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Research Letter

A Phase 1 study Combining Pexidartinib, Radiation Therapy, and Androgen Deprivation Therapy in Men With Intermediate- and High-Risk Prostate Cancer

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Abstract

Purpose: This study aimed to evaluate a combination of radiation therapy (RT), androgen deprivation therapy (ADT), and pexidartinib (colony-stimulating factor 1 receptor [CSF1R]) inhibitor in men with intermediate- and high-risk prostate cancer. CSF1R signaling promotes tumor infiltration and survival of tumor-associated macrophages, which in turn promote progression and resistance. Counteracting protumorigenic actions of tumor-associated macrophages via CSF1R inhibition may enhance therapeutic efficacy of RT and ADT for prostate cancer.

Methods and Materials: In this phase 1 study, the treatment regimen consisted of pexidartinib (800 mg, administered as a split-dose twice daily) and ADT (both for a total of 6 months), and RT that was initiated at the start of month 3. RT volumes included the prostate and proximal seminal vesicles. The delivered dose was 7920 cGy (180 cGy per fraction) using intensity modulated RT with daily image guidance for prostate localization. The primary objective was to identify the maximum tolerated dose based on dose-limiting toxicities.

Results: All 4 enrolled patients who were eligible to receive RT had T_1 stage prostate cancer, 2 were intermediate risk, and 2 were high risk. The median age was 62.5 years, and the prostate-specific antigen levels were in the range 6.4 to 10.7 ng/mL. The patients' individual Gleason scores were 3 + 3, 4 + 3, 4 + 4, and 4 + 5. All 4 patients reported ≥1 adverse events before RT. Grade 1

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hypopigmentation was observed in 1 patient, and grade 3 pulmonary embolus in another. One patient experienced fatigue and joint pain, and another elevated amylase and pruritus (all grade 3 toxicities). Five of the 6 adverse events noted in 3 patients were all grade 3 toxicities attributable to pexidartinib, qualifying as dose-limiting toxicities and ultimately resulting in the study closure.

Conclusions: The combination was not well tolerated and does not warrant further investigation in men with intermediate- and high-risk prostate cancer.

Introduction

The standard of care for patients with unfavorable intermediate- or high-risk localized prostate cancer includes radiation therapy (RT) with 4 to 6 months or 1.5 to 3 years of androgen deprivation therapy (ADT), respectively.[1] The combination has been shown to improve biochemical failure- and disease-free survival, as well as cancer-specific survival.[2,3] Despite receiving the combination, patients can experience a biochemical recurrence (ie, prostate-specific antigen increase), as well as distant metastases and prostate cancer-specific mortality; therefore, there is a need for treatment improvement.[4,5] Without such improvement, the administration of dose-escalated RT and long-term ADT will have failed for 45% of patients with high-risk prostate cancer by 6 years.[6]

To address the need for treatment intensification, we considered combining RT and ADT with the colony-stimulating factor 1 receptor (CSF1R) inhibitor pexidartinib. CSF1R signaling promotes tumor infiltration and survival of tumor-associated macrophages (TAMs), which in turn promote progression and resistance.[7] Preclinical evidence showed that pexidartinib counteracted TAM-mediated resistance to ADT and RT induced an increase in TAMs, resulting in slower tumor growth compared with RT alone.[8,9] Thus, counteracting the protumorigenic effects of TAMs via CSF1R inhibition may enhance therapeutic efficacy of RT and ADT for prostate cancer. We conducted a phase 1 study of RT + ADT + pexidartinib to assess the maximum tolerated dose and dose-limiting toxicities (DLTs).

Methods and materials

This was an institutional review board-approved prospective phase 1 trial of RT + ADT + pexidartinib. We planned to enroll eligible patients (n = 24) in 2 cohorts: Dose escalation cohort (using 3 + 3 design applied to 2 preselected doses of pexidartinib), followed by an open-label randomized extension cohort with 12 patients (6 patients receiving and 6 patients not receiving pexidartinib).

The proposed treatment regimen included pexidartinib 800 mg or 1000 mg given orally at a split-dose every day of a 28-day cycle over 6 cycles. ADT was to be received for a minimum of 6 months starting with day 1 of the first cycle. RT was to be initiated at the beginning of month 3 and administered daily for 8 weeks. Actual RT volumes included the prostate and proximal seminal vesicles. The delivered dose was 7920 cGy (180 cGy per fraction) using intensity modulated RT with daily image guidance for prostate localization.

