Anti-Cancer Drugs, 4, pp. 301–309

Review paper

Update of hormonal treatment in cancer of the prostate

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Prostate carcinomas are heterogenous tumors composed of hormone sensitive and hormone insensitive cells. Although all androgens have an effect on prostatic cells, it is believed that dihydrotestosterone (DHT) is the active metabolite primarily utilized by prostatic cancer cells for growth and division. Hormonal therapies are therefore designed to lower tissue levels of DHT or prevent its binding to receptors on prostatic cancer cells. The Veterans Administration Cooperative studies in the 1960s and 1970s laid the groundwork for the use and timing of hormonal therapy. Until recently orchiectomy and estrogens were the two main alternatives, but new compounds such as luteinizing hormone releasing hormone analogs and antiandrogens have shown to be as effective and less toxic than estrogens. Today, important controversies concerning the selection of the best primary treatment and the timing of initiating the hormonal therapy still exist. Second line hormonal strategies are used, but they still have to prove their impact on overall survival.

Key words: Hormonal treatment, prostate cancer.

Introduction

Prostate cancer is one of the most common malignancies of the male population worldwide. In 1992 it was diagnosed more often than any other cancer in men in the US and it is estimated that it has caused the death of 32 500 people.[1]

This malignancy is rarely diagnosed before the fifth decade of life but increases in frequency between 60 and 80 years of age.[2] It has been estimated that the lifetime probability of developing prostate cancer is 9.6% in black men and 5.2% in white men within the US.[3] Jewett was among the first to demonstrate that patients with tumors confined to the prostate gland (stages A and B) undergoing radical prostatectomy had a survival comparable to that of age-matched controls without prostate cancer.[4] Unfortunately, at the time of diagnosis 50–60% of the patients are found to have advanced disease;[5] 30–40% of these men will have advanced local disease (stages C and D1) and the remainder will have distant metastases (stage D2).[6] For this group of patients no definite cure can be offered and it has been estimated that their median survival is 24–36 months.[7] The treatment for these patients with metastases is androgen withdrawal. Huggins and Hodges were the first to demonstrate, back in 1941, that androgen withdrawal decreases the levels of acid phosphatase and produces a significant tumor response in most patients.[8–10] Despite the fact that over 50 years have passed since this original observation, many controversies and unsolved dilemmas still exist concerning the implementation of hormonal treatment.

In this review paper we will refer to the different therapeutic options that are available in the armamentarium of the practising urologist.

First line hormonal treatment

Orchiectomy and estrogens

Bilateral orchiectomy and the oral administration of estrogens, usually diethyl-stilbestrol (DES), were the first and only options urologists had for almost three decades after the historical observation of Huggins and Hodges.[8] The main advantage of orchiectomy is that it reduces circulating testosterone levels to less than 50 ng/dl in a short time. Plasma luteinizing hormone (LH) and follicle stimulating hormone (FSH) are elevated because of the loss of normal feedback by gonadal steroids. Bilateral orchiectomy continues to be the 'golden standard' of hormonal therapy for metastatic

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prostate cancer, even today. The main drawback of this surgical procedure, apart from the loss of libido and erectile function, is the psychological trauma associated with castration. Some patients also complain of hot flushes but this side effect is usually transient and can be controlled with short-term use of 1 mg of DES daily or antiandrogens.

The main effect of estrogens is the suppression of LH release from the pituitary, consequently reducing testosterone synthesis and secretion by the testis.[11]

The first clinical trials performed in the late 1940s utilizing orchiectomy and estrogens concluded that hormonal therapy prolonged survival in patients with metastatic prostate cancer.[12–14] These studies were later criticized mainly because they were not randomized and because they did not use concurrent controls.

In the following 20 years the Veterans Administration Cooperative Urological Research Group (VACURG) performed three major studies in an effort to clarify the true biological and clinical effects of orchiectomy and estrogens. The first VACURG study, commenced in 1960 and published in 1967, was a randomized clinical trial including 2200 men.[15] The important conclusions of this study came from the 1764 patients with stage C and D who were divided into four treatment groups: (i) placebo, (ii) bilateral orchiectomy, (iii) 5 mg of DES per day and (iv) orchiectomy plus DES. Those patients in the placebo group who progressed would receive hormonal treatment, so this study evolved to be at the same time a comparison of early versus delayed hormonal treatment. The historical conclusions of this study are: (i) the combination of bilateral orchiectomy and DES does not offer any advantage over each treatment used alone, (ii) high dose (5 mg/day) DES is associated with a significant increase of cardiovascular complications and (iii) delayed hormonal treatment does not affect overall survival.

