Treatment of Localized Prostate Cancer With Intermittent Triple Androgen Blockade: Preliminary Results in 110 Consecutive Patients

ROBERT L. LEIBOWITZ, STEVEN J. TUCKER

Compassionate Oncology Medical Group, Los Angeles, California, USA

Key Words. *Prostate cancer · Triple androgen blockade*

ABSTRACT

***Objectives*. To determine the effectiveness of triple androgen blockade as an alternative to watchful waiting, radical prostatectomy or radiation therapy in the management of patients with clinical stage T1 to T3 prostate cancer.**

***Methods*. The records of 110 consecutive patients were retrospectively evaluated. Patients were treated with a three-drug androgen blockade regimen, consisting of a luteinizing hormone-releasing hormone agonist (leuprolide or goserelin) plus an antiandrogen (flutamide or bicalutamide) plus finasteride (a 5-alpha-reductase inhibitor), followed by finasteride maintenance therapy, as the sole intervention. All patients refused local therapy and had their prostates intact. Determinants of efficacy included serum prostate-specific antigen (PSA) levels and disease-specific survival.**

***Results*. Patients were treated for a median of 13 months with triple androgen blockade. At baseline, mean PSA level was 13.2 ± 1.2 ng/ml (range, 0.39-100 ng/ml), and mean Gleason score was 6.6 ± 0.1 (range, 4-10). During treatment, PSA levels declined to ≤0.1 ng/ml in all patients, with a median time of 3 months. After a median follow-up of 36 months since initiation of treatment, PSA levels have remained stable in 105 of 110 patients (95.5%). At a median follow-up of 55 months (range, 38-125 months), the mean PSA level for the first 57 patients treated in this series is 1.88 ± 0.1 (range, 0-11.0 ng/ml). Only 9 of 110 (8.1%) patients have a PSA level ≥4.0 ng/ml. To date, no patient has received a second cycle of hormone blockade.**

Conclusions*. Although median follow-up is short, triple androgen blockade therapy followed by finasteride maintenance appears to be a promising alternative for the management of patients with clinically localized or locally advanced prostate cancer. Further study of this approach is warranted. *The Oncologist* *2001;6:177-182

INTRODUCTION

Current treatment options for clinically localized or locally advanced cancer of the prostate include radical prostatectomy, radiation therapy, brachytherapy, cryotherapy, or "watchful waiting" (i.e., surveillance). Approximately two-thirds of patients are treated with either prostatectomy or radiotherapy. Although local therapies are potentially curative, they are associated with long-term, often permanent, side effects, and to date none have been demonstrated to provide a statistically significant survival benefit compared with surveillance in prospectively randomized trials. In the only prospective randomized trial comparing placebo to radical prostatectomy plus placebo, the Veterans Administration Cooperative Urological Research Group failed to demonstrate an overall survival benefit with a median follow-up of 23 years for patients undergoing prostatectomy compared to patients receiving no initial treatment [1, 2]. Moreover, reported 10-year disease-specific survival rates for prostatectomy (88% to 93%) and external beam radiotherapy (66% to 86%) are not different from those reported for surveillance (84% to 85%) [3, 4]. The curative potential of surgery or radiation has been further called into question by measurements of prostate-specific antigen (PSA), which indicate persistent or recurrent disease in up to 27% to 53% of patients treated for clinically localized prostate cancer [5-7]. This implies that only a limited number of patients treated with local therapy will enjoy long-term PSA failure-free survival. For men presenting with known adverse risk factors such as Gleason

Correspondence: Robert L. Leibowitz, M.D., Compassionate Oncology Medical Group, 2080 Century Park East, #601, Los Angeles, California 90067, USA. Telephone: 310-229-3555; Fax: 310-229-3554; e-mail: help@drsteventucker.com *Received October 18, 2000; accepted for publication January 4, 2001.*

scores [8-10], PSA values greater than 10 ng/ml, or locally advanced disease and treated with radical prostatectomy or radiotherapy, the 5-year PSA biochemical failure-free survival is only between 21% and 32% [7-9]. Sensitive PSA assays, including reverse-transcriptase polymerase chain reaction for PSA, suggest that a large proportion of patients with clinically localized disease have occult micrometastatic disease in peripheral blood, lymph nodes, and/or bone marrow prior to prostatectomy [10-14]. Given these data and the well-documented morbidity associated with surgery and radiation, including impotence and urinary incontinence, the clinical benefit of local therapy for prostate cancer continues to be debated.

