Prostate cancer: 9. Treatment of advanced disease

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The case

A 70-year-old man is referred to a urologist for recommendations on the management of metastatic prostate cancer. His cancer was diagnosed 5 years ago, and he underwent radical prostatectomy at that time. The tumour was confined to the prostate gland (Gleason score 7), and during surgery the lymph nodes were assessed as being clear of cancer. Before the surgery, the patient's prostate-specific antigen (PSA) level had been 8 ng/mL. After the prostatectomy, PSA was at first undetectable, but recently the PSA level rose to 2 ng/mL and then, at the most recent test, to 16 ng/mL. A bone scan was ordered to investigate back discomfort, which has been persistent but easily controlled with acetaminophen. Unfortunately, the bone scan shows several sites of metastatic disease. The man's medical history includes type 2 diabetes, which has developed during the past 3 years and which is controlled by diet, as well as asymptomatic hypertension, which is managed by means of a thiazide diuretic. The patient asks what treatments are available, what impact they are likely to have on his disease and what risks are associated with the therapies.

The patient in this case exemplifies the consequences of failed local therapies and presents a scenario that is altogether too familiar to any practitioner who cares for men with prostate cancer. Current systemic therapies include alterations in the patient's hormonal milieu or the use of a cytotoxic agent. The impact of both approaches is discussed here.

Androgens and the prostate gland

The male sex hormones are collectively known as androgens — from the Greek *andros* (man) and *gennan* (to produce). Testosterone is the principal circulating androgen in men, and its presence is necessary for normal development of the penis, scrotum, testicles and male secondary sex characteristics at puberty. Testicular androgens are critical in the formation of the prostate gland in the embryo and for its normal function throughout adulthood, including production of prostate-specific antigen (PSA).

Testosterone has long been implicated as a possible promoter of prostatic cancer growth. Prostate cancer does not develop in eunuchs or other men castrated before puberty, and latent prostate cancer is less frequent among men with cirrhosis, who often have low testosterone levels.

The normal pathways for endocrine control of gonadal function are summarized in Fig. 1. Testosterone synthesized in the testes is a precursor for 90%

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of the dihydrotestosterone produced in the prostate; the remaining 10% is derived from the less-potent adrenal androgens — androstenedione and dehydroepiandrosterone — and from extrinsic sources. Testosterone provides a negative feedback signal for the hypothalamic secretion of luteinizing hormone releasing hormone (LH-RH) and, subsequently, release of luteinizing hormone from the pituitary gland.

Testosterone circulates in association with 2 major plasma proteins: sex-hormone-binding globulin and albumin. Only 2% of the testosterone is unbound and available for diffusion into the target cell, where it is converted to dihydrotestosterone by the enzyme 5α-reductase.[1] Dihydrotestosterone then binds to and activates androgen receptors, which bind to the promoter regions of specific genes, thereby regulating transcription and hence protein synthesis, cell growth and differentiation.[2]

No treatment equals or surpasses androgen ablation in checking the growth of prostate cancer and reducing tumour volume; biochemical and objective responses are achieved in 80% of patients.[3–11] Withdrawal of androgen induces apoptosis, a form of programmed cell death, in normal and malignant prostatic epithelial cells. However, this fails to eliminate the entire population of malignant cells, and progression to androgen independence almost inevitably occurs, which leads to the development of symptoms (e.g., bone pain, weight loss and fatigue) and death.

