

Preliminary Results of Bicalutamide Monotherapy on Biochemical Failure of Localized Prostate Cancer

Fadil Akyol, MD; Ugur Selek, MD; Gokhan Ozyigit, MD; Cem Onal, MD; Bulent Akdogan, MD; Erdem Karabulut, PhD; and Haluk Ozen, MD

Ankara, Turkey

Objectives: To prospectively assess the efficacy and tolerability of bicalutamide monotherapy on biochemical failure of localized prostate cancer following total androgen deprivation (TAD) and 3D-conformal radiotherapy (3D-CRT).

Methods: Between January 1998 and January 2002, we prospectively evaluated 20 eligible patients with biochemical failure. All patients were initially treated with neoadjuvant TAD of 12 weeks before 3D-CRT (73.6 Gy at isocenter) and same regimen of TAD after completion of radiotherapy for 24 weeks in high-risk patients. We prescribed 150 mg/day bicalutamide monotherapy for 24 weeks in patients with biochemical failure according to American Society for Therapeutic Radiology and Oncology 1997 consensus definition. Primary end points were biochemical control (BC) and metastasis-free survival (MFS).

Results: Median follow-up was 28 months after biochemical failure date. At last visit, the median PSA level of all patients was 2.80 ng/dl while 1.28 ng/dl for nonmetastatic and 30.7 ng/dl for metastatic patients. BC was successfully obtained in five of them with only bicalutamide. Ten patients developed distant metastasis among 15 patients receiving salvage TAD. MFS was 55% at three years for all 20 patients. Temporary gynecomasty was observed in 11 patients as the only serious toxicity.

Conclusions: Bicalutamide monotherapy seems to be a tolerable regimen for patients with biochemical failure following 3D-CRT, and TAD and may be effective in patients with low PSA levels at biochemical failure.

Key words: prostate adenocarcinoma ■ radiotherapy ■ androgen deprivation ■ bicalutamide ■ PSA

© 2006. From the Departments of Radiation Oncology (Akyol, professor of radiation oncology; Selek and Ozyigit, assistant professors of radiation oncology; Onal, instructor of radiation oncology), Urology (Akdogan, instructor of urology; Ozen, professor of urology) and Biostatistics (Karabulut, instructor of biostatistics), Faculty of Medicine, Hacettepe University, Ankara, Turkey. Send correspondence and reprint requests for *J Natl Med Assoc.* 2006; 98:1058-1061 to: Dr. Ugur Selek, Assistant Professor of Radiation Oncology, Hacettepe University, Faculty of Medicine, Department of Radiation Oncology, Ankara, Turkey 06100; phone: +90 312 305 2900; fax: +90 312 309 2914; e-mail: ugurselek@yahoo.com

INTRODUCTION

Prostate-specific-antigen (PSA)-only relapse after radiotherapy for prostate cancer is a common phenomenon that clinicians have to deal with. The definition of biochemical failure following radiotherapy has not been established so far. The American Society for Therapeutic Radiology and Oncology (ASTRO) consensus panel in 1997 agreed to define PSA relapse as three consecutive increases in PSA values and biochemical failure were stated as an appropriate early end point for clinical trials.¹ No level of PSA relapse is an adequate surrogate for clinical outcome, and no absolute level was stated as a valid cut-off point for successful versus unsuccessful treatment. Furthermore, the majority of patients with biochemical failure are otherwise healthy and need to preserve their clinical well-being while conserving quality of life. The treatment approach swings between broad categories of local salvage to systemic therapies. Local therapies such as salvage surgery for postradiation failure, prostate bed radiation for postsurgery recurrence or cryotherapy or brachytherapy are mainly reserved for men with organ-confined disease.

Hormonal therapy is frequently given for the management of PSA-only relapses with suspicion of nodal or distant metastasis. Typical approaches vary such as orchiectomy or luteinizing hormone-releasing hormone (LHRH) agonist therapy or combined hormonal treatments. However, those therapies are not curative but associated with serious side effects,²⁻⁴ and androgen resistance is another important issue in this setting.⁵ Intermittent androgen deprivation is an approach that could reduce side effects and prolong the time period to hormone resistance.

