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THERAPY FOR ADVANCED AND HORMONE REFRACTORY CANCER OF THE PROSTATE

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ABSTRACT

Cancers of the prostate are categorized as follows: 1)- hormone-naive (never having previously received hormone manipulation); 2)- androgen-dependent (having received hormonal manipulation but a less than continuous application, i.e., intermittent androgen blockade or with an agent that does not produce a castrate testosterone level, i.e., antiandrogen); 3)- androgen independent (progressive disease when serum testosterone levels are in the castrate range) but still potentially responsive to other hormone therapy, i.e., second line hormone therapy; 4)- hormone-independent or hormone refractory (progressive disease when castrate serum testosterone levels have been documented and one or more further hormonal manipulations have failed).

Here in, we present an extensive review of current modalities of therapy for advanced and hormone refractory cancer of the prostate. This revision includes a discussion of how hormone therapy should be delivered, when hormone therapy should be delivered, and appropriate monitoring for response in androgen-independent disease.

The chemotherapy and other strategies for hormone refractory prostatic cancer are discussed and we present the guidelines of the National Comprehensive Cancer Network for standard chemotherapy options. A discussion on the state of the art palliative radiotherapy as an alternative or adjunct to chemotherapy is presented. Finally, we present the new areas of research in advanced prostatic cancer, including vaccines, antibodies, gene therapy, anti-angiogenesis therapy, antisense therapy and blocking signal transduction

Key words: prostate, prostate cancer, advanced, therapy, hormone refractory
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INTRODUCTION

The definition of advanced prostate cancer is in evolution. Classically, patients with advanced prostatic cancer are those with node (N1, M1a) or visceral (M1c) or bone metastases (M1b). However, clinical stage T3 and T4 disease at diagnosis and pathologic T3 (extra-capsular extension, seminal vesical extension) after radical prostatectomy could reasonably be included in the category of advanced prostate cancer. An argument could also be made for including patients with a pretreatment PSA > 20 ng/ml and / or a high Gleason sum (> 8), as they have a diminished probability of organ-confined prostate cancer and are at higher risk for eventual disease recurrence. PSA monitoring after therapy has further modified the definition of advanced disease to include patients with a rising PSA after androgen deprivation even among those patients where there is absence of clinical or radiological disease.

When discussing advanced carcinoma of the prostate and potential treatment options, it is important to categorize disease status accurately. An outline developed by Scher (1) is very useful in segregating the heterogeneous advanced prostate cancer population into subgroups that have clinical relevance with regard to treatment choice and treatment response. Cancers of the prostate are categorized as follows: 1)- hormone-naive (never having previously received hormone manipulation); 2)-

androgen-dependent (having received hormonal manipulation but a less than continuous application, i.e., intermittent androgen blockade or with an agent that does not produce a castrate testosterone level, i.e., antiandrogen); 3)- androgen independent (progressive disease when serum testosterone levels are in the castrate range) but still potentially responsive to other hormone therapy, i.e., second line hormone therapy (2); 4)- hormone-independent or hormone refractory (progressive disease when castrate serum testosterone levels have been documented and one or more further hormonal manipulations have failed). A rather intriguing and newly recognized circumstance documents that the initial hormonal regimen will, at times, determine the response to subsequent hormonal manipulations (3). As an example, patients who had failed combined androgen blockade with an LH-RH analogue and Flutamide responded more frequently to a trial of the antiandrogen Casodex (150 mg) than did a group of patients who had progressed after androgen deprivation with an LH-RH analogue alone.

HOW SHOULD HORMONE THERAPY BE DELIVERED?

In 1999, hormone naive patients with N+/M+ disease are usually treated by androgen deprivation by either combined androgen blockade or monotherapy to achieve castrate "T" levels. Two large clinical trials one from the EORTC (#30583) and one from the NCI (#036) reported a statistically significant survival benefit for combination therapy when compared to monotherapy (4,5). The rationale for blocking adrenal androgens is the potential for conversion of the large amounts of adrenal DHEA to DHT (6). A very important subsequent NCI trial (#0105) of more than 1,300 patients demonstrated that there was no statistically significant advantage in survival or time to progression between orchiectomy combined with the antiandrogen Flutamide versus orchiectomy + placebo (7).

The NCI INT-0105 trial was initiated in December 1989 (7). Accrual was completed in September 1994. It was a prospective study of the relative benefits of combined androgen blockade and monotherapy based on extent of disease for patients randomized to orchiectomy plus placebo or orchiectomy plus Flutamide. With 1,378 patients accrued, this trial represents the largest to date to study the benefits of combined androgen blockade. This trial was constructed to answer objections raised by the NCI INT-0036 trial. They were that daily subcutaneous injections of leuprolide might have driven a subclinical period of disease progression "flare", and that flutamide in the combination arm only served to block flare.

