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Endocrine treatment of prostate cancer

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Abstract

Although androgen deprivation as a treatment for patients with prostate cancer was described more than 60 years ago its optimal use remains controversial. The widespread use of prostate-specific (PSA) assay has lead to earlier diagnosis and earlier detection of recurrent disease. This means that the systemic side effects of androgen deprivation and quality of life have become more important. Debates continue regarding the proper use and timing of endocrine therapy with orchiectomy, oestrogen agonists, gonadotropin hormone-releasing hormone (GnRH) agonists, GnRH antagonists, and androgen antagonists. A critical review of the literature was performed.

Data support that androgen deprivation is an effective treatment for patients with advanced prostate cancer. However, although it improves survival, it is not curative, and creates a spectrum of unwanted effects that influence quality of life. Castration remains the frontline treatment for metastatic prostate cancer, where orchiectomy, oestrogen agonists and GnRH agonists produce equivalent clinical responses. Maximum androgen blockade (MAB) is not significantly more effective than single agent GnRH agonist or orchiectomy. Nonsteroidal antiandrogen monotherapy is as effective as castration in treatment of locally advanced prostate cancer offering quality of life benefits. Adjuvant endocrine treatment is able to delay disease progression at any stage. There is, however, controversy of the possible survival benefit of such treatment, including patients having PSA relapse after definitive local treatment for prostate cancer. Neoadjuvant endocrine treatment has its place mainly in the external beam radiotherapy setting. Intermittent androgen blockade is still considered experimental. The decision regarding the type of androgen deprivation should be made individually after informing the patient of all available treatment options, including watchful waiting, and on the basis of potential benefits and adverse effects.

Several large studies are under way to investigate the role of adjuvant endocrine treatment in the field of early prostate cancer, intermittent androgen deprivation and endocrine therapy alone compared with endocrine therapy with radiotherapy. The real challenge, however, is to develop better means to avert hormone-refractory prostate cancer and better treatments for patients with hormone-refractory disease when it occurs.

Keywords: GnRH agonists; GnRH antagonists; Antiandrogens; Oestrogens; Timing of treatment; Adverse effects

1. Introduction

It has been more than 60 years since Huggins and Hodges published their Noble Prize-winning paper where they reported studies on eight patients with prostate cancer and skeletal metastases to determine the effects of castration and oestrogen administration on elevated acid phosphatases [1]. After that androgen deprivation has been the mainstay of treatment for locally advanced and metastatic disease. Despite the long pedigree for this treatment, the optimal use of androgen deprivation remains controversial.

Monitoring the level of prostate-specific antigen (PSA) has created a dramatic shift in the population of patients in whom the endocrine treatment is initiated. The percentage of patients having bone metastases at the time of diagnosis of prostate carcinoma has decreased enormously. Patients with recurrent prostate carcinoma after the failure of local therapy are now diagnosed with recurrence on basis of a rising PSA level. These patients have a median life expectancy of 10–15 years, which is in sharp contrast to patients who present with metastatic disease having that of 3 years [2]. They are treated with androgen deprivation when their PSA level begins to rise. However, there is substantial uncertainty with regard to the benefit of initiating treatment this early, and there is no consensus about optimal PSA threshold for initiating

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treatment. Whether treatment needs to be continuous, which has been the traditional practice, is open to question. The impact of long-term androgen deprivation on quality of life is much greater for the patient who is facing 15 years treatment than for the patient whose treatment duration will be short due to the progression of metastatic bone disease.

The basis for endocrine treatment of prostate cancer is to deprive the cancer cells of androgens. Apoptotic regression of an androgen-dependent tumour can be induced by any procedure that reduces intracellular concentration of dihydrotestosterone by 80% or more [3]. This can be done by elimination of the testosterone production of the testes. Alternatively the androgen receptors of the prostate cancer can be blocked. Not more than 6% of all the cancers do not respond to androgen deprivation [4]. Every type of endocrine treatment carries adverse events, which influence quality of life in different ways. Debates continue regarding the proper use and timing of endocrine therapy with orchiectomy, oestrogen agonists, gonadotropin hormone-releasing (GnRH) agonists, GnRH antagonists, and androgen antagonists.

