Urologia Internationalis

Urol Int 2004;72:91–98
DOI: 10.1159/000075960

Review

Alessandro Sciarra
Antonio Cardi
Franco Di Silverio

Department of Urology,
University La Sapienza,
Rome, Italy

Antiandrogen Monotherapy: Recommendations for the Treatment of Prostate Cancer

Abstract

Objective: The concept of antiandrogens as monotherapy for the treatment of prostate cancer is discussed. ***Methods:*** Both Medline and Current Contents were used to identify studies on antiandrogen monotherapy in prostate cancer. We tried to analyze this database critically to estabilish whether or not there is evidence for using this monotherapy. ***Results:*** In particular, bicalutamide in monotherapy has been compared with castration in large international trials. Results show that antiandrogen monotherapy is inferior to castration in patients with metastatic tumour but the difference in median survival is limited. In locally advanced M0 prostate cancer bicalutamide 150 mg monotherapy seems equivalent to castration in terms of overall survival and time to progression. Analysis of quality of life showed that there is evidence of some benefits from bicalutamide when compared to castration in both sexual interest and physical capacity. ***Conclusion:*** Antiandrogens in monotherapy can be effective and well tolerated. However, more research is needed because none of the available compounds have definitively been proven to be equivalent to castration.

Introduction

Hormonal treatment of prostate cancer is based on the demonstration that malignant prostate cells are target tissues of androgen action. The goal of the therapy is therefore to reduce the androgenic support to prostatic cancer growth by removing the primary source of circulating androgens. This may be achieved by means of orchiectomy, by suppressing the gonadotropin secretion using LHRH analogues or blocking the androgens at receptor levels with antiandrogens.

Today, more than 50 years after the first evidences, endocrine manipulation remains one of the principal corner stones in the management of prostate cancer (PC).

Unfortunately, the use of androgen deprivation in patients with PC has limitations. Most importantly, endocrine treatment can be considered palliative in nature, and relapse of the malignancy occurs if the patient survives competing with causes of death [1]. Also, side effects and toxicity associated with endocrine manipulation are common. With loss of sexual function a number of side effects such as fatigue, depression and lack of energy, result in reduced quality of life.

Castration has been the treatment of choice for many years. Total androgen blockade cannot be considered to be the 'gold standard' for various reasons, mainly because of marginal advantages in effectiveness and the very high costs. During the last two decades a number of new pharmacological approaches for androgen deprivation has been introduced. Different issues are still open for discussion: timing of therapy, the use of endocrine therapy in very early cancer, non-steroidal antiandrogen monotherapy, intermittent androgen suppression, neoadjuvant and adjuvant therapy.

In this review, the concept of antiandrogens as monotherapy for prostate cancer is discussed.

In the first-line endocrine treatment of PC, antiandrogens have been used in long-term combination with either surgical or medical castration, as well as antiflare therapy when initiating treatment with LHRH agonists.

KARGER
Fax + 41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0042–1138/04/0722–0091/$21.00/0

Accessible online at:
www.karger.com/uin

Dr. Sciarra
Via Nomentana 233
I–00161 Rome (Italy)
Tel./Fax +39 06 446 1950
E-Mail sciarrajr@hotmail.com

The antiandrogens developed so far include compounds with steroidal structure, such as cyproterone acetate (CPA) and megestrol acetate, displaying also progestational and antigonadotropic effects, and compounds without steroidal structure, such as nilutamide, flutamide and bicalutamide, which are considered pure antiandrogens. The latter substances, inhibit the negative feedback of the gonadal steroids, so that more gonadotropins are released by the hypophysis and more testosterone and estradiol by the gonads; therefore, serum testosterone levels are not lowered and patients may retain sexual function. During pure antiandrogen therapy the peripheral aromatisation of testosterone, and therefore serum levels of estradiol increase, which frequently causes gynecomastia and breast tenderness. A rise of up to 50% in serum testosterone [2] may be disturbing because it may 'overcome' the blockade of the androgen receptor by antiandrogens.

Materials and Methods

Both Medline and Current Contents database were used to identify studies on antiandrogen monotherapy in prostate cancer. We tried to analyze this database critically to establish whether or not there is an evidence for using this monotherapy. In particular, we evaluated large randomized studies with enough statistical power and we analyzed whether data can be considered mature to estimate differences in survival.

