Docetaxel Followed by Gemcitabine and Irinotecan in Solid Tumors

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Docetaxel (Taxotere), gemcitabine (Gemzar), and irinotecan (Camptosar, CPT-11) are active single agents in a variety of solid tumors. In combination, synergism may be schedule dependent. Preclinical studies suggested

Introduction

Irinotecan (Camptosar, CPT-11), gemcitabine (Gemzar), and docetaxel (Taxotere) are chemotherapeutic agents with different intracellular targets and complementary, rather than overlapping, mechanisms of action.

The taxanes induce polymerization of tubulin’s alpha and beta subunits, resulting in stabilization of microtubules and disruption of the cell cycle.[1,2] Difluorodeoxycytidine triphosphate (dFdCTP), the predominant intracellular metabolite of gemcitabine, is incorporated as a substrate during DNA synthesis, causing inhibition of DNA elongation and chain termination after the addition of another base or another molecule of dFdCTP. In addition, the diphosphate form of gemcitabine leads to a decrease in the normal intracellular triphosphate pools.[3,4] The active metabolite of irinotecan SN-38 stabilizes the covalent linkage between the topoisomerase I enzyme and the DNA backbone formed during the enzymatic relaxation of DNA torsional strain. This slows DNA religation during the catalytic cycle.[5]

All three agents—irinotecan, gemcitabine, and docetaxel—are individually active in a variety of malignancies as first- and second-line treatment. In preclinical studies, interactions between these agents have been demonstrated, with the magnitude of beneficial interaction at least somewhat schedule related. A marked synergistic effect was observed when CAEP cells, a cell line derived from squamous cell carcinoma of the lung, were exposed to docetaxel followed 24 hours later by gemcitabine; less synergy was observed with the reverse sequence.[6] The two sequences also produced moderate synergistic killing of RAL cells, a cell line derived from adenocarcinoma of the lung. In this cell line, enhanced synergism was encountered when a 48-hour washout was used between docetaxel and gemcitabine exposures.[6] A similar sequence, docetaxel given first followed 24 hours later by irinotecan, resulted in synergistic interactions between these two drugs in cancer cell lines.[7,8]

Simultaneous exposure to gemcitabine and irinotecan resulted in antagonism at low concentrations but synergism at concentrations of gemcitabine above 0.1 mM and irinotecan above 3.2 µM in the SCOG small-cell lung cancer cell line. In MCF7 breast cancer cells, synergism occurred at gemcitabine concentrations of 0.1 to 2 mM and irinotecan concentrations of 0.2 to 10 µM. However, antagonism occurred at high concentrations (ie, > 2 mM of gemcitabine and > 20 mM of irinotecan).[9]

Phase I data from our institution showed that gemcitabine administered at 1,000 mg/m² over 30 minutes followed by irinotecan at 100 mg/m² over 90 minutes (IrinoGem) could be administered on a day 1 and 8 schedule every 3 weeks.[10] This IrinoGem regimen has recently been studied in a phase II trial for chemotherapy-naive advanced and metastatic pancreatic cancer patients. In that trial, almost 90% full doses of both drugs were delivered on days 1 and 8. The regimen has been well tolerated and active with modest toxicity.[11]

To build on the clinical activity of IrinoGem and take advantage of the available preclinical synergy data, we conducted a phase I trial of the combination of docetaxel, gemcitabine, and irinotecan (the
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DIG regimen) in patients with solid tumors. The schedule and doses chosen were based on the preclinical synergistic interactions and our prior experience delivering almost full doses of gemcitabine and irinotecan in combination. In this trial, the doses of gemcitabine and irinotecan were initially fixed at 1,000 mg/m² and 100 mg/m², respectively. Docetaxel doses were to be escalated until the maximum tolerated dose for the combination was defined.

Two different schedules were studied: docetaxel was either administered on days 1 and 8, followed 24 hours later by gemcitabine and irinotecan on days 2 and 9 (schedule A), or docetaxel was administered on day 8, with gemcitabine and irinotecan on days 1 and 9 (schedule B). As was done in our prior studies with the gemcitabine/irinotecan combination, irinotecan was given immediately following gemcitabine.

The objectives of the study were to determine the maximum tolerated dose of docetaxel that could be administered with fixed doses of gemcitabine and irinotecan, to describe the pattern of dose-limiting toxicity, and to define the recommended phase II doses for each of the tested schedules of this three-drug regimen.

