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Phase Ib Trial of Cabazitaxel and Tasquinimod in Men With Heavily Pretreated Metastatic Castration Resistant Prostate Cancer (mCRPC): The CATCH Trial

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Abstract

BACKGROUND.—Tasquinimod is an immunomodulating and anti-angiogenic oral agent with anti-prostate cancer activity in preclinical studies and in clinical trials of men with metastatic castration resistant prostate cancer (mCRPC), including single agent activity and in combination with taxanes. We sought to identify the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of tasquinimod in combination with cabazitaxel and prednisone in men with chemorefractory mCRPC.

METHODS.—Men with mCRPC who had failed prior docetaxel chemotherapy received cabazitaxel 25 mg/m² every 3 weeks with oral tasquinimod at 1 of 3 escalating dose levels (0.25, 0.5, and 1.0 mg once daily) with prednisone and PEG-filgrastim support, using a 3+3 dose escalation design. Treatment continued until progressive disease or unacceptable toxicity.

RESULTS.—We enrolled 25 men with chemorefractory mCRPC. The RP2D was 0.5 mg tasquinimod based on excess DLTs (two of three men) observed at dose level 3 (1.0 mg) including grade 3 sensory neuropathy and grade 3 atrial fibrillation. Dose level 2 was expanded to 14 men, where 3 DLTs were observed: grade 3 fatigue, grade 4 febrile neutropenia, and grade 3 liver function abnormalities. The proportion of men with a 30% PSA decline was 63% and the median composite progression-free survival (PFS) was 8.5 months (95% CI 4.2–16.4 months) based on 12

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CONFLICTS OF INTEREST

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PFS events. The median number of cycles of cabazitaxel was 6 (range 1–13), with six men receiving >10 cycles. Best overall RECIST responses (CR + PR) were observed in three men (12%), with stable disease in 12 (48%). No pharmacokinetic interactions were observed.

CONCLUSIONS.—We determined the RP2D of tasquinimod combined with cabazitaxel to be 0.5 mg daily following a 3 week lead-in of tasquinimod 0.25 mg with growth factor support. No unexpected toxicities occurred. *Prostate* 77: 385–395, 2017.

Keywords

mCRPC; prostate cancer; tasquinimod; cabazitaxel; chemotherapy; immunotherapy; clinical trial; angiogenesis; phase I

INTRODUCTION

Tasquinimod is an oral quinolone-3-carboxamide agent with immunomodulating and anti-angiogenic properties [1,2]. Preclinical studies have demonstrated several anticancer mechanisms of tasquinimod in prostate cancer. These include binding to and inhibiting the activity of S100A9, a ligand for receptor for advanced glycation end products (RAGE), and important for myeloid-derived suppressor cell activity [3,4]. When RAGE is activated in prostate cancer tissue, the mitogen-activated protein kinase (MAP kinase) pathway and NF- κ B pathway are subsequently activated and can lead to cell survival, tumor growth, and metastasis [5,6].

Tasquinimod has been shown to upregulate thrombospondin-1 (TSP1) [7]. TSP1 has anti-angiogenic properties through various means including binding to CD36 to cause apoptosis of endothelial cells and suppression of nitrogen oxide dependent pathways. TSP1 also blocks the vascular endothelial growth factor (VEGF) pathway and down regulates hypoxia-inducible factor 1 α (HIF-1 α) leading to an overall block of the “angiogenic switch” from being turned on in a hypoxic state [7]. Finally, tasquinimod may also inhibit epigenetic modification of DNA in hypoxic states by acting as a specific histone deacetylase 3–4 inhibitor (HDAC), leading to reduced invasion and tumor growth [8], including reduced tumor microenvironment-based signaling important for growth and metastasis in both bone and visceral sites [9,10].

