Nadir Testosterone after Long-Term Followup Predicts Prognosis in Patients with Prostate Cancer Treated with Combined Androgen Blockade

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Abbreviations and Acronyms

ADT = androgen deprivation therapy
BMI = body mass index
CAB = combined androgen blockade
LHRH = luteinizing hormone-releasing hormone
OS = overall survival
PFS = progression-free survival
PSA = prostate specific antigen
TST = testosterone

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Purpose: We examined the clinical significance of long-term serum testosterone monitoring to predict the prognosis of patients with prostate cancer treated with combined androgen blockade.

Materials and Methods: We retrospectively analyzed the records of 225 patients who underwent combined androgen blockade as first line therapy for prostate cancer. The prognostic values of testosterone and other clinical factors were evaluated with respect to prostate specific antigen progression-free and overall survival.

Results: Median patient age was 73.0 years, median prostate specific antigen was 42.6 ng/ml and median followup was 45.8 months. No variable associated with testosterone was predictive of progression-free survival. With regard to overall survival on univariate analysis nadir testosterone less than 16 ng/dl ($p = 0.0190$), less than 20 ng/dl ($p = 0.0020$) and less than 32 ng/dl ($p = 0.0146$) were significant together with other clinical factors. In contrast, nadir testosterone less than 8 and less than 12 ng/dl were not significant. Multivariate analysis showed that nadir testosterone less than 20 ng/dl was the significant prognostic factor ($p = 0.0048$). In addition, time to nadir testosterone was about 1 year (11.3 months). Patients were divided into rapid and slow types based on time to testosterone less than 20 ng/dl before and after 6 months, respectively. No significant difference in overall survival was observed between the 2 types. The current results suggest that the critical factor for prognosis was not a rapid decrease but whether nadir testosterone achieved a level of less than 20 ng/dl.

Conclusions: Nadir testosterone 20 ng/dl was the most significant cutoff level for overall survival in Japanese patients with prostate cancer treated with combined androgen blockade.

Key Words: prostatic neoplasms, testosterone, antiandrogens, mortality, prognosis

PROSTATE cancer is one of the most commonly diagnosed cancers in men.[1] ADT is the mainstay of therapy for locally advanced or metastatic prostate cancer ineligible for local regional treatments and some patients with early stage disease choose ADT depending on age or medical status.[2,3] A low TST level in men on ADT is thought to be associated with a longer

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duration of response.[2,3] According to current guidelines the target TST level during ADT for prostate cancer is defined as less than 50 ng/dl.[4] However, a castration cutoff of TST 50 ng/dl was derived from old assay methods.

Recently a new method using chemiluminescence has made it possible to more accurately measure serum TST below 50 ng/dl. It has shown that most patients who undergo orchiectomy achieved serum TST less than 20 ng/dl. van der Sluis et al reported that medically castrated men had significantly lower TST than those who were surgically castrated (median 4.0 ng/dl, range less than 2.9 to 20.2 vs 9.2 ng/dl, range less than 2.9 to 28.8, $p < 0.001$).[5] The most clinically significant castration level during ADT remains controversial. Several studies provide evidence about the correlation between castration level and prognosis.[2,3,6] Although some evidence exists, few groups have assessed the relationship between serum testosterone levels during ADT and prognosis, especially in Japanese patients on CAB. In the current study we examined the clinical significance of long-term serum TST monitoring to predict the prognosis in Japanese patients with prostate cancer treated with CAB.

MATERIALS AND METHODS

Patient Selection and Clinical Variables

We retrospectively analyzed the records of a total of 225 patients who underwent CAB as first line therapy for prostate cancer at Chiba University Hospital and Yokohama Rosai Hospital between 1999 and 2014.

The prognostic value of the serum TST level and other clinical factors was evaluated in association with PSA-free PFS and OS. We selected Japanese patients with prostate cancer who received CAB as first line therapy and we measured serum testosterone several times. Patients treated with radiation as first line therapy or radical prostatectomy and those with a history of radiation to the pelvis, systemic chemotherapy, use of 5α-reductase inhibitors and missing data on TST were excluded from analysis. Patients who underwent salvage radiation therapy after ADT were assessed only for PFS.

Variables included in analysis were age, BMI, clinical T stage, lymph node metastasis, bone metastasis, Gleason score, PSA at baseline, nadir PSA, time to nadir PSA, TST at baseline, nadir TST at 6 months (nadir within the first 6 months of ADT), nadir TST less than 8, less than 12, less than 16, less than 20 and less than 32 ng/dl, and time to nadir TST.

The Architect® Testosterone II assay was mainly used to determine serum TST. The Total Testosterone Kit (LSI Medience, Tokyo, Japan) was used for a period.

Statistical Analysis

Univariate and multivariate Cox proportional models, and the Kaplan-Meier method were used for statistical analysis. The Student t-test, and chi-square and Wilcoxon signed rank tests were used to assess the associations of nadir TST less than 20 ng/dl with other clinical variables. Statistical calculations were done using JMP® 11.0.0.

RESULTS

The study population included 225 patients, of whom 28 died of prostate cancer and 5 died of other disease. Median followup was 45.8 months. Table 1 shows patient characteristics. Median age was 73.0 years and median PSA was 42.6 ng/ml. Overall 65.2% of cases were clinical T3 stage or greater. The rates of lymph node metastasis and bone metastasis were 30.6% and 47.1%, respectively. The rates of Gleason score 6 or less, 7, 8 and 9 or greater were 8.7%, 34.3%, 20.3% and 36.7%, respectively. First line antiandrogen medication was bicalutamide in 93.3% of patients while 96.4% received LHRH antagonist, including leuprolide acetate in 64.9%, goserelin acetate in 28.4% and degarelix acetate in 3.1%, and 3.6% underwent surgical castration. Systemic chemotherapy with docetaxel was given to 23.1% of patients after several courses of ADT.

Table 1. *Characteristics of 225 patients*

Median/av mos followup	45.8/49.8
Median/av age	73.0/72.3
Median/av BMI (kg/m^2)	23.2/23.2
Median/av alkaline phosphatase (IU/l)	248.5/523.4
Baseline PSA (ng/ml):	
Median/av	42.6/498.9
No. less than 100 (%)	127 (56.4)
No. 100—less than 500 (%)	48 (21.3)
No. 500 or greater (%)	50 (22.2)
Median/av baseline TST (ng/dl)	514/550
No. T stage (%):	
T1c	38 (18.9)
T2	32 (15.9)
T3	99 (49.3)
T4	32 (15.9)
TX	24
No. lymph node metastasis (%):	
N−	152 (69.4)
N+	67 (30.6)
NX	6
No. bone metastasis (%):	
No	117 (52.9)
Yes	104 (47.1)
MX	4
No. Gleason score (%):	
6 or Less	18 (8.7)
7	71 (34.3)
8	42 (20.3)
9 or Greater	76 (36.7)
GSX	18
No. antiandrogen medication (%):	
Bicalutamide	210 (93.3)
Flutamide	9 (4.0)
Chlormadinone	6 (2.7)
No. LHRH agonist/antagonist/surgery (%):	
Leuprorelin	146 (64.9)
Goserelin	64 (28.4)
Degarelix	7 (3.1)
Surgical castration	8 (3.6)
No. systemic docetaxel chemotherapy	52