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Luteinizing Hormone-releasing Hormone Agonist Monotherapy for Prostate Cancer: Outcome and Prognostic Factors

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Abstract

Background: We assessed the outcome and prognostic factors in men with prostate cancer after luteinizing hormone-releasing hormone agonist monotherapy.

Methods: Between April 1998 and August 2002, 62 men with prostate cancer who were treated with monotherapy at our institution were included in this analysis. Prostate-specific antigen (PSA) failure-free (bNED) survival was calculated using Kaplan-Meier methods. Prognostic factors were evaluated using Cox proportional hazards regression model.

Results: We reviewed the data of patients, with a median follow-up from the commencement of monotherapy of 26 months. The overall survival rate at 3 years was 89.9%. The bNED survival rate was 63.7% at 3 years. Of the 20 patients with clinical stage B, 2 progressed to PSA failure, whereas PSA failure was seen in 8 of 30 patients with stage C and 8 of 12 patients with stage D. The significant factors for bNED status were an initial PSA level of <30 ng/m*l* ($p=0.0044$), achievement of PSA nadir level of <2.0 ng/m*l* ($p<0.001$), and Gleason score of ≤ 6 ($p<0.001$).

Conclusions: Patients with high clinical stage, a high initial PSA level of ≥ 30 ng/m*l*, and high Gleason score of ≥ 7 are at increased risk for PSA failure. Failure to achieve PSA nadir level of <2.0 ng/m*l* is an important predictor of the progression. The use of PSA nadir can provide useful guidelines for the reconsideration of treatment in patients who have received monotherapy.

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Key words: prostate cancer, luteinizing hormone-releasing hormone agonist monotherapy, prostate-specific antigen nadir

Introduction

Prostate cancer is the most commonly diagnosed visceral malignancy and the second leading cause of cancer death among men in the United States[1], yet Japan has one of the lowest age-adjusted death rates from prostate cancer in the world[2]. However, the incidence of, and death rate from, prostate cancer are rising rapidly even in Japan[3].

The optimal treatment for prostate cancer still remains controversial. However, castration and combined androgen blockade (CAB) in the hormone therapy for prostate cancer are well accepted

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Table 1 Patient characteristics

	Mean (range) or %
No. assessable patients	62
Age (years)	74.8 (53 ～ 86)
Median follow-up (months)	26 (12 ～ 47)
Clinical stage, %	
B0	4 (6.5)
B1	8 (12.9)
B2	8 (12.9)
C	30 (48.4)
D1	1 (1.6)
D2	11 (17.7)
Gleason score, %	
2 ～ 4	8 (12.9)
5 ～ 6	23 (37.1)
7 ～ 10	31 (50.0)

Data presented as the number of patients, except age and median follow-up.

practices. Furthermore, medical castration using luteinizing hormone releasing hormone agonist (LHRHa) therapy represents an important progress and is preferred to surgical castration because of the postoperative appearance.

Expected to produce an effective treatment, CAB therapy, with which blockade of adrenal androgen secretion is considered to be achieved, has been used in the hormone therapy for advanced prostate cancer. Although CAB therapy has remarkable roles in the therapy for advanced prostate cancer, a recent review reported that CAB does not have a new role in the treatment of advanced prostate cancer, in view of the multiple possibilities of aberrant androgen receptor response to antiandrogens[4]. Based on a reference[5], the meta-analysis found no difference in 2-year survival for CAB versus LHRHa monotherapy arm. There continues to be controversy about the efficacy of CAB versus LHRHa monotherapy.

CAB therapy has a greater adverse effect on quality of life than monotherapy[6] and implies increased costs. Therefore, LHRHa monotherapy seems to be an effective first line hormone therapy for prostate cancer because of the equivalence between monotherapy and CAB. Recently, the 3-month formulation of LHRHa offers an effective alternative treatment[7] and a decreased cost. Most patients appear minimally bothered by the pain at injection above all. Furthermore, some studies[8–10] have documented that the addition of antiandrogens in patients who progressed after initial hormone therapy with castration or LHRHa monotherapy might benefit several patients. Therefore, it is very meaningful to evaluate LHRHa monotherapy.