Antiandrogen Monotherapy in Prostate Cancer: Rationale, Indications and Open Questions

The goal for an improved endocrine manipulation is twofold: first, improved anticancer efficacy in terms of increased rate and duration of response as well as prolongation of survival, and, second, minimal toxicity and improved quality of life [1]. Potential advantages of the use of antiandrogens may be the quick achievement of a maximal effect, the reversibility of the antiandrogenic effect, the oral application and the potential preservation of libido and potency with the use of nonsteroidal monotherapy [3].

Antiandrogen monotherapy can be analyzed as:

(1) monotherapy in metastatic PC, and

(2) monotherapy in nonmetastatic PC (immediate or as adjuvant of primary curative intent).

Surgical or pharmacological castration will probably remain standard treatment for hormone-sensitive PC.

Table 1. Open questions on antiandrogen monotherapy

- If complete androgen blockade (CAB) is not necessary in every patient, is it not better to initiate endocrine treatment in a less aggressive fashion and step it up later on when progression occurs?
- May this concept delay the occurrence of hormone-refractory PC?
- Is it necessary to treat patients with locally advanced M0 PC with castration or may antiandrogen monotherapy be indicated as endocrine manipulation?
- After primary curative intent (radical prostatectomy, radiotherapy), is it necessary to treat patients in progression with castration or can antiandrogen monotherapy be proposed?
- After primary curative intent, is there an indication to treat all PC patients with antiandrogen monotherapy as secondary chemoprevention, independently of progression?
- Can libido and potency, at least temporarily, be preserved using antiandrogen as monotherapy?
- Would less aggressive therapies used in an adjuvant setting provide a better quality of life and decrease costs?
- If quality of life could really be improved for a prolonged period of time and the therapies were less effective in terms of disease-specific and overall survival, would patients be ready to exchange quality of life for life time?

However some questions may be proposed and they are presented in table 1.

All these questions [4] are currently being addressed and the field is now open for research into other options that have been understudied in the past.

Antiandrogen Monotherapy: Can It Improve Quality of Life of Patients?

Within a relatively short period of time, quality of life (QL) assessment has become an established part of oncology. This is partly due to the understanding that extension of life is not always the best option [5].

Criteria for inclusion of QL issues in clinical trials are well defined by EORTC [5]. They state that QL assessment can be a relevant end-point if:

– no improvement in overall, recurrence-free or systemic disease-free survival is expected, but significant changes or differences in one aspect of QL are expected;
– one treatment results in a better survival, but has more toxic effects;
– patients have an extremely poor prognosis with or without treatment;

– treatment is known to be very burdersome for patients;
– a new treatment is to be evaluated.

As a result of the use of hormone therapies in the management of patients with early prostate cancer, there is a strong likelihood of patients receiving this therapy for a longer duration. Therefore, a major consideration in the choice of hormone treatment is the physiological and psychological impact it has on patients [6]. Moreover, recognizing that endocrine manipulation of advanced prostate cancer conceptually remains a palliative treatment, we should regard the maintenance of QL as an important therapeutic goal.

Side effects of castration can have a profound effect on QL. With castration being used for longer periods of time, reports of osteoporosis and subsequent risk of fractures have received considerable attention [7, 8]. Sexual function is one aspect of QL that has increased in importance over recent years as the profile of PC patients has changed from the elderly man with metastatic disease to that of the younger man with early stage disease and much longer life expectancy. A large number of patients with nonmetastatic disease is physically active before treatment and the reduction of energy and muscular mass following castration is likely to significantly reduce patients' physical capabilities.

Antiandrogens represent a treatment modality for oral administration, which given as monotyherapy is associated with few adverse effects. Further, antiandrogen monotherapy holds the potential of preserving sexual function.

