Management of Hormone-Sensitive and Hormone-Refractory Metastatic Prostate Cancer

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The current options for the treatment of advanced prostate cancer are reviewed.

Background: Prostate cancer is a significant health problem in the United States and is the focus of increasing attention in our society. With the aging of the US population, it is likely that prostate cancer will continue to grow in importance. The options for systemic therapy of metastatic prostate cancer should be familiar to physicians, including nonspecialists, whose patients seek their advice and counsel.

Methods: Past and recent literature was surveyed to provide an understanding of the systemic treatment of advanced prostate cancer. The author presents a review of the systemic treatment of metastatic prostate cancer in different clinical circumstances and addresses the current status of chemotherapy in the management of advanced prostate cancer.

Results: Early androgen deprivation used over prolonged periods appears to be modestly superior to delayed androgen deprivation with a small potential survival advantage and an advantage in delaying disease progression in advanced prostate cancer. Patients with hormone-refractory prostate cancer may benefit from secondary hormonal therapy (eg, adrenal enzyme inhibitors, antiandrogens, glucocorticoids) and chemotherapy.

Conclusions: The choices of therapy for metastatic prostate cancer depend on individual patient preference. Patients and physicians should be aware of the possible side effects associated with the therapeutics options for treatment of metastatic prostate cancer.

Introduction

It is estimated that 185,000 new cases of prostate cancer will be diagnosed in the United States in 1998.1 New prostate cancer diagnoses have fallen significantly for the first time after climbing steadily for a number of years. This is likely due to the efficacy of screening efforts that have detected many of the readily detected cases of prostate cancer. Mortality rates, however, have been more constant, with approximately 40,000 men dying of prostate cancer each year. Very recent trends have shown a small decrease in mortality that, if continued, may indicate that therapy can delay or prevent prostate cancer deaths. Although uncertain, it is hoped that the interventions of screening and treatment for localized prostate cancer will lead to fewer deaths resulting from prostate cancer.

Prostate cancer-related deaths occur as a result of complications of metastatic disease. Metastatic disease is incurable, and the goals of treatment should be to prolong survival and improve the patient’s quality of life. Metastatic disease may be found on presentation or may develop after treatment for localized disease. Metastatic prostate cancer refers to tumor metastatic to regional pelvic lymph nodes (D1) or distantly metastatic to other sites (D2), most often bone.

The concept of what constitutes advanced disease has evolved to include disease documented only by a rising prostate-specific antigen (PSA) after local therapy has been used or considered. PSA testing is largely responsible for this shift. Often in these patients, metastatic disease cannot be definitively documented by biopsy, physical examination, bone scan, computed tomography scan, magnetic resonance imaging scan, or ProstaScint (Cytogen Inc, Princeton, NJ), scan. It often is not possible to determine whether PSA comes from tumor localized to the prostatic bed, from distant sites, or from both. Virtually all of these patients are destined to develop metastatic prostate cancer, and receiving systemic therapy is an option.

Systemic treatment of metastatic prostate cancer includes hormonal therapy, chemotherapy, radiopharmaceuticals, investigational therapy, and supportive therapy. Hormonal therapy is the mainstay of systemic therapy. Traditionally, hormonal therapy was reserved until late in natural history of the disease when patients became symptomatic from metastatic bone involvement. However, hormonal therapies are being used increasingly earlier in the course of prostate cancer for poor-risk patients, for locally advanced prostate cancer, or for PSA failures after definitive local therapy. Chemotherapy is used and being developed for stage D2 prostate cancer as well as in the adjuvant setting. Radiopharmaceuticals are used in the setting of bone pain.

This paper focuses on the systemic treatment of metastatic prostate cancer and provides an overview of therapy. The topic of early vs delayed use of androgen ablation in advanced disease is reviewed more extensively. Information on systemic treatment of early-stage disease is included where it relates to treatment of metastatic disease. The first part of this article addresses hormone-sensitive disease, and the second part focuses on hormone-refractory disease.

