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Endocrine approaches in the therapy of prostate carcinoma

F.C.H.d'Ancona[1,2] and F.M.J.Debruyne[1]

[1]Department of Urology, Radboud University Nijmegen Medical Centre, Geert Grooteplein 10, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands

[2]To whom correspondence should be addressed. E-mail: f.d'ancona@uro.umcn.nl

At present, the management of non-organ confined prostate cancer, whether it is a recurrence or metastasis, continues to evolve based on prostate cancer detection using prostate-specific antigen and the development of medications as alternatives for the classical orchiectomy, which induced irreversible implications for quality of life. Diethylstilbestrol therapy was associated with cardiovascular side-effects; GnRH agonists were able to create a castration level, but again considerable side-effects were described. Combination therapies using antiandrogens and GnRH agonists do not improve survival and have additional toxicity. GnRH antagonists, which also suppress FSH, represent the latest class of agents introduced for hormonal treatment, but phase III studies with survival data are not yet available. In spite of all these achievements, hormonal manipulation has resulted in only modest improvements during recent decades and new targets are needed to improve the clinical outcome. Selectively modifying the androgen receptor is currently one of the most promising developments.

Key words: androgen receptor modification/antiandrogens/hormonal therapy/prostate cancer

Introduction

Huggins and Hodges (1941) described the androgendependent nature of prostate cancer by the observation that surgical castration resulted in prompt relief of pain in patients with bone metastatic prostate cancer, and since that time hormonal manipulation in the treatment of prostate cancer has evolved.

To date, hormonal manipulation has been the keystone treatment for patients whose localized prostate cancer has not been treated effectively with surgery or radiation therapy. In advanced disease, androgen deprivation therapy stabilizes >80% of the patients. However, the median duration of the response after initiating this hormonal regimen in metastatic disease is only 2–3 years! (Eisenberger *et al.*, 1998).

It should be evident that the endocrine treatment of prostate cancer is a palliative treatment. Convincing evidence for cure of prostate cancer under endocrine treatment has rarely been presented. Manipulation of the male hormonal axis may result in lower prostate-specific antigen (PSA) levels in patients with androgen-insensitive tumours, but eventually the majority of tumours will progress to a hormone refractory state with a median survival of ~1 year (Nishimura *et al.*, 2000).

Conventional management of nonorgan confined, recurrent or metastatic prostate cancer is still evolving due to earlier diagnosis and new medications. In this review we describe the current treatment strategies as well as the controversies related to the hormonal therapy for advanced prostate cancer, such as monotherapy versus maximum androgen blockade, early versus delayed hormonal therapy and intermittent versus continuous hormonal treatment.

An important goal for chemoprevention is the maintenance of an androgensensitive clinical state, and prevention and/or delay of an androgenindependent state (Lieberman, 2001).

Working mechanism; biological basis of androgen dependence/independence

The major source of androgens in the male is the Leydig cells located at the testes. After castration, serum testosterone decreases to 5–10% of the original values. The remaining testosterone is derived from adrenal androgens, which may be metabolized to testosterone and 5α-dihydrotestosterone (DHT), the most potent androgen at the level of the prostate, which is derived from testosterone through the activity of the enzymes 5α-reductase (5α-R) type 1 and type 2. The biological activity of androgens is determined by their structure and by their affinity to the androgen receptor (AR), which is ~7-fold higher for DHT in comparison to testosterone. Adrenal androgens are rather weak but can be metabolized to DHT within the prostate and outside through the availability of the enzymes 17β-hydroxysteroid dehydrogenase and 5α-R.

Androgen production in the Leydig cells and adrenals is under pituitary control through LH and adrenocorticotrophic hormone (Figure 1).

The action of androgens at the target cell is mediated by the AR. The steroid–AR complex binds to specific DNA sites and leads to the initiation of transcription. Without this receptor, steroid hormones cannot exert their biological effect. Antiandrogens interfere with the formation of the AR complex at the level of the receptor.

