available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer
Editorial by XXX on pp. x–y of this issue

Plasma Cell-free DNA Concentration and Outcomes from Taxane Therapy in Metastatic Castration-resistant Prostate Cancer from Two Phase III Trials (FIRSTANA and PROSELICA)

Niven Mehra[a], *David Dolling*[b], *Semini Sumanasuriya*[a], *Rossitza Christova*[b], *Lorna Pope*[b], *Suzanne Carreira*[b], *George Seed*[b], *Wei Yuan*[b], *Jane Goodall*[b], *Emma Hall*[b], *Penny Flohr*[b], *Gunther Boysen*[b], *Diletta Bianchini*[a], *Oliver Sartor*[c], *Mario A. Eisenberger*[d], *Karim Fizazi*[e], *Stephane Oudard*[f], *Mustapha Chadjaa*[g], *Sandrine Macé*[g], *Johann S. de Bono*[a,*]

[a] *Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, UK;* [b] *The Institute of Cancer Research, London, UK;* [c] *Tulane University School of Medicine, New Orleans, LA, USA;* [d] *The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA;* [e] *Department of Medical Oncology, Institut Gustave Roussy, University of Paris Sud, Villejuif, France;* [f] *Department of Medical Oncology, Hôpital Européen Georges Pompidou, Paris, France;* [g] *Sanofi, Paris, France*

Article info

Article history:
Accepted February 12, 2018

Associate Editor:
Stephen Boorjian

Statistical Editor:
Andrew Vickers

Keywords:
Circulating cell-free DNA
Cell-free DNA
Taxane chemotherapy
PROSELICA
FIRSTANA
Cabazitaxel
Docetaxel

Abstract

Background: Noninvasive biomarkers are needed to guide metastatic castration-resistant prostate cancer (mCRPC) treatment.
Objective: To clinically qualify baseline and on-treatment cell-free DNA (cfDNA) concentrations as biomarkers of patient outcome following taxane chemotherapy.
Design, setting, and participants: Blood for cfDNA analyses was prospectively collected from 571 mCRPC patients participating in two phase III clinical trials, FIRSTANA (NCT01308567) and PROSELICA (NCT01308580). Patients received docetaxel (75 mg/m^2) or cabazitaxel (20 or 25 mg/m^2) as first-line chemotherapy (FIRSTANA), and cabazitaxel (20 or 25 mg/m^2) as second-line chemotherapy (PROSELICA).
Outcome measurements and statistical analysis: Associations between cfDNA concentration and prostate-specific antigen (PSA) response were tested using logistic regression models. Survival was estimated using Kaplan-Meier methods for cfDNA concentration grouped by quartile. Cox proportional hazard models, within each study, tested for associations with radiological progression-free survival (rPFS) and overall survival (OS), with multivariable analyses adjusting for baseline prognostic variables. Two-stage individual patient meta-analysis combined results for cfDNA concentrations for both studies.
Results and limitations: In 2502 samples, baseline $\log_{10}$ cfDNA concentration correlated with known prognostic factors, shorter rPFS (hazard ratio [HR] = 1.54; 95% confidence interval [CI]: 1.15–2.08; $p = 0.004$), and shorter OS on taxane therapy (HR = 1.53; 95% CI: 1.18–1.97; $p = 0.001$). In multivariable analyses, baseline cfDNA concentration was an independent prognostic variable for rPFS and OS in both first- and second-line chemotherapy settings. Patients with a PSA response experienced a decline in $\log_{10}$ cfDNA concentrations during the first four cycles of treatment (per cycle −0.03; 95% CI: −0.044 to −0.009; $p = 0.003$). Study limitations included the fact that blood sample collection was not mandated for all patients and the inability to specifically quantitate tumour-derived cfDNA fraction in cfDNA.

* Corresponding author. The Institute of Cancer Research, The Royal Marsden NHS Foundation Trust, London SM2 5NG, UK. Tel. +44 20 8722 4028.
E-mail address: johann.de-Bono@icr.ac.uk (J.S. de Bono).

https://doi.org/10.1016/j.eururo.2018.02.013

Conclusions: We report that changes in cfDNA concentrations correlate with both rPFS and OS in patients receiving first- and second-line taxane therapy, and may serve as independent prognostic biomarkers of response to taxanes.