Since 1998, we have been performing a prospective study of LHRHa monotherapy for prostate cancer. It has been reported that there are multiple prognostic factors including clinical stage, the Gleason score, initial PSA level and the level of the posttreatment PSA nadir in patients with prostate cancer treated with LHRHa. In this study we evaluated the efficacy and the prognostic factors of LHRHa monotherapy in patients with prostate cancer.

Our study provides more information into the prognostic factors that affect biochemical failure, and into the question, "What is the advantage of LHRHa monotherapy for treatment of prostate cancer ? ".

Patients and Methods

From April 1998 through August 2002, 62 patients selected patients with previously untreated advanced prostate cancer were entered in this study at a single medical center. Eligible patients were required to have a histologic diagnosis of adenocarcinoma of the prostate and have any of the following characteristics: age ≥76 with any stage, asymptomatic stage D2 disease with any age, or a patient's selection of the LHRHa monotherapy (any age or stage). All patients gave full informed consent before treatment. Pretreatment clinical evaluation for all patients consisted of a history and physical examination with assessment of performance status, and labolatory studies including complete blood count, serum chemistry profile, serum PSA, a digital rectal examination (DRE), transrectal ultrasound (TRUS), magnetic resonance imaging (MRI) scan of the pelvis, and radionuclide bone scan. The Tandem-R monoclonal method was used to measure serum PSA[11]. The Gleason score[12] of biopsy tissue was also determined by a single uropathologist at our institution. The clinical and pathologic characteristics of these 62 patients are

Table 2 Initial PSA and posttreatment PSA (3 months, 12 months, 24 months)

PSA (ng/ml)	Initial PSA	3 months	12 months	24 months
n	62	61	58	36
Mean (ng/ml)	163.7	7.4	4.9	2.8
Maximum (ng/ml)	3,400	120	80.5	70.0
Minimum (ng/ml)	2.0	0.2	0.03	0.01

Abbreviations: PSA = prostate-specific antigen.

listed in **Table 1**.

LHRHa monotherapy consisted of either 3.75 mg leuprolide or 3.6 mg goserelin acetate every 28 days, until progression or the appearance of toxicity. All patients received antiandrogen therapy for two weeks before LHRHa monotherapy, in order to avoid disease flare. Serial PSA levels of the patients were obtained at one to three month intervals after initiation of the treatment. PSA failure was defined as three consecutive elevations in PSA level after reaching the PSA nadir.

PSA failure-free (that is, biochemically no evidence of disease, bNED) survival was calculated from the time of the first elevation in PSA. The tolerability and adverse events of LHRHa monotherapy have been also evaluated.

bNED probabilities were estimated using an actuarial calculation according to the Kaplan-Meier product limit method[13]. A clinical staging, initial PSA, Gleason score, and PSA nadir was performed. The log rank test was used to compare differences between probabilities and survival probabilities. Multivariate analysis was performed using the Cox hazard model[14] with the Stat Flex program[15].

Results

Table 1 lists the number of patients, patient age, clinical stage, and Gleason score. The mean age of the patients at the commencement of treatment was 74.8 years (range, 53～86 years). The mean follow-up after treatment was 26 months (range, 12～47 months). The median initial PSA level was 23.0 ng/ml, and the median biopsy Gleason score was 7. Of the 62 patients 33 had an initial PSA level of <30, whereas 29 had a higher initial PSA level. Mean PSA levels were 7.4 and 4.9 ng/ml at 3 months and 12 months, respectively, compared with an initial PSA level of 163.7 ng/ml (**Table 2**). A total of 31 patients had a Gleason score of ≤6, and 31 had a higher score. Of the 18 patients with Gleason score 7 disease, 9 had a Gleason score of 3+4 and 9 had a score of 4+3.

