KJU
Korean Journal of Urology

www.kjurology.org
http://dx.doi.org/10.4111/kju.2012.53.3.149

Urological Oncology

Clinical Significance of Free-to-Total Prostate-Specific Antigen (PSA) Ratio in Advanced Prostate Cancer Patients with PSA Less than 0.1 ng/ml after Hormone Treatment

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Purpose: We analyzed the pattern of change in the free-to-total prostate-specific antigen (f/t PSA) ratio and the progression to castration-resistant prostate cancer (CRPC) in patients with advanced prostate cancer who received hormone treatment and whose PSA nadir was below 0.1 ng/ml.

Materials and Methods: We retrospectively analyzed the medical records of 52 patients with advanced prostate cancer. All patients were treated with maximum androgen blockade (gonadotrophin-releasing hormone agonist and anti-androgen agents). The patients were divided into two groups: those with a nadir f/t PSA ratio above 60% and those with a nadir f/t PSA ratio of 60% or below. Age, initial PSA, clinical stage, lymph node metastasis, bone metastasis, and follow-up data, including PSA, free PSA, and f/t PSA ratio, were collected. The Mann-Whitney U-test, Fisher exact test, chi-square test, Kaplan-Meier survival analysis, and log rank test were used.

Results: There were 24 patients in the group with a nadir f/t PSA ratio above 60% and 28 patients in the group with a nadir f/t PSA ratio of 60% or below. After hormone therapy, the median f/t PSA ratio in each group increased from 37% and 34% at 3 months to 75% and 60% at 6 months, respectively. At 9 months, however, the f/t PSA ratio increased to 80% in the group with a nadir f/t PSA ratio above 60%, whereas it decreased to 31% in the group with a nadir f/t PSA ratio of 60% or below. From 9 to 15 months, the f/t PSA ratio showed a tendency to decrease (75 to 37% and 27 to 20%, respectively). The progression to CRPC was significantly different between the two groups (10 vs. 24).

Conclusions: Progression to CRPC was significantly higher in the group with a lower f/t PSA ratio. Additionally, the pattern of change in the f/t PSA ratio was significantly different after 9 months. Collectively, the f/t PSA ratio can be used as an additional marker for prognosis of hormone treatment.

Key Words: *Hormone replacement therapy; Prostate-specific antigen; Prostatic neoplasms*

Article History:
received 14 August, 2011
accepted 25 October, 2011

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INTRODUCTION

Prostate cancer is the most common cancer in the United States [1]. In Korea, prostate cancer is the fifth most common malignancy in men [2]. Because of prostate-specific antigen (PSA)-based screening, the clinical stage of newly diagnosed prostate cancer has been migrating downward in the United States [3]. According to the American Cancer Society-National Prostate Cancer Detection Project, the proportion of locally advanced (clinical state T3) and metastatic (stage T1-4N0-1M1) prostate cancer (advanced prostate cancer) was reduced to less than 5% of all newly diagnosed cancers [4]. In Korea, however, more than half of newly diagnosed prostate cancer is of an advanced stage

[5].

For localized prostate cancer, radical prostatectomy and radiation therapy have been the recommended treatment modalities [6]. Hormone treatment has been considered a gold standard for the treatment of advanced prostate cancer [7]. Hormone treatment is a feasible option as the primary treatment of choice for localized prostate cancer, depending on the patient's age at diagnosis, life expectancy, and socioeconomic status [5]. However, after 18 to 24 months of hormone treatment, advanced prostate cancer progresses to castration-resistant prostate cancer (CRPC) [8]. Therefore, it is important to be able to forecast which patients have cancer that may progress to CRPC in order to improve the efficacy of hormone treatment and to perform additional treatments.

Recent studies have reported that changes in the free-to-total PSA (f/t PSA) ratio in patients with advanced prostate cancer whose PSA level has reached the nadir is an important prognostic factor. Therefore, we investigated the pattern of change in the f/t PSA ratio and the progression to CRPC in patients with advanced prostate cancer who received hormone treatment and whose PSA nadir was below 0.1 ng/ml.