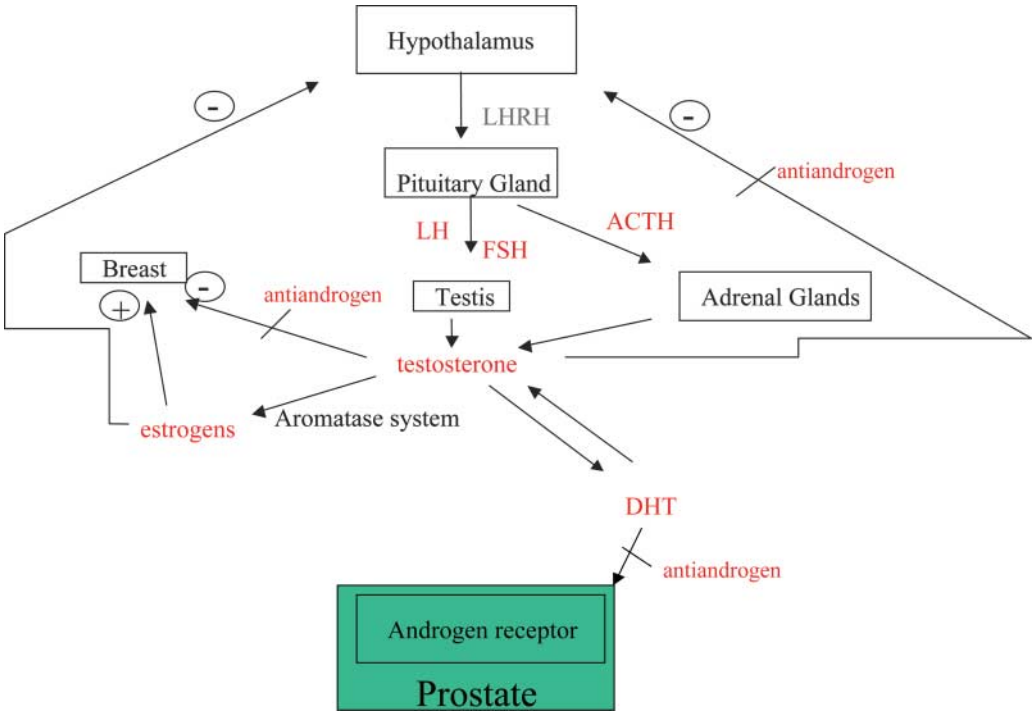

Figure 1. Endocrinologic pathway and antiandrogen effect. ACTH = andrenocorticotrophic hormone; DHT = dihydrotestosterone; FSH = follicle stimulating hormone; LH = luteinizing hormone; LHRH = luteinizing releasing hormone; + = stimulates; − = inhibits.

Several publications (Taplin *et al.*, 1995, 1999; Tilley *et al.*, 1996) suggest that androgen ablation provides selective pressure on the androgen signalling pathway for mutation development.

Androgen deprivation can be achieved by: surgical castration; medical castration: estrogens, GnRH agonists and antagonists; androgen blockade at target cells: steroidal antiandrogens, pure antiandrogens, maximal androgen blockade and 5αR inhibition.

Prostate tissue shrinks if androgen is withdrawn by an average of 30–40%. The possibility of relapse is best explained by the presence of hormone-resistant cell populations, which through clonal overgrowth eventually lead to the presence of a hormone-insensitive tumour.

There is a pathological continuum starting with normal-appearing glandular epithelium that evolves to dysplastic prostatic intra-epithelial neoplasia (carcinoma *in situ*) and then to invasive carcinoma. The early stages are androgen dependent. However, as disease progresses over time, androgen independent clones emerge, either *de novo* (stem cell theory) or in response to androgen deprivation therapy and clonal selection (Lieberman, 2001).

Five mechanisms to explain the antiandrogen resistant state have been described (Patterson *et al.*, 2002). (i) The hypersensitive pathway: more AR is produced (by gene amplification) or the AR has enhanced sensitivity to compensate for low androgen levels, or more testosterone is converted to the more potent DHT by 5α-R. (ii) The promiscuous pathway: the specificity of the AR is broadened and it can be activated by nonandrogenic molecules. This pathway may explain the clinical observation of the antiandrogen withdrawal syndrome, in which patients who progress on antiandrogen therapy tend to improve when antiandrogens are stopped. (iii) The outlaw pathway: receptor tyrosine kinases are activated, and the AR is phosphorylated by either kinase B or the mitogenactivated protein kinase pathway, producing a ligandindependent AR. (iv) The bypass pathway: parallel survival pathways, such as that involving the antiapoptotic protein B-cell lymphoma 2, obviate the need for AR or its ligand. (v) The lurker cell pathway: androgen-independent cancer cells that are present in the prostate might be selected by therapy.

Considering these pathway theories, the current target of antiandrogen therapy strategies is the creation of an androgen-sensitive clinical state or to delay the androgen-independent state.

Current approaches to hormonal treatment

In view of the hormonal pathway in men, several therapeutic strategies have been proposed in recent decades.