Based on the results of the NCI INT-0036 trial, the NCI INT-0105 trial was constructed to have a 90% power at a 0.05 level of significance (one sided) to detect a 25% improvement in survival from a median of 28.3 months (death hazard ratio of 1.25). Information regarding treatment benefits for the subgroup of patients with minimal disease was considered of vital importance as this subgroup of patients currently represents the majority of men with M1 disease as a result of the early complete radiologic evaluation triggered by a rising PSA profile.

For most physicians caring for patients with metastatic prostate cancer who based their treatment recommendations to employ complete androgen blockade on the results of NCI trial 0036 published in the New England Journal of Medicine in 1989 which showed a survival advantage to combined androgen blockade, the final publication of NCI 0105 trial 10 years later was quite startling, disturbing and confusing for urologist and patient alike. By the parameters used to construct the trial there was no statistical advantage to orchiectomy plus flutamide versus orchiectomy alone. While the trial did show an approximately 10% survival difference in favor of the combination, this did not reach statistical significance because the trial had been powered to demonstrate a 25% difference in survival between the two arms, a difference comparable to the 0036 trial published 10 years previously. However a difference as large as 20% between the two groups could be missed. NCI 0105 had been constructed to randomize patients by performance status and extent of disease to either monotherapy or combined therapy, to test the validity of the hypothesis that patients with minimal disease would derive the greatest advan-

tage from combined androgen blockade as had been noted in trial 0036. However, in NCI 0105 there was no statistically significant advantage to the combination for the good performance and minimal disease subgroups. Again this outcome illustrated the danger of extrapolating post trial sub analysis, no matter how logical or attractive, to standard practice without confirmation as a primary question in a subsequent randomized trial.

An interesting caveat to consider is the possible consequence of cross over to flutamide at the time of failure among patients taking placebo which was permitted by trial design. Could this have favorably modified the control arm survival outcome so as to reduce the difference between the 2 arms? The NCI 0105 trial analysis also provided critically important information about the biomarker prostate specific antigen. This was the first large trial to systematically include PSA as a marker of tumor status and response and to correlate its profile with survival endpoints. There was a statistically higher incidence of normalization to a PSA < 4.0 ($p = 0.018$) in the combination arm. This intuitively might lead to the prediction that a better clinical and survival outcome was assured. If PSA response were truly a surrogate for survival, then this statistically significant reduction in PSA in the combination arm would predict a survival benefit for this arm. This was not the case and therefore in the context of a large perspective randomized trial, which is the only mechanism for assigning surrogate endpoints, this discordance between PSA response and survival rendered PSA invalid as a surrogate endpoint. In fact the discussion of results contained the statement “PSA has no role as surrogate marker for survival in patients with metastatic prostate cancer”.

The NCI 0105 trial was also unique in the fact that it measured quality of life parameters and therefore was able to assess the incremental morbidity, if any, of combination therapy as compared to monotherapy. A separate publication analyzing quality of life issues has been reported (8). A sobering conclusion was reached. Patients on the combination arms suffered a statistically higher incidence of gastrointestinal effects, anemia, and abnormality of liver function tests. In this setting the patients receiving combination of orchiectomy and flutamide not only failed to achieve a response benefit, but also paid a price both economically, the additional cost of the antiandrogen, and qualitatively with depreciation in quality of life. The attention to quality of life in this clinical trial is especially important because hormonal treatment of metastatic disease can be considered largely palliative rather than curative. Since relief of symptoms may be brought about at the expense of some treatment related toxicity it is important that overall quality of life is maintained, namely the treatment will not worsen the patient’s current status. As was done in this trial, quality of life measurement should be gathered through patient reported instruments.

Metaanalysis is a methodology to investigate the overall conclusions that can be drawn from a number of trials addressing the same questions with disparate outcomes and/or a methodology to combine the results of a number of small trials to gain statistical power for determining differences that these small trials, individually, are unable to detect. There are several metaanalyses dealing with combined androgen blockade that warrant discussion. The largest was conducted by the Prostate Cancer Trialists collaborative group (9,10). Twenty-two of the 25 possible trials that could be included were subject to metaanalysis and the results were published in 1995. The NCI 0105 trial data was not included as it was in the process of accrual. Individual data for 5,710 patients, 87% of whom had metastatic disease were obtained. At the time of the study 52.7% of patients had expired. No statistical benefit to combined androgen blockade was recorded. The overall mortality among patients randomized to castration alone was 58.4% compared with 56.3% among those randomized to combined androgen blockade. When patients were grouped by type of castration or type of antiandrogen therapy, no significant difference between subgroups was detected. A separate analysis of patients with M0 and M1 disease did not alter the results.

The five-year survival estimates were 22.8% for castration alone versus 26.2% for combined androgen blockade. This absolute difference of 3.5% was not statistically significant. Although a large

improvement in survival among patients with advanced disease had been excluded by this study, the existence of a more moderate benefit was not. The Prostate Cancer Trialists Collaborative Group plans to update results with inclusion of new studies and extended follow-up of existing studies.

