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Efficacy and tolerability of Casodex in patients with advanced prostate cancer

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The efficacy and tolerability of Casodex, a new non-steroidal antiandrogen, were studied in 267 patients with advanced prostate cancer. All patients received Casodex, 50 mg daily, as monotherapy. The objective response rate was 55.5% and the subjective response rate was 56.1%. The most common adverse events were the expected pharmacological effects of breast tenderness, gynecomastia and hot flushes. No other adverse events were reported in more than 5% of patients. There was minimal occurrence of impotence, loss of libido and diarrhea. The results show that Casodex 50 mg is effective and well tolerated in the treatment of advanced prostate cancer.

Key words: Antiandrogen, bicalutamide, Casodex (ICI 176,334), prostate cancer.

Introduction

Antiandrogens have been widely used in the treatment of prostate cancer, usually in combination with orchidectomy or luteinizing hormone releasing hormone (LHRH) analogs in order to achieve maximal androgen blockade.[1] Steroidal antiandrogens, such as cyproterone acetate, have progestational effects, which result in loss of libido and potency. The non-steroidal antiandrogens, flutamide and nilutamide, lack progestational activity and thus may preserve libido and potency, but their usefulness has been limited by other adverse events, notably gastrointestinal disturbances, alcohol intolerance and other adverse effects.[1,2] Moreover, flutamide is normally given three times daily; such a regimen may produce poor compliance, resulting in a failure to maintain effective drug concentrations in serum.[2]

Casodex (Zeneca Pharmaceuticals, ICI 176,334, bicalutamide) is a new non-steroidal antiandrogen that was synthesized in a programme to find a non-steroidal antiandrogen, devoid of progestational activity, with a long half-life and with fewer adverse effects than other antiandrogens. Casodex binds to prostate androgen receptors with an affinity four times that of hydroxyflutamide, the active metabolite of flutamide.[2] It is slowly absorbed after oral administration, having an elimination half-life of about 1 week,[3] thereby making Casodex suitable for once-daily dosing. Preliminary reports of phase II clinical trials and dose-ranging studies showed that treatment with Casodex 50 mg daily as monotherapy reduced prostatic acid phosphatase to an extent similar to that with standard hormonal therapy, produced an objective response in patients with advanced prostate cancer and may cause fewer side-effects than other non-steroidal antiandrogens.[4,5] This paper presents the final results of a large European Phase II multicenter study of the efficacy and tolerability of Casodex 50 mg monotherapy in patients with advanced prostate cancer.

Patients and methods

The trial was an open study, conducted in 46 centers in Europe (see Appendix). All patients had histologically- or cytologically-proven prostate cancer, with either metastatic or locally advanced disease (stage T_3 or T_4). Patients who had undergone previous endocrine or cytotoxic treatment for prostate cancer were excluded, as were patients who had received radiation therapy within 3 months previously and patients with ECG abnormalities.

All patients were treated with Casodex, 50 mg daily, until an endpoint was reached; patients who completed 48 weeks of treatment underwent no further assessment other than monitoring of serious adverse events. The treatment endpoints were objective disease progression, a serious adverse event, unwillingness or inability of the patient to continue treatment, death, or discontinuation of treatment if this was felt by the investigator to be in the patient's best interests. Objective assessment of prostate size (usually measured by ultrasound or computerized tomography, although digital rectal examination was also acceptable) and clinically-measurable metastases were obtained before treatment and every

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12 weeks for at least 6 months. Similarly, bone metastases (assessed by bone scan, radiography or both) were assessed before treatment and every 24 weeks for at least 6 months. Objective regression or progression were defined according to the criteria presented in Table 1.

