ELSEVIER

Archives of Medical Research 44 (2013) 259–265

Archives of Medical Research

ORIGINAL ARTICLE

Correlation of Serum β2-Microglobulin Levels with Prostate-specific Antigen, Gleason Score, Clinical Stage, Tumor Metastasis and Therapy Efficacy in Prostate Cancer

Yun-xin Zhang,[a,b,*] Li Wang,[c,*] Peng-yu Ji,[d] Gang-gang Zhao,[a,b] Gan-ping Zhong,[a] and Zhi-ping Wang[a,b]

[a]*Department of Urology, The Second Hospital of Lanzhou University, Lanzhou, Gansu, China*
[b]*Institute of Urology, The Second Hospital of Lanzhou University, Key Laboratory of Urological Diseases in Gansu Province, Gansu Nephro-Urological Clinical Center, Lanzhou, Gansu, China*
[c]*Key Laboratory of Preclinical Study for New Drugs of Gansu Province, Department of Pharmacology, School of Basic Medical Sciences, Lanzhou University, Lanzhou, Gansu, China*
[d]*Department of Clinical Laboratory, The Second Clinical Medical College of Lanzhou University, Lanzhou, Gansu, China*

Received for publication September 24, 2012; accepted March 12, 2013 (ARCMED-D-12-00531).

Background and Aims. Despite previous reports implying a role of β2-microglobulin (β2M) in the development of prostate cancer (PCa), the correlation of serum β2M with the clinicopathological features, therapy efficacy and prognosis of patients with PCa have not been fully clarified. The present study aims to investigate the serum levels of β2M in patients with PCa and explore the potential use of β2M as a tumor marker for diagnosis, treatment and prognosis of PCa.

Methods. Serum β2M levels in 120 patients with PCa, 50 patients with benign prostate hyperplasia (BPH) and 85 healthy age-matched controls were measured by enzyme immunoassay. The correlation of serum β2M with the clinicopathological features, therapy efficacy and the prognosis of PCa were subsequently assessed.

Results. Our results showed that: (i) PCa patients had significantly higher levels of β2M compared to those of patients with BPH or those of healthy controls. (ii) Serum β2M were markedly elevated in patients with high stage or grade PCa as compared to patients with low stage or grade PCa. (iii) We measured significantly higher levels of β2M in patients with metastasis as compared to patients lacking metastasis. (iv) During follow-up, serum β2M showed a marked decrease after successful therapy and a significant further increase in recurrent disease.

Conclusions. Our results demonstrate that serum β2M is correlated closely with the clinical stage, Gleason grade, PSA, distant metastasis and therapy efficacy in patients with PCa. Serum β2M may be a useful biomarker for clinical diagnosis, follow-up and prognosis of PCa.

Key Words: Prostate cancer, β2-microglobulin, Clinical pathology, Prognosis, Metastasis.

Introduction

Prostate cancer (PCa) is the most commonly diagnosed visceral cancer in males and is responsible for the second highest cancer-associated male mortality rate in Western countries, with increasing rates being reported in China, Japan, and Korea (1). Although several biomarkers have been identified and tested as diagnostic and prognostic markers for PCa, to date, only prostate-specific antigen (PSA) is routinely used in diagnosis (2). The introduction of the PSA test in the late 1980s has resulted in a marked increase in the diagnosis of PCa, but has not subsequently led to a significant reduction in deaths from PCa (3). Additionally, use of PSA as a cancer-specific diagnostic test has well-recognized limitations. Many unnecessary biopsies are performed because in some cases high PSA values reflect a large prostate volume rather than a high risk of PCa. Moreover, the use of PSA velocity, PSA

*These authors contributed equally to the work.

Address reprint requests to: Zhi-ping Wang, Department of Urology, The Second Hospital of Lanzhou University, Cuiyingmen No.82, Linxia Road, Lanzhou City, Gansu Province 730030, China; Phone and Fax: +86 931 894 2821; E-mail: erywzp@lzu.edu.cn

0188-4409/$ - see front matter.
http://dx.doi.org/10.1016/j.arcmed.2013.03.008

density and the free-to-total PSA ratio has provided only marginal improvements in terms of specificity. These limitations of PSA contribute to the ongoing debate about the benefits of population-based screening for PCa (4). Therefore, additional biomarkers may be useful in the diagnosis and treatment of patients with PCa.