Hormone-Sensitive Metastatic Disease

When prostate cancer progresses after definitive local therapy or when stage D prostate cancer is documented, the patient and physician are confronted by options for the choice and timing of systemic therapy. Several questions and controversies exist with respect to these options. This decision process is complicated in asymptomatic individuals as the therapies have side effects and are questionable able to prolong survival. Patients tend to be proactive and prefer treatment to observation in many instances. The costs to society through additional health care expenditures are great. Information on the timing and choice for hormonal therapy is reviewed to aid in this decision process.

Androgen Deprivation

The primary treatment for symptomatic metastatic prostate cancer since the 1940s has been the removal of the testicular androgen. Prior to routine PSA testing,
patients with D2 disease were shown to respond to androgen deprivation on average for 14 to 17 months.\textsuperscript{2} Failure of androgen deprivation is recognized earlier with serial PSA testing.

Testicular androgen deprivation is accomplished with bilateral orchiectomy, diethylstilbestrol (DES), or a luteinizing hormone-releasing hormone (LHRH) agonist. These three therapies are considered to be therapeutically equivalent. DES is inexpensive but has fallen out of favor since at least higher doses are associated with thromboembolic disease and excess mortality.\textsuperscript{3} DES is no longer available due a lack of interest in its use. Orchiectomy is chosen by some patients for its convenience. Patients have been shown to prefer the use of LHRH agonist to orchiectomy.\textsuperscript{4} The LHRH agonists used in the United States are leuprolide and goserelin, both of which are available in three-month depot formulations. LHRH agonists are well tolerated but are costly compared to orchiectomy or DES.

Androgen deprivation is associated with numerous side effects including decreased libido, impotence, anemia, hot flashes, hair loss, osteoporosis, fatigue, and psychologic factors. These quality-of-life issues as well as costs need to be considered when androgen deprivation is utilized. A LHRH agonist or orchiectomy with or without an antiandrogen is the standard form of androgen deprivation used in the United States.

**Intermittent Androgen Deprivation**

The intermittent use of LHRH agonists has been proposed\textsuperscript{5,6} and is the focus of a current Intergroup clinical trial. This investigational approach seeks to use PSA response to indicate the need for administration of LHRH agonist. Potential benefits have been suggested, including a delay in the progression to the hormone-refractory state and quality-of-life benefits. Patients interested in this concept should be encouraged to participate in a clinical trial since the outcome is uncertain.

**Adrenal Androgen Production**

In addition to testosterone produced by the testicles, the adrenal glands produce three androgenic steroid hormones: dehydroepiandrosterone (DHEA), DHEA-sulfate, and androstenedione. These weak androgens can be converted peripherally to dihydrotestosterone (DHT) to provide growth stimulus to prostate tumors. Theoretically, these adrenal androgens can be blocked at the level of the adrenal receptor with nonsteroidal antiandrogens, or their production can be decreased at the level of the adrenal gland with agents that cause a medical adrenalectomy (ketoconazole, aminoglutethimide).

**Antiandrogens**

The current generation of antiandrogens are nonsteroid agents that are intended to act as androgen receptor antagonists. The antiandrogens approved in the United States are flutamide, bicalutamide, and nilutamide. At the present time, they are differentiated by side-effect profiles, dosing, and cost. Antiandrogens have been used as monotherapy without suppression of testicular androgens; however, this approach has been shown to be inferior to androgen deprivation. The rationale for antiandrogen monotherapy has been to inhibit tumor growth without having to remove testosterone in the hope of maintaining libido and potency. This concept has been expanded on by the idea of combining an antiandrogen with finasteride\textsuperscript{7} and is the subject of several investigations.

**Combined or Maximal Androgen Blockade**

It was proposed in the 1980s that testicular androgen deprivation combined with an antiandrogen would be more effective than testicular androgen deprivation alone.\textsuperscript{8} This is referred to as \textit{combined androgen or maximal androgen blockade}. This concept is based on the theory that the antiandrogen will block the additional androgens produced by the adrenal glands at the level of the tumor.