**Patients and Methods**

**Patient Selection**

Adult patients with pathologically confirmed solid tumors that were refractory to standard therapy, or for whom no standard therapy of proven efficacy was available, were eligible if they had adequate organ function, performance status of 0 to 2, and resolution of toxic effects from prior therapy. Adequate organ function was defined as granulocyte count of at least 1,500/mL, platelet count of at least 100,000/mL, serum creatinine < 2.1 mg/dL, and serum bilirubin < 2.1 mg/dL. Female patients with child-bearing potential must have had a negative pregnancy test.

Patients were ineligible if they had known bone marrow metastases, a history of congestive heart failure requiring medical therapy (New York Heart Association class III or IV), unstable angina, atrial fibrillation, or myocardial infarction within the 6 months prior to study entry, uncontrolled bacterial, viral, or invasive fungal infection, prior whole pelvic radiation, or a psychiatric condition that would prevent informed consent. Prior chemotherapy with any or all three of the agents under study was allowed. Measurable or evaluable disease was not required. All patients gave written informed consent by signing an informed consent document approved by the Institutional Review Board of the Medical University of South Carolina.

**Treatment Plan**

Docetaxel was administered as a 60-minute (later amended to a 30-minute) intravenous infusion on days 1 and 8 (arm A) or day 8 only (arm B). This was followed 24 hours later, on either days 2 and 9 (arm A) or day 9 (arm B) of each 3-week treatment cycle by a 30-minute intravenous infusion of gemcitabine at 1,000 mg/m² immediately followed by irinotecan at 100 mg/m² over 90 minutes. On arm B, the day 1 doses of gemcitabine and irinotecan were given without docetaxel pretreatment. The dose levels tested in this phase I trial are shown in Table 1. Cohorts of at least three patients were evaluated at each dose level. No dose escalation was permitted within individual patients.

Patients were removed from protocol if they demonstrated progressive disease or allergic reaction with diffuse rash or anaphylaxis, or if treatment termination was deemed in the best medical interests of the patient. Patients experiencing a dose-limiting toxicity, but also demonstrating clinical or radiographic response or stable disease with subjective benefit, could continue treatment at the next lower dose level.

**Drug Administration**

All patients received prophylactic antiemetic therapy chosen by their treating physician. Antiemetics generally included an HT3 blocker not only before docetaxel, but also before gemcitabine and irinotecan. Oral dexamethasone at 8 mg was taken the night before and bid on the same day as
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docetaxel for a total of three doses (dexamethasone at 20 mg IV was given 30 minutes before the infusion of docetaxel if the patient had not taken the dexamethasone the night before).

Gemcitabine at 1,000 mg/m² was prepared in 250 mL of normal saline and given over 30 minutes by IV infusion on days 2 and 9 (arm A) or days 1 and 9 (arm B) of each treatment cycle. Immediately following completion of each dose of gemcitabine, irinotecan at 100 mg/m², prepared in 500 mL of normal saline or 5% dextrose in water (D5W) solution, was administered over 90 minutes by IV infusion. Docetaxel at the cohort-specific dose was prepared in 100 mL of normal saline or D5W, and given over 60 minutes (later amended to 30 minutes) by IV infusion on days 1 and 8 (arm A) of each treatment cycle, or only on day 8 if the arm B dose escalation was being employed. The treatment cycles were repeated every 3 weeks.

Prophylactic atropine was not routinely given. In patients who developed cholinergic diarrhea during the infusion of irinotecan, 0.5 mg of atropine was administered IV. These and any other patients who reported diarrhea within the first 8 hours after completing irinotecan were given prophylactic atropine just before all subsequent doses of irinotecan. Patients were instructed to begin taking oral loperamide (Imodium) at the earliest signs of diarrhea and/or abdominal cramping that occurred more than 8 hours after receiving irinotecan. Loperamide was prescribed as 4 mg orally at the onset of cramps and/or diarrhea, and then 2 mg every 2 hours around the clock until the patient was diarrhea-free for at least 12 hours. During the night, patients were advised to take 4 mg of loperamide every 4 hours instead of 2 mg every 2 hours.

Growth factors were not permitted during the first cycle of therapy, unless profound neutropenia and severe or life-threatening infection were present. Patients received full supportive care (ie, transfusions of blood products, antibiotics, antidiarrheals, analgesics, etc, as appropriate).

