Artigo de Revisão

MANAGEMENT OF ADVANCED PROSTATE CANCER

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SUMMARY

Geriatricians and general practitioners often follow patients with metastatic prostate cancer. The epidemiology and basic treatment principles of metastatic prostate cancer are discussed aiming to update the topic for the non-oncologist. Hormone manipulation remains the basis of treatment, usually up to a second line of therapy. Selected cases are treated successfully with intermittent androgen ablation. When new hormone-independent clones arise, chemotherapy should be added to therapy that confers improved survival as well as better quality of life when based on taxanes. In specific situations, additional measures such as bisphosphonates and radiation therapy should be included in the treatment. As a rule, the public health system makes available the necessary medication to ensure treatment for the vast majority of patients in Brazil.

KEY WORDS: Prostatic neoplasms/therapy. Hormones/therapeutic use. Hormonal antineoplastic agents. Drug therapy. Epidemiology.

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This review aims to familiarize general practitioners and geriatricians practicing in Brazil and neighboring countries with the current treatment of advanced prostate cancer. Most of what is presented is readily available through the public health system in Brazil.

Stage IV prostate cancer comprises patients with locally advanced tumors (T4, indicating invasion of the bladder, rectum, pelvic wall), involvement of lymph-nodes (N1) or presence of distant metastasis (M1, which includes non-regional lymph-nodes or metastasis to other organs, usually bones). Imaging studies of some patients may not disclose an evident site of metastatic disease, although they present with a high PSA (prostate specific antigens). A PSA level above 20ng/ml is highly suggestive of advanced disease, and a level > 50ng/ml is virtually diagnostic of metastatic disease. Using nomograms based on mathematical models[1, 2] such as those available at the site http://www.mskcc.org/mskcc/html/10088.cfm, which take into consideration PSA level, Gleason Score, clinical stage and age, we are able to predict fairly accurately the probability of advanced disease for a given patient. While even metastatic prostate cancer may have a variable clinical course, sometimes with very slow progression, factors such as age, co-morbidities, disease-related symptoms, time of disease progression and functional status play a very important role in the decision making process related to therapy. Considering that the vast majority of patients are elderly, such additional factors, more often than not are limiting factors for one or more treatment modalities.

Epidemiology

According to the Ministry of Health in Brazil, the estimated number of new cases of prostate cancer in 2006 was approximately 47,000, with estimated incidence of 51/100,000 men. The same government-released statistics show a surprisingly wide variation in the incidence between different regions in the country (13/100,000 men in the North, up to 81/100,000 men in the South), rising questions about low reporting or underdiagnosis. The available data suggest an incidence of prostate cancer-related deaths of 8/100,000 men between 1995 and 1999. No recent Brazilian data are available regarding either prostate cancer-related deaths or the percentage of cases with advanced disease at diagnosis. In the United States, the Surveillance Epidemiology and End Results, linked to the National Cancer Institute, estimated that in 2006 the number of patients who died from prostate cancer was approximately 27,000, with 234,000 new patients being diagnosed with the disease. The estimated incidence of prostate cancer was of 170 new cases /100,000 men.

Diagnosis at an advanced stage

The majority of symptomatic patients with prostate cancer present either bone pain, other bone-related symptoms or symptoms related to urethral obstruction. As such, the vast majority of patients diagnosed with metastatic disease remained asymptomatic for months to years. The patients under discussion are, therefore, those who present with symptoms due to advanced disease, asymptomatic patients with the finding of very high PSA levels, with findings compatible with metastatic disease upon further investigation or who were previously treated with curative intent and eventually progress to metastatic disease. Since the disease can be asymptomatic for a long period of time, for younger patients diagnosed as having metastatic disease based on very high PSA levels only, treatment and consequent side effects, such as impotence are frequently difficult to accept. For these patients, strong consideration must be given to enrollment in clinical trials, and even to treatment strategy adjustments described below.