A number of large, prospective, randomized clinical trials have examined this question by comparing testicular androgen ablation with combined androgen blockade. Even though a number of these trials demonstrated a significant benefit with combined androgen blockade, a larger confirmatory trial of orchiectomy with or without flutamide involving more than 1,300 men did not reveal a significant improvement in overall or progression-free survival.\textsuperscript{9} Lingerings issues from these trials question whether statistical considerations are responsible for these differences and whether orchiectomy and LHRH agonists are truly equivalent when combined with an antiandrogen.

Two meta-analyses have been published\textsuperscript{10,11} that examine the value of combined androgen blockade by pooling data from published trials of testicular androgen deprivation vs combined androgen blockade. These studies gave contrasting opinions about the benefit of combined androgen blockade. It is probable that there is a small benefit for combined androgen blockade, based on the positive results of the larger prospective, randomized trials\textsuperscript{2,12,13} and the lack of studies that do not exclude this possibility. These agents are costly, and their early use affects health care costs.

**Timing of the Treatment of Metastatic Disease With Androgen Deprivation**

The question of when to treat metastatic disease with androgen deprivation has important implications for patients and society. While patients and their physicians place survival as the major goal of therapy, they also are placing ever-increasing emphasis on quality-of-life issues. It is difficult to advocate a long-term therapy with significant side effects in a population in which many of the individuals treated may not benefit from the therapy. Additionally, the routine use of early LHRH agonists and antiandrogens are associated with significantly higher costs compared to delayed therapy.

A limited number of modern studies have examined the benefit of early vs delayed androgen deprivation in stage D prostate cancer. For this reason, several large radiation therapy and surgical studies that examined the benefit of immediate or delayed androgen deprivation are also reviewed. These studies addressed the question of whether early androgen deprivation is superior to delayed androgen deprivation in advanced prostate cancer. Studies that used androgen deprivation neoadjuvantly or briefly during or after therapy are not included.

Many patients in these adjuvant hormonal radiation therapy trials were pathologic stage D1 or clinical stage C. Patients who are clinical stage C are often upstaged if pathologically staged. These patients have tumor that is not thought to be organ confined and have a high rate of progression, such that an adjuvant therapy can be ideally tested. Stage C and D1 prostate cancers represent a population with lower tumor burden compared with D2 disease, which is an attractive setting to test early vs late androgen ablation.

**Adjuvant Androgen Deprivation and Radiation Therapy**

A number of early studies\textsuperscript{14-18} examined the question of whether early or delayed hormonal therapy had an influence on outcome when combined with radiation.
therapy. These trials did not show an advantage to early hormonal therapy; however, all are significantly flawed such that conclusions are in doubt. Many of these trials were single-institution, retrospective analyses that neither were designed nor were statistically powerful enough to adequately answer the question of whether early or delayed androgen deprivation improved outcome. In many of these studies, DES was utilized as a hormonal therapy. This was in an era before higher doses of DES (5 mg daily) were recognized to cause excess cardiovascular morbidity. Most of these reports recognized this problem by the time of publication, and some documented an increase in noncancer mortality with this type of hormonal therapy. Treatment with hormonal therapy often varied with respect to timing of onset and duration of therapy, such that they were not used in a true adjuvant setting.

Several recent adjuvant hormone studies were better designed, and their initial results are available. A trial by the European Organization for Research on Treatment of Cancer (EORTC) studied the use of standard external-beam irradiation with or without adjuvant LHRH agonist (goserelin) in 415 patients. Of the eligible patients, 91% had stage C (T3 and T4) prostate cancer, and 89% were nodal status N0. LHRH agonist was started on the first day of irradiation and was continued for three years. Androgen ablation was performed at the time of progression in the delayed androgen ablation group, most often with LHRH agonist (72%). Local control and survival improved with the use of goserelin. In 401 patients at a median follow-up of 45 months, survival at five years was 79% with the LHRH agonist compared to 62% without the LHRH agonist ($P=0.001$). These results may reflect a survival advantage as a result of enhanced local control with the combined treatment as well as a benefit from early hormone treatment.

