Blackwell Publishing

Asian J Androl 2007; 9 (2): 253–258
DOI: 10.1111/j.1745-7262.2007.00074.x

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·*Clinical Experience*·

Long-term effectiveness of luteinizing hormone-releasing hormone agonist or antiandrogen monotherapy in elderly men with localized prostate cancer (T1–2) : a retrospective study

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Abstract

Aim: To evaluate the long-term effectiveness, side effects and compliance rates of two types of drugs (luteinizing hormone-releasing hormone [LHRH] agonist and antiandrogen) that were used individually to treat patients with localized prostate cancer (T1–2) at our institution. **Methods:** Ninety-seven patients who were diagnosed in the period from April 1997 to January 2000 as having clinically localized prostate cancer (T1–2) received either LHRH agonist (leuprolide acetate 7.5 mg/month) monotherapy (group 1, n = 62) or antiandrogen monotherapy (group 2, n = 35; 18 received bicalutamide 50 mg q.d., 13 received nilutamide 150 mg t.i.d. and 4 received flutamide 250 mg t.i.d.). The mean age in both groups was 76 years. **Results:** The mean follow-up time was (50.8 ± 8.5) months in group 1 and (43.1 ± 2.2) months in group 2. Prostate-specific antigen (PSA) levels rose in only 1 of the 62 patients (1.6%) in group 1, and in 20 of the 35 patients (57.1%) in group 2. In group 2, 10 of the 20 patients (50%) with increasing PSA levels were treated with LHRH salvage therapy, and eight (80%) responded. Hot flashes (54.8%) and lethargy (41.9%) were the most common side effects in group 1. In contrast, nipple-tenderness (40%) and light-dark adaptation (17.1%) were more often seen in group 2. Only 1 of the 62 patients (1.6%) in group 1 switched to another medication because of adverse side effects; whereas 8 of the 35 patients (22.9%) in group 2 did so. **Conclusion:** Unlike antiandrogen monotherapy, LHRH agonist monotherapy provided long-term durable control of localized prostate cancer (T1-2). It can also be an effective treatment option for patients whose disease failed to respond to antiandrogen monotherapy. The limitations of our study are the lack of health outcomes analysis and a small sample size. *(Asian J Androl 2007 Mar; 9: 253–258)*

Keywords: localized prostate cancer; antiandrogen; prostate-specific antigen; luteinizing hormone-releasing hormone agonist; androgen; ablation; monotherapy

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Received 2004-07-19 Accepted 2005-05-08

1 Introduction

Prostate cancer is the most common cancer in men and the second leading cause of cancer-related male deaths in western countries [1]. The incidence of prostate can-

cer is rising, partly because the growth of public awareness of the disease has increased the number of men being screened for it [2–3]. In turn, more men are presenting with localized prostate cancer than ever before [3–5].

In addition, the life expectancy of the American man is increasing. The averagely 65-year-old men can now expect to live additional 17 to 20 years compared to mean age of 10 years after diagnosis of prostate cancer [6]. As a result, the incidence of prostate cancer in the elderly has dramatically increased. At the same time, many elderly patients with prostate cancer who in the past would have died of comorbidities (e.g. ischemic cardiac disease or hypertensive cerebrovascular accidents) while under observation no longer do so because of better medical care. Thus, we are now faced with the issue of how to best treat elderly patients in order to prevent metastatic prostate cancer death.

Treatment options for patients older than 70 years with localized prostate cancer remain controversial. Current options include radical surgery [7], radiation therapy [8], expectant management (observation) [9, 10] and hormone therapy [9]. Because many elderly men are ineligible or unsuitable candidates for definitive radiation therapy or radical prostatectomy, or are unwilling to undergo an observation protocol, hormone therapy is now being looked at more closely.

In 1941, Huggins *et al.* [7] were the first to pro-pose hormone therapy for the management of advanced prostate cancer. However, there are few data on the use of hormonal treatment to control localized prostate cancer. Small tumors are highly sensitive to androgen deprivation, suggesting that androgen blockade could be given at the early stages of prostate cancer [11]. Aggressive definitive treatment may result in a lower cancer-specific mortality at 10 years after diagnosis of prostate cancer, but the difference between aggressive and hormonal treatments appears to be small. Finally, patients between the ages of 65 years and 75 years with clinically localized, well-differentiated prostate cancer who have been treated with delayed endocrine therapy incur no greater loss of life expectancy than the general population [12].

