A phase I study of paclitaxel, estramustine phosphate and vinorelbine (Pacl-E-Vin) in advanced malignancies: triple tubulin targeting

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Anti-tubulin couplets have activity in hormone-resistant prostate cancer. This study was designed to define the dose-limiting toxicity (DLT) and recommended phase II dose (RPTD) of the unique triplet combination of paclitaxel, estramustine phosphate (EMP) and vinorelbine (Pacl-E-Vin). Patients with advanced malignancies who had failed standard therapy, ECOG performance status (PS 0–2) and adequate organ function were included. Dose of EMP was fixed at 300 mg/m^2/dose p.o. t.i.d. on days 1–3 and 8–10. Vinorelbine dose was 20 mg/m^2/day i.v. on days 3 and 10. Paclitaxel was dose escalated from 40 to 50 mg/m^2/day i.v. on days 3 and 10. Cycles were repeated every 3 weeks. Twelve adults (median age 72) were entered on this study. Primary tumors included prostate ($n = 7$), cervix ($n = 2$), melanoma ($n = 1$), colon (1) and lung with synchronous prostate cancer ($n = 1$). Nine patients had received no prior chemotherapy, one had received a prior regimen and two had received two or more prior regimens. Of four evaluable patients at dose level 1, one patient had grade 3 neutropenia leading to the day 10 dose being withheld. Of five evaluable patients at dose level 2, there was one DLT (febrile neutropenia) and two grade 3 neutropenias leading to the day 10 dose being withheld. One patient had a lower extremity deep vein thrombosis. Other side effects were mild and reversible. Nine patients were evaluable for efficacy: three with prostate cancer had a greater than 50% prostate-specific antigen (PSA) response, and a patient with synchronous prostate and lung cancer had a greater than 50% PSA response. We conclude that the DLT of Pacl-E-Vin is neutropenia. RPTD is vinorelbine 20 mg/m^2, paclitaxel 40 mg/m^2, both administered on days 3 and 10, and EMP 900 mg/m^2/day on days 1–3 and 8–10, q3w. Dose omission at day 10 followed by 20% dose reduction of paclitaxel and vinorelbine is recommended in the event of grade 3 neutropenia. Activity in hormone-refractory prostate cancer is promising and warrants phase II evaluation.

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Introduction

Paclitaxel and vinorelbine both target microtubules via differing mechanisms of action. Taxanes polymerize the microtubules and inhibit Bcl-2 and Bcl-x_L phosphorylation, inducing G_2/M arrest and apoptosis [1]. Vinorelbine destabilizes microtubules leading to apoptosis [1].

In vitro studies suggest synergistic cytotoxic effects of taxanes and vinca alkaloids on human breast cancer and human adenocarcinoma A549 cell lines when given simultaneously [2]. Moreover, animal studies have demonstrated *in vivo* synergy of paclitaxel and vinorelbine combinations in P388 leukemia [2].

A number of *in vitro* studies show cytotoxic synergy against a variety of murine cancer cell lines when vinorelbine exposure precedes paclitaxel [3,4]. Synergy between vinorelbine and paclitaxel was demonstrated in experiments using human prostate cancer cell lines LNCaP, DU-145, PC-3 and PC-3 M [5].

Various phase I studies have shown that the dose-limiting toxicity (DLT) for the combination of paclitaxel and vinorelbine was grade 3 and 4 hematologic toxicity (neutropenia with and without fever) and peripheral neuropathy [6–8]. The findings of these studies are summarized in Table 1.

Docetaxel and vinorelbine have also shown enhanced antitumor effects on mice bearing solid tumors, and such a combination is being extensively explored clinically [9].

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Table 1 **Phase I trials of paclitaxel and vinorelbine**

Investigator	Disease	N	RPTD	DLT
Ibrahim *et al.* [9]	breast cancer	51	Pac 150 mg/m^2, VNR 36 mg/m^2, q3wk $\pm$ G-CSF	without G-CSF: febrile neutropenia; with G-CSF: peripheral neuropathy
Chang *et al.* [7]	breast cancer, lung cancer	7	Pac 90 mg/m^2, VNR 25 mg/m^2, day 1 and 2, q3w	1 death (from pneumonia and neutropenia), neutropenia, peripheral neuropathy
Cohen *et al.* [8]	advanced cancers	10	Pac40 mg/m^2/week, VNR 22.5 mg/m^2/week, $\times$ 6, q8w	neutropenia

G-CSF: granulocyte colony stimulating factor; Pac: paclitaxel; VNR: vinorelbine.