Four patients died of prostate cancer during the study period and two of unrelated causes (chronic cardiac disease and cerebral vascular accident). However, treatment interruption because of toxicity did not occur in the patients.

bNED survival rates were 68.6% at 2 years, and 63.7% at 3 years. Of the 20 patients with clinical stage B, two progressed to PSA failure, whereas PSA failure was seen in 8 of 30 patients with stage C and 8 of 12 patients with stage D. A 3-year bNED survival was significantly higher for men with stage B than those with D, respectively (79.2% vs. 33.3%, p=0.00077). Of the 29 patients with an initial PSA level of ≥30 ng/ml, 13 progressed to PSA failure, whereas PSA failure was seen in 5 of 33 patients with a lower initial PSA level. Of the 62 patients, 88.7% achieved a PSA nadir of <2.0 ng/ml (**Table 3**). Of 55 patients who achieved a PSA nadir of <2.0 ng/ml, 43 were bNED, whereas only one of 7 with a higher PSA nadir kept PSA control (p<0.001) (**Table 4**). At 3 years, 89.8% vs. 29.6% (p<0.001) of the patients were bNED status for those with Gleason score of ≤6 and ≥7, respectively.

The clinical stage, initial PSA level, PSA nadir, and Gleason score significantly predicted for PSA failure on univariate analysis. The bNED survival curves were significantly different for initial PSA level (<30 vs. ≥30 ng/ml) (**Fig. 1**), PSA nadir level (<2.0 vs. ≥2.0 ng/ml) (**Fig. 2**), and Gleason score (≤6 vs. ≥7) (**Fig. 3**). A higher clinical stage, higher initial PSA level, higher PSA nadir, and higher Gleason score were significantly associated with PSA failure on univariate analysis (**Table 3**).

Table 3 Results of univariate and multivariate analysis of prognostic factors for PSA failure-free survival

	No. Pts. (%)	Median Mos. Survival	p Value	
			univariate	multivariate
Clinical stage				
B	20 (32.3)	24.4		
C	30 (48.4)	23.3	0.2111	
D	12 (19.3)	16.3	0.0106	0.0086
Initial PSA (ng/ml):				
< 30	33 (53.2)	26.3		
≧ 30	29 (46.8)	18.0	0.0044	—
PSA nadir (ng/ml):				
< 2.0	55 (88.7)	24.0		
≧ 2.0	7 (11.3)	11.6	< 0.001	0.0068
Gleason score:				
< 7	31 (50.0)	29.6		
≧ 7	31 (50.0)	17.4	< 0.001	0.0168

Abbreviations: PSA = prostate-specific antigen.

Table 4 Number of patients with PSA failure according to PSA nadir

PSA nadir (ng/ml)	No. Pts./Total No. (%)
< 2.0	12/55 (21.8)
< 0.5	6/26 (23.1)
0.5 ～ 0.99	4/19 (21.1)
1.0 ～ 1.99	2/10 (20.0)
≧ 2.0	6/7 (85.7)

Abbreviations: PSA = prostate-specific antigen.

On multivariate analysis, clinical stage (p = 0.0086), Gleason score of ≤6 (p = 0.0168), and PSA nadir of <2.0 ng/ml (p = 0.0068) were significant predictors of bNED survival (**Table 3**).

The incidence of side effects occurred in nearly 8% of the patients (data not shown). The majority of side effects that patients experienced were hot flashes and liver dysfunction, which were mild in most cases and well tolerated by all patients.

Discussion

The assessment of PSA level in the serum, which has been used to detect prostate cancer and its recurrence and monitor the response to treatment, is an important prognostic factor of the biochemical control[16,17]. Other prognostic factors in prostate cancer treated with hormone therapy include clinical stage, Gleason score, performance status, etc[18,19]. Although the initial PSA level is important in treating patients who receive hormone therapy for prostate cancer, some studies have reported on the relationship between PSA nadir after treatment and biochemical control. Benaim et al.[20,21] demonstrated that PSA nadir was significantly lower in patients with advanced or metastatic prostate cancer who were experiencing longer biochemical responses. Dijkman et al.[22] observed that monitoring PSA early in therapy had predicted the disease outcome in patients with stage D2 prostate cancer. Furthermore, histologic assessment of Gleason score in prostate cancer is an important prognostic indicator. Fowler Jr et al.[23] analyzed that the only demographic or tumor related variable that influenced cause specific survival was Gleason score less than 8 versus 8 or greater in men with clinical stages T3 to 4 NXM0 prostate cancer.