A similar trial by the Radiation Therapy Oncology Group (RTOG) studied radiotherapy with or without adjuvant goserelin in locally advanced disease. All patients were given definitive radiotherapy and were randomized either to receive no further therapy or to receive goserelin begun during the last week of radiation therapy and continued indefinitely. Goserelin was administered to those who did not receive it adjuvantly at the time of relapse. A total of 73% of patients had stage C disease and 26% of patients had stage D1 disease. In the adjuvant LHRH arm, there was a significantly improved rate of local recurrence, freedom from distant metastasis, disease-free survival, and PSA relapse rate. However, overall five-year survival was not significantly different. In patients with Gleason score 8–10 tumors, five-year overall survival was significantly different ($P=0.03$) in the adjuvant LHRH arm (66%) compared with the control arm (55%). Additional follow-up from this trial is needed to be confident about the lack of significance of overall survival.

A prospective, randomized trial of external-beam radiotherapy was performed using orchietomy or no orchietomy as an adjuvant therapy. Ninety-one patients were studied with a median follow-up of 9.3 years. Primary tumors were mostly stage T2 (65%), and 43% of patients had positive pelvic lymph nodes (D1). Disease progression ($P=0.005$) and overall survival ($P=0.02$) were significantly better with early androgen deprivation. These differences were due primarily to the improved outcomes for patients with node-positive disease.

An additional study examined the question of radiation with early or delayed androgen deprivation. The authors first performed a retrospective analysis of all patients who underwent radiation therapy alone for T1–4 and N0 or NX prostate cancer in a certain time period. Only 10% of the 938 men underwent staging lymphadenectomy; the remainder were NX. They used prognostic features, pretreatment PSA, Gleason score, and T classification to identify a poor-risk population of 185 patients. These patients were categorized as poor risk with PSA $>20$ ng/mL or PSA 10 to 20 ng/mL with Gleason scores $>7$. The authors then applied these factors to the next cohort of 100 poor-risk patients treated with radiation and added androgen deprivation. Androgen deprivation was intended to be continued lifelong and was composed of $30\%$ orchietomy, $55\%$ LHRH agonists, and $15\%$ LHRH agonists and antiandrogens. The prognostic features were significantly worse for the patients who received androgen ablation in the second cohort. The failure rate at five years was $82\%$ for the radiation-alone group compared to $15\%$ in the radiation-and-androgen-deprivation group. At five years, there was no survival advantage, and a subsequent survival analysis is anticipated.

It is apparent that there is a benefit for the use of adjuvant hormonal deprivation and radiation. This is seen as a delay in disease progression and is possibly associated with a survival advantage. These patients represent a population with locally advanced disease and in many cases with metastatic disease. While the benefit from enhanced local control for the combined therapy cannot be excluded, it likely also represents an improvement in control of metastatic disease with early hormonal therapy.

**Stage D1 Disease**

A number of important questions remain with regard to the timing of androgen deprivation in metastatic prostate cancer (D1 and D2). Many studies in early metastatic disease (D1) are retrospective or single-institution adjuvant trials and suffer multiple criticisms. D1 disease is most commonly treated as advanced disease with observation or androgen ablation. It is believed that the nodal biopsy is predictive rather than therapeutic. Despite the metastatic state, some groups will proceed with local therapy to the prostate in the form of radiation or a prostatectomy. The proponents of this approach cite local disease control and possible benefit in preventing later metastasis.

A retrospective study in 68 patients with D1 disease demonstrated a median interval to progression to D2 disease of 43 months with late androgen deprivation as compared to 100 months for early androgen deprivation ($P=0.0087$). Survival was not significantly different but was 90 months for the group receiving late androgen deprivation and 150 months for immediate androgen deprivation ($P=0.111$). Another retrospective study of 266 D1 patients revealed a significantly improved rate of nonprogression ($P<0.0001$) in patients who had immediate orchietomy as compared to no immediate orchietomy. Survival was not significantly different ($P>0.32$); 6% of patients with immediate orchietomy died compared with 18% of patients without immediate orchietomy. A third retrospective study in D1 patients showed a significant difference in nine-year disease-free survival ($P=0.03$) of 67% for early endocrine treatment compared with a 32% estimated nine-year survival for late endocrine treatment. The nine-year cause-specific survival was not significantly different ($P<0.194$). In summary, it appears that androgen ablation can delay disease recurrence in stage D1 disease but has not been shown to improve overall survival.