The primary objective was to establish the maximum tolerated dose and DLTs of pexidartinib. A DLT is a clinically significant adverse event (AE) or abnormal laboratory value that is grade 3 or 4 (per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0) and unrelated to disease progression, intercurrent disease, or concomitant medications. Based on the 3 + 3 design, if at least 2 patients ($\geq$2 of 3, or $\geq$2 of 6) experienced a DLT at dose level 0 (800 mg/day), the study would be terminated.

Results

Eight patients provided informed consent between July 2015 and October 2017. Because of screen failure (n = 2) or consent withdrawal (n = 2), only 4 patients were enrolled in the trial. Tables 1 and 2 display the patients' baseline characteristics. The median age was 62.5 years (range, 48-85 years), and 2 patients were black and 2 were white. The patients' Eastern Cooperative Oncology Group performance status scores were 0 and 1 (50% each). Prostate-specific antigen levels were in the range 6.4 to 10.7 ng/mL, and individual Gleason scores were 3 + 3, 4 + 3, 4 + 4, and 4 + 5. All 4 patients had T_1 stage prostate cancer. Two patients were designated as having intermediate-risk disease, and 2 as having high-risk disease.[10]

Table 1 Baseline patient characteristics (N = 4)

Characteristic	Descriptive statistics	
Median age, year (range)	62.5	(48-85)
Race, n (%)		
White/Middle Eastern	2	(50)
Black/African American	1	(25)
Black/Native American	1	(25)
Eastern Cooperative Oncology Group performance status score at baseline, n (%)		
0	2	(50)
1	2	(50)

Table 2 Baseline patient characteristics (N = 4)

ID number	PSA, ng/mL	Gleason score	T-stage	D'Amico's risk group
1	10.7	3+3	T1c	intermediate-risk
2	6.4	4+4	T1c	high-risk
3	8.7	4+5	T1b	high-risk
4	8.5	4+3	T1c	intermediate-risk

Abbreviations: ID = identification; PSA = prostate-specific antigen

The treatment characteristics of the patients are depicted in Table 3. Only patient #1 completed all 3 treatments in the course of the study. He received 6 months of pexidartinib at 800 mg per day (with 1 week interruption), in addition to 6 months of ADT and 4 months of RT. His RT took longer than planned due to inconsistent compliance with radiation visits. The AEs he suffered did not contribute to RT treatment breaks. Patient #2 completed 6 days of pexidartinib at 800 mg per day, and then withdrew from the study because he was unable to tolerate the drug. However, he completed 6 months of ADT and RT off-study. Patient #3 completed 6 weeks of pexidartinib at 800 mg per day. Because his overall condition worsened due to noncancerous comorbidities, the patient did not start RT. He completed 6 months of ADT off-study. Patient #4 completed a total of 5 weeks of pexidartinib at 800 mg per day for 3.5 weeks on and 1 week off, at 600 mg per day for 1 week on and 1 week off, and at 400 mg per day for 3 days on and off. The dose deescalation regimen with interruptions were related to AEs that he was experiencing. He also completed 6 months of ADT and RT off-study.

All 4 patients presented with at least one AE (Table 4). Patient #1 had grade 3 fatigue and joint pain. Grade 1 hypopigmentation was observed in patient #2, leading to discontinuation of treatment at his request. Patient #3 presented with grade 3 pulmonary embolus. Patient #4 experienced grade 3 elevated amylase (asymptomatic) and pruritus (symptomatic). Five of the 6 AEs (83%) noted in 3 patients were grade 3 toxicities and attributable to pexidartinib, qualifying as DLTs and ultimately resulting in the study closure. Notably, all AEs occurred before RT, and took 5 to 154 days from onset to resolution.