Progression to androgen independence is a complex process. It involves selection and growth of pre-existing clones of androgen-independent cells; adaptive up-regula-
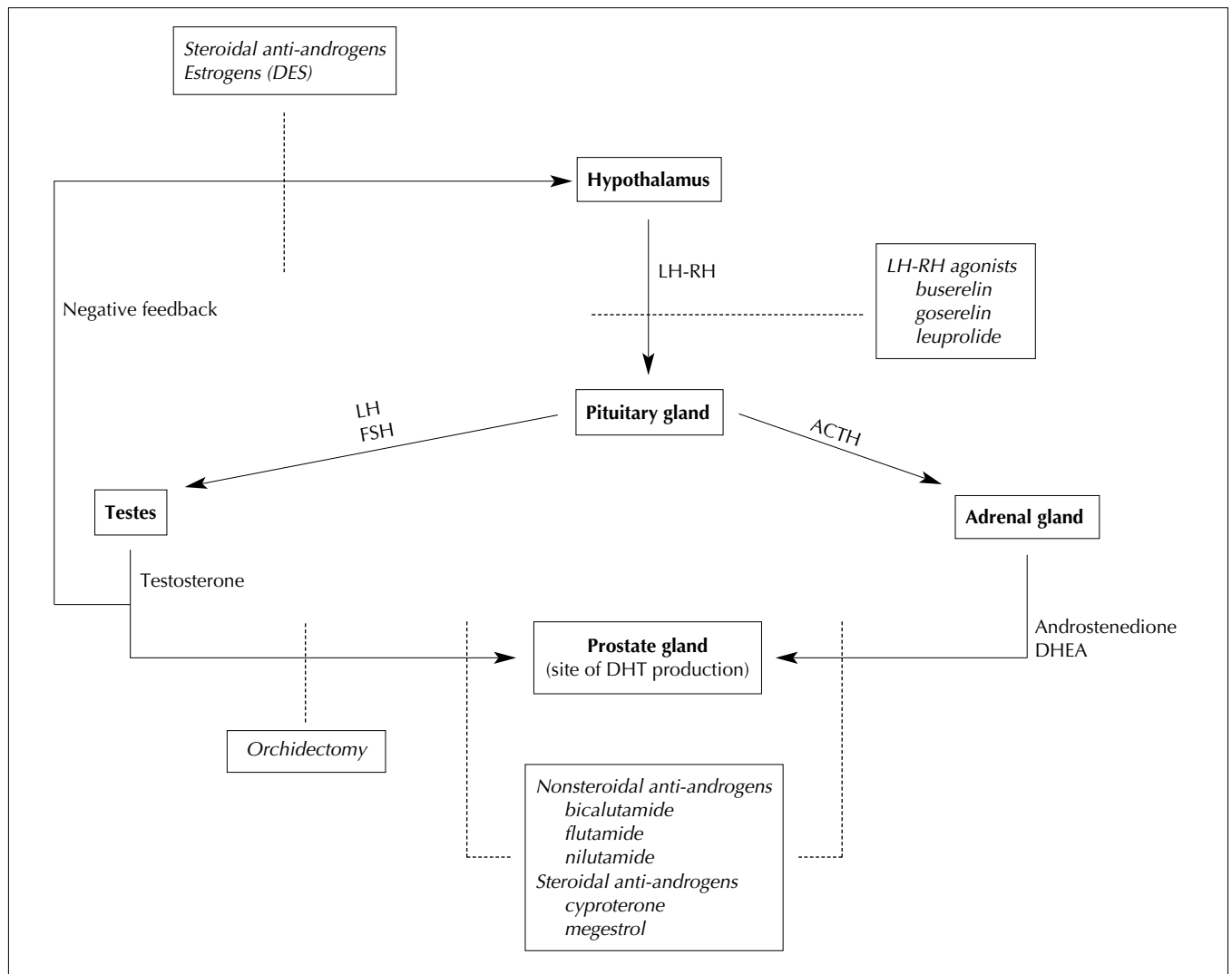
Fig. 1: Pathways of endocrine control of gonadal function and sites of action of hormonal agents. The tissues involved in regulation of gonadal function are indicated by bold type. Direction of action of endocrines is indicated by arrows. Dotted lines indicate where various hormonal agents (shown in italic) interfere with normal endocrine flow. ACTH = adrenocorticotropic hormone, DES = diethylstilbestrol, DHEA = dehydroepiandrosterone, DHT = dihydrotestosterone, FSH = follicle-stimulating hormone, LH = luteinizing hormone, LH-RH = luteinizing hormone releasing hormone.

tion (i.e., increased expression) of genes that help the cancer cells survive and grow after androgen ablation; and androgen-receptor mutations or interactions with alternative transcription factors.[12] Better understanding of the molecular basis of apoptosis and progression to androgen independence will provide clinicians with novel therapeutic targets in the future.