Estramustine phosphate (EMP) is nor-nitrogen mustard linked to estradiol. It exerts very little alkylating activity and acts primarily as an anti-tubulin agent [10]. EMP binds to tubulin and to microtubule-associated proteins, depolymerizing cytoplasmic microtubules and disrupting the nuclear matrix [11–13]. *In vitro* studies indicate that EMP potentiates paclitaxel and vinca alkaloid cytotoxicity [14–17]. This potentiation may be a consequence of the effects on microtubules by both drugs and/or due to inhibition of P-glycoprotein-mediated resistance to paclitaxel by EMP [16,17].

A phase I trial of EMP and 3-h paclitaxel infusion at the University of Southern California in women with metastatic breast cancer who had failed prior paclitaxel showed a partial response (PR) in three out of eight subjects [18]. Paclitaxel was escalated to a dose of 225 mg/m^2 on day 2, combined with EMP 300 mg/m^2/dose t.i.d. p.o. on day 1, without apparent increase in toxicity [18].

Combinations of EMP and paclitaxel in phase II trials involving hormone-refractory prostate cancer (HRPC) patients have shown some objective and major prostate-specific antigen (PSA) responses. Hudes *et al.* gave 34 subjects with HRPC 120 mg/m^2 paclitaxel as a 96-h infusion, and EMP 600 mg/m^2/day p.o. continuously, on a 3-week cycle. The objective response rate was 44% (four of nine evaluable patients). The PSA-50 response rate was 53% (where PSA-50 response is defined as a 50% or greater decrease in PSA sustained for more than 4 weeks) [19]. In a similar subject population, Smith *et al.* gave oral EMP 280 mg t.i.d. and oral etoposide 100 mg/day, both given from days 1 to 7, while paclitaxel 135 mg/m^2 (1-h infusion) was administered on day 2. He observed an objective response rate of 63% (10 out of 16 evaluable patients) and a PSA-50 response rate of 65% [20].

Borrega-Garcia *et al.* reported on the results of their phase II trial at the 2000 Annual Meeting of the American Society of Clinical Oncology. They gave 22 patients with HRPC vinorelbine 25 mg/m^2/day on days 1 and 8, and EMP 280 mg p.o. daily, from days 1 to 14, cycled every 3 weeks. The objective response rate was 53%. There were two toxic deaths, (one due to pulmonary embolism, and the other due to aggravation of chronic obstructive pulmonary disease and progressive disease) [21]. Grade 3 or 4 toxicities were as follows: anemia (1 cycle), edema (16 cycles), thrombocytopenia (1 cycle), gynecomastia (1 cycle) and impotence (1 cycle).

The activity of EMP with vinorelbine and EMP with paclitaxel in pre-clinical models as well as phase I and II trials provide a strong rationale for the development of the triplet of paclitaxel, EMP and vinorelbine (Pacl-E-Vin). The primary objective of this study was to determine the toxicity profile and recommended phase II dose (RPTD) of this combination.

Materials and methods

This was a single institution phase I study performed by the Kaplan Comprehensive Cancer Center (KCCC) of the New York University (NYU) School of Medicine. The study accrued patients between December 1998 and June 2001. The protocol was reviewed by the Clinical Executive Management Committee (Scientific Review Committee) of the KCCC and by the Institutional Board of Research Associates (IRB) of the NYU School of Medicine. Informed consent was obtained in accordance with Food and Drug Administration guidelines.

