Treatment of hormone sensitive prostate cancer

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Introduction

Prostate cancer is the second most frequent cancer in men and the most frequent in men over 70. Metastatic prostate cancer is a well defined entity which is characterized by painful bone metastases [1]. Metastatic prostate cancer is an incurable disease. The main objectives of treatment are symptom control and good quality of life. The hypothesis that prostate cancer may be as sensitive to androgens as normal prostate gland had been made but had not been demonstrated until Huggins demonstrated the activity of hormone manipulation [2]. He treated several patients by either surgical castration or estrogens. He observed that patients experienced fast pain relief, and that the level of serum prostate acid phosphatase (a marker of prostate cancer which is not used anymore) decreased. As a result, castration and estrogens became the standard treatment for advanced symptomatic prostate cancer. The second step of progress occurred when the knowledge of the physiology of androgens increased; the discovery of the hypothalamo-pituitary axis and of its mediators (Luteinizing hormone (LH), Luteinizing Hormone-Releasing Hormone (LH–RH)). A. Schally described the structure of LH-RH and synthesized agonists of this mediator [3].

Definition of hormone sensitivity

It became evident that a majority of patients benefited from castration, either surgical or chemical. They experienced pain relief, and increase in their quality of life. Biological effects were also observed, due to tumour cell death: decrease in serum Prostatic Specific Antigen (PSA) levels (PSA reflects directly the tumour burden), in serum Alkaline Phosphatase (ALP) levels (ALP reflects indirectly the bone metastases burden), and in some cases Lactate dehydrogenase (LDH) levels. These effects reflect hormone sensitivity and are observed in 80% to 90% of patients. Primary hormone refractoriness is rare except in case of very undifferentiated or even primary neuro-endocrine tumours.

Mechanisms of hormone sensitivity

Androgen receptors

Structure

The androgen receptor is a member of the superfamily of nuclear receptors that are ligand dependant transcription factors [4]. Serum testosterone passively diffuses through the cellular membrane and then is transformed into dihydro-testosterone by 5-α reductase. It binds to a heat shock protein 90 (HSP90) chaperone complex. This complex helps to fold the protein into a ligand-binding conformation which catalyses the interaction with multiple signalling kinases. Nevertheless this complex is not mandatory for nuclear translocation.

Transcriptional activity

Three major functional domains have been described: a transcriptional regulation domain (AF-1, very variable in length and sequence, which has dominant activity), a DNA-binding (DBD) domain (leucine-zipper dimerization interface, highly conserved,) and a ligand-binding domain (LBD) (AF-2 has transcriptional regulatory activity which is not dominant). The region between DBD and LBD, called ' hinge region' , is important because it contributes to dimerization, nuclear localization and binding to co-activator proteins. Androgen receptors bind to a palindromic response element of the DNA as homodimers [5]. The target genes which are androgen-regulated are not extensively known. Early studies showed that their number in any given cell type is small; however recent studies have shown that a large number of genes are concerned in prostate cancer, but that the variability between models or samples is wide. It is thus difficult to define exactly which genes are concerned by androgen regulation.

Different hormones

LH-RH, LH, testosterone, adrenal androgens

Androgens are derived from steroid metabolism. Cholesterol is transformed into pregnenolone. Preg-

nenolone is then transformed into progesterone by the 3-α hydroxysteroid dehydrogenase. The next step is the transformation of progesterone into androstenedione which is catalysed by the 17-α hydroxylase-C 17–20 lyase. Androstenedione is then transformed into testosterone by 17-α keto-reductase. The most important physiological natural androgens are testosterone and dehydroandrosterone (DHEA).

Testosterone is produced by the Leydig cells of the testicle. It is produced since puberty until a very advanced age. Its production is directly dependent on the stimulation by the pituitary hormone (LH). Testosterone is active after it has been metabolised into dihydro-testosterone (DHT) in the cytoplasm of target cells, under the enzymatic activity of 5-α reductase. Testosterone represents around 80% of physiological androgens. The other source of androgens (mainly DHEA and 11-α hydroxy-androstenedione) is the adrenal gland.