These preclinical data motivated the clinical development of tasquinimod in phase I and determined the safe dosing of this agent using a fixed schedule or using inpatient dose escalation from 0.25 to 1.0 mg once daily over 4–6 weeks to improve tolerability given the ability to dose patients at their own individual maximum tolerated dose (MTD) [11]. Following this dose finding study, a randomized double-blind, placebo controlled phase II trial was performed in 201 men with CRPC and documented metastatic disease [12]. Patients received oral tasquinimod or placebo (2:1) at 0.25 mg daily for 2 weeks followed by 0.5 mg daily for 2 weeks and then 1.0 mg daily thereafter if tolerated. The primary outcome was the progression free proportion at 24 weeks, defined as requiring any of the following: (i) opioid pain medicine wither any intravenous dose or orally for more than 10 of 14 days; (ii) radiographic progression by RECIST; (iii) progression on bone scan per prostate cancer working group two criteria; and (iv) need for palliative radiotherapy or cord compression

needing radiotherapy or surgery. The 24 week proportions free of progression were 69% in the tasquinimod group versus 37% in the placebo group ($P < 0.001$). The median progression-free survival (PFS) was 7.6 months versus 3.3 months ($P = 0.0042$), with greater differential activity observed in men with bone metastases. A dose reduction or termination was needed in 55% of the tasquinimod patients, whereas grade 3 or 4 adverse events were seen in 40% of the tasquinimod patients versus 12% with placebo, including deep vein thromboses 4% versus 0% and myocardial infarction 1% versus 0%. The most common reason to stop therapy was for musculoskeletal pain or constipation. Long term follow up of this study demonstrated an association of tasquinimod with improved overall survival (OS), with specific benefits in men with bone metastases and low volume/risk disease, and in men with low serum TSP-2 levels [13].

These results prompted the development of a global randomized, placebo-controlled phase III trial of tasquinimod in 1245 men with bone metastatic castration resistant prostate cancer (mCRPC). This trial confirmed an improvement in radiographic PFS using PCWG2 guidelines [14] (HR 0.64, $P < 0.001$) but an OS benefit was not observed [15]. Although well tolerated in general, these data suggested that single agent tasquinimod was not sufficiently active to extend life despite a delay in progression in these men.

Given this single agent activity, combination approaches of active agents have been evaluated preclinically with tasquinimod including androgen deprivation therapy (ADT) and docetaxel [16]. These studies demonstrated an additive impact on tumor growth delay than either single agent alone. Given the ability of tasquinimod to delay radiographic and symptomatic progression in men with mCRPC, the additive activity of tasquinimod with taxane chemo-therapy preclinically, and the lack of overlapping toxicities, we conducted a phase Ib clinical trial of tasquinimod with cabazitaxel, another taxane approved for mCRPC for men who have progressed despite initial docetaxel therapy [17].

PATIENTS AND METHODS

Patient Selection

Eligible men had to be 18 years of age or older and have confirmed prostate adenocarcinoma without small cell features, ongoing ADT with a baseline serum testosterone of less than 50 ng/dl, and castrate resistant disease progression defined by having at least 1 of 3 criteria: (i) PSA progression defined by consecutive PSA rise with a minimum of three rising PSA levels with an interval of 1 week between each determination and a screening PSA of ≥ 2 ng/ml; (ii) soft tissue disease progression defined by RECIST1.1 [18]; and (iii) bone metastatic disease progression defined by one or more new lesions on bone scan that are not clinically consistent with tumor flare. Patients were required to have radiographic evidence of metastatic disease and have a KPS of 70 or higher. Patients could have no more than three prior chemotherapy regimens with at least one regimen having docetaxel, or be intolerant of docetaxel.

Patients were required to be < 80 years of age in the phase I dose escalation phase, but the dose expansion phase did not have age limits. All patients were required to have a life expectancy of at least 3 months, and patients could not have major infectious co-morbidities,

untreated brain or epidural metastases, significant renal, hepatic, cardiac or bone marrow dysfunction, or grade 3 or more neuropathy judged by NCI Common Toxicity Criteria v4.0. Patients had to have been able to swallow the study drug and comply with study requirements. All participants signed an informed consent. This trial was registered with clinicaltrials.gov under NCT01513733 and was conducted through the Department of Defense Prostate Cancer Clinical Trials Consortium. The lead site was the Duke Cancer Institute with one participating site, the University of Chicago. This trial was done in accordance with the principles of the Declaration of the Helsinki and Good Clinical Practice guidelines and was approved by the Institutional review board of each participating institution.

