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European Association of Urology

Prostate Cancer

Effects of Cabozantinib on Pain and Narcotic Use in Patients with Castration-resistant Prostate Cancer: Results from a Phase 2 Nonrandomized Expansion Cohort

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Article info

Article history:
Accepted February 10, 2014
Published online ahead of print on February 20, 2014

Keywords:
mCRPC
Pain control
Patient-reported outcomes
Phase 2 trial
Quality of life
Tyrosine kinase inhibitor

Abstract

Background: Pain negatively affects quality of life for cancer patients. Preliminary data in metastatic castration-resistant prostate cancer (mCRPC) suggested a benefit of the oral tyrosine kinase inhibitor cabozantinib to pain palliation.
Objective: Prospective evaluation of cabozantinib's benefits on pain and narcotic use in mCRPC.
Design, setting, and participants: This was a nonrandomized expansion (NRE) cohort (n = 144) of a phase 2 randomized discontinuation trial in docetaxel-refractory mCRPC patients. Pain and interference of symptoms with sleep and general activity were electronically self-reported daily for 7-d intervals at baseline and regularly scheduled throughout the study. Mean per-patient scores were calculated for each interval. Narcotic use was recorded daily during the same intervals.
Intervention: Open-label cabozantinib (100 mg or 40 mg).
Outcome measurements and statistical analysis: The following stringent response definition was used: clinically meaningful pain reduction (≥30% improvement in mean scores from baseline) confirmed at a later interval without concomitant increases in narcotics. Only patients with moderate or severe baseline pain were analyzed.
Results and limitations: Sixty-five patients with moderate or severe baseline pain were evaluable. Of these, 27 (42%) experienced pain palliation according to the stringent

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http://dx.doi.org/10.1016/j.eururo.2014.02.013

response definition. Thirty-seven patients (57%) had clinically meaningful pain relief at two consecutive intervals, reported ≥6 wk apart in the majority. Forty-four patients (68%) had palliation at one or more intervals; 36 (55%) decreased narcotics use during one or more intervals. Clinically meaningful pain reduction was associated with significant ($p \leq 0.001$) improvements in sleep quality and general activity. A limitation of this study was its open-label design.
Conclusions: Cabozantinib demonstrated clinically meaningful pain palliation, reduced or eliminated patients' narcotic use, and improved patient functioning, thus meriting prospective validation in phase 3 studies.
Patient summary: We evaluated the potential of cabozantinib to improve symptoms in patients with metastatic prostate cancer that no longer responds to standard therapies. We saw a promising reduction in pain and reduced need for narcotic painkillers. Larger, well-controlled trials are necessary to confirm these findings.

1. Introduction

Most patients with advanced castration-resistant prostate cancer (CRPC) develop bone metastases frequently associated with debilitating pain that is, itself, associated with shorter survival [1]. For those with severe pain, symptoms are rarely eliminated despite optimal management with narcotic analgesics [2], which carry numerous side effects, thus reducing overall functioning even further. Anticancer treatments are needed in this disease that effectively control pain and enable reduction of narcotics.

The receptor tyrosine kinase MET and the vascular endothelial growth factor (VEGF) signaling pathway are implicated in development and progression of CRPC [3]. MET expression appears to be greater in bone metastases than primary tumors and lymph node metastases [4]; the VEGF pathway promotes bone lesion development and activates MET in advanced prostate cancer [3]. Cabozantinib is an orally bioavailable tyrosine kinase inhibitor of MET and VEGF receptor 2 that has demonstrated clinical activity in multiple types of solid tumors [5,6]. In a recent phase 2 randomized discontinuation trial (RDT) that enrolled 171 patients with metastatic CRPC (mCRPC), single-agent cabozantinib demonstrated increased progression-free survival compared with placebo, along with reductions in soft-tissue lesions, bone metastasis burden, and bone-turnover markers; common toxicities seen at the 100-mg dose in this population included fatigue, hand–foot syndrome, and diarrhea, which were typically manageable with either a dose reduction, treatment interruption, or supportive measures [7]. Randomization was halted early due to the clinical activity observed [7]. In a prospective, nonrandomized expansion (NRE) cohort of the phase 2 study, cabozantinib resulted in improvements on bone scans as well as reductions in bone biomarkers, soft-tissue disease, and circulating tumor cells [8,9].

Separately, a retrospective survey of participating investigators found widespread perceptions of pain benefits in the RDT. To explore this further, a formal prospective evaluation of pain using a rigorous measurement approach in accordance with relevant US Food and Drug Administration (FDA) guidance on patient-reported outcomes (PROs) [10,11] that met contemporary standards for pain assessment was needed [12,13]. Evaluating pain is no different from the development of other biomarkers, requiring analytically valid measurements and demonstrated clinical validity in appropriately designed and powered prospective trials. Studies of approved anticancer therapies in mCRPC have demonstrated modest pain palliation [14–16], but have not consistently evaluated PROs in line with current FDA guidance and contemporary methodology [13,17–21]. Supplemental Table 1 provides an overview of these requirements.

Since pain palliation is a stand-alone primary end point for which therapies have been approved in this disease, we explored whether the pain benefit observed in the RDT was sufficient to warrant the design of a phase 3 registration trial in mCRPC with a dedicated pain end point. To this end, we applied contemporary pain assessment methodology to the NRE cohort [13,22], exploring changes in pain, interference of symptoms with patients' daily living, and narcotic analgesia use.

2. Patients and methods

The patients described in this report were from the NRE cohort of the fully enrolled, phase 2 RDT XL184-203 [7]. Patients with progressive mCRPC (according to standard, objective criteria [23,24]) during treatment with a taxane- or abiraterone-containing regimen (or within 6 mo following the last dose), evidence of bone metastasis on bone scans, and previous docetaxel treatment were sequentially enrolled to two starting doses of open-label cabozantinib, first 100 mg then 40 mg daily, as part of a dose-ranging evaluation. Patients taking prednisone ≤10 mg/d were eligible for enrollment. The study design is described in detail elsewhere [22] and in the Supplement.

The study was approved by all local institutional review boards and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. The trial is registered at ClinicalTrials.gov (identifier: NCT00940225).

Once daily, patients were to self-report pain and interference of symptoms with daily living, using an automated, telephone, interactive voice-response system (IVRS), over 7-d intervals at screening (within 14 d before the first dose), at week 3, week 6, and every 6 wk thereafter, using select items from the Brief Pain Inventory short form (BPI-SF) and MD Anderson Symptom Assessment Inventory (MDASI) questionnaires [25,26]. Pain assessments were halted at patient request or if patients discontinued study treatment other than for progression. During each interval, patients reported their worst pain in the prior 24 h (item 3 on the BPI-SF) and the interference of cancer symptoms with sleep and general activity over the same period (items 4 and 14, respectively, on the MDASI). All three items use a 0–10 numeric rating scale, with higher scores representing greater pain intensity or symptom interference.