Practical management of advanced prostate cancer

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Abstract

Prostate cancer is the most common cancer in men and the second leading cause of cancer death in this population. Androgen deprivation is the basis of first line treatment for advanced prostate cancer providing disease control in over 80 percent for a median duration of 18 months. This can be achieved by either bilateral orchiectomy or LH-RH agonist administration. Complete androgen blockade provides similar survival benefit when compared to LH-RH agonist alone, however with a higher incidence of side effects and thus it is not recommended as a standard first line treatment for advanced disease. Early hormonal suppression is mandatory since it reduces the risk of progression and cancer related complications. Continuous hormonal suppression is the most acceptable mode of LH-RH agonist administration. Second line hormonal manipulation has generally low response rate. It includes the addition of anti-androgen, estrogens, aromatase inhibitors or ketoconazole. LH-RH agonists must be continued during the second line hormonal treatment and the hormone refractory phase. Two chemotherapeutic agents have been approved in hormone refractory prostate cancer (HRPC): mitoxantrone and docetaxel. Three- weekly Docetaxel and prednisone is currently the standard of care chemotherapy treatment for first line HRPC. The adjunction of Zoledronic acid should be considered for metastatic bone disease.

Introduction

Prostate cancer is the most common malignancy in men [1]. The incidence of prostate cancer increased dramatically in the early 1990s and surpassed that of lung cancer [1]. These changes resulted from prostate-specific antigen (PSA) screening that detected many early-stage prostate cancers [2-3].

Advanced prostate cancer is an incurable disease and treatment objective is only palliation. The major observation is that prostate cancer is a hormone-sensitive tumor. Median duration of hormone sensitivity is 18 months. Progression of prostate cancer from the hormone sensitive to the hormone resistance status occurs in all patients with advanced disease. This article is focused on the practical hormonal and chemotherapeutic options for patients with advanced prostate cancer.

Hormone- sensitive stage

Mechanism of action of anti androgen therapeutics.

Prostate normal and malignant cells are sensitive to androgens. There are two major sources of androgens: testicles which produce testosterone (95% of all androgens) and adrenal glands (dehydroandrosterone, dehydroandrosterone sulfate and androstenedione). Testicles and, to a lower extent, adrenal glands are under the control of the anterior lobe of the pituitary. Luteinuzing hormone (LH) stimulates testosterone production by testicles. LH secretion is under the control of hypothalamic LH-RH (LH-releasing hormone). Production of LH-RH is pulsatile. It is reduced as a function of the serum testosterone level (feed-back mechanism).

There are specific androgen receptors on normal and malignant prostate cells which allow the internalisation of testosterone. Testosterone is then transformed into dihydrotestosterone (DHT), the active form of the hormone, which is translated into the nuclear and induces cell proliferation [4] (figure 1).

Huggins and Hodges were the first to demonstrate that castration and oestrogen injection had therapeutic activity in men with metastatic prostate cancer [5-6]. Hormonal suppression options include orchiectomy, the most simple androgen suppressor, LH-RH antagonists, steroidal and non steroidal androgen blockers and estrogens (figure1). The different mechanisms of action for hormone manipulation drugs are listed in table 1. The major side effects of hormone suppression are loss of potency. Other toxicities are shown in table 1. A particular side effect of LH-RH agonists is the flare syndrome which must be prevented [7]. At the beginning of treatment with LH-RH agonists, a surge of LH, and a secondary increase of serum testosterone level is observed. This may induce pain increase and, more importantly, tumor growth with bladder retention, and spinal medulla compression. It can be prevented by anti-androgens administrated 15 days before the first injection of LH-RH agonist [8-10]. Long-term hormone suppression results in osteoporosis. This phenomenon has been well demonstrated in patients who receive hormone suppression for local-stage prostate cancer without bone metastasis. These patients have elevated markers of osteoporosis: osteocalcin pro-collagen, C-terminal propeptide, and collagen C-telopeptides and their estimated risk of fracture is 5% [11].

