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The development of risk groups in men with metastatic castration-resistant prostate cancer based on risk factors for PSA decline and survival

Andrew J. Armstrong [a,*], *Ian F. Tannock* [b], *Ronald de Wit* [c], *Daniel J. George* [a], *Mario Eisenberger* [d], *Susan Halabi* [e]

[a] *Duke Comprehensive Cancer Center and the Duke Prostate Center, Divisions of Medical Oncology and Urology, Departments of Medicine and Surgery, DUMC Box 102002, Durham, NC 27715, USA*
[b] *Division of Medical Oncology, Princess Margaret Hospital and University of Toronto, Toronto, Canada*
[c] *Department of Medical Oncology, Rotterdam Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands*
[d] *Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD 21231, USA*
[e] *Department of Biostatistics and Bioinformatics, and the CALGB Statistical Center, Duke University, Durham, NC, USA*

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ABSTRACT

Aims of the study: There are no known predictive factors of response in men receiving chemotherapy for metastatic castration-resistant prostate cancer (mCRPC). We investigated pre-treatment factors that predicted a ⩾30% PSA decline (30% PSAD) within 3 months of starting chemotherapy, and assessed performance of a risk group classification in predicting PSA declines and overall survival (OS) in men with mCRPC.

Methods: In TAX327, 1006 men with mCRPC were randomized to receive docetaxel (D) in two schedules, or mitoxantrone (M), each with prednisone: 989 provided data on PSA decline within 3 months. Predictive factors for a 30% PSAD were identified using multivariable regression in D-treated men ($n = 656$) and validated in M-treated men ($n = 333$).

Results: Four independent risk factors predicted 30% PSAD: pain, visceral metastases, anaemia and bone scan progression. Risk groups (good: 0–1 factors, intermediate: 2 factors and poor: 3–4 factors) were developed with median OS of 25.7, 18.7 and 12.8 months ($p < 0.0001$); 30% PSAD in 78%, 66% and 58% of men ($p < 0.001$); and measurable disease response in 19%, 9% and 5% of men ($p = 0.018$), respectively. In the validation cohort, similar predictive ability was noted for 30% PSAD, tumour response and OS. PCWG2 subtypes were also predictive but resulted in unequal grouping. C-indices were 0.59 and 0.62 for 30% PSAD and OS in the validation dataset, respectively.

Conclusions: Risk groups have been identified and validated that predict PSAD and OS in men with mCRPC and may facilitate evaluation of new systemic regimens warranting definitive testing in comparison with docetaxel and prednisone. Prospective validation of this classification system is needed.

* *Corresponding author:* Tel.: +1 919 668 8797; fax: +1 919 668 7117.
E-mail address: andrew.armstrong@duke.edu (A.J. Armstrong).
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1. Introduction

Metastatic castration-resistant prostate cancer (mCRPC) remains a common and often fatal disease in Europe and the United States in 2009.[1,2] Docetaxel and prednisone were reported in 2004 to improve survival, response and quality-of-life in men with mCRPC, but since then no approved agents have further improved outcomes over docetaxel in phase III studies.[3,4]

Barriers to the identification of active agents in clinical trials of men with mCRPC include the lack of strong surrogates of survival and the potential length of time necessary to reach survival-based end-points.[5–7] The identification of potentially effective agents in phase II trials is confounded by the presence of prognostic factors that may lead to selection bias and to apparently favourable results that are not confirmed in definitive phase III clinical trials. Validated prognostic nomograms have identified risk factors for survival that have been used to stratify men with mCRPC in clinical trials.[8–10] However, these risk factors have not been fully utilised to restrict eligibility in conducting clinical trials or to identify risk groups of men with CRPC who may benefit from more aggressive intervention.[11,12] In addition, no known factors reliably predict the PSA declines in men with mCRPC and this may identify groups at higher risk for rapid disease progression.