### Dose Escalation and Maximum Tolerated Dose

For this phase I trial, the maximum tolerated dose was defined as the dose level immediately below the dose level at which two out of the first three patients in any cohort, or at least two out of six patients in any expanded cohort, experienced a dose-limiting toxicity. The following dose-escalation rules were used: Three patients were initially studied at the first dose level. If none of these patients experienced a dose-limiting toxicity during the first cycle of therapy, the dose was escalated to the next higher level for the next three patients. If one of three patients at any dose level experienced a dose-limiting toxicity, three additional subjects were accrued at that dose. If none of these three additional patients experienced a dose-limiting toxicity, the dose was escalated in subsequent recipients. If one or more of these three additional patients experienced a dose-limiting toxicity, the dose was escalated in subsequent cycles. If one or more of these three additional patients experienced a dose-limiting toxicity, the maximum tolerated dose was exceeded, and three more study subjects were treated at the next lower dose. The maximum tolerated dose defined in this trial was considered the recommended starting dose for subsequent phase II testing.

### Dose-Limiting Toxicity

Toxicity was graded according to the National Cancer Institute (NCI) Common Toxicity Criteria. For the purposes of defining the maximum tolerated dose, the dose-limiting toxicity pertained only to toxicity during the first cycle of treatment. The dose-limiting toxicity was defined as one or more of the following: (1) grade 3 and 4 nonhematologic toxicity (excluding nausea, vomiting, fever, and anorexia), (2) grade 4 neutropenia lasting ≥ 4 days, and (3) failure to recover neutrophils (≥ 1,500/mL) or platelets (≥ 100,000/mL) by day 29. During this phase I trial, days 8 and 9 treatment in cycle 1 were given at full doses if the neutrophil count was > 1,500/mL, platelets ≥ 100,000/mL, and there were no nonhematologic toxicities worse than grade 1. Day 8 and 9 treatments in cycle 1 were held in patients with either counts below this level or nonhematologic toxicity worse than grade 1 on that day. Dose adjustments for cycle 2 or later are enumerated in Table 2.

### Patient Evaluation

At enrollment, patients were evaluated with a complete history and physical examination, including a performance status assessment. Required blood counts, serum chemistries, and urinalysis were completed within 14 days of study entry. Any x-ray, scan, computed tomography, magnetic
reasonance imaging, or ultrasound that was utilized for tumor measurement in patients with measurable or evaluable disease had to have been performed within the 28 days prior to study entry. During the first cycle of chemotherapy, a physician monitored patients at least weekly. For subsequent cycles, patients were assessed at each chemotherapy visit. A complete blood count (CBC) with differential and serum chemistries was performed on days 1 and 8, with additional CBCs with differential on days 11, 14, 17, and 20 (if indicated) of each cycle.

In patients with measurable or evaluable disease, evaluation of tumor response was performed every two cycles. A complete response was defined as disappearance of all clinically detectable malignant disease, and a partial response was a ≥ 50% decrease in the sum of the products of perpendicular diameters of all measured lesions. No new lesions could appear, and no existing lesions could enlarge by > 25%. Progressive disease was defined as a ≥ 25% increase in the sum of products of measured lesions over the smallest sum observed (over baseline, if there was no decrease), reappearance of any lesion that had disappeared, or appearance of any new lesion. Stable disease was defined as findings that did not qualify for complete or partial response, or progressive disease.

Results

Patient Characteristics

A total of 25 patients were registered onto study at the Hollings Cancer Center, Medical University of South Carolina (the baseline characteristics and tumor types of all 25 patients are listed in Table 3 and Table 4, respectively). Nineteen patients were accrued in arm A: 15 males/4 females, median age: 61 years, with a Zubrod performance status of 0/1/2 (n = 3/12/4, respectively). Seventeen of these patients were evaluable (one died of an unrelated cause on cycle 1, and another withdrew consent before beginning treatment). Forty-two cycles of schedule A therapy have been delivered (mean: 2.5 cycles/patient).

In arm B, six patients were accrued: 2 males/4 females, median age: 61 years, with a Zubrod performance status of 0/1/2 (n = 0/5/1, respectively). Five patients were evaluable for maximum tolerated dose; one patient inadvertently received granulocyte colony-stimulating factor (G-CSF) on cycle 1. Twenty-five cycles of schedule B chemotherapy have been delivered (mean: 4.1 cycles/patient).