Subjective assessments of performance score, cancer-related pain and analgesic use, urological symptoms and urine flow rates were made before treatment, after 4, 8 and 12 weeks, and every 12 weeks thereafter for at least 6 months. The scoring systems used to assess performance status, pain and analgesic use are shown in Table 2. The total subjective score was derived from the sum of the three individual scores; a subjective response was defined as no increase in any individual score, and either a decrease of at least 3 in the total score or a decrease of at least 2 in any individual score. Only patients who were symptomatic at entry (total score of 3 or above or a score of at least 2 in one individual measure) were included in the analysis of subjective responses. Blood samples were taken at the same time as the subjective investigations, for standard haematological and biochemical tests.

A standard 12-lead ECG was recorded before treatment, after 4, 8 and 12 weeks, and every 12 weeks thereafter for at least 6 months. A subset of 20 patients was monitored by means of 24 h ambulatory ECG recording.

Adverse events were identified from the patients' responses to the question 'Has anything bothered you since your last visit?'. Patients were also asked

Table 1. Critera for objective responses

Complete objective response
Absence of evidence or residual lesions from clinical, radiological, isotope bone scan or biochemical assessment.

Partial objective response
Any of the following:
- A reduction in prostatic acid phosphatase, total acid phosphatase or prostate-specific antigen of at least 90%, or into the normal range, in patients in whom the values at entry were more than twice the upper limit of the normal range.
- A reduction in prostatic size (product of two largest diameters) of at least 50%; for this criterion to be acceptable, one of the two largest diameters had to be at least 3 cm at the start of the trial.
- Radiological evidence of improvement of bone metastases or isotopic evidence of improvement uncontradicted by radiological findings.
- Radiographic evidence of healing of osteolytic bone metastasis.
- A reduction of at least 50% in any measurable extra-skeletal metastases.

Stable disease
Lack of objective evidence of progression and insufficient evidence of partial response.

Objective progression
Any of the following:
- An increase in prostatic dimensions (product of two largest diameters) of at least 50%, compared with the minimum dimensions during the study (one of the two largest diameters had to be at least 3 cm at the start of the trial).
- Appearance of new bone metastatis.
- Evidence of worsening of existing bone metastasis.
- Appearance of new extra-skeletal metastasis or an increase of at least 25% in the size of existing metastases.

Best objective response
First occurrence of progression or partial response or stable disease after 24 weeks.

Time to first treatment failure
Time to cessation of therapy for any of the following reasons:
- Adverse event.
- Patient unwilling or unable to continue.
- Objective progression.
- Death.
- Withdrawal of Casodex by the investigator.

Table 2. Scoring systems for performance status, cancer-related pain and analgesic use

Performance status or activity score
0 fully active; asymptomatic
1 ambulatory; capable of light work
2 in bed ⩽50% of the time; capable of self-care but not work
3 in bed >50% of the time; capable of only limited self care
4 completely bed-ridden; incapable of self-care
Cancer-related pain score
0 none
1 mild
2 moderately severe
3 severe
4 intractable
Cancer-related analgesic use score
0 no analgesia
1 occasional non-narcotic analgesia
2 regular non-narcotic analgesia
3 occasional narcotic analgesia
4 regular narcotic analgesia

specifically about the adverse events that would be predicted for a non-steroidal antiandrogen (breast tenderness, gynecomastia and hot flushes). Follow-up was continued for a minimum of 3 months after the recording of an adverse event.

Objective and subjective response rates were expressed as percentages with 95% confidence limits. Kaplan–Meier Product Limit Survival methods were used to assess time to treatment failure.

Results

A total of 267 patients were included in the study. Their demographic characteristics and tumour status are shown in Table 3.

The mean duration of treatment with Casodex was 49.4 weeks (range 0.4–113 weeks). During the course of the study, treatment was discontinued in 140 patients (52%). The most common reasons for treatment discontinuation were disease progression (71 patients), adverse events irrespective of their relationship to the study drug (37 patients, of whom 15 died) and investigator's, patient's or relative's choice (21 patients); other reasons were deterioration of disease or protocol violations (three patients each), non-medical reasons (one patient) or a combination of reasons (four patients). Ten patients did not satisfy the selection criteria, mainly because of coexisting malignant disease, previous endocrine therapy or ECG abnormalities. Data from these patients were included in the analysis of safety, but four patients were excluded from the efficacy analysis because of coexisting malignancy or previous hormonal therapy.

