

Maximal androgen blockade: facts and fallacies

L J Denis

Oncology Centre Antwerp, Apartment 2, Blok H, Lange Gasthuisstraat 35-37, 2000 Antwerp, Belgium

Prostate cancer in its natural course is a single, biological process with an unusually slow but constant growth. This growth can be temporarily arrested by endocrine treatment but there are proven data that the clinical stage and grade of the tumor, as well as a number of other prognostic factors, define the outcome of the disease independently of a given treatment (Denis 1993).

It is a fine point to know that the landmark publication by Huggins and Hodges (1941) on the effect of estrogens, castration, and androgens on serum phosphatases in metastatic carcinoma of the prostate claimed no more than a decrease of these serum markers as well as a net relief of pain in patients with symptomatic, widespread clinical prostate cancer. However, this publication led to the widespread use and abuse of diethylstilbestrol (DES), bilateral orchiectomy, or both. The equivalent efficacy of 5 mg DES and surgical castration was demonstrated in a large, randomized trial (Nesbit & Baum 1995), but it took a number of trials, the famous VACURG studies, to demonstrate the lethal side-effects of estrogens (Blackard 1975).

Now, more than half a century later, we know that prostate cancer growth is partly dependent on androgens, with the dihydrotestosterone-androgen receptor complex (DHT-AR) regulating the gene expression. We also know that androgens are essential, but not directly or solely responsible, for cellular proliferation of prostate cancer cells. The homeostasis of the organ is secured by a balance between the growth and inhibiting factors. We also know that all endocrine treatment is based on the withdrawal or blockade of androgen stimulation from the androgen receptors in the prostate cells, with a subsequent temporary arrest of the cancer growth in about 60% of all treated cases. The happy clinician only remembers that the subjective response in symptomatic cases can reach up to 80% of all treated cases, making endocrine treatment the first primary choice treatment in these men. The marker response on prostate specific antigen (PSA) drives the clinician to ecstasy, since endocrine treatment is able to lower the serum values of these markers in up to 90% of treated patients.

Once again, history repeated itself and, instead of concentrating on why 20% to 40% of the patients did not show objective response to endocrine treatment, extensive

clinical research followed the easy road and sustained a wide array of first-line endocrine treatments utilized in daily practice to palliate symptomatic prostate cancer, while at the same time hoping to prolong the time to progression or, even better, to decrease the mortality due to prostate cancer. The scheme of routinely used endocrine treatments is listed in Table 1. It is regrettable that clinical practice completely abandoned DES treatment and adequate randomized, prospective trials were never performed after the publication of the cardio-vascular complications associated with its use.

The Urological Group of the European Organization for Research and Treatment of Cancer (EORTC GU Group) followed the same cautious path, even after demonstrating that the response rates for DES (3 mg/per day) were the highest compared with medroxy-progesterone acetate and cyproterone acetate in two randomized protocols (30761 and 30762) (Pavone-Macaluso *et al.* 1986, Smith *et al.* 1986).

Instead, they followed the reported results of Bracci (1979), who noted an improved response and outcome of patients with advanced prostatic cancer when cyproterone acetate (CPA) treatment was combined with bilateral orchiectomy. The Group decided to gamble on the combination treatment and in the EORTC study 30805 bilateral orchiectomy, the then 'gold standard', was compared with DES (1 mg/per day), and with bilateral orchiectomy and CPA (50 mg 3 times per day). No difference in time to progression and overall survival was noted between the three treatment arms. Once again, the final analysis demonstrated that the outcome of the disease was determined more by the initial prognostic factors than by the allocated treatment (Robinson *et al.* 1995). With the

Table 1 First-line endocrine treatments in clinical use

Androgen withdrawal	
Surgical castration	Bilateral orchiectomy (subcapsular, subepididymal)
Medical castration	Estrogens, progesterones, LHRH analogues, antagonists
Androgen blockade	
Steroidal anti-androgens	Cyproterone, chlormadinone, megestrol
Non-steroidal anti-androgens	Flutamide, nilutamide, bicalutamide

Table 2 EORTC 30853 – measured advantages for MAB treatment over castration

Parameters (time to:)	P value	Hazard ratio	95% CI
Subjective progression	0.009	0.67	0.50-0.90
Objective progression	0.008	0.64	0.46-0.89
First progression	0.002	0.64	0.49-0.84
Death	0.02	0.73	0.56-0.95
Death from cancer	0.007	0.67	0.49-0.90

CI, confidence interval

development of the luteinizing hormone-releasing hormone agonist (LHRH A), a reliable medical castration which was reversible became available and became the preference of patients as the first primary treatment for prostate cancer. The equivalence of the subjective and objective response rates and time to treatment failures between LHRH A and bilateral orchiectomy or estrogens (3 mg/per day) was confirmed in randomized trials and paved the way for the widespread use of medical castration (The Leuprolide Study Group 1984, Kaisary *et al.* 1991).