While the first cycle of the analysis in 1995 found that combined androgen blockade gave no survival advantage with the caveat of larger confidence limits which did not exclude the possibility of a small improvement the latest results effectively eliminate significant benefit from combined androgen blockade.

The Ontario Cancer Treatment Practice Guidelines Initiative suggested that the Prostate Cancer Collaborative Group metaanalysis had a series of methodological weaknesses (11,12) in data collection and statistical decisions. The Canadian group conducted a metaanalysis based only on published data (20 studies) and showed a clear benefit in 2-year survival with combined androgen blockade over castration alone.

Yet another metaanalysis evaluated the current outcome of nine clinical trials, which had in common the use of flutamide as the antiandrogen. This study also included the NCI 0105 trial. The analysis of 4,128 patients demonstrated a 10% difference between monotherapy and combined therapy and this effect size was statistically significant (13). It is of interest that the NCI 0105 trial indeed had found a 10% survival benefit with flutamide; however the NCI 1015 trial had been sized to detect a larger difference, 25%, parallel to the difference of the first NCI study. However with more subjects and more events the same difference was statistically significant in the combined androgen blockade with flutamide metaanalysis!

A recently updated European metaanalysis of trials using combined androgen blockade by orchiectomy ± showed that nilutamide added to orchidectomy significantly reduced the odds for disease progression by 17% and death from any cause by 16% compared with orchidectomy alone (14,15). Lastly, an Agency for Health Care Policy and Research report was completed in 1999 (16). It concluded that there is no statistically significant difference in survival at 2 years between patients treated with combined androgen blockade or monotherapy. However metaanalysis of the limited data available shows a statistically significant difference in survival at 5 years in favor of combined androgen blockade. The magnitude of this difference is of uncertain clinical significance.

An important question is, therefore, raised; namely, the choice between surgical castration as monotherapy or combination therapy by medical castration and an antiandrogen. Androgen deprivation will variably decrease the quality of life of the asymptomatic patients, e.g., hot flashes, lethargy, loss of vigor and interest and libido, weight redistribution. In some circumstances, these quality of life issues will lead to cessation of androgen deprivation or intermittent androgen deprivation as an alternative protocol. Using initial medical castration, which is reversible, permits this option. In addition to the unpleasant short-term side effects of androgen deprivation long-term morbidity, including osteoporotic fracture have been reported. The option for an intermittent androgen deprivation regimen and rather than surgical castration is a viable option. When employing medical castration to this purpose the results of the NCI 036 trial and the EORTC 30583 trial support the addition of an antiandrogen.

Intermittent androgen therapy has garnered interest recently based on the work of Bruchovsky et al. (17). They have demonstrated that quality of life is improved by cycling androgen deprivation and avoiding the continuous morbidity/side effects of the regimen. The effect of this strategy on overall survival outcome is unknown; however this question is being addressed by a Phase III prospective randomized trial by the Southwest Oncology Group (#9346). The trial randomizes patients who have achieved a normal serum level (< 4.0 ng/ml) of PSA after a seven month induction period of combined androgen blockade to either continuous androgen deprivation or to the withdrawal of androgen deprivation with repetitive recycling based on PSA defined trigger points. Another multigroup clinical trial will test continuous or intermittent androgen deprivation for patients with a rising PSA after external beam radiotherapy.

WHEN SHOULD HORMONE THERAPY BE DELIVERED?

The question of appropriate timing of hormonal therapy has witnessed pendulum swings since the sentinel work of Huggins & Hodges (18). Initially, based on comparison with historical series, before the recognition of the pitfalls of using historical controls, early hormone therapy was recommended. The VACURG trials changed this practice and the pendulum swing to the opposite direction; namely, deferring therapy until symptomatic progression. It is important to recognize that these trials, while randomized, were not designed to answer the specific question of timing of androgen deprivation and were influenced by the significant cardiovascular effects of the hormone therapy employed, DES 5 mg/day. Nevertheless, they directed opinion towards deferring therapy. It should be noted that Byar, the VACURG statistician, in his 1973 review stated that "these data support the concept that treatment can be delayed" (19). He did not state that the data irrefutably concluded that therapy should be delayed. A later review of the VACURG trials by Byar did raise the possibility that early hormone therapy could be beneficial (20). The current delivery of androgen deprivation therapy with pharmaceutical agents much less toxic than DES and which avoid the psychological impact of surgical castration has once again raised the issue of appropriate timing. To delay therapy assumes that the results of therapy can be initiated at a later date without any detrimental loss. The medical research council of Great Britain investigated this issue and the results are noteworthy. A large randomized trial accrued 938 patients (21). The pertinent findings were as follows: a)- progression from M0 to M1 disease was significantly delayed among patients who received initial treatment; b)- among patients with M1 disease, bone pain was delayed if initial treatment was given; c)- local progression was more rapid in the deferred than in the initially treated group and transurethral resection of the prostate was more frequently necessary in the deferred group; d)- a statistically significant increase in extraskeletal metastasis and ureteral obstruction was noted in the deferred group. These results are consistent with the anticipated ability of androgen deprivation to delay disease progression. Of major importance was the increased incidence of spinal cord compression among the patients whose therapy was deferred. Of specific interest was that 19 of the 23 patients who were randomized to deferred treatment developed spinal cord compression after hormonal therapy had been started for another indication. In other words, the event of spinal cord compression was not a result of failure to follow or recognize its presence, but a failure of delayed therapy to effectively prevent it. This finding challenges the premise that has been used to justify delayed androgen deprivation; namely, that delayed therapy in the long-term would produce results similar to initially administered therapy. Also, of major importance was the finding that both cause-specific and overall survival of those patients treated initially was superior to those receiving deferred therapy. The benefit was specifically important for those patients with M0 disease. Critiques of the study read as follows: a)- PSA monitoring was not employed and for those patients who wish to avoid initial therapy with androgen deprivation and the pace of disease activity could be assessed by a period of PSA monitoring to determine the need or wisdom of therapy, b)- a protocol of intermittent androgen deprivation could have been employed, c)- quality of life instruments were not measured, d)- approximately 10% of patients who died from prostate cancer did so before receiving hormone therapy. Rebuttal statements include the nonavailability of PSA at trial initiation and the fact that patients with initial androgen deprivation suffered fewer complications of spinal cord compression, pathologic fractures, and obstructive events intuitively translates to improved quality of life. Without the defined monitoring provided by a clinical trial protocol, the patients in routine practice who fail to receive necessary androgen deprivation are unknown. In fact this unfortunate circumstance might be best addressed by the earlier administration of androgen deprivation therapy.

