Tolerability Assessment of Maximal Androgen Blockade with 50 mg Daily of Bicalutamide and Castration in Patients with Advanced Prostate Cancer

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Background: Androgen is the most important growth factor for the development and growth of prostatic adenocarcinomas. For patients with advanced prostate cancer, hormonal manipulation including castration and antiandrogen therapy is a well-established mode of treatment. The choice of hormonal therapy for prostate cancer depends not only on the desired progression-free and overall survival, but also on the patient's quality of life, treatment costs, and treatment toxicities.

Methods: This was an open, non-comparative trial to determine the tolerability of 50 mg bicalutamide (Casodex®) in combination with castration; we also investigated whether the prostate-specific antigen (PSA) rates of change at weeks 4 and 12 were indicative of an increased risk of progression.

Results: Thirty-seven patients were enrolled in the study from December 1996 to June 1999 in Chang Gung Memorial Hospital, Taoyuan. The overall incidence rate of adverse events was 27%. The most frequent adverse event was hot flushes (5.4%). The rate of overall disease response was 85.3%. No evidence was found for any predictive relationship between serum PSA concentration and risk of progression.

Conclusion: The overall results indicate that bicalutamide administered as a 50-mg daily dosage in combination with castration is a well-tolerated therapy for the treatment of patients with advanced prostate cancer.

(Chang Gung Med J 2002;25:577-82)

Key words: prostate cancer, prostate, antiandrogen, maximal androgen blockade.

Carcinoma of the prostate gland is now recognized as one of the principal medical problems confronting the male population of the world.[1] In the US, prostate cancer is the second most commonly diagnosed cancer after skin cancer with an incidence of 101/100,000 in Caucasian people to 137/100,000 in black Americans.[2] Prostate cancer is also the second most common cause of death from cancer after lung cancer in the US, with an age-adjusted mortality rate of 55.5/100,000 in black

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Received: Feb. 1, 2002; Accepted: Jul. 2, 2002
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men.[2] In Taiwan, the incidence of prostate cancer is 14.25/100,000, ranking sixth in reported incidence and with a mortality rate of 4.80/100,000 in the male population.[3] Despite recent advances in the early detection of prostate cancer, 10% to 50% of clinically localized cases will progress. However, the percentage of newly diagnosed cases that present with advanced disease is unknown. In the US from 1989 through 1994, 8% to 14% were stage D2 at diagnosis, and there is a much higher percentage of metastatic prostate cancer in Taiwan.[3]

Prostate cancer is heterogeneous and is composed of hormone-sensitive and -insensitive tumor cell populations. There is also a spectrum of different degrees of hormone sensitivity. In recent years, treatment of advanced prostate cancer has largely focused on androgen-ablative therapies, by either surgical castration or by medical (LHRH-analogue) means.[4,5] However, while castration is successful in suppressing testicular androgen production, androgen produced by the adrenal cortex is unaffected. In order to achieve complete androgen blockade, additional or alternative therapies are therefore required; this has led to the use of antiandrogens.[6-8] Antiandrogens provide therapy that has great potential in terms of patient compliance and quality of life. By competing for androgen receptors, antiandrogens antagonize the action of androgens irrespective of their sources. Commercially available antiandrogens include steroidal antiandrogen (cyproterone acetate) and non-steroidal antiandrogens (flutamide, nilutamide, and bicalutamide).[9-13] The extensive database on bicalutamide (Casodex) has provided a detailed assessment of its safety and pharmacokinetics.[14] The pharmacological effects of Casodex in combination with LHRH analogues studied in approximately 400 patients included breast pain (3%), gynecomastia (5%), hot flushes (49%), asthenia (15%), diarrhea (10%), constipation (17%), nausea (11%), and vomiting (3%). Hepatic adverse events occurred with a frequency of 6%, but with clinically relevant changes in only 2% of patients.[9] We conducted a clinical trial using Bicalutamide and castration in treating advanced prostate cancer patients. We assessed the tolerability of 50 mg of Casodex and investigated the rate of changes in the prostate-specific antigen (PSA) and progression of the disease.