The immediate popularity of the LHRH A was somewhat offset by the clinical side effects of the physiological burst of testosterone which occurred in some patients after the initial injection. This prompted the need for a temporary association with an anti-androgen for a few weeks, and the first real indication for combination treatment was established (Schulze & Senge 1990).

The EORTC GU Group launched a second randomized trial on combination treatment, this time comparing an LHRH A arm with CPA given only for the first two weeks, LHRH A with long term CPA, and bilateral orchiectomy. Again, no difference was shown between the three arms for response rate, time to progression, and duration of survival. These results were confirmed after a ten-year follow-up review (de Voogt *et al.* 1998).

The newly developed non-steroidal anti-androgen, flutamide, received a more spectacular welcome in the clinical field. Not only did Sogani *et al.* (1984) describe excellent results with flutamide in monotherapy, but also unbelievably successful results were reported for the ‘total or complete androgen blockade’, based on phase II studies

combining a non-steroidal anti-androgen (first nilutamide and later flutamide) with an LHRH A agent (Labrie *et al.* 1983, Sogani *et al.* 1984). This development of the combination treatment led to one of the great controversies in urological oncology and, 27 randomized trials later, we are still debating the clinical value of the combination treatment.

The controversy was started on the one hand by the skepticism within the EORTC GU Group after two failed randomized trials and on the other hand by the enthusiasm for the combination treatment in other study groups boosted by the landmark trial of the US International 0036 (Crawford *et al.* 1989). This prompted the EORTC GU Group to use a two-pronged approach. First, a third phase III two arm trial (EORTC 30853) was launched comparing bilateral orchiectomy with LHRH A and flutamide and secondly, a decision was taken to organize a series of workshops to discuss the issues and launch a metaanalysis of all reported phase III trials in the hope of coming to a consensus conclusion.

Surprisingly, the EORTC 30853 trial, run with extensive quality control, 21 objective and subjective parameters of progression and 6 independent committees to monitor pathology, endocrine results, bone scan, response criteria, quality of life and PSA evaluation, resulted in a statistical advantage for combination treatment by faster response on markers, increased progression-free survival, overall survival and more specifically a decreased death rate due to prostate cancer. The advantages of the combination treatment in protocol EORTC 30853 in terms of P values, hazard ratios, and confidence intervals after a median follow-up of 5 years are shown in Table 2 (Denis *et al.* 1993).

Three workshops in collaboration with the American Cancer Society, the EORTC and the International Prostate Health Council (Table 3) established the feasibility of a metaanalysis based on the collected data. It also brought some common sense to the discussion and the exalted term of ‘total or complete androgen blockade’ was replaced by ‘maximal androgen blockade’ (MAB) in Europe and ‘combined androgen blockade’ (CAB) in the US. The conclusions of the third workshop are summarized in Table 4 (Denis & Murphy 1993). A second report on the metaanalysis published by the Prostate Cancer Trialists’ Collaborative Group (1995) showed a 9% decrease in the

Table 3 Workshops leading to the organization of an overview (meta-analysis) of MAB treatment in prostate cancer

Date	Venue	Organization	Purpose
1989	Atlanta, USA	American Cancer Society (ACS)	Comparability of 4 MAB trials
1990	Paris, France	European Organization for Research and Treatment of Cancer Genito-Urinary Tract Co-Operative Group (EORTC GU Group)	Feasibility of an overview
1992	Paris, France	International Prostate Health Council (IPHC)	Organizing an overview

Table 4 Prerequisites for a meta-analysis of MAB trials: conclusions of MAB Workshop III

1. Prognostic factors must be analyzed before initiating therapy
2. Carefully designed, statistical analysis is a prerequisite for success
3. The initial definition of the aims and endpoints of trials will increase reliability
4. Response and time to progression, as well as quality of life in the perception of the patient, is a secondary but vital element in any clinical decision
5. Preliminary results should not be published on the endpoints if statistical relevance is not reached
6. A monitoring committee, not participating in the trial, should evaluate interim results
7. For progress to be made in this overview effort, both patience and more data are needed

annual reports of deaths in the patients treated with flutamide ($P=0.09$) compared with a 2% increase in deaths in patients on CPA, both combined with testicular androgen ablation.

