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CLINICAL TRIAL REPORT

# A phase I trial of gemcitabine in combination with patupilone in patients with advanced solid tumors

**William Schelman · Sherry Morgan-Meadows · Howard Bailey · Kyle Holen · James P. Thomas · Jens Eickhoff · Heidi Brandon · Kate Oliver · Dona Alberti · George Wilding**

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**Abstract**
*Introduction* Chemotherapy regimens including gemcitabine in combination with microtubule inhibitors such as docetaxel and paclitaxel have wide clinical application. Patupilone is a novel tubulin-polymerizing agent with activity against paclitaxel-resistant cell lines. We conducted a phase I trial to assess the maximum tolerated dose, dose limiting toxicity (DLT) and antitumor activity of gemcitabine and patupilone.
*Methods* Patients with refractory solid tumors enrolled in cohorts of three. Cohorts received fixed doses of gemcitabine (1,000 or 750 mg/m$^2$) along with escalating doses of patupilone (1.5–3 mg/m$^2$) on days 1 and 8 of a 21-day cycle.
*Results* Twenty-seven patients received a total of 99 courses of treatment on study. Hematologic toxicity in the first cohort required a modification of the protocol to decrease the gemcitabine dose. Subsequent patients received gemcitabine 750 mg/m$^2$ and escalating doses of patupilone from 1.5 to 3 mg/m$^2$. DLTs were grade 3 asthenia and grade 3 dehydration. There was also one treatment-related death due to neutropenic infection. Other clinically significant toxicities were persistent asthenia and persistent nausea. Four patients, one each with pancreatic cancer, esophageal carcinoma, cholangiocarcinoma and gallbladder carcinoma, experienced a partial response.
*Conclusions* The dose-limiting toxicities of gemcitabine and patupilone were asthenia and dehydration. Dose reductions also occurred due to persistent fatigue that was not dose-limiting. However, patients with advanced malignancies were able to tolerate gemcitabine and patupilone at doses that resulted in clinical benefit. The recommended phase II dose for this schedule is gemcitabine 750 mg/m$^2$ and patupilone 1.5 mg/m$^2$ on days 1 and 8 of a 21-day cycle.

**Keywords** Gemcitabine · Patupilone · Chemotherapy · Phase I

W. Schelman (✉) · S. Morgan-Meadows · H. Bailey · K. Holen · J. P. Thomas · J. Eickhoff · H. Brandon · K. Oliver · D. Alberti · G. Wilding
University of Wisconsin Paul P. Carbone Comprehensive Cancer Center, 600 Highland Avenue, K4/530 CSC, Madison, WI 53792, USA
e-mail: wrs@medicine.wisc.edu

*Present Address:*
S. Morgan-Meadows
Southern Cancer Center, Mobile, AL, USA

*Present Address:*
J. P. Thomas
The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA

## Introduction

Microtubules are essential for many cellular processes including mitosis, motility, secretion and proliferation. Agents that interfere with tubulin polymerization disrupt these cell functions, resulting in mitotic arrest. Microtubule inhibitors have become an important class of antineoplastic compounds in the treatment of solid tumors and hematologic malignancies. Unlike the vinca alkaloids, vinblastine and vincristine, which inhibit tubulin polymerization [1], the taxanes, paclitaxel and docetaxel, promote tubulin polymerization and stabilize preformed microtubules [2]. While paclitaxel is currently used as first-line therapy in a number of solid tumors including breast, ovarian, lung, colon and liver neoplasms, its

efficacy has been limited by acquired resistance to genes such as the P-glycoprotein MDR gene [3].

The epothilones are a group of non-taxane, tubulin-polymerizing agents that have preclinical activity in taxane-resistant cell lines [4]. Patupilone (epothilone B, EPO906) induces polymerization of tubulin dimers into stable microtubules [5, 6] and inhibits cell growth in a variety of human cancer cell lines. In preclinical models, patupilone displayed activity against paclitaxel-resistant cell lines and retained its activity in cells expressing either increased P-glycoprotein-mediated efflux or tubulin mutations. In addition, patupilone had a higher potency than paclitaxel in growth inhibition trials [7, 8].