Androgen withdrawal therapy

The ablation of testicular function in the palliative treatment of prostate cancer was first attempted in the 1930s by means of radiation of the testes. This proved less effective than surgical removal, which was introduced a decade later.[3] Bilateral orchidectomy has become the gold standard of hormonal therapy for metastatic prostate cancer. Its advantages include low cost, low morbidity and the avoidance of compliance problems that may arise with drug therapy. However, the psychologic trauma associated with surgical castration has increased the use of medical castration.

Over the past 2 decades, drugs affecting the hypothalamic production of LH-RH and those blocking the peripheral effects of androgens (steroidal and nonsteroidal antiandrogens) have been used alone and in various combinations to achieve medical castration. The advent of these agents has increased the options for suppressing the influence of androgens on the growth of prostate cancer (Table 1). The general side effects of androgen ablation include hot flushes, gynecomastia, loss of libido and potency, lethargy, and loss of bone and muscle mass over time.

Several classes of drugs induce castrate levels of testosterone by suppressing the release of luteinizing hormone from the pituitary gland. For example, diethylstilbestrol (DES) suppresses hypothalamic release of LH-RH and increases levels of testosterone-binding globulin; these ef-

fects combine to decrease the serum level of free testosterone. DES is the least expensive of the synthetic estrogens, and castrate testosterone levels are achieved at doses of 1 mg/day.[4] However, its low cost must be weighed against the increased risk of thromboembolic and cardiovascular complications.[4]

LH-RH agonists include goserelin and leuprolide (available as monthly subcutaneous and intramuscular injections respectively and, more recently, as 3-month formulations) and buserelin (available as a 2-month depot formulation). Pulsatile release of LH-RH from the hypothalamus normally stimulates the release of luteinizing hormone from the pituitary gland, but when this periodicity is disrupted by continuous administration of LH-RH agonists, hypothalamic regulation of the pituitary is lost.

LH-RH agonists produce a biphasic response — an initial rise in levels of luteinizing hormone and testosterone, termed the "flare phenomenon," followed in 2 weeks by a fall in these levels.[5] The flare phenomenon can be prevented by administering cyproterone acetate or DES 1 week before the LH-RH agonist; alternatively, it can be blocked by nonsteroidal anti-androgens.[6] Although LH-RH agonists appear equivalent to DES and orchidectomy, the flare phenomenon is one disadvantage of using these drugs alone. Their main advantages are reversibility and the avoidance of cardiovascular complications, but these are achieved at high cost ($400/month).

Anti-androgens compete with androgens for receptor sites in target cells. Current indications for their use are outlined in Table 2. The nonsteroidal anti-androgens — which include flutamide, nilutamide and bicalutamide — have no direct gonadotropic or progestational effects and therefore do not suppress testosterone levels. Most studies do not support the use of nonsteroidal anti-androgens alone,[6] although recent data suggest that higher-dose (150 mg/day) bicalutamide monotherapy may be equivalent to

Table 1: Relative beneifts of various forms of medical castration*

| Benefit | Therapeutic option; degree of benefit | | | | | |
	LH-RH alone	CPA alone	Lead-in CPA + CAB†	CAB + nonsteroidal anti-androgen	CAB + CPA	CPA + DES
Rapid onset	−	+	++	+	+	++
Reversibility	++	++	++	++	++	++
Absence of flare	−	++	++	+	+	++
Absence of hot flushes	−	+	+	−	+	+
Low toxicity	+	+	++	−	+	+
Low cost	−	+	−	−	−	++
Ease of administration	++	++	+	+	+	++