Study Design

This was a phase I dose finding study with the primary objective of finding the recommended phase 2 dose (RP2D) of tasquinimod in combination with cabazitaxel and prednisone based on safety and tolerability and predefined dose limiting toxicities in men with docetaxel-treated mCRPC. The secondary objective was to describe the radiographic progression-free survival (rPFS), rates of PSA decline and radiographic response by PCWG2 and RECIST1.1 criteria [14,18], circulating tumor cell (CTC) responses using the Cellsearch method, OS, and overall safety and tolerability. Exploratory objectives included pharmacokinetic (PK) analysis and pain response. This was a single arm, dose escalation, open label, prospective trial. Oral tasquinimod was evaluated at three dose levels (0.25, 0.5, and 1.0 mg all daily) in combination with cabazitaxel 25 mg/m² every 3 weeks. Treatment for all cohorts started at 0.25 mg once daily, with dose escalation at dose level 2–0.5 mg after 3 weeks, and at dose level 3–1.0 mg after 3 weeks and to 1.0 mg daily after 6 weeks if tolerated. All patients were given oral prednisone 10 mg daily and pre-emptive PEG-filgrastim support starting at cycle 1 day 2 given the relatively high risk of neutropenic fever with cabazitaxel alone. Treatment was given continuously until progressive disease, withdrawal of consent, or unacceptable toxicity.

Dose limiting toxicities (DLT) were defined per protocol by NCI CTC v4.0 as grade 4 febrile neutropenia, grade 4 thrombocytopenia, grade 3 thrombocytopenia associated with a clinically significant bleeding event, or grade 3–4 non-hematologic toxicity, including grade 3–4 persistent nausea or vomiting despite maximum supportive care. The DLT time period was different for each dose level given the need for intra-patient dose escalation of the tasquinimod dose. Transient non-hematologic toxicities including laboratory or electrolyte abnormalities of grade 3–4 that lasted less than 48 hr were not considered a DLT.

Withdrawal or dose reductions of cabazitaxel during the DLT observation period were considered a DLT. The MTD was defined as the highest dose at which <1 of 6 subjects had a DLT during the period from study drug initiation through two cycles (42 days) of therapy and the MTD. A 3/3 dose escalation design was used with a prolonged DLT observation period of 6 weeks (dose level 1), 9 weeks (dose level 2), and 12 weeks (dose level 3) due to an intra-individual dose escalation of tasquinimod from a starting dose of 0.25 mg for the first 3 weeks. The protocol was amended for dose level 2, to permit dose escalation if 4 or fewer DLTs were observed out of 12 treated subjects. Dose expansion at the MTD was

planned for an additional 14 patients with a total sample size of up to 38 men to assess further safety and drug–drug PK interaction analysis.

Pharmacokinetics

Blood samples to evaluate the tasquinimod and cabazitaxel concentrations were collected weekly for the first four cycles. Tasquinimod concentration was determined using a validated method based on liquid chromatography and tandem mass spectrometry [19]. Cabazitaxel concentration was determined using a validated method based on supported liquid extraction, stable isotope dilution, and liquid chromatography with tandem mass spectrometry [20]. PK parameters including area under the concentration–time curve (AUC), Clearance (CL), and volume of distribution (V_z) were calculated using the Phoenix WinNonlin 6.4 software.