MATERIALS AND METHODS

We retrospectively analyzed the medical records of 52 patients who received hormone treatment after a diagnosis of advanced prostate cancer between January 2007 and April 2009. Data on age, initial PSA, clinical stage, lymph node metastasis, and bone metastasis were collected. The follow-up data of the patients included PSA, free PSA (fPSA), and f/t PSA ratio every 3 months for 15 months. The 2010 American Joint Committee on Cancer/tumor-node-metastasis staging system and Gleason system were used for the pathologic staging and tumor grading [9]. The clinical stage was locally advanced (T3-4) or metastatic (stage T1-4N0-1M1) prostate cancer. The pathologic diagnosis was confirmed with transrectal ultrasonography-guided prostate biopsy. All patients underwent magnetic resonance imaging and bone scans for staging workup.

All patients were treated with maximum androgen blockade (gonadotrophin-releasing hormone agonist and anti-androgen agents) [10]. The patients who underwent radical prostatectomy or radiation therapy before hormone therapy, antiandrogen monotherapy, or other forms of chemotherapy were excluded. According to the European Association of Urology Guideline, CRPC was defined as 2 consecutive increases in PSA despite a testosterone level in the castration range [6]. The PSA nadir was defined as the lowest PSA level during hormone treatment [11,12]. The patients were divided into two groups with a nadir f/t PSA ratio above 60% (group 1) and a nadir f/t PSA ratio of 60% or below (group 2). The pattern of change in the f/t PSA ratio during the course of hormone treatment and progression to CRPC were compared between the two groups.

The Mann-Whitney U-test, Fisher exact test, and chi-square test were used to compare the two groups of patients. Kaplan-Meier survival analysis and the log rank test was used to analyze the difference in progression to CRPC between the two groups. All statistical analyses were performed with SPSS ver. 18.0 (IBM, New York, NY, USA), and p-values less than 0.05 were determined to be statistically significant.

RESULTS

Table 1 summarizes the clinical characteristics and CRPC progression in the two groups. The median age of the patients was 75 years (interquartile range [IQR], 70 to 80 years), and the median Gleason score was 7 (IQR, 6 to 9). PSA and the f/t PSA ratio at the time of diagnosis were 16.27 ng/ml (IQR, 9.32 to 88.06 ng/ml) and 8.80% (IQR, 0.01 to 11.50%), respectively. The PSA nadir of all patients was lower than 0.1 ng/ml. The median nadir f/t PSA ratio and the time to PSA nadir were 60% (IQR, 60 to 87%) and 6 months (IQR, 5 to 9 months), respectively. Progression to CRPC occurred in 34 patients, and the median time elapsed

TABLE 1. The clinical characteristics and CRPC progression in the two groups

Characteristic	Total (n=52)	Group 1 (n=24)	Group 2 (n=28)	p-value
Age (yr)	75 (70-80)	75 (55-87)	75 (70-81)	0.713[a]
Biopsy Gleason score	7 (6-9)	8 (7-9)	6 (6-8)	0.007[a]
Initial PSA (ng/ml)	16.27 (9.32-88.06)	23.53 (6.39-84.02)	13.73 (9.32-100.00)	0.567[a]
Initial f/t PSA ratio (%)	8.80 (0.01-11)	10 (2-15)	6 (0.01-10)	0.283[a]
Nadir f/t PSA ratio (%)	60 (60-87)	90 (80-90)	60 (30-60)	0.001[a]
Time to PSA nadir (mo)	6 (5-9)	5 (4-8)	7 (6-9)	0.111[a]
LN invasion (%)	7 (13.4)	3 (12.5)	4 (14.2)	0.654[b]
Bone metastasis (%)	22 (42.3)	10 (41.6)	12 (42.8)	0.578[b]
Progression to CRPC (%)	34 (65.3)	10 (41.6)	24 (85.7)	0.002[b]
Time to CRPC (mo)	15 (12-24)	15 (12-24)	15 (12-24)	0.792[a]

Values are presented as □ (interquarile range).

PSA, prostate-specific antigen; f/t PSA ratio, free-to-total PSA ratio; LN, lymph node; CRPC, castration-resistant prostate cancer.

[a]: Mann-Whitney U-test, [b]: Fisher exact test and Chi-square test.

