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A Phase 2 Study of Intravenous Panobinostat in Patients With Castration-Resistant Prostate Cancer

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Abstract

Purpose—Panobinostat, a pan-deacetylase inhibitor, increases acetylation of proteins associated with growth and survival of malignant cells. This phase 2 study evaluated the efficacy of intravenous (IV) panobinostat in patients with castration-resistant prostate cancer (CRPC) who had previously received chemotherapy. The primary end point was 24-week progression-free survival. Secondary end points included safety, tolerability, and the proportion of patients with a prostate-specific antigen (PSA) decline.

Methods—IV panobinostat (20 mg/m²) was administered to patients on days 1 and 8 of a 21-day cycle. Tumor response was assessed by imaging every 12 weeks (4 cycles) according to modified Response Evaluation Criteria In Solid Tumors (Scher HI et al, 2005), and PSA response was defined as a 50% decrease from baseline maintained for 4 weeks. Safety monitoring was routinely performed and included electrocardiogram monitoring.

Results—Of 35 enrolled patients, 4 (11.4%) were alive without progression of disease at 24 weeks. PSA was evaluated in 34 (97.1%) patients: 5 (14.3%) patients demonstrated a decrease in PSA but none 50%; 1 patient (2.9%) had carcinoembryonic antigen as a marker of his prostate cancer, which declined by 43%. Toxicities regardless of relationship to panobinostat included fatigue (62.9%), thrombocytopenia (45.7%), nausea (51.4%), and decreased appetite (37.1%).

Conclusions—Despite promising preclinical data and scientific rationale, treatment with IV panobinostat did not show a sufficient level of clinical activity to pursue further investigation as a single agent in CRPC.

Keywords

Prostate cancer; Deacetylase inhibitor; Panobinostat; Prostate-specific antigen

Introduction

Prostate cancer is driven by progressive genetic and epigenetic aberrations. Emerging data strongly indicate that the entire epigenome is dysregulated during prostate cancer development, therefore representing a target for therapeutic intervention [1].

Several lines of evidence have demonstrated the importance of deacetylases (DACs) in the progression of prostate cancer [2–5]. The presence of overexpressed histone deacetylases (HDACs), particularly the class I isoforms, has been documented in tumor samples and associated with poor patient outcomes after radical prostatectomy [6–8]. Experimental data have suggested that castration-resistant prostate cancer (CRPC) could respond to agents inhibiting heat shock protein 90 (HSP90), a molecular chaperone regulated by HDAC6 [9], because the activity of several HSP90 client proteins—including androgen receptor (AR)—remains crucial for disease progression [10, 11].

DAC inhibitors (DACi) have been noted to have greater antiproliferative effects on AR-positive prostate cancer cells than their AR-negative counterparts and inhibit tumor growth in both castration-sensitive and -resistant xenograft models [12, 13]. In addition to targeting HDAC6—which affects AR stability via HSP90 hyperacetylation—direct suppression of AR transcription and modulation of the acetylation of nonhistone proteins, such as the transcription factors E2F1 and p53, have been implicated in DACi's complex mode of action in experimental models [14–16]. In light of their high potency to inhibit tumor cell growth in vivo, several DACi have entered clinical development [17].

Panobinostat is a novel pan-DACi that demonstrates potent inhibition of a broad range of histone and nonhistone DACs, leading to acetylation of intracellular targets involved in oncogenesis such as p53, hypoxia-inducible factor-1 α , α -tubulin, and HSP90 [17, 18]. In a study by Liu et al [19], panobinostat was able to revert the resistance of androgen-independent (AI) LNCaP cells to bicalutamide and apoptosis. Single-agent panobinostat was also found to block AR activity in CRPC models [14], and to have antitumor activity in combination with docetaxel in AR-positive AI xenografts [20].