Statistical Analysis

The MTD was defined as the highest dose of cabazitaxel/tasquinimod at which no more than 1 of 6 (initial protocol) or 4 of 12 (amended protocol) evaluable patients has had a DLT during the first treatment cycle, given that two patients encountered DLT at the next higher dose level. Effectively, the MTD is the highest dose associated with first/second-cycle DLT in <33% of patients. Following the determination of the RP2D from the initial phase of the study, a dose expansion of 14 total patients was performed at this dose to further evaluate the toxicity profile for future phase II testing. With 14 patients enrolled in the study, the toxicity rate can be estimated with a standard error of no greater than 13.4% points. Subjects who withdrew consent prior to receiving study treatment were replaced.

Ninety-five percent confidence intervals for the MTD were calculated using the exact Binomial distribution. The Kaplan–Meier approach was used to estimate the PFS and OS distributions. PFS was defined from time of treatment to the time of first progression or death from any cause whichever occurred first or last follow up if alive. Patients were followed for survival after coming off study. Furthermore, the Kaplan–Meier product-limit method was used to estimate the survival distribution (which will be defined as the time from the date of study entry [date of first dose] to the date of death from any cause) and PFS (defined as the time from the date of study entry to the date of disease progression or death, whichever occurs). In addition, objective response rate (defined as either partial or complete response using the RECIST 1.1 criteria) and post therapy decline in PSA were estimated. Furthermore, descriptive statistics were used to summarize the patient characteristics (baseline clinical and laboratory variables) and the adverse events.

RESULTS

Patient Characteristics

Between August 8, 2012 and March 4, 2015, 25 evaluable men were treated on the study with 8 at dose level 1, 14 at dose level 2, and 3 at dose level 3 (see Fig. 1 for CONSORT diagram), and 23 of these men were evaluable for DLT determination. Two subjects were replaced at dose level 2 due to rapid disease progression in cycle 1 without toxicity, and they were considered not evaluable for DLT determination. A summary of the baseline

characteristics can be found in Table 1. The majority of patients were non-Hispanic Caucasian men (76%), with 24% African American male enrollment, with a median age of 66 years. The median baseline PSA was 220 ng/ml, and 44% had excellent functional status (KPS 90–100). All men had prior docetaxel, with 68% having prior abiraterone acetate, and 32% having prior enzalutamide. The pattern of metastatic spread at baseline included 60% with a visceral (liver, lung metastases $\pm$ node/bone) pattern, 36% with bone $\pm$ lymph node, and 4% with lymph node only patterns of spread. The median CTC count at baseline was 6 cells per 7.5 ml whole blood (Cellsearch method), and 12% had clinically significant pain requiring opioids.

Trial Conduct and MTD Determination

One DLT was observed at dose level 1 (grade 3 thrombocytopenia) and the dose was escalated per protocol after a total of 8 subjects were treated at this dose level per protocol. We observed four DLTs out of 12 patients at dose level 2, where additional patients were enrolled at this dose level to better estimate the precision of DLTs. In addition, 2 subjects were replaced due to progression prior to the end of the DLT period, and were declared unevaluable for DLT determination, although they were included for efficacy evaluations. DLTs at dose level 2 included AST and ALT elevation (G3), grade 3 fatigue, and grade 4 febrile neutropenia, and based on protocol rules for DLT determination using $<4/12$ DLTs for dose escalation, we further dose escalated to level 3 (1.0 mg daily of tasquinimod). At dose level 3, we observed that two of three patients experienced a DLT (grade 3 peripheral sensory neuropathy and atrial fibrillation), and therefore dose level 2 (0.5 mg daily) was declared the MTD for subsequent phase II studies based on the pre-specified protocol rules. See Table 2 for a full listing of the DLTs observed. A total of 14 subjects were treated at this MTD for efficacy and PK assessments, including the two who were replaced and considered not evaluable for MTD determination.