The second VACURG study was commenced in 1967 and showed that in patients with stage C and D disease a dose of 1 mg of DES was as effective as a dose of 5 mg and was significantly more effective than the dose of 0.2 mg or placebo in the prevention of death from prostatic cancer, without being associated with an increased frequency of cardiovascular mortality.[16]

The third VACURG study evaluated the efficacy of estrogens other than DES and concluded that there is no advantage in terms of overall survival of these other therapeutic modalities in comparison with 1 mg of DES per day.[17]

There is no doubt that the VACURG studies influenced the practice of urological oncology worldwide, but at the same time gave rise to certain invalid interpretations which will be discussed in a subsequent section of this article.

In concluding the discussion concerning the role of estrogens in the treatment of metastatic prostate cancer we can say that despite the negligible cost of DES, the cardiovascular side effects have severely limited its use in the US and Europe during recent years.

The LH releasing hormone agonists

The term gonadotropin releasing hormone (GnRH or LHRH) was given to the isolated hypothalamic decapeptide that stimulates the synthesis and release of LH and FSH from the pituitary.[18] After isolating this hormone, Schally went on synthesizing this compound[19] and later a series of analogs named agonists or superagonists were manufactured by different companies. The administration of an analog causes an initial increase in LH and then in serum testosterone. This increase in testosterone may cause worsening of pain (flare phenomenon) during the first 7–14 days of treatment. Pretreatment with a variety of antiandrogen compounds can block this flare phenomenon.[20] After the first 7–14 days it was found that LHRH analogs suppress pituitary release by a paradoxical desensitization (downregulation) of receptors in the pituitary. Eventually LH secretion from the anterior pituitary lobe is suppressed and as a result plasma testosterone levels are decreased to castrate levels for as long as the duration of therapy.[21] Leuprolide was the first LHRH analog studied in randomized clinical trials in the US. The leuprolide study group compared 3 mg/day of DES with a subcutaneous dosage of 1 mg/day of leuprolide and concluded that these two therapeutic regimens were equal in terms of both disease-free survival and overall survival.[22]

Numerous other reports have verified these results and have compared LHRH analogs with other hormonal regimens.[23,24] They all proved that LHRH agonist monotherapy is as effective as any classic hormonal therapy.

LHRH analogs do not produce the cardiovascular side effects associated with estrogens. Apart from impotence the flare effect is the major side effect and for this reason they should not be used alone in patients who have impending spinal cord compression. An advantage of these analogs

lies in the avoidance of the psychological effect of surgical castration.

Finally, it must be mentioned that these agents may be prohibitively expensive for some elderly patients in many countries.

Today many such agonists are available on the market and although they differ from a physicochemical point of view there is little reason to believe that one agonist is more effective than another.

The antiandrogens

These agents act at the cellular level and inhibit the binding of testosterone and dihydrotestosterone (DHT) in prostatic cells, and are classified into two groups: steroidal and non-steroidal.

Cyproterone acetate (CPA). CPA is a synthetic 21-carbon hydroxyprogesterone derivative whose most important action is the competitive inhibition of the binding of DHT to the cytosol androgen receptors preventing the translocation of this complex into the nuclear concentration of DNA.[25,26] At the same time CPA possesses progestational activities and thus inhibits gonadotrophin secretion and the production of testosterone. CPA was introduced in clinical practice by Scott and Schrimer in 1966, who observed a 70% objective response rate in a small number of previously untreated patients with metastatic disease.[27]

The European Organization of Research on Treatment of Cancer (EORTC) Genitourinary Group has conducted a thorough randomized phase III trial comparing CPA 250 mg/day, medroxyprogesterone acetate (MPA) 200 mg/day and DES 3 mg/day.[28] The final reports of this trial demonstrated that MPA was less efficient than CPA and DES as far as survival and time to progression are concerned, which were the same for CPA and DES. Cardiovascular side effects from CPA were less than half of those seen with DES treatment.

