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# A phase II trial of docetaxel and vinorelbine in patients with hormone-refractory prostate cancer

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**Abstract** Recent studies of docetaxel have demonstrated improved survival over mitoxantrone and prednisone in patients with hormone-refractory prostate cancer (HRPC), supporting the study of novel docetaxel-containing regimens as primary therapy or following initial docetaxel-based therapy. To evaluate the combination of docetaxel and vinorelbine in the treatment of patients with HRPC, 40 patients with proven adenocarcinoma of the prostate with progressive metastatic disease despite androgen ablation were enrolled onto this phase II trial. Patients were treated with docetaxel 60 mg/m$^2$ on day 1 and vinorelbine 15 mg/m$^2$ on days 1 and 8 of a 21-day cycle. All patients received dexamethasone 8 mg twice daily for 4 days starting 1 day prior to the docetaxel infusion. After the first three patients were enrolled, filgrastim was added on days 2–6 and 9–13. Of the 40 patients enrolled, 19 had no prior chemotherapy and 21 had received at least one prior chemotherapy regimen. Of the 19 patients without prior chemotherapy and the 21 with prior chemotherapy, 7 (37%) and 6 (29%), respectively, demonstrated a decrease in prostate specific antigen by $>50\%$ maintained for at least 4 weeks. Out of eight patients with measurable disease, one achieved a partial response and four demonstrated stable disease. There was one patient with deep vein thrombosis, and febrile neutropenia was noted in only three patients after the protocol was modified to include filgrastim support. The combination of docetaxel and vinorelbine with filgrastim was well tolerated and active against HRPC in patients with or without prior chemotherapy.

**Keywords** Hormone refractory prostate cancer · Docetaxel · Vinorelbine

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## Introduction

In 2005, approximately 200,000 men will be diagnosed with prostate cancer and 30,000 men will die secondary to metastatic prostate cancer [1]. Androgen deprivation is only temporarily effective in metastatic prostate cancer secondary to the development of molecular mechanisms of tumor resistance [2]. Following androgen deprivation, therapy is limited to a few active chemotherapy regimens and a lack of salvage regimens when first-line chemotherapy fails.

Treatment with mitoxantrone and prednisone decreases prostate specific antigen (PSA) and improves quality of life in 30% of patients [3, 4]. Single-agent docetaxel or paclitaxel induces a biochemical response in approximately 40% of patients [5–9]. The addition of estramustine to either vinblastine or a taxane may increase PSA response, but the median overall survival is approximately 20 months, and thrombotic events occur in 10–25% of patients [10–20]. Recent landmark studies of docetaxel alone or in combination with estramustine have demonstrated improved survival over mitoxantrone and prednisone [21, 22]. Additional novel combi-

nation regimens are now needed to further improve the first-line and salvage therapy.

Vinorelbine has shown activity in the treatment of prostate cancer [23, 24] and preclinical models have demonstrated synergy when combined with taxanes [25–27]. Vinorelbine acts as an antimicrotubule agent that induces a $G_2$/M cell cycle arrest, similar to estramustine, with less thromboembolic toxicity [27, 28]. In this phase II trial, we hypothesized that the combination of docetaxel and vinorelbine in patients would be well tolerated and have clinical activity in patients with hormone-refractory prostate cancer (HRPC) either as first-line therapy or after initial chemotherapy, including docetaxel-based primary therapy.

## Materials and methods

### Patients

Patients with histopathologically proven adenocarcinoma of the prostate with progression despite androgen ablation therapy were eligible. Patients must have had documented metastasis. Other inclusion criteria were as follows: absolute neutrophil count (ANC) ≥1500/μl and a platelet count ≥100,000/μl; normal liver function tests defined as total bilirubin below the upper limit of normal (ULN) and transaminases (SGOT, SGPT) not more than 2.5 times the ULN; an estimated life expectancy of at least 6 months; and an ECOG performance status less than 2. Any radiation therapy had to have been completed at least 4 weeks prior to the initiation of therapy, and full recovery from any effects of surgery or radiation therapy was required. Patients with active infections, unstable or coexisting medical or social conditions precluding full compliance with the study, or HIV-positive patients who met the CDC criteria for AIDS, were excluded. Patients were also excluded if prior irradiation included more than 30% of the marrow-containing skeleton; if the patient had grade >2 peripheral neuropathy; if an epidural or spinal cord compression was present; if the patient had received an investigational drug within 3 weeks of registration or sumarium within 8 weeks of initiating therapy; or if there was any known contraindication or hypersensitivity reaction to dexamethasone, Polysorbate 80, or *Escherichia coli*-derived products. Patients on antiandrogens were required to either stay on such therapy for the remainder of the study or have demonstrated progression after the discontinuation of flutamide or bicalutamide for 4 weeks and 6 weeks, respectively. Patients were maintained on androgen ablation therapy (LHRH agonists or orchiectomy). The study was reviewed and approved by the Institutional Review Board of the UMDNJ/Robert Wood Johnson Medical School and all patients provided written informed consent.