2. Elimination of testosterone production

Castration, the time-honoured frontline treatment for metastatic prostate cancer, was previously defined by induction of a serum testosterone level of <50 ng/ml. However, recent literature redefines this upper limit to <20 ng/ml [5]. The first method of permanent castration was bilateral orchiectomy, and the first reversible method was diethylstilbestrol (DES) [1]. Medical castration may be obtained with oestrogen agonists, GnRH agonits, GnRH antagonists, and ketoconazole.

2.1. GnRH agonists

GnRH is a small hormone, composed of 10 amino acids that is synthesized in hypothalamic neurones and secreted directly into the hypophyseal–portal blood circulation in a pulsatile manner. GnRH interacts with high-affinity receptors on the gonadotropic cells in the anterior pituitary, stimulating the synthesis and release the gonadotropins, LH and FSH. Short pulses of GnRH increase pituitary sensitivity, presumably by increasing GnRH-receptor number and LH/FSH levels. The episodic release of endogenous GnRH prevents receptor desensitisation and is mandatory for continuing androgen production. Continuous stimulation of the pituitary with high concentrations of GnRH agonist induces regulatory changes, possibly down regulation of the GnRH-receptors [6,7]. This results in receptor desensitisation and inhibition of LH release, which further inhibits the production of testosterone by the testicle.

Endogenously produced GnRH has a very short half-life because of peptidase degradation. By altering the basic amino acid structure of synthetically produced analogues, compounds with a prolonged half-life time and increased resistance to peptidase degradation have been developed for systemic administration. Depot GnRH agonists have revolutionised the treatment of patients with advanced prostate carcinoma. They are administered by subcutaneous injection at intervals of 1–3 months. Current studies demonstrate that only about 5% of patients being treated with GnRH agonist therapy fail to achieve testosterone suppression <50 ng/ml [8].

GnRH agonists initially impose an increase in LH production, and therefore, an increase in plasma testosterone levels lasting 1–2 weeks [9]. In prostate cancer this is responsible for the tumour flare effect. This represents androgen-induced stimulation of tumour growth as a result of the testosterone surge. In particular, increased activity in bone metastases can cause severe pain and spinal cord compression. Therefore, co-treatment with antiandrogen should be used during the commencement of GnRH agonist for 2–3 weeks. This kind of therapy is now a standard especially in patients with bone metastases and, therefore, spinal cord compression and increased bone pain is rarely seen in contemporary urological practice.

The equivalence of orchiectomy, oestrogen agonists and GnRH agonists has been well demonstrated in several studies as well as in a recent meta-analysis [8]. When compared to 5 mg of DES, GnRH analogues have a more favourable cardiovascular safety profile with a reduced risk of deep vein thrombosis and congestive heart failure. Given the strong preference patients have expressed for injections as opposed to orchiectomy, GnRH agonists have largely replaced orchiectomy as the castrative treatment of prostate carcinoma. There are several GnRH agonists available, including goserelin, leuprorelin, buserelin and tritorelin. Although there are no proven differences in the efficacy of each preparation, no prospective, randomised, controlled trials have been undertaken to compare their efficacy and side effect profiles directly.

2.2. Maximum androgen blockade

GnRH agonists block testicular testosterone production. However, testosterone is also produced from the adrenal glands under independent control. This accounts around 5% of serum testosterone concentration. An important quantity of total androgen (40–50%) is produced in the peripheral tissues, including the prostate, from inactive precursors dihydroxyepiandrosterone (DHEA) and its sulfide (DHEA-S) of adrenal origin [10]. Since the first description of the effect of androgen deprivation on prostate cancer, the survival rates of non-curatively treated prostate cancer patients have not increased [11]. Many investigators have been convinced that androgen-independent prostate cancer and relapse following medical or surgical castration were caused by the adrenal androgen source. Therefore, GnRH agonists have been used in conjunction with specific antiandrogens.

Terms complete androgen blockade (CAB), combined androgen blockade (CAB) or maximum androgen blockade

(MAB) describe the use of two forms of androgen blockade, first, to inhibit the production of testosterone using either orchiectomy or GnRH agonists, and second, by blocking the androgen receptor to inhibit the effects of andrenal and locally-produced androgens using steroidal or nonsteroidal antiandrogens.

Conclusive evidence for superiority of MAB over castration alone as primary treatment of metastatic prostate cancer has not been provided, despite of a large number of randomised trials. One meta-analysis found that MAB improved 5-year-survival by 3.5%, compared with orchiectomy and GnRH agonist treatment alone [12], whereas a more recent meta-analysis showed only a marginally significant improvement in 5-year-survival in patients receiving MAB, but this benefit was confined to the subgroup of the patients with best prognosis [13]. The results of these meta-analyses are not consistent with those of a large randomised trial [14], which showed no significant difference in survival between patients receiving MAB and those undergoing orchiectomy without concomitant antiandrogen therapy. This inconclusive evidence has placed more emphasis on therapies that confer a side effect advantage, such as monotherapies.