Wenderoth has performed a similar study in which he compared CPA, parenterally injected weekly in doses of 300 mg, to estadiol undecylate. No difference in clinical response among these two regimens was noted and again the side effects in the CPA-treated patients were much less.[29] In the past 10 years after the introduction of the concept of total androgen blockade by Labrie, which will be discussed later, CPA has often been used in combination with other antiandrogenic drugs. The EORTC Genitourinary Group has studied the additional effect of CPA on orchiectomy in trial 30805 by comparing orchiectomy versus orchiectomy plus CPA versus DES 1 mg/day. The final analysis demonstrated no difference in time to progression and survival among the three different groups.[30] In study 30843 the EORTC has also examined the combination of an LHRH analog, Buserelin, administered in combination with CPA 150 mg/day for 2 weeks versus orchiectomy and, again, no difference among the various therapeutic modalities was noted.[31] Numerous other studies have been performed with different combinations of antiandrogenic drugs including CPA and they all have in common the same response in objective and subjective regression.

Today, CPA is rarely used as monotherapy because of its cardiovascular complications seen in approximately 10% of treated men,[32,33] and because of its other adverse effects such as impotence,[34] infertility,[35] gynecomastia and breast tenderness.[36] It is frequently used in conjunction with LHRH agonists to block the flare phenomenon,[37,38] and it can also be used to suppress the hot flushes associated with orchiectomy and LHRH agonist therapy.[39,40]

Non-steroidal (pure) antiandrogens. Drugs that exclusively block the binding of DHT to its cytosol receptors, being devoid of any other endocrine effect, are called pure or non-steroidal antiandrogens.

Flutamide was the first pure antiandrogen discovered[41] and it has been shown that it is effective in the treatment of metastatic prostate cancer.[42,43] Since it is a non-steroidal antiandrogen, it does not lead to thromboembolism and since it does not suppress testicular function like CPA, it rarely causes loss of libido.[44] Gynecomastia is the most frequently reported side effect, and other toxicities include breast tenderness, diarrhoea, nausea, vomiting and liver function abnormalities which are reversible.[44]

Flutamide alone has been used in the treatment of prostate cancer and compared with DES[45] and estramustine phosphate.[46] The results obtained from these trials are not conclusive and somewhat contradictory, and this is due to the small number of patients included in these trials and to the lack of uniform criteria of response.

Flutamide, like most pure antiandrogens, inhibits the negative feedback of androgens at the pituitary level, resulting in rises of serum LH and testosterone levels. This peripheral rise of testost-

erone can hamper the antiandrogenic effect of flutamide in the target tissues.

Today the use of flutamide alone as a primary treatment for metastatic prostatic carcinoma is limited and its common use in total androgen blockade will be discussed later.

Nilutamide is another non-steroidal antiandrogen with some structural similarities to flutamide. It has a longer half-life of approximately 2 days. Toxicities reported have included nausea, alcohol intolerance, problems with light adaptation and interstitial pneumonitis.[48,49] All of the main clinical trials performed with nilutamide have focused primarily on its combination with surgical or medical castration.[50,51]

Casodex is a pure antiandrogen with a mean half-life of 7 days.[52] The manufacturers of this compound (ICI Pharmaceuticals), when introducing this pure antiandrogen, claimed that Casodex at once daily oral dose maintains stable serum drug concentrations devoid of central effects that cause an increase of LH secretion and consequently of androgen production in the testes. This peripheral selectivity was first shown in animals;[53] however, early studies in humans suggested that this selectivity was not maintained.[54,55] The first phase II trial was an open, non-randomized, multicenter, dose-sighting study, in patients with advanced prostate cancer.[54] The conclusion of this study was that 50 mg/day was a well-tolerated dose that produced a response rate equivalent to conventional therapy. The most frequent side effects of Casodex are breast tenderness, gynecomastia and hot flushes.[56] Today there are many phase II and phase III trials ongoing in Europe and North America, seeking to evaluate the actual biologic effect of Casodex in patients with advanced prostatic carcinoma.

Controversies concerning primary hormonal treatment

Despite its acknowledged usefulness, hormonal therapy remains controversial with respect to both the preferable form of treatment and the optimal timing of therapeutic intervention.