MONITORING FOR RESPONSE IN ANDROGEN-INDEPENDENT DISEASE

In order to evaluate treatments for androgen-independent disease it is necessary to identify response by selection of measurable endpoints. The

well-recognized difficulty in assessing such a response with prostate cancer is the infrequency of measurable metastatic disease (and when such measurable soft tissue disease is present, the applicability of its response to a more common osseous disease is questionable). PSA remains the most consistently used benchmark for establishing a response to therapy. Observation of PSA declines clarified the Flutamide withdrawal syndrome and later the responses to withdrawal of other antiandrogens. The antiandrogen withdrawal (AAW) effect first described in 1993 is now an well-accepted phenomena (22) and AAW represents the first therapeutic option for any patient failing combined androgen blockade. These observations also reawakened the possibility that subsequent second and third line hormonal maneuvers could be successful. Therefore the following pathways are reasonable considerations: a)- if CAB has been the initial therapy then withdraw the antiandrogen, b)- if monotherapy has been the initial therapy then add an antiandrogen, c) if failure occurs while receiving one antiandrogen change to another antiandrogen. Antiandrogen withdrawal has already been discussed. Fowler has reported (23) the benefit of adding flutamide to patients failing monotherapy. Armed with this information, exploratory trials by Liebertz (24) and later Joyce (25) reported that patients who failed combined androgen blockade, had a response to Flutamide withdrawal and, subsequently, failed once again demonstrated another response to Casodex. It is clear that antiandrogens are not identical in their mechanism of action, although they belong to the same antiandrogen drug class, namely, nonsteroidal antiandrogens. Also, it seemed logical that with AAW, a certain number of androgen receptors might be again exposed to unblocked adrenal androgens and that the response to AAW could be enhanced by adding an agent to block adrenal androgens. Thus the addition of aminoglutethimide or Ketoconazole to antiandrogen withdrawal has demonstrated an increase in the overall PSA response to 50 to 60% compared to the 20 to 30% response with AAW alone (26). Ketoconazole, low dose prednisone and DES 1.0 mg daily are effective in reducing PSA and alleviating symptoms in some patients and are worthwhile second line hormonal therapies to apply in selected circumstances. A number of patients are taking PC SPES (P.C. = prostate cancer; spes = hope) either as primary or second line therapy. A recent publication analyzed the components of PC SPES and found it to contain a number of estrogenic compounds (27). Both its therapeutic effect (decrease in PSA levels) and its adverse effects (DVT, CHF, gynecomastia/dynia) are consistent with this finding.

The interest in second line hormonal therapy was obvious at the 1999 American Society of Clinical Oncology meeting where several abstracts describing hormone strategies were presented (28,29).

A great deal of activity has centered around the development of strategies for disease which no longer responds to hormonal manipulation and is classified as hormone refractory. Chemotherapeutic agents are being reinvestigated. Interest also has developed in cytostatic agents rather than cytotoxic therapy. These new strategies avoid cell destruction in favor of cell manipulation and redirection. Assuming that a cancer is a normal cell with a number of aberrant characteristics, pharmacological agents that can force the aberrant cell towards a more disciplined cell cycle are quite attractive. Recently significant insight into the biologic activity of single agent and combination cytotoxic therapy based on monitoring PSA have appeared.