**Stage D2 Disease**

It has long been considered standard in the United States to offer patients with D2 disease androgen deprivation only after the development of symptomatic disease. Studies by the Veterans’ Administration Cooperative Urological Research Group (VACURG) suggested no clear survival advantage to early hormone therapy compared with delayed hormone therapy in prostate cancer. This group’s initial recommendation was to delay hormone treatment with DES (1 mg daily) for prostate cancer until the time symptoms appeared. In a later analysis of the VACURG data, this recommendation was questioned as patients treated with DES 1 mg daily survived longer than those treated with placebo. Subset analysis suggested that younger patients with high-grade disease had the greatest benefit from early hormone treatment.

The Medical Research Council Prostate Cancer Working Party Investigators Group examined the effect of immediate vs delayed androgen deprivation by orchietomy or LHRH agonist in patients who were not operative candidates with T2 to T4 tumors or asymptomatic metastatic disease. In the first report of their results, 203 of 469 patients in the immediate-treatment group died of prostate cancer compared to 257 of 465 patients in the delayed-treatment group during to follow-up period. This was significant with a $P$ value of $<0.001$. Unfortunately, 29 of the deaths in the delayed-treatment group occurred in patients who never received androgen deprivation. The difference in survival of the two groups may have been less had the delayed-treatment group been monitored more closely and treated with...
androgen deprivation. The subsequent reports of this study may provide additional information. In summary, early androgen deprivation used over prolonged periods appears to be modestly superior to delayed androgen deprivation with a small potential survival advantage and an advantage in delaying disease progression in advanced prostate cancer. It is important to discuss with patients the side effects of androgen deprivation, which include decreased libido, impotence, anemia, hot flashes, hair loss, osteoporosis, fatigue, and psychologic factors. It is evident that the earlier the use of androgen deprivation, the longer the duration of any perceived ill effects. Sexually active men who place a great emphasis on maintaining sexual function may choose to delay therapy with androgen deprivation in spite of a potential small survival advantage. Reasonable patient requests should be honored. A note documenting the physician-patient discussion of the decision process should be included in the chart. Ultimately, the decision to begin hormone treatment will be based on a patient’s choice of a possible benefit in survival and disease progression vs the side effects.

Hormone-Refractory Metastatic Disease

A rising PSA, progressive symptoms, or progression on imaging studies signals the failure of androgen deprivation. Hormone-refractory prostate cancer is a term commonly used to describe prostate cancer that has progressed in spite of primary androgen deprivation by removal of testicular androgens using orchiectomy, DES, LHRH agonists, or combined androgen blockade. These patients retain hormonal sensitivity in that they can demonstrate a flare in symptoms with exogenous androgen administration and may respond to secondary hormonal therapy. Two retrospective analyses of cooperative group trials have been completed examining for a benefit for continuation or discontinuation of an LHRH agonist. One demonstrated a modest survival advantage for the continuation of an LHRH agonist, and the other did not show an advantage to continuation. It seems reasonable to continue with a life-long regimen of LHRH agonists. It is standard to recommend that a testosterone level be measured to assure the patient’s testosterone value is in the castrate range.

There is no one standard of care for patients with hormone-refractory prostate cancer. It is preferable that patients participate in clinical trials to answer important questions. Available clinical trials may affect choices in the timing and sequence of secondary hormonal treatments. In the absence of a clinical trial, efficacy and quality-of-life concerns of treatment dictate choices. The sequence of second-line hormone treatments, chemotherapy, radiation therapy, and supportive care is a judgment decision.

Secondary Hormonal Therapy

Any hormone therapy used following primary androgen ablation or combined androgen blockade can be considered a secondary hormonal therapy. These secondary hormonal treatments can be used alone or in combination with other systemic therapies. These need to be recognized individually as active therapies and considered in reporting response data. The following sections list some secondary hormone treatments that have demonstrated significant responses.

