Metastatic prostate cancer – EML

The application sought endorsement of medicines already listed on the Model List of Essential Medicines for the treatment of metastatic prostate cancer: docetaxel, dexamethasone, calcium and vitamin D. The application also sought the addition of leuprorelin (as representative of the class of luteinizing hormone-releasing hormone (LHRH) agonists), bicalutamide and diethylstilbestrol to the core list of the Model List for the same indication.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Prostate cancer is the second most common cancer among men globally, with an estimated 1.1 million new cases and more than 300 000 deaths annually *(1)*. Although the majority of patients in resource-abundant regions are diagnosed with localized (and potentially curable) disease, patients in resource-limited regions typically present with advanced disease.

Androgen suppression, via either surgical or medical castration, is the mainstay for advanced disease. Both options are equally efficacious; multiple randomized trials have documented improvements in disease progression with the use of androgen suppression *(2)*. Androgen suppression reduces tumour volume, improves symptoms and delays progression; however, it poses serious limitations since it is a palliative therapy and may reduce quality of life. Surgical castration, via bilateral orchiectomy, is a more cost–effective option and overcomes the problems of medication non-compliance and poor access to healthcare *(2)*. For patients whose quality of life would diminish substantially if they underwent orchiectomy, medical castration may represent a reasonable alternative. The primary forms of medical castration are gonadotropin-releasing hormone (GnRH) agonists, administered either alone or in combination with an antiandrogen (complete androgen blockade) *(3)*.

The effect of androgen suppression on prostate cancer progression is finite and the disease will eventually progress from "castration-sensitive" to "castration-resistant". Despite initial response rates of 80–90%, nearly all men eventually develop progressive disease following androgen suppression. Castration-resistant prostate cancer, potentially treated with the addition of chemotherapy, is characterized by a median overall survival of between 1 and 2 years.

Public health relevance

Prostate cancer is known to be the sixth most common cancer in the world and the third most common among men *(4)*. Prevalence varies hugely with geography and ethnicity,

which may be attributed to differences in genetic susceptibility or external factors, such as environment and differences in health care. Unfortunately, only limited information is available on the specific epidemiology of metastatic prostate cancer. The mean age of men with prostate cancer is 72–74 years *(4).*

Requirements for diagnosis, treatment, and monitoring

Diagnostics

The diagnosis of prostate cancer is most often made by histological examination of a biopsy of the primary tumour/prostate gland (common) or metastasis (less common) using haematoxylin–eosin staining *(5)*. Core needle biopsy of the prostate is often performed with imaging assistance (e.g. transrectal ultrasound); a minimum of 12 cores are typically obtained to reduce sampling error. In advanced disease, however, a biopsy of a distant metastatic site can confirm extraprostatic disease. A surgeon usually performs the prostate biopsy under local anaesthesia. In addition to a morphological description, the pathologist should grade the cancer using the Gleason grading system, which not only characterizes the architecture of the prostate cancer but also provides prognostic information *(6)*.

Serum prostate-specific antigen (PSA) serves as a sensitive but not specific tumour marker, providing both diagnostic and prognostic information. If PSA is elevated, imaging studies (plain X-rays, ultrasound, radionuclide bone scan and/or computerized tomography scan, or magnetic resonance imaging) can clarify potential sites of distant disease. A rise in PSA during treatment indicates the need for further testing and/or treatment. Imaging studies should also be directed toward symptomatic areas (e.g. back pain, bone pain) and again can confirm the presence of metastatic disease.

Metastatic disease is further classified depending on the site of disease (e.g. regional lymph node involvement, non-regional lymph node involvement, involvement of bone, or involvement of another site).

On occasion, a presumptive diagnosis of metastatic prostate cancer can be reasonably made on the basis of concurrent findings of widespread metastatic disease in an expected distribution (e.g. bones, lymph nodes) along with a markedly elevated PSA (hundreds to thousands range), particularly if a biopsy cannot be performed or reasonably evaluated by an experienced individual.

Testing

Once the diagnosis of metastatic prostate cancer has been established, the following investigations should be carried out: PSA, comprehensive metabolic panel to assess renal and hepatic function, and complete blood count. For patients actively undergoing therapy with androgen deprivation, PSA is monitored every 3–6 months. If PSA is rising, a serum testosterone should be obtained to determine whether therapy is suppressing testosterone into the castrated range. Rising PSA despite castrated levels of testosterone reflects the

development of castration-resistant prostate cancer, the lethal form of advanced prostate cancer.

