INTERMITTENT ANDROGEN DEPRIVATION THERAPY MAY PROLONG THE DURATION OF ANDROGEN DEPENDENCE OF WELL-DIFFERENTIATED PROSTATE CANCER

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We previously reported the results of a pilot study of intermittent androgen deprivation (IAD) therapy in which surveillance was performed when PSA level fell below 0.3 ng/ml and androgen deprivation was resumed when PSA level exceeded 2.0 ng/ml. In the present study, we compared the duration of androgen dependence in patients treated with IAD with that in patients with continuous androgen deprivation (CAD) therapy. Forty-six patients with clinically localized or metastatic prostate cancer, or biochemical recurrence after radical prostatectomy were treated with IAD from 1995 to 2003. Patients in or after the second cycle of IAD (30 patients) were evaluated for duration of androgen dependence. Patients whose serum PSA nadir became <0.3 ng/ml (33 patients) represented a control group of CAD. The overall 5-year biochemical progression-free rate was 58% and 89% in the IAD and CAD groups, respectively; there was no significant difference between the two groups ($p=0.5$). Subgroup analysis showed that, irrespective of metastasis, the 5-year biochemical progression-free survival rate in the IAD group was not significantly different from that in the CAD group. However, IAD offered significantly better results for well-differentiated prostate cancer, whereas CAD offered significantly better results for moderately or poorly differentiated prostate cancer. The results obtained from this retrospective and nonrandomized study suggested that IAD may be a feasible treatment for well-differentiated prostate cancer.

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Key words : Prostate cancer, PSA, Endocrine therapy, Intermittent androgen deprivation

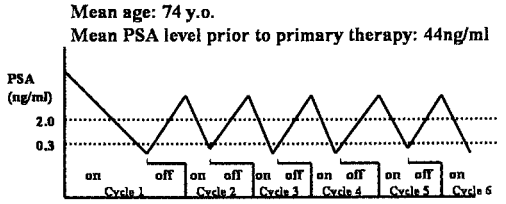
INTRODUCTION

Continuous androgen deprivation (CAD), although not curative, remains the mainstay of systemic treatment for metastatic or locally advanced prostate cancer[1]. Androgen deprivation offers temporary palliation but all cancers eventually progress to an androgen-independent stage. Whether cancer progression results from an adaptive mechanism to androgen withdrawal or selective growth of pre-existing androgen-independent clones remains uncertain. In vitro and in vivo animal studies have suggested that cancer cells that survive androgen withdrawal will undergo repeated cycles of apoptosis and growth when exposed to intermittent episodes of androgen withdrawal and replacement[2-5] This process may improve the duration of androgen dependence in patients with prostate cancer. Thus, intermittent androgen deprivation (IAD) therapy has recently been proposed as an alternative to CAD.

Clinical trials are currently ongoing to compare the feasibility, safety and quality of life measurements of IAD therapy with those of CAD[6-19]. We previously reported the results of a pilot study on IAD in which androgen deprivation was resumed at a low PSA level (2.0 ng/ml)[9]. CAD is associated with numerous adverse effects, which are either immediate (impotence and hot flushes) or late (loss of bone density and anemia) effects[20]. Naturally, IAD has been reported to reduce some of the immediate adverse effects[10-12], but, whether IAD indeed improves the duration of androgen dependence remains to be established. In this study, we evaluated the duration of androgen dependence in patients treated with IAD compared to those treated with CAD. The results suggested that IAD may be a feasible treatment for well-differentiated prostate cancer.

SUBJECTS AND METHODS

Among patients treated with CAD from 1995 to 2003, 84 patients with clinically localized (M (−)) or



Mean duration (days)	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5
On therapy	580	213	186	235	168
Off therapy	333	213	172	144	154

Fig. 1. Cycling characteristics of patients entered in IAD therapy.

metastatic prostate cancer (M (+)), or biochemical recurrence after radical prostatectomy showed PSA nadir < 0.3. Informed consent of IAD was obtained from 46 patients and 38 patients refused the intermittent protocol. The clinical history of cancer, dates of biopsies, pathology, stage at diagnosis and N-M status at

Table 1. Factors which influence time to progression

	Hormone refractory (−) (n=39)	Hormone refractory (+) (n=7)	p (univariate)	p (multivariate)
Age (y)	74.7±5.5	68.6±7.8	0.014*	0.0634
Pre-PSA (ng/ml)	42.4±109.8	67.4±109.2	0.5812	0.1061
Stage A	7	0	0.0012*	0.1172
B	26	1		
C	3	2		
D	3	4		
Patho well	24	0	0.0069*	0.212
mod	9	3		
poor	6	4		

univariate: unpaired t-test (age/pre-PSA) and χ^2 test (stage/pathology). multivariate:logistic regression analysis. * $p<0.05$.