The safety profile of bicalutamide monotherapy was evaluated in two large phase III trials, with more than 1,400 patients with either metastatic M1 or T3/T4 M0 PC receiving treatment with bicalutamide or castration [9,10]. As predicted by its pharmacological action, about 50% of patients experienced some degree of gynecomastia and breast pain during the first year of treatment with bicalutamide, with few new cases arising thereafter. In addition, only 4.1% of patients withdrew due to drug-related adverse events. In these two phase III trials, quality-of-life measurement was assessed in a questionnaire covering 10 quality of life dimensions [11]: general health, pain, emotional well-being, vitality, social functioning, physical capacity, sexual interest, sexual functioning, activity limitation and bed disability. In patients with M0 disease, bicalutamide when compared with castration, was favored in 8 of 9 evaluable dimensions, and in 2 of the dimensions, sexual interest and physical capacity, this difference was statistically significant ($p = 0.029$, $p = 0.046$, respectively). Only the domain of overall health favored castration, and this was not statistically significant. Although, as expected after a diagnosis of PC, sexual interest declined in both bicalutamide and castration treatments: in these two comparative studies [9,10], the percentage reduction from baseline in sexual interest after 12 months for M0 patients was 23% in the bicalutamide monotherapy group and 47% in the castration group ($p = 0.029$). For patients with sexual interest on entry to the trial, significantly more patients receiving bicalutamide maintained an interest in sex ($p < 0.01$) compared with the castration group. A significant advantage of bicalutamide over castration was also shown for physical capacity ($p = 0.046$). Generally, nonsteroidal antiandrogens are not associated with a fall in testosterone and consequently a loss of physical activity or the presence of other psychological effects, loss of muscle mass or strenght linked to low testosterone levels, are not expected with these drugs.

Moreover, experimental studies suggest that nonsteroidal antiandrogens do not affect bone mineral density (BMD) [12]. In particular BMD in patients who received bicalutamide 150 ng daily for more than 5 years were similar to age-matched healthy individuals, and higher than that of patients who had been castrated.

In table 2, a conclusive analysis on the effect of antiandrogen monotherapy on QL is reported.

Antiandrogen Monotherapy: Is Treatment Efficacy Comparable to That of Castration Therapy in Metastatic PC?

In monotherapy, three antiandrogens have been used in large scale: CPA, flutamide and bicalutamide.

Nilutamide monotherapy has not been widely investigated with randomized studies. Decensi and Boccardo [21] administered nilutamide at a dose of 300 mg daily to untreated patients with metastatic PC. Partial response was demonstrated in 38.5% of patients. Median survival was 23 months with a progression-free survival of only 9 months. A relatively high incidence of side effects was reported. At now, nilutamide has been generally not poposed as a valid option in the treatment of advanced PC.

CPA Monotherapy

The clinical trials that have compared CPA monotherapy with castration or CAB did not fulfil the statistical requirements for contemporary equivalence studies [22]. In smaller series, the steroidal antiandrogen CPA has been found comparable to orchidectomy and estrogen therapy in terms of treatment results [20, 23]. Other studies showed that CPA monotherapy results in shorter progression-free and overall survival when compared to LHRH agonist therapy [18, 24]. The European Organization for Research and treatment of Cancer (EORTC) protocol 30761 compared CPA 250 mg with diethylstilbestrol (DES) 3 mg [25]. This study showed that patients treated with CPA achieved better results in terms of objective response of local tumor and bone metastases, progression rate and time to progression. Recently another study on CPA has become available; protocol 30892 of EORTC Genitourinary Group compared flutamide monotherapy with CPA monotherapy in untreated metastatic PC patients with good-risk prognostic factors [15]. In order to qualify for the study, patients had to have at least two of the three favorable prognostic factors: performance status WHO 0, a normal alkaline phosphatase level and less than T4 classification of the primary tumor. Patients with a history of myocardial infarctions who presented with active coronary disease were not eligible. A total of 308 patients were recruited between 1990 and 1996: the final analysis with regards to effectiveness is still pending.

Flutamide Monotherapy

Flutamide has been studied in about 700 PC patients in a randomised fashion, usually in comparison with estrogens [2, 19]. In most of these relatively small studies there were no significant differences with respect to response and survival rate. Nonetheless, large randomised studies with enough statistical power to allow conclusions about equivalence with castration therapy do not exist and the question of whether flutamide monotherapy can be considered a treatment of PC cannot be answered from the informations currently available. In 1992, Boccon-Gibod et al. [26] studied 100 patients who were randomised to receive flutamide or orchidectomy and reported no significant differences in response rate. Most importantly, when stratifying patients according to PSA level at entry, it was shown that patients with PSA of <120 ng/ml did relatively better on flutamide monotherapy compared to castration than did patients with higher levels of PSA.