Initial clinical development of panobinostat included both oral and intravenous (IV) formulations in solid tumors and hematologic malignancies [18]. Oral panobinostat (20 mg) showed minimal clinical activity in CRPC, whereas the combination of the same schedule of oral panobinostat (15 mg) given 3 times weekly with standard docetaxel resulted in a 50% reduction in prostate-specific antigen (PSA) in 5 of 8 (63%) CRPC patients, including 2 patients who achieved a partial response by modified Response Evaluation Criteria In Solid Tumors (RECIST) [21–23]. These studies, along with preclinical data suggesting a dose-dependent effect of panobinostat on PSA expression [14], led to the decision to expand the clinical investigation in CRPC to the IV formulation, which demonstrated higher peak concentrations (> 20- to 30-fold) and exposures (area under the curve, 3.5 to 5 $\times$) than the oral formulation [24]. This decision was supported by the initial evidence of clinical activity in a patient with Gleason grade 9, stage IV CRPC treated with single-agent IV panobinostat 20 mg/m² in a phase 1 trial. Therefore, the development of panobinostat in CRPC was continued with this phase 2 trial exploring single-agent IV panobinostat in patients previously treated with chemotherapy.

Patients and Methods

Study Design

This open-label, single-arm, multicenter phase 2 study evaluated the efficacy and safety of single-agent IV panobinostat in patients with CRPC. The primary end point was rate of

progression-free survival (PFS) at 24 weeks using modified RECIST criteria [22, 25]. Secondary end points included safety, tolerability, overall survival (OS), tumor response, duration of stable disease, and PSA response per Prostate-Specific Antigen Working Group (PSAWG) 1999 Guidelines [26]. This study adhered to the Declaration of Helsinki and the International Conference on Harmonisation ICH Harmonised Tripartite Guidelines for Good Clinical Practice. Approval was obtained from each independent ethics committee and local institutional review board and all patients provided written informed consent. This study is registered in www.clinicaltrials.gov as NCT00667862.

Patient Selection

Adult patients with metastatic CRPC that progressed on or after 1 or 2 cytotoxic therapies with evidence of progressive disease (PD)—defined as ≥ 2 new lesions on a bone scan and/or per RECIST criteria—were eligible for this study [22, 25]. Patients with 2 consecutive increases in PSA over a previous reference value per PSAWG guidelines, an Eastern Cooperative Oncology Group performance status of ≤ 1, and normal laboratory tests were eligible. Patients without surgical castration required a serum testosterone level < 50 ng/mL with continuation of luteinizing hormone-releasing hormone (LHRH) agonist/antagonist therapy. Medically castrated patients willing to continue LHRH agonist/antagonist therapy during study treatment were eligible. Patients who received prior first-line antiandrogen therapy or responded to second-line therapy had to have had PD documented by rising PSA levels after 4 to 6 weeks. Treatment discontinuation from flutamide (≤ 4 weeks), bicalutamide, megestrol acetate, cyproterone acetate, or nilutamide (≤ 6 weeks) prior to study enrollment was required. Patients with active central nervous system disease, impaired cardiac function, liver or renal disease, history of invasive malignancies, peripheral neuropathy, and/or Common Terminology Criteria for Adverse Events (version 3) grade ≥ 2 diarrhea were not eligible. Prior treatment-related exclusion criteria included chemotherapy or bisphosphonates ≤ 4 weeks prior to study; immunotherapy ≤ 2 weeks prior to study; prior DACi treatment for prostate cancer; and concomitant use of valproic acid, medications that may prolong the QT interval or induce torsade de pointes, and CYP3A4/5 inhibitors or inducers.

Treatment Plan

Patients received 20 mg/m² panobinostat (IV infusion over 30 minutes) on days 1 and 8 of a 21-day cycle. Patients remained on treatment until PD, intolerable toxicity, start of new cancer therapy, withdrawal of consent, or death. Dose adjustments and interruptions were permitted but patients could not receive doses < 10 mg/m². A maximum 4-week break in treatment for toxicity resolution was permitted. Patients could be considered for dose reescalation if they met protocol-specified criteria for ≥ 3 weeks at the lower dose.

Duration of Therapy, Monitoring, and Response Assessment

Patients were monitored by history and physical exam, toxicity assessment, and PSA level every 3 weeks. Laboratory evaluations included coagulation, urinalysis, and thyroid function tests once per cycle; hematology and biochemistry once per week; blood and urine for bone markers once per cycle after cycle 2; electrocardiogram (ECG) on days 1 and 8 of cycle 1; and serum testosterone every 3 months. Response assessment by bone and computed tomography (CT) scans and/or other appropriate imaging was performed every 12 weeks. Patients were removed from the protocol if there was evidence of PD by PSA or RECIST criteria or symptomatic PD [25]. Patients with PD by bone scan only at first assessment continued treatment, with reassessment after 6 additional weeks of therapy. Patients with documented PD at ≥ 24 weeks were considered as having PD not requiring confirmation. Patients were followed for survival until the protocol was amended to remove the collection of this parameter due to lack of clinical activity.