CHEMOTHERAPY AND OTHER STRATEGIES

At University of Michigan we believe that a decrease of pretreatment PSA by 50% is a useful predictor for survival and disease response for most drugs, however, a Phase III trial to accurately answer this question is needed. We looked at the relationship between PSA response with soft tissue disease response in 115 androgen independent prostate cancer patients who had chemotherapy with oral estramustine and oral etoposide as part of a phase II trial and demonstrated a strong correlation between PSA response and shrinkage of measurable tumors as well as increased survival for patients who decreased their PSA by greater than 50% from their baseline value (30).

PSA response has also been researched as a possible marker of prognosis and survival, i.e., a prognostic factor. Researchers at Memorial Sloan

Kettering analyzed the PSA response in 110 patients at that institution (31). They found a longer average survival for patients who experienced at least a 50% decline in PSA. In fact, this greater than a 50% decrease in PSA was one of the most significant variables that could actually predict how long a patient could survive with androgen independent prostate cancer. Another study from the National Cancer Institute analyzed the PSA response in 50 androgen independent prostate cancer patients (32). They found that 15 patients experienced a greater than 75% decrease in PSA. The average survival for this group was about 21 months. This value was significantly different ($p = 0.003$) from the non-responders whose average survival was about 6.9 months. A clinical trial of suramin in androgen independent prostate cancer showed a 1-year survival rate of 80% in patients with a greater than 75% decrease in PSA versus 20% for those without this response. In a trial of estramustine phosphate and vinblastine, patients who experienced a PSA decrease of greater than 50% on three successive measurements at least two weeks apart were found to have a significantly prolonged overall and progression free survival (33). However, it is important to mention that not all studies have found the same association. In two phase I studies of suramin, a PSA decrease did not predict for increased survival (34).

It is important to note two other special points or misconceptions about PSA in the hormone refractory setting. First, each person's hormone refractory tumor makes a different amount of PSA. In early disease we can use a PSA of 4 ng/ml as an upper limit of normal to screen for cancer. This is not true in the androgen independent setting. Patients in the androgen independent setting may have a small amount of cancer and a high PSA or a large amount of cancer and a low PSA. This is also mirrored clinically, i.e., we have patients in our clinic with a PSA of < 10 who have many bone metastases and need narcotics to control their pain. We have other patients with PSAs of > 1000 who have no pain. Therefore, there is no absolute PSA level, which correlates with symptoms.

Several researchers have looked for other prognostic factors in an attempt to explain differences in survival. Factors associated with decreased survival have included: increasing age, presence of bone pain, decreasing performance status, increased levels of blood LDH and SGOT, decreased levels of blood albumin, and low hemoglobin. Currently, however, there is no exact pretreatment prognostic factor, which can be used to accurately predict survival or patient response to treatment. Though the treatment of hormone refractory prostate cancer has improved dramatically, there is still no therapy that has been demonstrated to improve survival. The first choice of treatment for patients with hormone refractory prostate cancer, therefore, is still a clinical trial.

CONTINUED ANDROGEN SUPPRESSION

A controversial area in the treatment of androgen independent prostate cancer has been the role of continued androgen ablation. A retrospective review of patients enrolled in chemotherapy trials for androgen independent disease concluded that continued androgen ablation was not a significant factor in patient survival (35). However, another review showed a modest survival advantage for patients with continued testicular androgen ablation. Also, many patients feel more secure staying on hormone therapy. It is reasonable in the evaluation of new therapies for hormone refractory prostate cancer that patients maintain androgen ablation including LH-RH agonists.

NCCN GUIDELINES (NATIONAL COMPREHENSIVE CANCER NETWORK) FOR STANDARD CHEMOTHERAPY OPTIONS

The NCCN, an organization of cancer centers from around the country committed to promoting the best interests of cancer patients, recently updated their practice guidelines for the treatment of androgen independent prostate cancer. The guidelines published by this organization are rapidly evolving to be the standards of care for cancer treatment. The guidelines for the relief or palliation of androgen independent prostate cancer, outside of experimental protocols, list three different areas of care: a)- Supportive care usually with prednisone and other drugs, b)- Local and/or systemic radiation, c)- Palliative chemotherapy (Table).

Table - *National Comprehensive Cancer Network (NCCN) practice guidelines: hormone refractory prostate cancer.*

REGIMEN	SCHEDULE
Supportive Care	
Prednisone	7.5 - 10 mg/d
Dexamethasone	0.75 mg/bid
Chemotherapy	
Ketoconazole	1200 mg/d
Doxorubicin	20 mg/m^2 IV over 24h each week
Vinblastine	4 mg/m^2/week/for 6 weeks
Estramustine	600 mg/m^2/d for 42 days
Etoposide	50 mg/m^2/d for 21 days
Estramustine	10 mg/kg/d for 21 days
Mitoxantrone	12 mg/m^2 IV every 21 days
Prednisone	10 mg/d
Paclitaxel	120 mg/m^2 IV over 96h every 3 weeks
Estramustine	600 mg/ m^2/d continuously
Radiotherapy	
Standard external-beam radiation	
Strontium 89	

Supportive Care and Steroids

Currently, no drug combination has been shown to increase survival for androgen independent prostate cancer in a randomized phase III trial. Therefore, supportive care is a reasonable and logical alternative to active treatment. This should involve: aggressive pain management, aggressive control of symptoms, and hospice care if desired.

