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Original article

Alkaline phosphatase velocity predicts overall survival and bone metastasis in patients with castration-resistant prostate cancer

Kai H. Hammerich, M.D., Ph.D.[a], Timothy F. Donahue, M.D.[b], Inger L. Rosner, M.D.[c,d,e], Jennifer Cullen, Ph.D., M.P.H.[d,e], Huai-Ching Kuo, M.S.[d], Lauren Hurwitz, M.H.S.[d], Yongmei Chen, M.D., M.P.H.[d], Melanie Bernstein, B.A.[b], Jonathan Coleman, M.D.[b], Daniel C. Danila, M.D.[b], Adam R. Metwalli, M.D.[a,*]

[a] *Urologic Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD*
[b] *Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY*
[c] *Urology Service, Department of Surgery, Walter Reed National Military Medical Center, Bethesda, MD*
[d] *Center for Prostate Disease Research (CPDR), Rockville, MD*
[e] *Department of Surgery, Uniformed Services University of the Health Sciences, Bethesda, MD*

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Abstract

Introduction and objectives: Identifying patients with prostate cancer (CaP) who will ultimately develop bone metastasis (BM) or die of disease is essential. Alkaline phosphatase velocity (APV) has been shown to predict overall survival (OS) and bone metastasis–free survival (BMFS) in an earlier study of an equal access military patient cohort of patients with castrate-resistant prostate cancer (CRPC). To confirm these findings, we examined a cohort of patients from a high-volume cancer center to validate a previous observation that faster alkaline phosphatase (AP) kinetics are predictive of OS and BMFS in this second cohort of patients.

Materials and methods: A retrospective cohort study was conducted of patients with CRPC treated at Memorial Sloan Kettering Cancer Center between 1989 and 2010. All patients who received androgen deprivation therapy (ADT) as primary treatment in response to a rising PSA after definitive surgery for CaP were eligible. For those who received primary ADT or surgery followed by ADT, CRPC was defined as one rising PSA value after a PSA nadir $\leq$4 ng/ml, and confirmed by a second rising PSA value, with concurrently documented testosterone levels $<$50 ng/dl. APV was computed as the slope of the linear regression line of all AP values ($>$2 values per patient) plotted against time. Study outcome included BMFS and OS. Univariable Kaplan-Meier analysis was used to examine time-to-event outcomes. Multivariable Cox proportional hazards regression analysis was used to model time to BMFS and OS.

Results: Of 89 patients with CRPC with evaluable data and CRPC, 17 (19%) experienced BM and 26 (29%) died. APV was dichotomized at the uppermost quartile split of all observed APV values: $\geq$5.42 U/l/y vs. the lower 3 quartiles combined, $<$5.42 U/l/y. Patients with faster APV had significantly worse outcomes, including faster progression to BM and poorer OS when compared with those with slower APV ($P = 0.0451$ and $P = 0.0109$, respectively). There was strong correlation between PSA doubling time (PSADT) ($<$10, $\geq$10 mo) and APV ($\geq$5.42 U/l/y vs. $<$5.42 U/l/y) ($P = 0.0289$), preventing simultaneous evaluation of both factors in multivariable analysis. Kaplan-Meier analysis showed that PSADT was also predictive of BM and OS (log-rank $P < 0.0001$). Separate multivariable Cox proportional hazards regression models were used to examine PSADT and APV, as predictors of each study outcome (BMFS and OS). Both PSADT and APV were strongly predictive of BMFS and OS (respectively).

Conclusions: APV and PSADT were predictors of BM and OS in patients with CRPC, respectively. These data are additional evidence of the potential value of AP kinetics in patients with advanced CaP. Prospective studies will be required to clarify these associations. However, given the restrictions on the current patient population in excluding metastatic disease within 12 months of ADT and a PSA nadir $>$4 ng/ml, the findings are not inappropriately generalized to other men. Published by Elsevier Inc.

Keywords: Prostate cancer; Castrate-resistant prostate cancer; Prostate; Cancer-specific death; Prostate cancer progression; Biomarker

* Corresponding author. Tel.: +1-301-496-6353; fax: +1-301-480-5626.
E-mail addresses: adam.metwalli@nih.gov, kai.hammerich@nih.gov (A.R. Metwalli).

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1. Introduction

Despite recent controversy, prostate-specific antigen (PSA) remains the primary screening parameter for all stages of prostate cancer (CaP). Since its clinical application nearly 3 decades ago, patients present at an earlier stage with predominantly low-grade, organ-confined disease at younger age [1]. However, despite increased screening with PSA-based strategies, almost 4% of patients continue to be diagnosed with advanced-stage disease at the time of initial presentation [2–4]. More importantly, approximately 12% of the patients with organ-confined CaP at the time of initial presentation ultimately go on to develop bone metastases (BM) and less than 1% of those patients with BM have survival of 5 or more years [3,5].

