Prostate cancer: management of advanced disease

J.-P. Droz, A. Fléchon & C. Terret
Centre Léon-Bérard, Department of Medical Oncology, Lyon, France

Introduction

Advanced prostate cancer is an incurable disease. Treatment objective is palliation only. The major observation is that prostate cancer is a hormone-sensitive tumour. Huggins and Hodges [1] were the first to demonstrate that castration and estrogen injection had therapeutic activity in men with metastatic prostate cancer. The most frequent metastatic sites in prostate cancer are bone (85%), lymph nodes and further visceral metastases (liver, central nervous system, lungs) (45%) [2]. However, consequences of widespread metastases are important: bone pain, nervous compression and haematological and metabolic consequences. All these conditions must be taken into account in order to select the best treatment options leading to a better quality of life for the patient. This chapter focuses on the practical management of patients with advanced disease; treatment evaluation criteria and new therapeutic approaches will be developed in another section of this educational program.

Metastatic hormone-sensitive prostate cancer

Hormone deprivation is the major treatment at this stage of the evolution.

Mechanism of action of therapeutics

Normal and malignant prostatic 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 sulphate and androstenedione). Testicles and, to a lesser extent, adrenal glands are under the control of the anterior lobe of the pituitary. Luteinizing hormone (LH) stimulates testosterone production by the testes. Luteinizing hormone secretion is under the control of hypothalamic luteinizing hormone-releasing hormone (LH-RH). Production of LH-RH is pulsatile. It is reduced as a function of the serum testosterone level (feedback mechanism).

There are specific androgen receptors on normal and malignant prostate cells which allow the internalization of testosterone. Testosterone is then transformed into dihydrotestosterone (DHT), the active form of the hormone, which is transported into the nucleus where it induces cell proliferation (Figure 1). Drug and hormone manipulations have different mechanisms of action. The most simple androgen suppressor is castration. The mechanism of action of other hormone treatments are shown in Table 1. LH-RH agonists act as orchidectomy, other drugs are peripheral inhibitors of androgens. The major side effect of hormone suppression is loss of potency. Other toxicities are shown in Table 1. However, one particular side effect of LH-RH agonists, the flare syndrome, must be prevented. 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 an increase in pain and, more importantly, tumour growth with bladder retention, and spinal cord compression. It can be prevented by anti-androgens administered 15 days before the first injection of the LH-RH agonist.

Principles of first-line hormone suppression

The basis of first-line hormone suppression is castration by either bilateral orchidectomy or LH-RH agonist administration. Three questions are important at this stage: what is the role of complete anti-androgen blockade (CAB)? What is the impact of hormone suppression on survival? What is the optimal timing of hormone suppression?

Role of complete androgen blockade

Different trials were designed to study the impact of anti-androgen addition to castration. Only several trials included a sufficient number of patients. One Intergroup trial in the USA, 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 [3]. However, further large-scale trials failed to demonstrate such a significant difference [4] even when trials were designed to study good-prognosis patients. Meta-analysis was performed [5] but failed to demonstrate any significant impact of CAB on survival. Consequently, CAB cannot be recommended as standard treatment of metastatic prostatic cancer.

Impact of androgen blockade on overall survival

A UK randomized trial has demonstrated a slight impact of immediate versus deferred hormone suppression in advanced prostate cancer [6]. The majority of patients had non-
metastatic but locally advanced disease (55%) at the time of randomization. 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 M0 to M1 disease, development of pain, need of transuretheral resection for local progression, pathological fractures, spinal cord compression, ureteral obstruction and development of visceral metastases.

Early androgen blockade in patients with PSA level increase after treatment of local disease

The rise of serum PSA levels after curative treatment (either surgery or radiotherapy) is an indicator of infraclinical metastatic disease. Large randomized trials of immediate versus delayed androgen blockade have been performed. No data are yet available. Early treatment may not be recommended on the basis of current knowledge.

Role of intermittent androgen blockade

The aim of this intermittent treatment is to delay the occurrence of androgen refractoriness and to decrease adverse events of hormone suppression. Different phase II trials have been published, phase III trials are on-going. This type of treatment is still not standard [7].

Anti-androgen withdrawal syndrome

When patients are treated with the combination of LH-RH agonist (or orchidectomy) and anti-androgens, it is observed that anti-androgen withdrawal may induce some form of benefit in almost 30% of patients, such as a decrease in pain or a reduction of serum PSA levels [8]. This phenomenon seems to be dependent on the occurrence of mutations on androgen receptors and their ability to use anti-androgens as substrate. It is thus recommended that anti-androgen therapy be stopped when hormone resistance occurs after CAB.

Hormone resistance

Progression of prostate cancer to the hormone refractory status is a universal phenomenon which is not well understood. It may be the result of an altered structure or expression of androgen receptors or altered androgen receptor signalling and interactions with other signal transduction pathways, which possibly involve growth factor receptors [9].