Hematologic Toxicities

Hematologic toxicities during cycle 1, which were dose limiting in this phase I trial, are shown in Table 5. At dose level 1 in arm A (docetaxel at 20 mg/m²), no dose-limiting hematologic toxicities were noted. However, one patient at dose level 1 with previously treated esophageal cancer experienced a grade 4 neutropenic episode for < 4 days. This patient received cycle 2 on schedule when again he had a grade 4 uncomplicated neutropenia of short duration. He was taken off study after cycle 2 due to disease progression. At dose level 2 (docetaxel at 25 mg/m²), one patient with previously treated renal cell carcinoma experienced a febrile neutropenic dose-limiting toxicity, and another patient with previously treated head and neck cancer had cycle 2 held for 1 week due to a neutrophil count of 1,400/mL.

Dose level 3 (docetaxel at 30 mg/m²) was associated with significant hematologic toxicity. One patient with previously treated head and neck cancer experienced a grade 3 infection with grade 4 neutropenia, and died after completing cycle 1 due to disease progression. The other two patients—one with previously treated head and neck cancer and another with previously treated hepatocellular carcinoma—had cycle 1, day 8 and 9 therapy held due to low neutrophil counts. At the confirmatory cohort level 2 (docetaxel at 25 mg/m²), three hematologic dose-limiting toxicities were observed. Two patients—one with previously treated colon cancer and the other with previously treated head and neck cancer—experienced grade 3 infection. The patient with colon cancer also experienced grade 4 neutropenia lasting > 4 days. The head and neck cancer patient withdrew consent after completing the first cycle, and the colon cancer patient had disease progression after two cycles.
On arm B (docetaxel at 45 mg/m² given on day 8 only), one patient with a previously untreated breast cancer and a new pancreatic mass had neutropenia for > 4 days. Since her breast cancer shrank during the first cycle, she received additional chemotherapy at a 25% dose reduction of all three drugs, per protocol. With the dose reduction, she had uncomplicated grade 4 neutropenia for < 4 days on cycle 2. On cycle 3, she had grade 3 neutropenia on day 11 and grade 4 neutropenia on day 14. Also on cycle 3, she had a red blood cell transfusion on day 9 to correct a hemoglobin level of 6.8 g/dL.

A patient with previously treated non-small-cell lung cancer had cycle 1, day 8 and 9 therapy held due to low neutrophil counts. This patient could not be evaluated for cycle 1 dose-limiting toxicity due to a weather-related interruption in his planned evaluation of blood counts. This patient was treated on cycle 2 at the full dose and did not experience dose-limiting toxicities; he was removed from the study after two cycles due to disease progression. Another patient on arm B could not be evaluated for dose-limiting toxicity due to erroneous administration of G-CSF on cycle 1. This patient, with previously untreated pancreatic cancer, withdrew consent after one cycle reporting that "she had felt much better" before starting the treatment with chemotherapy; on cycle 1 she had developed nausea/vomiting for an unspecified number of days.

In arm A, no cumulative hematologic toxicities have been demonstrated. However, none of the patients had more than six cycles of chemotherapy on protocol. In arm B, one patient with previously treated non-small-cell lung cancer had cumulative hematologic toxicity despite a 25% dose reduction of docetaxel and irinotecan due to grade 3 diarrhea experienced during cycle 1. He was transfused during cycle 6 for grade 3 anemia, and was admitted to the hospital on cycle 8 with grade 4 thrombocytopenia and severe epistaxis and hematochezia; he stopped therapy after eight cycles with stable disease.

Nonhematologic Toxicities

Nonhematologic toxicities are enumerated in Table 6. In dose level 1 of schedule A, no nonhematologic dose-limiting toxicities were observed. One patient with previously treated non-small-cell lung cancer had reversible grade 3 acute renal failure along with grade 2 diarrhea and nausea/vomiting, which occurred on cycle 5. The renal failure was thought to be secondary to dehydration, and the patient was taken off protocol following this episode.

At dose level 2, one patient with previously untreated renal cell carcinoma experienced grade 3 diarrhea for 1 day; he did not take loperamide as instructed. Per protocol requirement, this patient then received an additional five cycles at 75% of the initial dose, and he did not have additional grade 3 diarrhea. In addition, one patient on cycle 2 with previously untreated malignant mesothelioma experienced grade 3 diarrhea and asthenia. The doses of chemotherapy were reduced by 25%, with improvement of this symptomatology on the following cycles.