Since advanced disease is not curable, the first question is whether earlier initiation of treatment (for example, when PSA rises but patient has no symptoms) will be advantageous for survival or at least in delaying

symptoms. A recent review by the Cochrane Collaboration suggests that early initiation of treatment may indeed lead to a longer symptom-free period and possibly to a longer overall survival [3], although this remains controversial[4,5]. Adenocarcinoma of the prostate is dependent on hormonal stimulation (by testosterone) until a very late stage of the disease, at which point new clones of hormone-independent cells arise[6]. Although at this stage, a non-hormonal therapy must be added to the treatment, hormone manipulation still has to be continued for life, due to presence of a residual hormone-dependent clone.

Treatment

Treatment starts with hormone manipulation while the disease is hormone sensitive. Though hormone manipulation can control the disease for several years, eventually addition of cytotoxic medication is required due to development of hormone-independent cancer cells.

A small fraction of prostate cancers have neuroendocrine differentiation. These tumors neither synthesize PSA, nor respond to hormone manipulation. They usually progress with soft tissue metastasis and osteolytic lesions when compared to the osteoblastic nature of bone metastasis in the majority of patients with prostate cancer. This group of patients is best treated with chemotherapy regimens commonly used for other neuroendocrine tumors, that is to say platinum based.

A basic treatment nomogram is depicted in Figure 1. A more detailed treatment nomogram can be found at http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf .

First line hormonal therapy

First line hormone therapy consists of blocking testosterone synthesis, either by orchiectomy (testis synthesize more than 85% of testosterone in men, the remainder synthesized mainly in the adrenal glands), or by using a gonadotrophin releasing hormone analog (aLHRH). Examples of aLHRH are goserelin and leuprolide, both injectable drugs, which can be given monthly and every three months. There is no evidence that either orchiectomy or aLHRH may be better than the other.

The most common side effects are hot flushes, decreased libido, sexual impotence and osteopenia. Another potentially serious side effect is the so-called tumor flare, where the aLHRH initially has a stimulatory effect on the receptor, leading to an increased LH/FSH synthesis, with consequent increase of testosterone level and tumor stimulation. If this flare occurs in a patient with incipient spinal cord compression or urethral obstruction, it may lead to significant worsening of these problems with catastrophic consequences. To avoid this clinically significant flare, androgen receptor blockers (such as flutamide or bicalutamide), are given blocking the effect of the testosterone flare for a few weeks, before and after initiation of aLHRH. Although anti-androgens (androgen receptor blockers) are still widely used as first line hormone therapy, current data suggest that, with few exceptions, they should be kept for second line therapy (discussed below). Patients who want to try to maintain the sexual function (seldom possible with use of an aLHRH) could try to use nonsteroidal androgen receptor blockers first. Steroidal androgen receptor blockers (such as Cyproterone) have poorer results for treatment of prostate cancer.

One question lacking a definitive answer is whether, once minimally symptomatic or asymptomatic metastatic disease is diagnosed, therapy should be initiated immediately or deferred until required by symptoms. Compiling data from trials addressing the question, it seems that early treatment does in fact have a beneficial (although small) impact on time to symptom progression and even on survival. Most interestingly, length of time to initiation of symptom-driven treatment can take a median of seven years, and time to development of hormone-independent prostate cancer does not seem to differ if hormone treatment is initiated earlier or later[7]. Furthermore, a new strategy of intermittent androgen ablation is prospectively being tested, with encouraging preliminary results[8,9,10]. From a perspective of the public health system, with limited resources as in Brazil, both strategies, delayed and intermittent androgen blockade should be seriously considered.

Second line hormone therapy

There are several options for second line hormone manipulation.