Hormone refractoriness is clinically expressed in different situations: increases in serum PSA levels, progression of

Figure 1. Regulation of androgens. T, testosterone; 5αR, 5-α-reductase; DHT, dihydrotestosterone; DHEA, dehydroandrosterone.
metastases, progression of pain and other symptoms while hormone deprivation is continued.

Other therapeutic problems in the treatment of advanced prostate cancer

The major observation is that no treatment has survival impact at this disease stage. Only a few trials have studied the survival impact of therapeutics, but none have shown any survival benefit. Thus, treatment only has symptomatic (palliative) impact. Symptoms are either local or diffuse. Treatment options are based on the observation of symptoms. Symptoms and therapeutic tools are summarized in Table 2.

Systemic treatment of metastatic hormone refractory prostate cancer is discussed elsewhere in this issue.

Therapeutic tools

Radiotherapy

Radiotherapy is active in the treatment of localized pain with a response rate of 80%. It is administered in split courses because its objective is only palliative.

Radiopharmaceuticals

Two radiopharmaceuticals are used in the routine treatment of diffuse metastatic bone pains: strontium [10] and samarium [11]. They induce a 40% objective diminution of diffuse pains. Toxicity is rare: patients may experience slightly increased pain for several days after treatment, whereas moderate thrombocytopenia is observed in 5% of cases. This treatment is indicated when diffuse pain is due to diffuse osseous metastases on bone scan.

Second- and third-line hormone therapy

The most frequently used further hormone therapy lines are anti-androgens, inhibitors of aromatase and estrogens [12]. Response rate is generally low at 10–20%. However, estrogens have a symptomatic effect, even in heavily pretreated patients. Estramustine phosphate must be considered as a chemotherapeutic agent, even though it is partly composed of an estrogen molecule, because it acts as an inhibitor of microtubules. It is more active when combined with other cytotoxic drugs.

Clinical problems

Pain

Pain is the most frequent problem. The origin of pain is most often central, sometimes neuropathic. Pharmacological treatment is specific for each mechanism. However, specific treatments, mostly radiotherapy and radiopharmaceutics, are indicated.

Spinal cord compression

Spinal bone involvement is observed in 80% of patients. However, spinal cord compression occurs only 6% of patients.
Symptoms are local pain with characteristic metameric irradiations, dysesthesia in the same area and neurological central nervous compression signs in the legs, and eventually paraplegia [13]. Treatment is difficult. The risk of spinal compression is evaluated by magnetic resonance imaging (MRI). Radiotherapy is active in reducing pain, but may be insufficient to prevent spinal compression. Surgery is difficult because the benefits of laminectomy are generally only short-lived and more extensive surgery with consolidation procedures is generally impossible due to multiple vertebral involvement. Further prospective strategies must be developed.

**Consequences of long-term hormone suppression**

Patients with hormone suppression develop osteoporosis. This phenomenon has been well demonstrated in patients who receive hormone suppression for local-stage prostate cancer without bone metastasis. These patients have markers of osteoporosis: osteocalcin pro-collagen, C-terminal propeptide and collagen C-telopeptides. The estimated risk of fracture is 5% [14]. However, a majority of patients have osteoblastic bone metastases. Thus, a combination of osteoblastic and osteolytic metastases occurs in roughly 30% of patients. Bisphosphonates have been studied in this patient population in randomized trials. They support the use of bisphosphonates that have been shown to improve pain control and quality of life. A large National Cancer Institute Canada Protocol comparing mitoxantrone plus prednisone with or without intravenous clodronate for patients with symptomatic bone metastases has been completed.

**Surgery of bone metastases**

As in other bone metastases, several orthopedic procedures may be used: vertebrectomy with consolidation, intramedullar nail, total hip replacement. The principal problems are linked to the fact that bones are grossly involved and material may not be well fixed. After surgery bone is generally irradiated in split courses.

**Urinary system compression**

Urinary system compression is a frequent symptom in patients who have not received previous specific local treatment for prostate cancer, but may also occur after prostate radiotherapy and, rarely, after prostatectomy. It induces bladder retention requiring transurethral resection. The major risk is urinary incontinence. Sometimes the tumour involves the trigon and spreads around the ureters. Unilateral or bilateral hydronephrosis is then observed, with a risk of renal failure. This evolution generally requires the use of an intraureteral catheter. Follow-up by urinary tract ultrasonography is proposed.

**Intracranial central nervous system involvement**

Intracranial involvement is classically infrequent, with only a 7% incidence in autopsy studies. Recent clinical experience may suggest an increased incidence of these types of metastases. They are most commonly related to dural involvement. The most frequent symptoms are jugular foramen syndrome (pain of occiput, auricular region and shoulder), clivus syndrome (headache and VI to XII palsies), cavernous sinus syndrome (III to VI palsies, ophthalmoplegia, facial numbness), orbital syndrome (pain and exophthalmy), and mental neuropathy [15]. Several patients have true encephalopathy syndrome. Diagnosis of dural involvement is often made by MRI imaging. Radiotherapy is often active against symptoms. However, all these symptoms must be differentiated from cerebrovascular disorders which are frequent in this elderly patient population.

