Original Article

Gemcitabine and Docetaxel in Metastatic, Castrate-Resistant Prostate Cancer

Results From a Phase 2 Trial

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BACKGROUND: Docetaxel is the standard of care for patients with metastatic, castrate-resistant prostate cancer (CRPC). Gemcitabine is a nucleoside analogue with broad antitumor activity. In a phase 2 study of combined docetaxel and gemcitabine, the authors assessed its safety and activity in patients with chemotherapy-naive, metastatic CRPC. **METHODS:** Eligible patients had untreated, metastatic CRPC with radiologic and/or biochemical evidence of progression after antiandrogen withdrawal with castrate testosterone levels, an Eastern Cooperative Oncology performance status (ECOG PS) of 0 to 2, and adequate organ function; no previous chemotherapy was permitted. Patients received gemcitabine (800 mg/m^2) Days 1 and 8 and docetaxel (75 mg/m^2) on Day 8 every 21 days for a maximum of 6 cycles. Response was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) for measurable disease. A prostate-specific antigen (PSA) response was defined as a decline $\geq$50% in baseline PSA level. **RESULTS:** Thirty-five patients with chemotherapy-naive, metastatic CRPC were enrolled. The median age was 67 years, and 60% of patients had an ECOG PS of 0. PSA responses were observed in 49% of patients. Among the patients who had measurable disease (n = 25), 3 patients (12%) had a confirmed, RECIST-defined partial response (PR); 4 patients (16%) had an unconfirmed PR; and 15 patients (60%) achieved stable disease. The most common adverse events included grade 1 and 2 fatigue (69%), alopecia (80%), and nausea/vomiting (54%). No treatment-related deaths were noted, but an unusually high incidence of grade 3 and 4 neutropenia was observed. **CONCLUSIONS:** The efficacy of combined gemcitabine and docetaxel in metastatic CRPC was similar to that observed with single-agent docetaxel. In contrast to single-agent docetaxel, the combination was moderately toxic and had an impact primarily on bone marrow reserve. ***Cancer*** **2011;117:752–7.** *© 2010 American Cancer Society.*

KEYWORDS: castrate-resistant prostate cancer, chemotherapy, gemcitabine, docetaxel, prostate-specific antigen.

Prostate cancer is the second leading cause of death among men in the United States, and >192,280 new cases were diagnosed in 2009.[1] Although the majority of patients with advanced prostate cancer have an initial response to androgen-deprivation therapy, all patients eventually will progress to a castrate-resistant state, which is manifested by rising levels of prostate-specific antigen (PSA), progressive disease on imaging studies, worsening of symptoms, and, ultimately, death.[2] Patients with progressive prostate cancer despite anorchid testosterone levels are considered "castrate resistant." The treatment of patients with metastatic, castrate-resistant prostate cancer (CRPC) has evolved significantly in the last several years. Chemotherapeutic options for patients with advanced disease, once considered a futile endeavor, have changed significantly with the understanding that docetaxel-based chemotherapy produces palliative benefits and leads to an overall survival improvement in patients with CRPC.[3,4] Despite its clinical benefits, the response to docetaxel often is short lived, and all patients eventually develop progressive disease.

Gemcitabine is a nucleoside analog that has activity against a broad spectrum of solid tumors.[5] Although in vitro work has suggested significant activity in prostate cancer cell lines,[6] existing clinical data suggest modest clinical activity when gemcitabine is used as a single agent in CRPC.[7] A series of phase 1 and 2 trials that evaluated the combination of gemcitabine plus docetaxel provided some evidence of a potential synergistic or additive effect when these 2 agents are

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used together.[8-13] The objective of the current, multi-institutional, phase 2 trial was to evaluate the efficacy, safety, and tolerability of this combination in patients with previously untreated, metastatic CRPC.