Antiandrogen Withdrawal Syndrome

Patients with progressive prostate tumors while on antiandrogens or other steroidal hormonal therapies can have PSA and tumor regression after the withdrawal of these agents. It has been postulated that the androgen receptor allows the antagonist antiandrogens to act as an agonist through a mutation in the steroid-binding domain. This is best described for the withdrawal of flutamide with reported PSA response rates of 14% to 80%. Patients with longer use of flutamide appear to have a greater response proportion to withdrawal. Most of these responses last several months but can last longer. Antiandrogens with longer half-lives appear to need a longer trial of withdrawal to see a response. The withdrawal of an antiandrogen is so benign and has such a large potential benefit that it is standard practice to do this prior to instituting a new therapy. Antiandrogen withdrawal must be considered as an active therapeutic intervention when writing clinical trials and when interpreting results of trials that did not control for this effect.

Glucocorticoids

Glucocorticoids have modest response rates in patients who have failed androgen deprivation. They are used in conjunction with agents that cause a medical adrenalectomy and with a number of chemotherapy agents. Glucocorticoids may have direct antitumor effects and effects on bone metabolism, as well as contributing to the suppression of adrenal androgens.

Antiandrogens

Antiandrogens have been examined for their ability to cause antitumor effects following failure of primary androgen deprivation. PSA responses are seen in a significant proportion of patients - 29% in one study and 64% in another study. Despite these response rates, deferred flutamide treatment was not shown to enhance survival. Higher doses of bicalutamide have been examined in patients progressing after primary androgen deprivation, after combined androgen blockade, or after other secondary hormonal therapies have failed. At 150 and 200 mg per day, some responses were seen, but these were small in number.

Adrenal Enzyme Inhibitors

Several recent trials using PSA as an endpoint have demonstrated the efficacy of ketoconazole and hydrocortisone as a secondary hormone therapy. This therapy was advanced by carefully controlling for H2-blockers and using PSA endpoints. Ketoconazole is absorbed in an acid environment, and patients must avoid H2 blockers. In a recent larger series of 48 patients, ketoconazole and hydrocortisone after antiandrogen withdrawal has demonstrated a PSA response rate of 63% (>50% decline). Response duration on average was 3.5 months. A number of potential side effects of this combination necessitate that the treating physician be familiar with the side effects and their management. Hydrocortisone is administered with ketoconazole to prevent Addissonian crisis. Patients may experience increased liver enzymes, peripheral edema, hypertension, congestive heart failure, hyperglycemia, rash, or nausea. Patients must avoid drugs that have dangerous interactions with ketoconazole, which inhibits their metabolism. These drugs include cisapride, astemizole, terfenidine, phenytoin, cyclosporine, and coumadin. Ketoconazole (Nizoral, Janssen Pharmaceuticals Inc, Titusville, NJ) at 1200 mg per day is expensive, typically costing over $500 per month. This should become less expensive when Nizoral goes off patent in June 1999. Due to disappointing efficacy and toxicity, a second imidazole compound, liarozole, is no longer being developed for advanced prostate cancer.

Aminoglutethimide is thought to work by similar mechanisms as ketoconazole. Several series have demonstrated similar efficacy to ketoconazole. In the PSA era, flutamide withdrawal combined with aminoglutethimide and hydrocortisone demonstrated a 48% PSA response rate (>80% decline) among 29 patients.
These medical adrenalectomies provide a good point for the medical oncologist to work jointly with the urologist. The relative low toxicity, high response rate and, in some cases, prolonged response durations have made this therapy an acceptable standard of care in patients who have failed androgen deprivation and undergone antiandrogen withdrawal.

Chemotherapy

Patients with disease progression after primary androgen deprivation may or may not have had trials of secondary hormonal therapy. They may retain some hormone sensitivity to secondary hormones. A number of trials and standard chemotherapy treatments for hormone-refractory disease include glucocorticoids. This, in addition to antiandrogen withdrawal, would be considered an adequate trial of secondary hormone therapy prior to initiating chemotherapy.

Numerous reviews have been written about chemotherapy for hormone-refractory prostate cancer in the pre-PSA era with significant pessimism. In the PSA era, this has been replaced by cautious optimism. This discussion is limited to a few large trials and concepts regarding chemotherapy in the pre- and post-PSA era.