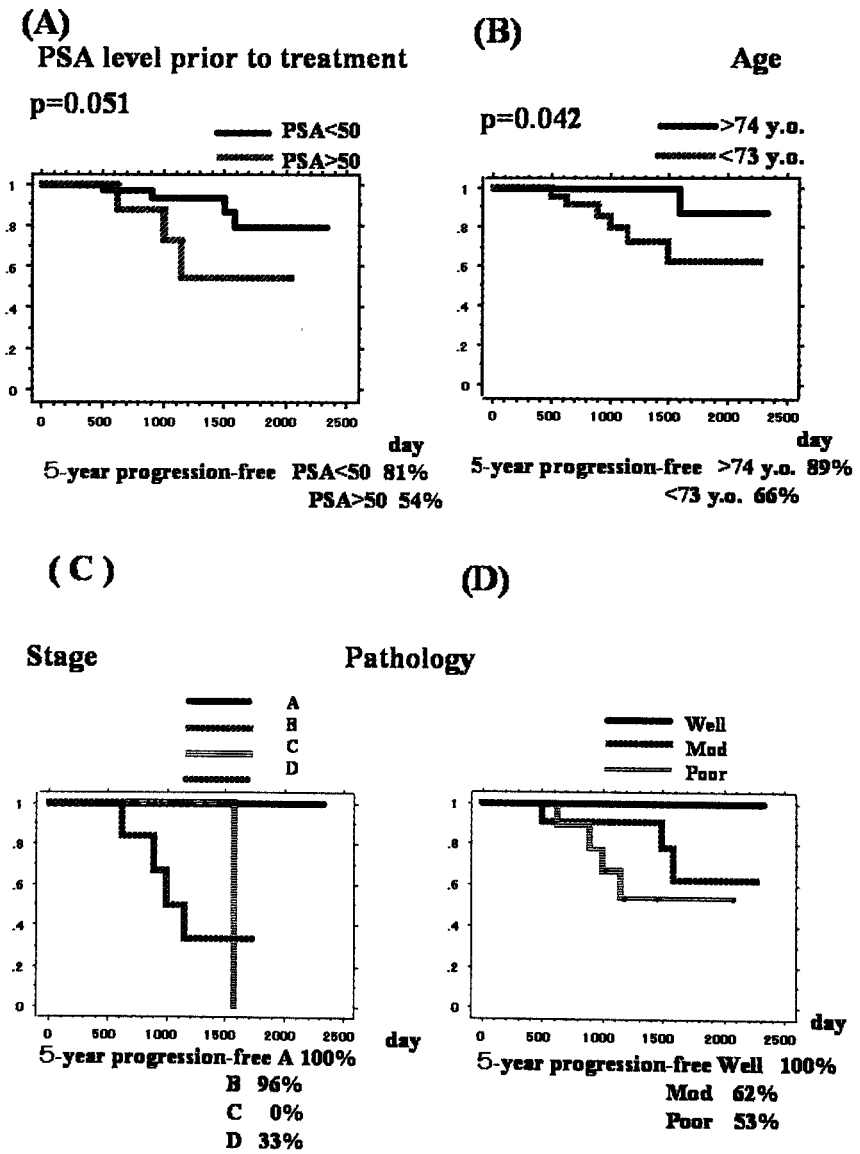


Fig. 2. Kaplan-Meier analysis of patients treated with IAD. Subgroup analyses according to PSA prior to primary treatment (A), patient age (B), tumor stage (C) and pathological grade (D).

the start of endocrine therapy were recorded. Serum PSA assay (Tandem-R) was performed at the beginning of the protocol and systematically repeated every month.

Patients were treated with either LH-RH analogue (Leuprolide acetate 3.75 mg or Goserelin acetate 3.6 mg) plus bicalutamide (80 mg) or LH-RH analogue alone. Discontinuation of endocrine therapy during the surveillance phase (off phase) was performed when the PSA level fell below 0.3 ng/ml after at least six months' duration of the treatment phase (on phase). Endocrine therapy was resumed when the PSA level exceeded 2 ng/ml (Fig. 1). When serum PSA increased at 3 continuous points during the treatment phase, the cancer was considered to have progressed to androgen-independent stage and the patient was excluded from this study.