2.3. GnRH antagonists

GnRH antagonist treatment causes a major and rapid reduction in serum testosterone level, after only 1 day of treatment, which is similar to that caused by castration [15]. This offers potential benefit compared to GnRH agonists because the tumour flare effect is avoided. In addition, GnRH agonists do not reduce testosterone levels as rapidly as GnRH antagonist, which may influence the efficacy of the treatment [15].

Extra-pituitary effects of GnRH have also been reported. In the prostate and in prostate tumours there is now evidence of a functional local GnRH regulatory system. This system is thought to consist of locally produced GnRH, or a GnRH-like peptide, mediating its effect via specific GnRH bindings sites [16]. The exact physiological role and regulation of this local system is largely unknown.

Despite equally rapid reduction of testosterone level, the GnRH antagonist was more effetive in suppressing the rat ventral prostate epithelial cell proliferation probably by interfering with effects of locally produced GnRH [7]. Differences between castration and GnRH antagonists treatment could also be related to the fact that castration increases whereas the antagonist decreases LH and FSH levels. The clinical significance of these findings is unclear and it will be a topic of further clinical trials testing GnRH antagonists in clinical settings.

2.4. Oestrogen agonists

Oral oestrogen treatment with DES, once the most common method for hormone manipulation of prostate cancer, was largely abandoned in the 1970s due to its significant thromboembolic and cardiovascular toxicity [17]. In the mid 1980s, interest in oestrogen therapy was renewed when it was found that oestrogen administered parenterally did not induce these side effects. The significant changes in liver metabolism and grave deviations in blood levels of coagulation factors seen after oral therapy were reported to be absent or only marginally present after parenteral therapy [18]. Anticancer efficacy of parenteral polyestradiol phosphate (PEP) was found to be equal to orchiectomy or MAB in terms of time to biochemical and clinical progression and overall and disease-specific survival [19,20]. No significant increase in cardiovascular mortality with PEP was observed. There was, however, a significant increase in non-fatal ischemic heart disease and heart decompensation. Therefore, before there are enough data to make it possible to identify the risk factors for cardiovascular complications attributable to the PEP regimen the concern to use oestrogens in the treatment of prostate cancer will remain, as there are other forms of medical androgen deprivation available not having these complications. In addition, prominent breast enlargement and feminisation as a rule are unwanted side effects.

2.5. Castration syndrome

A group of symptoms connected to medical or surgical castration can be referred to as the castration syndrome which does not only include the most well-known loss of libido and erectile function, and hot flushes, but also anaemia, obesity, decrease in muscular strength, fatigue, decline in physical activity and general vitality, mood changes and depression. In addition, castration induces osteoporosis in long-term. These effects on quality of life should be concerned when planning to start a castrative treatment in patients who will need it for a long time due to slow progression of the disease like those who have biochemical failure (a rising PSA) after radical prostatectomy or radiotherapy.

A typical symptom of hot flushes is an attack of warmth starting in the face, and spreading down to the neck and body, immediately followed by sweating. It lasts from 30 s to 5 min, and may recur more than 10 times per day. Even though being intensively studied, the exact pathogenesis of hot flushes has not been entirely clarified. It is postulated that there is a disturbance in the hypothalamic thermoregulatory centres due to decrease in beta-endorphin and noradrenaline [21]. Hot flushes develop in 50–75% of patients after orchiectomy or treatment with GnRH agonist while they have been registered in 17–30% of patients treated with oestrogen [21]. Contrary to what is generally thought, hot flushes do not vanish quickly, but persist in a practically unchanged intensity in more than half of patients who get them [22,23]. Treatment with small doses of oestrogen, cyproterone acetate or medroxyprogesterone can decrease or completely abolish hot flushes, probably by increasing endogenous betaendorphins [21].

Androgens are important activators of erythropoesis by stimulating haematopoetic stem cells and the production of

erythropoetin. Patients on androgen deprivation therapy develop a decrease in haemoglobin and haematocrit within 3–6 months [24]. This is typically normocytic, normochromic anaemia with a 10–25% reduction of haemoglobin. It is more prominent when combined androgen blockade is used. If necessary, this anaemia can be treated successfully by recombinant human erythropoetin [21].