Because of the limited data that suggest that hormone therapy might be an effective treatment for localized prostate cancer and the well-documented approach of using a luteinizing hormone-releasing hormone (LHRH) agonist or antiandrogen monotherapy for metastatic prostate disease, we sought to compare the effectiveness, side effects, and patient compliance rates of these two types of drugs in patients with localized prostate cancer (clinical stages T1 and T2, T1-2) who were ineligible for definitive local therapy (radical surgery and radiation therapy) or unwilling to undergo observation. Although other studies have evaluated the effects of these drugs in patients with T3 tumors, this is the first study to compare these drugs in patients with clinical T1–2 prostate cancer.

2 Materials and methods

2.1 Patients and treatments

Our study consisted of 97 patients diagnosed as having localized prostate cancer (T1–2) and were treated with LHRH agonist or antiandrogen at our tertiary care institution. Diagnosis was based on a digital rectal examination (DRE), a total PSA level and negative bone scans. Of the 97 patients, 62 (group 1) were placed on the LHRH agonist leuprolide (22.5 mg for 3 months or 7.5 mg for 1 month). In the remaining 35 patients (group 2), 18 received bicalutamide (50 mg q.d.), 13 received nilutamide (50 mg t.i.d.), and four received flutamide (250 mg t.i.d.).

The patients' charts were reviewed for the following data: age at the beginning of treatment, pre- and post-treatment PSA levels, Gleason score, tumor stage, treatment side effects, PSA nadir, tolerance (whether or not the patient switched to another medication) and follow-up time. PSA nadir was taken to mean the failure of treatment once the PSA levels rise more than 0.5 ng/mL. All patients included in the study were from the single urologists' (Dr Craig D Zippe) series. Data collection and analysis were carried out by the principal investigator (Dr Rupesh Raina). There were no mortalities caused by progression of the disease reported during the study period. Most of the patients were switched to hormonal therapy from androgens.

2.2 Statistical analysis

Comparisons between groups 1 and 2, and among patients within group 2, were performed using the Wilcoxon rank sum test or Fisher's exact test as appropriate. The results of the former test are presented as median and interquartile ranges and those of the latter were presented as percentages. All analyses were performed with the SAS statistical software package (SAS Institute, Cary, NC, USA). $P < 0.05$ was considered significant.

3 Results

Baseline patient characteristics (mean age at the beginning of treatment, mean follow-up time, mean initial PSA and mean Gleason score) are presented in Table 1. There were no statistically significant differences between the two groups.

Table 1 shows the mean PSA nadir as well as other biochemical characteristics and the number of patients who switched medications (patient tolerance). Not only was the mean PSA nadir lower in group 1, but it also occurred more quickly (with a mean of 3 months *vs*. 23 months for group 2). Moreover, only one patient in group 1 experienced PSA progression, and only one patient in this group switched to another medication.

Table 2 lists the side effects associated with each medication. Hot flashes (54.8%) and lethargy (41.9%) were the most common side effects of LHRH agonist therapy. The one patient in group 1 who switched medication to antiandrogen monotherapy did so because of persistent hot flashes. In contrast, no patients in group 2 experienced these effects. However, nipple-tenderness (40%) and light-dark adaptation (17.1%) was experienced significantly more often by group 2 patients. Patients who experienced the side effect of reduced light-dark adaptation received nilutamide.

In group 2, 20 of the 35 patients (57.1%) broke through their PSA nadir. Ten of these patients were switched to the LHRH agonist therapy, where upon eight responded (a successful LHRH rescue was defined as PSA nadir < 0.5) and two did not. The other 10 patients who showed PSA progression, either continued on antiandrogen therapy (n = 5), chose observation (n = 1), chose to have a radical prostatectomy (n = 1), or died of comorbid diseases (n = 3). We compared the baseline characteristics of those patients showing PSA progression while on antiandrogen monotherapy with those who did not. These results are displayed in Table 3. Both the groups had an equivalent frequency of follow-up. The mean follow-up time, initial PSA, and PSA nadir were all higher in the patients showing PSA progression. However, only follow-up time was significantly different between the two groups.

Finally, we analyzed the characteristics of the patients who did not respond to antiandrogen monotherapy and who received LHRH salvage therapy based on their initial PSA levels. Patients with low initial PSA levels (< 30 ng/dL, n = 6) responded better to LHRH salvage therapy (100 %) than those with high initial PSA levels (≥ 30 ng/dL, n = 4) (25%). These results are shown in Table 4, where it can be seen that the mean PSA nadir while on monotherapy was higher in the poor responders (P < 0.05).

Table 1. Baseline characteristics, biochemical characteristics and compliance of 97 patients with localized prostate cancer (T1-2) that were treated with luteinizing hormone-releasing hormone (LHRH) agonist (group 1) or antiandrogen monotherapy (group 2). Values are presented as mean ± SD unless specified. Comparisons between groups 1 and 2, and among patients within group 2, were made using the Wilcoxon rank sum test or Fisher's exact test as appropriate. P < 0.05 was considered significant. PSA: prostate-specific antigen.

