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 medroxyprogesterone 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

<table>
<thead>
<tr>
<th>Androgen withdrawal</th>
<th>Surgical castration</th>
<th>Bilateral orchiectomy (subcapsular, subepididymal)</th>
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<tbody>
<tr>
<td>Medical castration</td>
<td>Medical castration</td>
<td>Medical castration</td>
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<tr>
<td>Androgen blockade</td>
<td>Steroidal anti-androgens</td>
<td>Cyproterone, chlormadinone, megestrol</td>
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<tr>
<td></td>
<td>Non-steroidal anti-androgens</td>
<td>Flutamide, nilutamide, bicalutamide</td>
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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 Voo 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).

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

<table>
<thead>
<tr>
<th>Date</th>
<th>Venue</th>
<th>Organization</th>
<th>Purpose</th>
</tr>
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<tbody>
<tr>
<td>1990</td>
<td>Paris, France</td>
<td>International Prostate Health Council (IPHC)</td>
<td>Organizing an overview</td>
</tr>
<tr>
<td>1992</td>
<td>Paris, France</td>
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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


de Voogt HJ, Studer U, Schröder F, Klyn JG, de Pauw 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.