This road from basic simplicity to confusing complexity was not helped by the negative results of a long awaited statistical analysis of 1300 patients in a randomized INT 0105 trial to confirm or refute the advantage of MAB in patients with prostate cancer. This complexity again led clinical research into different, diverging ways. The first is followed by those who believe that a more careful analysis will show an advantage for MAB (Caubet *et al.* 1997). The second continues to study the equivalent efficacy of different combinations, and a double-blind study of 813 patients with metastatic prostate cancer treated with a combination of bicalutamide and LHRH A as compared with flutamide and LHRH A therapy showed similar results regarding progression and survival (Schellhammer *et al.* 1997). The third way is to consider this stalemate as an excellent time to try out other combinations such as estrogens and CPA, finasteride and flutamide, or comparing treatment times as neo-adjuvant or adjuvant endocrine treatment, or, last but not least, early versus delayed or intermittent treatment. The point being made is that we probably have to pay more attention to the quality of life, which is not very well studied in trials with prostate cancer, versus the mathematical endpoint of death by prostate cancer or by concomitant diseases. The fourth way is the realization that, for the time being, we are unable to classify patients with different prognostic factors in one treatment setting. A very important and practical prognostic factor is the immediate response to endocrine treatment based on the decrease of the initial PSA (Oosterlinck *et al.* 1997, Sylvester *et al.* 1998).

Conventional wisdom tells us that all of these directions have a point. The most important fact is that

there is probably a small statistical difference in favor of the MAB treatment in some patients with prostate cancer. This is reversed by the price of submitting to the side-effects of two drugs and the possibility that a non-steroidal anti-androgen just in the patients that may profit from the combination for a long time have to face the possibility of agonist effects of these agents mediated through mutant androgen receptors (Scher & Kolvenbag 1997).

The bottom line is that the small increase in benefit, even in survival, from adding an anti-androgen to monotherapy carries the burden of serious long-term side-effects such as anemia, osteoporosis, and depression among many others. Tailored treatment for the individual patient means that all the options, including monotherapy with anti-androgens and intermittent treatment, have to be discussed, but the patient has to realize that endocrine treatment really starts in earnest after initiation of therapy allowing for a period of evaluation of treatment response. A periodic three-month clinical evaluation of the progression or arrest of the disease process should be considered as a safeguard for the patient during endocrine treatment.

References

- Blackard CF 1975 The Veterans Administration Cooperative Urological Research Group studies of carcinoma of the prostate: a review. *Cancer and Chemotherapy Reports* **59** 225-232.
- Bracci U 1979 Anti-androgens in the treatment of prostatic cancer. *European Urology* **5** 303-306.
- Caubet JF, Tosteson TD, Dong EW, Naylon EM, Whiting GW, Ernstoff MS & Ross SD 1997 Maximum androgen blockade in advanced prostate cancer: a meta-analysis of published randomized controlled trials using nonsteroidal anti-androgens. *Urology* **49** 71-78.
- Crawford ED, Eisenberger MA, McLeod DG, Spaulding JT, Benson R, Dorr FA, Blumenstein BA, Davis MA & Goodman PJ 1989 A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. *New England Journal of Medicine* **321** 419-424.
- Denis LJ 1993 Staging and prognosis of prostate cancer. *European Urology* **24** 13-19.
- Denis L & Murphy GP 1993 Overview of phase III trials on combined androgen treatment in patients with metastatic prostate cancer. *Cancer* **72** 3888-3895.
- Denis LJ, Whelan P, Carneiro de Moura JL, Newling D, Bono A, De Pauw M, Sylvester R & Members of the EORTC GU Group and EORTC Data Center 1993 Goserelin acetate and flutamide versus bilateral orchiectomy: a phase III EORTC trial (30853). *Urology* **42** 119-129.
- Huggins C & Hodges CV 1941 Studies in prostate cancer. I. The effects of castration, of oestrogen, and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Research* **1** 293-297.