Orchiectomy

The most logical way of reducing testosterone levels to castrate levels is to perform an orchiectomy. This is a simple surgical procedure and it results in a rapid reduction of circulating androgen levels. However, it has no effect on the production or suppression of FSH, which may continue to stimulate prostate cancer cell growth. The procedure is irreversible and it will inevitably lead to impotence.

Currently with the possibility of medical hormonal blockade, simple orchiectomy is reserved for patients with extensive bony metastases, at risk for spinal compression, bladder neck obstruction and retroperitoneal adenopathy (Debruyne, 2002).

The profile of the prostate cancer patient has been changing over the years, leading to earlier detection at younger age. These patients are sexually and physically active and have a life expectancy of >10 years, making quality of life issues increasingly important while making a choice for treatment (Kolvenbag *et al.*, 2001).

Diethylstilbestrol (DES)

Treatment with DES achieves complete testosterone blockade by blocking LH. It leaves FSH unaffected. The Veterans Administration Cooperative Urological Research Group (VACURG) I study (Byar and Corle, 1988) showed that the endocrine treatment delays progression and also the time to progression increased in non-metastatic disease. Because of the switch of the majority of patients from the placebo arm to the endocrine treatment arm at the time of progression, the findings do not exclude the possibility of an effect of endocrine treatment on survival.

However, the side-effects are also well known; a 5 mg dose was associated with increased mortality from cardiovascular causes compared with castration (Blackard, 1975; Byar and Corle, 1988), but low dose did show a decrease in cancer-related death per year in high risk patients. However, de Voogt *et al.* (1986) found in a total of 226 patients a lethal complication rate of 16.1% with DES versus 7% in estramustine phosphate.

To avoid cardiovascular complication, a combination with prophylactic aspirin was suggested; Rosenbaum *et al.* (2000) treated patients with oral DES 1 mg three times daily or 2 mg twice daily with aspirin 100 mg once daily. Of 18 patients, 66% had PSA levels reduced to <0.6 or had a ≥50% reduction. Gynaecomastia was noted in 2 of 18 patients. No thromboembolic complications were noted.

Estrogenic therapies induce secondary responses in patients with an androgen-independent state of prostate cancer, which suggests an additional mechanism of action besides that of suppression of the pituitary–gonadal axis. Several studies (Smith *et al.*, 1998; Orlando *et al.*, 2000; Shadidi *et al.*, 2001) suggest that DES can produce PSA responses in a significant proportion of patients in an androgen-independent state of prostate cancer. The mechanism is yet unclear but may represent a direct cytotoxic effect on the cells, probably by apoptotic mechanisms (Robertson *et al.*, 1996).

GnRH agonists

Treatment with GnRH analogues offers reversible medical castration, with side-effects similar to those of orchiectomy.

Following an initial rise in LH and FSH due to the stimulation of GnRH, prolonged occupation of the LH receptors in the pituitary results in a reduction in testosterone to levels equivalent to those seen after administration of DES. GnRH agonists do not influence FSH with unknown implications since FSH stimulates growth factors and may induce progress of prostate cancer.

The testosterone surge must be distinguished from tumour flare. This surge is a hormonal increase in testosterone, LH or FSH following GnRH agonist therapy. The flare phenomenon is a clinical presentation of worsening of the symptoms such as pain, which may or may not follow the surge but is not described without the testosterone surge (Kuhn *et al.*, 1989; Thompson *et al.*, 1990). The surge is reported in nearly all patients receiving GnRH agonist therapy, leading to a transient over-stimulation of receptors and a surge of testosterone secretion within the first few days of therapy, while flare is reported in 4–33% of patients, even up to 63% of those with advanced disease (Kuhn *et al.*, 1989).

Oefelein (1998) studied 13 patients to determine the duration of androgen suppression (leuprolide) after a single 3 month injection and found persisting castrate levels of testosterone in 10 of the 13 patients at 6 months and hypogonadal symptoms persisting for a median of 13.6 months. Although an overwhelming majority of patients treated with GnRH agonists achieve castrate levels of testosterone, some do not. In another study by Oefelein and Cornum (2000), 5% of patients failed to reach a serum testosterone <50 ng/dl and 13% failed to reach <20 ng/dl. In cases of hormonal-dependent prostate cancer, this phenomenon may be of clinical significance and provides a rationale for the use of antiandrogens in addition to GnRH agonist. Sharifi *et al.* (1998) stated that a testosterone escape can occur during GnRH analogue therapy in ~10% patients projected over an average course of treatment.