### Evaluations

Pretreatment evaluations required on all patients included a complete history, physical examination, ECOG performance status determination, body surface area, chest radiograph, bone scan, measurement of serum PSA, serum testosterone, serum biochemistry, and complete blood count (CBC). Patients returned to the clinic weekly for a CBC. On day 1 of each 3-week cycle, patients were reevaluated and assessed for performance status, toxicity, serum biochemistry, CBC, and PSA.

### Treatment plan

Patients received docetaxel (Taxotere; Aventis, Bridgewater, N.J.) 60 mg/m$^2$ as a 1-h infusion every 3 weeks on day 1 and vinorelbine (Navelbine; GlaxoSmith Kline, Research Triangle Park, N.C.) 15 mg/m$^2$ IV push on days 1 and 8. On day 1 of each cycle, vinorelbine was administered first, followed by the docetaxel infusion. All patients received dexamethasone (8 mg twice daily for 4 days starting 1 day prior to the docetaxel infusion). Each cycle was 3 weeks in duration. After the first three patients experienced fever and neutropenia, all other patients were started on filgrastim (Neupogen; Amgen, Thousand Oaks, Calif.) 5 μg/kg beginning 24 h after day 1 for 5 days and 24 h after day 8 for 5 days or to an ANC of 10,000/μl.

### Dose modifications

Chemotherapy was held in patients with an ANC less than 1500/μl or platelets less than 100,000/μl on day 1 of the cycle. Therapy was not made up during the cycle. Patients with afebrile grade 4 leukopenia (according to the National Cancer Institute Common Toxicity Criteria, version 2.0) or neutropenia 7 days or longer, or grade 4 neutropenia or leukopenia associated with fever (one reading of oral temperature >38.5°C, or three readings of oral temperature >38.0°C in a 24-h period) were retreated after recovery with a 25% dose reduction of docetaxel and vinorelbine in all subsequent cycles. Grades 1, 2 and 3 myelosuppression (leukopenia, neutropenia, thrombocytopenia) and grade 4 leukopenia or neutropenia except as previously defined, did not require a dose reduction when recovery was within 21 days. If patients had any grade 3 or 4 nonhematologic toxicity, except nausea, vomiting or alopecia, they were removed from the trial.

Patients who developed abnormal liver function for any reason required a dose adjustment. Patients with a bilirubin less than the ULN and transaminases 1.6–5 times greater than the ULN required a dose reduction of docetaxel by 25%. A dose was held for up to 3 weeks if the bilirubin was greater than the ULN or transaminases were greater than five times the ULN. When the liver enzymes recovered, the docetaxel dose was reduced by

25% or the patient was removed from the study. A maximum of two dose reductions, for any reason, per patient was allowed.

### Criteria for response

Biochemical response was determined by the measurement of PSA every 3 weeks while the patient was receiving therapy. A biochemical response was defined as a reduction of PSA by ≥50% and maintained for at least 4 weeks. An increase in PSA of less than 25% from baseline was considered stable disease. Disease progression was defined as an increase in PSA greater than 25% above baseline. A complete measurable disease response was defined as complete disappearance of all measurable disease and symptoms/signs accompanied by PSA normalization, maintained for at least 1 month. A partial measurable disease response was defined as a greater than or equal to 50% decrease in tumor size by physical examination or radiographic studies using the summed products of the perpendicular diameters of all measured lesions with no appearance of new lesions. A less than 50% decrease or less than 25% increase in size without the appearance of new lesions was considered stable disease, and disease progression was defined as a greater than or equal to 25% increase in tumor size by physical examination or radiographic studies using the summed products of the perpendicular diameters of all measured lesions or the appearance of new lesions.