In this study, we tested prospectively the efficacy and toxicity of bicalutamide monotherapy in patients with biochemical failure following total androgen deprivation (TAD) and 3D-conformal radiotherapy (3D-CRT).

MATERIALS AND METHODS

Patient Characteristics

Between January 1998 and January 2002, 141 patients with T2-T3N0M0 prostate adenocarcinoma, according to 1997 American Joint Committee for Cancer Staging System (AJCC), were treated with 3D-CRT and TAD in our intradepartmental protocol.⁶ During follow-up, biochemical failure was detected in 20 patients, and we prospectively evaluated the therapeutic results of this subgroup of patients eligible for this study. There was no loss to follow-up.

The details of our institutional protocol were described elsewhere.^{7,8} Briefly initial treatment criteria to define high-risk patients in case of positivity of ≥ 1 were stage T3, PSA level of ≥ 10 ng/dl and Gleason Score of ≥ 7 . All patients were prescribed neoadjuvant TAD of 12 weeks with either triptoreline acetate 3.75 mg intramuscularly or goserelin acetate 10.8 mg subcutaneously combined with ciproterone acetate 100 mg PO two times daily or bicalutamide 50 mg PO once daily before 3D-CRT (73.6 Gy at isocenter). The same regimen was given after completion of radiotherapy in high-risk patients for 24 weeks. Informed consent was obtained from all patients.

Patients were followed up every three months for the first two years, four months for the third and fourth years, and every six months thereafter. In each visit, total serum PSA, free PSA, total testosterone, complete blood count and liver function tests were measured, and transrectal ultrasonography (TRUS) was performed.

Management of Biochemical Failure

The patients with documented biochemical failures according to the ASTRO consensus definition were evaluated with TRUS, bone scan and abdominopelvic computerized tomography to rule out local, nodal or distant relapses. Those patients who had given informed consent and had biochemical failure were treated immediately with 150 mg/day bicalutamide (Casodex®, AstraZeneca Pharmaceuticals, Wilmington, DE) for 24 weeks. Additional courses of bicalutamide monotherapy were given to three patients who responded well to the initial bicalutamide therapy and who subsequently failed with a PSA rise of ≥ 2 ng/dl (range 2.25–4.26 ng/dl) above the initial postbicalutamide PSA level after the treatment off period.

Further salvage TAD was given to 15 patients with only PSA increments insisted, and 10 of them developed nodal or distant clinical relapses. The salvage TAD regimen consisted of goserelin acetate (10.8 mg/3 months, subcutaneously) and ciproterone acetate (200 mg/day, PO). Taxane-based salvage chemotherapy was prescribed to three patients who were with nodal or distant metastasis and unresponsive to salvage TAD.

Statistical Analysis

The primary end points were biochemical control and metastasis-free survival. The biochemical failure date was calculated and backdated according to ASTRO consensus definition.¹ Kaplan-Meier method was used for survival estimates.⁹ Mann Whitney-U test was per-

Table 1. Patient characteristics at initial diagnosis and treatment schedule with final status

N	Age	T Stage	GS	PSA at Initial	PSA at Biochemical	Number of	TAD	Metastasis	CT	Status
				Diagnosis	Failure					
1	60	T3a	7	4.20	4.27	1	No	-	No	A
2	62	T2b	9	44.94	2.82	1	No	-	No	A
3	60	T2a	6	11.40	2.65	2	No	-	No	A
4	64	T2b	4	13.66	2.25	2	No	-	No	A
5	73	T3b	5	17.98	3.43	3	No	-	No	A
6	70	T2b	4	4.70	2.71	1	+	-	No	A
7	70	T2a	6	5.50	2.48	1	+	-	No	A
8	53	T3a	7	11.60	3.65	1	+	-	No	A
9	66	T3a	8	26.40	2.94	1	+	-	No	A
10	67	T3a	8	33.91	2.52	1	+	-	No	A
11	67	T2b	6	41.00	4.60	1	+	+	No	AWD
12	59	T3b	9	47.00	7.40	1	+	+	No	AWD
13	61	T3b	6	14.80	4.89	1	+	+	+	AWD
14	63	T3a	6	16.30	9.50	1	+	+	+	AWD
15	59	T3a	8	28.60	7.76	1	+	+	+	AWD
16	61	T3a	4	16.40	5.58	1	+	+	No	DWD
17	54	T3a	8	19.40	4.69	1	+	+	No	DWD
18	62	T3a	6	23.30	3.07	1	+	+	No	DWD
19	75	T2b	7	66.70	7.75	1	+	+	No	DWD
20	72	T3a	7	73.00	4.20	1	+	+	No	DWD