Table 2. Conclusion on QL under antiandrogen monotherapy

- Analysis of quality-of-life questionnaires demonstrated several statistically significant differences between castration and antiandrogen monotherapy; in particular there is evidence of some benefits from treatment with bicalutamide in both sexual interest and physical capacity
- Other antiandrogens are associated with significantly more side effects; CPA has been associated with thrombosis, gynecomastia and loss of libido in a significant percentage of cases [13, 17]; flutamide has been associated with diarrhea and liver abnormalities [18, 20]; however, also about 50% of patients under bicalutamide experienced some degree of gynecomastia and breast pain during the first year of treat ment [9, 10]
- Evaluation of QL should be continued to be included in clinical trials of PC treatments: the instruments used should assess both overall and disease-specific QL

These results suggested that flutamide monotherapy was best used in patients with less advanced disease. Results from EORTC protocol 30892 on the effectiveness of flutamide monotherapy in metastatic PC patients are still pending [15].

Bicalutamide Monotherapy

Bicalutamide in monotherapy has been compared with castration in large international trials. A daily dose of 50 mg was found to be inferior to castration in terms of progression-free and overall survival thus nourishing the fear that the androgen blockade with antiandrogen monotherapy may be insufficient [27]. In particular a total of 1,196 patients with advanced metastatic PC were recruited to compare bicalutamide with castration in three studies [28]. The median duration of follow-up was 72.3 weeks for the bicalutamide group and 75.1 weeks for the castration group. The analysis of efficacy showed a statistically significant difference in favor of castration in terms of time to treatment failure, time to objective progression and survival time. For this reason, higher doses of bicalutamide in monotherapy have been more recently studied, demonstrating that also the 150 mg dosage was well tolerated and showed QL benefits [29] . In two studies (protocol 306 and 307) [9] more than 1,400 patients with locally advanced or metastatic PC were randomized between surgical/pharmacological castration and bicalutamide 150 mg daily. A protocol ad interim analysis after a median follow-up of approximately 100 weeks revealed a statistically significant qualitative interaction between treatment group and stage of dis-

ease and, consequently, data from the M0 and M1 subgroups were analyzed separately. In the metastatic prostate cancer group data were considered mature as 43% of M1 patients had died. Bicalutamide at this dosage of 150 mg daily is inferior to castration in patients with metastatic disease with respect to time to death with a hazard ratio of 1.304. This difference was statistically significant but the difference in median survival was only 6 weeks [9]. Similarly, this analysis showed a significant difference in favour of castration when compared to bicalutamide also in terms of time to treatment failure (hazard ratio 1.43) and time to objective progression (hazard ratio 1.44). Again, most of the parameters on QL, including sexual function, showed a positive treatment effect in favour of bicalutamide, with sexual interest and physical capacity showing statistically significant advantages ($p = 0.041$ and 0.032, respectively).

A multicenter study was conducted in France to compare the efficacy of bicalutamide with that of the combined treatment of castration plus nilutamide [30] in metastatic PC. Castration was achieved either by orchidectomy or pharmacologically and nilutamide was administered at the dosage of 300 mg/day for the first month, followed by 150 mg/day. Most of the patients randomized to bicalutamide received 150 mg/day. The population analysed was limited to 235 cases and overall survival curves were immature.

In a smaller study conducted by Boccardo et al. [31], 220 patients with advanced (M0 and M1) previously untreated PC were randomised to receive bicalutamide 150 mg daily or goserelin plus flutamide. A survival trend (but not statistically significant: $p < 0.6$) favored CAB in metastatic disease.

Antiandrogen Monotherapy in Nonmetastatic PC

Recently, there has been an increased interest in the use of hormone therapy for the management of early PC, in addition to its established indication in treating advanced disease. In these settings, hormone treatment with minimal side effects and a favorable impact on QL will become more important [6].