GnRH agonists are used in a variety of settings for patients with prostate cancer. Despite their efficacy they are expensive. Another well-known phenomenon is that when the patients are diagnosed with advanced prostate cancer and treated with GnRH agonist, most continue taking this medication indefinitely. Long-term GnRH results in impaired testicular testosterone and leads to low serum testosterone and PSA levels for a long time, even after cessation of hormonal treatment (Pedraza and Kwart, 2003).

GNRH antagonists

GnRH antagonists work by directly inhibiting GnRH receptor without any initial stimulation of GnRH. The physiological response is a direct and rapid decrease in LH, FSH and testosterone with no flare. Stricker (2001) investigated a GnRH antagonist depot (abalerix, i.m. injections every 28 days) and not only noticed a prostate gland volume reduction of 19–46% depending on the initial volume, but also an immediate androgen ablation within 4 weeks (72% at 8 days; reached castration levels).

Completed phase II data showed a fast reduction of testosterone level (and PSA levels) within 10 days in contrast to 30% treated with GnRH analogues (Tomera *et al.*, 2001) and when therapy is stopped, a quick recovery in testosterone levels is measured. No surge and no clinical flare are noticed and FSH is suppressed. The expansion of indications for androgen deprivation, such as down-sizing or intermittent therapy, could provide many opportunities for their use. Despite these encouraging advances, however, their routine use for advanced prostate cancer may depend on demonstration of a survival advantage in avoiding flare and further phase III studies are needed to evaluate their efficacy, compared to the GnRH analogue therapy.

Antiandrogens

Steroidal antiandrogens have progestational and antigonadotrophic properties and, therefore, inhibit the release of LH, decreasing serum testosterone levels and causing suppression of libido and loss of erectile potency.

Pure androgen (non-steroidal) therapy leads to LH increase in endocrinologically intact males.

Non-steroidal antiandrogens are often used in conjunction with orchiectomy to establish combined androgen blockade (CAB). Non-steroidal antiandrogens act through competitive inhibition of androgen binding at the receptor level, inhibiting the action of androgens from adrenal glands and testis. Testosterone levels remain more or less stable, because LH production is limited by an increase in serum estrogens (because of increased availability of androgens for peripheral conversion when treated with these agents). The primary advantage of these agents is the preservation of sexual potency.

There are three non-steroidal antiandrogens: flutamide, nilutamide and bicalutamide, of which bicalutamide (Casodex; Astra Zeneca) is the most extensively evaluated.

The tolerability of non-steroidal antiandrogens has been extensively evaluated with bicalutamide appearing to have a more favourable adverse effects profile than flutamide or nilutamide. Hot flashes are less common with non-steroidal antiandrogens, with gynaecomastia and breast pain being the most frequent adverse events associated with monotherapy (Tyrrell *et al.*, 1998b; Boccardo *et al.*, 1999; Iversen *et al.*, 2000). Gastrointestinal side-effects, such as diarrhoea and nausea, are more common with flutamide. Hepatotoxity and asymptomatic elevations of aminotransferases are also more likely to occur in flutamide treatment (Wysowski and Fourcroy, 1996).

Available data suggest that breast pain by gynaecomastia during treatment may be prevented by prophylactic irradiation. Gynaecomastia is caused by an increase of estrogen-to-androgen activity due to aromatization of testosterone by cytochrome P450, especially in peripheral fat. Estrogen antagonists and aromatase inhibitors (blocking the conversion of androgens to estrogens) may also have a place in prophylactic treatment of gynaecomastia. Treatment with tamoxifen 10 mg showed a reduction of flutamide-induced breast pain and enlargement (Staiman and Lowe, 1997; Serels and Melman, 1998).

Cyproterone acetate Androcur (CPA), is a steroidal antiandrogen, immediately effective and does not have the cardiovascular side-effects seen with oral estrogens. Schröder *et al.* (2000) compared flutamide and CPA in a prospective randomized study, which did not confirm earlier data on cardiovascular toxicity, although patients were selected as not having coronary diseases. Side-effects were loss of libido and potency, which developed slowly with a median time of 8–12 months; ~20% of men remained potent for poorly understood reasons. Hot flashes and gynaecomastia are rare in CPA therapy, and CPA at dosages of 50–100 mg per day seems to prevent the hot flashes that present frequently under GnRH agonist therapy or castration. Also muscle wasting, osteoporosis and anaemia may be less pronounced. However, current data are too inconclusive to determine whether CPA is as effective as castration or the use of GnRH agonists.