Efficacy

A partial response occurred in 146 patients; no patient experienced a complete response and thus the overall objective response rate was 55.5% (95% confidence limits 49.5–61.6%). Of the 146 patients who showed a partial response, 96 had metastases on entry to the study. The objective response rate in these patients was 52.7% (confidence limits 45.4–60.0%) compared with 61.7% (51.0–72.5%) in patients with locally advanced prostate cancer without metastases at entry.

Treatment failure occurred in 174 patients. Of these patients, 69% experienced objective progression of disease, 9.8% stopped Casodex therapy because of an adverse event, 7.7% stopped therapy because of investigator's choice, 4.6% died (as a result of prostate cancer of other causes) and 2.3% stopped therapy because of patient's choice (6.9% of patients were classed as treatment failures for other reasons). The product limit survival estimate of the median time to treatment failure was 35.6 weeks. Patients with disease progression could continue treatment and have another reason for treatment discontinuation.

A group of 66 patients had subjective symptoms on entry to the study. The subjective response rate in these patients, based on the performance status, cancer-related pain and cancer-related analgesic use scores, was 56.1% (confidence limits 43.8–68.3%). Urological symptoms were present in 201 patients on entry to the study. Treatment with Casodex improved symptoms in more than 50% of the eligible patients for up to 48 weeks. Similarly, there was an increase in maximum urine flow rate during treatment, which was maintained for up to 48 weeks. This increase was greatest after 12 weeks of treatment, when the median flow rate was 12 ml/s compared with a baseline value of 9 ml/s.

Additional second-line endocrine treatment (orchidectomy, LHRH agonist, estrogen, antiandrogen or combination therapy) was given to 72 patients after disease progression. The subsequent response could be assessed in 42 of these patients; five (11.9%) showed a partial response, 17 (40.5%) had stable disease and the remainder showed progression.

Table 3. Demographic characteristics and tumor status of the patients

No. of patients	267
Mean age (years)	72.4
Age range (years)	52–86
Mean weight (kg) ($n=261$)	72.6
Weight range (kg)	45–106
Mean plasma testosterone (nmol/l) ($n=241$)	14.6
Testosterone range (nmol/l)	1.0–35.3

Tumor category	No metastases (%)	Metastases (%)
T_0 (no tumor palpable)	0 (0)	2 (0.7)
T_1 (intracapsular)	0 (0)	2 (0.7)
T_2 (intracapsular, deforming contour)	0 (0)	25 (9.4)
T_3 (extracapsular)	66 (24.7)	101 (37.8)
T_4 (invading surrounding tissue)	15 (5.6)	54 (20.2)
T_x (cannot be assessed)	0 (0)	2 (0.7)

Tolerability

Adverse events were reported by 229 of the 267 patients. The most common were the pharmacological effects that would be predicted for a potent antiandrogen: breast tenderness, gynecomastia or hot flushes (Table 4). No other adverse event was reported by more than 5% of the patients. The most common non-endocrine adverse events were asthenia (4.9%), pelvic pain, peripheral edema and pruritus (3.4% each). Impotence and decrease in libido were reported in only eight patients and one patient, respectively (3 and 0.4%), and diarrhea occurred in only five patients (1.9%).

Of the 21 patients out of 267 who discontinued treatment because of non-fatal adverse events, 16 were thought by the investigator to have events 'unlikely to be related to therapy' and only nine were thought to have events 'probably related to therapy'. During the study, seven patients died from prostate cancer alone and a further eight died from other causes, which were considered by the investigators unlikely to be related to therapy. Three died from causes 'possibly' related to therapy (thrombotic or hemorrhagic disease in two patients, and complete heart block in one). A further two patients died 3 weeks after stopping treatment because of adverse events. These events (pneumonia and cerebral arteriosclerosis) were not regarded as treatment-related by the investigators.