Definition of Response and Progression

Disease progression in the study was defined by 1 or more of the following criteria: PSA progression (50% increase from nadir and an absolute increase in PSA by 2 ng/mL maintained for 3 weeks); measurable disease progression (progression of target lesions) and nonmeasurable lesion progression (worsening of bone scan defined by development of 2 new lesions confirmed on a second scan at least 6 weeks later); appearance of new metastatic lesions outside the bone; or unequivocal progression of existing nontarget lesions [25].

Objective responses were defined using RECIST criteria [25]. PSA response was defined based on the PSAWG 1999 guidelines [26]. Bone disease was evaluated by bone scan, with disease characterized as complete response if there was disappearance of all osseous lesions; stable or improved if there were no new lesions and/or no new or worsening pain; and progression if there was the appearance of 2 new skeletal lesions. An increase in the size or intensity of lesions was not considered progression.

End Points and Statistical Design

The primary objective of this trial was to evaluate activity of panobinostat, with the primary end point defined as the proportion of patients who did not demonstrate PD or death at 24 weeks. Panobinostat was considered inactive if the PFS rate was 10% and active if the PFS rate was 30%, based on published analyses in this disease setting [22, 27, 28]. Given the late time point for measuring progression, a single-stage design was used. A sample size of 35 patients achieved 90% power to detect the 20% difference in PFS rate at a 5% significance level using a chi-square test. Kaplan-Meier method was to be used to estimate median PFS and OS and 95% confidence intervals. Data from participating centers were combined and analyzed as a single treatment group using SAS[®] Version 9.2

Results

Patient Population

A total of 35 patients were enrolled in this study. Median age was 67 years (range, 51–85 years; Table 1), with 11 patients (31.4%) 75 years of age. All 35 patients had a history of several lines of prior antiandrogen therapy, including bicalutamide (97.1%), and at least 1 cytotoxic therapy, including docetaxel (88.6%). In the majority of patients (80.0%), baseline disease progression was assessed by PSA level, but progression was also determined by measurable disease and bone scan in 37.1% and 34.3% of patients, respectively.

Patient Disposition

Of the 35 patients enrolled in the study, 34 (97.1%) were taken off study; 29 (85.3%) of these were due to disease progression (Fig. 1). There were 3 deaths (8.6%) on study, none of which were suspected to be treatment related.

Mean duration of exposure to panobinostat was 59 days (median, 49 days; range, 7–175 days). Eighteen patients (51.4%) received 2 cycles ($\approx$ 6 weeks) of therapy, of whom 8 (44.4%) had PD and 6 (33.3%) had toxicity. For the remaining 4 patients, early withdrawal of consent (n = 3, 16.7%) and death (n = 1, 5.6%) were the reasons for ending the study treatment. An additional 13 (37.1%) patients received between 2 and 4 cycles, while 4 patients (11.4%) received > 4 cycles (range, 5–9 cycles). All 4 of these patients were taken off study due to PD; 1 patient had to stop the study drug after 8 treatment cycles due to grade 3 thrombocytopenia and neutropenia.

Efficacy and Response

In the 35 treated patients, there were no documented objective responses. PSA was assessed in 34 patients (Table 2, Figure 2), of whom only 5 (14.7%) had a decline from baseline during treatment, none reaching a decrease of 50% or more. Of the 5 patients with a decline in serum PSA, 4 had a < 30% decrease in PSA: 1 after 2 cycles, 2 after 3 cycles, and 1 after 5 cycles of treatment. One patient with a > 30% decrease in PSA completed 9 cycles. One patient had carcinoembryonic antigen as the only marker of his prostate cancer, which declined by 43% after 1 treatment; however, he discontinued panobinostat due to recurrence of baseline atrial fibrillation with a rapid ventricular response. PD or death was reported for 28 patients (80.0%) within 24 weeks from the start of study treatment. All of these patients had PD with an increase in PSA, and the majority (71.4%) also showed radiological PD with bone and/or soft tissue disease. At the end of 24 weeks, only 4 (11.4%) patients were alive without PD.