Of the three patients at dose level 3, one patient with head and neck cancer had grade 3 nausea/vomiting for 3 days. Another patient with previously treated hepatocellular carcinoma had reversible grade 3 asthenia and fatigue, leading to reduction in the doses of all three drugs by 25%. One of the four patients on cohort dose level 2.1 with previously treated colon cancer experienced grade 3 diarrhea starting on cycle 1, day 10, and lasting for 3 days. This patient did not take loperamide as recommended.

On arm B, two patients had nonhematologic dose-limiting toxicities. One patient with previously treated non-small-cell lung cancer had grade 4 diarrhea, and was admitted to the hospital with orthostatic hypotension; he was removed from the study after one cycle due to disease progression. The other patient, also with non-small-cell lung cancer, experienced grade 3 diarrhea for 14 days, and was also admitted to the hospital. This resulted in a 25% dose reduction of docetaxel and irinotecan, and the diarrhea was improved in all subsequent cycles. The patient with previously untreated pancreas cancer who was erroneously given G-CSF during cycle 1 had grade 3 nausea and vomiting for several days during the first cycle.

Response Evaluation
The response data for arms A and B are shown in Table 7. No patients had a confirmed partial or complete response, while a total of five patients experienced stable disease for \( \geq 4 \) cycles. Five additional patients had some evidence of initial tumor shrinkage, but then either progressed rapidly or were removed from study for other reasons. For example, at dose level 1 of schedule A, one patient with heavily previously treated non-small-cell lung cancer showed tumor shrinkage for five cycles. She had multiple, too small to count, small lung nodules, many of which significantly decreased in size and some that disappeared. She was removed from protocol due to renal toxicity.

At dose level 2, two patients showed tumor shrinkage: one had a previously untreated malignant mesothelioma that had tumor shrinkage after two cycles and stable radiologic findings after four cycles when he was taken off protocol; the other, with a previously treated composite non-small-cell lung cancer and small-cell lung cancer, had tumor shrinkage after the first course of chemotherapy, but declined further treatment due to personal reasons. At dose level 3, one patient with previously treated head and neck cancer demonstrated \( \geq 50\% \) tumor regression after two cycles of therapy; this patient was taken off protocol after his third cycle of chemotherapy because of worsening of his performance status and nutritional problems.

On arm B, the patient with an untreated breast cancer and a coincident pancreatic mass of uncertain etiology had rapid reduction in her breast cancer without shrinkage of the pancreatic mass. She declined additional protocol treatment after four cycles of chemotherapy.

**Recommended Doses for Phase II Studies**

The maximum tolerated dose of docetaxel given intravenously on days 1 and 8 followed by the combination of gemcitabine at 1,000 mg/m\(^2\) and irinotecan at 100 mg/m\(^2\) given on days 2 and 9, every 3 weeks as described here (schedule A) is 20 mg/m\(^2\). This regimen is appropriate for phase II testing. We do not plan additional phase I testing of our schedule B and cannot recommend a phase II regimen using day 8-only docetaxel in combination with day 1 and 9 gemcitabine and irinotecan.

**Trial Course**

In arm A at dose level 1, no cycle 1 dose-limiting toxicities were noted. At dose level 2, one of the three original patients experienced a cycle 1 dose-limiting toxicity (febrile neutropenia). This cohort was then expanded to include three additional patients (one of these patients died of a cause unrelated to the study). Therefore, an additional patient was accrued at the cohort 2 level. Among these four patients, one experienced 1 day of grade 3 diarrhea, but no other dose-limiting toxicities were observed. Due to the disparate nature of the dose-limiting toxicities noted at dose level 2 plus the brief, barely grade 3 diarrhea leading to one of the dose-limiting toxicity designations, written permission was obtained from the MUSC Institutional Review Board to proceed with dose level 3 accrual.

At dose level 3, all three patients experienced significant toxicities during cycle 1; one patient had two dose-limiting toxicities—grade 3 infection and grade 4 neutropenia for \( \geq 4 \) days. The other two patients were unable to receive cycle 1, day 8 and 9 chemotherapy due to grade 2 neutropenia. No additional patients were entered at this dose level.

