Original Study

Characterization of Differences Between Prostate Cancer Patients Presenting With De Novo Versus Primary Progressive Metastatic Disease

Antoine Finianos,[1] Kanika Gupta,[1] Brandon Clark,[2] Samuel J. Simmens,[2] Jeanny B. Aragon-Ching[3]

Abstract

Men who present with metastatic prostate cancer can have distant metastases as their first presentation of cancer (de novo) or develop progression to metastases after a history of curative intent therapy (primary progressive). We found that men presenting with de novo metastatic disease have a shorter duration of hormone sensitivity and worse survival compared with those with primary progressive metastatic disease, suggesting a more aggressive disease course.

Background: Men who present with metastatic disease can have de novo or primary progressive disease. We characterized and compared the outcomes between these 2 groups. **Patients and Methods:** A retrospective cross-sectional analysis from a single institution of de novo versus primary progressive metastatic patients during a 2-year consecutive period was undertaken. Patient characteristics such as demographics, Gleason score, duration of hormone sensitivity, and treatment were obtained. The *t* test, Mann-Whitney *U* test, and Fisher exact test were used to test differences in patient and disease characteristics between the de novo and primary progressive metastatic groups. Differences in the Kaplan-Meier survival curves were compared using the log-rank test. **Results:** A total of 90 patients (n = 38 with de novo and 52 with primary progressive disease) were included. Statistically significant median differences were found for the prostate-specific antigen level at the development of metastases: de novo, 279.42 ng/mL versus primary progressive, 12.5 ng/mL ($P = .0002$; albumin and hemoglobin, $P = .03$ and $P = .045$, respectively). The median duration of hormone sensitivity was 372 days (range, 54-3753 days) in the de novo group versus 1613 days (range, 7-4314 days) in the primary progressive group ($P = .00006$). Overall survival was worse in the de novo arm, with a median survival of 6.2 years compared with a median survival in the primary progressive group of 11.6 years ($P = .027$). **Conclusion:** Although the reported samples were small, our data revealed a potential difference in disease aggressiveness in those presenting with de novo metastatic cancer with higher risk disease and shorter time to castration resistance and worse survival. These data could have implications for earlier and more aggressive treatment for men presenting with de novo metastatic prostate cancer.

Clinical Genitourinary Cancer, Vol. ■, No. ■, ■-■

Keywords: Castration resistance, De novo metastatic disease, Metastatic prostate cancer, Prostate specific antigen, Treatment

Introduction

Prostate cancer continues to be the most common noncutaneous cancer among American men. In 2017, the estimated new prostate cancer cases will be ~161,360 male patients, with estimated deaths at 26,730.[1] According to the Surveillance, Epidemiology, and End Results database, ~4% of patients with prostate cancer will have distant disease and metastases at their first presentation, termed de novo metastatic disease. However, a subset of men initially treated with curative intent

This study was presented in part at the American Society of Clinical Oncology Genitourinary Cancers Symposium, February 2015 and 2017, both in Orlando, Florida.

[1]Division of Hematology and Oncology, The George Washington University School of Medicine and Health Sciences, Washington, DC
[2]Department of Epidemiology and Biostatistics, The George Washington University Milken Institute School of Public Health, Washington, DC
[3]GU Medical Oncology, Inova Schar Cancer Institute, Fairfax, VA

Submitted: Jun 20, 2017; Revised: Aug 12, 2017; Accepted: Aug 12, 2017

Address for correspondence: Jeanny B. Aragon-Ching, MD, FACP, GU Medical Oncology, Inova Schar Cancer Institute, 8501 Arlington Boulevard, Suite 340, Fairfax, VA
E-mail contact: Jeanny.Aragon-Ching@inova.org

1558-7673/$ - see frontmatter
http://dx.doi.org/10.1016/j.clgc.2017.08.006

with either radiation or prostatectomy, or both, will develop progression to metastatic disease during the disease course, termed primary progressive disease. Although the incidence of prostate cancer has been declining as a result of less stringent prostate-specific antigen (PSA) screening recommendations in recent years,[2] the reported 5-year relative survival for all prostate cancer stages combined has also notably increased from ~83% in in the late 1980s to ~99% in the more contemporary period of 2005 to 2011, which might have been resulted from a lead time bias or overdetection[3] but also perhaps because of more efficacious treatment options. Moreover, with less PSA screening, it is conceivable that the incidence of de novo metastatic disease might soon increase, which has already been evidenced in some series.[4] However, in a study of men with de novo metastatic disease from a California Cancer registry, no significant improvement in overall or disease-specific survival was observed during a 20-year period (1988-2009).[5] Although the Groupe d'étude des tumeurs urogénitales (GETUG) AFU 15,[6] chemohormonal therapy versus androgen ablation randomized trial for extensive disease in prostate cancer (CHAARTED),[7] Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy: A Multi-Stage Multi-Arm Randomised Controlled Trial (STAMPEDE),[8,9] and LATITUDE (A Study of Abiraterone Acetate Plus Low-Dose Prednisone Plus Androgen Deprivation Therapy [ADT] Versus ADT Alone in Newly Diagnosed Participants With High-Risk, Metastatic Hormone-Naive Prostate Cancer [mHNPC])[10] trials have included a mixture of patients with de novo and primary progressive metastatic prostate cancer, no data to date have evaluated the clinical, phenotypic, molecular, or treatment outcome differences between these 2 groups of patients. Therefore, we sought to retrospectively characterize and compare the differences in disease characteristics and outcomes between patients who had presented with de novo disease and those who had presented with primary progressive metastatic disease in a single institutional study.