Combination hormone blockade has been suggested as an option in the management of patients with clinically localized or locally advanced prostate cancer. The combination of the 5-alpha-reductase inhibitor finasteride and a pure antiandrogen such as flutamide (Eulexin®, Schering-Plough Corporation; Kenilworth, NJ) is an effective form of androgen blockade. Finasteride inhibits the intraprostatic conversion of testosterone to 5-alpha-dihydrotestosterone, whereas flutamide blocks the interaction of androgens with their cytoplasmic receptors [5]. The advantage of this combination over traditional hormone therapy (e.g., chemical or surgical orchiectomy) is that it does not affect plasma concentrations of testosterone, thereby maintaining potency and quality of life. Long-term treatment (i.e., four years) with finasteride monotherapy has been shown to produce continuous improvement in PSA over time in patients with benign prostatic hyperplasia in the PLESS Study Group trial [15], and finasteride in combination with flutamide has been shown to substantially decrease PSA levels in patients with metastatic prostate cancer [16].

Antiandrogens are typically used in combination with luteinizing hormone-releasing hormone (LHRH) super-agonists such as leuprolide or goserelin. This combination has been shown to provide a substantial survival benefit in patients with metastatic prostate cancer compared with an LHRH agonist or orchiectomy alone [17-19]. While these studies suggest a benefit for combined androgen blockade, other well-designed studies dispute the benefit including four large meta-analyses [17, 20-24]. Some authors suggest that patients with minimal disease burden receive a more pronounced survival benefit with combined androgen ablation [19, 25, 26]. In patients with localized or locally advanced prostate cancer, long-term treatment with flutamide plus an LHRH agonist reduced PSA to undetectable levels in 39 of 46 (85%) patients with stage T2 and T3 disease who were treated continuously for a median of 7.2 and 9.9 years, respectively [27].

The triple combination of an LHRH agonist, an antiandrogen, and finasteride has also recently been studied in patients with localized prostate cancer [28, 29]. In this trial, 59 patients were randomized to an LHRH agonist plus an antiandrogen with or without the addition of finasteride. Finasteride was added both as part of the three-drug induction regimen and maintenance therapy. Patients who received the three-drug combination plus finasteride maintenance had a significantly shorter median time to undetectable PSA (three versus five months; $p = .0095$) and a significantly longer median time to relapse, defined as PSA increase to ≥2.5 ng/ml (34 versus 19 months; $p = .013$). These data suggest that this three-drug combination androgen-blockade regimen may be a highly effective alternative to prostatectomy, radiotherapy, or watchful waiting for the treatment of localized prostate cancer.

We have treated 110 consecutive patients who presented with clinical stage T1 to T3 prostate cancer and refused local therapy with this three-drug combination androgen-blockade regimen in a community-based medical oncology practice. Preliminary results suggest that the majority of patients maintain long-term, stable, low PSA levels following triple androgen blockade therapy with finasteride maintenance.

Materials and Methods

Patients

The records of 110 consecutive patients presenting with clinical stage T1 to T3 prostate cancer and treated between June 1990 and June 1999 were retrospectively reviewed. All patients had biopsy-proven adenocarcinoma of the prostate; biopsies were performed and interpreted at each patient's local institution. Routine staging with bone scans, magnetic resonance imaging, computer tomography, and/or indium-111 capromab pendetide (ProstaScint®; Cytogen Corporation; Princeton, NJ) was not performed. Any patient with clinical evidence of metastatic disease was excluded from study. Patients were not surgically staged to differentiate clinically localized (stage T1 and T2) from locally advanced (stage T3) disease, nor were baseline scans routinely ordered. No patient had undergone any form of local therapy. All patients, in fact, refused local therapy and were offered triple androgen blockade therapy. Patients were informed of the risks, benefits, and alternatives to hormone blockade before therapy was initiated.

Treatment

Patients were treated with an LHRH agonist (either leuprolide acetate [7.5 mg] or goserelin acetate [3.6 mg] every 28 days) plus an antiandrogen (either flutamide [750 mg] or bicalutamide [150 mg] daily) plus finasteride (5 mg daily) for a median of 13 months [30]. Induction therapy was followed by maintenance therapy with finasteride (5 mg daily) for an indefinite period.