Patient selection

The inclusion criteria for this study stipulated that patients have advanced cancer that had failed standard treatment or cancer that was not amenable to therapy with standard approaches. Patients had to be 18 years or older and give signed informed consent. It was required that subjects have adequate organ function: neutrophils $>1.5 \times 10^9$/l, platelets $>100 \times 10^9$/l, hemoglobin >9 g/dl, serum creatinine <2 mg/dl, AST and ALT $<4 \times$ upper limit of normal, and bilirubin <2 mg/dl. Patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2 and measurable or evaluable disease. Female subjects of childbearing potential were required to have a negative pregnancy test and were counseled to avoid pregnancy. Breast-feeding was not allowed. The protocol specifically excluded patients with prior neuropathy of any grade because a previous study had shown an unacceptably high neurotoxicity rate with vinorelbine and paclitaxel in patients with pre-existing neuropathy [22]. Subjects who had previously received vinorelbine or paclitaxel could not be included. Radiotherapy to more than 25% of the bone

marrow, radiotherapy within 21 days of study entry or chemotherapy within 14 days of study entry was not allowed. Also ineligible were patients who had suffered a myocardial infarct within one year of enrollment, had congestive heart failure (New York Heart Association class 2 or greater), uncontrolled cardiac dysrhythmias, angina pectoris, uncontrolled hypertension or cardiomyopathy.

Therapeutic plan and toxicity evaluation

The dose of EMP was fixed at 300 mg/m^2/dose p.o. t.i.d. on days 1–3 and 8–10. The planned dose levels are outlined in Table 2, but only dose levels 1 and 2 were explored. Although dose escalation of vinorelbine (Navelbine; Glaxo SmithKline, Philadelphia, PA), was planned from dose level 3, at the dose levels explored the dose of vinorelbine was fixed at 20 mg/m^2/day, given i.v. on days 3 and 10. Paclitaxel was administered i.v. on days 3 and 10 at 40 mg/m^2/day (dose level 1) or 50 mg/m^2/day (dose level 2). Cycles were repeated every 3 weeks.

The total daily dose of estramustine (900 mg/m^2) was divided into three doses and given 1 h before meals to prevent nausea. Since EMP is available as a 140 mg capsule, this number was divided into the total daily dose and then rounded off into a whole number. If the number of capsules could not be evenly distributed between the three doses, then the larger number of capsules was given in the morning and afternoon.

During cycle 1, patients received a premedication of dexamethasone 20 mg i.v., diphenhydramine 25 mg i.v. and cimetidine 300 mg i.v. over 30 min. On subsequent cycles dexamethasone could be decreased to 10 mg i.v. if there was no allergic reaction in the previous cycle. Vinorelbine was given prior to paclitaxel, as this sequence has been shown to be synergistic [4,5]. Since vinorelbine is a moderate vesicant, 100 ml of normal saline was administered first and then the dilute vinorelbine was given i.v. over 6–10 min in a free-flowing vein. Paclitaxel was administered i.v. in 250 ml of 5% dextrose over 1 h.

Colony stimulating factors were not to be given prophylactically in this study, but were allowed at the discretion of the treating physician in the event of neutropenic fever or sepsis.

Table 2 **Planned dose levels**

Dose level	EMP p.o. dose days 1–3, 8–10 (mg/m^2/dose t.i.d.)	Vinorelbine i.v. days 3 and 10 (mg/m^2/day)	Paclitaxel i.v. days 3 and 10 (mg/m^2/day)
1	300	20	40
2	300	20	50
3	300	25	50
4	300	25	60

Toxicity was assessed according to National Cancer Institute Common Toxicity Criteria, version 2 (www.ctep.info.nih). DLT was defined as grade 4 neutropenia lasting more than 5 days, febrile neutropenia or grade 3/4 non-hematologic toxicity occurring in the first two cycles of treatment, excluding alopecia.

Retreatment at cycle 1, day 10 (C1D10), C2D1 or C2D10 required non-hematologic toxicities to be either grade 0 or 1 (except for alopecia), and neutrophils $>1 \times 10^9$/l and platelets $>75 \times 10^9$/l. If these criteria were not met, then that treatment was omitted, and at the subsequent cycle the dose of paclitaxel and vinorelbine was reduced by one dose level. If the subject was already at dose level 1, the doses of paclitaxel and vinorelbine were lowered by 20%.

If liver enzymes (AST, ALT, alkaline phosphatase) became elevated 3 times or more greater than baseline, then EMP was to be stopped until recovery to baseline levels, after which the dose was to be reduced by 20%.

Patients experiencing grade 3/4 injection-site toxicity could continue therapy via a central venous catheter.

