD that is independent of the myelosuppressive effects of the agent. Escalation of the docetaxel dose with G-CSF support identified the nonhematological dose-limiting toxicity of docetaxel. We would predict that 185 mg/m² of docetaxel without G-CSF would be the MTD in relapsed leukemia patients, but because the myelosuppressive effects did not seem to be dose-related at the higher dose levels, it is unclear if this dose would be myeloblastic.

The use of G-CSF after high doses of docetaxel seems to be well tolerated, and G-CSF effectively circumvents the dose-limiting neutropenia caused by docetaxel. Consideration should be given to administering G-CSF after docetaxel in future trials.

REFERENCES

Phase I Trial of Docetaxel with Filgrastim Support in Pediatric Patients with Refractory Solid Tumors: A Collaborative Pediatric Oncology Branch, National Cancer Institute and Children's Cancer Group Trial

Nita L. Seibel, Susan M. Blaney, Michelle O'Brien, et al.

*Clin Cancer Res* 1999:5:733-737.

Updated version Access the most recent version of this article at: [http://clincancerres.aacrjournals.org/content/5/4/733](http://clincancerres.aacrjournals.org/content/5/4/733)

Cited articles This article cites 18 articles, 8 of which you can access for free at: [http://clincancerres.aacrjournals.org/content/5/4/733.full#ref-list-1](http://clincancerres.aacrjournals.org/content/5/4/733.full#ref-list-1)

Citing articles This article has been cited by 5 HighWire-hosted articles. Access the articles at: [http://clincancerres.aacrjournals.org/content/5/4/733.full#related-urls](http://clincancerres.aacrjournals.org/content/5/4/733.full#related-urls)

E-mail alerts Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at [pubs@aacr.org](mailto:pubs@aacr.org).

Permissions To request permission to re-use all or part of this article, contact the AACR Publications Department at [permissions@aacr.org](mailto:permissions@aacr.org).