In an attempt to confirm dose level 2 as the maximum tolerated dose, four additional patients were then accrued to the docetaxel cohort dose of 25 mg/m\(^2\). Two of these patients experienced dose-limiting toxicities (grade 3 diarrhea and grade 4 neutropenia for \( \geq 4 \) days), one patient with previously treated colon cancer experienced grade 3 infection, and a patient with previously treated head and neck cancer also had grade 3 infection. The next lower cohort dose (docetaxel at 20 mg/m\(^2\) days 1 and 8, with gemcitabine at 1,000 mg/m\(^2\) followed by irinotecan at 100 mg/m\(^2\), on days 2 and 9) was then considered the maximum tolerated dose.

Because the maximum tolerated dose was the original starting dose of the trial, written approval was obtained from the Institutional Review Board to amend further the study protocol. In this revision, the dose of irinotecan was reduced to 80 mg/m\(^2\) to maintain the sequence with gemcitabine at 1,000 mg/m\(^2\) on days 2 and 9. Docetaxel was again given at 25 mg/m\(^2\) on days 1 and 8. The first patient...
enrolled at this dose level experienced no dose-limiting toxicities; we plan to continue accrual with docetaxel at 25 mg/m on days 1 and 8 along with gemcitabine at 1,000 mg/m followed by irinotecan at a modified dose of 80 mg/m on days 2 and 9.

In arm B, significant dose-limiting toxicities were observed at the starting docetaxel dose of 45 mg/m. The dose-limiting toxicities in arm B were grade 3 diarrhea in one patient with previously treated non-small-cell lung cancer, grade 4 diarrhea in another patient with previously untreated non-small-cell lung cancer, and prolonged grade 4 neutropenia in a previously untreated breast cancer patient with a concomitant pancreatic mass. In addition, a patient with previously untreated pancreas cancer had grade 3 nausea/vomiting. It was felt that dose deescalation was not worth pursuing at this time, and arm B ended after the first dose level had been investigated.

Discussion

Our previous phase I work[10] with gemcitabine and irinotecan defined the recommended phase II dose of gemcitabine at 1,000 mg/m over 30 minutes followed by irinotecan at 100 mg/m over 90 minutes. Doses of each drug were given weekly for 2 consecutive weeks (days 1 and 8) every 3 weeks, and the dose-limiting toxicity was diarrhea; myelosuppresion was modest. These findings suggested the possibility that an additional drug could be combined with the IrinoGem regimen. Based on preclinical data from our institution and the substantial single-agent activity of docetaxel in several solid tumors, we developed two schedules of the three-drug regimen of docetaxel, irinotecan, and gemcitabine for phase I testing. The findings of this phase I work suggest that the combination of low doses of docetaxel on days 1 and 8, with full doses of IrinoGem on days 2 and 9, is feasible without growth factor support. However, toxicity is not insignificant, and attempts at escalation of the dose of docetaxel above the initial cohort dose level of 20 mg/m resulted in an excess of dose-limiting toxicities.

In our phase I trial of IrinoGem,[10] no episodes of febrile or prolonged neutropenia were observed during the first cycle of therapy at any dose level. In a phase II trial of IrinoGem in pancreatic cancer,[11] only a 2.2% rate of grade 4 neutropenia (and no neutropenic fevers) was reported during the 394 cycles administered in 45 patients. However, the addition of even docetaxel at 25 mg/m on days 1 and 8 to full doses of IrinoGem on days 2 and 9 led to several episodes of grade 4 neutropenia lasting > 4 days and/or grade 3 infection. Disappointingly, this marked augmentation in hematologic toxicity and infectious episodes was not accompanied by a similarly dramatic increase in efficacy.

As single agents, docetaxel, irinotecan, and gemcitabine all showed schedule-dependent dose-limiting toxicities. On weekly or "3 weeks out of 4" schedules, gemcitabine was associated with dose-limiting myelosuppression.[12,13] For irinotecan, severe neutropenia (78% grade 3/4) was the dose-limiting toxicity when the agent was given in an every-3-week schedule by Merrouche and colleagues.[14] With docetaxel, severe neutropenia occurred on the every-3-week or the days 1 and 8 every-3-week schedule.[15] Weekly × 4 every-6-week administration of irinotecan had severe diarrhea as the dose-limiting toxicity, despite the use of an aggressive regimen of loperamide at the onset of diarrhea.[16,17] In the study by Hainsworth et al[18] assessing weekly docetaxel, grade 4 asthenia was limiting at dose levels that rarely produced severe myelosuppression.