Note: LH-RH = luteinizing- hormone releasing hormone, CPA = cyproterone acetate, CAB = combined androgen blockade (LH-RH + steroidal anti-androgen), DES = diethylstilbestrol.
*The relative merits assigned in this table represent the authors' views, which are based on the use of multiple drug regimens over the years to produce androgen ablation.
†CPA used as lead-in therapy for first month to prevent flare.

surgical castration.[7] The reported side effects of these nonsteroidal anti-androgens are summarized in Table 3.

Steroidal anti-androgens (cyproterone acetate and megesterol) have progestational activity in addition to their anti-androgenic activity at peripheral receptors; thus, they inhibit secretion of gonadotropin and production of testosterone.[6] The combination of low-dose cyproterone acetate (50 mg twice daily) and mini-dose DES (0.1 mg daily) achieves potent androgen ablation at one-third the cost of LH-RH agonists.[9] The advantages of steroidal anti-androgens include reversibility, suppression of hot flushes and intermediate expense. Specific side effects include the potential for fatigue and depression.[9]

Responses to androgen withdrawal therapy

Up to 80% of patients with metastatic disease exhibit objective responses to androgen ablation; median overall progression-free survival is 23 to 37 months.[8,10,11] Serum PSA level remains the most useful indication of response and prognosis in these patients. Almost all treated patients have an initial response accompanied by a rapid decrease in serum PSA, which falls into the normal range in about 70% of patients.

Table 2: Indications for use of anti-androgens

To prevent the flare phenomenon during the first month of LH-RH agonist treatment:
 cyproterone acetate (50 mg twice daily) plus DES (0.1 mg daily)
 or cyproterone acetate (150 mg orally, twice daily)
 or cyproterone acetate (150 mg orally, twice daily)
 or a nonsteroidal anti-androgen

To treat hot flushes after medical or surgical castration:
 cyproterone acetate (50 mg once daily)

To treat biochemical (indicated by rising PSA level) or clinical progression of disease in patients treated with LH-RH agonists, orchidectomy or low-dose cyproterone acetate and mini-dose DES:
 3-month trial with a nonsteroidal anti-androgen (bicalutamide, flutamide or nilutamide), to be continued only if there is a decrease in serum PSA level

Note: PSA = prostate-specific antigen.

Table 3: Summary of side effects of nonsteroidal anti-androgens

Anti-androgen	Side effects
Bicalutamide[8]	Gynecomastia (25%)
Nilutamide[6]	Decreased adaptation of vision to darkness (33%)
	Nausea (25%)
	Alcohol intolerance (20%)
	Possibility of interstitial pneumonitis
Flutamide[9,11]	Gynecomastia (60%)
	Diarrhea (10%)
	Nausea
	Possibility of idiosyncratic hepatocellular toxicity resulting in death

The level of serum PSA after 6 months of treatment indicates whether the response will be prolonged.[13–15] PSA levels greater than 4 ng/mL after 6 months of therapy are associated with a median survival of 18 months, whereas levels below 4 ng/mL are associated with a median survival of 40 months.[13–15] Furthermore, a rising PSA level is the earliest sign of progression, predating clinical recurrence by 6 to 12 months.

The flutamide withdrawal syndrome[6] is characterized by a 50% decrease in serum PSA level after discontinuation of this anti-androgen. Despite its name, the syndrome has been reported in approximately 20% of patients after discontinuation of both steroidal and nonsteroidal anti-androgens. This phenomenon highlights the potential role for androgen receptor mutations and anti-androgens in tumour progression and implies that partial antagonists (like nonsteroidal anti-androgens) may become partial agonists during progression to androgen independence, probably because of subtle changes in androgen receptor structure and protein–protein interactions.