First-line hormone suppression: principles.
The basis of first-line hormone suppression is castration by either bilateral orchiectomy or LH-RH agonist administration [12]. Three questions are important at this stage: what is the role of complete anti-androgen blockade (CAB)? What is the optimal timing of hormonal suppression? And what is the optimal duration of treatment?
As for the first question, different trials were designed to study the impact of anti-androgen addition to castration or LH-RH agonist [13- 23]. Only several trials included a sufficient number of patients. One American Intergroup trial, which compared leuprolide with and without flutamide, demonstrated a significantly longer progression-free survival and median overall survival in the group of patients who received CAB [14]. However, further large-scale trials failed to demonstrate such a significant difference even when trials were designed to study good-prognosis patients [23]. Meta-analysis published in Lancet included 8275 patients from 27 randomized trials, 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. Patient on CAB present more significant side effects [24]. Consequently, CAB cannot be recommended as standard treatment of metastatic prostatic cancer.
To respond to the second question, a Bristish randomised trial has demonstrated a slight impact of immediate versus deferred hormone suppression in advanced prostate cancer [25]. The majority of patients had non metastatic but locally advanced disease (55%) at the time of randomisation. Patients of the deferred treatment group were treated when clinically significant progression occurred. All events occurred more rapidly in the deferred treatment group: progression from Mo to M1 disease, development of pain, need for transuretheral resection for local progression, pathological fractures, spinal cord compression, ureteric obstruction, and development of visceral metastases [25]. These data represent clear evidence that early androgen suppression is a must in patients with metastatic prostate cancer or locally advanced disease who have failed local treatment.
Androgen blockade must be continued indefinitely. Intermittent treatment consists of stopping the hormonal treatment when PSA reach its nadir level (6 to 9 months). Reintroduction of hormonal blockade could be done when symptoms reappear or when PSA reach 10 to 20 ng/ml. The aim of this intermittent treatment is to delay the occurrence of androgen-refractoriness and to decrease adverse events of hormone suppression [26]. Different phase II trials have been published [27- 34]; phase III trials are on-going [35-36]. This treatment option could be considered for patients with metastatic asymptomatic disease who have cancer responsive to hormonal treatment, aged more than 70 years with lower tumour volume or aged less than 70 years with Gleasson score less than 6. This type of treatment is not still standard [37].

Second line hormone-therapy.
Second line hormonal manipulation has generally low response rate ranging from 10 to 20%. The most frequently used further hormone therapy lines are: addition of anti-androgens, inhibitors of aromatase, estrogens, or Ketokonazole. Estramustine phosphate must be considered as a chemotherapeutic agent, even it is partly composed of estrogen molecule, because it acts as an inhibitor of microtubules and it is more active when combined to other cytotoxic drugs. If patients are treated with CAB, the anti-androgen agent must be stopped [38-39].
The observation of the development of gynecomastia in patients treated by ketoconazole for fungal infection set the stage for a totally new application for this drug. Oral Ketoconazole reduces serum testosterone to the castrate level range. In addition, the adrenal androgens androstenedione and dihydroepiandrosterone are dramatically reduced. The effect is due to an interaction with cytochrome P450-dependent enzymes active in the sex steroid-synthesizing organs [40-41]. The CALGB 9583 phase III study randomized 260 patients at the time of progression on combined androgen blockade to undergo either antiandrogen withdrawal (AAWD) simultaneous with ketoconazole or AAWD followed by ketoconazole at the time of PSA progression. The PSA response proportion to those undergoing antiandrogen withdrawal alone was 13% compared with 30% in the combination arm ($P < 001$). Fourteen percent of patients treated with ketoconazole/AAWD experienced objective responses. Overall survival in the two arms was not different approximatively 16 months, however this study allowed cross over and 108 (82%) of 132 of patients who were randomly assigned to AAWD eventually did receive ketoconazole. These data confirmed that ketoconazole is an active drug and may be considered an acceptable secondary hormonal therapy [42].

Hormone-resistant stage

Progression of prostate cancer to the hormone refractory status is a universal phenomenon which is not well understood. It may result of altered structure or expression of androgen receptors, altered androgen receptor signalling and interactions with other signal transduction pathways which possibly involve growth factor receptors [43]. Occurrence of hormone refractoriness is the major event during metastatic prostate cancer evolution.

Hormone resistance is clinically expressed in different situations: serum PSA level increase, progression of metastases, progression of pain and other symptoms while hormone deprivation is continued. Physicians must not forget that LH-RH antagonists must be continued during hormone refractory stage.

Chemotherapy

Chemotherapy was studied very early, in the 70s-80s, particularly in the setting of the National Prostate Cancer Project (NPCP) group [44]. Actually, only two cytotoxic agents are approved by the United States Food and Drug Administration for palliative treatment of HRPC. These are mitoxantrone and docetaxel.

