Bicalutamide for Advanced Prostate Cancer: The Natural Versus Treated History of Disease

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Purpose: **To determine the therapeutic effects of bicalutamide 200 mg in patients with prostate cancers of different hormone sensitivities.**

Methods: **Patients with progressive prostate cancer were treated with bicalutamide 200 mg daily. Before treatment, patients' tumors were classified on the basis of prior hormone exposure and by serum testosterone levels into androgen-dependent and androgen-independent groups. Prior exposure to flutamide and response to flutamide withdrawal was also considered. Outcomes were reported independently on the basis of posttherapy changes in prostate-specific antigen (PSA), measurable disease, and radionuclide bone scans.**

Results: **Outcomes varied by prior hormone exposure as a higher proportion of patients with progression of androgen-dependent tumors showed posttherapy PSA decreases of more than 50% or more than 80%, measurable disease regression, and improvement on radionuclide bone scans than did patients with androgen-independent progression. Within the category of androgen-independent progression, clinical benefit was observed in patients who had previously progressed on flutamide, independent of the response to flutamide withdrawal. Patients who had progressed on a gonadotropin-releasing hormone (GnRH) analog alone had a low response proportion, whereas those who progressed after two or more hormone therapies did not respond. Overall, the drug was well tolerated. After progression on bicalutamide monotherapy, one third of patients with androgen-dependent progression responded to medical castration with a GnRH analog.**

Conclusion: **Classifying patient tumors on the basis of prior hormone exposure permits a more precise estimate of the potential benefit of a specific hormone therapy for the individual patient. The precision is further increased by reporting the effects of a drug on each parameter of disease independently. The difference in outcomes for patients with androgen-independent progression suggests that the specific hormone therapy administered and the response to that therapy can influence the biology of the relapsing tumor and the sensitivity to subsequent therapies. The sensitivity to bicalutamide after progression on flutamide deserves further study.**

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HORMONAL THERAPY has served as the mainstay of treatment for advanced prostate cancer for more than five decades. Controversies remain as to the optimal timing—initial versus delayed, the optimal type—combined androgen blockade versus monotherapy, and the role, if any, as second- and third-line treatment. When first described, hormone treatments were used primarily for patients with symptomatic metastatic disease. More recently, it is being used in the neoadjuvant setting before surgery or radiation therapy[1] in patients with increasing prostate-specific antigen (PSA) values after surgery or radiation as the sole manifestation of progression, or as part of a formal intermittent (on and off) approach.[2]

The role of hormones as second- and third-line treatment in patients who have progressed on first-line therapy is less clear because a range of response proportions have been reported. This is the result of patient- and tumor-related factors.[3-5] One pretreatment predictive factor rarely considered is the influence of the specific hormonal therapy(ies) used on the response to a subsequent hormone treatment. For example, a patient who has relapsed on an antiandrogen alone, with an elevated serum testosterone level, might be expected to respond to a hormonal maneuver that lowers serum testosterone. In contrast, a lower response proportion would be anticipated to a hormone treatment in a patient who is showing progression of disease despite castrate levels of testosterone (androgen-independent progression).[6]

Bicalutamide (Casodex; Zeneca Pharmaceuticals, Wilmington, DE) is a pure antiandrogen that blocks the binding of dihydrotestosterone to the androgen receptor. It has a fourfold higher binding affinity to the androgen receptor than the active metabolite of flutamide, hydroxyflutamide.[7] Advantages over other medications in this class include an improved safety profile,[8] a long-terminal half-life that permits once-daily administration, and a direct correlation between response proportions and drug

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exposure calculated from the area under the plasma-concentration times time curve (AUC).[9] In one trial using sequentially higher doses of bicalutamide, 73% of patients normalized their PSA at a dose of 50 mg daily, 97% at 150 mg, and 98% at a dose of 200 mg daily.[10]

The present study evaluated bicalutamide 200 mg in patients with progressive prostate cancer who were at different points in their illness with respect to disease extent and prior hormone exposure. It sought to determine the points in the natural and treated history of prostate cancer that an antiandrogen might be beneficial. Included were patients with androgen-dependent progression who had not received hormones, those who had relapsed after neoadjuvant therapy, and those with androgen-independent progression who had progressed after one or more hormonal agents. Associations with prior response to flutamide withdrawal were also considered. In recognition of the controversial nature of outcomes reporting in this disease, and the lack of uniform outcome criteria that have been validated using the end point of survival, the results were reported independently on the basis of post-therapy declines in PSA, changes in measurable disease, and changes in radionuclide bone scans.[11]

