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Original article

Elevated alkaline phosphatase velocity strongly predicts overall survival and the risk of bone metastases in castrate-resistant prostate cancer[1,2]

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Abstract

Objectives: In patients with a rising prostate-specific antigen (PSA) level during treatment with androgen deprivation therapy, identification of men who progress to bone metastasis and death remains problematic. Accurate risk stratification models are needed to better predict risk for bone metastasis and death among patients with castration-resistant prostate cancer (CRPC). This study evaluates whether alkaline phosphatase (AP) kinetics predicts bone metastasis and death in patients with CRPC.

Methods and materials: A retrospective cohort study of 9,547 patients who underwent treatment for prostate cancer was conducted using the Center for Prostate Disease Research Multi-center National Database. From the entire cohort, 347 were found to have CRPC and, of those, 165 had 2 or more AP measurements during follow-up. To determine the AP velocity (APV), the slope of the linear regression line of all AP values was plotted over time. Rapid APV was defined as the uppermost quartile of APV values, which was found to be $\geq$6.3 IU/l/y. CRPC was defined as 2 consecutive rising PSA values after achieving a PSA nadir $<$4 ng/ml and documented testosterone values less than 50 ng/dl. The primary study outcomes included bone metastasis–free survival (BMFS) and overall survival (OS).

Results: Rapid APV and PSA doubling time (PSADT) less than 10 months were strong predictors of both BMFS and OS in a multivariable analysis. Faster PSADT was a stronger predictor for BMFS (odds ratio [OR] = 12.1, $P < 0.0001$ vs. OR = 2.7, $P = 0.011$), whereas rapid APV was a stronger predictor of poorer OS (OR = 5.11, $P = 0.0001$ vs. OR = 3.98, $P = 0.0034$). In those with both a rapid APV and a faster PSADT, the odds of developing bone metastasis and death exceeded 50%.

Conclusion: APV is an independent predictor of OS and BMFS in patients with CRPC. APV, in conjunction with PSA-based clinical parameters, may be used to better identify patients with CRPC who are at the highest risk of metastasis and death. These findings need validation in prospective studies. Published by Elsevier Inc.

Keywords: Prostate cancer; Bone metastasis; Bone metastasis–free survival; Overall survival; Alkaline phosphatase; Prostate-specific antigen (PSA); PSA doubling time (PSADT); Alkaline phosphatase velocity (APV)

1. Introduction

Alkaline phosphatase (AP) has long been known as 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) [1–4]. Currently, prostate-specific antigen (PSA)-based methods are employed to stratify men by risk of developing bone metastases [5,6] despite evidence that this may not enrich clinical trials sufficiently [7]. Given the conflicting data currently available and the resulting lack of

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accurate predictive models, this study analyzed the Center for Prostate Disease Research (CPDR) Multi-center National Database in an attempt to identify whether AP velocity (APV) identifies patients who are at the highest risk of developing bone metastases. AP has long been known as a bone turnover marker with very stable intraindividual measurement kinetics, thus it was hypothesized that APV might improve the current PSA-based risk stratification [8,9].

Men who progress to CRPC and then to bone metastases are much more likely to die of their disease than patients with any other stage of prostate cancer (PCa). In addition, the morbidity and the cost of caring for these patients increase dramatically as they enter this late stage of their disease. As such, it is a clinical imperative to improve identification of patients who are most likely to progress to this terminal stage of the disease.

2. Materials and methods

2.1. Study population

The study population comprised men who were enrolled in the institutional review board–approved CPDR Multi-center National Database as previously described [10]. The study population included patients with biopsy-confirmed PCa detected between January 1, 1989 and December 31, 2010 who had undergone androgen deprivation therapy (ADT) as the primary treatment or secondary to either radical prostatectomy or external beam radiation therapy. Indication for ADT was not recorded, though patients were excluded if detectable metastases were observed before or at the time of ADT initiation or within the first 12 months following ADT initiation to reduce the likelihood of occult metastases. In this retrospective cohort, as in most settings apart from randomized clinical trials, the rationale and the timing for bone imaging are variable. This study population was restricted to subjects with CRPC who achieved a PSA nadir of ≤ 4 ng/ml, had rising PSA levels despite ADT, and had a testosterone value <50 ng/dl ($n = 347$). Hussain et al. [11] demonstrated that men who have a PSA nadir >4 ng/ml have a very short median survival of 13 months, therefore we excluded these individuals so that the effect of APV would be evaluated in men who better reflect most men with CRPC. Rising PSA level was defined as 2 consecutive increases above the nadir for subjects who underwent radiation or primary ADT and 2 consecutive rises more than undetectable levels for subjects who underwent prostatectomy. Patients taking medications, such as bisphosphonates, that could affect AP levels or kinetics were excluded. Finally, only those with no radiographic evidence of metastasis at baseline and 2 or more AP measurements at least 3 months apart following initiation of ADT were considered ($n = 165$).

2.2. Demographic and clinical characteristics

The following demographic and clinical data for each subject were obtained: age at PCa diagnosis, race/ethnicity, PSA level at diagnosis (ng/ml), clinical T category (T1-T2b, $\geq$T2c), biopsy Gleason sum (2–7 and 8–10), and PSA doubling time (PSADT). The PSADT was calculated as previously described by Pound et al. [12]. The PSADT was computed using all available PSA values at least 3 months apart after the diagnosis of CRPC. If the slope of the linear regression line was 0 (i.e., elevated but constant PSA levels), the PSADT was arbitrarily set to 120 months. Too few subjects were observed per PSADT strata of Freedland et al. [13]; therefore, the cut points of Pound et al. [12] were used to dichotomize PSADT as <10 vs. ≥ 10 months.

Finally, a kinetics measure of APV was calculated by using the slope of the linear regression line of the AP values plotted against time in years. This was computed using all AP values drawn at least 3 months apart obtained after CRPC developed but before the radiographic scan detected bone metastases. The APV was dichotomized at the upper quartile of all observed AP values in this study sample (<6.3 vs. ≥ 6.3 U/l/y) so as to compare those with the fastest rate of change with all other patients. The APV measure could not be treated continuously because of nonnormality and skew in its distribution.

An indicator variable was used to examine treatment as primary ADT vs. ADT secondary to radical prostatectomy, or ADT secondary to external beam radiation therapy (EBRT). The time variables of interest included time elapsed between (1) date of PCa diagnosis and ADT initiation, (2) date of ADT initiation and PSA nadir, and (3) date of ADT initiation and time at which rising PSA status was documented.

2.3. Study end points

The study end points included bone metastasis–free survival (BMFS) and OS. Presence of bony metastases was ascertained by a review of each patient's complete radiographic scan history, which was captured as part of ongoing data collection activities for the CPDR Multi-center National Database. The duration of BMFS was calculated as the number of years elapsed from the time point of documented rising PSA status until the end of the study period. Subjects who had no evidence of bone metastases were censored at the end of the study period. OS was used because OS data are recorded and available in CPDR and because determining prostate cancer–specific mortality (PCSM) is challenging under the best of circumstances [14].

2.4. Statistical analysis

The Student t test or the Wilcoxon and the Mann-Whitney tests were used to compare distributions in continuous patient characteristics, including age and time variables, across APV groups. Mantel-Haenszel chi-square tests were used to examine whether there were significant