Controversial issues in advanced prostate cancer

Is combined androgen blockade superior to castration alone?

The term "combined androgen blockade" describes the addition of an anti-androgen to medical or surgical castration to block the action of residual (adrenal) androgens. Although this concept dates back to 1945[16] and has been the subject of randomized controlled trials for 15 years, it remains controversial.

Dihydrotestosterone is detectable in prostate tissue after castration. Early attempts to eliminate the source of residual androgens by adrenalectomy were ineffective, but the development of nonsteroidal anti-androgens in the late 1970s revived interest in this approach. However, the numerous trials conducted to date have had mixed results. For example, a National Cancer Institute (NCI) intergroup study[10] found that among patients with previously untreated metastatic prostate cancer, progression-free and median survival were statistically significantly longer for those treated with a combination of the LH-RH agonist leuprolide and the nonsteroidal anti-androgen flutamide than for those treated with leuprolide and placebo. However, critics have correctly pointed out that leuprolide therapy may be subject to problems with compliance and that the inferior results for leuprolide with placebo may have resulted from untreated flare.

The difficulty in analyzing and integrating the results of numerous trials arises from heterogeneity in type of

castration and type of anti-androgen, as well as differences in study design, randomization procedures, assessment of treatment outcomes, statistical evaluation and length of follow-up. A meta-analysis of 22 randomized trials evaluating combined androgen blockade found no significant improvement in 5-year survival.[11] Continuing debate regarding this therapy prompted the largest trial to date for advanced prostate cancer, in which 1387 patients were randomly chosen to undergo orchidectomy combined with either flutamide or placebo; recent reports indicate no differences in survival in any subgroup.[17]

One explanation for the differences between this study and the earlier NCI intergroup study is that untreated flare with LH-RH monotherapy adversely affects overall survival. At present, the data do not convincingly show a benefit of combined androgen blockade over castration alone for patients with metastatic prostate cancer, which implies that the role for adrenal androgens in disease progression after castration is insignificant.

When should androgen ablation be initiated?

Although early studies found that delayed and immediate endocrine therapy were equivalent, any apparent benefit of immediate therapy may have been obscured by the cardiovascular side effects of DES.[18] Furthermore, theoretical and animal-model data suggest that early androgen ablation is more effective.[19] A recent randomized controlled study of patients with locally advanced disease compared radiation therapy plus 3 years of adjuvant hormone therapy with radiation therapy initially plus hormone therapy only at disease recurrence; 5-year overall survival was significantly better in the first group.[20] The results of a British study comparing early and delayed endocrine therapy in metastatic prostate cancer also supported immediate therapy.[21] Taken together, accumulating evidence supports initiation of treatment as soon as locally advanced, recurrent or metastatic disease is diagnosed.

Quality-of-life issues

Patients with metastatic prostate cancer have a median survival time of only 2–3 years, so there is not enough time for the long-term effects of androgen ablation to be manifested; therefore, these effects are not clinically relevant. However, awareness of potential adverse effects of long-term continuous androgen ablation is increasing. PSA testing has shifted diagnosis to an earlier stage, which means that diagnosis of locally advanced or metastatic disease is less frequent, and diagnosis of clinically confined disease (stage T1c or T2) more frequent. Moreover, PSA detection of recurrence after radical prostatectomy or radiotherapy identifies men who may benefit from early

therapy and who may have a life expectancy exceeding 10 years. These trends are forcing clinicians to balance the potential benefits of early adjuvant therapy with the risks of metabolic complications and the increased expense associated with long-term continuous androgen withdrawal therapy. The metabolic complications include osteoporosis and fractures, loss of muscle mass, anemia, fatigue and lethargy, changes in lipid profile (with an increased risk of cardiovascular complications), glucose intolerance and personality changes, including depression or irritability.