Recent clinical studies have evaluated patupilone. Two schedules of patupilone, weekly i.v. and every 3 weeks i.v., have been evaluated in phase I trials [9, 10]. Diarrhea was dose limiting in both schedules. The recommended phase II dose was 2.5 mg/m$^2$ for the weekly schedule and 6 mg/m$^2$ for the every 3-week schedule. Subsequent phase II studies have demonstrated activity in prostate [11], ovarian and breast cancer [12] and in renal cell carcinoma [13].

Gemcitabine has clinical activity in a variety of cancers, both alone and in combination with either paclitaxel or docetaxel [14–20], resulting in wide application in metastatic cancer. These agents have non-overlapping toxicity, and myelosuppression is the major dose limiting toxicity (DLT) observed in combination studies. Clinical activity has been seen in a number of tumors including breast cancer [17, 21, 22], non-small cell lung cancer [16, 23–26], unknown primary [27], urothelial carcinoma [28–30], biliary tract [31] and pancreatic cancer [32, 33].

Based on the observed clinical activity of patupilone and the clinical utility of gemcitabine–microtubule agent combinations, we conducted a phase I dose escalation trial of gemcitabine in combination with patupilone.

## Methods

### Patient population

Eligible patients had, (a) histologically confirmed, incurable malignancy refractory to standard therapy or for which no standard therapy exists, (b) an ECOG performance status of 0, 1, or 2, (c) preserved organ function as demonstrated by platelet count $\geq$100,000 mm$^{-3}$, ANC $\geq$ 1,500 mm$^{-3}$, hemoglobin $\geq$ 10 g/dl, bilirubin $\leq$ 1.5 mg/dl, serum creatinine $\leq$ 1.5 mg/dl, (d) sensory neuropathy $\leq$ grade 1, (e) diarrhea $\leq$ grade 1 and (f) age $\geq$ 18 years. Pregnant and lactating females were not eligible. In addition, 4 weeks must have elapsed since prior chemotherapy or radiotherapy, and patients must have recovered fully from toxicity.

### Study agents and regulatory information

Treatment consisted of gemcitabine and patupilone. The Health Sciences Institutional Review Board of the University of Wisconsin approved this trial, and all patients gave written informed consent for participation.

### Study design

The study was an open-label, single institution, phase I trial using a standard dose escalation schedule with sequential cohorts receiving gemcitabine with increasing doses of patupilone (Table 1). Patients received patupilone over 5 min followed by a 30-min infusion of gemcitabine on days 1 and 8 of a 21-day cycle. Gemcitabine doses on days 1 and 8 were initially fixed at 1,000 mg/m$^2$; however, grade 2 neutropenia at dose level 1 prompted an amendment to decrease the gemcitabine dose to 750 mg/m$^2$ on days 1 and 8. DLT was defined as any toxicity occurring in cycle 1 considered definitely related to patupilone or gemcitabine and met the following criteria: $\geq$grade 3 diarrhea despite appropriate intervention, grade 4 neutropenia for $\geq$5 days, febrile neutropenia, grade 4 hemoglobin of any duration, platelet count $<25 \times 10^9\,l^{-1}$ of any duration, $\geq$grade 3 neuropathy or any other non-hematologic toxicity $\geq$grade 3. Maximum tolerated dose (MTD) was defined as the highest safely tolerated dose where $\geq$1 patient out of six experienced DLT. Patients enrolled in cohorts of three. If no patients in a cohort experienced DLT, escalation proceeded according to table one. If one of the first three patients experienced a DLT, three additional patients were added in that cohort. If no additional DLTs occurred, escalation continued.