Safety

Overall, the most common adverse events included diarrhea (52% grade 1–2, 4% grade 3), fatigue (52% grade 1–2, 8% grade 3), nausea (48% grade 1–2, 4% grade 3), and peripheral sensory neuropathy (40% grade 1–2, 4% grade 3). Other adverse events that occurred in more than 10% of patients included taste alterations, anemia, anorexia, musculoskeletal pains, leg swelling, vomiting, headache, abdominal pain, constipation, insomnia, dizziness, dyspepsia, oral mucositis, asymptomatic lipase or amylase elevations, and thrombocytopenia. These were largely grade 1–2 (Table 3). Grade 3–4 common adverse events included vomiting (4%), asymptomatic lipase increases (8%), anemia (12%), and thrombocytopenia (4%). The following grade 3–4 toxicities only occurred in one subject: AST elevation, atrial fibrillation, febrile neutropenia, gastric ulcer, gastritis, hypotension, pustular rash, sepsis, and urinary tract infection. One subject experienced a grade 5 colonic perforation in the setting of a combination of constipation, opiate use and possibly study drugs. Refer to Table 2 for a complete list of the DLTs by dose level and see Table 3 for a listing of the most commonly observed toxicities at least possibly related to study drugs at a rate of 10%.

Pharmacokinetic Evaluation

We observed no drug–drug interactions between tasquinimod and cabazitaxel according to the PK parameters obtained for both drugs in cycle 1 and in later cycles, using intensive PK analysis at all drug levels. The PK parameters of tasquinimod and cabazitaxel were comparable to those reported in the literature. For example, the mean oral CL and V_z at 0.5 mg of tasquinimod were 0.28 L/h and 13 L, respectively compared to 0.28 L/h and 15 L previously reported [13]. For cabazitaxel, the clearance values were generally about 20–30 L/h/m² with a volume (V_z) of about 3000 L compared to reported values of clearance and volume (V_{ss}) after 1-hour infusions at 25 mg/m² every 3 weeks, of 25 L/h/m² and 2,000 L, respectively [21,22].

Antitumor Activity

Although considered exploratory given that this was a dose finding safety study, all patients were followed for response and radiographic PFS using PCWG2 criteria and for OS (Fig. 2A and B). The median number of every 3 week treatment cycles administered was 6 (range 1–13) with six men (24%) receiving over 10 cycles of cabazitaxel. Five patients continued tasquinimod monotherapy after stopping cabazitaxel for a median of 2 months. Efficacy data are summarized in Table 4. The median OS of all the patients was 16.0 months [95% confidence interval (CI) 7.8–17.9 months] with a 6 month OS rate of 85.7% [95% CI 62–95.2%], 12 month OS rate of 63.1% [37.2–80.7%], and 18 month OS rate of 12.6% [0.7–41.8%] (Table 4, Fig. 2A and B). The median rPFS was 8.5 months [95% CI 4.4–11.4 months] with a 6 month rPFS rate of 70.2% [95% CI 47.4–84.5%], 12 month rPFS rate of 25.5% [95% CI 9–46.1%], and 18 month rPFS rate of 6.4% [95% CI 0.4–24.7%].

The mean PSA best percent change of 24 patients was a decline of 44% and median decline of 65% (Fig. 3A). Sixty three percent of men achieved a PSA decline of >30% from baseline, whereas 58% achieved a 50% or greater decline, and 25% achieved a 90% or greater PSA decline. The median time to nadir of PSA was 2.9 months. The best radiographic response by RECIST 1.1 criteria was partial response (PR) in three men (12%), followed by stable disease (SD) in 12 men (48%), and progressive disease (PD) in four men (16%). Two men were not evaluable for a response. A swimmer plot describing the patient experience (toxicity, progression, treatment duration) per dose level is shown in Figure 3B.

DISCUSSION

Tasquinimod is an immunomodulatory anti-angiogenic agent that has demonstrated the ability to delay radiographic progression free survival in randomized phase II and III trials of men with mCRPC and preclinically has demonstrated synergistic combination activity with taxane chemotherapy [13,15,23–26]. Based on these results, we conducted a phase I trial of tasquinimod with the standard-of-care taxane chemo-therapy cabazitaxel in men with heavily pre-treated mCRPC in the post-docetaxel setting. We determined the MTD to be 0.5 mg of tasquinimod with full dose cabazitaxel and prednisone, along with concurrent growth factor support, and following a lead-in period of 0.25 mg once daily for 3 weeks. The efficacy results obtained in this phase Ib clinical trial suggest a higher than expected PSA decline rate as well as longer than expected progression-free and OS rates and treatment

immune modulatory agents with or without taxanes in this heavily pretreated patient population. As such tasquinimod could be tolerated with other taxane-based chemotherapeutic regimens in other cancer types as indicated in the future.

