Management of Advanced Prostate Cancer

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Prostate cancer is one of the most common cancers in men; with an incidence of 1369 new cases in 2008 (crude incidence rate 41.5 per 100000 people) in our locality, and it is now the third most common cancer in males in Hong Kong.\(^1\) Despite the fact that the disease is a highly curable disease if diagnosed at an early stage, still many people will suffer from advanced and metastatic disease, with about 300 patients died of the disease in 2008 in Hong Kong.

Both normal and malignant prostatic cells are dependent on androgens for growth, function and proliferation. Therefore, androgen deprivation therapy (ADT) has been used as the mainstay to treat advanced stage disease. Androgen mainly comes from the testicles, which produce testosterone (up to 95% of all androgens) and the adrenal glands (dehydroandrosterone, dehydroandrosterone sulphate and androstenedione). The testicles, and to a lesser extent, the adrenal glands are under control of the pituitary gland. The hypothalamic-pituitary-testis axis is the main target for ADT. Commonly used ADT is castration by either bilateral orchidectomy or lutenising hormone-releasing hormone (LH-RH) agonist administration. Both treatments can effectively decrease serum testosterone to less than 50ng/dL. Bilateral orchidectomy (surgical castration) is still considered as the “gold standard” for ADT in prostate cancer. The surgical approach can be total (removing both testes) or subcapsular (removing only the seminiferous tubules of the testis); and can be done under even under local anaesthesia. It provides the fastest action amongst all ADT and achieves the castration level within 12 hours. The side effects of bilateral orchidectomy include the intrinsic risks related to anaesthesia and surgery. Also some patients may not accept the concept of castration (loss of the “male-image”).

Under normal physiological conditions, the hypothalamus secretes luteinising hormone-releasing hormone (LH-RH) in a pulsating manner to simulate the secretion of luteinising hormone (LH) from the pituitary. Therefore by giving an injection of an LH-RH analogue, the constant serum level of LH-RH will mask the pulsating stimulation of LH-RH to the pituitary and hence results in a drop in testosterone level. Currently there are several LH-RH analogues with different dosing frequencies (from 1 month to up to 1 year) available for usage.\(^2\) In general, the usage of LH-RH analogues is quite safe with no major specific side effects. However, if patients have advanced disease, such as bone metastases, it will be safer to start the patient first on antiandrogen (androgen receptor blockers) at least 2-3 weeks prior to commencement of LH-RH analogues to avoid the “flare” phenomenon. This condition is related to a sudden increase in serum LH-RH analogue level after the initial injection and will lead to a strong stimulation to the pituitary and hence excessive release of LH and testosterone production. The development of an LH-RH antagonist, Degarelix, which has been shown to cause rapid and significant reductions in testosterone and prostate-specific antigen (PSA) levels, without the “flare” phenomenon as the LH-RH agonists.\(^3\) This rapid onset of action is particularly relevant in patients with symptomatic disease who require a more rapid effect of ADT.

While ADT provides very effective control of prostate cancers, it also has certain side effects that may have long-term consequences to patients.\(^4\) The early side effects of ADT include loss of libido, erectile dysfunction, hot flush, mood changes etc. After prolonged usage, patients may suffer from osteoporosis, increase in metabolic complications – such as dysglycaemia, dyslipidaemia, and also increased cardiovascular morbidities and mortalities. The long-term side effects are particularly important for those patients who have slow disease progression. Therefore, currently there are suggestions that the intermittent usage of ADT may provide a balance on disease control and the quality of life of the patients.\(^5\) However, further studies are needed to define the specific group and protocol for the application of this intermittent therapy in clinical practice.

Unfortunately, despite the effectiveness of these treatments, there are still a proportion of patients who will develop further disease progression and ultimately succumb as a result of advanced disease. Anti-androgen receptor blockers (anti-androgens, e.g. bicalutamide, flutamide, etc) could be used to further block the androgen receptors, which will help to minimise the effects of adrenal androgen on the tumour cells and lead to a drop in serum prostate specific antigen and disease control. Unfortunately, the effects of anti-androgen typically result in only a transient response in terms of 4 to 6 months only. Then these patients will be considered as in a “hormonal refractory stage”. Classically, the patients may try some further hormonal manipulation, including anti-androgen withdrawal, oestrogen, steroids etc.\(^6\) However, the response rate is usually low and also with only a short duration.