Table 1. Baseline patient demographics

	Mean	Standard error	Range	*n*
Age (years)	67.0	0.8	51-86	110
Gleason score	6.6	0.1	4-10	110
Serum PSA (ng/ml)	13.2	1.2	0.39-100	110
Serum testosterone (ng/dl)	373.0	n.a.	154-819	54

Efficacy variables included: A) PSA levels; B) time to achieve undetectable PSA level (defined as ≤0.1 ng/ml), and C) disease-specific survival. Measurements of PSA were made at 3-month intervals or less during treatment with triple androgen blockade and at approximately 3-month intervals during maintenance therapy. Blood samples were assayed for PSA at our clinic or by local community laboratories. The AIA® 600 immunoassay analyzer (Tosoh Medics, Inc.; South San Francisco, CA) was used at our clinic, which employed a two-site immunoenzymetric assay and Tosoh AIA-PACK methodology. Baseline and follow-up testosterone levels were also measured at 3-month intervals until testosterone levels reached baseline levels or a plateau. Testosterone was also measured during finasteride maintenance to assess androgen recovery.

At the majority of patient visits, clinical symptoms and adverse effects were recorded. In addition, complete blood counts and comprehensive chemistry panels including liver function tests were performed.

Results

Patients

Baseline patient characteristics are shown in Table 1 for 110 consecutive patients who completed treatment by May 2000. The median age was 67 years (range, 51 to 86 years), and the mean Gleason score was 6.6 ± 0.1 (range, 4-10). The mean baseline PSA level was 13.2 ± 1.2 ng/ml (range, 0.39-100 ng/ml). Mean baseline serum testosterone level was available in 54 patients and was 373 ng/dl (range, 154-819 ng/dl). Table 2 summarizes the Gleason score, clinical stage, and PSA risk group (PSA <10, 10-20, and >20 ng/ml) for men receiving triple androgen blockade. Forty-four percent of patients had clinical stage T1c and 40% of patients had clinical stage T2a. Patients with higher stages (T2b/T3) comprised 16% of the study population. Fifteen patients had Gleason scores of 8 to 10; 25 patients had PSA 10-20; and 20 patients had a baseline PSA >20. The mean PSA for patients presenting with a baseline PSA greater than 20 was 35 ng/ml.

Efficacy

The median duration of triple androgen blockade therapy was 13 months. All 110 patients in this series achieved undetectable PSA levels (≤0.1 ng/ml). The median time to achieve undetectable PSA was 3 months (range, 1-10 months).

With a median follow-up of 36 months from the start of hormone blockade therapy, the majority of patients have maintained low PSA levels. As shown in Table 3, the mean PSA level for the entire cohort is 1.3 ± 0.1 ng/ml (range, 0-11.0 ng/ml). Eighty-five patients have now been off triple hormone blockade therapy for ≥12 months and have a mean PSA level of 1.6 ± 0.1 ng/ml. These men continue to receive finasteride 5 mg daily. For the first 57 patients who completed therapy, the mean PSA level is 1.88 ± 0.1 ng/ml at a median follow-up of 55 months (range, 38-125 months). Only 9 out of 110 patients (8%) have a PSA level ≥4.0 ng/ml. Moreover, six of eight patients who have been off therapy for >5 years have maintained stable low PSA levels without relapse. As of May 2000, no patient in this series has required further treatment.

Disease-specific survival is 100%. Although 10 patients have died, none of these deaths were considered to have resulted from prostate cancer or a treatment-related

Table 2. Clinical characteristics of 110 men treated with triple androgen blockade

Clinical stage		Gleason score		PSA risk group	
T1c	44%	4-6	51%	<10	59%
T2a	40%	7	34%	10-20	23%
T2a/T3	16%	8-10	15%	>20	18%

Table 3. Post-treatment PSA levels

	Mean PSA(ng/ml)	Standard error	Range (ng/ml)	Median follow-up (months)	*n*
All patients off treatment	1.30	0.1	0-11.0	36	110
Patients off treatment ≥12 months	1.60	0.1	0-11.0	42	85
Patients off treatment ≥24 months	1.88	0.1	0-11.0	55	57

Table 4. Baseline and post-treatment testosterone values

	Testosterone	Range	*n*
Baseline	373	154-819	54
Patients off treatment ≥12 months	412	9-942	91

complication. In each case, prostate cancer was reported by the local attending physician to be controlled and in remission.

Safety and Toxicity

Nearly all patients reported adverse events typically associated with hormone blockade therapy, including hot flashes, loss of libido, and loss of potency; however, these side effects resolved in nearly all patients on discontinuation of hormone blockade. No unexpected adverse events were reported. Return of testosterone to greater than 180 was attained by all men who had a normal baseline testosterone level; the mean pretreatment testosterone level was 373 (n = 54); the mean post-treatment testosterone level is 412 ng/dl (range, 9-942 ng/dl; n = 91) among patients who have been off treatment for ≥12 months. Available testosterone data are summarized in Table 4.