PATIENTS AND METHODS

Patient Demographics

Patients with histologically confirmed progressive prostate cancer were eligible for the study. All had documented progression of disease manifest by one or more of the following: (1) an increase of prostate-specific antigen of greater than 50% from an individual baseline value on three successive occasions; (2) new metastatic lesions on radionuclide bone scan; or (3) a greater than 25% increase in a bidimensionally measurable tumor mass. Patients with new symptoms of tumor growth as the sole manifestation of progression were not considered.

Baseline Parameters

All patients underwent a complete history and physical examination with a determination of the Karnofsky performance status (KPS). Disease-related symptoms were recorded at each visit, at which time patients were asked to evaluate their libido as well as their ability to achieve an erection sufficient for penetration. Laboratory studies included an automated blood and platelet count and an assay of serum alkaline phosphatase, lactate dehydrogenase, aspartate transglutaminase, blood urea nitrogen, creatinine, calcium, phosphorus, uric acid, total protein, albumin, total bilirubin, and in the majority of cases, a baseline serum testosterone. Acid phosphatase was measured in the Department of Clinical Chemistry at Memorial Sloan-Kettering Cancer Center using an enzymatic assay with thymophthalein phosphate as substrate.[12] Prostate-specific antigen was analyzed in the same laboratory with the Tandem-E prostate-specific antigen immunoenzymatic assay (Hybritech Corporation, San Diego, CA). Imaging studies included a radionuclide bone scan, a computed tomography scan or magnetic resonance imaging of the abdomen and pelvis, and a chest radiogram.

Hormonal Sensitivity

Patients' tumors were categorized on the basis of prior hormone exposure as previously described.[11] A tumor was considered to be androgen dependent if the serum testosterone level was in the noncastrate (> 35 ng/mL) range. Operationally, this included patients who had not received hormones, those who were being treated with an intermittent approach, and those who had been treated with neoadjuvant therapy before surgery or radiation and who subsequently relapsed off hormonal therapy. Androgen-independent tumors were those proliferating despite castrate levels (< 35 ng/mL) of testosterone. This category was subdivided further into relapse-1 (relapse after orchiectomy or gonadotropin-releasing hormone analog monotherapy); those who had progressed on combined androgen blockade with a gonadotropin-releasing hormone (GnRH) analog and flutamide who did or did not respond to flutamide withdrawal; and those who progressed on two or more hormone treatments exclusive of antiandrogen withdrawal (Table 1).

Extent of Disease

Disease extent was recorded on the basis of PSA values, the presence or absence of metastatic disease on bone scan, and the presence or absence of measurable disease by physical examination or imaging studies. Sites of measurable disease included lymph nodes, pulmonary nodules, or visceral sites. All imaging studies were reviewed independently (L.S.) without knowledge of the patient's clinical status.

Treatment and Follow-Up

Patients who met the eligibility criteria for the study were asked to sign a statement of informed consent that was reviewed by the Memorial Hospital Institutional Review Board. Bicalutamide was then administered at a fixed dose of 200 mg: four 50-mg tablets given once daily. Pill counts were performed at each outpatient visit to ensure compliance. Different follow-up schedules were used for patients with androgen-dependent versus those with androgen-independent tumors based on the anticipated response to the study agent. Those with androgen-dependent tumors were monitored monthly for the first 3 months and at 3-month intervals thereafter. At each visit, symptoms and adverse events were recorded, and biochemical studies including a screening profile and PSA were obtained. Imaging studies that were abnormal at baseline were repeated at 3 months, 6 months, and at 6-month intervals thereafter until disease progression was documented. Imaging studies that were negative at baseline were only repeated if clinically indicated. After progression on bicalutamide monotherapy, a hormonal intervention that lowered serum testosterone level (eg, a gonadotropin-releasing hormone analog or orchiectomy) was added and the patient was evaluated for a secondary response while bicalutamide was continued. Patients were then followed-up until a second progression or nonresponse was documented. At that point, bicalutamide was discontinued while GnRH analogs were continued, and the patient was evaluated for a bicalutamide withdrawal response.

