Circulating Tumor Cells in Biochemical Recurrence of Prostate Cancer

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Abstract

Circulating tumor cells (CTCs) have shown prognostic importance in men with metastatic castration–resistant prostate cancer. Little information exists as to the yield of CTCs in men presenting with biochemical recurrence. This study sought to determine whether CTCs are detectable in such men and whether it correlates with known clinicopathologic parameters. Although the overall yield was low (8%), finding a detectable CTC raises a suspicion for metastatic disease in our series.

Objective: Circulating tumor cells (CTCs) have known prognostic implications in metastatic castration–resistant prostate cancer, but little is known regarding its utility in biochemical recurrence (BR) of prostate cancer. The primary objectives were to determine whether CTCs are measurable in patients with BR and whether it can reliably predict prostate-specific antigen (PSA) increase and PSA doubling times (PSADTs). **Methods:** BR was identified in patients after prostatectomy or radiation or both, with a PSA increase of $\geq$ 0.2 for prior prostatectomy or $>$ 2 mg/dL increase for post-nadir in prior radiotherapy. CTCs were enumerated at baseline at the time of study entry using the CellSearch (Janssen Diagnostics, Raritan, NJ) test. **Results:** The median age for all 36 patients accrued was 69.5 years (range, 51-91) with a median PSA of 1.65 ng/mL (range, 0.2-65.8). Gleason scores ranged from 5 to 9 (median, 7). The majority had prostatectomy (n = 25), external beam radiotherapy (n = 9), CyberKnife (Accuray, Sunnyvale, CA) (n = 1), and combined radiohormonal therapy (n = 1). PSADT ranged from 0.35 to 55 months, with a median of 7.43 months. The incidence of positive CTCs was 8.3% (3 patients), of whom 2 had biopsy-proven bony lesions on presenting with equivocal scans and PSADTs of 2.27 and 3.08 months, respectively. The third CTC-positive patient had a PSADT of 4.99 months. **Conclusions:** Obtaining CTCs in unselected patients presenting with BR has a relatively low yield. However, obtaining a positive CTC raises the suspicion of the presence of metastatic disease and may have utility for longitudinal follow-ups of patients with BR.

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Introduction

Prostate cancer is the leading noncutaneous malignancy among American men.[1] Although prostate-specific antigen (PSA) has been used as a biomarker for screening, diagnosis, prognostication, and measurement of treatment responses for men with advanced prostate cancer, certain limitations exist regarding the use of the PSA. For instance, in the setting of metastatic castration–resistant prostate cancer (mCRPC), PSA may be discordant with radiographic or clinical response.[2-4] The PSA Working Group 2 recommends that in the absence of objective signs of progression, switching therapies on the basis of PSA results alone may not be warranted.[5] To this end, the search for a viable surrogate biomarker for predicting survival and response to therapy has been more widespread over the past few years. One such Food and Drug Administration–approved method of predicting response to chemotherapy and aid in prognostication of progression-free survival and overall survival in men with mCRPC is the use and quantification of circulating tumor cells (CTC).[5-8] However, use of CTCs has not been widely studied in

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men with earlier phases of disease,[9] such as those presenting with biochemical recurrence (BR).

BR occurs in approximately one third of men who present after curative prostatectomy or radiotherapy. In patients who have BR, no standard treatment currently exists.[10] The clinical implications and prognosis for patients presenting with BR are also varied. Although some patients have only localized disease, others may have occult or overt metastatic disease. Therefore, providing better prognostic markers for this heterogeneous population of patients is critical, because offering salvage therapies may be appropriate in some with truly localized recurrence, which offers a second chance for cure, whereas offering early androgen deprivation therapy to those with occult or overt metastatic disease or those who have rapid PSA doubling times (PSADTs) may be appropriate in others, especially in the context of a rapidly evolving landscape of treatment in metastatic prostate cancer.

The primary objective of this study was to determine whether CTCs were measurable in patients who have undergone primary treatment with surgery or radiation with or without prior hormonal therapy manifesting with BR and whether this correlates with PSA increase and varying categories of PSADT. Secondary objectives included description of correlates of CTC detection, including testosterone, body mass index, PSA, lactate dehydrogenase, alkaline phosphatase, and stage and grade of prostate cancer.