Glucocorticoids like prednisone have been used frequently to manage symptoms in advanced prostate cancer patients and many studies have shown improved symptom control and increased quality of life in patients. In one study, 40% of patients given low dose prednisone (7.5 - 10 mg/day) experienced objective improvement in pain control and 20% experienced improvement in overall quality of life. Another study using low dose dexamethasone (0.75 mg twice a day) showed improved symptom control in 63% of patients (36).

Recently, the use of bisphosphonates, drugs which alter bone metabolism, have regained popularity in relieving bone pain for advanced prostate cancer. The use of these drugs will probably increase over the next few years.

Chemotherapy (Sometimes called "Palliative" Chemotherapy)

The NCCN guidelines recommend that two drugs be used in combination. The drugs suggested were chosen based on demonstrated anti-cancer activity and acceptable toxicity and include: ketoconazole and doxorubicin; estramustine and vinblastine; estramustine and etoposide; mitoxantrone and prednisone; estramustine and paclitaxel.

Ketoconazole (Nizoral) and Doxorubicin (Adriamycin)

The combination of doxorubicin and ketoconazole has been evaluated in a phase II trial (37). Thirty-nine patients who had progressed following initial hormone ablation therapy were treated with weekly infusions of doxorubicin (20 mg/M^2 over 24 hours) and daily ketoconazole (1,200 mg daily). Patients received hydrocortisone only at the time of developing clinical adrenal insufficiency; 63% required this intervention at some time during the therapy. A PSA decrease of more than 50% was seen in 21 of 38 (55%) patients. Seven of the 12 patients (58%) with bi-dimensionally measurable disease showed a partial response. Twenty-nine percent of the patients developed significant complications like acral erythema (redness of the hands and feet) and stomatitis (mouth sores). These symptoms resolved when the doxorubicin was stopped. The doxorubicin was started again and the symptom did not return. Also, 2 patients with a history of heart disease died suddenly while on this therapy. One other patient experienced congestive heart failure. Seventeen patients (45%) required hospitalization for complications.

Vinblastine (Velban) and Estramustine (Emcyt)

Vinblastine has shown little response as a single agent in androgen independent prostate cancer. Single agent estramustine phosphate in androgen independent prostate cancer has shown response rates of 0 - 20% and is an approved drug by the Food and Drug Administration for patients with hormone refractory prostate cancer. The combination of vinblastine and estramustine demonstrated enhanced tumor killing in preclinical models. Vinblastine (4 mg/ M^2) given weekly with estramustine phosphate (600 mg/ M^2 or 10 mg/kg) daily for 6 weeks followed by a 2 week rest period has been tested in clinical trials (4). Response rates of 14 - 40% were demonstrated for patients with bi-dimensionally measurable disease. PSA decreases of more than 50% were found in 54 - 61% of patients, and this therapy was well tolerated. One trial showed that patients who experienced a greater than 50% decline in PSA on 3 separate occasions had significantly increased overall and progression free survival (38).

Etoposide (VP - 16, VePesid) / Estramustine (Emcyt)

Both drugs were given orally (estramustine 15/mg/kg/daily in 4 divided doses and etoposide 50 mg/ M^2/daily in 2 divided doses) for 3 weeks with a 1-week rest period. Of the 18 patients with bi-dimensionally measurable disease, 50% had objective responses: 3 complete and 6 partial. A PSA decrease of greater than 50% was demonstrated in 55% of patients. Estramustine caused significant nausea in about 30% of patients and 2 patients had to withdraw from the study because of this problem. A second trial used a lower dose of estramustine (10 mg/ kg/daily). This trial had 62 patients and demonstrated a PSA decrease of greater than 50% in about 40% of the patients and objective partial responses in 8 of 15 (53%) patients with measurable disease. Less nausea, because of the decreased estramustine dose, was noted. Average survival was around 14 months. A third trial using an even lower dose of estramustine (140 mg, 3 times a day) with etoposide (50 mg/M^2/ day) in 56 patients demonstrated similar results, 45% of the 33 patients with bi-dimensionally measurable disease had an objective response: 5 complete and 10 partial responses. A PSA decrease of greater than 50% was seen in almost 60% of patients. Average survival was about 13 months. The combined results of the above 3 trials showed soft tissue responses in about 45 - 55% of patients, PSA decreases of greater than 50% in about 40 - 60%, and average survival of 52 - 56 weeks.

Currently, it is our practice to treat patients with 280-mg estramustine 3 times a day and etoposide 50 mg 2 times a day. Patients are told to take the estramustine with food while avoiding calcium rich products (milk, yogurt, ice cream, calcium containing antacids, and calcium supplements or other supplements and multivitamins with calcium can interfere with absorption of these drugs). This combination produces only mild nausea and is generally well tolerated.