MATERIALS AND METHODS

Eligible patients had histologically confirmed adenocarcinoma of the prostate with metastases and evidence of disease progression (worsening disease observed on bone scans, an increase in measurable disease, or a PSA >5 ng/mL and increasing on 2 consecutive measurements 1 week apart) despite at least 1 endocrine manipulation and testosterone levels <50 ng/dL. Patients who had received antiandrogen therapy were required to demonstrate progressive disease after appropriate withdrawal from therapy. Androgen-deprivation therapy with a luteinizing hormone-releasing hormone (LHRH) agonist or orchiectomy was required for the duration of the study. Other inclusion criteria were a Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and adequate bone marrow, hepatic, and renal function (as defined by a white blood cell count $\geq$1500/μL, a platelet count $\geq$100,000/μL, hemoglobin $\geq$8.0 g/dL, aspartate and alanine aminotransferase levels $\leq$2 times the upper limit of normal [ULN], and serum bilirubin $\leq$1.5 times the ULN. Patients who had received previous chemotherapy for CRPC were excluded; however, the receipt of neoadjuvant or adjuvant (nontaxane) chemotherapy was allowed >1 year before study entry. Other exclusion criteria included previous radiation therapy within 4 weeks of study entry and a history of severe cardiovascular disease (class III/IV intra-abdominal hypertension), uncontrolled congestive heart failure, or ventricular arrhythmia. The Cleveland Clinic Institutional Review Board reviewed and approved this study in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. All patients provided written informed consent before registration.

Treatment consisted of Gemcitabine (Gemzar; Lilly Pharmaceuticals, Indianapolis, Ind) 800 mg/m^2 administered intravenously over 30 to 60 minutes on Day 1 and 8 of each treatment cycle and docetaxel (Taxotere; Sanofi-Aventis Pharmaceuticals, Bridgewater, NJ) 75 mg/m^2 administered intravenously over 30 to 60 minutes on Day 8 followed the Day 8 infusion of gemcitabine. All patients received oral prednisone 5 mg twice daily with standard antiemetic and supportive care. Prophylactic use of white blood cell and erythrocyte growth factors was not permitted.

All patients were required to have an absolute granulocyte count $\geq$1.5.10^9/L and/or a platelet count $\geq$100.10^9/L on Day 1 and Day 8 of any cycle before they received treatment. Dose reductions of 25% and 50% were implemented for any initial and subsequent delay of Day-8 chemotherapy. Adverse events were graded according to version 3.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events. Treatment was administered weekly for 2 consecutive weeks on a 21-day cycle for a maximum of 6 cycles or until disease progression was assessed by the investigators according to Response Evaluation Criteria in Solid Tumors (RECIST),[14] unacceptable toxicity, or consent withdrawal.

Baseline evaluations included medical history and physical examination, laboratory parameters (hematology and blood chemistry, including testosterone level and PSA), and tumor imaging (computed tomography [CT] scans or magnetic resonance imaging [MRI] studies of the chest, abdomen, and pelvis; bone scan; and brain CT or MRI scans). Tumor assessments were performed at baseline and every 8 weeks.

Efficacy Assessment

PSA values were obtained before each cycle of chemotherapy. A PSA response was defined as a decline >50% that was maintained for at least 4 weeks. PSA progression was defined as a 25% increase in PSA over the nadir value that was confirmed by a second PSA evaluation at least 1 week later. A complete PSA response required normalization of PSA (<4 ng/mL) for at least 21 days. Patients with measurable soft tissue disease were assessed according to RECIST. Complete responses required the complete disappearance of all evidence of all sites of measurable or osseous disease with normalization of the PSA level (defined as PSA <4 ng/mL). A partial response was defined according to RECIST as a reduction $\geq$50% in PSA without the appearance of new osseous lesions, and worsening pathologic findings. Progressive disease was defined as a progression in the PSA level, an increase in the size of existent bone lesions, or the appearance of 1 or more new bone lesions identified on bone scan. The time to progression was measured from the first day of treatment to the time of disease progression. Overall survival was measured from the initiation of therapy to the date of death or last follow-up.

Statistical Methods

The primary endpoints of the study were to determine the safety and efficacy of combined gemcitabine plus docetaxel in patients with untreated, metastatic CRPC. A 2-stage accrual design with a maximum goal of 34 eligible and evaluable patients was used to test the hypothesis that the underlying overall response rate (PSA for patients with nonmeasurable disease and RECIST-defined for patients with measurable disease) was essentially $\leq$20% versus $\geq$40%, respectively. The study was designed with $\alpha = .11$ and power of 0.90. Seventeen eligible and evaluable patients were enrolled in the first accrual stage, and an additional 17 patients were enrolled in stage 2 if $\geq$4 of the 17 stage 1 patients responded. Survival was calculated from the date of study registration to the date of death or last follow-up; and was summarized using the method of Kaplan and Meier. Spearman rank correlations were used to assess associations, such as the relation between a PSA decrease and a measurable disease reduction.