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Fig. 1.
CONSORT Diagram of patient enrollment and flow.

Fig. 2.
(A) Kaplan–Meier estimates of radiographic progression-free survival (rPFS). (B) Kaplan–Meier estimates of overall survival (OS).

Fig. 3.
(A) Waterfall plot of best overall PSA decline from baseline. **(B)** Swim lane plot of patient experience according to dose level, toxicity, progression, and death over time.

TABLE 1.

Baseline Characteristics of All Evaluable Patients

Baseline characteristic	N	% or value
Age, median (range)	25	66 (50–79)
Race		
White	19	76
Black	6	24
Ethnicity		
Hispanic	2	8
Non-Hispanic	23	92
Dose level		
1 (0.25 mg TASQ)	8	32
2 (0.5 mg TASQ)	14	56
3 (1.0 mg TASQ)	3	12
Karnofsky performance status		
70–80	14	56
90–100	11	44
Baseline median PSA, ng/ml (range)	25	220 (0.6–4059)
Gleason sum (8–10%)	25	64
Baseline median hemoglobin, g/dl	25	11.6
Baseline median alkaline phosphatase, IU/L (range)	25	90 (49–760)
Pattern of spread		
Lymph node only metastases	1	4
Bone metastases ± node (non-visceral)	9	36
Visceral (liver/lung) metastases ± bone/node	15	60
Pain score (0–10 scale), %	20	12
Median circulating tumor cells (cellsearch), per 7.5 ml blood (range)	11	6 (0–202)
Prior therapy with Abi/Enza/Docetaxel (%)	25	68/32/100

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TABLE 2.

Dose Limiting Toxicities (DLTs) According to Dose Level

Dose level	CTC AE v4.0 term	Grade	Attribution
1	Thrombocytopenia	3	Probable
2	Febrile neutropenia	4	Definite
2	ALT elevation	3	Probable
2	AST elevation	3	Probable
2	Fatigue	3	Probable
3	Peripheral sensory neuropathy	3	Possible
3	Atrial fibrillation	3	Possible

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

TABLE 3.

Most Commonly Observed Toxicities With Cabazitaxel and Tasquinimod According to NCI Common Toxicity Criteria v4.0

Toxicity terms	Grade 1–2 (%)	Grade 3–4 (%)
Diarrhea	52	4
Fatigue	52	8
Nausea	48	4
Peripheral sensory neuropathy	40	4
Dysgeusia	36	0
Anemia	28	12
Anorexia	28	0
Pain	28	0
Edema limbs	24	0
Vomiting	24	4
Headache	20	0
Abdominal pain	16	4
Alopecia	16	0
Constipation	16	0
Insomnia	16	0
Pain in extremity	16	0
Dizziness	12	0
Dyspepsia	12	0
Lipase increased	12	8
Mucositis oral	12	0
Serum amylase increased	12	0
Thrombocytopenia	8	4

TABLE 4.

Estimates of Efficacy With Combination Tasquinimod and Cabazitaxel

Estimate	Total	Number failed	Median time in months (95% CI)	6-month survival (95% CI)	1-year survival (95% CI)	18-month survival (95% CI)
Overall survival (OS)	25	12	16 (7.8, 17.9)	85.7% (62%, 95.2%)	63.1% (37.2%, 80.7%)	12.6% (0.7%, 41.8%)
Radiographic progression-free survival (rPFS)	25	20	8.5 (4.4, 11.4)	70.2% (47.4%, 84.5%)	25.5% (9%, 46.1%)	6.4% (0.4%, 24.7%)