Maximum androgen blockade (MAB): this strategy consists of associating an androgen receptor blocker (such as bicalutamide or flutamide) to the aLHRH already in use or to the orchiectomy already performed as first line therapy. The androgen receptor blockers are administered per oral (PO) on a daily basis (or three times per day). Two metanalyses evaluating the strategy of MAB as first line hormonal therapy have not shown that it can prolong survival[11,12] as compared to

Figure 1 - Basic treatment nomogram for metastatic disease

Metastatic	Bone disease	Blastic	Orchiectomy or aLHRH Add ARB at progression Stop ARB at progression Add Ketoconazole at progression	at progression: Docetaxel-based CT
		Lytic	If neuroendocrine: platinum based CT Not neuroendocrine: as above but length of response usually shorter	
	Soft tissue (lymph-nodes)			

aLHRH: LHRH analog; ARB: androgen receptor blocker; CT: chemotherapy

Table 1 - Hormonal medications most frequently used

Drug	Mechanism of action	Dose and administration	Main side effects	Approximate price
Leuprolide	aLHRH	22.5mg IM every 3 mo.	Osteoporosis Hot flashes Depression Gynecomastia impotence	U$ 1,700 / 3 months
Goserelin	aLHRH	10.8 mg SC implant every 3 mo.	Osteoporosis Hot flashes Depression Gynecomastia impotence	U$ 900 / 3 months
Bicalutamide	Androgen receptor blocker	50-150 mg PO daily	Hepatotoxicity Hot Flashes Edema Gynecomastia Constipation	U$ 350 (50mg/day) monthly
Flutamide	Androgen receptor blocker	250 mg PO q8 hs	Hepatotoxicity Hot Flashes Edema Gynecomastia Constipation	U$ 300 monthly
Ketoconazole	Adrenal and testicular inhibition	1,200 mg PO daily	Hepatotoxicity Adrenal Insufficiency Nausea Diarrhea Gynecomastia	U$ 160 monthly

surgical (orchiectomy) or medical (aLHRH) castration alone. In a subgroup analysis, of patients receiving modern anti-androgens (such as flutamide and bicalutamide as opposed to cyproterone) as part of MAB, there was a suggestion of a survival benefit for patients receiving MAB as compared to castration alone. Used as second line hormone manipulation, it is fairly common to see patients respond temporarily to MAB after failure of first line hormone therapy, potentially delaying onset of chemotherapy treatment and accompanying side effects. Though never prospectively evaluated in comparison to other treatments in second line, MAB is well tolerated by the majority of patients. The main side effects of androgen receptor blockers consist of worsening hot flushes, gynecomastia, abnormal liver function tests, worsening hypertension and decreased libido. The added toxicity of aLHRH with androgen blockers includes muscular wasting, anemia, and worsening of the individual side effects, already described for each class of drug. It should be noted that when the disease progresses during MAB, prior to initiation of alternative therapy, the androgen receptor blocker has to be discontinued. There is a chance of the so-called anti-androgen withdrawal effect, where a temporary (usually short-lived) partial response can be seen even before starting a new treatment.

Diethylstilbestrol (DES): the mechanism of DES action is through inhibition of LHRH production by the hypothalamus. From a clinical standpoint, the effect of this estrogen is comparable to orchiectomy but due to its thrombogenic and cardiovascular side effects, it is being progressively less prescribed throughout the world and banned altogether in some countries.

Cyproterone acetate (CyA): this steroidal anti-androgen continues to be widely used in many countries, but is gradually being replaced by modern non-steroidal anti-androgens. It not only blocks androgen receptors, but has a mild progesterone-like effect leading to partial inhibition of release of LH by the pituitary gland, with consequent decrease in testosterone level [13]. Though its direct comparison to flutamide as first line treatment in metastatic disease did not show a difference in the overall survival and progression free survival [14], we prefer to use orchiectomy or aLHRH as first line and MAB with modern androgen blockers as second line therapy based on the favorable outcome, when compared to association of aLHRH with cyproterone acetate [11].

Ketoconazole: this well-known antifungal can decrease serum testosterone both through inhibition of testicular as well as adrenal hormone synthesis, when administered in large doses (800 to 1200 mg/day). It has been employed for over a decade, mostly after progression of disease post- anti-androgen withdrawal [15, 16]. We frequently prescribe ketoconazole to treat patients with oligosymptomatic or asymptomatic disease confined to bones, who have already failed MAB as third-line hormone manipulation. The main toxicity consists of hepatotoxicity, mandating serial liver function tests assessment. Though duration of response is usually limited to few months, patients who have long-term responses with acceptable toxicity and preservation of quality of life are often found.

