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Review

Endocrine prevention and treatment of prostate cancer

Teuvo L.J. Tammela *

Department of Surgery, Tampere University Hospital, Teiskontie 35, P.O. Box 2000, FIN-33521 Tampere, Finland

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ABSTRACT

The major androgen within the prostate is dihydrotestosterone (DHT). DHT and 5α-reductase are highly associated with prostate cancer. It has been hypothesised that inhibition of 5α-reductase activity might reduce the risk of prostate cancer development, slow tumour progression and even treat the existing disease. The basis for endocrine treatment of prostate cancer is to deprive the cancer cells of androgens. Every type of endocrine treatment carries adverse events which influence quality of life in different ways.

5α-Reductase inhibitors (5-ARI) reduce risk of being diagnosed with prostate cancer but they do not eliminate it. By suppressing PSA from BPH and indolent prostate cancers 5-ARI enhances the ability of a rising PSA to define a group of men at increased risk of clinically significant prostate cancer. Also fewer high-grade cancers are missed because biopsy is more accurate in smaller prostates.

Androgen deprivation is an effective treatment for patients with advanced prostate cancer. However, 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, GnRH agonists and antagonists produce equivalent clinical responses. 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. Neoadjuvant endocrine treatment has its place mainly in the external beam radiotherapy setting. Increasing data suggest IAD is as effective as continuous ADT. 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. There are new promising secondary or tertiary forms of endocrine therapies under evaluation, like CTP17A1 inhibitors and more potent antiandrogens including MDV3100, which give new hope for patients developing castration resistant prostate cancer.

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* Fax: +358 3 31164371.
E-mail address: teuvo.tammela@uta.fi

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1. Introduction

Although androgen deprivation as a treatment for patients with prostate cancer was described more than 60 years ago its optimal use remains controversial (Huggins and Hodges, 1941). After that androgen deprivation therapy (ADT) has been the mainstay of treatment for locally advanced and metastatic disease. Despite the long pedigree for this treatment, the optimal use of ADT remains controversial.

Although testosterone is the primary circulating androgen in men, within the prostate it is converted to a more potent dihydrotestosterone (DHT) by the action of intracellular 5α-reductase enzymes including type 1 and type 2 isoforms (Zhu and Sun, 2003). Circulating DHT levels are low (1:10) when compared with testosterone, whereas in the prostate, this ratio is reversed, making DHT the primary androgen in the prostate. DHT has stronger affinity of binding to androgen receptor (AR) and slower dissociation rate. DHT is also more potent at stimulating prostatic growth than testosterone.

DHT and 5α-reductase are highly associated with prostate cancer. Expression of type 1 5α-reductase in the prostate is elevated in the different stages of prostate cancer (PIN, localised, recurrent and metastases) when compared with benign prostatic hyperplasia (BPH), while type 2-reductase, normally the most prevalent isoform within the prostate, is elevated in BPH (Thomas et al., 2003, 2005, 2008). It has been hypothesised that inhibition of 5α-reductase activity might reduce the risk of prostate cancer development, slow tumour progression and even treat the existing disease. Specific inhibition of DHT production maintains the levels of testosterone and avoids the androgen depletion associated adverse effects (Andriole et al., 2005).

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 (Kyprianou and Isaacs, 1987). This can be done by elimination of the testosterone production of the testes. Alternatively the androgen receptors (AR) of the prostate cancer can be blocked. Only 6% of all the cancers do not respond to androgen deprivation (Palmberg et al., 1999). 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 (antiandrogens).

In spite of initial response to ADT advanced prostate cancer progresses eventually to castration resistant prostate cancer (CRPC). However, CRPC often remains responsive to other hormonal therapies (Scher and Sawyers, 2005; Attard et al., 2008; Shafiri, 2010) in large part due to the intratumoural regeneration of androgens (Montgomery et al., 2008). Therefore these patients are often treated with secondary hormonal therapies which further delete androgen concentrations or directly bind and inhibit AR (Ryan and Smith, 2005).

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. 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 year, which is in sharp contrast to patients who present with metastatic disease having that of 3 years (Klotz, 2000). They are treated with ADT when their PSA level begins to rise. However, there is substantial uncertainty with regard to the benefit of initiating treatment this early. Whether treatment needs to be continuous, which has been the traditional practice, is open to question. The impact of long-term ADT 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.

2. Endocrine prevention of prostate cancer

There are currently available two 5α-reductase inhibitors (5-ARI). finasteride specifically inhibits type 2 5α-reductase and at the therapeutic dose (5 mg daily) reduces circulating DHT by 70% and intraprostatic by 68–86%. Dutasteride inhibits both type 1 and type 2 5α-reductase and at the therapeutic dose (0.5 mg daily) reduces circulating DHT levels by 95% and intraprostatic levels by 94% (Rittmaster, 2005). Large-scale clinical trials in BPH patients have shown ARIs to be safe and generally well tolerated over long-term treatment.

Both 5-ARIs have been studied in large-scale trials as possible protective agents to reduce the developing of prostate cancer. The Prostate Cancer Prevention Trial (PCPT) tested finasteride. This study enrolled approximately 18,000 healthy men aged more than 55 years. All of them were at low risk for prostate cancer determined by a normal digital rectal examination (DRE) and a prostate specific antigen (PSA) value <3 ng/ml. These men were randomised into two groups receiving either 5 mg finasteride daily or placebo for 7 years. Annual DREs and PSA values were recorded. Biopsy was recommended for an abnormal DRE or PSA >4 ng/ml. At baseline no biopsy was required, but at the end of the study the biopsy was requested of all participants who had not yet received one to assess the presence of prostate cancer (Thompson et al., 2003). The finasteride-treated men had a significantly lower rate of prostate cancer (18.4%) than the placebo arm (24.4%), resulting a 24.8% relative reduction in cancer prevalence over the 7-year period. In addition, there was a significant reduction in the rate of acute urinary retention, BPH, transurethral resection of the prostate and urinary tract infection. There was, however, an increase in the detection of high-grade prostate cancer (HGPC) in the finasteride treated population compared with the placebo group (6.4% vs. 5.1%). This is probably mostly explained by decrease in prostate volume allowing a greater proportion of the prostate to be sampled by biopsy and so increased chances to detect prostate cancer (Thompson et al., 2007; Lucia et al., 2007). The PCPT data suggest that finasteride does not reduce the volume of HGPC as effectively as in low-grade disease.

As type 1 5α-reductase is more highly expressed in prostate cancer, it is probable that inhibition of both type 1 and 2 5α-reductase would be more effective than inhibition of type 2 only. Dutasteride inhibits both types and could therefore be more ideal for chemoprevention of prostate cancer. A retrospective analysis of three phase 3 trials involving BPH patients revealed that the cumulative incidence of prostate cancer as an adverse event

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