### Statistical assessment

The study had a two-stage design, requiring an initial 14 patients and a maximum of 40 patients. If four or more patients responded, the null hypothesis was rejected. The probability of rejecting the null hypothesis with a true probability of response in all patients enrolled of 0.2 was 0.86. Patients were enrolled with or without prior chemotherapy; response rates for the combined group were reported, along with response rates for the group of patients with and without prior chemotherapy, although stratification to prior chemotherapy was not planned.

**Table 1** Patient characteristics

| | |
|---|---|
| No. of patients | 40 |
| Age (years) | |
| Mean | 70 |
| Range | 47–88 |
| PSA (ng/ml) | |
| Median | 123 |
| Range | 4.4–4542 |
| Alkaline phosphatase (units) | |
| Mean | 304 |
| Range | 58–1077 |

## Results

A total of 40 men were enrolled on the study. Their pretreatment characteristics are summarized in Tables 1 and 2. The median age was 70 years (range 47–88 years). Of the 40 patients, 21 (52.5%) had received some form of prior chemotherapy, 13 had received prior chemotherapy with progressive metastatic HRPC (7/13 received prior taxane therapy), and 8 had received prior chemotherapy (5 received docetaxel, 2 received mitoxantrone, and 1 had received both mitoxantrone and docetaxel) for biochemical progression after local therapy on a clinical trial.

### PSA response

Of the 40 patients enrolled, 13 (33%) demonstrated a decrease in PSA by >50% maintained for at least 4 weeks (Table 3). Of the 13 patients with a decrease in PSA >50%, 4 demonstrating partial responses to therapy had a decrease in PSA of greater than 75%, and 7 had received no prior chemotherapy, 3 had received prior docetaxel for biochemical progression after local therapy on a clinical trial, 1 had received prior paclitaxel for metastatic disease, and 2 had received prior chemotherapy (non-taxane) for metastatic disease (Table 3). Out of 8 patients with measurable disease, 1 achieved a partial response and 4 demonstrated stable disease.

Of 13 patients treated on this study who had prior chemotherapy that progressed on prior treatment for metastatic HRPC (Table 3), 3 demonstrated a PSA decrease of >50%. Of the 7 patients who progressed despite prior taxane therapy for metastatic HRPC, 1 had a decrease in PSA of >50%. The median time to progression was 17 weeks in all enrolled patients and 28 weeks in patients with response on-study.

**Table 2** Prior chemotherapy

| Chemotherapy regimen | No. of patients[a] |
|---|---|
| Taxane-based therapy | |
| Paclitaxel alone | 1 |
| Docetaxel alone | 7 |
| Paclitaxel/13-*cis*-retinoic acid/interferon alpha | 3 |
| Paclitaxel/estramustine | 3 |
| Non-taxane-based therapy | |
| 13-*cis*-retinoic acid/interferon alpha | 2 |
| L-377202 (investigational agent) | 7 |
| L-778123 (investigational agent) | 1 |
| Tamoxifen/onconase (investigational agent) | 2 |
| Mitoxantrone | 3 |
| Epothilone B | 1 |
| Vaccine | 3 |

[a]Represents 21 patients who received multiple prior therapies

**Table 3** Biochemical PSA response rates in evaluable patients by prior systemic therapy

| | Prior systemic therapy | | | |
|---|---|---|---|---|
| | All evaluable patients ($n=40$) (%) Responders (%) | None ($n=19$) Responders (%) | For PSA progression[a] ($n=7$) Responders (%) | For metastatic disease ($n=14$) Responders (%) |
| Partial response | 13 (33) | 7 (37) | 3 (43) | 3 (21) |
| ≥50% decrease | 9 (23) | 3 (16) | 3 (43) | 3 (21) |
| ≥75% decrease | 4 (10) | 4 (21) | – | – |
| Stable disease | 18 (45) | 11 (58) | 3 (43) | 4 (29) |

[a]Represents patients on prior clinical studies with PSA progression after local therapy, without metastasis

### Toxicity

The regimen was generally well tolerated (Table 4). A total of 285 cycles of chemotherapy were administered, with each patient receiving an average of 7 (range 1–33) cycles of therapy. During the course of the study, 90% of doses of chemotherapy were given on time; 56 doses were held because of low ANC. The first three patients on-study were treated without filgrastim support and were limited to eight cycles of therapy. All three patients developed fever and neutropenia, requiring a total of nine held doses. The trial was then amended to include filgrastim support for all subsequent patients. In subsequent patients treated with chemotherapy and filgrastim, three patients developed fever and neutropenia. Dose reductions due to abnormal liver function, an alkaline phosphatase of 2.5 times the ULN occurred in one patient.