Two corner-stone studies for mitoxantrone have been performed [45-46]. Both studies compared prednisone alone versus prednisone plus mitoxantrone. The trial designs were different: the Canadian study was designed to demonstrate a palliative advantage of mitoxantrone [45], the American CALGB study was armed to demonstrate a survival advantage [46]. Both studies failed to demonstrate any survival advantage. CALGB study randomly assigned 242 men with HRPC (65 percent of whom were taking analgesics for bone pain) to mitoxantrone (14 mg/m2 IV every three weeks) plus hydrocortisone (40 mg daily) or the same dose of hydrocortisone alone. Median survival was similar (approximately 12 months in both groups), and pain control was significantly better with combination therapy. Although the greater PSA response with combined therapy (38 versus 22 percent) achieved statistical significance, it was quantitatively similar to the earlier study, and the median time to disease progression was short in both groups (3.7 and 2.3 months, respectively) [46]. Another confirmatory study in asymptomatic patients showed a significantly prolonged PFS in the mitoxantrone arm but failed to prolong survival, its primary objective [47]. These study set mitoxantrone as standard first line treatment for hormone refractory metastatic prostate cancer.

Multiple phase II trials have tested the efficacy and toxicity of docetaxel in HRPC with weekly or three weekly regimen [48-54]. The TAX 327 trial published by Tannock in 2004 was the basis for the shifting of standard from mitoxantrone to docetaxel [55]. In this study, 1006 men with chemotherapy-naive metastatic HRPC were randomly assigned to docetaxel 75 mg/m2 every three weeks (D/P), or docetaxel 30 mg/m2 weekly
(WD/P)or mitoxantrone 12 mg/m2 every three weeks (M/P), with all patients receiving prednisone 5 mg orally twice daily. The primary endpoint was overall survival. At a median follow-up of 21 month, patients receiving every three week had a significantly longer median survival 18.9 when compared to the weekly docetaxel arm 17.4 months or the mitoxantrone arm 16.5 months. Moreover, three weekly docetaxel had a higher pain response rate (35 versus 31 versus 22 percent). As expected, grade 3 or 4 neutropenia during therapy was most common with D/P (32 versus 1.5 and 22 percent with wD/P, and M/P, respectively), although rates of neutropenic infection were low (3 versus 0 and 2 percent, respectively), and few patients discontinued therapy because of adverse effects (11, 16, and 10 percent with D/P, wD/P, and M/P, respectively). With longer follow-up, the survival benefit of every three week docetaxel has persisted (median survival 19.3 versus 16.3 months for mitoxantrone/prednisone). The corresponding three year survival rates were 18 versus 14 percent [56].
Another trial compared the combination of docetaxel and estramustin to mitoxantrone and prednisone and similarly showed a mild but significantly survival benefit of the docetaxel/estramustin arm [57]. This treatment arm was also associated with significantly more grade 3 or 4 gastrointestinal, cardiovascular, metabolic, and neurologic toxicity. Although these results confirm the superiority of docetaxel/Estramustin over mitoxantrone/prednisone, it is difficult to endorse the continued use of Estramustin in view of the similar survival benefit and better tolerability of docetaxel plus prednisone compared to mitoxantrone/prednisone in the TAX-327 study, and the elevated risk of venous and arterial thromboembolism in patients receiving Estramustin.
Vinorelbine was also evaluated in a phase III trial [58]. Patients with metastatic prostate cancer, progressive after primary hormonal therapy, were randomised to receive intravenous vinorelbine (VRL) 30 mg/m2 on days 1 and 8 every 3 weeks, and hydrocortisone (HT) 40 mg/day or hydrocortisone alone until disease progression. Second line hormonal manipulation was allowed for all patients. PFS was significantly prolonged in the VRL plus HT arm compared with the HT alone arm (p= 0.055). Clinical benefit, defined as a decrease in pain intensity or analgesic consumption or an improvement of Karnofsky PS for at least 9 weeks, and at least stable assessment in the other two, was also more frequently observed in patients who received VRL plus HT versus HT alone (30.6% and 19.2%; P = 0.008). There was no statistical difference in overall survival. This therapeutic gain is similar to that previously reported with mitoxantrone in combination with low-dose corticosteroids. The authors concluded that the combination Vinorelbine/HT is well tolerated in this elderly group of patients, who often present cardiac co-morbidities, and therefore offers an active and safe therapeutic option for patients with hormone-refractory prostate cancer.