For patients in the first cycle of IAD it is not possible to judge whether androgen-independent cancer is present (Fig. 1). Thus, patients in or after the second cycle who were treated with LHRH plus bicalutamide (33 patients) were evaluated for duration of androgen dependence. Moreover, according to our protocol, only those patients whose serum PSA became <0.3 ng/ml after primary androgen deprivation therapy were eligible to receive IAD. Thus, among patients treated with CAD using LHRH plus bicalutamide, those whose serum PSA nadir became <0.3 ng/ml (38 patients) represented a control group of CAD. The mean follow-up periods for patients treated with IAD and patients treated with CAD were 1,239+/−477 and 826+/−654 days, respectively. The grade was assessed by a single pathologist using the Japanese Urological association histological grading system. Statistical analyses including multivariate logistic regression analysis, Kaplan-Meier analysis, non-parametric analysis (Mann-Whitney's U test) and Student's t-test were performed using StatView 5.0. The Kaplan-Meier curves were statistically analyzed by using the Logrank test. The definition of difference is a p-value less than 0.05. If there were no drop outs in a group, the p value could be calculated using StatView 5.0.

RESULTS

The cycling characteristics of patients treated with IAD are summarized in Fig. 1. Patients received 1-6 cycles of IAD; the longest duration of off therapy was 1,331 days and the longest duration of IAD treatment was 1,605 days. Seven patients had biochemical progression during the second or third cycle; all of them required chemotherapy. Both univariate and Kaplan-Meier analyses showed that patient age, tumor stage and pathological grade significantly influenced time to biochemical progression, whereas PSA level prior to primary endocrine therapy did not (Table 1 and Figs. 2 A-D). Additionally, a multivariate analysis suggested that, among patient age, tumor stage and pathological grade, patient age most predominantly influences time to biochemical progression (Table 1). The characteristics of 30 patients in or after the second cycle of IAD and 33 patients treated with CAD whose PSA nadir became <0.3 ng/ml are summarized in Table 2. Four patients treated with CAD had biochemical progression. There were no significant differences in PSA level prior to primary endocrine therapy, stage, pathological grade or method of endocrine treatment between the two groups, but patients treated with IAD were significantly younger than those treated with CAD (p=0.0011).

Table 2. Characteristics of patients treated with IAD and CAD

	IAD	CAD	p-value
Number	30	33	
Age	73.5±6.0	80±7.8	0.0011*
Pre-PSA (ng/ml)	60±132	344±992	0.13
Stage M (−)	24	24	0.72
M (+)	6	9	
Pathology well	12	9	0.11
mod+poor	18	24	

* $p<0.05$.

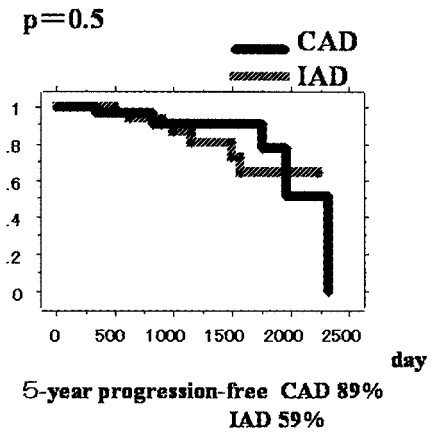


Fig. 3. Kaplan-Meier analysis of all patients treated with IAD, compared with CAD.

The overall 5-year biochemical progression-free survival rate was 58% and 89% in the IAD and CAD groups, respectively (estimated from the Kaplan-Meier curve); there was no significant difference between the two (p=0.5) (Fig. 3). Subgroup analysis showed that, irrespective of metastasis, the 5-year biochemical progression-free survival rates in both the CAD and IAD groups were not significantly different (Fig. 4A). However, IAD offered significantly better results for well-differentiated prostate cancer, whereas CAD offered significantly better results for moderately or poorly differentiated prostate cancer (Fig. 4B).

DISCUSSION

Clinical trials are currently ongoing to evaluate the feasibility of IAD. However, there is no standard regime between the trials; in most of them endocrine therapy is resumed when the PSA level exceeds 10-20 ng/ml[6-19] We employed a regime for IAD in which