Regulation of androgen production

The most important phenomenon is the regulation of testosterone by a feedback mechanism which involves the pituitary gland and the hypothalamus (Fig.1). The hypothalamus produces a regular pulse of a mediator called LH-RH. The pulsatile activity of this centre is abrogated by the serum testosterone level. LH-RH reaches the anterior pituitary gland through the pituitary portal system. Then it stimulates the secretion of LH and FSH by binding to a LH-RH receptor on the pituitary gonadotrope cells. LH stimulates the synthesis of testosterone in the testis by acting on the Leydig cells. Conversely to the regulated production of testosterone by the testicle, androgen production by the adrenal gland is stimulated by ACTH without any feedback regulation. Growth Hormone (GH) stimulates testosterone and oestradiol secretions by Leydig cells. But it also seems to increase the secretion of androgens by the adrenal gland in the presence of ACTH [6]. GH and Insulin-like Growth Factor-1 may be involved in prostate growth and may be important in the general evolution of prostate cancer [7].

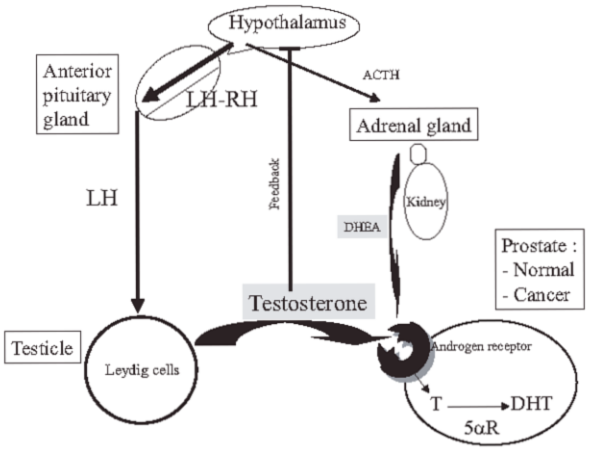

Fig. 1. Regulation of androgens. T: testosterone; 5∝R: 5-∝-reductase; DHT: dihydro-testerone; DHEA: dehydro-androsterone; LH: luteinising hormone; LH-RH: luteinising hormone-releasing hormone; ACTH: adrenal corticotrophin hormone.

Hormonal therapy

Hormonal treatment of prostate cancer is composed of a wide variety of techniques (Table 1) with different mechanisms of action (Fig. 2).

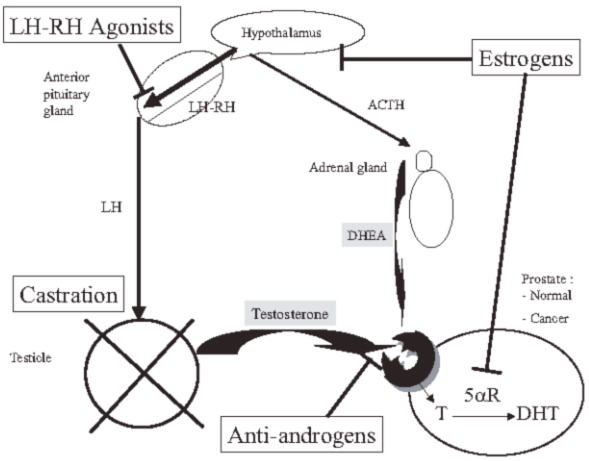

Fig. 2. Mode of action of hormonal treatment. T: testosterone; 5∝R: 5-∝-reductase; DHT: dihydro-testerone; DHEA: dehydro-androsterone; LH: luteinising hormone; LH-RH: luteinising hormone-releasing hormone; ACTH: adrenal corticotrophine hormone.

Surgical castration

Orchidectomy is performed through a scrotum incision under local anaesthesia. It is the most radical, effective and cheap technique [2]. Another technique is the intra-albugineal excision of the gland (pulpectomy). However it may favour residual endocrine gland, thus the serum testosterone level must be controlled after this procedure. Surgical castration must be discussed with the patient, considering the psychological impact and the definitive effect of this procedure.