Parameter	Group 1 (n = 62)	Group 2 (n = 35)	P value
Age (years)	76.0 ± 1.0	76 .0 ± 1.2	1.00
Ethnicity			
Caucasian	47	24	
African American	10	8	
Asian	5	3	
Smoking	21	19	
Follow-up (months)	50.8 ± 8.5	43.1 ± 2.2	0.50
Initial PSA (ng/mL)	13.5 ± 4.1	19.6 ± 4.6	0.35
Gleason score	5.8 ± 0.4	6.14 ± 0.6	0.85
PSA nadir (ng/mL)	0.5 ± 0.2	2.1 ± .6	0.003
Patients who experienced a decline in their PSA (%)	95.5 ± 3.0	85.7 ± 2.6	0.03
Patients who experienced PSA progression (%)	1.6 (1/62)	57.1 (20/35)	< 0.001
Patients who switched medication (%)	1.6 (1/62)	22.9 (8/35)	< 0.001

Table 2. Side effects associated with luteinizing hormone-releasing hormone (LHRH) agonist (group 1) and antiandrogen monotherapy (group 2). P < 0.05 was considered significant. †Observed only with patients in the nilutamide group. Wilcoxon rank sum and Fisher's exact test were used to assess the P-values.

Side effects	Group 1 (n = 62)	Group 2 (n = 35)	P value
Nipple tenderness (n, %)	10 (16)	14 (40)	0.01
Light-dark adaptation† (n, %)	0 (0)	6 (17)	0.002
Diarrhea (n, %)	0 (0)	2 (6)	0.13
Abdominal discomfort (n, %)	0 (0)	1 (3)	0.36
Nausea and vomiting (n, %)	0 (0)	2 (6)	0.13
Hot flashes (n, %)	34 (55)	0 (0)	< 0.001
Lethargy (n, %)	26 (42)	0 (0)	< 0.001

Table 3. Baseline characteristics of patients experiencing PSA progression while on antiandrogen monotherapy. $P < 0.05$ was considered significant. †Clinical stage not available for one patient. Values are presented as mean ± SD. Wilcoxon rank sum and Fisher's exact test were used to assess the *P*-values. PSA: prostate-specific antigen.

Parameter	No PSA progression (n = 15)	PSA progression (n = 20)	*P value*
Age (years)	75.8 ± 0.8	75.8 ± 2.0	1.00
Follow-up (months)	37.4 ± 3.8	46.8 ± 2.4	0.04
Initial PSA (ng/mL)	12.8 ± 2.8	24.4 ± 7.8	0.22
Gleason score	6.4 ± 0.1	6.5 ± 0.2	0.71
Clinical stage (%)†			
T1C/T2A	71.4 (10/14)	60.0 (12/20)	0.72
T2B	28.6 (4/14)	40.0 (8/20)	0.72
PSA nadir (ng/mL)	1.9 ± .8	2.3 ± 1.0	0.72
Decline in PSA (%)	83.2 ± 5.0	87.2 ± 2.9	0.46

Table 4. Response of low (PSA < 30 ng/dL) and high volume (PSA ≥ 30 ng/dL) tumors to LHRH salvage therapy following PSA progression on antiandrogen monotherapy (values are mean ± SEM). $P < 0.05$ was considered significant. †Successful luteinizing hormone-releasing hormone (LHRH) rescue was defined as PSA nadir < 0.5. PSA: prostate-specific antigen.

Parameter	Initial PSA (< 30 ng/dL)	Initial PSA (≥ 30 ng/dL)	*P value*
Age (years)	78.0 ± 1.3	80.5 ± 3.8	0.49
Follow-up (months)	50 ± 4.0	51.0 ± 5.2	0.88
Initial PSA (ng/mL)	8.9 ± 1.3	80.1 ± 25.2	< 0.05
PSA nadir- antiandrogen	1.1 ± .33	6.0 ± 4.6	0.21
PSA at antiandrogen failure	6.3 ± 2.0	27.3 ± 9.2	0.03
PSA nadir-LHRH (ng/mL)	0.2 ± 0.1	3.65 ± 1.8	0.047
LHRH rescue (%)†	100 (6/6)	25 (1/4)	0.03

4 Discussion

As can be seen, the LHRH agonist therapy controlled PSA progression better than antiandrogen monotherapy. One of the most important aspects of this study (as it related to the effectiveness of the two drugs) was that only 1 of 62 patients (1.6%) taking LHRH agonist therapy broke through his PSA, as opposed to 20 of 35 patients (57.1%) taking the antiandrogen monotherapy. These results may have been different if higher doses of bicalutamide had been administered, a practice that has become increasingly common. Indeed, literature have shown 150 mg of bicalutamide to be more efficacious than the 50 mg which was administered in this study.