2.6. Osteoporosis

Endocrine treatment of prostate cancer with GnRH agonists or orchiectomy has been shown to have negative effects on bone mass [25–27]. Accordingly, the risk of osteoporotic fractures is greatly increased in men undergoing androgen suppression therapy for prostate cancer [26–28]. Both prevalence of osteoporosis and relative risk of hip fracture increase according to the length of androgen suppression. After 5 years of treatment the prevalence of osteoporosis was 50% while the relative risk of hip fracture had doubled during the same time [27]. For that reason a bone densitometry is recommended before androgen suppression because it could detect those patients at high risk to develop osteoporosis. Exercise and calcium supplementation are recommended for men receiving hormonal treatment, as these are often beneficial [29]. As therapeutic approaches to treat and avoid the loss of bone mass have been studied mainly treatments with oestrogens and bisphosphonates with encouraging results [29,30]. Also, in patients treated with intermittent androgen blockade mineral density has stabilised or increased during off periods [31].

3. Antiandrogens

Antiandrogens, steroidal and non-steroidal, can be used as monotherapy, neoadjuvant therapy prior to radical prostatectomy or radiation therapy, or in combination with castration.

Cyproterone acetate, a steroidal anti-androgen, competitively inhibits the binding of dihydrotestosterone (DHT) and testosterone to the androgen receptor. Due to combined androgenic and progestogenic action it binds progesterone receptors in the pituitary, inhibiting also the release of LH and production of testosterone by the testicles [32]. The adverse effects of cyproterone acetate are more or less the same as those of castration therapy [33]. There are also concerns over hepatotoxicity with long-term use. In addition, thromboembolic complications are possible due to the progestogenic action of the compound [21].

Nonsteroidal antiandrogens such as bicalutamide, flutamide and nilutamide inhibit the activity of androgens by blocking competitively the interaction of testosterone and DHT with the androgen receptor. They still cross the blood–brain barrier raising LH secretions and, therefore, testosterone secretion in the testes. Treatment with nonsteroidal antiandrogens is the only established way to avoid castration in the endocrine treatment of prostate cancer. Nausea, diarrhoea and some liver toxicity are commonly observed in patients treated with flutamide whereas in those treated with bicalutimide they are uncommon [34,35]. Nilutamide induces often alcohol intolerance and visual problems with adaptation darkness [36]. Currently, bicalutamide is the best-tolerated agent in this group [37–39].

There has been an increased interest in nonsteroidal antiadrogens as monotherapy, partly because of the side effects of castration. In contrast to that, a slight increase rather than a decrease in serum testosterone occurs after bicalutamide monotherapy [40]. Bicalutamide has been evaluated as monotherapy for advanced prostate cancer in a number of studies. When it was compared (150 mg/day) to MAB with either flutamide or nilutamide as antiandrogen [37], no significant differences in regard to progression-free or overall survival was observed. When compared with castration this was also true in patients with nonmetastatic cases but there was a small survival advantage for castration in the M1 subgroup [38,41].

In Early Prostate Cancer Programme (with 8115 patients enrolled), bicalutamide is being assessed as adjuvant or primary treatment for early (i.e. clinically non-metastatic) prostate cancer. The programme comprises three double-blind, parallel trials all of which enrolled and randomised patients on a 1:1 basis to either bicalutamide 150 mg/day or placebo. In the North American study more than 80% had previously undergone radical prostatectomy, compared with about 60% in the European and 20% in Scandinavian ones. After a median follow-up of 2.6 years, a significant reduction in the risk of objective progression and significant delay in the time to PSA doubling were observed in the bicalutamide group [39,42]. For survival, however, further maturation of data is required and, therefore, the study is still going on.

Bicalutamide offers quality of life benefits in terms of sexual interest, physical capacity and potentially, preservation of bone mineral density [38]. Therefore, bicalutamide monotherapy may be a preferred option to castration for younger, sexually active men with locally advanced prostate cancer who wish to optimise their physical activity. Also hot flushes occur less frequently than after castration. However, gynaecomastia and breast pain are common adverse events and develop to most patients. The main pathogenesis for this is that the antiandrogen blocks androgen receptors in the breast tissue while aromatisation of increased testosterone results in higher concentrations of estradiol, which further induces development of gynaecomastia. There are, however, prophylactic and treatment measures, such as radiotherapy, surgery and possibly some medical treatments, may offer relief or prevention [43].