Patients with androgen-independent tumors were monitored monthly with serial examinations, symptom and adverse event assessments, and biochemical studies. Abnormal imaging studies were repeated at months 3, 6, and every 6 months thereafter, at which time overall response assessments were made. Patients were continued on treatment until progression of disease was documented.

Table 1. Patient Characteristics

No. of patients	104		
Median age, years	70		
Range	48-82		
Median KPS	90		
Range	70-90		
Prior therapy			
Surgery			
Prostatectomy	22		
Prostatectomy and EBRT	12		
Cryosurgery	3		
Radiation			
External beam	55		
I-125 implantation	3		
External beam/palliative	9		
Palliative	11		
Baseline biochemical parameters			
Hemolgobin			
Median	14 1		
Range	9 1-16 5		
AST			
Median	19		
Range	11-49		
LDH			
Median	167 0		
Range	106-351		
Creatinine			
Median	1 1		
Range	6-2 4		
Acid phosphatase			
Median	60		
Range	1-72		
PSA			
Median	22.9		
Range	10-1,300		
	No of Cases	Testosterone Median	Range
Hormonal Status			
Androgen dependent	53		
Naive	37	384	146-778
Intermittent/sensitive	16	500	299-987
Androgen independent	51		
Relapse-1	13	12	0-34
Flutamide withdrawal responders	14	12	0-34
Flutamide withdrawal nonresponders	12	6	0-23
≥ 2 Hormone therapies	12	3	0-18

Abbreviations: EBRT, external-beam radiation therapy, LDH, lactate dehydrogenase

Outcomes

Posttherapy changes in PSA, and if present at baseline, measurable disease and/or radionuclide bone scanning, were evaluated independently in the following manner.

Posttherapy PSA changes. The percentage decline in PSA from baseline was calculated from the lowest posttherapy nadir relative to the pretreatment baseline for groups of patients on the basis of hormonal status. To meet the criteria for a given degree (> 50% or > 80%) of decline required a minimum of three measurements taken at a minimum of monthly intervals. The duration of the decline was measured from the start of therapy to the date of the first sequential increase that was confirmed by a subsequent value.

Measurable disease. Standard phase II response criteria were used. A partial response required a more than 50% reduction in the sum of the products of the largest perpendicular diameters of all measured lesions with no growth of other lesions or appearance of new lesions. Progression required a more than 25% increase or appearance of new lesions. All other responses were classified as stable.

Radionuclide bone scan. Posttherapy bone scans were classified as showing improvement, stability, or progression relative to the baseline scan on the basis of a visual inspection[13] by a blinded independent review. Progression required the appearance of new lesions. An increase in the intensity of a preexisting lesion was not considered to be progression.

Statistical Analysis

The time to progression was calculated from the start of therapy to the time of the first confirmed increase in PSA, increase in measurable disease, new lesions on bone scan, or increase in disease-related symptoms, whichever was shorter. For patients with androgen-dependent tumors, the time to treatment failure was calculated from the start of treatment to the time of progression after the addition of a GnRH analog or surgical castration to bicalutamide monotherapy. Progression-free survival distributions were estimated by the method of Kaplan and Meier.[14]

RESULTS

One hundred five patients were entered, 104 of whom were assessable. One patient was enrolled but opted not to receive treatment after signing informed consent. The demographics including prior therapy and baseline biochemical parameters are listed in Table 1. As illustrated, the median age was 70 years, and median KPS was 90%. The predominant local treatment was external beam radiation therapy, whereas 34% of the patients had undergone a radical prostatectomy. The high median hemoglobin reflects the good performance status of the patient population. Approximately half of the patients had androgen-dependent tumors (hormone naive, relapse after prior neoadjuvant or intermittent treatment) and half androgen-independent progression (relapse after orchiectomy or GnRH analog alone, 12 patients; in one case, diethylstilbestrol), combined androgen blockade with flutamide (26 patients), or multiple (two or more) hormonal therapies (12 cases).