Since treatment with patupilone can cause diarrhea, patients were prospectively monitored for diarrhea. Patients with grade 1 or 2 diarrhea were initially treated with loperamide 4 mg followed by 2 mg after each loose stool (standard dose) and were reassessed at 24 h. If the diarrhea had not resolved, the loperamide was increased to 4 mg followed by 2 mg every 2 h (high dose), and they were

**Table 1** Dose escalation schema with number of subjects and courses

| Dose level | *n* | Gemcitabine (mg/m$^2$)[c] | Patupilone (mg/m$^2$)[c] | Courses number |
|---|---|---|---|---|
| 1 | 5 | 1,000 | 1.5 | 15 |
| 1a[b] | 6 | 750 | 1.5 | 29 |
| 2a | 6 | 750 | 2 | 18 |
| 3a[a] | 6 | 750 | 2.5 | 27 |
| 4a | 4 | 750 | 3 | 10 |

[a] MTD

[b] Recommended phase II dose

[c] Administered i.v. on days 1 and 8 of a 21-day cycle

again reassessed at 24 h. Grade 3 or 4 diarrhea was treated in the hospital with high-dose loperamide and tincture of opium. Patients were reassessed at 24 h and if diarrhea persisted, octreotide was administered. At presentation, patients were assessed for secondary causes of diarrhea. Persistent diarrhea was treated in a manner identical to grade 3 or 4 diarrhea.

### Adverse events monitoring

All toxicities were graded according to the National Cancer Institute Common Toxicity Criteria Grading System, version 2, and assigned an attribution of unrelated, unlikely, possible, probable, or definite in relation to treatment with the combination of gemcitabine and patupilone.

### Clinical response evaluation

Clinical response was not a primary endpoint of this study. However, all patients with measurable disease were assessed for clinical response after each even numbered cycle. Disease response and progression were determined using standard RECIST criteria [34].

## Results

Twenty-seven patients enrolled in this trial over 24 months. Patient characteristics appear in Table 3. Two-thirds of the patients had a gastrointestinal primary tumor (pancreas-8, esophagus-3, gallbladder/cholangiocarcinoma-5). The initial patient cohort received gemcitabine 1,000 mg/m$^2$ and patupilone 1.5 mg/m$^2$ on days 1 and 8; however, three of five patients treated at this dose level had hematologic toxicity requiring the elimination of the day 8 dose. Therefore, this dose was felt to be excessively toxic, and the protocol was amended to decrease the gemcitabine dose to 750 mg/m$^2$. Dose escalation then resumed at dose level 1a.

Escalation proceeded to dose level 4a without DLT (Table 2). Two patients at this dose level experienced DLT (grade 3 fatigue, grade 3 dehydration). Consequently, further enrollment to dose level 4a ceased, and an additional two patients were enrolled at dose level 3a. Of the additional two patients, one experienced a DLT (grade 5 pneumonia), and enrollment to this cohort also ceased. Dose level 3a met the predefined criteria for MTD; however, three of the six patients treated at this dose level had persistent, low-grade asthenia that, although not meeting the definition of DLT, prompted discontinuation of therapy. These three patients received therapy for a total of five, six and six cycles, respectively. One additional patient at dose level 3a who was treated for six cycles also suffered persistent low-grade asthenia, but opted to remain on therapy until disease progression. Due to the intolerable asthenia observed with prolonged therapy, this dose was not felt to be clinically tolerable, and accrual resumed at dose level 2a (Table 3).

Two additional patients were subsequently enrolled to cohort 2a, and two patients from higher dosing cohorts on active treatment were also dose-reduced to this dose level. One of the patients from a higher dose cohort experienced persistent low-grade asthenia despite dose reduction. Consequently, this dose was also considered clinically intolerable,

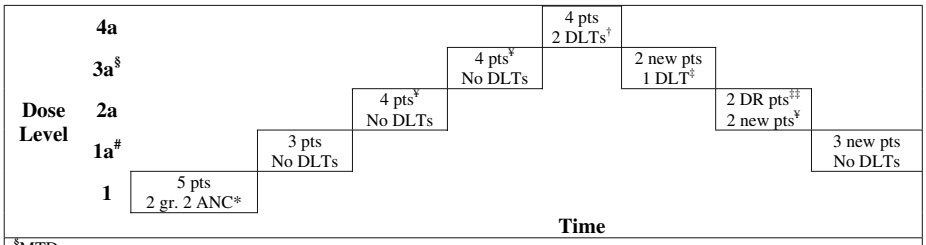
**Table 2** Flow chart of dose escalation