Monotherapy versus maximum androgen blockade

Boccardo *et al.* (1999) investigated the results of bicalutamide (Casodex) monotherapy versus flutamide (Eulexin) and goserelin in prostate cancer patients and found no difference in survival outcome. Bicalutamide monotherapy, 150 mg once daily, was compared to flutamide, 250 mg three times daily, in combination with goserelin. This was studied in 220 patients, half of whom had nonmetastatic disease. No statistically significant differences in overall or progression-free survival were noted. Quality of life issues were in favour of the monotherapy group.

Also, bicalutamide was found to be better tolerated than CAB with flutamide.

Another study from Fourcade *et al.* (1998) compared the effect and safety of bicalutamide (Casodex) 150 mg monotherapy with castration and nilutamide (Anandron) in metastatic prostate cancer. In 235 patients, no differences were noted in objective response or time to disease progression. However, time to treatment failure was significantly longer in bicalutamide monotherapy patients compared to those on CAB. Bicalutamide was also better tolerated. Hot flushes were noted in 47% of CAB patients compared to 11% of monotherapy patients. Gynaecomastia and breast pain were the most frequent adverse events in the bicalutamide group (37 and 33%), compared to 3 and 1.5% in the CAB group.

In a meta-analysis Samson *et al.* (2002), comparing CAB with monotherapy, there was no statistically significant difference between survival in a subgroup of patients with a good prognosis, whereas adverse effects leading to withdrawal from therapy occurred more often with CAB.

Non-steroidal antiandrogen therapy as monotherapy was described in a small study with nilutamide where the median progression-free survival was 9 months with a median overall survival of 23 months (Decensi *et al.*, 1991). Flutamide as monotherapy was compared with castration or CAB; in both studies (Pavone-Macaluso, 1994; Boccon-Gibod *et al.*, 1997) there was a similar outcome to the compared therapy.

Bicalutamide monotherapy, 150 mg once daily, achieves a PSA response similar to castration and is well tolerated (Tyrrell *et al.*, 1998a). Survival analyses in patients with M1 (metastasizing) disease showed that Casodex 150 mg was less effective than castration, although the survival advantage was only 6 weeks. However, a *post hoc* evaluation, however, showed that PSA level at time of entry to the study was related to outcome, and that PSA levels <400 and M1 disease patients had a similar outcome.

Kaisary *et al.* (2001), in a *post hoc* analysis of randomized controlled trials for metastatic prostate cancer patients, concluded that monotherapy with bicalutamide 150 mg/day may be of benefit when PSA levels are <400 ng/ml. Especially for subjective response, the preservation of physical activity and sexual interest monotherapy appeared to give a significant advantage.

There are only limited data on the use of steroidal antiandrogen monotherapy. Moffat (1990) randomized 137 patients with no contraindications to DES:goserelin:CPA at 2:1:1, and 223 patients with proposed contraindications to DES:goserelin or DES:CPA at 2:1. CPA-treated patients had a significantly poorer median survival than goserelin in the first group but not in the second. Thorpe *et al.* (1996) found that the CPA was less effective than goserelin, but no survival data were published. The only advantage of CPA over castration appears to be the lower incidence of hot flushes when it is prescribed.

Early versus delayed hormonal therapy

The decision to start hormonal therapy is not only a decision concerning the medical complications and survival benefit, but it also involves quality of life issues and health costs.

Should treatment start directly at the time of diagnosis or should the treatment be postponed until symptoms develop? Several studies have been performed. The VACURG study suggests that the hormonal treatment with DES could be delayed until the development of symptoms (Byar, 1973), but the study design was probably not good enough to support this statement: patients progressing on placebo were eligible to cross over to DES without changing the study arm. VACURG I reported that patients with metastatic disease were randomized to 5 mg of DES, 5 mg of DES and orchiectomy, orchiectomy alone, or placebo. Patients were allowed to cross over to DES when progression occurred, but the original study arm was not adapted. No differences in survival were seen between the treatment arms. Patients in the DES group had a higher incidence of cardiovascular death, but lower incidence of prostate cancer-related death. In VACURG II, patients were randomized to three different dose regimes (0.2, 1 and 5 mg DES) versus placebo (Byar and Corle, 1988); there was a cross-over design, but concerns about toxicity of DES therapy led to withholding patients at DES 0.2 mg and placebo therapy from cross-over. Therefore, this study more or less investigated hormonal treatment versus placebo treatment, but some survival benefit of hormonal treatment was seen.