METHODS

From December 1996 to June 1999, there were 37 patients with advanced prostate cancer who consented to enter this study. Among them, the mean age was 70.9 (range, 59-89) years. All patients received a once daily dose of 50 mg of Casodex in combination with castration. Patients choosing medical castration (26 cases) received a 3.6-mg Zoladex depot injection every 4 weeks and comprised the Casodex-Zoladex group. Patients choosing surgical castration (11 cases) underwent an orchiectomy and comprised the Casodex-orchiectomy group. Assessments were made at 4-week intervals for the first 12 weeks after beginning treatment, and at 12 weeks intervals thereafter. A 4-ml blood sample was taken before treatment and at weeks 4, 8, and 12 weeks, then at 12-week intervals for estimation of serum PSA. Disease response was defined either as a decline in the PSA level or as pain relief. Adverse events (AEs) were assessed at all visits during therapy. The trial was stopped if there was any disease progression or if the patient died.

All hypothesis testing was conducted at the 5% level of significance. All tests were 2-sided. Paired t-test was used to test the mean changes from the baseline for serum PSA concentration, and Fisher's exact test was used to test the incidence of adverse events between the Casodex-Zoladex and Casodex-orchiectomy groups.

RESULTS

Of the 37 patients enrolled in the study, 9 (24.3%) patients discontinued the study during the treatment period: 6 were lost to follow-up at different periods, 1 quit due to an AE of severe anemia due to upper gastrointestinal (UGI) bleeding, and 2 due to death; 1 died in week 36 due to a cerebrovascular accident and the other died of hemopneumothorax after thoracoscopic surgery in week 8. Thirty-four patients had at least 3 blood samplings after treatment, among which 29 (85.3%) patients had the response of a decline in PSA concentrations.

At the baseline, 37 patients had a median serum PSA concentration of 57.2 ng/ml (mean ¡ SD, 291.88 ¡ 765.22). At week 48 post treatment, the median PSA value was 0.56 ng/ml, and the mean

PSA (mean ¡ SD) was 17.89 ¡ 38.18 ng/ml; both median and mean serum PSA concentrations decreased significantly from the baseline, and the maximum decline was observed at week 4 post-treatment ($p < 0.037$) (Figs. 1, 2).

Of all 37 patients studied, 10 (27%) patients reported adverse events: 7 (7/26; 26.9%) patients in the Casodex-Zoladex treatment group, and 3 (3/11; 27.3%) patients in the Casodex-orchiectomy treatment group. No statistically significant difference between the 2 treatment groups was found. The incidence rate of hot flushes was 5.4% for all patients, being 3.8% in the Casodex-Zoladex group and 9.1% in the Casodex-orchiectomy group (Table 1). All hot flushes were classified as being mild AEs. Other observed adverse events included abdominal distension, chest pain, constipation, gynecomastia, leg edema, left upper quadrant (LUQ) pain, rash, sweating, tinnitus, turbid urine, and UGI bleeding. Aside from hot flushes, none of these adverse events was found in more than 1 patient. Among all adverse events, hot flushes and gynecomastia are expected pharmacological effects.

Four (11%) of the 37 enrolled patients had progressive disease. The Kaplan-Meier probability of time to progression is shown in Fig. 3.

Table 1. Incidence of Adverse Events

Adverse event (n, %)	Total no. of patients N = 37	Casodex + Zoladex N = 26	Casodex + orchiectomy N = 11
Patients with any AE	10 (27%)	7 (26.9%)	3 (27.3%)
Hot flushes	2 (5.4%)	1* (3.8%)	1* (9.1%)

*: Mild adverse event.

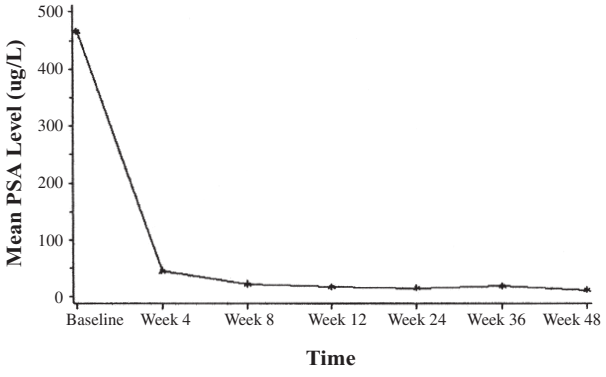

Fig. 1 Plot of mean PSA levels over time.

