Treatment of Androgen-Independent Prostate Cancer

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ABSTRACT
Androgen-ablative therapy for metastatic prostate cancer is effective for 60%-80% of men, but its effects are always finite and the majority of men develop androgen-independent disease within two years. Although current therapies for androgen-independent disease have not been shown to impact on survival, recent clinical and laboratory insights offer hope for effective therapy. For instance, recent data indicate that androgen-independent disease may still be dependent on hormonal stimulation, suggesting that hormonally based therapies may provide continued benefit. Chemotherapy, especially with estramustine and etoposide, seems to be an effective combination for a majority of patients. Treatment with suramin had been hampered by its side effects, but new dosing schedules are effectively circumventing toxicity. Radioisotopes such as strontium 89 have been shown to provide effective palliation for a majority of androgen-independent patients. Overall, these and other emerging efforts may be the foundation for therapies that offer hope for a significant survival benefit.

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INTRODUCTION
There has recently been an increase in emphasis on prostate cancer awareness among the general public, including the possible benefits of prostate-specific antigen (PSA) screening. Despite these efforts, an increasing number of deaths from prostate cancer has been observed in each of the past several years [1]. The reasons for the increasing death rate from this disease are not known with certainty, but are not solely the result of the aging of the population [1]. Whatever the causes, the fact remains that many patients still progress to, or are diagnosed with, stage D2 prostate cancer and will eventually require therapy that reduces serum androgens. Androgen-ablative therapy is typically achieved by orchiectomy or luteinizing-hormone-releasing hormone (LHRH) analog administration, with diethylstilbestrol now being used less commonly [2]. These methods appear to be equivalent with respect to reduction in serum androgens and approximately 60%-80% of D2 patients respond, independent of the method of androgen ablation used [3]. Unfortunately, however, the remissions induced by these therapies are always of limited duration and most patients exhibit progressive disease within 12 to 18 months after the initiation of therapy [2, 3]. This stage of the disease is often called hormone-refractory or androgen-independent (AI) prostate cancer, although as will be discussed below, neither of these terms may be entirely accurate.

Patients with AI prostate cancer represent a difficult challenge for the oncologist because historically there have not been many effective therapies. Although many prostate cancer patients are elderly and, therefore, often have lower performance status, all oncologists are faced with prostate cancer patients who are physiologically vigorous and lack significant co-morbid disease. There is, therefore, a vital need not only for more effective and well-tolerated palliative therapies, but potentially more aggressive therapies capable of providing a survival advantage.

THE DECISION TO TREAT HORMONE-REFRACTORY PROSTATE CANCER
In the current era of PSA testing, often both the patient and his physician become aware at the same time that the androgen-ablative treatment the patient received is losing effectiveness. Increasing PSA values typically presage clinical relapse [3, 4], resulting in understandable anxiety for patients and physicians alike. Although patients necessarily consult their oncologists for options, as will be discussed below, no single regimen can be considered standard therapy. In fact, because therapy has not yet been shown to improve survival [5], the usual therapeutic goal is palliation. In this setting a rising PSA, in and of itself, in the asymptomatic patient usually should not dictate treatment. In fact, outside the confines of a clinical study, it may be
well advised to delay treating the patient who has only increasing PSA values because it may be months before symptoms requiring palliation are present. As is true for some other patients with advanced malignancies, in the absence of a clear survival benefit, therapy should often be directed at improving the quality of life.

Even for palliative therapy it is important to have objective methods of determining the effectiveness of the treatment regimen. However, hormone-refractory prostate cancer is notoriously difficult to assess by the typical radiographic examinations. This is because bone is the only site of metastatic disease in approximately 80%-85% of patients [2, 3, 6], and responding bone metastases resolve only very slowly on bone scan or plain films. Although about 15% of patients have sites of evaluable soft-tissue disease, these sites are often involved either late in the course or in patients with less typical and more aggressive forms of disease [3, 6]. Therefore, it might not be possible to extrapolate the response rate of hormonal therapy from the responses of this patient subset. For these reasons it is fortunate that PSA values have, for the most part, been shown to improve the ability to objectively assess therapy. For instance, in one large study of hormone-refractory patients on a variety of different therapies, PSA declines by >50% were associated with an improved survival [7]. It should be emphasized, however, that PSA levels alone may not be a completely reliable marker for the disease in all patients and, therefore, do not replace the need to assess pain, performance status, or when possible, objective signs as response indicators.

