Systemic treatment for prostate cancer

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Treatment of metastatic prostate cancer

Hormone therapy

Patients with symptomatic metastatic prostate cancer should be treated by androgen deprivation. Historically this was accomplished by surgical castration. However, the standard treatment in modern medicine is the use of a luteinizing hormone-releasing hormone (LHRH) agonist such as goserelin acetate (Zoladex®) or leuprorelin acetate (Prostap®), which have an effect equivalent to castration on testosterone level and on prostate cancer response [1]. They act by downregulation of pituitary receptors and the consequent inhibition of release of follicle stimulation hormone (FSH) and leutinizing hormone (LH) with a decrease in testosterone production from the testis. These agents initially mimic the natural hormone and cause a transient rise in testosterone and their inception should be covered by an anti-androgen at full dose to prevent worsening of symptoms such as bone pain or urinary obstruction. A standard approach is to use anti-androgens for 7 days prior to the first LHRH agonist injection and for 14 days following it. Depot preparations of LHRH agonists lasting at least 3 months are as effective as the 1-month preparations.

Direct LHRH antagonists such as abarelix have been developed that avoid the tumor flare phenomenon. Preliminary assessments suggest equivalent response rates to the agonists [2].

In hormone-naïve patients with symptomatic metastatic disease, approximately 85% have a symptomatic response for a median of 12–18 months. Duration of response appears to relate to the burden of disease and patients treated with hormone therapy for localized or soft tissue disease tend to have longer responses than those with multiple bone metastases. The non-steroidal anti-androgen, bicalutamide appears to be less effective than castration in patients with metastatic disease [3].

A range of trials investigated the concept of complete androgen blockade in which an anti-androgen was added long-term either to surgical castration or to an LHRH agonist. A report based on more than 8000 patients randomized to either androgen ablation or to androgen ablation plus an anti-androgen showed no meta-analysis that combined androgen blockade is not more effective than simple medical or surgical castration with 5-year survival rates of 25.4% and 23.6%, and 10-year survivals of 6.2% and 5.5%, respectively [4].

Another issue, addressed in a more limited way, is whether asymptomatic patients with metastases should be treated immediately or whether hormone therapy should be deferred until they develop symptoms. A Medical Research Council (MRC) trial [5] suggested an advantage to early treatment. However, the advantage was seen in patients with locally advanced rather than disseminated disease. There seemed a clear benefit to early treatment in preventing some of the more distressing complications of metastatic prostate cancer. The advantage of early hormone therapy in locally advanced prostate cancer was also seen in a European Organization for Research and Treatment of Cancer (EORTC) trial [6].

Side-effects of androgen ablation

Common side-effects of androgen ablation include loss of libido and hot flashes, but a range of others have been reported such as fatigue, weight gain, depression, memory loss and loss of bone mineral density. Osteopenia is a particular problem of long-term therapy, but may be prevented by bisphosphonates [7].

Intermittent hormone therapy

This is based on the idea that allowing reversal of the castrate state may prolong the period to development of androgen-independence and improve quality of life [8]. Results from phase III trials are needed to evaluate the place of this approach.

Hormone-refractory prostate cancer

There are a number of systemic management approaches for the patient with prostate cancer progressing while on hormone ablation therapy. These include secondary hormone manipulation, cytotoxic chemotherapy, systemic isotope therapies and bisphosphonate therapy. Since the predominant pattern of metastatic prostate cancer includes bone and pelvic lymph node metastases the most prevalent clinical problems are bone pain, urinary obstruction, spinal cord compression, lymph edema of the lower limbs, anemia and cachexia.

Management of patients who have failed hormone ablation therapy is more difficult than treating patients who are hormone-naïve since second-line treatments tend to have only transient benefit. Early referral for palliative and supportive care should be considered, including radiotherapy for bone pain, spinal cord compression, lymph edema or hematuria. The sequence of further therapeutic attempts is influenced by factors such as the disease-free interval induced by primary hormone therapy, the grade and growth rate of the cancer and the specific symptoms, general health and performance status of the patient.

Second-line hormones

The first approach to patients who become refractory to hormone ablation is usually with an additional hormone...
treatment such as an anti-androgen or simple use of prednisone to cause adrenal suppression, either of which leads to a further remission in about 15%–20% of patients [9]. The thinking behind these interventions is that low levels of androgen continue to be produced from other organs, especially the adrenal glands, and access of these to the prostate cancer can be blocked by an anti-androgen or, alternatively, production from the adrenal can be stopped by physiological levels of replacement adrenal steroid such as prednisone 7.5 mg/day.