More recent studies investigated treatment timing. In 1997, the Medical Research Council (MRC Prostate Cancer Working Party Investigators Group, 1997) presented their results on 938 patients with locally advanced or asymptomatic metastatic prostate cancer. Patients were randomized to immediate or delayed treatment with orchiectomy or GnRH analogue. Progression from M0 to M1 disease and development of metastatic pain occurred more rapidly in the deferred treatment patients. Moreover, skeletal-related events, ureteral obstruction and development of extra-skeletal metastases were more common in this group. A significant improvement in survival was detected in patients without evidence of metastases. In those with metastatic disease, there was no survival benefit, but there appeared to be significantly fewer side-effects from their metastases when treated early.

When reviewing the data, as was performed by the group in 2000, the advantage for early treatment on survival in the 938 patients studied had disappeared. For the group without metastases, still there was a benefit in cancer-specific survival for the early hormonal treatment.

A major concern for the MRC study was whether patients in the delayed treatment arm were allowed to progress too far, before they were offered hormonal treatment, which can of course create a bias for the outcome. The MRC study has been criticized on other major issues: exact causes of death related to prostate cancer were not clear; the data recovery occurred only once a year and the presence or absence of metastases at a time when PSA measurement was not routinely available in all UK centres. The final conclusion this study provides is that early hormonal treatment can prevent serious complications of metastatic prostate cancer, but does not necessarily prolong survival.

Bolla *et al.* (2002) performed a study with 415 patients with locally advanced prostate cancer. Randomization was performed between radiotherapy and goserelin immediately for 3 years and radiation therapy alone. With a median followup of 45 months, the overall survival at 5 years was 79% in the combined group versus 62% in the radiation group. Of the surviving patients free of disease at 5 years, the difference between the combined group and the radiotherapy group was 85 versus 48%!. Bolla *et al.* also concluded that there was improved local control in locally advanced prostate cancer when goserelin therapy was started simultaneously with external beam radiotherapy.

A publication of the Radiation Therapy Oncology Group (Pilepich *et al.*, 1997) investigated the use of adjuvant goserelin in radiated patients with locally advanced prostate cancer in 977 patients. They were randomly assigned to achieve external beam radiotherapy alone (65–72 Gy) or external beam radiotherapy combined with 3.6 mg goserelin administered s.c. every 4 weeks beginning the last week of radiation and continuing until the first sign of progression. The 5 year survival rate appeared to be 75% in the adjuvant arm versus 71% in the radiotherapy arm ($P = 0.52$). However, patients with a poorly differentiated tumour (Gleason 8–10) had a significantly better 5 year survival (66 versus 55%, $P = 0.3$). In this study the goserelin therapy was started at the end of the radiation course, which might be the explanation for the differences. The synergistic effect of hormonal therapy combined with radiation therapy upon apoptotic activity could have played a role in the study by Bolla *et al.* (2002).

Granfors *et al.* (1998) performed a study with 91 patients with locally advanced prostate cancer. After pelvic node staging, patients were randomized to receive external beam radiation therapy or a combination of radiation therapy and orchiectomy. When clinical progression occurred in the monotherapy group, patients were treated with androgen ablation. Clinical data showed 61% progression in the radiation group versus 31% in the combination group ($P = 0.005$). Cancer-specific death was 44 versus 27% ($P = 0.06$). Combined treatment had favourable outcome in the lymph node-positive patients whereas node-negative patients showed no significant differences in survival rate. Progression-free, disease-specific and overall survival rates are better in patients with pelvic lymph node involvement in prostate cancer when treated with androgen ablation therapy combined with radiation therapy. Because the androgen ablation is performed at the start of the treatment, these data are in favour of early androgen deprivation.

Messing *et al.* (1999) studied data of 98 patients with prostate cancer who were treated with radical surgery and had positive pelvic lymph node dissection. Patients were randomized for immediate antiandrogen therapy with goserelin or orchiectomy or to be followed until disease progression. The study was designed to recruit 204 patients, but was closed earlier because there appeared to be a marked improvement in overall and cancer-specific survival in the group receiving early hormonal treatment. At a median of 7.1 years follow-up, 15% of patients in the immediate group died versus 35% in the observational group. However, this study lacks reference pathology analyses; and it is known that 85% of patients with Gleason scores >8 and positive lymph nodes at radical prostatectomy will develop distant metastases within a period of 5 years (Cheng *et al.*, 1998). So it

could be that patients were unequally distributed according to their prognostic factors upon entry to the study, which could well affect the outcome in a relatively small number of patients.