N: patient number, GS: Gleason score, PSA: prostate-specific antigen, TAD: total androgen deprivation, CT: chemotherapy, A: alive with no evidence of clinical disease, AWD: alive with disease, DWD: death with disease

formed to analyze the differences between groups. All statistical analyses were performed by SPSS 11.0 (SPSS Inc., Chicago, IL).

RESULTS

Median follow-up after the biochemical failure date of 20 patients was 28 months (range 8–53 months). The median time to initial biochemical failure was 21 months (range 8–42 months). Patient characteristics at initial diagnosis and treatment schedule with final status were summarized in Table 1. The median PSA level of the 20 patients at last visit after salvage hormonal treatment and chemotherapy was median 2.80 ng/dl (range, 0.42–750 ng/dl) and 1.28 ng/dl (range 0.55–4.33 ng/dl) for non-metastatic and 30.7 ng/dl (range 0.42–750 ng/dl) for metastatic patients. Biochemical control was obtained in two patients after the first course and in two after two and in one after three courses of bicalutamide monotherapy. All of them were alive with no evidence of nodal or distant metastasis. Salvage TAD was required in 15 patients who had PSA increment insisting under bicalutamide monotherapy, and five of them were alive at the last visit with no evidence of biochemical failure. We observed nodal or distant metastases in another 10 of 15 patients after salvage TAD, and five of them died of disease. The median time to metastasis and to death after bicalutamide monotherapy was 17 months (range 6–42 months) and 27 months (range 10–31 months), respectively. The median PSA level at biochemical failure was lower in patients who responded well to bicalutamide therapy compared with nonresponders (2.8 ng/dl vs. 4.6 ng/dl, $p=0.07$). In statistical analysis, no significant factors were found to be predictive for bicalutamide response. In metastatic patients, PSA doubling time was <1 year between the completion of initial treatment and the first PSA relapse, and the median PSA value at initial diagnosis was significantly higher compared with the nonmetastatic group (26 ng/dl vs. 12.6 ng/dl, $p=0.02$). The MFS was 75% at two years and 55% at three years in our 20 patients with biochemical failure.

Temporary gynecomasty was observed in 11 patients as the only serious evaluable toxicity related with bicalutamide in our cohort. Some of them required anti-inflammatory prescriptions for breast pain.

DISCUSSION

After definitive local treatment, the relationship between cancer mortality and biochemical failure is questionable, as evident metastatic disease might take many years to appear after biochemical failure. In radical prostatectomy series, patients with posttreatment rising serum PSA values had a similar survival rate to those without biochemical failure, and approximately one-third developed clinically evident metastatic disease at an average of eight years while the median time to death after metastases was five years.^{10,11} In contrast to the literature, metastasis-free survival seems to be lower, and median time to metastasis

and death after hormonal treatment is shorter in our cohort. A possible explanation might be significantly higher PSA values, stages and Gleason scores of metastatic patients at initial diagnosis. It is also noteworthy that PSA doubling time of those patients was <1 year between the completion of initial treatment and the first PSA relapse. Thus, these patients might have metastatic foci at initial presentation that available diagnostic methods could not detect.