Administration and care of patients

Given the role of testosterone in the pathogenesis of prostate cancer, the initial treatment for patients with castration-sensitive metastatic disease is androgen deprivation therapy (ADT). Androgen deprivation can be induced either medically or surgically (i.e. orchiectomy) with equivalent efficacy, although bilateral orchiectomy is the more cost–effective option *(7, 8)*.

Bilateral surgical orchiectomy – the removal of both testicles via a scrotal incision – should be performed by a trained surgeon under sterile operating conditions. This procedure, performed as an outpatient operation, immediately reduces testosterone level and may be particularly useful when testosterone reduction is needed urgently.

GnRH agonists are the mainstay of medical castration and achieve a reduction in serum testosterone similar to that achieved by surgical orchiectomy *(9, 10)*. Administration of GnRH agonists results in the down-regulation of luteinizing and follicular-stimulating hormones; however, initiation of treatment with GnRH agonists may cause a surge of testosterone *(9)*. Consequently, a short course of an oral antiandrogen, such as bicalutamide, is recommended at the start of therapy to prevent transient worsening of cancer-related symptoms, such as urinary retention or pain, which are considered as "flare" responses *(7, 11)*. GnRH agonists are administered either intramuscularly or subcutaneously and the duration of effect (typically 1–6 months) varies with formulation. Patients should be monitored for local reactions (including allergic skin reactions) as well as adverse effects secondary to androgen suppression. Importantly, patients should be monitored for the behavioural and neurological effects of ADT, including depression.

PSA should be measured every 3–6 months. Although most patients will respond to ADT, the effect of ADT is finite and the cancer will subsequently progress as evinced by PSA, imaging or worsening of cancer-related symptoms despite castrate levels of testosterone (castration-resistant prostate cancer).

Additional treatment options for castration-resistant prostate cancer include therapies that target the androgen pathway (abiraterone and enzalutamide), immunotherapy (sipuleucel-T), and radiopharmaceuticals (radium-223). However, these agents are still in development and thus far have provided a relatively small benefit; moreover, current costs limit the use of these agents, which are therefore not proposed to for addition to the EML at this time.

A phase II trial and other small series have shown a benefit of using low-dose conjugated estrogens (diethylstilbestrol or fosfestrol), together with warfarin therapy, with PSA responses of up to 79% *(12, 13)*. This has been recommended as an alternative second-line approach in resource-deprived regions that do not have access to other standard medications *(14, 15)*.

Overview of regimens

The following provides basic information on administration and dosing for ADT with surgical orchiectomy and LHRH agonists.

Surgical option for castration-sensitive metastatic prostate cancer when LHRH agonists are not available or affordable

- **ADT: bilateral orchiectomy and supportive measures**
  - surgical orchiectomy
  - calcium 1000 mg orally daily
  - vitamin D 2000 IU orally daily

Standard regimens for castration-sensitive metastatic prostate cancer

- **ADT: LHRH agonist (when bicalutamide is not available)**
  - leuprorelin 7.5–22.5 mg IM every 1–3 months
  - calcium 1000 mg orally daily
  - vitamin D 2000 IU orally daily

- **ADT: LHRH agonist**
  - leuprorelin 7.5–22.5 mg IM every 1–3 months
  - bicalutamide 50 mg orally daily
  - calcium 1000 mg orally daily
  - vitamin D 2000 IU orally daily

Note: Leuprorelin is proposed to be added to the EML as a class agent, to include similar LHRH agonists.

Regimen for castration-sensitive metastatic prostate cancer with high volume of disease (visceral metastases and/or four or more bone metastases)

- **ADT plus docetaxel**
  - leuprorelin 22.5 mg IM every 3 months
  - bicalutamide 50 mg orally every day
  - docetaxel 75 mg/m^2 IV every 3 weeks x 6–9 cycles
  - dexamethasone 8 mg orally twice daily for 3 days, beginning the day before docetaxel for patients not receiving prednisone
  - calcium 1000 mg orally daily
  - vitamin D 2000 IU orally daily

Alternative regimen for use when LHRH agonists are not available or affordable

- diethylstilbestrol 1–3mg orally daily (in conjunction with warfarin therapy)

Review of benefits and harms

Benefits

Androgen suppression, initially performed via orchiectomy, has been a recognized treatment for prostate cancer for approximately 75 years since the role of testosterone in the pathogenesis of prostate cancer was elucidated.

