# A phase I/II trial of fixed-dose docetaxel plus irinotecan and escalating doses of estramustine phosphate for second-line or greater treatment of selected advanced solid tumors

Walid Baz[a], Fadi Nakhl[a], Raymond El-Soueidi[a], Frank Forte[a], Joseph Lowry[a], Nelly Aoun[a] and Jack Burton[b]

**This phase I/II study evaluated the safety of the combination of irinotecan, docetaxel, and estramustine for selected advanced solid tumors and also obtained initial efficacy data. Twenty-two patients were enrolled in the study. The regimen consisted of docetaxel 30 mg/m$^2$ and irinotecan 60 mg/m$^2$ both given intravenously on days 1 and 8 every 21 days in combination with escalating doses of estramustine (500 mg/m$^2$/day escalated to 750 mg/m$^2$/day on days 0, 1, 2, 7, 8, and 9 given every 21 days) during phase I. Dose escalation was continued until the maximum planned dose level of estramustine (750 mg/m$^2$/day) was reached. After the appropriate phase II dose of estramustine was found additional patients were enrolled. Twenty-one of the 22 patients were evaluable for toxicity and 17 for tumor response. The recommended phase II dose of estramustine was found to be 750 mg/m$^2$/day orally on days 0, 1, 2, 7, 8, and 9 given every 21 days. Hematologic toxicity was fairly mild, with only one episode of grade 3 neutropenia. Diarrhea was the most common nonhematologic toxicity with grade 3 toxicity occurring in five of 21 patients. Only one episode of venous thrombosis was observed. Objective response rate was 15.8%, overall clinical benefit rate was 63%, and median time to progression was 15 weeks. Estramustine in combination with the doublet of docetaxel and irinotecan is a well-tolerated regimen with minimal hematologic toxicity, mild to moderate nonhematologic toxicity, and promising initial antitumor activity in previously treated patients with advanced solid tumors.** *Anti-Cancer Drugs* **20:508–512**


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[a]Department of Hematology/Oncology, Staten Island University Hospital, Staten Island and [b]Department of Hematology/Oncology, Coney Island Hospital, Brooklyn, New York, USA

Correspondence to Dr Walid Baz, MD, Department of Hematology/Oncology, Staten Island University Hospital, 256 Mason Avenue, Staten Island, NY 10305, USA
Tel: +1 718 226 6400; fax: +1 718 226 6404; e-mail: walidbazmd@hotmail.com

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## Introduction

Preclinical data demonstrate the activity of estramustine phosphate (EMP) in cancer models and indicate that this is a targeted agent that can selectively accumulate in tumor tissue by binding to an estramustine-binding protein expressed by different cancer types (including prostate, breast, ovarian, colon, lung, melanoma, and glioma) [1–5]. EMP has well-documented activity in hormone-refractory prostate cancer, and showed some clinical efficacy in breast and ovarian cancers [6–11].

Combination studies of irinotecan and docetaxel are justified because of their striking single-agent activity in several solid tumors. In one preclinical study, the combination of a topoisomerase inhibitor in combination with taxanes showed synergistic cytotoxicity [12]. Multiple phase II trials confirmed the efficacy and safety of this novel combination in lung [13,14], breast [15,16], pancreatic [17], and gastric [18] cancers.

Combining EMP to the docetaxel/irinotecan doublet is not anticipated to have significantly increased toxicity. In fact, EMP showed a myeloprotective effect when combined with other chemotherapy drugs such as docetaxel and vinblastine [19,20].

EMP's antimicrotubule properties, especially the unique interaction with microtubule-associated proteins, led to the hypothesis that synergistic antimicrotubule effects and cytotoxicity could be achieved by combining EMP with other microtubule inhibitors [21,22]. In support of the hypothesis, additive or greater antimicrotubule effects were observed preclinically with the combination of EM and other microtubule inhibitors such as taxanes and vinca alkaloids [23–25].

Other properties of EMP is the multidrug resistance inhibitory activity in ovarian and bladder cancer cells in terms of inhibiting the efflux of chemotherapy drugs by modulating the P-glycoprotein [26,27], and subsequently decreasing the resistance to these drugs.

A schedule as short as 1 day of EMP in combination with docetaxel [28] showed antitumor activity similar to that

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seen with the longer dosing schedules typically used with EMP (usually at least 5 days). Results of phase I and II trials of weekly schedules of EMP in combination with paclitaxel using 3 days of EMP given with the weekly chemotherapy doses suggest that antitumor activity is retained, with possible decreases in toxicity, particularly deep venous thrombosis, the most serious toxicity [6,29].