Dose escalation

Three evaluable patients were to be entered at dose level 1. If none of these patients experienced DLT, then the dose was escalated to the next level in three subsequent patients and so on. If one of the three patients experienced DLT at any dose level, then a further three patients were accrued. If none of the three additional patients experienced DLT, then the dose was escalated to the next level. If one or more of the three additional patients had DLT, then the patient entry at that dose level was halted. Up to three further patients were then to be treated at the next lower level (to a maximum of six patients). The maximum tolerated dose (MTD) was defined as the lowest dose level at which two or more of six patients experienced DLT. The RPTD was defined as MTD minus one dose level.

The criteria for removal from the study included: declining performance status, disease progression, patient wishes, grade 3/4 neurotoxicity, grade 3/4 non-hematologic toxicity or non-compliance with therapy. Patients requiring concurrent radiotherapy or oncologic surgery during the first two cycles were also to be removed from the study.

Response evaluation

All patients were restaged within 6 weeks of commencing therapy with a chest X-ray, computerized tomography scans, clinical tumor measurements and appropriate serum tumor markers (including PSA). World Health Organization response criteria were followed and all

responses were reconfirmed 4–6 weeks after the initial observation. A PSA-50 response was defined as a greater than 50% decline in PSA sustained on two separate determinations at least 4 weeks apart.

Results

Patient characteristics

Patient characteristics are described in Table 3. Twelve patients were enrolled on this protocol, of which five commenced treatment at dose level 1 and seven patients commenced treatment at dose level 2.

All 12 patients met the eligibility criteria. Ten out of the 12 were male. The median age of this population was 72, with a range of 41–79 years. At study entry, three patients had ECOG PS = 0, eight patients had a PS = 1 and one patient had PS = 2.

Seven patients had prostate cancer, two had cervical cancer, and one patient each had melanoma or colon cancer. One patient had both organ-confined prostate cancer and metastatic non-small cell lung cancer (NSCLC). All patients had advanced disease (stage 4).

All patients but one had received prior therapy. Six had received treatment for their primary cancer and nine for metastatic disease. Six patients had had previous surgery, while three had received prior radiotherapy. Six prostate cancer patients had failed prior hormonal therapy, while one patient with melanoma had been given biological therapy. Three patients had received prior chemotherapy.

Table 3 Patient characteristics at study entry

Characteristic	Total ($n = 12$)
Sex	
male	10
female	2
Age	
median	72
range	41–79
ECOG PS	
0	3
1	8
2	1
Diagnosis	
prostate cancer	7
cervical cancer	2
melanoma	1
colon cancer	1
NSCLC and prostate cancer	1
Stage 4 at study entry	12
Prior therapy	
none	1
surgery	6
radiotherapy	3
hormonal therapy	6
biological therapy	1
chemotherapy	3

Two patients were on warfarin at study entry for previous thromboses. The protocol was later amended to exclude this patient group as EMP can be thrombogenic.

Drug delivery

At the conclusion of this study, two patients remained on therapy (both having completed nine and 25 cycles of therapy respectively). Two patients were taken off the study because of minor toxicity, six patients because of progressive disease and two patients (one with stable disease and one in partial remission) who had been on treatment for greater than 1 year, for toxicity. Both patients who suffered grade 2 minor toxicities were unable to tolerate EMP due to vomiting, anorexia and diarrhea, and withdrew consent to continue on the study during the first cycle. The median number of cycles per patient was 4 (range 1–27).

Toxicity

Three patients were not evaluable for toxicity or efficacy because they received one or less than one complete cycle of therapy. Of these three inevaluable patients, one was non-compliant with the study protocol during cycle 1 and was taken off the study. The other two inevaluable patients had the following problems: grade 2 vomiting occurred in one patient at dose level 1 when he mistakenly took 5 continuous days of estramustine, while a second patient at dose level 2 had grade 2 anorexia and diarrhea, again attributed to EMP. Both subjects declined to continue on this study because of these toxicities. At dose level 1, four out of five patients were evaluable for toxicity and there was no DLT, but one patient had C1D10 dose withheld for grade 3 neutropenia. The same patient had grade 4 anemia requiring blood transfusion (but this was not defined as DLT). At dose level 2, five out of seven patients were evaluable for toxicity. There was one DLT (febrile neutropenia) and two day 10 doses withheld for grade 3 neutropenia. The toxicity data are summarized in Table 4.