Orchiectomy: Data from the Veterans Affairs Research Service Cooperative Urological Research Group revealed that progression from extraprostatic extension to distant metastases within 10 years was significantly improved in men receiving orchiectomy (32%) versus placebo (62%) *(16, 17)*. The Group also found an increased 5-year overall survival among patients in the treatment arm (32%) versus placebo (20%) *(18)*. The benefits of surgical treatment over medical androgen deprivation include cost and patient adherence.

LHRH agonists: Multiple studies have compared LHRH agonists with surgical orchiectomy. A systematic review covering 10 randomized trials and nearly 2000 men found no difference between LHRH agonists and surgical orchiectomy (hazard ratio, 1.13; 95% CI: 0.92–1.39) *(8)*. LHRH agonists are often the first line of therapy as they are greatly preferred by patients to surgical castration *(19)*.

An overview of randomized controlled trials and meta-analysis explored whether early ADT improves outcomes compared with deferred therapy *(20)*. The early initiation of androgen suppression reduced prostate cancer-related mortality but did not improve overall survival. Early therapy is associated with higher costs and greater frequency of treatment-related adverse effects *(21)*. Deferred treatment risks the development of hormone independence in the tumour as well as serious complications such as spinal cord compression. In fact, immediate treatment with either surgical orchiectomy or LHRH agonists was associated with reduced risk of pathological fracture, spinal cord compression and ureteric obstruction *(22)*. For these reasons, androgen suppression is often initiated early.

Docetaxel in combination with prednisone is still considered the reference systemic therapy for patients with metastatic hormone-refractory prostate cancer, and studies of combination therapy with docetaxel and other chemotherapeutic agents have been disappointing *(23, 24)*. Docetaxel plus prednisone achieved statistically significantly higher overall survival than mitoxantrone plus prednisone. Docetaxel was also associated with improved response rate, quality of life, pain response and PSA decline, with statistically significant benefits for all outcomes except response rate.

Harms and toxicity considerations

Adverse effects of ADT include sexual dysfunction, vasomotor symptoms (e.g. hot flushes), anaemia, behavioural and neurological effects, diabetes, cardiovascular disease and decreased bone density. Given the risk of osteoporosis and pathological fracture, a baseline measurement of bone density is recommended, as are calcium and vitamin D supplementation and exercise *(25)*. Anaemia is typically mild and does not usually necessitate specific therapy. Vasomotor symptoms can be treated supportively. In order to minimize the side-effects of ADT, researchers attempted to compare intermittent with continuous androgen deprivation. The results were inconclusive and continuous therapy remains the standard of care *(26)*.

Among ADT agents, diethylstilbestrol is known to be cardiotoxic at high doses. An intermediate dose (3 mg/day) seems to be as effective as orchiectomy and may have an acceptable adverse effect profile. However, the need to monitor patients for contemporary cardiac risk makes it a weak alternative.

Other than the adverse effects of ADT described above, risks of surgical orchiectomy include blood loss, haematoma and infection. Patients typically recover fully from surgery in 2–4 weeks.

Patients receiving docetaxel frequently experience dose-limiting neutropenia. Docetaxel is also associated with fluid retention, ranging from mild peripheral oedema to severe fluid retention and pleural effusion. To reduce this risk, patients should be treated with a corticosteroid before and after docetaxel doses *(27)*. Hypersensitivity reactions to docetaxel occur frequently but incidence is reduced to <5% with corticosteroid premedication *(28)*. Patients may also experience sensory neuropathy, although this is generally mild and reversible.

Recommendations

On the basis of the evidence presented in the application, the Expert Committee recommended the addition of bicalutamide and leuprorelin to the complementary list of the Model List of Essential Medicines for the treatment of metastatic prostate cancer. The Committee recommended listing of bicalutamide and leuprorelin each with a square box symbol as representative of the wider class of peripheral androgen blockers and GnRH agonists, respectively. In addition, the Committee endorsed the use of the already listed docetaxel for this indication.

The addition of diethylstilbestrol to the Model List was not supported because of its being associated with an increased risk of cardiovascular death and providing no advantage compared with surgical orchiectomy or other ADT in terms of overall survival.

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