Van Andel and Kurth (2003) evaluated the impact of bicalutamide monotherapy on health-related quality of life in 91 patients with lymph node-positive prostate cancer. Patients were randomized for immediate or delayed treatment when progression occurred. Time to progression was significantly shorter in the delayed treatment arm (33 versus 62 months) but no significant differences were found in survival. Patients with androgen deprivation therapy experienced a worse overall health-related quality of life, experienced more hot flushes and also showed worse sexual, emotional and physical function.

Studies performed to compare early versus delayed hormonal therapy in patients with metastatic disease suggest no clear survival advantage overall. However, when patients are lymph node positive there is an advantage of early hormonal treatment to influence progression-free survival and quality of life. A survival advantage in the early therapy regimen can be expected in patients with poorly differentiated prostate carcinoma (Denis *et al.*, 1998; Newling, 2001; Patterson *et al.*, 2002).

When distant metastases occur, early hormonal treatment has advantages, reducing the risk of related complications.

Intermittent versus continuous hormonal treatment

Intermittent androgen deprivation (IAD) therapy is proposed to delay the time to tumour progression in patients with prostate cancer due to castration therapy resistance. Other advantages include reduction of side-effects, reduction of costs. IAD therapy has been proposed as monotherapy in patients with advanced prostate cancer, but could also be applied in men who failed radical prostatectomy or radiation therapy by an increase in PSA levels. It has been stressed that prostate carcinoma with neuroendocrine (NE) differentiation tends to be more aggressive and resistant to hormonal therapy.

Serum levels of NE markers, particularly Chromogranin A (CgA), could reflect the NE activity of prostate carcinoma. It could be used during follow-up. Sciarra *et al.* (2003) demonstrated that intermittent administration of triptorelin and flutamide significantly reduced the increase in serum CgA during CAB therapy. Intermittent therapy was given following the PSA. The 'off-treatment phase' was initiated when PSA was <0.4 ng/l. This study only hypothesized that the IAD therapy may reduce the risk of NE hyperactivation in prostate cancer during androgen deprivation. No information was given about the clinical progression when comparing stable CgA cases and cases in which CgA was increasing.

Serial PSA determinations make intermittent androgen suppression possible by providing an easy way to determine the tumour activity during the non-treatment episodes. Intermittent hormonal therapy consists of a 6–9 month period of hormonal suppression followed by a corresponding length of time without hormonal therapy. When PSA levels reach threshold criteria, androgen suppression is reactivated. Many reversible medical therapies have been used to suppress testosterone intermittently (Klotz *et al.*, 1986; Goldenberg *et al.*, 1995; Higano *et al.*, 1996; Horwich *et al.*, 1998; Crook *et al.*, 1999; Grossfeld *et al.*, 2001). These six phase II trials investigated the effect of the intermittent hormonal therapy. Most of the reported cases used an 8 month period of androgen blockage followed by a non-treatment period in which PSA was monitored. Treatment varied between DES, maximal androgen blockade and GnRH analogues and was restarted most of the time at a PSA level of 10 ng/ml, but this varied between studies. Significant recovery of libido was reported in the off-treatment period in men with a normal libido prior to initial treatment. With regard to the effectiveness of the reinstituted hormonal therapy in prior responders, the overall subjective improvement in well-being was significant in all studies.