Table 1 summarizes the most frequently prescribed hormone drugs.

Hormone-independent prostate cancer

At some point, during progression of disease, new clones emerge. Eventually, among these clones one arises that is independent of hormone stimulation for its growth. It should be emphasized that there will still be some hormone-dependent cells, and therefore, if already in use, aLHRH has to be continued. It is known that hormone-independent prostate cancer cells are only modestly sensitive to chemotherapy and to radiation therapy. Therefore, after publication of two phase III clinical trials in 2004 [17, 18], docetaxel became the preferred first-line chemotherapy treatment for the majority of patients with hormone-independent prostate cancer. In these trials, the combination of docetaxel with low dose prednisone or with oral estramustine led to longer survival as compared to mitoxantrone, the standard care at the time. Although prolongation of survival was very modest (in the order of two months), it was statistically significant and most important, it was also associated with responses in about 50% os cases, and the quality of life of the responding patients was improved. There is no best second-line chemotherapy. Although options are multiple, none has proven to prolong survival. Depending on the patient's performance status and co-morbidities, we have administered oral cyclophosphamide, association of carboplatin with taxanes, vinorelbine with prednisone, mitoxantrone with prednisone or oral etoposide. Interesting research sponsored by the National Cancer Institute (NCT 00039221) is currently evaluating the association of docetaxel with ketoconazole. New drugs are about to become commercially available (satraplatin, ixabepilone), however with little impact on survival.

Other treatment measures

Parallel to the anti-tumor treatment, palliative measures such as radiation therapy for pain control and use of bisphosphonates should be mentioned.

Radiation therapy can be administered as external beam radiation, indicated mainly for control of pain arising from a localized metastatic lesion such as in one or a few vertebrae or pelvic bones. In recent years radiation has also been delivered through administration of strontium-89 or samarium-153, aiming to control diffuse bone pain in patients with intolerance to high doses of opiates[19]. The mechanism action relies on its preferential uptake in metabolically active bone lesions, with subsequent release of beta particles to the local environment. The main toxicity consists of bone marrow suppression, which may hamper subsequent administration of myelotoxic chemotherapy agents.

Regarding the use of bisphosphonates, although pamidronate apparently does not decrease bone pain[20], zoledronic acid was shown to decrease bone-related complications in the setting of hormone-independent disease[21]. Bisphosphonates also help to prevent osteoporosis induced by prolonged androgen deprivation[22].

In summary, proper assessment of the individual patient and likelihood of this patient's prostate cancer to be a life-determining factor is paramount. Hormone manipulation remains the backbone therapy of metastatic prostate cancer and is fortunately available to all patients through the public health system. The introduction of intermittent androgen ablation should be considered a valid treatment strategy in responding patients. Though chemotherapy has now shown to prolong survival, it should still be reserved for the more advanced setting of hormone-independent disease.

Conflict of interest: none

RESUMO

TRATAMENTO DO CÂNCER DE PRÓSTATA AVANÇADO

Pacientes com câncer de prostata metastático estão freqüentemente sob os cuidados de geriatras e clínicos gerais. Discutimos a epidemiologia e os princípios básicos do tratamento do câncer de próstata metastático, visando atualizar o não-oncologista no assunto. A base do tratamento continua sendo a manipulação hormonal, inclusive como tratamento de segunda linha. Casos selecionados podem ser tratados com ablação androgênica intermitente de maneira eficaz. Quando se desenvolvem clones de células hormônio-independentes, quimioterápicos são incorporados na terapia. A quimioterapia confere não só benefício em sobrevida, mas também na qualidade de vida, quando baseado em taxanos. Medidas adicionais como o uso de bisfosfonados e radioterapia devem ser incorporadas no tratamento em situações especiais. De modo geral, o sistema público de saúde do Brasil disponibiliza todas as medicações necessárias ao adequado tratamento dos pacientes no país. [Rev Assoc Med Bras 2008; 54(2): 178-82]

UNITERMOS: Neoplasias prostáticas/terapia. Hormônios/uso terapêutico. Antineoplásicos hormonais. Quimioterapia. Epidemiologia.

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