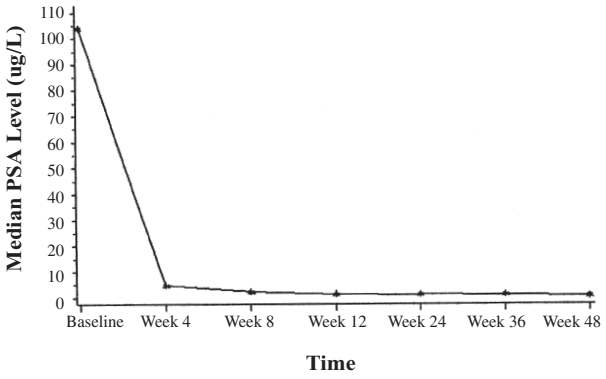

Fig. 2 Plot of median PSA level over time.

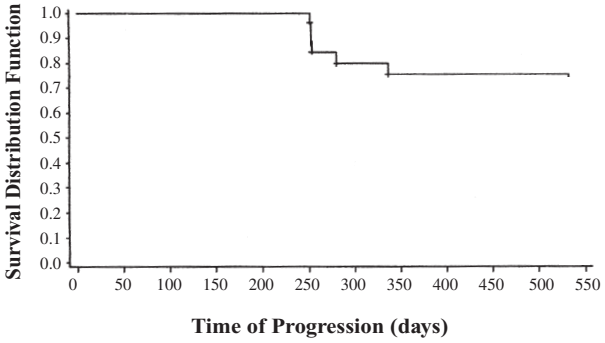

Fig. 3 Kaplan-Meier probability of time to progression.

DISCUSSION

The mainstay of the management for advanced or metastatic prostate cancer generally involves androgen deprivation. Castration alone is successful in suppressing testicular androgen but not for that produced by the adrenal glands. The rationale for combined androgen blockade, i.e., the complete elimination of testicular androgens by castration and pharmacological blockade of adrenal androgens, rests on the hypothesis that prostate cancer is composed of androgen-dependent cells with different requirements for maintaining function and growth.

The role of PSA as a sensitive marker for

prostate cancer has been well established since its isolation by Wang et al. in 1979.[15] Analyses of serum PSA have included free/total ratio PSA,[16] PSA density (PSA/prostate volume), age-specific PSA ranges, and PSA rate of change (PSA velocity). Several studies have demonstrated the value of PSA measurements in improving the detection and progression of advanced prostate cancer, and in monitoring the response to hormonal treatment.[17-21] Matzkin reported that a decline in PSA concentrations to a normal range and the percentage decrease in PSA were each associated with favorable clinical outcomes.[20] The PSA rate of change may be a more sensitive and accurate method of predicting clinical outcomes of advanced prostate cancer patients.

AEs with antiandrogen use are not uncommon, although most of them are temporary and not life-threatening. The notorious side effects of non-steroidal antiandrogens such as flutamide are hepatic dysfunction and diarrhea. In this trial, the most frequent adverse event observed was hot flushes (5.4%), which is an expected pharmacological effect. Other adverse events reported were abdominal distension, chest pain, constipation, gynecomastia, leg edema, LUQ pain, rash, sweating, tinnitus, turbid urine, and UGI bleeding. None of these events was observed in more than 1 patient.

The overall results indicate that Casodex administered at a 50-mg daily dosage in combination with castration is a well-tolerated therapy for advanced prostate cancer and has a low incidence of treatment-related withdrawal.

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使用Bicalutamide合併去勢治療完全阻斷雄性素法於進展性前列腺癌病患之經驗並評估其耐受度

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背 景： 雄性素是前列腺癌之重要生成因素。對於進展性前列腺癌病患，使用去勢療法合併抗雄性素是廣爲採用的方式。選擇賀爾蒙治療要著眼於疾病的控制，更要注重病患的生活品質，治療花費以及治療副作用。

方 法： 對於進展性前列腺癌病患使用每日50毫克Bicalutamide合併去勢治療，評估病患對藥物耐受度，以及利用前列腺特異抗原的變化評估是否可以作爲疾病進展之指標。

結 果： 自1997年12月至1999年6月期間，總共有37位進展性前列腺癌病患收納入此次研究。發生副作用之比率大約百分之27。最常見之副作用爲臉部潮紅 (5.4%)。85.3%之病患治療有效，其前列腺特異抗原明顯下降，但是前列腺特異抗原的變化與疾病進展並無明顯之相關性。

結 論： 每日50毫克Bicalutamide合併去勢療法對於治療進展性前列腺癌有相當的安全與耐受度。

(長庚醫誌 2002;25:577-82)

關鍵字： 前列腺癌，前列腺，抗雄性素，完全阻斷雄性素法。

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