RESULTS

Patient Characteristics

Between July 2004 and October 2006, 35 patients with chemotherapy-naive, metastatic CRPC were enrolled. Baseline characteristics are summarized in Table 1. The median patient age was 67 years, and most patients (60%) had an ECOG performance status of 0. All patients had undergone either surgical or medical castration and demonstrated castrate levels of testosterone during study treatment. Similarly, all but 3 patients (9%) had received antiandrogen treatment either as part of their initial androgen-deprivation therapy or as a second-line hormone manipulation. Twenty-four patients (69%) had received previous radiation therapy, and 8 patients (23%) had undergone radical prostatectomy. Only 1 patient had received previous chemotherapy in the adjuvant setting. Pretreatment PSA levels ranged from 1.50 ng/mL to 938.6 ng/mL. Although the vast majority of patients (71%) had RECIST-defined, measurable disease before study entry, 10 patients (29%) had documented bone disease with either radiographic progression, a rising PSA, or worsening clinical symptoms.

Efficacy Results

All patients were evaluable for response. The vast majority of patients (29 of 35; 83%) experienced some PSA decline while they were receiving treatment. Seventeen patients (49%) achieved a PSA response. Among these, 6 patients (17%) had a PSA decrease $\geq$95%. The median time to PSA nadir in these patients was 3.4 months (range, from 3 weeks to 5.4 months). Figure 1 summarizes the data as a waterfall plot. Of 25 patients who had measurable disease, 3 patients (12%) had a confirmed, RECIST-defined partial response; 4 patients (16%) had an unconfirmed partial response; and 15 patients (60%) had stable disease, including reduced tumor burden in 12 patients. Figure 2 illustrates the maximal change in tumor burden of the evaluable patients. The median reduction in tumor burden was a 26.5% decline (range, from a 72.1% decline to a 14.3% increase). At the time of this report, 26 patients had died, and the estimated median survival was 19.4 months (Fig. 3). The median follow-up for the 9 patients who remained alive at the time of the current analysis was 11.1 months (range, 0.9-48.5 months).

Table 1. Patient Characteristics

Variable	No. of Patients (%)
Median age [range], y	67 [55-84]
ECOG performance status	
0	21 (60)
1	12 (35)
2	2 (6)
Previous adjuvant/neoadjuvant chemotherapy	1 (3)
Previous RT	24 (69)
Previous RP	8 (23)
Median pretreatment PSA [range], ng/mL	35.0 [1.50-938.6]
Measurable disease	
Soft tissue only	17 (49)
Soft tissue and bone	8 (23)
Bone disease only	10 (28)

ECOG indicates Eastern Cooperative Oncology Group; RT, radiotherapy; RP, radical prostatectomy; PSA, prostate-specific antigen.

Treatment Administration and Adverse Events

Twenty-two patients (63%) completed all 6 of the planned treatment cycles. Thirty-two percent of the cycles were delayed at least by 1 week, primarily for neutropenia. Fourteen percent of patients required a dose reduction of gemcitabine by 25% (n = 4; because of grade 3 neutropenia) and by 50% (n = 1; because of grade 3 diarrhea). Docetaxel was reduced by 25% in 2 patients who developed grade 3 neutropenia and by 50% in the same patient who developed grade 3 diarrhea and required a 50% reduction in the dose of gemcitabine. Four patients discontinued therapy because of PSA progression. Other