New approaches that use reversible medical castration are being studied to reduce the negative impact of androgen ablation on quality of life, with the realization that androgen withdrawal therapy is rarely curative, that combined androgen blockade is not superior to orchidectomy and that progression to androgen independence is initiated and accelerated by androgen withdrawal. The treatment goal is no longer to kill all cancer cells by maximizing androgen ablation; rather, the goal is now to regain biological control of the growth of tumour cells, as well as their response to subsequent androgen ablation.

Intermittent androgen suppression is based on the hypothesis that if tumour cells that have survived androgen withdrawal are forced along a normal pathway of differentiation by re-exposure to androgen (i.e., interruption of the medical castration therapy), then apoptotic potential may be restored and progression to androgen independence delayed. Experimental animal data and clinical studies support this hypothesis.[22] Androgen withdrawal therapy was continued for 9 months, after which medications were discontinued (Fig. 2). When serum PSA levels increased to 10–20 ng/mL, treatment was resumed. The cycle of treatment followed by no treatment was repeated until regulation of PSA level became androgen-independent. Nearly half of each cycle involved no treatment, and
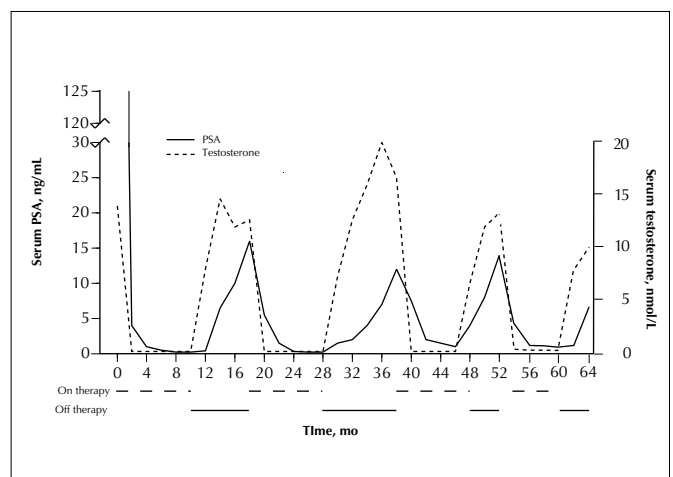
Fig. 2: Levels of prostate-specific antigen (PSA) and testosterone in serum of patients treated with intermittent androgen suppression.

off-treatment periods were associated with an improved sense of well-being and recovery of libido and potency in the men who reported sexual function before the start of therapy.

Observations from preliminary studies suggest that intermittent androgen suppression does not have a negative impact on time to progression or survival. This treatment option offers clinicians an opportunity to improve quality of life by balancing the benefits of immediate androgen ablation (i.e., delayed progression and prolonged survival) while reducing treatment-related side effects and expense. Phase III randomized studies of the efficacy of intermittent androgen suppression have been initiated in Canada, the United States and Europe. Until survival data are available, it should be considered an investigational form of therapy.

Another approach to reduce the side effects of therapy is the concept of sequential androgen blockade.[23] The relative potency of nonsteroidal anti-androgens such as flutamide is increased by inhibiting conversion of testosterone to the more potent dihydrotestosterone, which thereby obviates the necessity for castrate levels of testosterone. The usual side effects of androgen ablation are avoided because testosterone levels are not reduced. Libido and potency are preserved in most patients. Further follow-up and comparative studies are needed to determine whether time to progression or survival are adversely affected.

Hormone-refractory prostate cancer

Hormone-refractory prostate cancer, defined as symptomatic prostate cancer that is progressing despite optimal hormone therapy, is disabling and incurable. Patients have a serum testosterone level in the castrate range and, typically, the serum level of PSA is rising. Hormone-refractory prostate cancer is associated with a symptom complex that includes progressive bone metastases that may be painful, fatigue, weight loss and, occasionally, bone marrow failure.