Preferable form of treatment

It has been reported that after elimination of testicular androgens by medical or surgical castration, the intraprostatic concentration of DHT remains at approximately 40% of that measured in intact men.[57,58] This was the scientific proof Labrie needed to back up his earlier phase III reports in which non-steroidal antiandrogens were used in combination with orchiectomy and LHRH analogs. It was then that the term total androgen blockade (TAB) was introduced and in these early studies Labrie demonsrated a superior advantage of TAB over standard hormonal ablation.[59,60]

Labrie's theory states that TAB neutralizes the adrenal androgens as well, which could play an important role in priming prostatic cancer cells. In a recent paper Labrie presents all the enzymes required for the conversion of dihydroepiandrosterone (DHEA) and its sulfate (DHEAS) into testosterone and DHT, enzymes that are present in the human prostate and are responsible for the local formation of DHT.[61]

Many studies were undertaken in Europe and North America to test the TAB hypothesis, and the results are confusing if not contradictory. In the US, a large intergroup NCI study, comprising more than 600 patients, demonstrated longer progression-free survival and overall survival with TAB (leuprolide plus flutamide) than with leuprolide alone.[62] The difference in overall survival was only 7 months and it seems that patients with good performance status and minimal disease appear to benefit more from the combination therapy. In Europe, the EORTC has completed three studies addressing the question of TAB.[63]

In the first trial (EORTC 30805) bilateral orchiectomy was compared with 1 mg/day of DES and with bilateral orchiectomy plus CPA. In study 30843, orchiectomy was compared with buserelin and CPA, and in the latest study (EORTC 30853) bilateral orchiectomy was compared with goserelin plus flutamide. Overall survival was not improved by TAB in any of the above EORTC studies. In concordance with the EORTC results are the trials performed in Canada,[64] in Denmark[65] and the study performed by the International Prostate Cancer Study Group.[66]

In favor of TAB are the results of a recent multinational, double-blind randomized trial.[67] In this study 225 patients received orchiectomy plus nilutamide and 239 patients orchiectomy plus placebo. The group of patients treated with the combination regimen showed a 7 month survival benefit.

The conflicting messages from all these reports may be due to many factors. First, the criteria used in classifying responses are different; then comorbid illnesses are not thoroughly analyzed and it is known that the course of metastatic disease is

influenced by many factors. We also do not know what the impact of the flare phenomenon is in overall survival.

Lately, the role of 5α-reductase inhibitors in the treatment of advanced prostatic carcinoma has been introduced.[68,69] It has been shown that DHT is the responsible compound for the androgen mediated effects on the prostate gland.[70] Since testosterone is converted to DHT by 5α-reductase it is logical to use inhibitors of this enzyme and measure their effect on target tissues. Finasteride is the first 5α-reductase inhibitor used in man and it has been proven that it reduces the volume of the prostate in some patients with benign prostatic hyperplasia.[71] The administration of finasteride alone causes an increase in serum and intraprostatic testosterone levels and whether this intraprostatic high testosterone influences the growth of prostatic cancer cells must still be elucidated. Presti *et al.* have performed a multicenter randomized, double-blind study to investigate the effect of finasteride on stage D prostate cancer. They gave 10 mg/day to 13 patients and a placebo to 15 patients. The results were that the effect of finasteride was minor and inferior to that seen with medical or surgical castration.[72]

An attractive idea, as already proposed,[69] would be to combine an antiandrogen with finasteride; however, many experiments in animal models must first be performed before such combinations can be tried in humans.

Timing of endocrine treatment

As mentioned earlier, one of the conclusions drawn from the first VACURG study[15] was that delayed hormonal treatment does not affect the overall survival of patients with metastatic prostate cancer. A recent reanalysis of the data presented in that study revealed a survival benefit for younger patients who had high grade, stage D disease and who were treated early.[73]

Kramolowsky has studied a group of patients who had stage D1 disease and found that those treated with immediate hormone deprivation had a statistically significant longer interval to progression but a statistically insignificant prolonged survival.[74]

Zincke[75] and de Kernion[76] have also shown that patients who had stage D1 cancer and who were treated with radical prostatectomy and early androgen ablation had a significantly prolonged survival. In Zincke's study diploid tumors treated with radical prostatectomy plus immediate orchiectomy were associated with a non-progression rate of 100% at 10 years. Kozlowski *et al.*, in a recent review article, describe thoroughly a risk–benefit analysis of early versus delayed hormonal treatment and the view presented in this article is strongly supportive of early treatment.[77]

The controversy concerning the timing of initiation of hormonal treatment will persist, mainly because knowledge about the natural history of this disease is still insufficient. The EORTC and the Medical Research Council in the UK are conducting important trials at the moment in an effort to shed more light in this matter.

