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Original Research

Early PSA response is an independent prognostic factor in patients with metastatic castration-resistant prostate cancer treated with next-generation androgen pathway inhibitors

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Abstract ***Background:*** The optimal use of new therapies in metastatic castration-resistant prostate cancer (mCRPC) remains to be clarified. Prostate-specific antigen (PSA) response used as a pharmacodynamic end-point may help identify patients with early resistance to new androgen receptor-pathway inhibitors. We aimed to determine the clinical significance of early PSA response (EPR) during therapy with enzalutamide, abiraterone acetate (AA) and orteronel in mCRPC.

Methods: Data from patients recruited in clinical trials were studied. PSA values were obtained at baseline and 28 d after treatment initiation. EPR defined as a decline >50% from baseline was calculated according to the Prostate Cancer Working Group 2 criteria. The effects of clinical characteristics on radiographic progression-free survival (rPFS) and overall survival (OS) were examined using the Cox model.

Results: EPR was assessed in 118 patients treated in clinical trials and was found to be associated with longer rPFS and OS ($P < 0.0001$ for both). Median rPFS was 13.9 and 5.6 months (hazard ratio [HR]:0.38, $P < 0.001$) for patients with and without an EPR, respectively. Median OS was 32.2 months in patients with an EPR and 15.9 months in patients without an EPR (HR: 0.4, $P < 0.01$). EPR remained prognostic for OS in multivariate analyses (HR: 0.5, $p = 0.009$) that included validated pre-therapeutic prognostic factors for mCRPC. Prognostic values of EPR for rPFS and OS were confirmed in an independent cohort of 95 AA-treated non-trial patients.

Conclusions: EPR is an independent prognostic factor in patients with mCRPC treated with

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next-generation androgen pathway inhibitors and may be useful for the therapeutic management of these patients.

1. Introduction

Prostate cancer (PCa) is the most common cancer in men and the third most common cause of cancer death [1–2]. Of particular significance is the understanding and identification of predictive and prognostic factors that would allow for an individual therapeutic strategy and estimation of expected benefit. Despite the efforts for early detection and the observed shift in the initial staging of PCa secondary to a wide use of prostate-specific antigen (PSA) screening as well as adequate and aggressive use of hormonal therapy, patients eventually become resistant to androgen deprivation therapy (ADT) and relapse. In contrast to other solid cancers, almost all patients with PCa initially respond to ADT; however, acquired resistance that leads to disease progression and dissemination is almost ineluctable, necessitating treatment modification [3–4].

Cancer therapeutics achieved an important progress following the identification of molecular changes such as *RAS* mutations that predict resistance to epidermal growth factor receptor inhibitors in colorectal cancer, amplifications and gene mutations of ER, PR, and *ERBB2* in breast cancer and *ALK* gene translocation in non-small cell lung cancer [5]. While the molecular progress in other cancers is substantial and has allowed us to address disease heterogeneity with tailored treatment, metastatic PCa is still invariably treated as a single disease.

Until 5 years ago, the only approved agent for metastatic castration-resistant prostate cancer (mCRPC) was docetaxel-based chemotherapy, with a modest improvement in survival rates [6]. Over the last decade, however, a number of treatments and agents have improved overall survival (OS) in mCRPC patients including sipuleucel T, abiraterone acetate (AA), enzalutamide, cabazitaxel, and radium 223. Androgen receptor (AR) signalling inhibition by new generation endocrine therapies such as enzalutamide and AA proved to provide an OS benefit in both chemotherapy-naïve and -treated mCRPC patients [7–10]. Nonetheless, one-third of patients treated with abiraterone [8], 20–25% of those treated with enzalutamide [9] and 15% of patients treated with orteronel [11] in the published mCRPC post-docetaxel studies show primary resistance to these agents, usually defined as progression within the first 3 months of treatment [12]. The percentage of primary resistance in the pre-docetaxel setting is reported to be <20% for all three agents [7,10,13]. How these agents should be used to achieve optimal medical management is yet be clarified, remaining a major topic of investigation. Identifying patients rapidly who will not respond to these therapies is therefore of major importance. We hypothesised that very early PSA decline would identify patients most likely to benefit from androgen pathway inhibitors and those who will survive longer.

2. Patients and methods

The patient selection for the main cohort was made using the Gustave Roussy clinical databases of patients participating in six prospective phase III trials evaluating three AR axis inhibitors: enzalutamide, AA, and orteronel. The cohort included patients participating in the following trials: AFFIRM (enzalutamide post-docetaxel) [9], PREVAIL (enzalutamide pre-docetaxel) [7], COU-301 (AA post-docetaxel) [8], COU-302 (AA pre-docetaxel) [10], C21004 (orteronel pre-docetaxel) [11] and C21005 (orteronel post-docetaxel) [13]. Following informed consent, treatments were administered at standard doses: AA 1000 mg once daily in combination with prednisone (10 mg daily), enzalutamide 160 mg once daily, and orteronel 400 mg twice daily in combination with prednisone 5 mg twice daily. In all cases, the patients continued the luteinizing hormone–releasing hormone agonist treatment they were receiving before the start of the new generation agent. The patients were evaluated as follows: clinical evaluation (day 28 [D28]), biological evaluation at D8 (AFFIRM), D15 (COU-301), D21 (COU-302), D28 (AFFIRM, PREVAIL, COU-301, C21004, and C21005) and thrice monthly thereafter until disease progression. Bone scans and computed tomography (CT) of the chest and abdomen/pelvis were performed every 4 months. Follow-up was continued until death, loss to follow-up, or withdrawal of informed consent.

Concurrently, another cohort of patients treated with AA outside these clinical trials was included in the analysis. The patients received the same doses of treatment while clinical and biological follow-up during the treatment was on D8, D15 (however not consistently), D28 and at thrice monthly thereafter. Restaging with CT of the chest and abdomen/pelvis was performed as clinically indicated and according to the judgement of the treating oncologist.