After the failure of ADT, chemotherapy will be the other treatment modality for these patients, in particular for those with relative good general condition.
Mitoxantrone, estramustine and docetaxel are three chemotherapy agents currently approved by FDA for first line treatment in hormonal refractory patients. Recent studies have established the combination of Docetaxel and prednisolone as the standard of care for these patients. The tolerability of docetaxel is relatively good, except for the risk of marrow suppression. Various other combinations of chemotherapy have been used with doxitacexal, but none has demonstrated superiority to the docetaxel/ prednisolone combination. Newer chemotherapy, cabazitaxel, has also been approved by the FDA for the treatment of hormone-refractory prostate cancers in 2010.

Sipuleucel-T immunotherapy is a vaccine-based immune therapy. It consists of two prostate cancer cell lines that have been modified to secrete granulocyte-macrophage colony-stimulating factor (GM-CSF), which is an immune-stimulatory cytokine that plays a key role in stimulating the body’s immune response. Although FDA has already approved this drug for use in hormonal refractory prostate cancers, analyses for its real benefits are still underway and it is also very expensive.

For those patients with bony metastases, external beam radiotherapy can be employed for the control of symptoms. Also for patients with known metastases to the spine and long limb bones, prophylactic irradiation may be considered to decrease possible future complications such as fractures, cord compression etc.

Bisphosphonates are potent inhibitors of bone resorption. Data have shown that they significantly reduce skeletal complications in patients with bone metastases from a variety of solid tumours. Zoledronic acid is the most potent bisphosphonates available, and is the only bisphosphonate shown to reduce the incidence and time to the development of skeletal-related events (SREs) in metastatic prostate cancers. Besides the use of zoledronic acid in the metastatic stage, there are also a few studies suggesting that zoledronic acid can also help in preventing ADT-related bone loss.

In recent years, there are many breakthroughs in the understanding of the development of various stages of prostate cancer, in particular the hormonal failure stage. In fact, there are many new proposed mechanisms to account for the development of the hormonal refractory stage, including the self production of androgen (autocrine action), the up-regulation of androgen receptors to adapt to the low androgen stage etc. Therefore, the most appropriate description of this stage of disease is “castration refractory”, rather than “hormonal refractory”, as the tumour is still responsive to the stimulation of androgen. These new observations have led to the development of many new agents that will target on these castration-refractory prostate cancers.

Abiraterone acetate is a potent and highly selective irreversible inhibitor of cytochrome P-17, a dual enzyme that blocks adrenal androgen production. Studies have shown that despite being “hormone refractory”, prostate cancer cells continue to express high androgen receptor expression. Use of Abiraterone and prednisolone has shown to slow down the disease progression, with good patient tolerance. MDV3100 is a novel AR antagonist selected for activity in prostate cancer cells. It blocks nuclear translocation of AR and DNA binding, and has no agonist activity when AR is over-expressed. Preliminary studies have shown favourable tumour response. Further data are awaited.

In summary, with further understanding on the pathophysiology of prostate cancer cells, those patients who progress after orchidectomy or traditional LH-RH antagonists are still “hormone responsive”. Newer agents are being developed to target these cancer cell characteristics and more options will be expected for CRPC in the future.

References
4. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak E, et al. Sipuleucel-T immunotherapy is a vaccine-based immune therapy. It consists of two prostate cancer cell lines that have been modified to secrete granulocyte-macrophage colony-stimulating factor (GM-CSF), which is an immune-stimulatory cytokine that plays a key role in stimulating the body’s immune response. Although FDA has already approved this drug for use in hormonal refractory prostate cancers, analyses for its real benefits are still underway and it is also very expensive.

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