**(a)**

| Dose level | n | Gemcitabine ( mg/m$^2$)† | Patupilone (mg/m$^2$)† | Courses No. |
|---|---|---|---|---|
| 1 | 5 | 1000 | 1.5 | 15 |
| 1a‡ | 6 | 750 | 1.5 | 29 |
| 2a | 6 | 750 | 2 | 18 |
| 3a* | 6 | 750 | 2.5 | 27 |
| 4a | 4 | 750 | 3 | 10 |

*MTD
‡Recommended phase II dose.
†Administered i.v. on days 1 and 8 of a 21 day cycle.

**(b)**




§MTD
#Recommended phase II dose
*Gr.2 ANC requiring dose delay C1D8
¥One pt unevaluable
†Gr.3 asthenia and Gr.3 dehydration
‡Gr.5 pneumonia
‡‡Pts dose reduced from next highest level due to persistent asthenia

**Table 3** Patient characteristics

| | *n* |
|---|---|
| Total | 27 |
| Median age, year (range) | 62 (29–77) |
| Gender | |
| Male | 15 |
| Female | 12 |
| ECOG performance status | |
| 0 | 6 |
| 1 | 18 |
| 2 | 3 |
| Primary tumor type | |
| Pancreas | 7 |
| Cholangiocarcinoma | 4 |
| Breast | 3 |
| Esophageal | 3 |
| Bladder | 2 |
| Leiomyosarcoma | 2 |
| Prostate | 1 |
| Ovarian | 1 |
| Uterine | 1 |
| Neuroendocrine | 1 |
| Gallblader | 1 |
| Unknown primary | 1 |
| Prior systemic therapy | |
| 0 | 6 |
| 1 | 7 |
| 2 | 7 |
| 3 | 4 |
| 4 | 3 |

and enrollment resumed at dose level 1a. Three additional patients were enrolled at dose level 1a, for a total of six patients. The initial three-person cohort at this level included two patients who were treated for 6 and 9 months without significant asthenia. The three additional patients enrolled at level 1a experienced grade 1 fatigue but were able to continue with treatment. For this reason, dose level 1a was the recommended phase II dose.

The most common toxicities are shown in Table 4. Consistent with prior patupilone experience, 33% of courses resulted in diarrhea. Despite an aggressive treatment regimen instituted for diarrhea on this protocol, two patients required intravenous hydration. Other gastrointestinal toxicity included persistent, low-grade nausea. The severity of nausea increased with escalating doses of patupilone and ultimately required a modification of the protocol to include aprepitant as standard premedication. Unlike prior experience with patupilone, neutropenia occurred in 15% of courses. As a result of two patients experiencing grade 2 neutropenia during cycle 1, the protocol was amended to decrease the dose fixed dose of gemcitabine to 750 mg/m$^2$. After the gemcitabine dose was reduced, only one additional patient required a dose modification for neutropenia at dose level 2a. Neutropenia-associated infections occurred in two patients. One patient with advanced prostate cancer entered at dose level 3a (received treatment on days 1 and 8) was hospitalized on day 13 for dyspnea and neutropenia and died due to sepsis secondary to pneumonia. The most clinically significant toxicity was asthenia which occurred in 25% of cycles administered. Although predominately grade 1, fatigue was persistent between cycles, increased with escalating doses of patupilone and resulted in discontinuation of therapy in three patients at dose level 3a. Two patients also experienced four episodes of grade 1 neuropathy (not shown).