We believed that adding 3 days of EMP to the weekly docetaxel/irinotecan doublet (2 weeks on/1 week off) might have a synergistic antitumor activity, multidrug resistance inhibitory effect, and an attenuated toxicity profile.

## Patients and methods

### Study protocol and eligibility criteria

The study protocol was reviewed and approved by the institutional review board of Staten Island University Hospital, which was the only clinical site where patients were enrolled. All participants provided written informed consent. In order to be eligible, patients had to be at least 18 years of age, have an Eastern Cooperative Oncology Group performance status $\leq 2$ with documented locally advanced or metastatic solid tumors of one of the following types: small cell or non-small cell lung, breast, colon, prostate, pancreatic, bladder, ovarian, stomach, esophageal, endometrial, or carcinoma of unknown primary site. Patients must have received at least one prior chemotherapy regimen that did not include EMP, irinotecan, or docetaxel (unless given more than 1 year before enrolment in adjuvant therapy).

### Treatment plan

This study involved a phase I dose escalation of EMP according to a modified Fibonacci design, in which two cohorts of three patients were enrolled and treated sequentially at the two planned dose levels of EMP. Irinotecan at 60 mg/m$^2$ (infused intravenously over 90 min) followed by docetaxel at 30 mg/m$^2$ (infused intravenously over 30 min) were given on days 1 and 8 of each 21-day treatment cycle. EMP was given orally, three times a day, on days 0,1,2,7,8, and 9 of each cycle. EMP doses were escalated as follows: 500 mg/m$^2$/day in the first dose cohort and 750 mg/m$^2$/day in the second cohort. For the initial cohort, the first cycle of docetaxel/irinotecan was given alone (i.e. without added EMP) to obtain initial data on the toxicity of this doublet. Dose escalation was continued until the maximum planned dose level of EMP (level 2=750 mg/m$^2$) was reached, providing no more than zero of three or one of six patients from the first EMP dose level experienced dose-limiting toxicity (DLT). Patients were then enrolled in phase II at the recommended dose of EMP determined in phase I (750 mg/m$^2$). For any of the DLTs defined below, the irinotecan dose was reduced to 45 mg/m$^2$. The docetaxel dose was fixed at 30 mg/ m$^2$. A maximum of eight cycles of treatment could be administered under this protocol. Prophylaxis for thrombosis was required using warfarin at a dose of 2 mg/day. The addition of low-dose aspirin (up to 325 mg/day) was optional.

The estimate of sample size for phase II was from basic Simon two-stage design parameters, as provided in the protocol; the calculations were based on an estimated baseline tumor response rate for a diverse group of relapsed/refractory solid tumors, expected to include lung cancer (set conservatively at 5%). Therefore, with this objective response rate (ORR), 10 was the minimum number calculated for the first stage of phase II. The number, *22*, was requested by the study sponsor.

### Endpoints

In phase I, the primary goal was to determine the maximal tolerated dose of EMP, which could be safely combined with the docetaxel/irinotecan regimen. The secondary endpoint was overall response rate. For phase II, overall response rate was the primary endpoint and toxicity was an important secondary endpoint. Due to the anticipated heterogeneity of the study population, time to progression (TTP) was a tertiary endpoint.

### Toxicity monitoring

Both hematologic and nonhematologic toxicities were determined and scored according to the common National Cancer Institute common toxicity criteria version 2.0. Monitoring was conducted by serial history and physical examinations together with serial blood counts and chemistries. Toxicity was assessed by determination of adverse events that occurred while on study or within 30 days of the last dose of study medication. Hematologic DLT was defined as the first episode of febrile neutropenia or recurrence of a grade 4 hematologic toxicity of more than 5 days duration after initial dose reduction of irinotecan for toxicity. Docetaxel, irinotecan, and estramustine were held up to 10 days if blood counts did not recover to white blood cells more than 3000/mm$^3$ or platelets more than 100 000/mm$^3$ by the time of next treatment cycle. Nonhematologic DLT was defined as any grade 3 toxicity except for nausea, vomiting, or diarrhea, for which grade 3 toxicity of up to 7 days will be allowed.

### Antitumor response

Tumor response was assessed and monitored by serial computed tomographic scans according to the Response Evaluation Criteria in Solid Tumors with chest and abdominal computed tomography performed at baseline, before the third cycle, every 3 months for 1 year, then every 3–6 months until disease progression or withdrawal from the study. In ovarian and prostate cancer patients without measurable disease, response was determined according to CA 125 Rustin's criteria [30] and Prostate-Specific Antigen Working Group's criteria [31] respectively.