Recently, intensive efforts have been focused on searching for molecular markers that may increase diagnostic and prognostic accuracy. For example, assessment of EZH2 protein in PCa tissue samples correlates with poor prognosis (5), whereas circulating levels of TGFβ1 in the blood predicts biochemical recurrence of PCa (6). Additionally, circulating tumor cells and circulating plasma DNA were recently shown to be correlated with PCa grade, stage, and metastasis (7).

Although there is evidence that β2M is closely related to growth, infiltration and metastasis of PCa, the clinical significance and implication of serum β2M in human PCa are not completely clear. The relationships between serum β2M and clinicopathological variables in PCa remain to be elucidated. In the present study we used enzyme immunoassay to analyze β2M expression in the serum of 120 patients with PCa, 50 patients with BPH and 85 healthy age-matched controls. The goals of this investigation were (i) to compare the serum levels of β2M in PCa patients to those of BPH patients and healthy controls, (ii) to evaluate the diagnostic and prognostic values of serum β2M in patients with PCa for the potential use of β2M as a tumor marker to diagnose human PCa and to monitor the prognosis of patients and (iii) to evaluate the values of serum β2M as a useful serological marker to monitor the efficacy of therapy and to follow-up metastasis in patients with PCa.

Subjects and Methods

Subjects

The study was approved by the clinical research ethics committees and informed consent was obtained from all of the patients. All specimens were handled in an anonymous manner according to the ethical and legal standards.

The present study included 120 patients who were diagnosed with PCa at our hospital between 2008 and 2012. Their ages ranged from 46 to 86 years (mean 64.6 ± 9.3). PCa was diagnosed by histopathological examination of specimens obtained by transrectal needle biopsy of the prostate. Before patients underwent digital rectal examination (DRE) and prostate biopsy, serum PSA and β2M levels were measured using the electrochemiluminescence immunoassay and enzyme immunoassay, respectively. The clinical stages of the disease were determined according to the TNM Prostate Cancer Staging System (American Joint Committee on Cancer) using a DRE, transrectal ultrasound (TRUS), X-ray, CT, MRI and bone scintigraphy. Biopsied specimens were fixed in 10% formalin and routinely embedded in paraffin; 3-μm sections were cut and stained with hematoxylin and reviewed by a pathologist to determine the Gleason score, based on the Gleason Grading System (8). Age, serum PSA levels, Gleason scores and clinical stages of the 120 patients are shown in Table 1. Additionally, 50 patients who were diagnosed with BPH and 85 healthy age-matched controls were included in the current study and used as controls.

Among the patients who were diagnosed with PCa, 42 were treated by radical prostatectomy as a definitive therapy. The other 78 patients were treated by hormonal therapy because of high stage, grade, or advanced age. Patients were followed-up with a periodic evaluation by DRE, serum PSA level, serum β2M level and imaging examination. Recurrence of PCa was defined as an increase in the serum PSA levels during two consecutive measurements (PSA failure) or the appearance of new soft tissue or metastatic lesions.

Serum Collection

For quantitative measurement of β2M and PSA levels, serum samples were collected from all 120 PCa patients before performing DRE and prostate biopsy. Serum specimens from 50 BPH patients and 85 healthy age-matched individuals were similarly collected to be used as controls. Moreover, in 42 patients who were treated with radical prostatectomy and 78 patients who were treated with hormonal therapy, serum β2M and PSA levels were measured before, during and after treatment. Among the 42 patients who were treated by radical prostatectomy, recurrence was observed in eight patients during the follow-up period. In these recurrent patients, serum samples were collected for evaluation of PSA and β2M levels. Serum samples were stored immediately at −20°C in plastic tubes until tested. All evaluated samples were tested simultaneously to minimize standard errors.

Determination of Serum β2M

β2M concentration in serum was determined by the Quantikine IVD human β2M ELISA kit (R&D Systems, Minneapolis, MN) according to the manufacturer's instruction.

Table 1. Clinical features of 120 patients with PCa

Clinical features	Mean ± SD (range) or number (%)
Age (years)	64.63 ± 9.32 (46–86)
Serum PSA (ng/mL)	37.04 ± 28.78 (2.33–130.20)
Clinical stage	
T1	7 (5.8%)
T2	35 (29.2%)
T3	58 (48.3%)
T4	20 (16.7%)
Gleason score	
≤6	54 (45.0%)
7	46 (38.3%)
≥8	20 (16.7%)

PCa, prostate cancer; PSA, prostate-specific antigen.