Although not a primary endpoint of this trial, patients underwent disease assessment prior to every even numbered cycle (Table 5). Partial responses (PR) were achieved in four patients, one each with pancreatic carcinoma, esophageal carcinoma, cholangiocarcinoma and gallbladder cancer. There were no complete responses. One patient at dose level 1a with esophageal cancer who had received three prior therapies, including one paclitaxel-containing regimen, had a 41% decrease in tumor size following two cycles of therapy and a 67% reduction after four cycles. Treatment was discontinued after a total of eight cycles due to patient wishes. Another patient at level 1a with previously untreated pancreatic cancer achieved a PR and did well until progressive disease was noted after 12 cycles of therapy. One patient at dose level 2a with cholangiocarcinoma who had received two prior treatment regimens had a documented PR following two cycles and remained on therapy for a total of 18 cycles before treatment was discontinued due to progressive disease. A patient with previously untreated gallbladder cancer at dose level 4a had a PR following four cycles of therapy. However, patupilone and gemcitabine were both dose-reduced during cycle 2 due to grade 3 fatigue which required treatment delays during cycle 1. Therapy was eventually discontinued after five cycles due to MD discretion for progressive toxicity.

## Discussion

This phase I study demonstrated that patupilone and gemcitabine resulted in persistent asthenia and nausea with prolonged treatment, but patients with pretreated malignancies were able to tolerate this combination at doses that resulted in clinical benefit. Significant myelosuppression was observed at dose level 1 (fixed-dose gemcitabine at 1,000 mg/m$^2$) which required a dose reduction in gemcitabine to 750 mg/m$^2$. Patupilone was well-tolerated over a

**Table 4** Drug-related adverse events, worst per course (99 total courses)

| Selected toxicities | Dose level | | | | | | | | | | | | | | | | | | | | Total (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | | | | 1a | | | | 2a | | | | 3a | | | | 4a | | | | |
| | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 | |
| Hematologic | | | | | | | | | | | | | | | | | | | | | |
| Anemia | | 2 | 1 | | | | | | | | 1 | | | 3 | | | | 2 | 1 | | 10 (10.1) |
| Neutropenia | 1 | 6 | | | | 1 | | | | 1 | 1 | 1 | | 1 | 2 | 1[a] | | | | | 15 (15.2) |
| Thrombocytopenia | 1 | 1 | 1 | | | | | | | 1 | | | 2 | 1 | 1 | | | 1 | | | 9 (10) |
| Non-hematologic | | | | | | | | | | | | | | | | | | | | | |
| Nausea | | | | | 3 | | 1 | | 4 | | | | 4 | 4 | | | 3 | | | | 19 (19.2) |
| Vomiting | | | | | 3 | 1 | | | 1 | | | | 2 | 3 | 1 | | 2 | | | | 13 (13.1) |
| Diarrhea | 3 | | | | 2 | 2 | | | 4 | 1 | 1 | | 6 | 4 | 3 | | | 7 | | | 33 (33.3) |
| Asthenia | 4 | 2 | | | 6 | 4 | 1 | | | | | | 4 | | | | | 2 | 2[b] | | 25 (25.3) |
| Anorexia | 2 | | | | | | 1 | | | | | | 3 | | | | 2 | 2 | | | 10 (10.1) |
| Dehydration | | | | | | 1 | | | | | | | | 1 | 2 | | | 2 | 2[b] | | 8 (8.1) |
| Weight loss | | | | | | | | | | | | | 1 | 2 | | | 2 | | | | 5 (5.1) |

[a] One patient experienced a grade 5 neutropenic infection resulting in death

[b] Includes single event that met criteria for dose-limiting toxicity

**Table 5** Response

| Best response | Number | Median duration (months) |
|---|---|---|
| Progressive disease | 10 | – |
| Stable disease | 6 | 4.5 |
| Partial response | 4 | 7 |
| Complete response | 0 | – |
| Not evaluable | 7 | |

wide range of doses when given along with gemcitabine at the reduced level aside from persistent fatigue. Based on the predefined criteria, the MTD was established at gemcitabine 750 mg/m$^2$ and patupilone 2.5 mg/m$^2$; however, three of the six patients treated at this dose level had persistent, low-grade asthenia that, although not meeting the definition of DLT, prompted discontinuation of therapy. One of the patients from level 3a who was dose reduced to level 2a (gemcitabine 750 mg/m$^2$ and patupilone 2 mg/m$^2$) also continued to experience unremitting fatigue that required discontinuation of treatment. Consequently, the recommended phase II dose for this schedule is patupilone 1.5 mg/m$^2$ over 5 min followed by gemcitabine 750 mg/m$^2$ over 30 min on days 1 and 8 of a 21-day cycle.