LH-RH agonists

LH-RH agonists have been synthesized since the early 1980' s. They act by inducing LH release from the anterior part of the pituitary gland. Therefore a high level of serum LH is observed during the

Table 1
Different hormonal treatments

Drug	Mechanism of action	Side effects
LH-RH agonists (injections)		
Leuprorelin[a] 3.75 mg * 11.25 mg **	Induction of LH release then inhibition of secretion	flare-up syndrom
Triptorelin 3 mg * 11.25 mg **		loss of potency
Goserelin 3.6 mg § 10.8 mg §§		hot flushes
Buserelin 6.3 mg §§§		weakness
		osteoporosis
Non-steroidal anti-androgens (oral)		
Flutamide 250 mg	competitive blockade of androgens to receptors	diarrhea
Bicalutamide 50 mg		hepatotoxicity
Nilutamide (1) 50 and 150 mg		flushing reactions
		dark-blindness (1)
		pulmonary fibrosis (1)
Steroidal anti-androgens (oral)		
Cyproterone acetate 50 mg	inhibition of LH release	loss of potency
	competitive blockade of androgens to receptors	gynecomastia
Oestrogens (oral)		
Diethyl-stilbestrol 1 mg	inhibition of LH release	loss of potenty
	inhibition of 5α-reductase activity	gynecomastia
		thromboembolism

[a] Mode of administration: Sub-cutaneous or intra-muscular depot preparations * monthly, ** every three months. Daily injections are not used anymore. Sub-cutaneous depot preparations: § monthly, §§ every three months, §§§ every two months. Daily injections and nasal spray (Buserelin) are not used anymore.

first 8 days of treatment. This leads to an increase of testosterone secretion by the testicle which may produce severe and life-threatening complications such as medullar compression with paraplegia, pain increase and urinary retention [8]. This has been called the ' flare-up syndrome' which is prevented by introduction of anti-androgens one week before the first injection of LH-RH agonists. The other major side effects of LH-RH agonists are hot-flushes, fatigue, muscular weakness and common complications of androgen blockade (see below). LH-RH agonists are given as subcutaneous depot preparations on a monthly or more often on a three-monthly basis. Randomised trials comparing castration to LH-RH agonists have shown no difference [8,9] between the two techniques. Nevertheless some cases of absence of activity of LH-RH agonists lead to recommend dosage of serum testosterone levels in patients who experience PSA rising after an initial period of activity of LH-RH agonists. Four LH-RH agonists are available: Goserelin, Leuprolid, Tripterelin and Buserelin. The first three drugs are available as a monthly and a three-monthly depot preparation, Buserelin as a two-monthly depot preparation.

Anti-androgens

Anti-androgens generally act as competitive inhibitors of testosterone on androgen receptors. There are two categories of drugs: those which have a steroid structure, very similar to androgens or sexual hormones, and those which have a non-steroidal structure.

Steroidal anti-androgens

Steroidal anti-androgens are progesterone derivates, commonly cyproterone acetate [10–12]. The structure explains the mechanism of action: it links to steroid receptors of cancer cells, but also inhibits the production of physiological LH-RH through a feedback on the hypothalamus. Its progestative structure explains the increased incidence of thrombo-embolic events and the suppression of hot-flushes when it is associated with LH-RH agonists. The other steroidal anti-androgen derivate, medroxyprogesterone acetate induced shorter survival when compared to cyproterone acetate [13].

Non steroidal anti-androgens

These drugs are synthetic competitive inhibitors which have pure anti-androgen activity [14]. Their pharmacokinetics may be different: flutamide and nitulamide have a short half-life and must be administered thrice daily, conversely bicalutamide has a longer half-life and is given once daily. They have common toxicities, as diarrhoea and toxic hepatitis, but nitulamide has specific toxicities: dark-blindness and interstitial pneumonitis.