At this stage of prostate cancer, radionuclide bone scans often reveal new progressive lesions, and diagnostic imaging procedures occasionally show soft-tissue lesions. Once symptoms develop, most patients become essentially incapacitated, and median survival time is 9–12 months.[24] These patients are generally elderly, they often have concurrent medical problems, and their bone marrow function may be compromised as a result of both disease and prior radiation therapy. They are generally intolerant of aggressive cytotoxic therapies.

With the widespread use of PSA testing, many patients receiving hormone therapy (but "resistant" to it) are now presenting when their PSA level first begins to rise, rather than when clinical symptoms develop. An apparent increase in median survival time, from 6–9 months in older studies of chemotherapy to 10–13 months in more recent ones, is probably due to initiation of treatment when PSA elevation indicates hormone-refractory disease, rather than when clinical progression becomes apparent.[24] As yet, no systemic therapies have been shown to have any meaningful impact on survival in randomized trials. Thus, any therapy must be recommended in light of its ability to diminish disease-related symptoms and improve quality of life.

Chemotherapy in hormone-refractory prostate cancer

Early studies of chemotherapy examined a variety of single agents and drug combinations.[25] Even though "responses" were noted (according to the criteria established by that group), they were infrequent; there was no impact on survival and, therefore, no convincing standard regimen was established. Many investigators concluded that, given the potential for toxic effects and the lack of demonstrable benefit, chemotherapy had little or no role in the management of hormone-refractory prostate cancer.[24]

More recently, many researchers have used changes in PSA level to infer that chemotherapy *is* effective in this form of the disease. However, some caution must be exercised in interpreting PSA changes in these patients. PSA is not as good an indicator of disease bulk in this situation as it is in earlier-stage disease. In addition, changes in PSA level do not provide information about the balance between toxic effects of the treatment and reduction of tumour-related symptoms. Furthermore, many agents reduce PSA gene expression without inducing death of tumour cells.

Recognition of the tremendous cost and overall burden that hormone-refractory prostate cancer places on patients and society has contributed to a continuing effort to develop and investigate new therapies. The most recent studies have investigated mitoxantrone plus prednisone, estramustine combinations and suramin. In addition, some older, well-tolerated regimens, such as cyclophosphamide given orally, are being re-examined for their potential palliative benefit.

Mitoxantrone plus prednisone

Mitoxantrone is an anthracenedione, a chemotherapy agent that acts by inhibiting topo-isomerase II. In initial studies of mitoxantrone in hormone-refractory prostate cancer the objective response rate was relatively low, but a larger number of patients experienced significant re-

duction of pain.[25] Recognizing that symptom control is important and that prolonging survival may not be a realistic outcome, pain relief may be regarded as a valid objective.

The primary endpoint in these trials was a "palliative response," defined as a significant reduction in pain with no increase in use of analgesics, or a 35% decrease in use of analgesics without any increase in pain.[26] On the basis of these criteria, a phase III study was undertaken to compare prednisone with prednisone plus mitoxantrone. A palliative response was achieved in 30 (38%) of 80 patients receiving the combined treatment and in only 17 (21%) of 81 who received prednisone alone (p = 0.025).[27] The median duration of the palliative response was longer for the combination treatment than for prednisone alone (43 and 18 weeks respectively; p < 0.001).

The patients who met the criteria for a palliative response also had improvements in most domains on quality-of-life scales, including highly significant improvements in overall well-being. There was no significant improvement in survival. A fall in PSA level of 75% or more was seen in 27% of those who received mitoxantrone plus prednisone and in only 9% of those who received prednisone alone. Mitoxantrone was well-tolerated, and the incidence of serious toxic effects was low. There was no evidence of deterioration in any quality-of-life domains associated with chemotherapy.

Estramustine combinations

Estramustine, composed of nornitrogen mustard and estradiol joined by a carbamate ester linkage, produces cytotoxic effects independent of its alkylating and hormonal constituents. The antineoplastic effects of estramustine are believed to arise from its effects on microtubule-associated proteins and consequent disruption of mitosis.