**HORMONAL THERAPY FOR AI PROSTATE CANCER**

Unlike breast cancer therapy, many clinicians view second-line hormonal therapy for prostate cancer as futile. This view is held even for patients who may have had longer-term responses to androgen ablation. The source for this belief probably comes from attempts to treat orchiectomized patients with LHRH analog therapy or vice versa. Responses after these maneuvers are typically very uncommon [5], probably because these therapies act similarly to reduce the level of serum testosterone. Despite this widespread belief, there is a considerable body of both past and emerging data that indicates that hormone-refractory prostate cancer is still, at least partially, hormonally sensitive.

Evidence that AI prostate cancer is still sensitive to hormonal stimuli is its behavior in the setting of recurrent exposure to testosterone. Unlike orchiectomy, LHRH analogs can be discontinued. Some clinicians prefer to stop therapy in progressing patients so as not to incur the cost, inconvenience and side effects of a possibly unnecessary therapy. Although there is some disagreement as to the effects of discontinuing LHRH analogs in these patients [8], at least one well-performed study has shown a modest survival advantage in patients continued on LHRH analogs [9]. This result may indicate that there is at least a component of AI disease that is responsive to androgenic stimulation, and suggests that androgen-ablative therapy should be maintained in most patients.

It should also be emphasized that androgen-ablative therapy does not, in fact, eliminate all circulating androgens. Even after orchiectomy, the adrenal cortex remains a significant source of so-called “weak” adrenal androgens [10], which may be able to stimulate the growth of prostate cancer cells (either directly or after peripheral conversion to testosterone and dihydrotestosterone). Hormones synthesize in the adrenal cortex have been the target for some of the therapies used for treating AI disease. For instance, early efforts to ablate adrenal androgens by adrenalectomy were sometimes successful [11]. More recent attempts using aminoglutethimide therapy, which is often referred to as a medical adrenalectomy, to block adrenal steroid biosynthesis have resulted in response rates of about 20%-25% [12, 13]. Approximately the same response rates have been demonstrated using ketoconazole [14], a therapy that might also be effective by reducing adrenal hormone synthesis. Both ketoconazole and aminoglutethimide typically require concomitant therapy with glucocorticoids [12-14]. Glucocorticoids have been shown to be sometimes effective alone [15, 16], possibly by decreasing adrenal androgen synthesis through suppression of adrenocorticotropic hormone.

Another approach in addressing androgens that may remain after conventional androgen ablation treatment has been to directly block the androgen receptor (AR) through the use of antiandrogens. The growth-promoting effects of androgens are the result of binding and activation of the AR in prostate cancer cells [17, 18]. The activated AR then stimulates the expression of a series of genes which results in tumor cell growth. Antiandrogens bind directly to the AR, but under normal conditions do not activate the receptor [19]. Therefore, by occupying the AR, antiandrogens can, in principle, prevent AR activation by residual androgens.

Currently, the most widely used antiandrogen in the USA is flutamide. The combined use of flutamide with orchietomy or LHRH agonist therapy appears to modestly prolong the survival benefit of initial androgen-ablative therapies [20]. This is presumed to be due to the ability of the antiandrogen to block residual adrenal androgens that may still be stimulating the AR [21]. In contrast, flutamide therapy for AI patients who have not been previously treated with this antiandrogen results in only a modest response rate of approximately 15% and no clear survival advantage [22]. This has been interpreted to mean that residual androgens do not play a major role in AI disease. However, this explanation is being reassessed in light of data indicating that the AR may be altered in some cases of AI prostate cancer.
THE AR IN AI PROSTATE CANCER

Recent observations suggest that the AR may continue to play an important role in the growth of AI prostate cancers. Several groups have now shown that the AR is expressed in the great majority of AI prostate cancers, possibly at increased levels [23, 24]. The significance of this AR expression in AI disease is suggested by the flutamide-withdrawal response. When flutamide is withdrawn from patients progressing on the combination of flutamide and LHRH analog therapy, or flutamide and orchietomy, approximately 40%-50% of patients will demonstrate a clinical response [25, 26].