Discussion

The results observed in this series indicate that patients with clinically localized or locally advanced prostate cancer can achieve undetectable PSA levels with short-term triple androgen blockade and maintain stable low PSA levels with finasteride maintenance. The advantage of finasteride maintenance is that it may prolong time to relapse [29]. Despite the retrospective nature of this study and the relatively short duration of follow-up, these results are provocative and, in conjunction with other published reports, support a reassessment of currently accepted approaches to the treatment of localized prostate cancer.

The clinical benefits of androgen blockade therapy appear to be greatest when patients are treated early. This conclusion is supported by a study in patients with locally advanced or asymptomatic metastatic disease that showed early intervention with hormone blockade was more effective than deferred intervention [31]. *Messing et al*. [32] also reported that immediate hormone blockade therapy following radical prostatectomy in pathologically node-positive patients significantly prolongs survival compared with either observation or delayed hormone therapy. This suggests that men with low tumor burden might be expected to have prolonged survival with the early use of hormone blockade and supports the rationale for use in localized disease.

Labrie has reported that combined hormone blockade is highly effective in controlling clinically localized or locally advanced prostate cancer [27]. In 46 patients with stage T2 to T3 prostate cancer treated only with an LHRH agonist plus flutamide for a median of 7 to 10 years, all patients achieved and maintained undetectable PSA levels; PSA failure occurred in only seven (15%) patients (two patients with stage T2 disease and five patients with T3 disease) after a median of 3 years. Moreover, *Strum et al*. have recently reported that intermittent androgen deprivation with an antiandrogen, an LHRH agonist, and finasteride (given during induction therapy and as maintenance) resulted in significantly prolonged time off intermittent androgen blockade in patients with clinically localized prostate cancer; only 5 of 27 (19%) patients required retreatment after a median of 36 months [28, 29].

Unlike the regimen described by *Strum et al*., we have used triple androgen blockade with finasteride maintenance for all our patients. Additionally we recommend utilizing "high-dose" bicalutamide,150 mg orally all at one time daily, rather than the 50 mg daily as used by *Strum*. Pharmacodynamic studies of bicalutamide demonstrate an increasing PSA response with higher dosing [33]. Studies suggest bicalutamide monotherapy at 150 mg daily may be equivalent to surgical castration or dual androgen blockade, and is associated with fewer side effects such as hot flashes, sexual interest, and physical capacity [34-36].

Thus far, none of our patients treated with this regimen have required retreatment with hormone blockade. Recurrences to PSA ≥ 4.0 ng/ml have occurred in 8% of patients (9/110), consistent with what others have observed [27, 29]. Follow-up PSA levels appear to have reached a stable PSA plateau in the majority of patients. However, if a patient experienced a progressive increase in PSA levels and his PSA was at or above pretreatment levels, retreatment with hormone blockade should be considered. Patients with PSA levels greater than 10 ng/ml may be candidates for further therapy.

Although PSA levels increased in nearly all patients when hormone blockade therapy was discontinued, one cannot assume that the relatively low levels of PSA observed in these patients result from residual or occult metastatic prostate cancer cells. At least some of this PSA is likely to originate from normal prostate-gland cells, as all of the men in this series still have their prostate glands intact. Therefore, as testosterone levels recover, as was the case in nearly all patients, normal prostate-gland cells will be stimulated to produce PSA. Remarkably, 18 patients (16%) in this series continue to have PSA levels less than 0.1 ng/ml, and seven of these patients have documented testosterone recovery to normal levels.

A particular benefit of the approach described here is its tolerability. The morbidities associated with radical prostatectomy or other forms of local treatment can substantially affect quality of life and are often permanent. While on

treatment most men reported loss of libido and potency as well as the occurrence of hot flashes. Surprisingly, six men in this series remained sexually active throughout the entire treatment period. No patients developed urinary incontinence or leakage. Approximately 25% of patients complained of some or all of the so-called "androgen deprivation syndrome" symptoms [37], including hot flushes, mood swings, mild arthralgias, and mild gynecomastia. Mild to moderate reductions in maximal athletic stamina were subjectively reported in our patients. These androgen deprivation symptoms generally resolved within a few months of testosterone recovery. With recovery of androgen production, patients reported an improved overall sense of well-being. Approximately 5% of patients reported persistent loss of libido and/or potency. While on therapy and during the testosterone recovery period, the use of Viagra® often improved sexual function and restored potency.