This study investigated the prognostic factors in patients with prostate cancer after LHRHa monotherapy. The results demonstrate that PSA failure predicting a poor outcome is significantly influenced by clinical stage, initial PSA level, Gleason score, and PSA nadir level. Patients whose PSA levels could not reach the nadir of <2.0 ng/ml after LHRHa monotherapy, presumably related to a high risk of PSA failure. Our study demonstrated that these patients were 28.6% for the 3-year bNED survival. The results also suggest that patients with

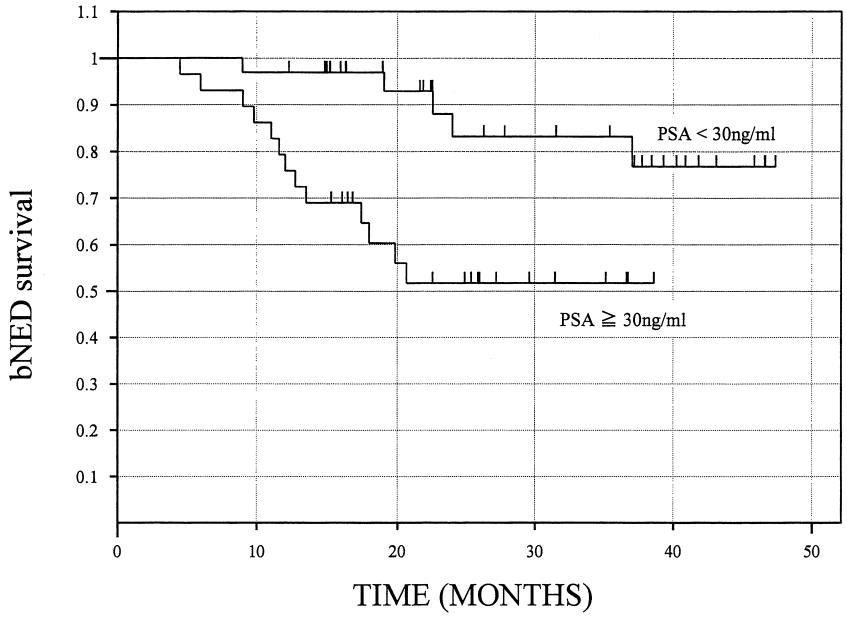

Fig. 1 PSA failure-free (bNED) survival stratified by initial PSA <30 ng/ml vs. ≥30 ng/ml. Survival was significantly more favorable in men with initial PSA <30 ng/ml compared with ≥30 ng/ml.