Ten patients were removed from the study because of toxicity. Three had febrile neutropenia, one had grade 3 ataxia (with a prestudy history of ataxia), two had grade 3 peripheral neuropathy, and three had grade 3 fatigue; one additional patient developed a deep vein thrombosis after the first dose of protocol therapy and was removed also from the trial.

**Table 4** Toxicity

| | Grade 2 No. of patients (%) | Grade 3 No. of patients (%) | Grade 4 No. of patients (%) |
|---|---|---|---|
| Neutropenia | 2 (5) | 2 (5) | 6 (15)[a] |
| Anemia | 1 (2.5) | | |
| Thrombocytopenia | | 1 (2.5) | – |
| Prolonged PT | | 1 (2.5) | – |
| Ataxia | | 1 (2.5) | – |
| Neuropathy | | 2 (5) | – |
| Fatigue | 2 (5) | 3 (7.55) | – |
| Myalgias | 2 (5) | | |
| Abdominal pain | 1 (2.5) | | |
| Bone pain | 3 (7.55) | 1 | |
| Mucositis | 1 (2.5) | | |
| Paresthesia | 2 (5) | | |
| Edema | 2 (5) | | |
| Dyspnea | 1 (2.5) | | |
| Alopecia | 3 (7.55) | | |
| Depression | 1 (2.5) | | |

[a]The first three patients enrolled on this study did not receive filgrastim and developed grade 4 febrile neutropenia. The trial was then amended for all subsequent patients to receive filgrastim support during therapy

## Discussion

This study demonstrated activity of the combination of docetaxel and vinorelbine in patients with HRPC with and without prior treatment with chemotherapy. In patients with HRPC, current treatment approaches are limited by chemotherapy regimens with poor response rates, poor long-term survival, and the lack of definitive salvage regimens when first-line chemotherapy fails.

In the current study, the combination of docetaxel and vinorelbine demonstrated activity even in patients who had prior treatment with chemotherapy (Table 3). Activity was demonstrated by both biochemical response and measurable disease response in some patients; the number of patients with measurable disease may have been limited because of the lack of requirement for CT scan at study entry. Although only a historical comparison, the activity of docetaxel in combination with vinorelbine was comparable to that found in studies with docetaxel alone as primary first-line therapy [22]. It was interesting, however, that the regimen had activity in patients despite prior chemotherapy, although prior stratification was not planned. Possible reasons for some activity in patients with prior chemotherapy include that vinorelbine is capable of overcoming mechanisms responsible for chemotherapy or that docetaxel alone would have had activity in this population. Given the small size of the current study, further study would be needed to define the true response in this population of patients.

The combination of docetaxel/vinorelbine combined with filgrastim resulted in only one detected thromboembolic complication. Studies of patients treated with combinations of estramustine with paclitaxel, estramustine with docetaxel, and estramustine with carboplatin combined with paclitaxel have demonstrated thromboembolic events in approximately 10–20% of patients along with significant gastrointestinal intolerance, most likely attributable to the estramustine [14, 15, 20, 21]. The current study demonstrated minimal toxicity after the inclusion of filgrastim (Table 4). Prior to the inclusion of filgrastim, the first three patients developed fever

and neutropenia. Following the addition of filgrastim, only three additional patients developed fever and neutropenia.

The mechanism of potential synergy between docetaxel and vinorelbine is currently unknown. Docetaxel acts by promoting polymerization of tubulin, thereby preventing microtubule breakdown and inducing cell death. Docetaxel has been shown to induce *bcl-2* phosphorylation and apoptotic cell death at concentrations 100-fold lower than paclitaxel [27]. Vinorelbine, a semisynthetic vinca alkaloid that acts by interfering with microtubule assembly is also capable of inducing *bcl-2* phosphorylation. Docetaxel has increased antitumor activity in tumors with a high percentage of cells in the $G_2$/M phase of the cell cycle. Efforts to increase the number of tumor cells in $G_2$/M, such as by the addition of vinorelbine, may theoretically enhance the activity of docetaxel against tumor cells and could be further studied. Preclinical models have demonstrated at least an additive, if not a synergistic, effect when both agents are used together [25–29]. Given the clinical activity of this regimen in patients with and without prior chemotherapy, further laboratory studies should to be performed to elucidate the mechanism of interaction, and clinical studies to better define the role of this combination as salvage therapy in patients with progression after first-line therapy.

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