Aromatase inhibitors

Trials have been done with aminogluthetimide, a drug which inhibits the aromatase in the adrenal gland [15]. The drug acts at an initial step of steroidogenesis and induces a deficiency in other steroid hormones (mainly glucocorticosteroids), thus patients must receive hydrocortisone substitution. Other aromatase inhibitors have not been extensively studied. The activity of these drugs is marginal: a 10% response rate has been reported, but tolerance is of concern. These drugs are not registered in this indication.

Estrogens

They are the first drugs which were investigated [2]. The most important is diethylstilbestrol (DES). Its derivate, Fosfestrol, is no longer produced nor available. Estrogens act through the inhibition of 5-α reductase which impairs the transformation of testosterone into its active derivate, dihydro-testosterone. But it also acts by a negative control on the pulsatile secretion of LH-RH in the hypothalamus. The major complication of DES is thrombo-embolic phenomenon. Randomized trials have compared DES to LH-RH agonists: activity was the same but thrombo-embolic events rates were 10% and 0% respectively [16].

LH-RH antagonists

LH-RH antagonists have the main property to abrogate the flare-up syndrome, but they induce very similar depletion of LH and of subsequent testosterone production [17,18]. They have been registered in the case of contraindication of LH-RH agonists.

Hormonal therapy side effects

Specific side effects to each drug have been mentioned previously. But androgen blocade induces common and universal side effects which impair patients' quality of life. The most important are impotency and osteoporosis.

Sexual side effects

The major consequence is the impotency with loss of libido. It is observed shortly after androgen blockade initiation (one to two months) and is sometimes reversible when androgen blockade is short. It is constant when LH-RH agonists or DES are administered. Potency may be preserved when non steroidal anti-androgens (mainly bicalutamide) are given alone, even at high dose. There is no way of palliation of androgen blockade-induced impotency: sildenafil, intra-cavernal injections of prostaglandin inhibitors are inactive.

Osteoporosis

Osteoporosis is a very frequent pathology observed in post-menopausal women. It is rarely observed in elderly males. Nonetheless, osteoporosis has been observed in patients who were treated for prostate cancer. Prospective studies have demonstrated the role of androgen blockade in the induction of this pathology in prostate cancer patients. Analysis of paired patients with prostate cancer who had localised controlled disease and were treated with or without androgen blockade allowed to define the impact of androgen blockade on bone metabolism. The methods used to detect osteoporosis were measurement of bone mineral density (BMD) by photon absorptiometry [19]. Hormone deprivation induces a significant decrease of BMD in around 40% of the patients. It is therefore recommended to carefully follow patients and to prevent osteoporosis by appropriate treatments which can be: the use of non-steroidal anti-androgens only [19], adjunctive treatment by vitamin D3 and calcium, with or without bisphosphonates [20].

Patient information

Patients should be informed of the objectives of the treatment and of its side effects. They should be aware that the main target is symptom control and not serum PSA level control. Thus the most important objective of patients' follow-up is to help them to continuously invest in the setting of quality of life (QoL) issues. It must be pointed out that this is often forgotten by patients and their families. Treatment side effects are differently experienced. Impotency is an important side effect but patients who have undergone prostatectomy or even radiotherapy are likely to be impotent already. The major impact of androgen suppression will be therefore loss of libido. The onset of some side effects are delayed and are forgotten by the patient. Nevertheless patients must be informed of their occurence and in some cases of their prevention. Finally, patients must be given the choice of surgical castration or LH-RH agonists prescription to attain testosterone suppression. Different factors should be taken into account: such as cost, definitive effect of castration and more importantly psychological impact.

