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Original Research

The association between health-related quality-of-life scores and clinical outcomes in metastatic castration-resistant prostate cancer patients: Exploratory analyses of AFFIRM and PREVAIL studies

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Abstract ***Background:*** Our exploratory analysis examined the association between health-related quality of life (HRQoL) (baseline and change over time) and clinical outcomes (overall survival [OS]/radiographic progression-free survival [rPFS]) in metastatic castration-resistant prostate cancer (mCRPC).
Methods: HRQoL, OS and rPFS were assessed in phase III trials comparing enzalutamide with placebo in chemotherapy-naïve (PREVAIL; NCT01212991) or post-chemotherapy (AFFIRM; NCT00974311) mCRPC. HRQoL was assessed using the Functional Assessment of Cancer Therapy-Prostate (FACT-P). Multivariate analyses evaluated the prognostic significance of baseline and time-dependent scores after adjusting for treatment and clinical/

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demographic variables. Hazard ratios (HRs) and 95% confidence intervals (CIs) represented the hazard of rPFS or OS per minimally important difference (MID) score change in HRQoL variables.

Results: In baseline and time-dependent multivariate analyses, OS was independently associated with multiple HRQoL measures across both studies. In time-dependent analyses, a 10-point (upper bound of MID range) increase (improvement) in FACT-P total score was associated with reductions in mortality risk of 19% in AFFIRM (HR 0.81 [95% CI 0.78–0.84]) and 21% in PREVAIL (HR 0.79 [0.76–0.83]). For baseline analyses, a 10-point increase in FACT-P total score was associated with reductions in mortality risk of 12% (HR 0.88 [0.84–0.93]) and 10% (HR 0.90 [0.86–0.95]) in AFFIRM and PREVAIL, respectively. rPFS was associated with a subset of HRQoL domains in both studies.

Conclusion: Several baseline HRQoL domains were prognostic for rPFS and OS in patients with mCRPC, and this association was maintained during treatment, indicating that changes in HRQoL are informative for patients' expected survival.

1. Introduction

Health-related quality of life (HRQoL) is an important end-point in oncology studies [1]. Patient-reported outcomes (PROs) can be associated with overall survival (OS) or progression-free survival (PFS) in various cancers [2–5]. Thus, the patient's perspective on changes in HRQoL, and more specifically PROs, is an important determinant of the value of cancer treatment.

The Prostate Cancer Clinical Trials Working Group 3 acknowledged the need to optimise assessment and analysis of PRO data and recommended evaluating the association between early changes in individual outcome measures (e.g. PROs) and later events such as radiographic PFS (rPFS) or OS [6]. In metastatic castration-resistant prostate cancer (mCRPC), improvement in HRQoL has been associated with improved clinical outcomes [7,8]. In addition, PRO data from 19 mCRPC clinical trials indicated that HRQoL and pain status augmented clinical efficacy data by providing better understanding of treatment impact [9]. However, information on relationships between commonly used efficacy outcome measures, such as rPFS or OS, and HRQoL in mCRPC is limited.

The AFFIRM (ClinicalTrials.gov, NCT00974311) [10] and PREVAIL (ClinicalTrials.gov, NCT01212991) [11] phase III trials showed that, compared with placebo, enzalutamide significantly prolonged OS and rPFS and displayed HRQoL benefits in men with mCRPC in post-chemotherapy and chemotherapy-naïve settings.

These exploratory analyses investigate the association between HRQoL and rPFS and OS in the AFFIRM and PREVAIL studies at baseline and during treatment.

2. Methods

2.1. Study populations and design

PREVAIL and AFFIRM were phase III, randomised, double-blind, placebo-controlled trials comparing oral enzalutamide 160 mg/day with placebo in post-chemotherapy (AFFIRM) or chemotherapy-naïve (PREVAIL) mCRPC patients. The trials' design, patient populations and results have been described previously [10,11].

Both trials were approved by local independent review boards and conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent.

2.2. Health-related quality of life

In both studies, HRQoL was assessed using the Functional Assessment of Cancer Therapy-Prostate (FACT-P), version 4, a 39-item instrument validated for use in mCRPC [12–14]. HRQoL data were collected at baseline (i.e. treatment day 1), at week 5 (PREVAIL only), at week 13 and every subsequent 12 weeks until study drug discontinuation.

2.3. Statistical analyses

In this *post hoc* exploratory analysis, we investigated the relationship between rPFS and OS and the following HRQoL measures: prostate cancer–specific subscale (PCS), PCS pain-related score, physical well-being (PWB), emotional well-being (EWB), social/family well-being (SWB), functional well-being (FWB), FACT-P total score, FACT-General (FACT-G) total score (the sum of PWB, FWB, SWB and EWB), FACT Advanced Prostate Symptom Index (FAPSI) and trial outcome index (TOI) (the sum of PWB, FWB and PCS). The analyses were performed on intent-to-treat patient populations (i.e. all patients who were randomised into the studies).

Cox proportional hazard models with baseline (i.e. fixed) or time-dependent covariates were fitted to time-to-event data (OS and, separately, rPFS). OS was defined as the time from randomisation to death from