Clinical assessment of patupilone has been conducted using three schedules, weekly, every 3 weeks and continuous infusion. Diarrhea was dose limiting in all schedules tested. Compared to bolus administration, continuous infusion resulted in more diarrhea. Phase II trials have been performed using both the weekly and every 3-week regimen with clinical activity being seen in prostate [11], ovarian and breast cancer [12] and in renal cell carcinoma [13]. Patupilone was fairly well tolerated in these studies with only three reported cases of grade 3 or 4 toxicities, including diarrhea, constipation, nausea and vomiting.

Given the interest in combinations containing anti-microtubule agents with gemcitabine, we chose to evaluate gemcitabine with weekly patupilone in patients with refractory malignancies. This combination had more toxicity than anticipated. Myelosuppression occurred commonly on this study, especially at higher doses of gemcitabine. Since myelosuppression was uncommon in other single-agent patupilone trials, it is most likely related to the combination. Another phase I study evaluating gemcitabine administered at 800 mg/m$^2$ in combination with increasing doses of patupilone, 3 weeks on, 1 week off has also been conducted. In that study, 11 out of 24 patients experienced grade 3 or 4 myelosuppression, but there were no DLTs related to hematologic toxicities [38]. Taken together, these findings suggest that the marrow suppression is likely related to the combination and may be dose-related.

Higher doses of patupilone in combination with fixed-dose gemcitabine resulted in more nausea as well as persistent, low-grade asthenia which was more pronounced with prolonged treatment. The asthenia in particular made higher doses of the combination difficult to tolerate. Reported rates of asthenia or fatigue related to patupilone have varied from none to 68% [9, 10, 13, 35–37]; however, preliminary data from other trials currently being conducted have not reported discontinuation related to asthenia, as occurred on this trial. Asthenia is a common toxicity related to treatment

with single agent gemcitabine, and it is possible that the additive affects of patupilone and gemcitabine may make this combination more difficult to tolerate. Interestingly, fatigue was reported in 50% (12 out of 24) of the patients being treated on the phase I study evaluating patupilone with gemcitabine at 800 mg/m$^2$ [38]. While DLTs in that study included grade 3 diarrhea ($n = 3$), nausea ($n = 1$) and dizziness ($n = 1$), none of those patients stopped treatment as a result of fatigue. Further, the MTD in that study was established at gemcitabine 800 mg/m$^2$ and patupilone 2.5 mg/m$^2$. The differences in tolerability between our study and the findings of Rinehart et al. [38] are difficult to ascertain but may be related to baseline patient characteristics, prior therapies or tumor types.

Consistent with the known clinical effectiveness of antimicrotubule agents in combination with gemcitabine, a number of patients appeared to experience clinical benefit in this study. It is also encouraging to note that many of the patients who had evidence of clinical benefit had received prior treatment with a number of chemotherapies, including taxanes. Most notably, PR occurred in four patients with pancreatic carcinoma, esophageal carcinoma, cholangiocarcinoma and gallbladder cancer. One patient with cholangiocarcinoma remained on therapy in partial remission for a total of 18 cycles before treatment was discontinued due to progressive disease. These findings support further investigation of this combination in the phase II setting.

In conclusion, the combination of gemcitabine and patupilone was tolerated at lower doses of each agent without myelosuppression or asthenia. Higher doses resulted in increased rates of myelosuppression as well as intolerable asthenia. The recommended phase II dose for this schedule is patupilone 1.5 mg/m$^2$ over 5 min followed by gemcitabine 750 mg/m$^2$ over 30 min on days 1 and 8 of a 21-day cycle. Further study of this combination may be warranted in pancreatic and biliary tract cancers.

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