If the patients showed at least stable disease after the first two cycles of treatment, they were allowed to remain in the study and to receive up to six additional cycles of treatment. If a patient showed progressive disease after the first two cycles, the patient was taken off study and considered a nonresponder. The radiologic review was performed by a single radiologist.

## Results

### Patients' characteristics (Table 1)

A total of 22 patients (four patients at dose level 1 and 18 patients at dose level 2) were enrolled in this study from February 2003 to January 2006 and treated at Staten Island University Hospital. Of the 22 patients, 21 were evaluable for toxicity and 19 for tumor response. A total of 94 cycles of treatment were administered (21 at dose level 1 and 73 at dose level 2). One patient of the first cohort (dose level 1) withdrew early from the study after two cycles secondary to disease progression. Another patient was added to that cohort for better evaluation of estramustine toxicity at dose level 1. All patients enrolled in the trial met eligibility requirements except one patient in phase II who had prior treatment and a prostate-specific antigen response to docetaxel monotherapy, and was granted an exception. Most of these patients were heavily pretreated metastatic cancers with two or more different chemotherapeutic regimen. No DLT occurred at dose level 1. Patients were then enrolled in phase II at the recommended dose of EMP determined in phase I (750 mg/m$^2$). All patients who were not on therapeutic doses of warfarin were treated with low-dose warfarin at 2 mg daily.

**Table 1 Patient characteristics**

| | *N* (%) |
|---|---|
| Age, mean (range) | 56 (46–74) years |
| Sex | |
| Male | 12 (54.6) |
| Female | 10 (45.4) |
| Race | |
| White | 21 (95.5) |
| Non-white | 1 (4.5) |
| ECOG performance status | |
| 0/1 | 20 (91) |
| 2 | 2 (9) |
| Types of cancer | |
| NSCLC | 8 (36.4) |
| SCLC | 4 (18.2) |
| Unknown primary | 3 (13.6) |
| Breast | 2 (9.1) |
| Ovarian | 1 (4.5) |
| Gastric | 1 (4.5) |
| Esophageal | 1 (4.5) |
| Prostate | 1 (4.5) |
| Cholangiocarcinoma | 1 (4.5) |

%, percentage of patients; ECOG, Eastern Cooperative Oncology Group; *N*, number of patients; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

### Hematologic toxicity (Table 2)

No grade 4 and only one (4.7%) grade 3 hematologic toxicity (neutropenia) occurred during the study. The episode of grade 3 neutropenia occurred at dose level 1. Anemia progressed from grade 1 to grade 2 in only three patients.

**Table 2 Hematologic toxicity**

| | Grade 1–2, *n* (%) | Grade 3, *n* (%) | Grade 4 |
|---|---|---|---|
| Anemia | 3 (14.28) | 0 | 0 |
| Neutropenia | 1 (4.7) | 1 (4.7) | 0 |
| Thrombocytopenia | 2 (9.5) | 0 | 0 |

%, percentage of patients; *n*, number of patients.

**Table 3 Nonhematologic toxicity**

| | Grade 3, *n* (%) | Grade 4, *n* (%) |
|---|---|---|
| Gastrointestinal | | |
| Diarrhea | 5(23.8) | – |
| Mucositis | 1(4.7) | – |
| Nausea/vomiting | 1(4.7) | – |
| Pulmonary | | |
| Dyspnea | – | 1(4.7) |
| Edema | 2(9.5) | – |
| Fatigue | 2(9.5) | – |
| Metabolic | | |
| Hyperglycemia | 1(4.7) | – |
| Hypokalemia | 1(4.7) | – |
| Neuropathy | – | – |

%, percentage of patients; *n*, number of patients.

### Nonhematologic toxicity (Table 3)

There was a total of 80 episodes (62 grade 1–2 and 18 grade 3–4) of nonhematologic toxicity in this study. Diarrhea was the most commonly observed nonhematologic toxicity with a total of six grade 3 episodes occurring in five of 21 patients. Most of the grade 1–2 adverse events were of gastrointestinal (diarrhea, nausea, and mucositis), metabolic (hypoalbuminemia, dehydration) and constitutional (fatigue ) origin. One episode of venous thrombosis, three episodes of grade 1–2 reversible hepatic toxicity, and one episode of grade 1 renal toxicity occurred during the study. No DLT occurred at dose level 1.