Table 2 shows the outcomes based on PSA decreases, changes in radionuclide bone scans, and changes in measurable disease based on the hormone sensitivity of the tumor. Overall, patients with androgen-dependent tumors had more favorable outcomes relative to those with androgen-independent tumors. For these two groups, 88% (47 of 53; 95% confidence interval, 77% to 96%) versus 10% (five of 51; 95% confidence interval, 8% to 31%) showed

Table 2. Outcomes Based on Overall Hormone Sensitivity

Disease Manifestation	Outcome	No	%	Androgen Dependent No	Androgen Dependent %	Androgen Independent No	Androgen Independent %
Increasing PSA		(n = 104)		(n = 53)		(n = 51)	
	80% decline	52	50	47	88	5	10
	50% decline	9	9	2	4	7	14
	Stable	11	11	2	4	9	17
	Progression	32	32	2	4	30	59
Bone		(n = 48)		(n = 15)		(n = 33)	
	Improved	11	23	7	48	4	12
	Stable	15	31	6	40	9	27
	Progression	21	44	0		19	58
	Nonassessable	1	2	2	12	1	3
Soft tissue		(n = 34)		(n = 19)		(n = 16)	
	> 50% decrease in area	7	21	7	37	0	
	Stable	10	29	8	42	3	19
	Progression	14	41	3	16	11	69
	Nonassessable	3	9	1	5	2	12

NOTE. One patient was entered onto the study but withdrew before receiving treatment. Nonassessable indicates that the specific site of disease was not reassessed

a more than 80% decrease in PSA, 48% (seven of 15; 95% confidence interval, 21% to 73%) versus 12% (four of 33; 95% confidence interval, 3% to 28%) an improvement in bone scan, whereas 37% (seven of 19; 95% confidence interval, 16% to 62%) versus 0% (zero of 16) showed regression of soft tissue disease. These differences in outcomes are reflected in Fig 1, which shows the time to progression based on PSA elevations for these

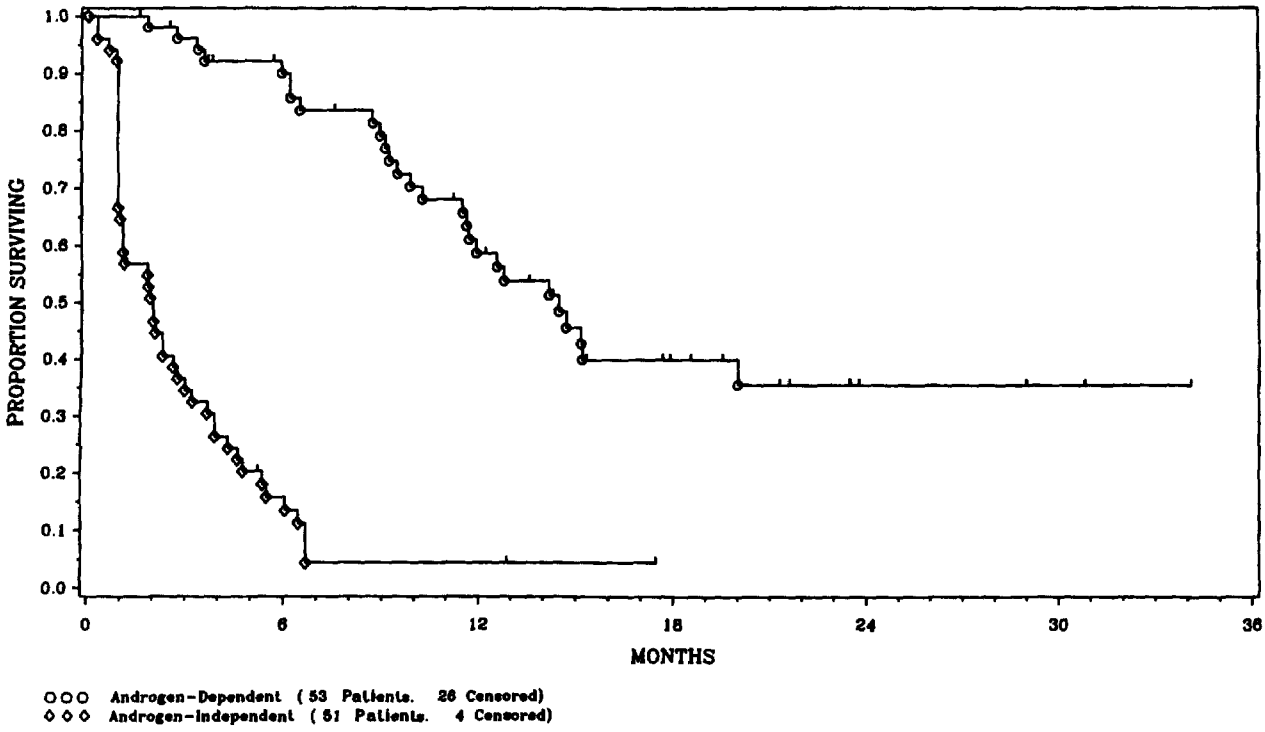

Fig 1. Time to progression based on PSA elevations for patients with androgen-dependent and androgen-independent progression.