Patients and Methods

Study Design and Statistical Analysis

This was a prospective, single-center study conducted at the George Washington University Medical Center, Washington, DC. All patients gave written, informed consent through a protocol approved by the Institutional Review Board (IRB). Eligible patients included men with prior histologically proven prostate adenocarcinoma identified in the departments of Urology or Radiation Oncology or Medical Oncology who have undergone primary definitive surgery or radiation who manifested with BR. Definition of PSA or BR varies among patients undergoing primary surgery or radiation.[11] This study used the definition of BR provided by the American Society of Therapeutic Radiation and Oncology—Phoenix consensus. For postradiotherapy, this is defined as a PSA increase of $\geq$ 2 ng/mL above the PSA nadir postradiotherapy.[12] For postsurgery, this is defined as exhibiting a PSA increase of $\geq$ 0.2 ng/mL.

The study sample size goal of 36 patients was determined to achieve 81% power to detect a Pearson correlation between CTC count and PSADT of 0.46, assuming alpha = 0.05 and a 2-sided Fisher Z test.

Patients consecutively presenting to the Hematology/Oncology clinic provided consent and were included in the study, which was reviewed and approved by the George Washington University IRB. Patients were evaluated as per standard of care testing with all patients having had imaging using computed tomography and technetium-99 scintigraphy bone scans obtained within 1 to 3 months of enrollment to determine the presence of any overt metastatic disease with radiographic interpretation rendered by the George Washington University Hospital Radiologists.

CTC Analysis Using CellSearch

Peripheral blood samples using 7.5 to 10 mL were obtained from each patient at the time of enrollment after referral and IRB consent were obtained. Samples were processed with the CellSearch Kit using the CellTracks System (Janssen Diagnostics, Raritan, NJ). CTCs were isolated using an automated sample preparation system (CellTracks II AutoPrep; Janssen Diagnostics) by an immunomagnetic capture that enriches for epithelial cells using antibodies to epithelial-cell adhesion molecule coupled with magnetic beads. The antibodies used in the CellSearch assay are targeted at cell markers (epithelial cell adhesion molecule [EpCAM] and cytokeratins 8, 18, and 19) that are expressed by adenocarcinomas and distinguished from leukocytes using a CD45 marker. Isolated cells were then stained with the dye DAPI stain, a fluorescent nucleic acid to identify these nucleated cells. CTC analysis was performed using the CellSearch CTC Kit. The results are reported as number of CTCs per 7.5 mL of whole blood.

Results

Patient Demographics

A total of 36 patients provided consent and were accrued from May 2010 to May 2012. The majority of patients were African-American. Most underwent prior primary prostatectomy with a median PSA of 1.65 (Table 1). The median time to BR from the

Table 1 Patient Demographic and Clinical Characteristics

No. of patients	36
Age at registration mean (SD, range)	69.6 years (8.4, 51-91)
Race	
Caucasian	11 (31%)
African-American	23 (64%)
Hispanic	2 (6%)
Primary treatment	
Prostatectomy	25 (69%)
EBRT	10 (28%)
CyberKnife (Accuray, Sunnyvale, CA)	1 (3%)
Prior hormone use	
Yes	11 (31%)
No	25 (69%)
Serum testosterone mean (SD, range) ng/mL	297 (161, 31-727)
PSA at enrollment median (range) ng/dL	1.65 (0.2-65.8)
PSADT median (range) mo	7.43 (0.35-55.2)
<3 mo	7 (19%)
3-15 mo	20 (56%)
>15 mo	9 (25%)
Time to BR median (range)	3.53 (0.44-16.30)
Hemoglobin g/dL mean (SD)	13.4 (1.4)
Alkaline phosphatase IU/L median (range)	69.5 (39-219)
LDH, median (range)	162 (82-329)
BMI kg/m^2 mean (SD, range)	28.4 (4.1, 20.7-36.8)
Albumin g/dL mean (SD, range)	4.3 (0.3, 3.9-4.8)

Abbreviations: BMI = body mass index; BR = biochemical recurrence; EBRT = external beam radiotherapy; LDH = lactate dehydrogenase; PSA = prostate-specific antigen; PSADT = prostate-specific antigen doubling time; SD = standard deviation.