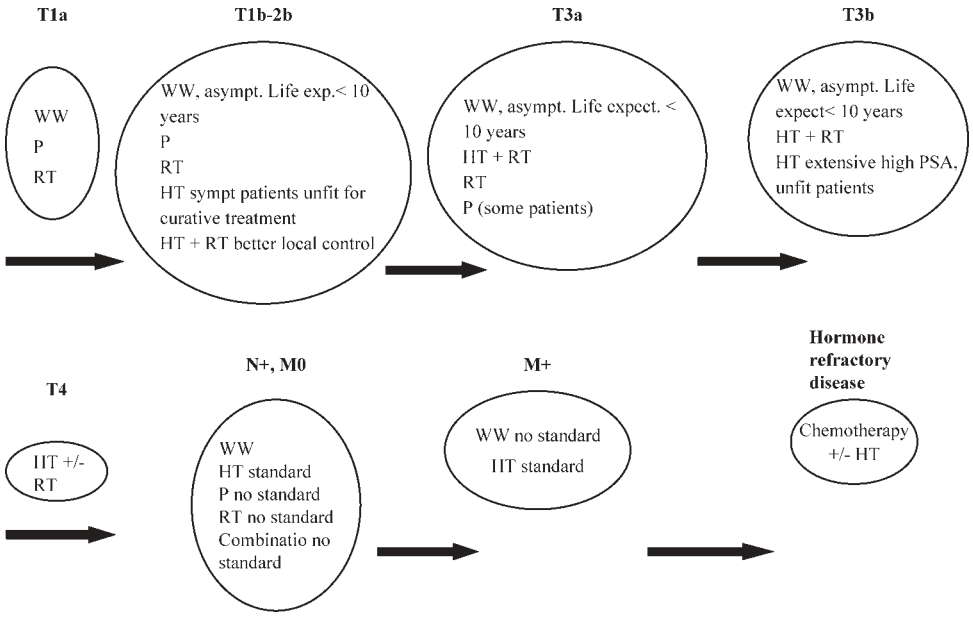

Figure 2. Stepwise treatment options stage by stage (according to TNM classification prostate carcinoma) for patients with prostate cancer. WW = watchfull waiting; P = radical prostatectomy; RT = radiotherapy; HT = hormonal therapy.

Intermittent treatment seems to deliver a better outcome in terms of survival than continuous hormonal therapy, though there have been no randomized trials so far.

Neoadjuvant hormonal therapy before radical prostatectomy

When dealing with hormonal therapy regimens for non-organ-confined prostate cancer, one must be aware that a potentially curative treatment may fail when the disease is incompletely resected or when micro-metastases are present at the time of the surgery. Some series report positive margin rates of >60% after radical prostatectomy in patients who were clinically staged pre-operatively to have localized prostate cancer (Jones, 1990; Rosen *et al.*, 1992; Frazier *et al.*, 1993; Trapasso *et al.*, 1994). With the availability and widespread use of reversible forms of medical castration, several investigators have postulated that hormonal ablative therapy before radical prostatectomy could improve outcome. Evaluating the prospective randomized trials comparing neoadjuvant androgen ablation before radical prostatectomy with radical prostatectomy alone, each study showed a significant reduction in margin-positive disease, decline in PSA and reduction of prostate volume in patients receiving neoadjuvant therapy (Soloway *et al.*, 1995; Van Poppel *et al.*, 1995; Goldenberg *et al.*, 1996; Hugosson *et al.*, 1996; Labrie *et al.*, 1997; Lee *et al.*, 1997). However, none of these studies reported a statistical improvement of survival, seminal vesicle or lymph node invasion, or biochemical disease-free interval at 3, 4 and 5 years after surgery. The neoadjuvant regimen contained androgen ablative therapy 6–12 weeks before surgery, and the duration of the therapy might explain these results (Gleave *et al.*, 1997, 2000a). Furthermore, the follow-up could be too short and the identification of residual tumour is difficult after hormonal treatment (Murphy *et al.*, 1991; Bazinet *et al.*, 1997).

Gleave *et al.* (2000b) reported that the neoadjuvant hormonal therapy for a period of 8 months yielded maximal tumour volume reduction, and in their uncontrolled study they described lower than expected PSA progression rates at 5 years in these patients.

A European 4 year follow-up study (European Study Group, 2000) did not show a lower PSA progression rate, but there was a trend towards a better local control of cT2 tumours in the neoadjuvant goserelin+flutamide-treated group. However, a subsequently higher survival rate could not been demonstrated at that time.

Currently, 3 months of neoadjuvant hormonal therapy is not recommended and controlled studies evaluating a longer period of hormonal neoadjuvant treatment are needed.

Conclusion

In the current treatment, strategies of prostate cancer hormonal therapy strategies are well established (Figure 2). Since Huggins and Hodges (1941) described the concept of hormonal dependence of prostate cancer, no new real differences in therapeutic approaches have been developed, although hormonal blockade itself has improved. Orchiectomy led to irreversible impotence, while DES treatment caused improvement in survival at the cost of considerable cardiovascular toxicity. GnRH agonists alleviated these drawbacks, but other problems such as hormone surge, causing clinical flare, were described. The combination therapy does not completely suppress androgens, has more side-effects and has almost no survival benefit compared to antiandrogen monotherapy.

GnRH antagonists cause androgen suppression as effectively as orchiectomy without the side-effects of surge and hormone flare, and act not only upon testosterone level but also upon FSH.

In T3+ M0 disease, the choice at the moment is either GnRH agonists or bicalutamide. Early hormonal therapy strategies do not influence survival significantly but could reduce the risk of skeletal-related events. However, in T3N+ disease there is a survival benefit.

New developments could be the use of less toxic agents and more clinical use of GnRH antagonists. However, the most promising would be the modulation of the AR itself, and many different specific androgens receptor modulators are currently under investigation.

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