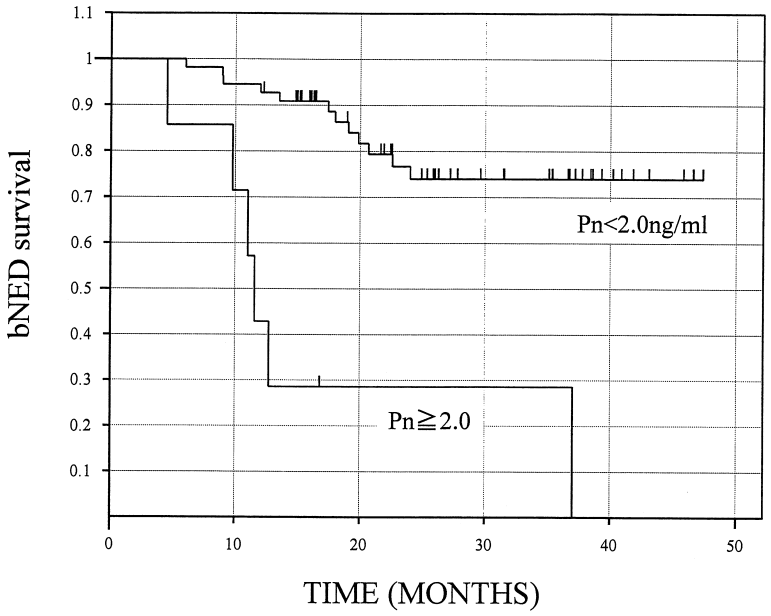

Fig. 2 PSA failure-free (bNED) survival stratified by PSA nadir (Pn) <2.0 ng/ml vs. ≥2.0 ng/ml. Survival was significantly more favorable in men with Pn <2.0 ng/ml compared with ≥2.0 ng/ml.

an initial PSA level of ≥30 ng/ml and Gleason score of ≥7 were at a high risk of PSA failure. On multivariate analysis, the most significant individual predictor of PSA failure was Gleason score of ≥7.

Based on literature reviews, Herr et al.[24] reported that combined androgen blockade was associated with greater fatigue, emotional distress, worrying about cancer and decreased general health over leuprolide alone. Schmitt et al.[25] reported that no difference between LHRHa monotherapy and CAB was statistically significant when evaluated at 1-year and 2-year follow-up periods, although recent

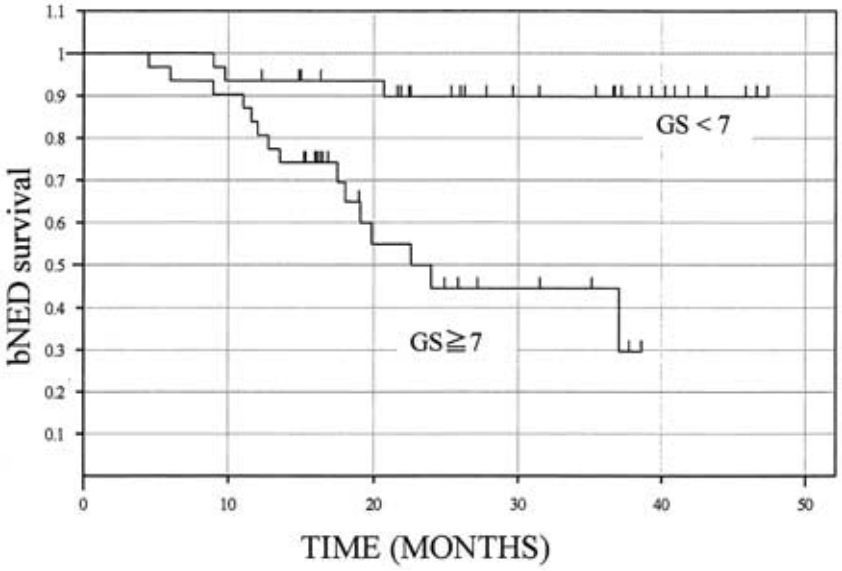

Fig. 3 PSA failure-free (bNED) survival stratified by Gleason score (GS) <7 vs. ≥7. Survival was significantly more favorable in men with GS<7 compared with ≥7.

overviews indicated that there was about a 2% to 5% improvement in 5-year survival rates with CAB. Conversely, LHRHa monotherapy might be better for two years after the commencement of hormone therapy because of monotherapy having less side effects. Furthermore, after LHRHa monotherapy, CAB therapy can be used as the strategy of second-line hormone therapy at signs of progression, which can be estimated by the prognostic factor, such as Gleason score.

In conclusion, patients with high clinical stage, a high initial PSA level of ≥30 ng/m*l*, and high Gleason score of ≥7 were at increased risk for PSA failure. Failure to achieve a posttreatment PSA nadir level of <2.0 ng/m*l* was the most important predictor of the progression. Finally, the use of PSA nadir level of <2.0 ng/m*l* can provide useful guidelines for the reconsideration of treatment in patients who have received LHRHa monotherapy.

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