4. Intermittent androgen deprivation

The proliferation of androgen independent cancer cell lines limits the long-term efficacy of hormone suppressive therapy. Data indicate that androgen independent progression

may begin early after the start of hormonal treatment, coinciding with the cessation of androgen-induced differentiation of stem cells [44]. It is possible that if androgen deprivation were stopped prior to the tumour progression of androgen-independent cells, any subsequent tumour growth would be due to the proliferation of androgen-dependent stem cells which would be susceptible once again to androgen withdrawal.

Intermittent androgen deprivation became feasible when medical castration became available. Serial serum PSA determinations make it possible by providing an easy method for early determination of tumour growth during periods of no treatment. There are several potential advantages. Libido and potency could be recovered during off-treatments in previously potent patients, and also other side effects of long-term androgen deprivation like osteoporosis, muscle atrophy and depression may be avoided, which would improve quality of life. In addition, intermittent androgen blockade might improve outcome by delaying the onset of hormonal resistance, but currently there are no clinical data available to verify this hypothesis.

Studies are currently in progress to determine the impact of intermittent androgen deprivation on survival and quality of life, and to compare intermittent therapy with continuous hormone deprivation [45]. Preliminary results suggest that intermittent androgen deprivation does not have a negative impact on time to progression, and it improves quality of life [45]. However, patients with large tumour burden like those with more than five spots on bone scan and/or non-lymphatic soft tissue metastases should be excluded as only one third of these could start three or more cycles [46]. On the other hand, intermittent androgen deprivation might be a feasible strategy in patients with PSA relapse after radical prostatectomy or radiation therapy. Data on long-term outcome are awaited with interest. At present, intermittent androgen blockade is still considered experimental.

5. Androgen deprivation in combination with surgery

5.1. Neoadjuvant treatment before radical prostatectomy

Although neoadjuvant androgen deprivation of three months before radical prostatectomy has been reported to reduce prostate size by 30–50% and incidence of positive margins by 18–37% in patients with clinically localised tumour (T1/T2), the outcome of the neoadjuvant treatments have been disappointing [47]. A recent report presented the 5-year results of a study comparing radical prostatectomy alone or proceeded by 3 months of treatment with MAB in patients having clinical T2b tumour [48]. Although a significant reduction in the rate of positive margins was observed with neoadjuvant hormonal treatment, there was no difference in the recurrence rate. For the neoadjuvant treatment of locally advanced T3 stages before radical prostatectomy, only a few studies, with a limited number of cases, are available [47]. They do not offer any valid evidence for the beneficial role of neoadjuvant androgen deprivation before surgery. Since a PSA decrease can be observed for up to 8 months, it has been speculated that neoadjuvant treatment of more than 3 months' duration might have a better effect [49].

It can be concluded that no advantage of neoadjuvant androgen deprivation before radical prosatectomy has been consistently and convincingly demonstrated so far [45,47,50,51]. In addition, no study has demonstrated that neoadjuvant treatment reduces the complications of radical prostatectomy [51].

5.2. Adjuvant treatment after radical prostatectomy

When studies in patients with seminal vesicle involvement or lymph node metastases are excluded, no conclusive data from randomised studies on the efficacy of adjuvant endocrine treatment after radical prostatectomy are available [47,50,52]. However, patients who do not achieve an undetectable PSA after radical prostatectomy although the surgical margins were negative are at high risk of unrecognised metastatic disease [53] which might favour the use of adjuvant androgen deprivation in these cases. The advantage for adjuvant treatment has been shown in patients who undergo radical prostatectomy and have lymph node metastases [54]. The ongoing Early Prostate Cancer Programme is assessing bicalutamide also as adjuvant therapy after radical prostatectomy [39].

The rationale for adjuvant hormonal therapy in patients with PSA progression after radical prostatectomy is based on the finding that most cases of PSA recurrence are not localised. In one study, 70% of cases were not localised [55]. Especially patients with early time to PSA recurrence, rapid PSA doubling time and adverse pathologic features (Gleason score 8–10, positive lymph nodes, seminal vesicle invasion) are suggestive of metastatic disease [5].