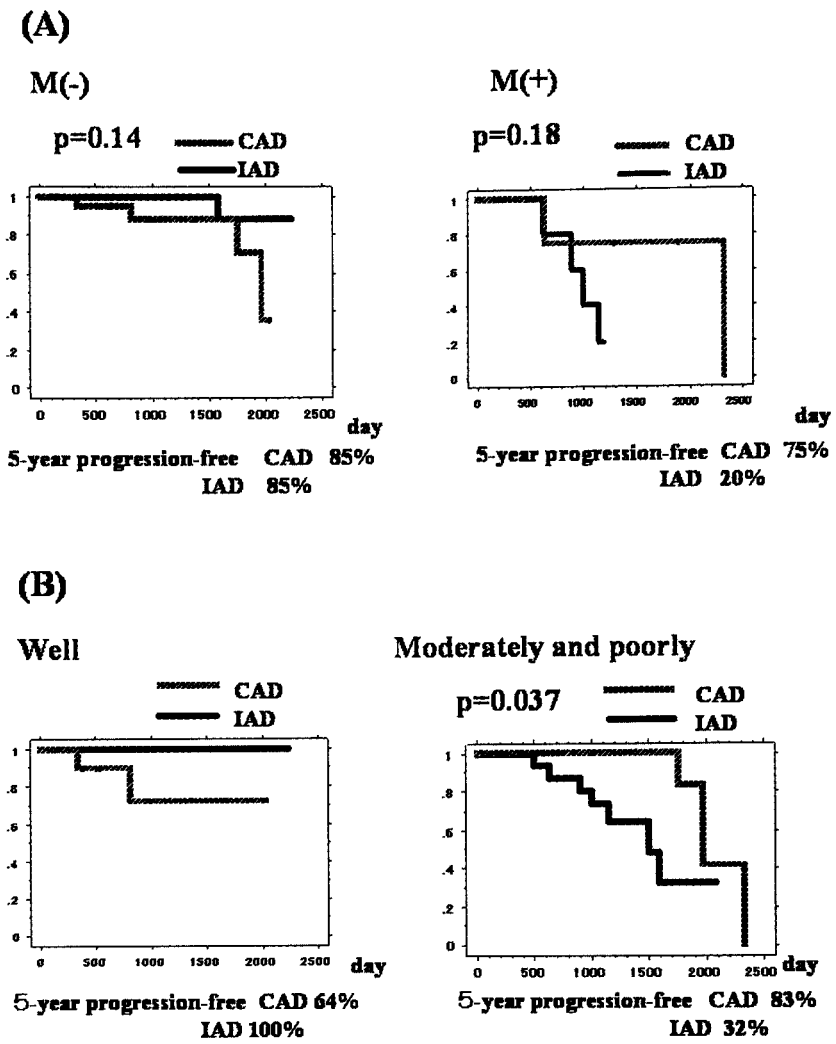


Fig. 4. Subgroup analyses of patients treated with IAD compared with those treated with CAD, according to M status (A) and pathological grade (B).

endocrine therapy is resumed at a low PSA level (>2 ng/ml). Since IAD is still an experimental treatment method, we assumed it safer to maintain PSA at a relatively low level (0.3–2.0 ng/ml) during the off phase. Previously, we reported that even this strict regime can provide sufficient duration of "off therapy" to restore the normal teststerone level[9] In this study, we showed that overall 5-year biochemical progression-free survival rates in the IAD and CAD groups were not significantly different (Fig. 3). Patient age, PSA level, stage and pathological grade were associated with biochemical progression, confirming the findings of Taille et al.[17] (Fig. 2 A–D). These results not only ensured the feasibility of IAD but suggested the necessity of properly selecting candidates for IAD therapy.

The present study is a retrospective and nonrandomized study, and currently, we do not have sufficient numbers of patients to allow subgroup analysis. However, it offers some insight into the variables that might need to be taken into consideration when designing prospective randomized trials. Subgroup analysis in this study showed that IAD is more effective than CAD for well-differentiated prostate cancer in terms of prolonging the duration of the androgen-dependent stage (Fig. 4 B). Since our regime selects good responders whose PSA nadir level fell below 0.3 ng/ml to the initial endocrine treatment, the effect of IAD to poor responders might be different. Although our results for localized prostate cancer were not compatible with findings obtained by another group using a different IAD-regime[18], our results suggested that, depending on pathological grade, IAD and CAD may have opposite effects (Fig. 4 B). Future studies are needed to show whether or not our unique regime for IAD can influence the therapeutic effects of IAD therapy.

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和文抄録

間欠的内分泌療法は高分化型前立腺癌が内分泌不応性となるまでの期間を延長するかもしれない

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われわれは過去にPSAが0.3 ng/ml以下になれば休薬し2.0 ng/ml以上になれば再開する方法で行った前立腺癌に対する間欠的内分泌療法の成績を発表した．今回は間欠療法と通常療法で内分泌不応性となるまでの期間を比較した．1995～2003年の間に限局性，転移性前立腺癌と診断された患者および根治的前立腺全摘出後に生化学的再発をきたした46人の患者を間欠的内分泌療法で治療した．この中で間欠的内分泌療法の第2サイクル以降に入った患者（30人）を研究対象にし，通常療法を受けPSAの底値が0.3 ng/ml以下になった患者33人をコントロールとした．間欠療法，通常療法の5年間生化学的非再発率はそれぞれ59％および89％で有意差はなかった（p＝0.5）．高分化型前立腺癌に対しては間欠療法が，中低分化型に対しては通常療法が有意に5年間生化学的非再発率が高い結果となった．これらの結果より高分化型前立腺癌に対して間欠的内分泌療法は通常の方法よりも有効な治療法であることが示唆された．

（泌尿紀要 **52**：259-264，2006）