Mitoxantrone (Novantrone) and Prednisone

Mitoxantrone is similar in its structure to doxorubicin. Early studies of mitoxantrone given alone demonstrated modest activity with the drug being well tolerated. A phase II study of 27 patients using mitoxantrone (12 mg/M^2 IV every 21 days) and prednisone (10 mg/day continuously) was started. The primary end points used were quality of life, pain levels, and analgesic or pain medication use. A complete response was the elimination of all disease-related symptoms. A partial response was defined to be a 50% decrease in pain medication (analgesic) use with no increase in pain, a decrease by 2 points in a six point pain scale with no increase in analgesic use. Progression was defined as either: an increase in analgesic use, an increase by one in the 6 point pain scale, or new bone pain requiring palliative radiotherapy. Using the above criteria, 36% of patients experienced a complete response, 44% experienced a partial response, and 20% had stable disease. Overall, there was a modest decrease in analgesic usage. Quality of life analyses showed decreases in pain throughout treatment and social functioning also improved. However, there was no improvement in global quality of life. Serious side effects was limited to neutropenia (a decrease in the number of a type of white blood cell that fights infection); however, no patients required hospitalization.

A larger, randomized Phase III trial using similar endpoints and definitions of response compared the combination of mitoxantrone (12 mg/M^2 every 21 days) and prednisone (10 mg/day continuously) to prednisone alone (39). In this trial of 161 men with androgen independent prostate cancer the primary endpoint was achieved in about 30% of the mitoxantrone/prednisone patients and 12% of the prednisone only patients. The average duration of response for the mitoxantrone/prednisone group was 43 weeks, which was significantly longer than the prednisone alone group (18 weeks). Patients who demonstrated a response had significant improvement in quality of life scales measuring global overall well being. This study and a similar Phase III study led to the approval of the combination of mitoxantrone/prednisone as a treatment for hormone refractory prostate cancer by the Food and Drug Administration.

Paclitaxel (Taxol) and Estramustine (Emcyt)

These 2 drugs have been shown to inhibit the way cancer cells divide. A phase II trial of paclitaxel alone in 24 patients with androgen independent disease demonstrated only one objective response. It is important to note that the combination of paclitaxel and estramustine phosphate has demonstrated tumor killing in both animal and human prostate cancer cell lines. One study looked at this combination in a trial using estramustine phosphate (600 mg/M^2/day continuously) and paclitaxel (120 mg/M^2 by 96 hr infusion every 21 days) in 34 patients. Four of nine (44%) of patients with measurable disease (2 of 3 patients or 66% had liver metastasis and 2 of 6 patients or 33% had lymph node disease) showed an objective response. A PSA decrease of more than 50% was achieved in 17 of 32 (53%) of patients. An average response time was about 37 weeks with an average survival time of about 69 weeks. The combination of paclitaxel and estramustine is now being tested in several other combinations. For example, Phase II trials where the paclitaxel is given every 3 weeks or even weekly have demonstrated early and promising results. These dosage schedules should make it to the clinic very rapidly.

PALLIATIVE RADIOTHERAPY AS AN ALTERNATIVE OR ADJUNCT TO CHEMOTHERAPY

Spot Radiation and Systemic Radiation with Strontium-89 (Metastron)

The majority of patients with hormone refractory disease do not have soft tissue disease. Rather, they develop metastasis to the bones. Autopsy studies done on patients with advanced prostate cancer have shown that the frequency of bone metastasis is between 65 - 100%. Skeletal metastasis can decrease a patient's quality of life in many ways.

External beam radiation therapy has been shown to be effective in controlling symptoms in a specific area. Strontium-89 (Metastron) follows the same path as calcium and so finds it's way to the bones where there is increased bone mineral production. This feature helps to minimize bone marrow suppression. In patients with advanced prostate cancer, partial relief of symptoms was demonstrated in 53 - 80% of patients. Complete pain relief was experienced in 10 - 22% of patients. In fact, the largest study of patients treated with strontium-89 showed not only symptom relief, but also decreased use of pain medication (analgesics), increased mobility and an improved quality of life (40). A randomized trial of palliative local radiotherapy with or without adjuvant strontium-89 showed a long-term benefit for combined therapy with strontium-89. Local symptom control was not improved; however, patients treated with strontium-89 had a significantly lower rate of developing new painful bone lesions (41% versus 66%) and those who developed new lesions had fewer of them. One potential side effect of strontium therapy is that it can lower the platelet count and, therefore, subsequent chemotherapy can be more toxic. Therefore we generally give strontium after our chemotherapy options have failed.