The comparative analysis of the 480 nonmetastatic patients with locally advanced T3/T4 M0 PC included in the two randomized studies of bicalutamide as monotherapy 150 mg daily and castration, has been performed after a median follow-up of 6.3 years with 56% deaths [32]. The authors did not specifically describe whether all patients received bicalutamide as immediate hormonal therapy or as adjuvant of primary curative intent [32]. Moreover, results are not analyzed classifying patients on the basis of stage (T3 vs. T4) or Gleason score. In these patients, bicalutamide monotherapy was statistically equivalent to castration in terms of overall survival, with a hazard ratio of 1.05. Having crossed the threshold for maturity, with more than half of the patients dead, it was possible to estimate median survival, which was 63.5 months in the bicalutamide group and 69.9 months in the castration group. Overall, 77% of patients had progressed and there was no significant difference in time to progression between the bicalutamide and castration groups (hazard ratio 1.20).

Two smaller studies comparing bicalutamide with CAB have also reported similar results with respect to time to progression and overall survival [30, 31]. These studies included both non-metastatic and metastatic patients but results have not been clearly analysed by disease stage.

To our knowledge, there are no large comparative studies analysing other antiandrogens (compared to castration) in the treatment of locally advanced PC.

Antiandrogen Monotherapy as Adjuvant Therapy

There is now considerable interest in the use of adjuvant therapies after primary treatment with surgery or radiotherapy in patients with early-stage disease. A significant proportion of men with early-stage PC will experience local or systemic progression and/or die from the disease despite receiving primary curative intent. Adjuvant therapy may have a role although not all patients can be expected to benefit: for example, given the generally favorable prognosis for organ-confined disease, it is probably unreasonable to administer a treatment which may have a negative impact on QL to all of these men [33].

The use of nonsteroidal antiandrogen monotherapy as adjuvant therapy after surgery or radiotherapy have been investigated. The 4-year results of an open randomized controlled study of flutamide 250 mg three times daily in 365 men with pT3-N0 disease after RRP, suggest an improvement in time to clinical recurrence and progression-free survival at 4 years (90% flutamide vs. 69% placebo controls; $p = 0.0029$), but data are not yet sufficiently mature to evaluate impact on survival [33, 34]. Moreover, when patients in whom the only indicator of progression after surgery was an increase in PSA are excluded, the proportion of men with progression is low and similar in the two groups [33] (flutamide vs. placebo). The incidence of study withdrawal due to

side effects in the flutamide group was disappointing with 20.1% men discontinuing therapy.

The bicalutamide Early Prostate Cancer (EPC) program is being undertaken to investigate the efficacy of bicalutamide as an adjuvant therapy of primary curative intent or as immediate hormonal therapy in men with M0 prostate cancer (T1b-4; N0-1; M0) [35]. A total of 8,113 men have been recruited to three studies in different geographic areas that comprise this program. Patients were assigned in a 1:1 ratio to receive either bicalutamide 150 mg daily or matching placebo tablets. Overall, 67.5% of patients had T1-2 disease, 31% T3 and 1.5% T4 disease. With respect to tumor grade 22.1% had Gleason score 2–4, 44.3% Gleason score 5–6 and 33.6% Gleason score 7–10 tumors. Only 3.1% of cases had N+ status. Overall, slightly more than half of patients underwent RRP, 17.7% radiotherapy, 0.6% brachytherapy, 0.1% other therapies and the remaining 28.2% of the cases were untreated [35].

Wirth et al. [36] reported results in terms of efficacy on 3,603 cases as part of the EPC program. The median follow-up was 2.6 years. Overall, 13.2% of cases developed disease progression, of whom 10.1% were in the bicalutamide group and 16.2% in the placebo group. A significant reduction of 43% was found in the risk of objective progression for bicalutamide compared with placebo (hazard ratio 0.57). This benefit was numerically consistent across the patients population, regardless of whether bicalutamide was given as adjuvant therapy or after management with watchful waiting and regardless of disease stage. The survival data were immature, with 7.2% overall mortality and less than 2% of patients dying of PC. The time of PSA doubling was significantly increased for the bicalutamide group compared with placebo (hazard ratio 0.37). Overall, the withdrawal rates were similar in the bicalutamide (40.3%) and placebo (37.2%) groups. In the bicalutamide group, 24.5% of patients withdrew because of adverse events, with gynecomastia and/or breast pain accounting for 15.4%. This is a very important study but a longer follow-up and a more detailed analysis stratifying patients included in the adjuvant treatment group is still pending.