Despite the lack of randomized studies to define long-term efficacy, antiandrogen monotherapy has an increasing initiative nowadays for the treatment of early PSA-only failure.^{2,3,12-15} The major advantages of these regimens include potential preservation of sexual function and fewer adverse effects than LHRH agonists such as hot flushes, anemia, osteoporosis and loss of muscle.²⁻⁴ The disadvantages consist of no current evidence to prolong survival besides the tendency for breast tenderness and/or gynecomastia.³ New strategies such as intermittent androgen deprivation are needed to maximize efficacy while minimizing cost and toxicity. Intermittency provides the patient time-off period from the side effects of castration as well as decreasing the costs. In addition, intermittent androgen deprivation might prevent the risk of continuous androgen suppression, which promotes androgen-resistant disease.⁵ Published studies have a small number of patients at all stages, and such heterogeneous populations make it difficult to assess the impact of intermittent androgen deprivation on survival and quality of life.¹⁶⁻²¹

Bicalutamide monotherapy at a dose of 50 mg once daily in patients with metastatic prostate cancer was found to be less effective than orchiectomy or LHRH agonist therapy with respect to time to treatment failure, time to objective progression, survival and subjective response rate in three randomized multicentric studies.²² Therefore, the bicalutamide monotherapy dose was subsequently increased to 150 mg once daily. Two large phase-3 studies have compared 150 mg/day bicalutamide monotherapy with orchiectomy or LHRH agonist therapy in patients with locally advanced or metastatic disease.^{23,24} Bicalutamide was not found as effective as castration, particularly in metastatic patients.²⁴ However, subgroup analysis revealed that bicalutamide and castration had similar efficacy in patients with a pretreatment PSA levels of <400 ng/dl.²⁵ Clinical characteristics have been studied in an effort to distinguish men with poor prognosis after biochemical failure treated with radiotherapy.^{11,26-28} PSA-only relapse within two years and PSA doubling times of <6 months after radiotherapy have been observed to be poor predictive factors for distant metastasis.²⁶⁻²⁸ Iverson et al. identified that bicalutamide 150 mg was as effective as LHRH agonist therapy in terms of overall survival or time to disease progression in nonmetastatic patients.²³ However, the efficacy of bicalutamide 50 mg or 150 mg once daily has not been investigated for PSA-only relapse.

In this context, we intended to find out whether bicalutamide monotherapy might achieve biochemical control,

prolong the duration to nodal or distant metastasis and to prevent initiating further hormonal treatment and chemotherapies in patients with low-level PSA relapse. All of our patients with biochemical failure had a PSA level of <10 ng/dl, anticipating much more benefit from bicalutamide monotherapy similar to the series of Kaisary et al.²⁵ To the best of our knowledge, this trial is the first using bicalutamide monotherapy in the management of biochemical failure after 3-D CRT and hormonal treatment. Biochemical control was successfully obtained with bicalutamide monotherapy in five patients without further salvage TAD, and all are alive and clinically disease free at last visit. Consequently, one-fourth of our patients were saved from further toxic salvage treatments up to now. Those patients responded well to bicalutamide monotherapy and had lower PSA levels than nonresponders, with a close to significant p value at the time of biochemical failure. The small number of patients in this cohort may not have enough power to detect if such a statistical significance exists. On the other hand, bicalutamide monotherapy seems to be ineffective in a large group of patients who further required salvage TAD. Their median PSA level at biochemical failure was higher compared with responders. Our findings in this subset of patients are in agreement with the literature, showing that bicalutamide monotherapy is ineffective for patients with high PSA levels. We have observed safe clinical application with minimum toxicity and experienced only temporary gynecomastia in about half of our patients as the only evaluable serious toxicity due to bicalutamide treatment. No side effects were detected requiring the discontinuation of bicalutamide monotherapy.

PSA-only relapse is an important source of anxiety and inconvenience for prostate cancer patients. The potency-sparing potential and the lessened degree of other adverse effects of oral antiandrogens are appealing, but the long-term efficacy in patients with PSA-only relapse is unknown. We believe that our approach with bicalutamide monotherapy in this limited number of patients is not enough for a definitive statement. However, it seems a start for certain subset of patients with low PSA level at biochemical failure who are otherwise healthy and need to preserve clinical well-being while conserving quality of life.

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