Indications of hormonal therapy

Metastatic disease

Role of single testosterone deprivation

In the past, surgical castration and DES were compared and demonstrated equal activity in random-

ized trials [8,12]. The testosterone castration level (<0.5 ng/ml) is obtained within several hours and is maintained indefinitely. Pain relief and symptomatic improvements are observed within few days, even few hours of treatment start in a majority (around 80%) of patients. The median survival in patients with painful bone metastases is 24 to 30 months and the progression-free survival being of around 14 months. Randomized trials have compared surgical castration to various dosages of DES (0.2, 1, 3 and 5 mg/day) [21–23]. The 3 and 5 mg daily doses were toxic (increased thrombo-embolic events and mortality) and were abandoned. The dose of 1 mg daily was equivalent to surgical castration. During the 1980s LH-RH agonists were tested and demonstrated activity. Randomized trials of LH-RH agonists compared surgical castration [8] and DES 8, [24]. Response rates and survival were equal in all arms. However patients treated with DES experienced more gynecomastia and thrombo-embolic events (10%). Even if surgical castration is the gold standard of treatment and is less expensive, LH-RH agonists are clearly equivalent in activity and have less psychological distressing consequence. It has become the gold standard of pharmacological castration.

Role of complete androgen blockade

Failure of androgen suppression and hormone refractoriness led to question the role of androgen from adrenal origin, and the mechanisms of resistance. The idea that suppression of testosterone production by the testicle seemed insufficient to completely suppress androgen production [25]. This led to explore the hypothesis that the combination of testicle testosterone production suppression (by either surgical or biochemical castration) and peripheral anti-androgen therapy, known as Complete Androgen Blockade (CAB) would be more active than simple androgen suppression. Several trials compared LH-RH agonists alone or in combination with flutamide. The US Intergroup 0036 trial showed a survival advantage of CAB [26]. Based on the fact that patients with less tumour burden may have benefited more evidently from CAB, a specific analysis was performed to delineate prognostic subgroups [27]. The US Intergroup conducted a prospective randomised trial of surgical castration with or without flutamide, the results of which were not in favor of CAB [28]. It is noteworthy that this study included a specific QoL assessement that demonstrated a better QoL in patients in the placebo arm [29]. These trials failed to clearly demonstrate a survival advantage of CAB. Other randomised trials compared surgical castration to LH-RH agonist with flutamide [30,31]. One trial [30] did not demonstrate any survival difference between the two groups, but less side effects after surgical castration. The other trial [31] showed survival prolongation in the CAB group but similar complications rates between the two groups. Meta-analyses were performed in 1995 [32] and 2000 [33]. The later included 8275 patients from 27 randomized trials. In this meta-analysis, 88% of patients had metastatic and 12% locally advanced disease; the median age was 70 years and the median follow-up was 5 years. A 1.8% 5-year survival gain was observed with CAB, but failed to reach statistical significance. Results were similar in the different subgroups according to age and disease stage. It was slightly different according to the type of anti-androgen blockade: cyproterone acetate had some disadvantages and was linked with more non-cancer deaths, while patients treated by non-steroidal anti-androgens had some significant survival benefit (2–3% five-year survival benefit). This meta-analysis demonstrated a 5-year survival advantage between 0% and 5%.

Role of single anti-androgen treatment

Antiandrogens have a different activity dependent on their structure: steroids have a double mode of action, one peripheral and the other central by inhibition of LH-RH production; non-steroidal anti-androgens have only peripheral activity. Treatment with single agent has been studied with both types of drugs [14]. Several studies failed to demonstrate any difference in activity with the different anti-androgens [34]. Different studies were performed with bicalutamide [35]. They demonstrated less skeletal side effects and some activity advantages in the setting of localised disease (see other section of this educational program).

Intermittent hormone deprivation

Since several years, investigators have explored the possibility of performing intermittent hormonal deprivation to decrease side effects of hormone suppression and particularly long-term effects such as induction of osteoporosis. Feasibility trials most often using CAB have been performed on patients with advanced or biochemical recurrent disease. Patients had sequential periods ' on' and ' off' therapy. Generally, criteria to stop CAB was an a priori fixed cut-off serum PSA value: fall below 4 ng/ml [36] or serum PSA nadir (80% serum PSA level reduction) less than 20 ng/ml [37]. Criteria to restart CAB were variable: serum PSA level more than a cut-off value (20 ng/ml) or a certain serum PSA velocity or occurrence of

symptoms. The overall ' on' /' off' therapy duration ratio was roughly 30 to 50% of the duration of each cycle. Duration of ' off' therapy decreases with subsequent cycles. The anti-proliferative effect seems very similar to continuous treatment. There were no major complications but the impact on osteoporosis needs further evaluation. However, no studies examining long-term side effects studies or therapeutic results between continuous and intermittent hormone deprivation have been conducted. An intergroup randomised US study is on-going [38].