Interestingly, flutamide was previously shown to stimulate the growth of a cell line, LNCaP, derived from a patient with AI prostate cancer [27]. Analysis of the AR from LNCaP cells showed that it contained a point mutation in the hormone-binding domain, which converted flutamide from being an AR antagonist to an agonist for these cells. A possible explanation for the flutamide withdrawal response, therefore, has been that similar mutations occur in some patients, resulting in tumors which are stimulated by flutamide.

Recent data demonstrate clearly that AR mutations do occur in AI prostate cancer [28-30] and may contribute to disease progression, although the frequency of these mutations and the contribution they make to AI disease have yet to be firmly established. We recently reported the isolation of ARs with mutations in the hormone-binding domain in five of 10 patients with AI prostate cancer [30]. Functional analyses of these ARs demonstrated activation by several hormones and drugs [30], including flutamide (unpublished data). These findings all indicate that hormonal- or anti-androgen-induced AR activation may continue to play an important role in AI prostate cancer.

Another nonsteroidal antiandrogen, bicalutamide, binds to the wild-type AR with increased affinity relative to flutamide [31], and may be more effective than flutamide in prolonging the response rate to androgen- ablative therapy in hormone-sensitive disease [32]. Interestingly, we have determined that bicalutamide remains an effective antagonist for several mutant ARs which are stimulated by flutamide (data not shown). Similar observations have been made regarding the mutant AR from the LNCaP cell line [27]. Based upon these in vitro data, we have begun a trial of bicalutamide in AI patients. The preliminary results, in conjunction with a recent report in abstract form [33], suggest that bicalutamide may be effective for some AI disease patients. Durable responses to this drug will probably be limited, however, and the report of a bicalutamide withdrawal response [34] may indicate that this agent can also be an agonist for some AI tumors. Nonetheless, the development and testing of new AR antagonists, and trials of additional hormonal treatments in AI prostate cancer, appear well justified.

CHEMOTHERAPY FOR AI PROSTATE CANCER

Cytotoxic chemotherapy has for the most part not been very successful for the treatment of AI prostate cancer. A host of single agents and combinations has been tried, but the results of therapy have usually been disappointing. For example, in 1993 the late Dr. Alan Yagoda, a pioneer in genitourinary oncology, and his colleague reviewed 26 recent drug trials of AI prostate cancer [35]. They found that only six trials had response rates of greater than 10%.

It is not known with certainty why prostate cancer is often less sensitive to chemotherapy than other cancers. Perhaps hampering therapy in this setting is the likelihood that prostate cancer cells in vivo divide very slowly, and many chemotherapeutics are better at killing cells in cycle. Also, of course, the typically older AI prostate cancer patient may be less able to tolerate intensive regimens that result in a host of side effects. Although to date no single agent or combination has been shown to result in a survival benefit, there are some active agents that can provide effective palliation for patients. Furthermore, as will be discussed below, recent trials offer encouragement that a greater number of AI patients might be aided by chemotherapy in the future.

DNA intercalating agents have some activity in prostate cancer. Adriamycin administered weekly at a dose of 20 mg/m\(^2\), a therapy shown to be very well tolerated for the treatment of breast cancer, resulted in a 25% response rate in studies of AI disease [36-38]. Mitoxantrone, a related agent, has been used in several studies, sometimes with a low dose of prednisone. This therapy has also been extremely well tolerated, and has been shown to provide effective palliation for between 20%-35% of patients [39, 40].

DNA alkylating agents have also been used for treating AI disease. Cyclophosphamide has been administered by a variety of treatment schedules, including high-dose therapy with GM-CSF [41]. But even low-dose daily oral therapy, well tolerated at a dose of 75 to 100 mg/m\(^2\) per day, was shown to result in PSA reductions of over 50% in 31% of patients [42].