A first analysis of the EPC therapy program, stratifying cases on the basis of lymph node status, showed that bicalutamide treatment significantly reduced the risk of objective disease progression or the risk of PSA doubling in patients with N0 prostate cancer (by 41 and 55%, respectively), but the largest decrease was seen in N+ cases (by 71 and 84%, respectively) [37]. Moreover, stratifying EPC cases on the basis of the initial Gleason score, bicalutamide significantly reduced the risk of objective disease progression or the risk of PSA progression either in Gleason score <7 (by 40 and 61%, respectively) or ≥7 cases (by 42 and 54%, respectively) [38].

Concluding Remarks on Antiandrogen Monotherapy in Nonmetastatic PC.

As nonsteroidal antiandrogens are associated with potential QL benefits when compared to castration, in early PC, submitted to endocrine manipulation, it may be preferable to use antiandrogens as first-line therapy. The treatment would then be stepped up with the use of more invasive forms of endocrine therapy. The treatment of patients who are initially treated by antiandrogen and then have progressive disease, has not been defined yet and only the analysis on small populations is reported [39].

In patients with nonmetastatic PC there is continuing controversy over the timing of the initiation of hormone therapy. At the time of VACURG studies [40], the clinicians' choice was fairly limited: surgical castration or estrogens which were associated with a high risk of cardiovascular complications. Conclusions from the VACURG studies might have been expressed as follows: 'When the only therapies available for immediate hormone therapy were castration or estrogens the price of therapy, in terms of the morbidity and mortality for the patient, was probably too high.' However, with the advent of better-tolerated hormone therapies, i.e. nonsteroidal antiandrogens, long-term hormone therapy is no longer associated with the morbidity seen in the early studies [41].

Our knowledge of adjuvant therapy for patients undergoing RRP is at least 15 years behind that for patients with breast and colorectal cancers. Through large randomized clinical trials, adjuvant therapy has been established as the standard for many women with breast cancer. The study reported as part of the EPC program [36] may be extremely important [Editor's comment, 36]. They demonstrated in a very large randomised trial that adjuvant therapy with a well-tolerated antiandrogen can delay progression. The ultimate endpoint of this trial should be an assessment of improved survival. Moreover, a more detailed analysis stratifying patients on the basis of stage, Gleason score, preoperative and postoperative PSA is still pending. A

Table 3. Recommendations

- Antiandrogens in monotherapy can be effective and well tolerated; however, more research is needed because none of the available compounds have definitively been proven to be equivalent to castration
- Studies comparing CPA, flutamide and in particular nilutamide with castration or CAB have all been relatively small, and carry far from the necessary statistical power to establish equivalence within reasonable limits
- At present, the appropriate dosage for bicalutamide monotherapy is 150 mg daily
- Concern that the blockade of androgen receptors during nonsteroidal antiandrogen monotherapy is insufficient in patients with metastatic tumor, is substantiated by the large bicalutamide studies finding the efficacy of antiandrogen slightly inferior to that of castration in M1 patients
- Bicalutamide 150 mg monotherapy seems equivalent to castration in locally advanced M0 PC patients; a more mature analysis, however, also in this case is awaited; if equivalence is confirmed, sequential therapy with 150 mg bicalutamide daily followed by castration will be an attractive option for nonmetastatic PC if endocrine manipulation is chosen for these patients
- Bicalutamide 150 mg may be an attractive option as adjuvant to therapy of primary curative intent in men with nonmetastatic PC; however, a more detailed analysis is needed and at present we cannot recommend bicalutamide 150 mg as adjuvant therapy for all PC patients

Table 4. Directions for future research include

- The search for more potent nonsteroidal antiandrogens
- Exploration of higher doses in order to achieve more complete blockade
- Definition of the optimal second-line therapy following antiandrogen monotherapy
- With longer duration of antiandrogen therapy in younger patients with nonmetastatic disease, ways to avoid or reduce troublesome gynecomastia will have high priority
- Definition of parameters able to select subgroups of patients with non-metastatic disease more suitable to positively respond to antiandrogen monotherapy

detailed comparative study of bicalutamide monotherapy versus castration only in patients in progression after primary curative intent may also give important indications for this category of patients.