The side effects of LHRH agonist therapy in the treatment of prostate cancer have been well described, particularly hot flashes and impotence [13–15]. In addition, lethargy, asthenia and bone demineralization (osteoporosis) have also been reported as side effects of chronic use of LHRH agonist therapy [9–12]. The current interest in intermittent androgen ablation protocols was stimulated by the issue of side effects [10] .

Flutamide was the first nonsteroidal antiandrogen used to treat prostate cancer [11]. Its side effects include diarrhea, gastrointestinal discomfort and gynecomastia; these have been shown to occur in up to 15% of the patients withdrawing from treatment [16]. Similar to flutamide, the most frequent side effects of bicalutamide include hot flashes, gynecomastia, breast tenderness and diarrhea. In general, bicalutamide has been reported to result in fewer gastrointestinal symptoms [11]. Nilutamide, another nonsteroidal antiandrogen, appears to have a similar effect on prostate cancer as flutamide [11]. Reported side effects include visual adaptation problems (light-dark adaptation), alcohol intolerance, and occasional severe pulmonary toxicity [11, 17]. In comparison to the other two antiandrogens, nilutamide has fewer gastrointestinal side effects. The incidence of reduced light-dark adaptation in 10%–30% of patients is the primary reason for discontinuation of this drug.

In our study, the most common side effects were hot flashes and lethargy in the patients on LHRH agonist, and nipple tenderness and light-dark adaptation in the patients on antiandrogen monotherapy. Interestingly, one patient in group 1 experienced breast tenderness, and he was placed on a 2-month course of tamoxifen, which resolved the pain. Almost one half (16/35) of the patients treated with antiandrogen monotherapy experienced side effects, with 8 of the 16 patients switching to another antiandrogen. Finally, recent quality of life studies have demonstrated that antiandrogen monotherapy allows patients to retain greater physical capacity and sexual interest than LHRH agonists [15]. Consistent with these findings, our study shows that 41.9% of patients on LHRH agonist reported lethargy, whereas no patient on antiandrogen monotherapy complained of fatigue. Data

on sexual interest and sexual function were not included in this study because accurate information regarding the pre-treatment status of the patients' erections was largely unavailable.

The role of antiandrogen monotherapy in localized prostate cancer is evolving.

It would be beneficial to identify risk factors that predict patients who are likely to break through their PSA nadir. However, our results show no difference between the baseline characteristics of those whose PSA levels progressed while on antiandrogen monotherapy and those whose PSA levels did not. However, these results may have been overstatement due to the fact that the group with PSA progression had a longer mean follow-up time.

Androgen insensitivity is a major problem associated with the hormonal control of prostate cancer. Patients who show PSA progression on antiandrogen monotherapy can often be rescued by the addition of an LHRH agonist. In the small population of patients in the present study who were placed on LHRH agonist salvage therapy (n = 10), nine responded and one did not. We analyzed the characteristics of these patients to determine the factors that might possibly put patients at risk of being insensitive to LHRH salvage therapy following progression on antiandrogens. Our results indicate that patients with higher initial PSA values showed a poorer response to LHRH salvage therapy. In addition, the PSA nadir of a patient, while on monotherapy, may be predictive of LHRH salvage therapy failure because the PSA nadir was significantly higher in the group showing poor response to the LHRH agonist. The elevated PSA nadir likely reflects progression to androgen-independence. We believe these data may be clinically important enough to warrant further investigation.

Our results are consistent with the findings of other researchers in that LHRH agonist therapy has been found to be more effective than antiandrogen monotherapy [18]. However, antiandrogen monotherapy may still play a role in the treatment of localized prostate cancer in two ways: 1) by acting as a short-term suppressant while the patient undergoes treatment for other medical conditions; or 2) by acting as step therapy for a patient who is sensitive to quality of life issues (i.e. potency or lethargy) and who would prefer to reduce the time required on LHRH agonist therapy. It should be emphasized that patients on antiandrogen monotherapy need to be monitored for PSA progression and often need to be switched to another antiandrogen because of side effects.

Most studies examining the role of hormone therapy for localized prostate cancer have included patients with clinical stage T3 tumors [19, 20]. Our data represent the first comparison between antiandrogen monotherapy and LHRH agonists for clinical T1–2 prostate cancer. Although our results are interesting, they are nonetheless preliminary. Additional studies with larger sample sizes are required before a definitive recommendation in favor of LHRH agonist therapy in the treatment of localized prostate cancer can be made.

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