Conclusion

The current series has demonstrated that a single cycle of 13 months of triple androgen blockade followed by finasteride maintenance therapy yielded promising preliminary results. Since the median follow-up is short, it is premature to form definitive conclusions about triple androgen blockade with finasteride maintenance as primary therapy for localized prostate cancer. Nevertheless, 57 patients have now been followed for a median of 55 months without requiring a second cycle of androgen blockade. If these results can be confirmed in prospective randomized clinical trials, it may suggest a new paradigm for the treatment of clinically localized or locally advanced prostate cancer.

Acknowledgment

We would like to express our gratitude to *Joni* and *Howard Miller* for their assistance in data management and preparation of this manuscript.

References

1 Byar DP. Proceedings: The Veterans Administration Cooperative Urological Research Group's studies of cancer of the prostate. Cancer 1973;32:1126-1130.

2 Iversen P, Madsen PO, Corle DK. Radical prostatectomy versus expectant treatment for early carcinoma of the prostate. Twenty-three year follow-up of a prospective randomized study. Scand J Urol Nephrol Suppl 1995;172:65-72.

3 Middleton RG, Thompson IM, Austenfeld MS et al. Prostate Cancer Clinical Guidelines Panel Summary report on the management of clinically localized prostate cancer. The American Urological Association. J Urol 1995;154:2144-2148.

4 Oesterling JE, Fuks Z, Lee CT et al. Cancer of the prostate. In: DeVita VT, Hellman S, Rosenberg SA, eds. Cancer Principles and Practice of Oncology (ed 5). Philadelphia: Lippincott-Raven, 1997:1322-1386.

5 Moul JW. Prostate specific antigen only progression of prostate cancer. J Urol 2000;163:1632-1642.

6 Pound CR, Partin AW, Eisenberger MA et al. Natural history of progression after PSA elevation following radical prostatectomy. JAMA 1999;281:1591-1597.

7 van den Ouden D, Hop WC, Schroder FH. Progression in and survival of patients with locally advanced prostate cancer (T3) treated with radical prostatectomy as monotherapy. J Urol 1998;160:1392-1397.

8 Roach M, Weinberg V, McLaughlin P et al. Does pretreatment PSA add to predicting long term survival from prostate cancer? In: Perry MC, ed. Proceedings of the American Society of Clinical Oncology 36th Annual Meeting. New Orleans, Louisiana, 2000:1282.

9 Fichtner J. The management of prostate cancer in patients with a rising prostate-specific antigen level [In Process Citation]. BJU Int 2000;86:II-III.

10 Melchior SW, Corey E, Ellis WJ et al. Early tumor cell dissemination in patients with clinically localized carcinoma of the prostate. Clin Cancer Res 1997;3:249-256.

11 Gao CL, Dean RC, Pinto A et al. Detection of circulating prostate specific antigen expressing prostatic cells in the bone marrow of radical prostatectomy patients by sensitive reverse transcriptase polymerase chain reaction. J Urol 1999;161:1070-1076.

12 Mejean A, Vona G, Nalpas B et al. Detection of circulating prostate derived cells in patients with prostate adenocarcinoma is an independent risk factor for tumor recurrence. J Urol 2000;163:2022-2029.

13 Okegawa T, Nutahara K, Higashihara E. Detection of micrometastatic prostate cancer cells in the lymph nodes by reverse transcriptase polymerase chain reaction is predictive of biochemical recurrence in pathological stage T2 prostate cancer. J Urol 2000;163:1183-1188.

14 Okegawa T, Noda H, Kato M et al. Value of reverse transcription polymerase chain reaction assay in pathological stage T3N0 prostate cancer. Prostate 2000;44:210-218.

15 Roehrborn CG, Boyle P, Bergner D et al. Serum prostate-specific antigen and prostate volume predict long-term changes in symptoms and flow rate: results of a four-year, randomized trial comparing finasteride versus placebo. PLESS Study Group. Urology 1999;54:662-669.

16 Kirby R, Robertson C, Turkes A et al. Finasteride in association with either flutamide or goserelin as combination hormonal therapy in patients with stage M1 carcinoma of the prostate gland. International Prostate Health Council (IPHC) Trial Study Group. Prostate 1999;40:105-114.