In tables 3 and 4 we propose final recommendations and directions for future research on the use of antiandrogen monotherapy in PC.

References

1 Iversen P: Endocrine therapy: Goals and limitations; in Schroder FH (ed): Recent Advances in Prostate Cancer and BPH. London, 1997, pp 147–158.
2 Boccon–Gibod L, Fournier G, Botter P: Flutamide versus orchiectomy in the treatment of metastatic prostate carcinoma. Eur Urol 1997;32:391–396.
3 Neumann F, Jacobi GH: Antiandrogens in tumor therapy. Clin Oncol 1982;1:41–64.
4 Eisemberger M, Crawford ED, McLeod D, Loehrer P: A comparison of bilateral orchiectomy with or without flutamide in stage D2 prostate cancer. 33rd Ann Meet American Society of Clinical Oncology, 1997, A1311.
5 van Andel G, Kurth KH: Quality of life in prostate cancer: Preliminary results of two studies in patients with extensive disease. 4th Int Symp Recent Advances in Urological Cancer, Paris, 1994, pp 191–203.
6 Iversen P: Quality of life issues relating to endocrine treatment options. Eur Urol 1999; 36(suppl 2):20–26.
7 Daniel HW: Ospeoporosis after orchoectomy for prostate cancer. J Urol 1997;157:439–444.
8 Townsend MF, Sanders WH, Northwat RO, Graham SD: Bone fracture associated with luteinizing hormone-releasing hormone agonists used in the treatment of prostate cancer. Cancer 1997;79:545–550.
9 Tyrrel CJ, Kaisary AV, Iversen P, Andersson JB, Baert L: A randomised comparison of Casodex 150 mg monotherapy versus castration in the treatment of metastatic and locally advanced prostate cancer. Eur Urol 1998; 33:447–456.
10 Iversen P, Tyrrel CJ, Kaisary AV, Anderson JB, Baert L: Casodex 150 mg monotherapy compared with castration in patients with previously untreated non-metastatic prostate cancer: Results from two multicenter randomised trials at a median follow-up of 4 years. Urology 1998;51:389–396.
11 Cleary PD, Morrissey G, Oster G: Health-related quality of life in patients with advanced prostate cancer: A multinational perspective. Qual Life Res 1995;4:207–220.
12 Calero JA, Diaz-Curiel M: Bicalutamide treatment does not produce bone effects in male Wistar rats. J Bone Min Res 1999;14 (suppl 1):S220(abstr F034).
13 Di SilverioF, Serio M: Zoladex vs. Zoladex plus cyproterone acetate in the treatment of advanced prostatic cancer: A multicentre italian study. Eur Urol 1990;18:54–61.
14 Schroder FH, Whelan P, Kurh KH, de Pauw M: Antiandrogens as monotherapy for metastatic prostate cancer: A preliminary report on EORTC protocol 30892; in Schroder FH (ed): Recent Advances in Prostate Cancer and BPH. London, Parthenon Publishing, 1997, pp 141–146.
15 Schroder FH, Collette L, de Reijke TM, Whelan P: Prostate cancer treated by antiandrogen: is sexual function preserved? Br J Cancer 2000;82:283–290.
16 Barradell LB, Faulds D: Cyproterone: A review of its pharmacology and therapeutic efficacy in prostate cancer. Drugs Aging 1994;5:59–80.
17 de Voogt HJ, Smith PH: Cardiovascular side effects of diethylstilbestrol, cyproterone acetate, medroxyprogesterone acetate, and estramustine phosphate used for the treatment of advanced prostatic cancer: Results from EORTC trials 30761 and 30762. J Urol 1986;135:303–307.