Estramustine has been extensively tested in patients with hormone-refractory prostate cancer, and as a single agent its benefits are minimal. However, it has been evaluated recently in combination with chemotherapeutic agents with which it has synergistic cytotoxicity in vitro (e.g., vinblastine, etoposide and paclitaxel). The results of 3 phase II trials of the combined regimen of estramustine and vinblastine have recently been published.[28]

The PSA response rate — defined as the percentage of patients with a decrease in PSA level of 50% or greater — for the 88 patients in the combined estramustine–vinblastine studies was 42%.[28] Partial responses were noted in 6 (24%) of 25 patients with bidimensionally measurable non-osseous disease. Recently completely randomized trials comparing estramustine plus vinblastine with vinblastine alone (by the Hoosier Oncology Group) and with estramustine alone (by EORTC, the European Organisation for Research on Treatment of Cancer) will better define the role of estramustine in hormone-refractory prostate cancer.

Recent phase II studies evaluating estramustine plus etoposide and estramustine plus paclitaxel have also been reported.[29,30] Both showed activity similar to that reported for estramustine plus vinblastine; however, these single-study results are early, and the toxicity of these regimens may be a problem.

Suramin

Suramin was originally synthesized 80 years ago and has been used to treat a variety of parasitic diseases. In the 1980s its cytotoxic activity against human prostatic cell lines in vitro was noted.[31] Although some clinical trials demonstrated activity against hormone-refractory prostate cancer, the relative merits of this agent are a subject of controversy. Eisenberger and colleagues[32] found a response in 6 of 12 patients with measurable disease, a reduction in PSA level of at least 50% in 77% of patients (24/31) and a reduction of 75% in 55% (17/31).

However, suramin is known to inhibit PSA release, and 9 of the 24 patients with a decrease in PSA level of 50% or more had evidence of disease progression at the same time. Treatment was discontinued in 80% of the patients (28/35) because of dose-limiting toxic effects, which presented primarily as a syndrome of fatigue, malaise and lethargy. Thus the palliative benefit of such a regimen must be questioned.

Suramin suppresses adrenocortical function and is given in conjunction with hydrocortisone. The concomitant use of steroids has made it difficult to establish the response attributable to suramin. In a study in which patients received suramin only, after progression on corticosteroids alone, only minimal activity was seen; there was no demonstrable response in patients with measurable disease.[33] A better understanding of suramin will come from a large, recently completed North American trial involving 500 patients, randomly chosen to receive suramin plus hydrocortisone or hydrocortisone alone.

Conclusion

Better therapies are needed for the prevention and treatment of hormone-refractory prostate cancer. Novel approaches currently being tested in early clinical trials include angiogenesis inhibitors, immunological therapies, gene therapy and differentiation therapies. Because of the high incidence of bone metastases in metastatic prostate cancer and their potential devastating effects, the role of bone-stabilizing agents, such as the bisphosphonates, is being explored in phase III studies.

However, until we have identified treatments that significantly affect survival, we must focus on relieving patients' distress and improving their overall quality of life. To this end, the only drug therapy with a documented benefit is the combination of mitoxantrone and prednisone. Although far from a cure, this combination has a role in treating symptomatic patients and can be the standard against which newer therapies are compared.

To return to the patient described at the beginning of this article, it seems that there is both good news and bad news for him. The bad news is that he cannot be cured and that available hormonal therapies produce side effects that will undoubtedly compromise his quality of life. The good news is that hormone therapies will almost certainly control his disease for a few years, and, if hormone-resistant disease develops, there is a chemotherapy regimen of known efficacy to palliate his symptoms. Although of little immediate benefit to this patient, the randomized controlled trial of intermittent hormone therapy may change the way we care for patients in the future. Furthermore, we now have a chemotherapy standard and a method of inquiry that permits an examination not only of conventional endpoints, such as survival, but also of others, such as pain control, that are of immediate relevance to patients.

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