Patient summary: In the past decade, several new therapies have been introduced for men diagnosed with metastatic prostate cancer. Although metastatic prostate cancer remains incurable, these novel agents have extended patient survival and improved their quality of life in comparison with the last decade. To further optimise treatment allocation and individualise patient care, better tests (biomarkers) are needed to guide the delivery of improved and more precise care. In this report, we assessed cell-free DNA in over 2500 blood samples from men with prostate cancer who were recruited to two separate international studies and received taxane chemotherapy. We quantified the concentration of cell-free DNA fragments in blood plasma, which partly originates from tumour. We identified that higher concentrations of circulating cell-free DNA fragments, prior to starting taxane chemotherapy, can be used to identify patients with aggressive prostate cancer. A decline in cell-free DNA concentration during the first 3–9 wk after initiation of taxane therapy was seen in patients deriving benefit from taxane chemotherapy. These results identified circulating cell-free DNA as a new biomarker of aggressive disease in metastatic prostate cancer and imply that the study of cell-free DNA has clinical utility, supporting further efforts to develop blood-based tests on this circulating tumour-derived DNA.

1. Introduction

Prostate cancer (PCa) remains a major global healthcare challenge and lethal PCa remains a major cause of male cancer deaths [1]. Although most men with metastatic hormone-sensitive PCa respond well to androgen deprivation therapy (ADT) alone, their disease invariably recurs as metastatic castration-resistant prostate cancer (mCRPC). Docetaxel was introduced as a life-prolonging treatment for mCRPC in 2004, with taxanes gaining importance in the management of mCRPC [2,3]. The TROPIC trial led to cabazitaxel being registered as a second-line taxane in 2010 [4]. Furthermore, the CHAARTED and STAMPEDE trials brought docetaxel to the hormone-sensitive setting in 2015, showing unprecedented survival benefit in combination with ADT for patients with metastatic disease [5,6].

Other approved therapies for mCRPC include abiraterone, enzalutamide, radium-223, and sipuleucel-T; however, no optimal sequence of treatment or patient selection strategies have yet been established [7]. Currently, patients are assigned specific treatment types pragmatically, often with fitter patients prescribed chemotherapy, and less toxic drugs assigned earlier [8]. Identifying patients who are likely to benefit from specific treatment options remains a critically important unmet clinical need, and biomarkers predictive of early response to taxane therapy would help minimise overtreatment.

Potential use of cell-free DNA (cfDNA) as a prognostic and predictive biomarker of PCa, facilitating diagnosis and response to treatment, has been suggested [9–11]. In healthy volunteers, cfDNA levels are <5 ng/ml and reported to largely arise from haematopoietic cells [12]. Conversely, elevated cfDNA concentrations are present in the plasma of patients with PCa, where it comprises both circulating tumour DNA and normal DNA, with tumour content averaging 30%. Circulating tumour DNA has been reported to represent multiple tumour sites and is released through necrosis, apoptosis, and even active secretion [13,14].

Cell-free DNA is amenable to qualitative, for example, genetic and epigenetic, and quantitative analyses [13,15–17]. In a study of patients with various advanced cancers, the median cfDNA concentration was 17 ng/ml, with the highest concentrations (53 ng/ml) seen in patients with mCRPC [18].

This substudy assessed the clinical utility of plasma cfDNA in patients with mCRPC who also received taxanes (docetaxel and cabazitaxel) in two phase III clinical trials (FIRSTANA [NCT01308567] and PROSELICA [NCT01308580]). We performed preplanned analyses of baseline and serial blood samples taken from 571 consenting patients, and investigated the prognostic value of baseline cfDNA concentration and whether changes in cfDNA concentration during the first 9 wk of taxane chemotherapy are associated with response.

2. Patients and methods

2.1. Patients

This study included patients participating in two prospective, randomised, open-label, international phase III trials: FIRSTANA (NCT01308567), evaluating superiority of cabazitaxel 20 mg/m^2 (n = 389) or cabazitaxel 25 mg/m^2 (n = 388) over docetaxel 75 mg/m^2 (n = 391), each with 10 mg/d prednisone, as first-line chemotherapy for patients with mCRPC [19]; and PROSELICA (NCT01308580), a noninferiority study evaluating cabazitaxel 20 mg/m^2 (n = 598) or 25 mg/m^2 (n = 602) with 10 mg/d prednisone, as second-line therapy for patients with mCRPC who progressed on docetaxel [20]. These study designs are shown in Supplementary Figure 1. The primary end point of both studies was overall survival (OS). Secondary end points included radiological progression-free survival (rPFS), tumour response in patients with measurable disease, and prostate-specific antigen (PSA) response ($\geq$50% response at week 12; $\geq$50% response at any time). As part of preplanned biomarker analysis, baseline and serial blood samples were collected from consenting patients for quantitative and qualitative evaluation of plasma cfDNA. Analyses of cfDNA were included in both PROSELICA and FIRSTANA study protocols; however, details of statistical analyses were not prespecified and are therefore to be considered exploratory.

Please cite this article in press as: Mehra N, et al. Plasma Cell-free DNA Concentration and Outcomes from Taxane Therapy in Metastatic Castration-resistant Prostate Cancer from Two Phase III Trials (FIRSTANA and PROSELICA). Eur Urol (2018), https://doi.org/10.1016/j.eururo.2018.02.013