6. Androgen deprivation in combination with radiotherapy

The addition of hormone therapy to radiation therapy may improve local control in a number of different ways [56]. In the neoadjuvant setting, hormone therapy may reduce the number of clonogens that the radiation is required to eradicate. Furthermore, there may be synergistic effect of radiotherapy and hormone therapy to enhance tumour cell kill in the prostate through a common mechanism of cell death, such as apoptosis [57,58]. Androgen deprivation by means of inhibiting angiogenesis reduces tumour bulk improving oxygenation of the remaining clonogenic cells, which further improves efficacy of radiotherapy [57]. Another possible mechanism for the effect of neoadjuvant hormone therapy is the removal of tumour cells from the active phase of cell cycle into the resting phase, thereby reducing the rate of accelerated

repopulation during radiation therapy [58]. In addition, hormone therapy may eliminate systemic metastases [59].

Neoadjuvant androgen deprivation is capable of reducing the volume of the prostate by 30–50%. This allows reduction of field size and dose of radiotherapy for prostate cancer, thus decreasing radiation exposure of the bladder, rectum and other adjacent organs and significantly reducing radiation-related adverse effects and complications [50,60]. Similar effects of neoadjuvant treatment before brachytherapy for prostate cancer have been reported [61]. In this setting, androgen ablation therapy serves to downsize the prostate to overcome anatomical limitations, including larger gland volume and pubic arch interference [62].

Large randomised trials, having locally advanced (T3–T4) or large T2 tumours, have shown significant improvements in overall or disease-specific survival, or both, in patients receiving adjuvant hormonal therapy with a GnRH agonists in addition to external beam radiotherapy, compared with those receiving radiotherapy alone [63–65]. In the study by Bolla et al. [63], in patients with locally advanced prostate cancer GnRH analogue therapy was continued for 3 years. After a median of 66 months' follow-up, 5-year overall survival was 78%, and the proportion of surviving patients who were free from disease was 74% in patients receiving adjuvant GnRH agonist therapy, compared with 62 and 40%, respectively, in those receiving radiotherapy alone. Disease progression occurred in 90 ($n = 208$) patients receiving radiotherapy alone, compared with 27 ($n = 207$) of those receiving adjuvant GnRH agonist.

The available data suggest that short-term (less than 6 months) adjuvant therapy significantly improves survival in patients with Gleason score 2–6 disease [65], whereas a longer duration of treatment is necessary in patients with Gleason score 8–10 disease [45,64]. However, the optimal duration of adjuvant hormone therapy has not been determined. To date, there are no data available showing that survival would be better when radiation therapy and hormone therapy are used instead of treatment with hormone therapy alone because studies comparing these two treatments are lacking. However, there are going on trials like The Intergroup randomised phase trial III led by the National Cancer Institute of Canada (NCIC PR-3, Medical Research Council in the UK PR-07 and the Southwest Oncology Group JPR.3) that are addressing the issue of hormone therapy alone [66]. Hormone therapy alone is being compared with hormone therapy combined with pelvic radiotherapy.

7. Timing of therapy

While there are potential benefits of adjuvant hormonal therapy after local treatment in locally advanced prostate cancer, a number of questions remain concerning the timing of the treatment, and it is unclear how early treatment should be given. Delayed therapy has been advocated, because hormonal therapy is not curative and is associated with adverse effects, and because there is usually a long delay between PSA relapse and the development of metastatic disease [67]. Several studies in different patient populations, including patients with locally advanced, lymph node-positive and metastatic disease, have suggested that early hormonal therapy improves overall or disease-specific survival [54,63–65,68,69].

The effect of early versus delayed hormonal therapy was investigated in a randomised study of 938 patients with locally advanced or metastatic prostate cancer [68]. The time to progression from M0 and M1 disease was significantly longer in patients receiving immediate therapy than those receiving deferred therapy, and significantly fewer patients in the immediate treatment group required transurethral resection for local progression. Complications like pathological fractures, spinal cord compression, ureteric obstruction and development of extraskeletal metastases, were twice as common in the deferred therapy group. The incidence of death from prostate cancer was significantly lower in patients receiving immediate therapy than in the deferred group (62% versus 71%, $p = 0.01$), particularly among patients with M0 disease (54% versus 70%, respectively, $p < 0.001$) but not in M1 patients. Another randomised trial ($n = 98$, median follow-up 7.1 years) comparing immediate hormonal treatment with observation in prostate cancer patients with minimal lymph node disease treated by radical prostatectomy and pelvic lymph node dissection showed a significantly reduced risk of tumour recurrence (77% versus 18%, $p < 0.001$) and death from prostate cancer (15% versus 35%, $p < 0.02$) in the arm treated immediately [54].