17 Denis LJ, Keuppens F, Smith PH et al. Maximal androgen blockade: final analysis of EORTC phase III trial 30853.

EORTC Genito-Urinary Tract Cancer Cooperative Group and the EORTC Data Center. Eur Urol 1998;33:144-151.

18 Dijkman GA, Janknegt RA, De Reijke TM et al. Long-term efficacy and safety of nilutamide plus castration in advanced prostate cancer, and the significance of early prostate specific antigen normalization. International Anandron Study Group [see comments]. J Urol 1997;158:160-163.

19 Crawford ED, Eisenberger MA, McLeod DG et al. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma [published erratum appears in N Engl J Med 1989;321:1420]. N Engl J Med 1989;321:419-424.

20 Maximum androgen blockade in advanced prostate cancer: an overview of 22 randomised trials with 3283 deaths in 5710 patients. Prostate Cancer Trialists' Collaborative Group. Lancet 1995;346:265-269.

21 Bertagna C, De Gery A, Hucher M et al. Efficacy of the combination of nilutamide plus orchidectomy in patients with metastatic prostatic cancer. A meta-analysis of seven randomized double-blind trials (1056 patients). Br J Urol 1994;73:396-402.

22 Caubet JF, Tosteson TD, Dong EW et al. Maximum androgen blockade in advanced prostate cancer: a meta-analysis of published randomized controlled trials using nonsteroidal antiandrogens. Urology 1997;49:71-78.

23 Schmitt B, Bennett C, Seidenfeld J et al. Maximal androgen blockade for advanced prostate cancer. Cochrane Database Syst Rev 2000;2:CD001526.

24 Eisenberger MA, Blumenstein BA, Crawford ED et al. Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. N Engl J Med 1998;339:1036-1042.

25 Denis LJ, Carnelro de Moura JL, Bono A et al. Goserelin acetate and flutamide versus bilateral orchiectomy: a phase III EORTC trial (30853). EORTC GU Group and EORTC Data Center. Urology 1993;42:119-129; discussion 129-130.

26 Sarosdy MF, Schellhammer PF, Johnson R et al. Does prolonged combined androgen blockade have survival benefits over short-term combined androgen blockade therapy? Urology 2000;55:391-395; discussion 395-396.

27 Labrie F, Cusan L, Gomez JL et al. Long-term combined androgen blockade alone for localized prostate cancer. Mol Urol 1999;3:217-226.

28 Strum S, McDermed J, Madsen L et al. Intermittent androgen deprivation (IAD) with finasteride (F) given during the induction and maintenance periods results in prolonged time off IAD in patients with localized prostate cancer (LPC). In: Perry MC, ed. Proc Am Soc Clin Oncol 1999:353a.

29 Strum SB, Scholz MC, McDermed JE. Intermittent androgen deprivation in prostate cancer patients: factors predictive of prolonged time off therapy. Oncologist 2000;5:45-52.

30 Leibowitz RL. Hormone blockade as the sole treatment of clinical stages T1-T3 prostate cancer: experience in 100 patients. In: Perry MC, ed. Proc Am Soc Clin Oncol 2000:377a.

31 Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council Trial. The Medical Research Council Prostate Cancer Working Party Investigators Group. Br J Urol 1997;79:235-246.

32 Messing EM, Manola J, Sarosdy M et al. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. N Engl J Med 1999;341:1781-1788.

33 Kolvenbag GJ, Nash A. Bicalutamide dosages used in the treatment of prostate cancer. Prostate 1999;39:47-53.

34 Boccardo F, Rubagotti A, Barichello M et al. Bicalutamide monotherapy versus flutamide plus goserelin in prostate cancer patients: results of an Italian Prostate Cancer Project study [see comments]. J Clin Oncol 1999;17:2027-2038.

35 Iversen P, Tyrrell CJ, Kaisary AV et al. Bicalutamide monotherapy compared with castration in patients with nonmetastatic locally advanced prostate cancer: 6.3 years of followup [In Process Citation]. J Urol 2000;164:1579-1582.

36 Tyrrell CJ, Kaisary AV, Iversen P et al. A randomised comparison of 'Casodex' (bicalutamide) 150 mg monotherapy versus castration in the treatment of metastatic and locally advanced prostate cancer. Eur Urol 1998;33:447-456.

37 McDermed J, Strum S, Scholz M. The androgen deprivation syndrome (ADS): the incidence and severity in prostate cancer (PC) patients (PTS) receiving hormone blockade (HB). In: Perry MC, ed. Proc Am Soc Clin Oncol 1998:316a.