18 Moffat LEF: Comparison of Zoladex, diethylstilbestrol and cyproterone acetate treatment in advanced prostate cancer. Eur Urol 1990; 18(suppl 3):26–27.
19 Lund F, Rasmussen F: Flutamide versus stilbestrol in the management of advanced prostatic cancer: A controlled prospective study. Br J Urol 1988;61:140–142.
20 Wysowski DK, Fourcroy JL: Flutamide hepatotoxicity. J Urol 1996;155:209–212.
21 Decensi AU, Boccardo F: Monotherapy with nilutamide, a pure antiandrogen, in untreated patients with metastatic carcinoma of the prostate. J Urol 1991;146:377–381.
22 Iversen P: Antiandrogen monotherapy; in Kurth KH (ed): Renal, Bladder and Prostate Cancer. Progress Controversies in Oncological Urology. London, Parthenon Publishing, 1999: pp 183–190.
23 Ostri P, Bonnesen T, Nilsson T: Treatment of symptomatic metastatic prostatic cancer with cyproterone acetate versus orchiectomy: A prospective randomised trial. Urol Int 1991; 46:167–171.
24 Thorpe SC: A prospective randomised study to compare goserelin acetate versus cyproterone acetate versus a combination of the two in the treatment of metastatic prostate carcinoma. Eur Urol 1996;29:47–54.
25 Pavone Macaluso M, de Voogt HJ, Viggiano G, Barasolo E: Comparison of of advanced prostate cancer: Final analysis of a randomized phase III trial of the EORTC. J Urol 1986;136:624–631.
26 Boccon-Gibod L, Fournier G, Battet P, Mallo C: Flutamide versus orchidectomy in patients with metastatic prostate carcinoma. J Urol 1992; 147:417A.
27 Tyrrell CJ: Casodex: A pure non-steroidal antiandrogen used as monotherapy in advanced prostate cancer. Prostate 1992;(suppl 4): 97–104.
28 Iversen P: Update of monotherapy trials with the new antiandrogen Casodex. Eur Urol 1994;26(suppl 1):5–9.
29 Bales GT, Chodak GW: A controlled trial of bicalutamide versus castration in patients with advanced prostate cancer. Urology 1996;47(suppl 1A):38–43.
30 Fourcade RO: An open multicentre study to compare the effect and safety of Casodex 150 mg monotherapy with castration plus nilutamide in metastatic prostate cancer. Eur Urol 1998;33(suppl 1):88A.
31 Boccardo R, Rubagotti A, Barichello M: Bicalutamide monotherapy versus flutamide plus goserelin in prostate cancer patients: Results of an italian prostate cancer project study. J Clin Oncol 1999;17:2027–2038.
32 Iversen P, Tyrrel CJ, Kaisay AV, Anderson JP: Bicalutamide 150 mg monotherapy compared with castration in patients with non-metastatic locally advanced prostate cancer: 6.3 years follow-up. J Urol 2000;164:1579–1582.
33 Wirth M, Froehner M: A review of studies of hormonal adjuvant therapy in prostate cancer. Eur Urol 1999; 36(suppl 2):14–19.
34 Wirth M, Frohmuller H, Marz F, Bolten M, Theib M: Randomized multicenter trial on adjuvant flutamide therapy in locally advanced prostate cancer after radical surgery: Interim analysis of treatment effect and prognostic factors. Br J Urol 1997;80(suppl 2): 263 (abstr 1033).
35 See WA, McLeod D, Iversen P, Wirth M: The bicalutamide early prostate cancer program: demography. Urol Oncol 2001;6:43–47.
36 Wirth M, Tyrrel C, Wallace M, Delaere KP: bicalutamide 150 mg as immediate therapy in patients with localized or locally advanced prostate cancer significantly reduces the risk of disease progression. Urol 2001;58:146–151.
37 Iversen P, Wirth M, See W, McLeod D: Is the efficacy of hormonal therapy affected by limph node status? New data from the bicalutamide EPC program. J Urol 2002;167: 1355A.
38 Wirth M, McLeod D, Iversen P, See W: Efficacy of bicalutamide in early non metastatic prostate cancer by initial desease state and grade. J Urol 2002;167:1367A.
39 Tan A, Tuckey J, Rice M: Orchidectomy following failure of antiandrogen monotherapy in patients with metastatic prostate cancer. Eur Urol 2001;40:130–134.
40 Byar DP: The Veterans Administration Cooperative Urological Research Group studies of cancer of the prostate. Cancer 1973;32: 1126–1130.
41 Newling D: Advanced prostate cancer: Immediate or deferred hormone therapy? Eur Urol 2001;39(suppl 1):15–21.