Combinations have not been shown to be clearly superior to single-agent therapy [43], but there is hope that this strategy may yet be fruitful. For instance, in one encouraging study the combination of 5-fluorouracil and weekly adriamycin resulted in PSA reductions in 11 of 18 patients [44]. Combinations of estramustine and etoposide or estramustine and vinblastine also seem to be very promising. The latter regimens have demonstrated responses, at least by the criteria of halving PSA values, in over 50% of patients in some studies [45, 46].

Estramustine, being an estrogen analogue, was developed to be a chemohormonal therapy. It was hoped that it might selectively alkylate DNA in those cells that express estrogen receptors, but this is not the way the drug seems to
work. Its mechanism of action is independent of hormonal status and the mustard moiety does not appear to alkylate DNA. Instead, estramustine binds to microtubules [47] or nuclear matrix associated proteins [48]. The molecular basis for any selective action it may have in prostate cancer is, therefore, unclear.

**Radiation Therapy**

Typical orthovoltage radiation therapy for relief of painful metastatic bone sites, for prophylaxis for impending fractures, or for treating incipient or frank cord compression, is effective palliative therapy for AI prostate cancer [3]. Radioactive isotopes have also recently been proven effective for palliation of widespread metastatic bone disease [49, 50]. Some of these isotopes, like the recently FDA-approved isotope strontium 89, seem to have the property of preferentially homing to metastatic sites in bone because of associated osteoblastic activity [50]. Strontium 89 therapy has been shown to result in subjective improvements in bone pain in approximately 75% of patients [49]. This therapy can be repeated in responding patients, and sometimes a second injection three months later proves beneficial for the initially non-responding patient.

**Suramin**

Suramin, an antitrypanosomal agent, has been the subject of multiple trials since it was first demonstrated to have utility for prostate cancer during phase II testing. Suramin’s exact mechanism of action is not known, since the drug can have antitumor effects by one or more possible mechanisms [51]. This agent has been reported to effectively block growth factors that may be critical for AI prostate cells, including epidermal and fibroblast growth factors. It is also possible that suramin’s antitumor properties are mediated via a hormonal mechanism, in that it is a potent adrenal corticolytic agent which can therefore suppress adrenal androgen synthesis. However, against an exclusive hormonal mechanism of action is the fact that the drug has activity in vitro against prostate cancer cell lines [51].

Hampering clinical progress with suramin has been associated toxicities. Among side effects attributed to suramin are rash, neuropathy, renal and adrenal insufficiency and pancytopenia [51-54]. Despite these toxicities, dosing schedules, both fixed and pharmacologically guided, have been devised [52-54]. These schedules have minimized some of the toxicities and in at least some trials antitumor activity has been retained [52, 53]. Response rates seem to vary widely, perhaps due to drug dosage and schedule. In one study which used an adaptive control dosing schedule, an objective response rate of 40% and PSA declines by more than 75% were observed [52]. In another study using a different schedule, the response rates were very much lower and suramin added little benefit over that achieved with hydrocortisone alone [54]. Based on these results, it is not yet certain how suramin will fit into the armamentarium for AI prostate cancer treatment.

**Future Directions**

Despite the lack of clear survival benefit offered by existing therapies for AI prostate cancer, many scientists and clinicians in this field are hopeful that the coming few years will see more effective therapies. Spurred by the magnitude of the problem, a resurgence in basic and clinical progress in prostate cancer has resulted in interesting new therapeutic strategies in various phases of development. It is further encouraging that these insights come from several areas of biology. Investigation of previously unknown properties of cytokines, including GM-CSF, have shown that sometimes the expression of these cytokines in tumor cells may re-awaken the immune system to provoke the systemic rejection of many cancers, including AI prostate cancer [55]. This type of “tumor vaccine” model may find utility for the treatment of AI disease. Monoclonal antibody trials are in progress, especially a variety of potentially specific target antigens [56], and these may yet prove promising. Conventional chemotherapy using drug combinations and, hopefully, new agents may prove useful. Finally, there have been significant advances recently in understanding how steroid hormones, and steroid hormone receptors such as the AR, function to control cell growth and development. Future trials may incorporate these advances, possibly in combination with conventional therapy. However, at the present time it is most important that overall research in prostate cancer continue in order to better understand the biology of this disease and identify new agents which may be useful for treatment.

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