Hormone refractoriness acquisition and the anti-androgen withdrawal syndrome

In patients who are treated with CAB by surgical or chemical castration and an anti-androgen, hormone suppression has a limited effect in time. The median time to hormone resistance is 24 months. After this time, either serum PSA level increases or metastases or symptom progress. Different investigators have observed that stopping the anti-androgen, while castration was maintained, led to a benefit in 30% of patients [39,40]. Patients may experience either serum PSA level decline or symptom relief and less frequently limited objective regression of metastases. Median duration of this phenomenon is 12 weeks. This is more often observed with non-steroidal anti-androgens, but may occasionally be seen with cyproterone acetate. Thus it is recommended to stop anti-androgen administration in patients with hormone refractoriness before starting a next treatment. Another question is the role of testosterone deprivation after development of hormone refractoriness. No randomised trials have been conducted to explore the hypothesis that testosterone deprivation maintenance may have some benefit. However retrospective studies recommend to continue basic androgen blockade because androgen stimulation may lead to life-threatening complications [41].

Second and further lines of hormone therapy

The second line treatment is dependant on the decision regarding first line hormone suppression. If the patient was treated by CAB, it is mandatory to stop the anti-androgen to evaluate the benefit of the anti-androgen withdrawal. Patients treated with testosterone suppression only, may benefit from the introduction of an anti-androgen. A response (serum PSA level decrease or symptom relief) is expected in 20 to 30% of patients. Further attempts to propose third-line hormonal treatment are more debatable. In some cases the use of drugs acting on adrenal gland androgen production is proposed. Aminogluthetimide and ketoconazole [42] have been studied. The response rate is generally smaller in third-line setting (around 10% of patients) and these drugs have notable side effects. One other possibility is the use of low-dose prednisone (10 mg/day): a 10% symptomatic improvement is likely to occur [43]. However prednisone is often used concomitantly with chemotherapy at this stage. Finally the role of estrogens must be discussed. Even in heavily pretreated patients, estrogens may have beneficial symptomatic effects. Only DES is still available. It is recommended to use low-dose DES (1 mg/day), to limit thrombo-embolic complications. Prophylactic use of coumarin is recommended. In the case of late stage acute complications (spinal cord compression [44] and intravascular disseminated coagulation [45]) high-dose estrogens may help to control the complications. Fosfestrol has been proposed in this setting, but since it is not available anymore, it may be replaced by higher doses of DES (5 mg/day).

Hormone deprivation schedule

Metastatic disease

Only few studies have addressed the issue of early versus differed hormone deprivation in advanced and metastatic non-pretreated disease. The Medical Research Council conducted the most important study [46] and compared early treatment in asymptomatic patients with delayed treatment when symptoms appeared. This study showed that early treatment with LH-RH agonist improves median survival by three months [47]. Indications of hormone deprivation in the other settings, neoadjuvant, adjuvant and PSA rising, are discussed in other sections of this educational program.

On-going recommendations on the use of hormonal therapy

The PDQ of the NCI recommends the primary use of hormone suppression in advanced (stage IV) disease. CAB is proposed as it increases median survival. Anti-androgens must be given before the start of LH-RH agonist to avoid the flare-up syndrome [48]. The European Society of Medical Oncology (ESMO) minimum recommendations are simple androgen deprivation in metastatic prostate cancer [49]. Orchidectomy and LH-RH agonists are both standard treatments to suppress testosterone production. Delayed treatment is an option depending of selection criteria and patients willingness.

Conflict of interest statement

The authors declare they have no financial and personal relationships that could inappropriately influence this work.

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