In the Early Prostate Cancer Programme testing immediate hormonal treatment with bicalutamide, significant reductions in the risk of disease progression, including the development of bone metastases, were seen not only patients who received immediate bicalutamide treatment as the primary treatment but also in those had received before that therapy of curative intent (radical prostatectomy or radiotherapy) [39]. However, longer follow-up is needed to determine the potential survival benefits of this approach.

Taken together, the data available support early initiation of androgen deprivation therapy not only in M1 patients but also in those with locally advanced or lymph node positive prostate cancer. Whether onset of treatment at PSA relapse produces the same results may be topic of further studies. To date there are no data supporting a particular PSA trigger point for the initiation of androgen deprivation therapy after failure of local radical therapy.

8. Sequental therapy

Patients who fail initial androgen suppression therapy and demonstrate evidence of disease progression may be treated with sequential therapy with other agents. In men who had initial androgen deprivation from either orchiectomy or GnRH agonist monotherapy, the addition of non-steroidal

antiandrogen therapy may be considered as around one third of patients respond for it at least short periods [70,71]. It has been found that tumours containing androgen receptor gene amplification at initial progression responded significantly better to MAB as second line therapy compared to those without amplification [70]. Androgen receptor amplification has also been reported in approximately a third of patients recurring during castration [72,73]. In addition, secondary responses with one antiandrogen in patients who have progressed on another antiandrogen are seen between 25 and 50% of cases [74].

If the initial therapy consisted of MAB, the nonsteroidal antiandrogen should be withdrawn. In all, around one third of patients will respond with a decrease in PSA lasting 4–6 months [75,76]. The mechanism for this withdrawal effect is not fully understood, but it is probably related to development of cancer cell clones that have mutated to be dependent on the antiandrogen as a substrate. The simultaneous reduction of adrenal androgens by taking ketoconazole and hydrocortisone can enhance this response observed as an increase in the PSA response in comparison to androgen withdrawal alone [77]. A variety of regimens including megestrol, aminoglutethimide and ketokonazole, retain activity as indicated by PSA decline even in patients who have failed to respond to MAB or androgen withdrawal. Corticosteroids can not only induce PSA responses but also produce regression of soft tissue disease in some patients [5].

Secondary hormonal therapy is of limited benefit in hormone refractory prostate cancer. Responses are subjective in nature, and there is no evidence of increase in survival. Treatment must be individualised based on the performance status of the patient, concomitant illness and primary hormonal therapy.

9. Conclusions

Androgen deprivation is an effective treatment for patients with advanced prostate cancer. However, although it improves survival, it is not curative, and creates a spectrum of unwanted effects that influence quality of life, particularly when its use is prolonged. Castration remains the frontline treatment for metastatic prostate cancer, where orchiectomy, oestrogen agonists and GnRH agonists produce equivalent clinical responses. MAB is not significantly more effective than single agent GnRH agonist or orchiectomy. Antiandrogen monotherapy with bicalutamide is as effective as castration in palliative treatment of locally advanced prostate cancer, offering quality of life benefits. Adjuvant endocrine treatment is able to delay disease progression at any stage. There is, however, controversy of the possible survival benefit of such treatment that has also to be balanced against its side effects and costs. Whether onset of androgen deprivation at PSA relapse in patients who have undergone definitive local treatment for prostate cancer produces survival benefit may be a topic of further studies. Neoadjuvant endocrine treatment has its place mainly in the external beam radiotherapy setting. At present, intermittent androgen blockade is still considered experimental.

Hormonal agents for treating advanced prostate cancer represent a wide range of treatment options. The decision regarding the type of androgen deprivation should be made individually after informing the patient of all available treatment options, including watchful waiting, and on the basis of potential benefits and adverse effects. The decision should be based on factors such as staging extent of the disease, the patient's performance status and the patient's requirements in terms of quality of life and survival.

Several large studies are under way to investigate the role of adjuvant endocrine treatment in the field of early prostate cancer and that of intermittent androgen deprivation in the treatment of prostate cancer. In addition, there are studies comparing endocrine therapy alone with hormone therapy with radiotherapy. Results of these studies are awaited with interest. However, the real challenge is to develop better means to avert hormone-refractory prostate cancer and better treatments for patients with hormone-refractory disease when it occurs.

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