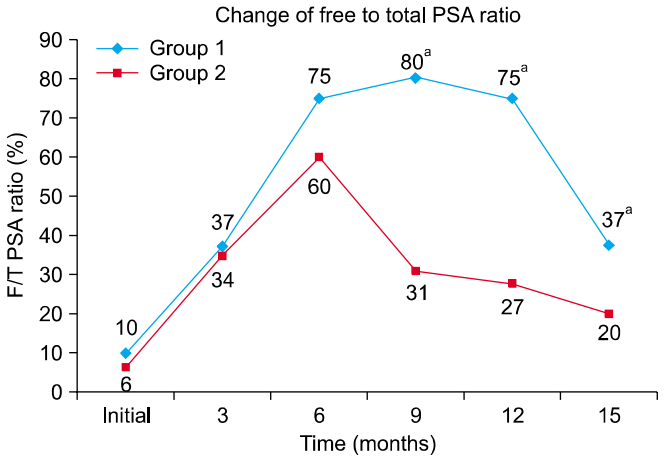

FIG. 1. The pattern of change in the free-to-total prostate-specific antigen ratio between the two groups during hormone treatment. [a]: $p<0.001$.

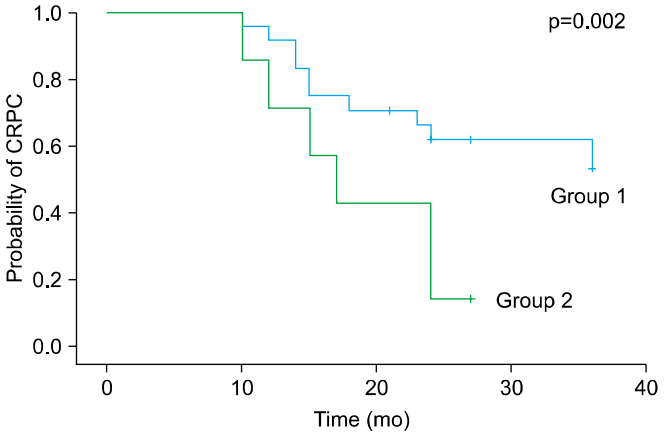

FIG. 2. The probability of progression to castration-resistant prostate cancer (CRPC) during hormone treatment in the two groups.

to progression to CRPC was 15 months (IQR, 12 to 24 months). There were 24 patients in group 1 and 28 patients in group 2. There were no significant differences in the median age, lymph node invasion, bone metastasis, initial PSA, initial f/t PSA ratio, or time to PSA nadir between the two groups. The median Gleason score was 8 (IQR, 7 to 9) in group 1 and 6 (IQR, 6 to 8) in group 2, which was statistically significant. The median nadir f/t PSA ratio was 90.00% (IQR, 80.00 to 90.00%) in group 1 and 60% (IQR, 30 to 60%) in group 2.

Fig. 1 shows the change in the f/t PSA ratio between the two groups. After PSA nadir, the median f/t PSA ratio of group 1 and group 2 increased from 37% (IQR, 30 to 76%) and 34% (IQR, 19 to 60%) at 3 months from the initiation of therapy to 75% (IQR, 40 to 87%) and 60% (IQR, 60 to 61%) at 6 months, respectively. There was no significant difference in the median f/t PSA ratio between the two groups. However, at 9 months, an increase in the ratio to 80% (IQR, 55 to 100%) was observed in group 1, whereas a decrease to 31% (IQR, 30 to 42%) was noted in group 2 ($p<0.001$). After 12 months, the ratio showed a tendency to decrease in both groups from 75% (IQR, 50 to 97%) to 37% (IQR, 27 to 90%) in group 1 and from 27% (IQR, 20 to 40%) to 20% (IQR, 10 to 28%) in group 2 ($p<0.001$ and 0.001, respectively). The difference in the median f/t PSA ratio between the two groups was significant from 9 to 15 months after the time of PSA nadir.

The probability of progression to CRPC during the follow-up period is illustrated in Fig. 2. The number of cases involving progression to CRPC was 10 in group 1 and 24 in group 2 (p=0.002). The median time to CRPC in both groups was 15 months (IQR, 12 to 24 months and 12 to 24 months, respectively), and it was not significantly different as shown in Table 1 (p=0.792).

DISCUSSION

In the United States, prostate cancer has the highest incidence of all noncutaneous malignancies and has the second-highest mortality rate in men [1]. Advances in screening and diagnostic techniques have resulted in a downward migration of stage [13]. In Korea, however, more than half of newly diagnosed prostate cancer is already of a locally advanced or metastatic stage [5].