A $\geqslant$30% decline in serum PSA in the 3 months (30% PSAD) following chemotherapy initiation has been identified as a valid surrogate of overall survival (OS) in men with mCRPC based on retrospective analyses from two pivotal phase III trials of docetaxel-based regimens.[7,13] Guidelines developed by the Prostate Cancer Working Group 2 (PCWG2) have since recommended the use of progression rather than response end-points to inform upon selection of active agents in phase II trials.[14] However, neither PSA or pain response nor progression-based end-points have been validated prospectively as surrogates of OS, and recent retrospective studies have shown quite modest surrogacy for current measures of progression-free survival (PFS) and PSA declines.[7,13,15–17] While recent definitions of PFS or changes in biomarkers such as circulating tumour cell count may improve upon surrogacy, a $\geqslant$30% PSAD and pain improvements following chemotherapy initiation are amongst the strongest predictors of OS, and can generally be ascertained within the first four cycles of chemotherapy.[14,17,18] We thus hypothesise that survival-based risk factors will also predict for PSA and tumour response outcomes and that these risk factors will facilitate communication with patients about expected responses to docetaxel chemotherapy and aid in selection of agents for definitive testing that surpass these expected outcomes in early phase studies.

2. Patients and methods

TAX327 was a randomized phase III study involving 1006 men with progressive metastatic CRPC, conducted from March 2000 to June 2002.[3] Eligible men had histologically documented metastatic PC despite castrate serum testosterone levels ($\leqslant$50 ng/dl), with disease progression defined clinically, radiographically or by PSA criteria. No prior chemotherapy other than estramustine was allowed, and men were required to have stable pain scores at entry. An Institutional Review Board approved the study at each participating institution.

Participants were randomised to one of three arms: three-weekly docetaxel (q3w, 75 mg/m^2), weekly docetaxel (q1w, 30 mg/m^2 5 weeks of 6) or q3w mitoxantrone (12 mg/m^2), all with prednisone 5 mg twice daily, with treatment planned for 30 weeks in the absence of progression. The present analysis is based on updated survival as of 7th November 2006, at which time 800 deaths had occurred.

2.1. Analysis of response-based outcomes

The primary objective of this analysis was the development of a predictive model for the attainment of a $\geqslant$30% decline in PSA within 3 months of treatment initiation (PSAD), without requirement for confirmation and irrespective of baseline PSA. Percent decline was taken as the nadir value during the 3-month interval as compared to baseline. Secondary end-points included a $\geqslant$50% confirmed PSA decline, PSA normalisation, pain response, tumour response and overall survival.[19] PSA normalisation required a PSA $\leqslant$4 ng/ml on protocol treatment amongst men with baseline PSA $\geqslant$20 ng/ml.[7] PSA was measured at each cycle.

Baseline pain was measured at each cycle using the Present Pain Intensity (PPI) score and an analgesic score (AS) was calculated from an analgesic diary where a standard dose of narcotic medication (e.g. 10 mg oral morphine) scored 4 points: a PPI of $\geqslant$2 and/or an AS of $\geqslant$10 were used as indicative of significant pain.[20] Pain response was defined as a $\geqslant$2 point-reduction from the baseline PPI without an increase in the AS or a >50% reduction in the AS without an increase in the PPI. Tumour response was evaluated every 2 months according to World Health Organisation (WHO) criteria.[3,4]

2.2. Model development

We first sought to identify independent factors that were predictive of 30% PSAD. We split the dataset into development and validation cohorts. Given the superiority of docetaxel to mitoxantrone and the larger sample size of docetaxel-treated men, we included men randomised to docetaxel (n = 656) in the development cohort. The validation cohort included men randomised to mitoxantrone/prednisone (n = 333). Baseline variables considered included the presence of visceral metastases, significant pain, alkaline phosphatase, investigator-determined mode of progression, haemoglobin, number of hot spots on bone scan, number of metastatic sites, PSA, PSA doubling time, time since diagnosis, tumour grade, prior therapies and Karnofsky performance status.[8–10] Multivariable logistic regression was performed, retaining variables that remained statistically significant (level of $p < 0.10$) after adjustment, and lacking co-linearity with other known prognostic factors. For each patient, a predictive score was computed from the estimated regression coefficients based on the fitted model and used to classify patients in risk groups. A concordance index was estimated as a measure of predictive ability in each cohort. Secondary outcomes were then assessed across risk groups. Differences in the proportion of men who achieved these outcomes across risk groups were