Safety

All 35 patients experienced adverse events (AEs), with most (71.4%) reporting at least one grade 3 AE. Four (11.4%) patients experienced grade 4 toxicity, primarily grade 4 thrombocytopenia. The most frequent AEs (all-causality) included fatigue (22 patients, 62.9%), nausea (18 patients, 51.4%), and thrombocytopenia (16 patients, 45.7%; Table 3). The most frequent AEs with a suspected drug relationship included fatigue (19 patients, 54.3%), thrombocytopenia (19 patients, 54.3%), and nausea (17 patients, 48.6%). Serious AEs were reported in 14 patients (40.0%) and were considered drug related in 7 (20.0%) patients. As shown in Table 4, QTcF prolongation between 30 and 60 ms was the most frequent QT abnormality (11 patients, 31.4%). Postbaseline QTcF > 480 ms was observed in 4 patients (11.4%), with only 1 patient experiencing a QTcF increase > 500 ms. Other common ECG abnormalities included asymptomatic changes in T-wave morphology (flat, inverted, and biphasic) and depressed ST segment.

Discussion

Recent phase 3 data for enzalutamide and abiraterone confirm the central role of the AR and AR signaling in the progression of prostate cancer throughout the spectrum of the disease [29, 30]. The role of epigenetic changes in regulating AR overexpression in CRPC remains to be further explored and, despite the lack of activity of oral vorinostat [31] and oral panobinostat [21] as monotherapy in the clinic, DACi have a strong scientific rationale for use in CRPC [32]. Since preclinical models demonstrated a dose-dependent effect of DACi on PSA expression [14] and IV panobinostat demonstrated much greater exposure compared with the oral formulation [24], the decision was made to evaluate the IV formulation of panobinostat at the recommended phase 2 dose (20 mg/m²) for patients with CRPC who had previously received docetaxel.

However, despite preclinical promise, the PFS rate at 24 weeks did not indicate a sufficient level of clinical activity, and no patients showed a PSA decrease of 50% qualifying as a protocol-defined response. All patients experienced toxicities, with most (71.4%) having at least one grade 3 AE. Grade 4 thrombocytopenia developed in 4 patients (11.4%). Analysis of scheduled ECGs revealed QTcF prolongation, a known yet manageable DACi class effect [33]. Maximum postbaseline QTcF of > 480 ms to 500 ms was reported in 3 (8.6%) patients, with 1 experiencing QTcF > 500 ms. No clinical sequelae were associated with these episodes of QTcF prolongation. Overall, treatment with panobinostat was not associated with new or unexpected AEs indicative of a specific risk in this population, but the lack of efficacy and the observed rate of grade 3–4 AEs did not justify further study in this population.

The mechanisms of DACi are complex, and methods of administration such as dose level and schedule are likely to influence intratumoral growth in ways that may not be apparent from standard imaging techniques (CT, bone scan) and PSA responses. To date, analysis of clinical activity of DACi has been limited to PSA response and histone acetylation in mononuclear cells, which may not accurately reflect the activity of these agents. Although histone acetylation in mononuclear cells occurs at very low doses of these agents, it is not a surrogate for effects on the tumor itself and does not correlate with clinical response [31]. Furthermore, intermittent low doses of oral panobinostat in patients with CRPC failed to demonstrate clinical activity and were associated with a more rapid posttherapy rise in PSA [21], suggesting a possible stimulatory effect of low doses of panobinostat as seen in preclinical models [14].

Given the toxicity seen in this and other DACi trials, it is possible that suboptimal cell inhibitory plasma concentrations of DACi can explain why there was less clinical activity than expected. In our study, 42.9% of patients required some adjustment in dose, potentially limiting the therapeutic efficacy of the drug. This underscores the importance of correlative studies within trials such as these to help determine the pharmacodynamic effects of the drug. It is unclear whether the dose and schedule were suboptimal or whether the drug itself was inactive against CRPC, thus raising the question of whether a different formulation and/or dose schedule would be effective in this patient population. At present, open questions remain regarding the optimal design of future studies for this class of agents in prostate cancer. These questions include the search for biomarkers predictive of clinical outcome beyond histone acetylation that may predict for response, and exploration of drug combinations using DACi, that may be effective in advanced CRPC.