Hormone therapy is the standard treatment for advanced prostate cancer [6,14]. Nonetheless, the timing of hormonal treatment in advanced prostate cancer remains controversial [6]. Although radical prostatectomy and radiation therapy have been recommended in localized advanced prostate cancer [15-18], Heidenreich [19] reported that hormone treatment has benefits in high-risk patients, such as those with poorly differentiated prostate cancer (Gleason score of 8 to 10) and those with a very short PSA doubling time (< 12 months). Also, Park et al. [5] reported that many of those with advanced prostate cancer have been treated with hormone treatment for various reasons, such as failure of surgical or radiation treatment, age at the time of diagnosis, or socioeconomic status. However, most patients with advanced prostate cancer who have received hormone treatment eventually progress to CRPC, despite the maintenance of castration serum testosterone levels [8]. In the present study, patients treated with hormone treatment showed biochemical improvements, with PSA decreasing to 0.01 ng/ml or lower in an average of 6 months, as well as progression to CRPC in an average of 15 months. Therefore, it is important to detect patients who may show early progression to CRPC and to perform other salvage therapies, including secondary hormone therapy, chemotherapy, and radiation therapy, early.

Although the pathophysiology of prostate cancer has not been elucidated completely, well-known prognostic factors include age, Gleason score, bone pain, serum hemoglobin level, PSA nadir, time to PSA nadir, and PSA level 3 months

and 6 months after treatment. However, the validity of these factors has not been clearly established. A previous report showed that Gleason score, PSA nadir, and PSA level 6 months after hormone treatment are prognostic factors that predict the progression to HRPC [5]. Kwak et al. [10] reported that the nadir PSA level after hormone treatment may be the most accurate prognostic factor. Huang et al. [20] suggested that the PSA nadir and time to PSA nadir are important prognostic factors. The PSA level is a useful marker in the diagnosis of prostate cancer, but there are disagreements about its prognostic importance after hormone treatment. Collette et al. [21] reported that PSA alone is not an appropriate marker of long-term therapeutic benefit in prostate cancer. Yoon [22] reported that free PSA is not a static factor, but rather a dynamic factor that is influenced by various conditions including hormone treatment. Therefore, free PSA and the f/t PSA ratio can be used to predict the prognosis of patients treated by hormone treatment. In this study, the number of patients progressing to HRPC was 10 in group 1 and 14 in group 2 (p=0.003). These findings suggest that the nadir f/t PSA ratio can be a prognostic factor.

Tanaka et al. [23] reported that whereas the f/t PSA ratio is unaffected by the stage of prostate cancer at the time of diagnosis, it does rise during the period in which the cancer is responsive to hormone treatment and then slowly returns to the pretreatment level as the cancer recurs. Recent literature has shown that the difference in the f/t PSA ratio between a group showing early biochemical recurrence and a group continuously responsive to hormone treatment becomes greater at 8 to 10 months after the initiation of treatment compared with the time of diagnosis. Some authors have argued that the pattern of change in the f/t PSA ratio is dependent on the response to treatment. In this study, the f/t PSA ratio of both groups steadily increased until 6 months after the initiation of hormone treatment. However, the f/t PSA ratio continuously declined since 9 months in group 2, whereas it remained elevated until 9 months and then slowly declined in group 1. The pattern of change in the f/t PSA ratio is thought to be related to the response to hormone treatment, similar to PSA. Such results are consistent with the results of previous studies showing that the f/t PSA ratio is affected not only by hormone treatment of advanced prostate cancer but also by the degree of response to hormone treatment. These results also demonstrate the importance of the f/t PSA ratio as a supplementary prognostic marker in the hormone treatment of advanced prostate cancer that can be used simultaneously with PSA.

CONCLUSIONS

When patients were divided into two groups on the basis of the nadir f/t PSA ratio, progression to CRPC was significantly higher in the group with a lower f/t PSA ratio. In addition, the pattern of change in the f/t PSA ratio was significantly different after 9 months. Collectively, the f/t PSA ratio can be used as an additional marker for the prognosis of hormone treatment. Further additional large-scale studies elucidating the clinical significance of f/t PSA ratio monitoring in the hormone treatment of advanced prostate cancer are necessary.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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