Discussion

Common pexidartinib-related AEs, which were experienced by our patients, include fatigue, hair color changes, and pain in extremity and pruritus.[11] Moreover, hepatotoxicity was an identified risk associated with the administration of pexidartinib in patients with tenosynovial giant cell tumors that led to stopping of enrollment into the phase 3 ENLIVEN study in 2016.[12] The drug was approved by the U.S. Food and Drug Administration in 2019 for these patients, and is available through a Risk and Evaluation Mitigation Strategy program due to hepatotoxicity.[13]

A pilot study of pexidartinib alone in patients with advanced castration-resistant prostate cancer did not meet its enrollment goal by the end of 2012 and was terminated, and the results were reported in October 2019.[14]

Table 3 Treatment characteristics of the patients (N = 4)

ID number	Pexidartinib		ADT	RT
	Dosage	Duration*	Duration	Status
1	800 mg†	6 months	6 months	Completed‡
2	800 mg	6 days	6 months off study	Completed off study
3	800 mg	6 weeks	6 months off study	None
4	800 mg (3.5 weeks)§ 600 mg (1 week)§ 400 mg (3 days)	5 weeks	6 months off study	Completed off study

Abbreviations: ADT = androgen deprivation therapy; ID = identification; RT = radiation therapy

* Duration refers to the length of time during which the patient takes treatment, without including interruptions.

† Patient #1 had a 1-week dose interruption.

‡ Patient #1 was not fully compliant with his radiation visits. RT per protocol was to occur over a 2-month period but his RT took 4 months to complete.

§ Patient #4 had a 1-week interruption after taking 800 mg of pexidartinib, and another week after taking 600 mg of the study drug.

Table 4 Adverse events experienced by the patients (N = 4)

ID number	Adverse event	Grade	DLT	Onset*	Resolution†
1	Fatigue	3	Yes	49 days	76 days
1	Joint pain	3	Yes	74 days	36 days
2	Hypopigmentation	1	No	Immediately‡	154 days
3	Pulmonary embolism	3	Yes	45 days	5 days
4	Elevated amylase	3	Yes	19 days	Unavailable
4	Pruritus	3	Yes	33 days	Unavailable

Abbreviations: DLT = dose-limiting toxicity; ID = identification

* Onset refers to the number of days from the pexidartinib start date until the appearance of an adverse event symptoms.

† Resolution refers to the number of days from the onset of an adverse event up to its resolution.

‡ Patient #2 had a history of mild hypopigmentation, which worsened during the study.

A total of 6 patients received pexidartinib but none completed the study because of disease progression (50%), withdrawal by the patient (33.3%), or an AE (16.7%). Similar to our patients, the patients in the study reported grade 2 fatigue (33.3%) and grade 3 pain in extremity (16.7%).

Pexidartinib as a monotherapy has also been tested in phase 1 and 2 trials for other cancers, including leukemias, melanoma, and glioblastoma.[11,15] Furthermore, combinations of pexidartinib with other agents have been investigated in phase 1 and 2 studies, including pexidartinib combined with durvalumab (pancreatic/colorectal cancer), paclitaxel (solid tumors), eribulin (breast cancer), vemurafenib (melanoma), sirolimus (sarcomas, malignant peripheral nerve sheath tumors), binimetinib or PLX9486 (both in gastrointestinal stromal tumors), and RT + temozolomide (glioblastoma).[11,15]

The design of early phase clinical trials that provide informative results for individual agents and combinations has been recognized as particularly challenging in the development of combination regimens.[16] Most combination trials do not show adequate safety and efficacy to progress to a later phase.[17] A survey of phase 1 combination trials conducted in between 2003 and 2017 revealed that only 25% of these studies advanced to phase 2 or further.[17] If no pharmacokinetic or pharmacodynamic interactions are anticipated, instead of conducting a full phase 1 study, a lead-in phase to assess tolerability before phase 2 is a reasonable design.[16,17] Notably, the toxicities observed in our study occurred in the lead-in, not the combination phase.

Similarly, a phase 1 study of sunitinib + ADT + RT in patients with localized high-risk prostate cancer used a lead-in phase of sunitinib + ADT, followed by sunitinib + ADT + RT.[18] Toxicities associated with sunitinib were reported precisely during the lead-in phase. Despite establishing the recommended phase 2 dose of sunitinib and safety of this combination, the study did not advance toward a phase 2 trial, which is consistent with the observation that only 67% of combinations with observed clinical promise progress past phase 1.[17]

Conclusions

RT + ADT + pexidartinib was not well tolerated by men with intermediate- and high-risk prostate cancer. Our findings support using a lead-in design for nonhormonal novel agents combined with RT and ADT, especially when an early phase combination is administered with curative intent. Moreover, androgen—receptor-axis targeted drugs combined with RT and ADT are under investigation,[19] and the results are highly anticipated.

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