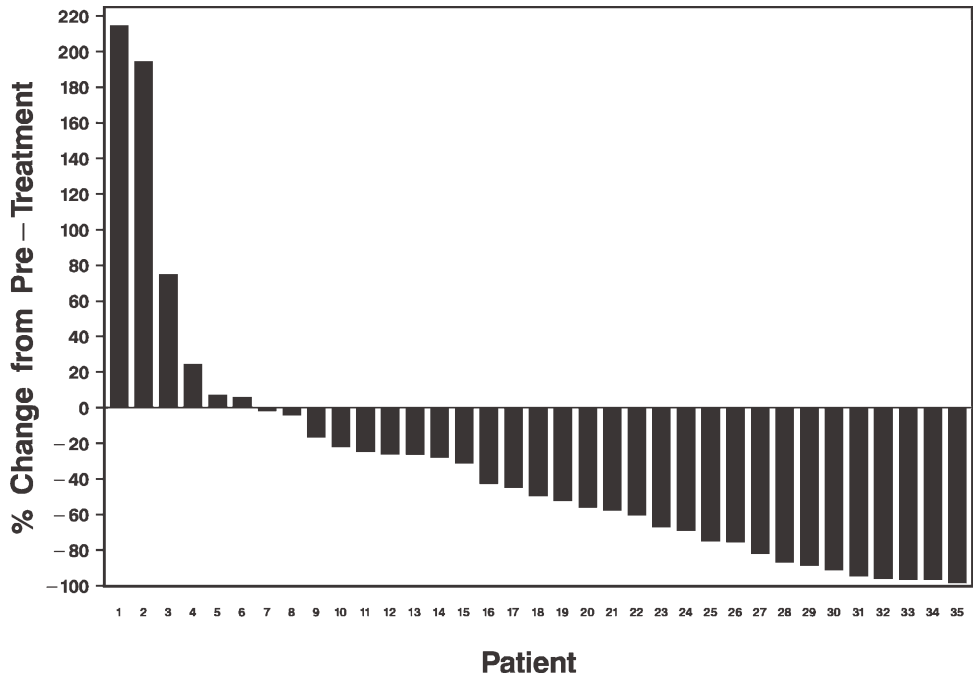

Figure 1. This waterfall plot illustrates the maximal prostate-specific antigen (PSA) change (%) from baseline. Negative values indicate a decrease in PSA compared with pretreatment levels, and positive values indicate an increase. PSA response was observed in 49% of patients, and 17% of patients achieved a PSA decline ≥90%.

reasons for stopping treatment included adverse events (17%), consent withdrawal (3%), physician discretion (3%), and death secondary to progressive disease (3%). The most commonly reported treatment-related adverse events were constitutional in nature and included grade 1 and 2 fatigue in 24 patients (69%), alopecia in 28 of 35 patients (80%), nausea/vomiting in 19 of 35 patients (54%), edema in 15 of 35 patients (43%), and peripheral neuropathy in 9 of 35 patients (26%). The most common laboratory abnormalities included grade 1 or 2 anemia (40%), thrombocytopenia (9%), and elevated aspartate and alanine aminotransferase levels (14%) (Table 2). The most commonly reported, treatment-related, grade 3 adverse events included neutropenia (34%) followed by fatigue (15%) and dyspnea (9%). Although there were no treatment-related deaths, 7 patients (20%) reported grade 4 toxicities (neutropenia in 5 patients, febrile neutropenia in 1 patient, and neutropenia and thrombocytopenia in 1 patient).

DISCUSSION

Metastatic, CRPC remains a therapeutic challenge. Although several novel agents are in late-stage development, there has been limited development beyond doce-

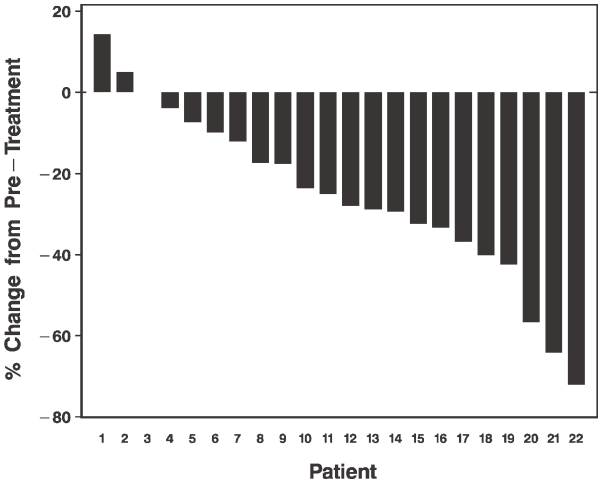

Figure 2. This waterfall plot illustrates the maximal change (%) in size among tumors that were evaluable with Response Evaluation Criteria in Solid Tumors from baseline.[11] The analysis excluded patients who had no follow-up measurements. Negative values indicate a decrease in measurable disease compared with pretreatment measurements, and positive values indicate an increase or a new lesion. The overall response rate was 12% (confirmed partial responses), an additional 16% of patients had unconfirmed partial responses, and 60% of patients had stable disease.