Table 3. Outcomes for Androgen-Dependent Disease

Disease Manifestation	Outcome	No	%	No Prior Hormones No	No Prior Hormones %	Prior Neoadjuvant or Intermittent No	Prior Neoadjuvant or Intermittent %
Increasing PSA		(n = 53)		(n = 37)		(n = 16)	
	80% decline	47	88	34	92	13	81
	> 50% to < 80% decline	2	4	1	2	1	7
	Stable	2	4	1	2	1	7
	Progression	2	4	1	2	1	7
Bone		(n = 15)		(n = 10)		(n = 5)	
	Improved	7	48	7	70	0	
	Stable	6	40	3	30	3	60
	Progression	2	13	0		2	40
	Nonassessable	0		0		0	
Soft tissue		(n = 19)		(n = 16)		(n = 3)	
	> 50% decrease in area	7	37	7	44	0	
	Stable	8	42	6	37	2	67
	Progression	3	16	3	19	0	
	Nonassessable	1	5	0		1	

NOTE. One patient was entered onto the study but withdrew before receiving treatment. Nonassessable indicates that the specific site of disease was not reassessed.

two groups of patients, the most stringent parameter for progression. As illustrated, the medians were 14 months and 3 months, respectively.

Table 3 subdivides patients with androgen-dependent progression into those who had no prior hormone exposure and those who were treated with neoadjuvant or intermittent therapy and later progressed. For those with no prior hormonal exposure, 92% (34 of 37; 95% confidence interval, 78% to 98%) had a greater than 80% decrease in PSA, 70% (seven of 10; 95% confidence interval, 35% to 93%) showed bone scan improvement, whereas 44% (seven of 16; 95% confidence interval, 20% to 70%) showed regression of a measurable lesion. A smaller proportion of patients who had been treated with neoadjuvant therapy or by a policy of intermittent treatment showed benefit. However, based on the number of patients evaluated, this difference was not significant. Only three patients had measurable tumor sites, two of whom remained stable. None of the five abnormal bone scans improved. The median time to progression for these two groups was 14 months (range, 3 to 33+ months) and not reached (range, 3 to 23+ months), respectively, with 62% of patients in each group having progressed based on PSA elevations.

Response to Chemical Castration After Progression on Bicalutamide

A total of 15 patients treated with bicalutamide with androgen-dependent disease was assessable for a response to the addition of a GnRH analog after sequential elevations in PSA were observed. Overall, five (33%; 95% confidence interval, 12% to 63%) showed a greater than 80% decrease in PSA for a median of 6 months (range, 6 to 11). Of these five patients, four had parallel improvements in an abnormal bone scan, but none had measurable disease at the start of bicalutamide therapy that could be assessed for response. Ten patients did not respond biochemically to subsequent chemical castration.

Response to Bicalutamide Withdrawal

Currently, eight of 15 patients who progressed after a GnRH analog was added to bicalutamide monotherapy are assessable for a bicalutamide withdrawal response. Of these, three showed significant (> 80%) decreases in PSA for 3, 5, and 5+ months. Of interest was that one of the patients who responded to bicalutamide withdrawal initially responded to bicalutamide but did not respond to the addition of a GnRH analog after progression on bicalutamide monotherapy. Figure 2 illustrates the sequential PSA values for a patient who had previously received neoadjuvant hormonal therapy and later relapsed. After a 12-month response to bicalutamide, a GnRH analog was added with a subsequent secondary response. At month 18, bicalutamide was discontinued while the GnRH analog was continued. As shown, 8 weeks after discontinuation of bicalutamide, the PSA level decreased for 5 months, after which progression of disease was observed.

Table 4 considers patients with androgen-independent progression. As shown, patients who relapsed after an orchiectomy or GnRH analog alone (relapse-1) showed modest benefit, as none of the 13 patients showed a more

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