A further effective hormonal agent, although probably more toxic, is estrogen such as stilboestrol [10]. The risks are thrombo-embolism, gastro-intestinal upset and, occasionally, fluid retention.

chemotherapy
Chemotherapy is being explored increasingly in the management of patients with prostate cancer especially now that sensitive measures of response based on prostate specific antigen (PSA) enable early detection of progression on hormone therapy. The recent demonstration of a survival advantage to inclusion of docetaxel in first-line chemotherapy has encouraged this trend.

In the past there has been investigation of estramustine as an anti-cancer agent specific to prostate cancer, based on a conjugate of nitrogen mustard and oestradiol. It has modest activity but it is associated with significant gastrointestinal toxicity. The modern era of prostate cancer chemotherapy was heralded by a seminal trial by Tannock et al. [11] who randomized patients between mitoxantrone at 12 mg/m² plus prednisone 10 mg versus prednisone alone. There was significant benefit to the use of mitoxantrone in terms of pain scores and analgesic use but no overall difference in PSA response or survival. This result was essentially confirmed in a CALGB trial.

Taxanes also have activity in prostate cancer and appeared on phase II and comparative studies to be more effective than mitoxantrone [12]. An industry-sponsored multi-national trial comparing docetaxel to mitoxantrone (both with prednisone) was reported recently. The TAX327 study was a three-armed phase II and comparative studies to be more effective than taxane-resistant cell lines. A small phase III trial showed evidence of biochemical response with minimal toxicity [17] and a larger international trial (SPARC) comparing satraplatin plus prednisone against placebo plus prednisone as second-line chemotherapy has completed recruitment.

As discussed further below, there is considerable interest in combining such cytotoxic chemotherapy with growth factor receptor inhibition or other targeted agents such as calcitriol [18]. Biologically targeted approaches are still in early trial [19], including investigations of anti-angiogenic drugs such as thalidomide [20], endothelin receptor antagonists [21] or vaccine immunotherapies.

isotope therapy and bisphosphonates
Patients with multiple sites of painful bone metastasis have been treated with the bone-seeking isotopes strontium-89, rhenium-186 or samarium-153 [22]. These technologies give effective pain relief in approximately 70% of patients and trials have suggested that in comparison with more localized palliation from external beam radiotherapy there is a delay in the time to the next skeletal-related event [23]. Treatment seldom causes any symptomatic toxicity, although myelosuppression may impair subsequent tolerance to cytotoxic chemotherapy.

There is also considerable interest in the role of bisphosphonates to inhibit prostate cancer metastases in bone. A placebo controlled phase III trial of pamidronate, a second generation bisphosphonate that has demonstrated in vitro activity against taxane-resistant cell lines. A small phase III trial showed evidence of biochemical response with minimal toxicity [17] and a larger international trial (SPARC) comparing satraplatin plus prednisone against placebo plus prednisone as second-line chemotherapy has completed recruitment.

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Bisphosphonates have the risk of a number of side-effects including fatigue, anemia, myalgia, edema, jaw necrosis and weight loss. Thus the role of bisphosphonates in patients with advanced metastatic prostate cancer requires further study.

**developments in drug therapy**

Increases in antitumor activity, which may be possible with combinations of currently available cytotoxic agents, are likely to be limited by unacceptable toxicities, especially in patients heavily pretreated with docetaxel or systemic isotopes. However, there is potential for combining chemotherapy with signal transduction inhibitors or other targeted agents.

For example, calcitriol [27], which binds the vitamin D receptor and has differentiation, anti-proliferative, pro-apoptotic and anti-angiogenic properties, has been assessed as a high-dose oral formulation (DN-101) in a small randomized trial (ASCENT) with weekly docetaxel and appeared to lead to a lower risk of skeletal events (hazard ratio 0.78) and a longer median overall survival (23.5 versus 16.4 months) [28].

The vascular targeting agent, bevazumab is also now in a phase II trial being studied with docetaxel, and there are early and encouraging studies of endothelin receptor antagonists [21] and of thalidomide [29].

Immunotherapeutic approaches include vaccines [30] and dendritic cells presenting a prostactic acid phosphatase antigen (Provenge) [31].

The systemic treatment of castration-independent prostate cancer has become a major focus of biological and therapeutic research.

**references**