- Kaisary AV, Tyrell CJ, Peeling WB & Griffiths K 1991 Comparison of LHRH analogues with orchiectomy in patients with metastatic prostate cancer. *British Journal of Urology* **67** 502-508.
- Labrie F, Dupont A, Belanger A, Levebre FP, Cusan L & Raynaud JP 1983 New hormonal therapy in prostate cancer: combined use of a pure anti-androgen and an LHRH agonist. *Hormone Research* **20** 18-27.
- Nesbit RM & Baum WC 1995 Endocrine control of prostatic carcinoma. Clinical and statistical survey of 1818 cases. *Journal of the American Medical Association* **143** 1317-1320.
- Oosterlinck W, Mattelaer J, Casselman J & Van Velthoven R 1997 PSA evolution: a prognostic factor during treatment of advanced prostatic carcinoma with total androgen blockade. *Acta Urologica Belgica* **65** 63-71.
- Pavone-Macaluso M, de Voogt HJ, Viggiano G, Barasolo E, Lardennois B, De Pauw M & Sylvester R 1986 Comparison of diethylstilbestrol, cyproterone acetate and medroxy-progesterone acetate in the treatment of advanced prostatic cancer: final analysis of a randomised phase III trial of the EORTC GU Group. *Journal of Urology* **136** 624-631.
- Prostate Cancer Trialists' Collaborative Group 1995 Maximum androgen blockade in advanced prostate cancer: an overview of 22 randomised trials with 3283 deaths in 5710 patients. *The Lancet* **346** 265-269.
- Robinson MRG, Smith PH, Richards B, Newling DWW, De Pauw M & Sylvester R 1995 The final analysis of the EORTC GU Group phase III clinical trial (protocol 30805) comparing orchidectomy, orchidectomy plus cyproterone acetate and low dose stilboestrol in the management of metastatic carcinoma of the prostate. *European Urology* **28** 273-283.
- Schellhammer PF, Sharifi R, Block NL, Soloway MS, Venner PM, Patterson AL, Sarosdy MF, Vogelzang WJ, Schellhammer JJ & Kolvenbag GJCM 1997 Clinical benefits of bicalutamide compared with flutamide in combined androgen blockade for patients with advanced prostatic carcinoma: final report of a double-blind, randomized, multicenter trial. *Urology* **50** 330-336.
- Scher HI & Kolvenbag GJCM 1997 The antiandrogen withdrawal syndrome in relapsed prostate cancer. *European Urology* **31** 3-7.
- Schulze H & Senge T 1990 Influence of different types of anti-androgens on luteinizing hormone releasing hormone analogue-induced testosterone search in patients with metastatic carcinoma of the prostate. *Journal of Urology* **144** 934-941.
- Smith PH, Suci S, Robinson MRG, Richards B, Bastable JRG, Glashan RW, Bouffieux C, Lardennois B, Williams RE, De Pauw M & Sylvester R 1986 A comparison of the effect of diethylstilbestrol with low dose estramustine phosphate in the treatment of advanced prostatic cancer: final analysis of a phase III trial of the EORTC. *Journal of Urology* **136** 619-623.
- Sogani PC, Vagawara MR & Whitmore WF 1984 Experience with flutamide in patients with advanced prostatic cancer without prior endocrine therapy. *Cancer* **54** 744-750.
- Sylvester RJ, Denis L & de Voogt H, for the EORTC GU Group 1998 The importance of prognostic factors in the interpretation of two EORTC metastatic prostate cancer trials. *European Urology* **33** 134-143.
- The Leuprolide Study Group 1984 Leuprolide versus DES for metastatic prostate cancer. *New England Journal of Medicine* **311** 1281-1287.
- de Voogt HJ, Studer U, Schröder F, Klyn JG, de Paur M, Sylvester R & members of the EORTC GenitoUrinary tract Cancer Cooperative Group 1998 Maximum androgen blockade using LHRH A buserelin in combination with short term (two weeks) or long term (continuous) cyproterone acetate is not superior to standard androgen deprivation in the treatment of advanced prostate cancer. *European Urology* **33** 152-158.