Second line hormonal treatment

Although the majority of patients with prostatic cancer respond to hormone treatment, an escape phenomenon occurs after an average of 2–3 years and the disease continues its course, despite continuation of hormone treatment. Clinical relapse results from the continued growth of androgen independent carcinoma cells following the suppression of androgen sensitive cells. It has been shown that patients refractory to primary hormonal treatment have a poor overall survival, in the range of 9–18 months, regardless of the subsequent therapeutic modality employed.[78] A number of patients do respond to second line hormonal treatment and may show some symptomatic improvement; however, objective tumor response is less than 10%.[78,79]

Orchiectomy has been used by many investigators as a second line therapy; the reported responses are less than 20% and do not last more than 6 months.[80–82] Ferro, by administrating 1104 mg daily of diethylstilbestrol diphosphate (fosfestrol) intravenously for 7 days, has shown impressive pain relief and some objective responses.[83] This effect is believed to be caused by a direct inhibitory cytotoxic effect of fosfestrol to prostatic carcinoma cells. Progestins, CPA and pure antiandrogens in high doses have also been used in the treatment of refractory prostatic carcinoma in an effort to block adrenal androgens, but the results of these trials are either disappointing or rare and short living.[84–86]

The idea of neutralizing adrenal androgens in patients with refractory disease is not new. Huggins and Scott were the first to carry out bilateral adrenalectomies in patients deteriorating after castration.[87] Similar effects to those surgical effects can be achieved today with drugs that block the

synthesis of adrenal hormones. Aminoglutethimide, trilostane ketoconazole and R75251, a new imidazole derivative of ketoconazole, have been used in patients as secondary hormonal treatment. Again, all of these drugs have severe side effects, most of them must be combined with cortisone to avoid Addisionian crises and, although they have been shown to have some subjective responses, they do not improve the overall survival.[89–92]

Estramustine phosphate (Estracyt) is a drug composed of estradiol bound to nitrogen mustard through a carbonate ester linkage. In this way it has simultaneous hormonal and cytotoxic effects by interfering with the cellular microtubular complex.[93] In relapsing patients a response rate of 30% has been reported and its side effects are similar to those of estrogens.[94] Other chemotherapeutic drugs such as endoxan, methotrexate, 5-fluorouracil, cisplatin and many others have been used for second line treatment in hormone resistant patients. Some of these drugs give short lasting subjective responses with considerable side effects and, when survival is the endpoint, the results are disappointing.[94]

Finally, somatostatin analogs and suramin, which is a growth factor inhibitor, have been introduced in early phase I studies in patients with refractory prostatic carcinoma. The first objective response rates of these compounds do not appear very impressive and their important side effects limit their wide use; however, it is still too early to draw final conclusions for these new drugs.[95,96] The analysis of the effects of cytotoxic chemotherapy in relapsed prostatic carcinoma is beyond the scope of this article and will not be discussed further.

Our capacity to prolong survival with secondary hormonal treatment is limited. This is why our main goal should be to maintain, or even improve if we can, the quality of life of our patients with general antitumor and supportive care.

Conclusions

Bilateral orchiectomy is a cheap and efficient method of reducing androgens to castrate levels and, although it was introduced 50 years ago, it still remains the golden standard of hormonal manipulations around the world. The use of estrogens has been limited today despite their low cost, mainly because new drugs such as LHRH analogs and antiandrogens have proven to be as efficient and with less side effects. Antiandrogens are used usually in combination with orchiectomy or LHRH analogs, but it has not been clarified yet whether TAB improved the overall survival of patients with metastatic prostate cancer. The timing of initiating hormonal treatment is another point of dispute among urologists, but the trend today is shifting towards early implementation of therapy. Second line hormonal treatment is available, but with toxic side effects and without any real impact in survival.

Finasteride, suramin and somatostatin analogs are new anticancer drugs that might be useful in the near future in the battle against prostatic carcinoma.

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(Received 22 March 1993; accepted 4 April 1993)