One particular problem is the evolution of hormone-refractory prostate cancer through neuro-endocrine components. Patients with such evolution generally have visceral metastases, low serum PSA level, increase of neuro-endocrine markers (neurone-specific-enolase, chromogramin A). Specific protocols based on platin analogues, etoposide and taxanes have been developed [59]. Response rate is 30-40%. However no trial has demonstrated any impact of chemotherapy on patients survival.

Biphosphonates treatment

Bisphosphonates are pyrophosphate analogs that inhibit bone resorption. Zoledronic acid (Zometa, Novartis Oncology) is a highly potent intravenous bisphosphonate that is

approved for the treatment of patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Patients with prostate cancer are at high risk of bone complications since the most frequent site of metastasis in prostate cancer is bone and since ADT is associated with osteoporotic effects. Preventing the adverse skeletal effects in prostate cancer is increasingly important, because these patients have relatively long life expectancies.

Zoledronic acid was compared with placebo in prostate cancer patients with a history of metastatic bone disease who had a rising serum PSA level despite treatment with ADT in a randomized, double-blind clinical trial [60]. Zoledronic acid demonstrated a 25% reduction in the proportion of patients with a skeletal-related event (P = .021). The time to the first skeletal-related event was at least 100 days later in patients receiving zoledronic acid compared with patients receiving placebo (P =.01). These improvements with zoledronic acid are clinically significant and offer a new therapeutic strategy in prostate cancer patients with skeletal metastases.

Conclusion

Advanced prostate cancer is an incurable disease and treatment must be focused on palliation of symptoms. In the hormone sensitive stage, castration by either bilateral orchiectomy or LH-RH agonist administration is the cornerstone of treatment. CAB is an option but does not have a survival benefit comparing to LH-RH agonists alone. Early continuous androgen suppression is the most acceptable mode of LH-RH agonists administration however future trials evaluating intermittent treatment are awaiting to completely answer this question. In the hormone refractory stage, three weekly docetaxel and prednisone is the standard of care. Biphosphonate must be added to the arsenal treatment especially in this category of patients at high risk of bone related complications.

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TABLES

Table 1. Hormone treatments in prostate cancer: mechanisms of action and side effects.

Drug	Mechanism of action	Side effects
	LH-RH agonists	
Leuprorelin Goserelin Buserelin Triptorelin	- negative feed-back of pulsatile secretion of LH - initial LH surge	- flare-up syndrom - loss of potency - hot flushes
	Non steroidal antiandrogens	
Flutamide Bicalutamide nilutamide	- competitive blockade of DHT to receptors	- diarrhea - hepatotoxicity - flushing reactions - hemeralopy - pulmonary fibrosis
	Steroidal antiandrogen	
Cyproterone acetate	- inhibition of LH release - competitive blockade of DHT to receptors	
	Oestrogens	
Diethyl-stilbestrol Fosfestrol	- inhibition of LH release - inhibition of 5 ∝ reductase activity - direct cytotoxic effect	- loss of potenty - gynecomastia - thromboembolism

FIGURES

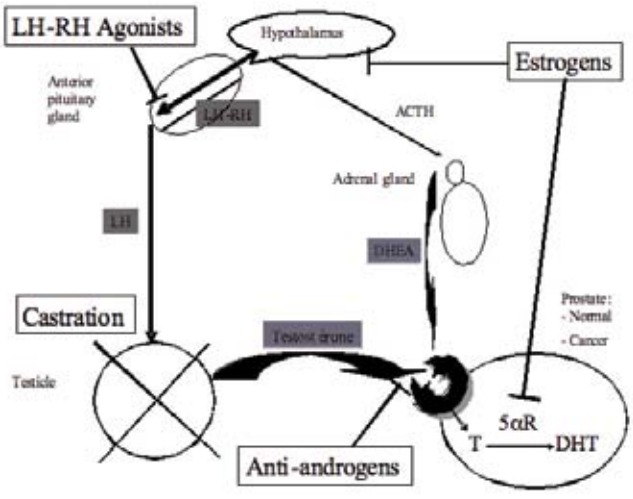

Figure 1