**Haematological disorders**

Pancytopenia (mostly anaemia and thrombocytopenia) may be due to bone marrow involvement. Haematological diagnosis must be made because it may lead to active treatment by chemotherapy and/or estrogens [16].

Intravascular coagulopathy is frequently observed. It includes thrombocytopenia, decrease of coagulation factors (II and VII), increase of D-dimers, of degradation products of
fibrin, and presence of schizocytes. It is often only a biological phenomenon without clinical significance. When clinically expressed (haemorrhage), it is treated by low-dose heparin, fibrinogen and platelet transfusions, and specific treatment (low-dose estrogens, high-dose estrogens, such as fosfostrol phosphate, or chemotherapy). However prognosis is poor.

**Inflammatory syndrome**

Patients with advanced disease and multiple treatment lines express inflammatory syndrome. At this end-stage, fever and weight loss are frequent. Treatment is only symptomatic, although corticosteroids and estrogens (diethylstilbestrol 1 mg) may induce some palliative benefit.

**Practical management of patients**

The median survival of patients with metastatic prostate cancer is 3 years, though it is only 1 year when the tumour is hormone refractory. The number of possible problems is great, but the major one is pain. The number of therapeutics is also great. They have only palliative and symptomatic impact. Early hormone suppression in patients with advanced disease may have slight survival impact. Thus, a general scheme of management can be proposed, based on several principles:

- Early hormone suppression is proposed in metastatic prostate cancer. Hormone suppression is achieved either by castration or treatment with LH-RH agonists.
- Powerful tools must be used to measure palliative impact: pain and analgesic scales, quality of life evaluation. PSA decrease may only be a surrogate of clinical response evaluation.
- After first-line hormone suppression, indication of further hormone therapy, chemotherapy and radiopharmaceutics is based only on symptomatic progression. It is not based on tumour progression as measured by PSA increase or metastasis evolution, because it is well established that, to date, treatment has only a palliative effect.
- Management of local problems (urinary obstruction, fracture, nerve compression) must be done depending on the situation.
- Other general problems occur which require specific management.
- Patients must be clearly informed of the palliative endpoints, therapeutic tools, current side effects and goals of treatment. The strategy must be prospectively explained in the early stages of treatment.

Table 3 summarizes the different problems encountered and proposes a timetable of successive treatments. Several questions still remain unsolved:

- Is simple androgen blockade or even anti-androgen alone sufficient?
- What is the true usefulness of third-line hormone treatment? However, it seems that second-line treatment, being either anti-androgen withdrawal or anti-androgen addition depending on first line treatment, has some symptomatic activity.

### Table 3. Proposed chronology of treatment

<table>
<thead>
<tr>
<th>Advanced disease: early first-line treatment</th>
<th>Specific treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androgen-blockade (castration or LH-RH agonist)</td>
<td>Local therapeutics</td>
</tr>
<tr>
<td>Hormone refractory disease: therapeutics are indicated on symptom occurrence</td>
<td>Local radiotherapy</td>
</tr>
<tr>
<td>General treatment</td>
<td>Transurethral resection</td>
</tr>
<tr>
<td>Second-line hormone therapy</td>
<td>Endoureteral catheter</td>
</tr>
<tr>
<td>Antiandrogens</td>
<td>Spinal cord compression surgery</td>
</tr>
<tr>
<td>Aromatase inhibitors</td>
<td>Orthopaedic surgery</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Drugs</td>
</tr>
<tr>
<td>Mitoxantrone prednisone</td>
<td>Analgesic</td>
</tr>
<tr>
<td>Trial</td>
<td>Bisphosphonate</td>
</tr>
<tr>
<td>Radiopharmaceutical</td>
<td>Calcium and vitamin D₃</td>
</tr>
<tr>
<td>Corticosteroid plus estrogens</td>
<td>Treatment of intravascular coagulopathy</td>
</tr>
<tr>
<td></td>
<td>Corticosteroids</td>
</tr>
</tbody>
</table>

**Terminal care**

LH-RH, luteinizing hormone-releasing hormone.
What are the maximal fields of radiotherapy which do not impair the use of chemotherapy and radiopharmaceuticals?

What is the best timing for chemotherapy and radiopharmaceuticals? The relative activity of different treatment sequences is unknown. Furthermore, these treatments have not been compared together. It may also be possible that chemotherapy induces more platelet toxicity after radiopharmaceutical administration.

What should the timing of treatment (radiotherapy, surgery) be in metastatic disease to the backbone?

Should there be a particular management strategy for elderly patients? There are arguments to think that comprehensive geriatric assessment may help to tailor more actively specific treatments [17].

However, it is recommended that patients with metastatic prostate cancer should be included in prospective trials armed to demonstrate either palliative or survival impact. Although these patients must be evaluated carefully before any decisions about treatment are made. Decisions are always multidisciplinary. Evaluation of treatment results must be performed at each step of therapy.

Acknowledgements

The authors thank Mrs Marie-France Mévellec for help in the preparation of the material and Mrs Marie-Dominique Reynaud for editing the manuscript.

References