Grade 3 asthenia and fatigue were not noted in either our phase I or II experience with IrinoGem. However, with the addition of low-dose docetaxel, these toxicities became evident in later cycles of therapy. In the DIG regimen, 1 of 10 patients at a docetaxel dose of 25 mg/m, and another 3 patients at 30 mg/m, experienced grade 3 asthenia and fatigue. In addition, grade 1 or 2 asthenia was frequently observed at docetaxel dose levels ≥ 25 mg/m on days 1 and 8. This toxicity was reminiscent of the current experience using 6 consecutive weeks every 8 weeks of single-agent docetaxel administration,[18] but occurred at lower dose levels than in prior work.

In the phase I study of weekly docetaxel, the incidences of asthenia and fatigue were clearly dose dependent. Grade 3 asthenia was the dose-limiting toxicity in 2 of 10 patients at a docetaxel dose of 43 mg/m; the maximum tolerated dose of docetaxel was 36 mg/m. At lower doses, fatigue and
asthenia were never dose limiting. In follow-up phase II trials testing the same weekly schedule of docetaxel in elderly lung cancer[19] and metastatic breast cancer patients,[20] the incidence of severe fatigue and asthenia was 14% and 10% at respective docetaxel doses of 36 and 40 mg/m².

In a trial of single-agent docetaxel administered on days 1 and 8 on an every-3-week cycle, asthenia was also dose dependent, but not dose limiting. In the phase I trial of Tomiak et al,[15] among 32 patients with refractory solid malignancies treated at doses between 20 and 110 mg/m² per course, 10 of 23 assessable patients receiving ≥ 50 mg/m² on days 1 and 8 experienced severe asthenia. However, no episodes of severe asthenia and fatigue were observed at lower dose levels. Our data suggest that the triple combination may potentiate this toxicity, and we will carefully assess this toxicity in additional patients treated with this combination.

As reported from the studies of Rowinsky and coworkers[16] and Rothenberg et al,[17] diarrhea is the dose-limiting toxicity of weekly single-agent irinotecan. However, significant diarrhea is a much less common toxicity with single-agent docetaxel or gemcitabine. For example, in a study of 730 patients with metastatic breast cancer (and normal liver function test values) given docetaxel at 100 mg/m², severe diarrhea was reported in 6% of patients. In the gemcitabine database of 973 patients treated at starting doses ranging from 800 to 1,250 mg/m², the incidence of severe diarrhea was only 1%. However, combinations may produce enhanced diarrheal toxicity.

Spridonidis and collaborators[21] reported that with gemcitabine at a fixed dose of 800 mg/m² on days 1, 8, and 15, and escalated doses of docetaxel on day 1 every 4 weeks, grade ≥ 2 diarrhea occurred in 17% of patients treated with docetaxel at 75 mg/m² and in 33% treated at 100 mg/m² in phase I investigation. In the two-drug IrinoGem combination, diarrhea was the dose-limiting toxicity at an irinotecan dose of 115 mg/m² on days 1 and 8. With the DIG regimen, diarrhea was also dose limiting in two patients in arm A at 25 mg/m² and in two patients in arm B at the initial dose of docetaxel at 45 mg/m².

This phase I trial accrued predominantly pretreated patients, and previous exposure to all three drugs under study did not exclude patients from study. Among the 25 patients accrued, five had radiologic tumor reductions that did not reach the formal criteria for a partial response, and two additional patients had stable disease for more than six cycles. The patients with tumor shrinkage did not have confirmed responses for a variety of reasons (none related to tumor regrowth).

Full doses of IrinoGem (30-minute infusion of gemcitabine at 1,000 mg/m² immediately followed by 90-minute infusion of irinotecan on days 2 and 9) combined with a 30-minute infusion of docetaxel at 20 mg/m² on days 1 and 8 can be used as the starting doses for this triplet in phase II trials. Myelosuppression should be manageable at this dose level, but cumulative asthenia and fatigue will be more prominent than with IrinoGem alone. Currently, we plan to evaluate the escalation of the docetaxel dose to 25 and 30 mg/m² on days 1 and 8, with gemcitabine at 1,000 mg/m² immediately followed by irinotecan at a reduced dose of 80 mg/m² on days 2 and 9.

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