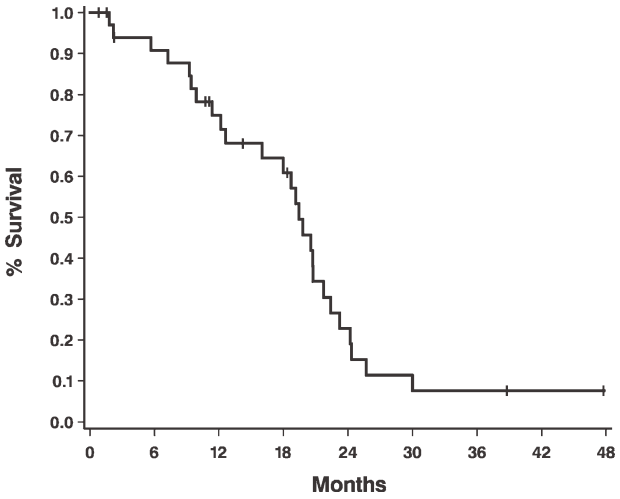

Figure 3. Overall survival is illustrated in months.

Table 2. Common Treatment-Related Adverse Events

	Percentage of Patients			
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Nausea/vomiting	43	11	3	—
Taste changes	37	6	—	—
Anorexia	31	3	3	—
Diarrhea	26	—	1	—
Alopecia	29	51	—	—
Dermatologic (nails/skin)	31	11	—	—
Fatigue	37	32	15	—
Dyspnea	20	6	9	—
Edema	34	9	3	—
Neuropathy	26	—	—	—
Neutropenia	—	11	34	14
Neutropenia/fever	3	—	—	3
Infection/no neutropenia	3	3	—	—
Thrombocytopenia	6	3	3	3
Anemia	29	11	6	—
Elevated AST/ALT	17	3	—	—

AST indicates aspartate aminotransferase; ALT, alanine aminotransferase.

taxel for patients with progressive, metastatic, CRPC.[15-17] Various phase 2 studies evaluating novel compounds administered in combination with docetaxel have been conducted.[18] Challenges in terms of study design, clinical endpoints, and the relative significant activity of docetaxel have made the identification of active docetaxel-based regimens problematic.

In our experience using gemcitabine combined with docetaxel-based chemotherapy in patients with untreated, metastatic CRPC, a high proportion of patients achieved significant PSA reductions. However, only 49% of patients demonstrated a PSA decline $\geq$50% compared with baseline. In addition, this PSA response did not differ substantially from that observed in the Southwest Oncology Group 9916 and TAX-327 studies.[3,4] For the patients who had measurable soft tissue disease, the objective response observed in our study was 28% (3 of 7 patients had a confirmed partial response). Although this objective response rate is somewhat similar to that reported in previous phase 2 and 3 docetaxel-based studies,[3,4,18] the similarity is probably because of patient selection and the inherent bias of phase 2 trial design.

Our study results differ somewhat with the results from a recent phase 1/2 experience evaluating the same combination in patients with CRPC in which PSA and RECIST-defined responses were observed in 74% and 48% of patients, respectively.[19] In that study, the median time to progression and overall survival also were 7.9 months and 13.9 months, respectively. These overall survival data clearly are inferior to observations in previous docetaxel-based studies. Although the estimated median overall survival in our study was longer (19.1 months), our trial was limited by a lack of progression-free survival data, because follow-up measurements were not continued once treatment stopped; thus, progression-free survival based on measurable disease could not be estimated. In addition, ours was a single-arm, nonrandomized study, a design that has limitations in determining the relative benefit of the combination compared with other treatment strategies in this setting. In addition, we did not incorporate a pain or quality-of-life measurement tool, and the endpoints used in the study were developed before the Prostate Cancer Clinical Trials Working Group recommendations of 2008.[20]

Toxicity also appears to be a major limitation of this combination. Similar to the Danish study, we observed a higher incidence of myelosuppression (59%; grade 3 in 34% of patients and grade 4 14% of patients) and fatigue (grade 3 only in 15% of patients) compared with other single-agent docetaxel trials. Similarly, a greater incidence of treatment delays was reported. In fact, approximately 33% of planned cycles were delayed because of adverse events, and almost 15% of patients required a dose reduction of 1 or both agents. Balancing treatment-related toxicity versus clinical efficacy versus quality of life remains a challenge when treating patients with metastatic CRPC; thus, such factors should be taken into consideration when designing clinical trials.

In conclusion, the current results suggest that the addition of gemcitabine to standard, docetaxel-based chemotherapy leads to significant toxicities without concomitant clinical benefits over those observed with single-

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