Currently, metrics such as PSA doubling time (PSADT) and PSA velocity are the only relevant measures commonly used to evaluate the risk for disease progression and BM in men diagnosed with CaP [6]. Nevertheless, the efficacy of PSADT in predicting the onset of BM in patients with rising PSA is limited [7].

Alkaline phosphatase (AP) has been shown to be a nonspecific bone turnover marker that has been used to evaluate efficacy of treatment and to predict overall survival (OS) in men with castration-resistant prostate cancer (CRPC) [8–10]. Historically, the clinical use of AP has been limited to detecting values above the upper limit of the reference range; only recently have AP kinetics been evaluated for clinical predictive value. A recently published study of a cohort of patients with CRPC demonstrated that alkaline phosphatase velocity (APV) has been shown to predict OS and bone metastasis–free survival (BMFS) [11].

It is well known that men who progress to metastatic CRPC have the highest probability of CaP-specific death compared with other stages of this disease. Furthermore, health care costs are significantly higher for patients who are diagnosed with this stage of disease [12,13]. Subsequently, from the clinical perspective of improved patient care as well as from an economic perspective, better tools are needed to identify and treat patients at risk for metastatic CRPC. The primary aim of this study was to confirm a prior observation that APV is a useful predictor of PCa progression in the interval between achievement of CRPC status and metastasis.

2. Methodology

2.1. Study population

Subjects of interest included those with biopsied-detected CaP between January 1, 1989 and December 31, 2010, who underwent androgen deprivation therapy (ADT) as primary CaP treatment or secondary to radical prostatectomy (RP) and provided written informed consent for study enrollment at Memorial Sloan Kettering Cancer Center (MSKCC). Patients with radiographic evidence of metastasis before or at the time of ADT initiation or within the first 12 months after ADT initiation were excluded from the study cohort to reduce the likelihood of occult metastases. The study cohort was further restricted to patients diagnosed with CRPC, defined as a PSA nadir of $\leq$4 ng/ml but with a rising PSA level despite ADT, and a testosterone level $<$50 ng/dl (n = 96). As patients with a PSA nadir $>$4 ng/ml have been shown to have a median survival of only 13 months [14], they were excluded so that the effect of APV would be evaluated for those who better reflect CRPC. A rising PSA level was defined as 2 consecutive increases above the PSA nadir for subjects who underwent primary ADT or RP followed by ADT. Patients taking medications that could affect AP levels or AP kinetics, including bisphosphonates, were excluded. Finally, only those with 2 or more AP measurements at least 3 months apart after initiation of ADT were considered (n = 89). A flow diagram of the study cohort is detailed in Fig. 1.

2.2. Demographic and clinical characteristics

The following demographic and clinical data for each subject were obtained: age at CaP diagnosis, race/ethnicity, PSA level at diagnosis (ng/ml), time from diagnosis to primary treatment (mo), time from ADT to PSA nadir (mo), time from ADT to CRPC (mo), follow-up time after ADT (mo), vital status, post-ADT PSA nadir (ng/ml), pre-CRPC AP level, post-CRPC AP level, clinical T stage (T1–T2b, $\geq$T2c), and biopsy Gleason sum (2–7 and 8–10). For patients who underwent RP, pathologic T stage (pT2, pT3–pT4) and pathologic Gleason sum (2–7 and 8–10) were examined. An indicator variable was created to examine treatment type as primary ADT vs. ADT after RP ("secondary ADT treatment"). Related time variables included

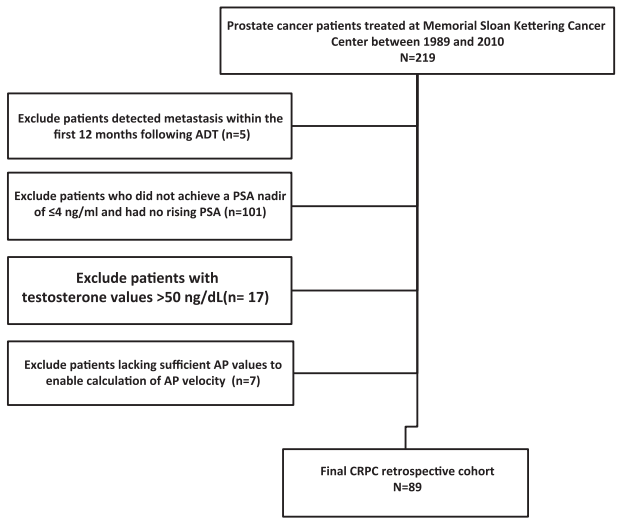

Fig. 1. A flow diagram of patient selection and inclusion criteria of the CRPC cohort.