Chemotherapy continues to be used and developed in hormone-refractory prostate cancer. Chemotherapy is often reserved for patients with D2 disease or in symptomatic patients where palliation is required. Responses to chemotherapy have traditionally been difficult to demonstrate. Most patients with D2 disease demonstrate only bone lesions. Even in responding patients, bone lesions are slow to show responses compared with other measures of response. Computed tomography scanning is useful only in the minority of patients with soft-tissue lesions. The benefit from chemotherapy has recently been advanced with some non-traditional outcome studies using pain and quality-of-life measures. PSA has the potential to be an excellent tumor marker to monitor chemotherapy response. Cytotoxic agents give PSA responses that correspond fairly well with traditional measures of response. Theoretically, PSA production may be affected by drugs to give a false response.

Single-agent chemotherapy was found to be superior to "standard" (radiation, secondary hormones) therapy for hormone-refractory prostate cancer by demonstrating a higher partial response rate and fewer cases of progression in National Prostate Cancer Project (NPCP) trials. In addition, in the NPCP series of trials, patients categorized with "stable disease" after receiving chemotherapy were judged as responders along with those who demonstrated partial responses. The significance of this "stable disease" category has been a source of controversy, and its importance has been debated. The population of patients classified as responders by NPCP criteria, including the "stable disease" category, demonstrated a survival time that was more than double that of nonresponders. There was no difference in survival between patients classified as having "stable disease" compared to those with partial responses. This leads to an important question whether the patients classified as "stable disease" in response to chemotherapy in the NPCP trials could have been shown to be responders by PSA measurements.

The partial response rate for patients who received 1000 mg/m² of cyclophosphamide intravenously every three weeks in NPCP trials 100, 300, and 700 was 6%, with an additional 31% of patients being classified in the "stable disease" category. These trials suggest an overall benefit of 30% to 40% with cyclophosphamide.

Similarly, single-agent doxorubicin was shown to be an active agent in the pre-PSA era. A related chemotherapeutic compound, mitoxantrone, has been studied in symptomatic D2 disease. While it is not clear that mitoxantrone is more active in prostate cancer, it likely is better tolerated in this population of men of advanced age. Mitoxantrone in combination with glucocorticoid has been shown to be superior in quality-of-life improvement and palliation of pain compared with glucocorticoid alone. A number of phase II trials of combination chemotherapy in the PSA era have shown relatively high response rates. These are often associated with relatively high toxicity. To date, no trial has demonstrated that combination chemotherapy has a survival benefit over single-agent chemotherapy.

Suramin is an antiparasitic agent that is being studied for its effect in advanced prostate cancer. A recent preliminary report of a phase III multicenter trial has shown suramin and hydrocortisone to be superior to hydrocortisone alone with respect to pain response, duration of pain response, PSA response, and disease progression. While the results of this study are modestly positive and encouraging, it is likely that suramin will undergo additional development.

Supportive Care

Many complications of advanced prostate cancer require multidisciplinary care. The urologist, medical oncologist, radiation oncologist, and support staff can dramatically affect the quality of life of individuals with metastatic disease. Careful attention to pain management by all involved care providers is crucial. Early attention to complications such as deep venous thrombosis, disseminated intravascular coagulation, infection, spinal cord compression, anemia, and ureteral obstruction can all improve a patient’s condition. Radiopharmaceuticals and external-beam therapy may be important resources in the management of bone pain, but they need to be utilized in a manner that does not prevent other systemic therapy.

Conclusions

In advanced prostate cancer, much enthusiasm has been generated on both sides by the questions of whether early or delayed androgen deprivation is superior and whether primary androgen deprivation or combined androgen deprivation is superior. The available evidence suggests a modest superiority for early androgen deprivation and combined androgen blockade. The more important issue is to ensure that patients are educated regarding the treatments and side effects and then make a choice based on their own wishes.

After failing androgen deprivation, palliation and quality of life take the highest priority. The use of secondary hormonal therapy, chemotherapy, and supportive measures can dramatically enhance a patient’s life. It is in every patient’s and physician’s interest to participate in clinical trials so that future patients may benefit from the accumulated knowledge.

References


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