Clinically relevant changes in hematological variables occurred in 22 patients and 12 patients showed clinically relevant changes in biochemical tests. All of these were considered to be attributable to spurious results or disease progression, with the exception of an inconfirmed gallstone in one patient. Results from the detailed cardiovascular study confirm that the use of Casodex for the treatment of prostate cancer does not appear to affect cardiac parameters as assessed by either 12-lead or 24-h ECG recording. In the elderly population recruited, many of the patients had underlying cardiac abnormalities which remained unchanged during the study period.

Table 4. Frequency of adverse events (total no. of patients = 267)

	No. of patients developing event (%)
Breast tenderness or pain	168 (63.4)
Gynecomastia	138 (52.5)
Hot flushes	61 (23.6)
Asthenia	13 (4.9)
Pelvic pain	9 (3.4)
Peripheral edema	9 (3.4)
Pruritus	9 (3.4)
Constipation	8 (3.0)
Impotence	8 (3.0)
Diarrhea	5 (1.9)
Libido decreased	1 (0.4)

Discussion

The results of this open study indicate that Casodex 50 mg monotherapy is effective and well tolerated when used as monotherapy in patients with advanced prostate cancer. The response rates obtained in these patients are comparable to those seen in studies with other forms of endocrine therapy.[6,7]

The main adverse events associated with Casodex are those that would be predicted for any potent antiandrogen, i.e. breast tenderness, gynecomastia and hot flushes. The incidence of hot flushes, however, appears to be lower in patients treated with Casodex than in patients undergoing orchidectomy.[8] The non-pharmacological side-effects were few and rarely necessitated discontinuation of treatment. Casodex did not produce the high incidence of gastrointestinal side-effects sometimes seen with flutamide,[8] or the alcohol intolerance and visual disturbances associated with nilutamide.[1] Moreover, Casodex had minimal effect on libido and potency, a finding consistent with a previous observation that Casodex 50 mg monotherapy does not interfere significantly with the erectile capability of men with prostate cancer.[10] The endocrinological effects of Casodex in a subgroup of patients in this study have been published separately.[11]

Casodex has been extensively evaluated, both as monotherapy and as combination therapy.[12,13] Monotherapy with Casodex, 50 mg daily, has been shown to be comparable to castration (orchidectomy or LHRH treatment) in terms of time to treatment failure and time to disease progression.[8] Other studies in which 50 mg Casodex has been compared with castration have, however, suggested that this dose may be insufficient as monotherapy to provide objective benefits equivalent to those with castration[14,15] and there is evidence that the antitumour effect can be enhanced by using higher doses, of up to 150 mg daily, without loss of tolerability.[12] Casodex is particularly suitable for monotherapy because of its good tolerability and long half-life, which permits once-daily dosing.[3] In these respects, Casodex offers advantages over other non-steroidal antiandrogens. Flutamide has a short half-life and is normally given three times daily, thereby potentially increasing the problems with patient compliance. Nilutamide is suitable for once-daily dosing, but the usefulness of this agent is limited by its side-effects.[16]

Combination treatment of prostate cancer aims to achieve total androgen blockade, minimizing the exposure of the tumor to both testicular and adrenal androgens. This can be achieved by combining antiandrogen treatment with either an LHRH agonist or orchidectomy. Several studies have shown that such treatment improves survival and response rates in patients with newly diagnosed prostate cancer.[17–19] Antiandrogens when given with LHRH analogs reduce the incidence of tumor flare associated with these drugs. Pharmacokinetic studies have shown that once-daily dosing with Casodex is an effective as flutamide in preventing tumor flare.[12,13]

In conclusion, this open study of monotherapy with Casodex 50 mg in 267 patients with advanced prostate cancer showed that this new antiandrogen was well tolerated and was effective in terms of objective and subjective responses. Further studies are in progress to evaluate the usefulness of Casodex as monotherapy in higher doses, to compare responses with those of medical or surgical castration and to study its effect in combination with LHRH analogs to produce maximum androgen blockade.

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Appendix

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