Patients and Methods

Patient Selection

All patients selected for review had histologically confirmed prostate adenocarcinoma and either de novo metastatic disease at presentation or primary progressive prostate cancer as evidenced by any of the following: primary treatment in the past with curative intent surgery or radiation, or both, with or without hormonal therapy, presenting with metastatic disease. The institutional review board approved the protocol to record the data from consecutive patients from 2008 to 2015. Patient demographics, including age and race, were recorded. Other clinical information, including sites of metastases, body mass index, receipt of previous hormonal therapy, PSA level, Gleason score at diagnosis, and laboratory parameters, including albumin, hemoglobin, creatinine, lactate dehydrogenase (LDH), and alkaline phosphatase, were all recorded. The interval to the development of castration resistance, various treatments received, date of metastases, and survival were also recorded.

Study Design and Statistical Analysis

The study data were collected and managed using REDCap electronic data capture tools hosted at Children's National Health System.[11] The software used was R, version 3.2.4 (R Foundation for Statistical Computing, Vienna, Austria). The study design was a retrospective descriptive analysis. Group differences were tested using the 2-sample t test, Mann-Whitney U test for skewed data, and the Fisher exact test. Kaplan-Meier survival curves were used to model subject survival. The log-rank test was used to compare the survival curves. The associations among demographic factors, laboratory values, prognostic and diagnostic factors, comorbidities, and treatment patterns were analyzed. $P < .05$ was considered statistically significant, with no adjustments for multiple testing.

Results

Patient Characteristics

A total of 90 consecutive patients with metastatic prostate cancer met the criteria for inclusion. Of these 90 patients, 38 were considered to have de novo and 52 to have primary progressive disease. The patient characteristics are summarized in Table 1. The de novo and primary progressive cancer groups were similar in age at diagnosis and race. The median PSA level at diagnosis was greater in the men with de novo than in the men with primary progressive cancer ($P < .001$). At the development of metastasis, the hemoglobin and albumin levels were significantly lower in patients with de novo cancer ($P = .03$ and $P = .045$, respectively). Although the PSA level increased from the diagnosis to the development of metastasis in those with primary progressive cancer, it was still significantly lower than that of those with de novo cancer at diagnosis; the difference was statistically significant ($P = .0001$). Both types of cancer were likely to metastasize to the bone and viscera; however, the de novo cancer cases were significantly more likely than the primary progressive cases to metastasize to lymph nodes ($P = .004$).

Treatment and Duration of Castration Sensitivity

In terms of primary local therapy, significantly more patients with primary progressive cancer will receive local therapy as a part of their initial treatment, as expected ($P < .001$). However, they also received significantly more intermittent androgen deprivation therapy (ADT) ($P = .003$). The duration of hormone sensitivity for those with de novo cancer was a median of 372 days compared with 1613 days for those with primary progressive cancer ($P \leq .0001$).

Overall Survival

The median follow-up period was 3.09 years and the mean follow-up period was 4.63 years for the whole cohort. The survival time was measured from the date of diagnosis for the men with de novo cancer and the date of diagnosis of metastatic disease for the men with primary progressive cancer. Two men (1 from each group) were not included in the survival analysis because of missing mortality data during the follow-up period. At the final follow-up examination, 13 men with de novo disease and 18 with primary progressive disease had died. The median survival in the de novo group was 6.2 years (95% confidence interval, 3.5-upper-bound not calculable) and 11.6 years (95% confidence interval, 8.1-15.7) in the primary progressive group ($P = .02$; Figure 1).

Discussion

The distinction between de novo and primary progressive metastatic prostate cancer has both clinical and practical implications. To date, published data describing well these 2 distinct cohorts of men are scarce. Although a single-institution study, which included only 1 arm of only metastatic patients, showed no particular difference in this cohort of patients,[12] our results, which included a primary progressive comparative