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Fig. 1.
Total time on study for each patient is shown in days. Reason for discontinuation is delineated by color: red (n = 29), disease progression; green (n = 3), death; blue (n = 2), withdrawal of consent; gray (n = 1), new therapy.

Fig. 2.
Best percentage change in prostate-specific antigen (PSA) from baseline for each individual patient is shown.

Table 1

Patient Characteristics

Baseline Characteristics	Total Patients N = 35
Age, median (range), y	67 (51–85)
ECOG performance status, n (%)	19 (54.3)
0	16 (45.7)
1	
Gleason score, median (range)	7 (5–9)
PSA level, median (range), ng/mL	134.6 (0.1–10,551.1)
Number of previous regimens, median (range)	5 (1–7)
Hormonal	1 (0–3)
Chemotherapy	
Extent of disease, n (%)	6 (17.1)
Soft tissue only	8 (22.9)
Bone only	21 (60.0)
Both soft tissue and bone	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen.

Table 2PSA Best Change From Baseline^a

PSA Best Change	Total Patients ^b N = 35
Increase from baseline, n (%)	28 (80.0)
All	11 (31.4)
50%	17 (48.6)
> 50 %	
Decrease from baseline, n (%)	5 (14.3)
All	4 (11.4)
0 to 30%	1 (2.9)
30% to 50%	
Unchanged from baseline, n (%)	1 (2.9)
All	

Abbreviation: PSA, prostate-specific antigen.

^a Best change from baseline defined as (lowest postbaseline – baseline)/baseline.

^b Thirty-four of 35 patients were followed for PSA. One patient was followed for carcinoembryonic antigen.

Table 3

Adverse Events (All Grades) Regardless of Study Drug Relationship in > 10% of Patients

Adverse Event, n (%)	Total Patients N = 35	
	All Grades	Grade 3/4
All	35 (100.0)	25 (71.4)
Fatigue	22 (62.9)	3 (8.6)
Nausea	18 (51.4)	1 (2.9)
Thrombocytopenia	16 (45.7)	9 (25.7)
Decreased appetite	13 (37.1)	1 (2.9)
Diarrhea	12 (34.3)	0
Back pain	11 (31.4)	2 (5.7)
Vomiting	11 (31.4)	2 (5.7)
Weight decrease	11 (31.4)	0
Dysgeusia	10 (28.6)	0
Constipation	8 (22.9)	1 (2.9)
Arthralgia	7 (20.0)	3 (8.6)
Anemia	6 (17.1)	1 (2.9)
Dehydration	6 (17.1)	0
Hemoglobin decrease	6 (17.1)	1 (2.9)
Hypophosphatemia	6 (17.1)	4 (11.4)
Hypotension	6 (17.1)	2 (5.7)
AST increased	5 (14.3)	1 (2.9)
Hypocalcemia	5 (14.3)	0
Muscular weakness	5 (14.3)	2 (5.7)
Pain in extremity	5 (14.3)	3 (8.6)
Pyrexia	5 (14.3)	1 (2.9)
Increased blood creatinine	4 (11.4)	0
Dyspnea	4 (11.4)	1 (2.9)
Hypokalemia	4 (11.4)	2 (5.7)
Hyponatremia	4 (11.4)	0
Leukopenia	4 (11.4)	1 (2.9)
Peripheral edema	4 (11.4)	0
Decreased platelet count	4 (11.4)	3 (8.6)

Abbreviation: AST, aspartate aminotransferase.

Table 4

Notable QT Interval Values

QTcF Value	Total Patients N = 35
Maximum postbaseline QTcF value, n (%)	13 (37.1)
> 450 ms and 480 ms	3 (8.6)
> 480 ms and 500 ms	1 (2.9)
> 500 ms	
Maximum QTcF increase from baseline, n (%)	11 (31.4)
> 30 ms and 60 ms	2 (5.7)
> 60 ms	