EMP is well known to cause thrombo-embolism [19,20,23–26]. A patient at dose level 2 developed a leg deep vein thrombosis after seven cycles of therapy and was anticoagulated with heparin, followed by warfarin. He has completed 20 cycles of chemotherapy.

The protocol did not specify whether grade 3/4 neutropenia on day 10 of the first two cycles was to be

Table 4 Toxicities encountered during the first two cycles

Dose level	*N* (total)	*N* (evaluable)	DLT	D10, G3 ANC
1	5	4	0	1
2	7	5	1 (febrile neutropenia)	2

D10, G3 ANC: dose withheld on day 10 for grade 3 neutropenia.

considered dose limiting, but advised omission of drug administration and 20% dose reduction in this case. In this analysis we list this event separately (refer to Table 4). However, these dose modifications clouded the data in terms of defining the MTD and recommending doses for phase II evaluation. Altogether the study points to dose level 1 as the RPTD, with D10 dose adjustments as needed.

No neuropathy above grade 1 was encountered in this group of patients.

Efficacy

Nine out of 12 patients were evaluable for efficacy. This group was moderately pretreated as nine subjects had received prior systemic therapy for metastatic disease. We observed three patients with a PR, five with stable disease (SD) and one with progressive disease (PD). The patient with synchronous NSCLC and prostate cancer had SD with lung cancer but a PSA-50 response for 11 weeks. Of the seven patients with prostate only disease, two were not evaluable, two had SD (with one patient continuing on treatment after 25 cycles) and three had a PR (with one patient continuing on treatment after nine cycles). All three patients with a PR had bone-only disease and they had a PSA-50 PR by cycles 2–6. These patients have completed nine, 20 and 27 cycles of treatment.

Discussion

The DLT of the combination of paclitaxel, estramustine and vinorelbine is neutropenia. We did not reach the MTD as originally defined in the protocol but dose modification for grade 3 neutropenia prohibiting day 10 therapy was frequently required and evidently prevented delivery of the prescribed doses (i.e. omission of D10 dose and 20% dose reduction with subsequent treatment). We have therefore taken D10 dose modification into consideration in our recommendation of dose level 1 for phase II evaluation, i.e. paclitaxel 40 mg/m^2/day, vinorelbine 20 mg/m^2/day, both given i.v. on days 3 and 10, with EMP 300 mg/m^2/dose given p.o. t.i.d. on days 1–3 and 8–10, with cycles being repeated every 3 weeks.

Previous studies have shown that thrombo-embolic events complicate the course of approximately 10% of patients treated with EMP and a taxane [19,20,23–26]. Although thrombo-embolism is not a prominent toxicity in single-agent estramustine studies, this event is most likely a consequence of the estrogen moiety of the estramustine. In our study two patients were on warfarin for previous thrombo-embolism, while a third patient developed a lower extremity DVT requiring full anticoagulation. The study of Sinibaldi *et al.* demonstrated that thrombo-embolic complications could be minimized with the use of prophylactic oral anticoagulation [26]. We therefore have incorporated prophylactic warfarin 1 mg p.o. daily in our phase II trial of Pacl-E-Vin. This dose of warfarin has been used extensively for thrombo-prophylaxis of central venous catheters, with minimal bleeding complications and requires only occasional monitoring of the International Normalized Ratio [27].

The efficacy seen in hormone-refractory prostate cancer in this study (three out of five evaluable patients with PSA responses) is encouraging. In hormone-resistant prostate cancer, combinations of taxanes and EMP offer clinically significant activity in a disease that was until recently effectively chemo-resistant. The taxane/EMP combinations are now the subject of frontline phase III studies against the combination of mitoxantrone and prednisolone (e.g. SWOG 9916). Studies of EMP with vinorelbine have also been performed in this disease, again with promising results [21].

Recently trials with weekly taxanes as opposed to 3-weekly regimens have been seen as having further promise, in terms of better tolerance and equivalent activity in prostate cancer [28,29]. Triple tubulin targeting by the Pacl-E-Vin combination is feasible and may offer a therapeutic advantage over couplet therapy. phase II evaluation of Pacl-E-Vin is now ongoing.

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