### Antitumor response

Of the 22 patients entered into the study, 19 of 22 patients were evaluable for tumor response. Three patients (15.8%) had partial response; one by Response Evaluation Criteria in Solid Tumors and two patients by major tumor marker response with more than 75% decrease of prostate-specific antigen (from 240 to 0.5 ng/ml) and CA 125 (from 580 to 80 U/ml). Stable disease (SD) was achieved in eight (42%) patients and seven (37%) experienced progressive disease. ORR was 15.8%, overall clinical benefit rate was 63% and median TTP was 15 weeks (range 3–24).

## Discussion

EMP has previously been combined with docetaxel, but not with this docetaxel/irinotecan doublet regimen

[8,20]. This regimen has antitumor activity across a wide range of solid tumors and the 2-week on/1-week off schedule allowed for intermittent pulse dosing of EMP to allow for interaction with these chemotherapy drugs while minimizing toxicity. The primary objective of the phase I portion of the study was to confirm safety of the planned maximal dose. The study was designed more as a phase II study with a safety lead-in cohort than a traditional phase I study.

The two dose levels of EMP (500 and 750 mg/m$^2$ on days 0, 1, 2, 7, 8, and 9 every 21 days) were selected because there were no expected new safety concerns, and a maximal tolerated dose for EMP had been defined with paclitaxel given up to 1200 mg/m$^2$/day for 3 days every 21 days and confirmed with docetaxel [15]. Given the above, and that there is no evidence for a dose–response effect for EMP and some safety concerns (mainly deep vein thrombosis), only these two dose levels were believed to be needed in the initial study design. Overall, nonhematologic toxicity was, on average, moderate and predominantly was anticipated. The most frequent grade 3–4 nonhematologic toxicity was diarrhea, which was an expected toxicity of irinotecan. This toxicity resulted in three withdrawals from the study, despite resolution with medical management, and was often because of under use of prescribed anti-diarrheals.

Hematologic toxicity was mild and less than anticipated. The mechanism of this myeloprotective effect of EMP is unclear. A phase III trial [19] showed that EMP significantly reduces the granulocyte toxicity of vinblastine (the incidence of grade 2–4 granulocytopenia was 15% in the EMP/vinblastine arm vs. 54% in the vinblastine-alone arm). Patients receiving single-agent EMP often demonstrate increased white blood cells and granulocyte counts [32], an observation that is consistent with increased mobilization or production of granulocytes.

Of particular note was the low rate of venous thrombosis, with only one subclinical episode observed in the entire study (4.5%). In earlier studies, the overall incidence of thromboembolic complications was approximately 10%, most likely related to EMP [28,33]. The use of low-dose aspirin (81 mg) and low-dose warfarin (1 mg) did not decrease the incidence of thromboembolic events [34]. In a phase II study [28] of docetaxel plus short-course EMP, 2 mg/day of warfarin was used as prophylaxis, which resulted in a low incidence of EMP-associated thromboembolic events (0 of 40 patients). This incidence may have been accomplished by shortening the duration of exposure to EMP. In our study, the use of 2 mg/day of warfarin also seemed to be effective.

Our trial enrolled a large number of patients with lung cancer. The best response in this group of heavily pretreated lung cancer patients was SD, but in several of the non-small cell lung cancer (NSCLC) patients there was prolonged SD or prolonged survival (one patient with NSCLC is alive at $>15$ months postenrolment). The antitumor activity of this regimen was encouraging in that, the ORR was 15.8%, overall clinical benefit rate was 63%, and median TTP was 15 weeks.

Two phase II trials [13,14] combining docetaxel and irinotecan as a second-line treatment in NSCLC showed similar ORR (14.3 and 20%) and TTP (3 and 5.6 months) but greater grade 3–4 hematologic toxicities (neutropenia: 54.3 and 46%, anemia: 25.7 and 23%, and thrombocytopenia: 0 and 17%). No antitumor responses were seen in the small cell lung cancer patients. This finding may be explained by the presence of an estramustine-binding associated protein in NSCLC cells but not in small cell lung cancer cells [5].

In conclusion, the regimen tested in this trial, consisting of docetaxel, irinotecan, and EMP was shown to have a favorable toxicity profile and promising antitumor activity against several tumor types. EMP showed a myeloprotective effect when combined with the docetaxel/irinotecan doublet. This regimen contains three radiosensitizing agents and warrants evaluation in combination with external beam radiation. Warfarin at 2 mg/day proved to be effective as deep vein thrombosis prophylaxis in EMP regimen. Further trials comparing docetaxel/irinotecan/estramustine to docetaxel/irinotecan are warranted especially that combining estramustine to docetaxel/irinotecan may have a better hematologic toxicity profile.

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