NEW CHEMOTHERAPY COMBINATIONS, CLINICAL TRIALS, AND AREAS OF RESEARCH OVER THE NEXT FIVE YEARS (41)

Estramustine (Emcyt) / Docetaxel (Taxotere)

Docetaxel is a similar drug to paclitaxel and the combination of estramustine and docetaxel has

been demonstrated to be very effective in preclinical models. In a recent study 33 patients were treated with estramustine 280 mg orally 3 times per day for 5 days and then with docetaxel, 60 - 80 mg/m^2 on day 2 every 21 days intravenously. Sixty three percent of the patients demonstrated a drop in their pretreatment PSA of > 50%. Five of 18 patients with soft tissue disease demonstrated a response to therapy. In another study of 12 patients treated with estramustine 280 mg orally 3 times per day for 5 days and 70 mg/M^2 on day 2 every 3 weeks, 92% of the patients demonstrated a response by PSA and 3 of 4 patients (75%) with soft tissue disease demonstrated a response. In a third study of 17 patients, 14 patients demonstrated a PSA response (82%). In all of these trials, toxicity was not extensive. The combination of estramustine and docetaxel will be studied in a Phase III trial comparing this regimen to the combination of prednisone and mitoxantrone.

Estramustine (Emcyt) / Etoposide (VP-16, Vepesid) / Paclitaxel (Taxol)

Since the combinations of estramustine and etoposide and estramustine and paclitaxel were so effective, there was good rationale to combine all three of these drugs into one regimen. In a phase II trial combining estramustine 280 mg orally 3 times per day for 14 days every 21 days and etoposide 50 mg/M^2 for 14 days every 21 days with paclitaxel (135 mg/M^2 over 3 hours on day 2), showed an improved response rate compared to the dual drug combinations: estramustine and etoposide alone. Of 40 patients, approximately 70% had a PSA decrease of greater than 50% and in the patients with measurable disease, 66% had a partial response. Toxicities included hair loss and decreased blood counts.

Cyclophosphamide (Cytoxan), Diethylstilbestrol (DES), and Prednisone

The combination of oral cyclophosphamide, diethylstilbestrol (DES), and prednisone was tested in 54 patients with hormone refractory disease at the University of Michigan. All of the patients had previously failed combined androgen ablation and had evidence of rising PSA following antiandrogen withdrawal. A decrease in pretreatment PSA by more than 50% was seen in almost 40% of patients; the average length of the response was 6 months. Two of 6 patients (33%) with measurable disease showed a partial response. This triple combination was well tolerated by patients. This combination appears to be an active and well tolerated combination against androgen independent prostate cancer.

Adriamycin (Doxorubicin) / Ketoconazole (Nizoral) alternating with Vinblastine (Velban) / Estramustine (Emcyt)

This regimen has been tested extensively at the M.D. Anderson Cancer Center and forms the backbone of many of their current clinical trials. The regimen is a bit difficult to follow because the treatment cycle is 56 days. This regimen was demonstrated to have a PSA response rate of 67% and a soft tissue response rate of 75%. Side effects were manageable, with 50% of the patients experiencing swelling in the legs and 18% DVT.

Suramin

Suramin was the first in a new class of drugs that inhibit growth factors (also called growth factor antagonists). It has been shown to inhibit the interaction between growth factors and their receptors to inhibit enzymes that help DNA to grow and replicate, inhibit angiogenesis, and inhibit growth in some prostate cancer cell lines. At least 6 clinical trials have already been published. These trials have demonstrated a response rate ranging between 10 – 50%. Recently suramin was rejected by the Food and Drug Administration as an agent for treatment for hormone refractory disease. The status of suramin for use in hormone refractory prostate cancer patients is unclear.

NEW AREAS OF RESEARCH

Vaccines, Antibodies and Gene Therapy

Lymphocytes fight infection from viruses and destroy cancer cells. They do this in 2 major ways. The first is through the T cells, which destroy cancer cells directly. A second is through the B cells, which, when they come across a foreign cell, produce antibodies. These antibodies attach to the cancer cell and activate another set of cells, the macrophages destroy

it. Since our B cells do not seem to recognize cancer very well, several researchers are trying to find prostate cancer specific antigens or proteins that are found on the surface of prostate cancer cells only. Gene therapy may enhance T and B cell activity.

Antibodies

Antibody trials will become more available over the next few years. Almost all of the current trials are by attaching a radioactive isotope to the antibody the prostate cancer cell and nearby cancer cells. Early phase trials usually test the antibody alone and later trials test the antibody with radioactivity.

Anti-Angiogenesis Therapy

All new tumors need new blood vessels to grow and no concept has more excited the scientific community and the public than anti-angiogenesis. Preclinical laboratory results with the drugs angiostatin and endostatin are provocative and although these drugs will not be ready for clinical trial soon, several trials of other anti-angiogenesis agents are already underway in the Phase I and Phase II trials.

Antisense Therapy

Proteins maintain the structural integrity of cells and organs and serve as catalysts for biological reactions (enzymes). The biological computer program that codes for proteins is contained within the nucleus of each cell in the deoxyribonucleic acid (DNA) molecule in the form of genes. Protein production takes place in 2 steps known as "transcription" and "translation". In the nucleus, a gene for a protein is copied or "transcribed" into an intermediary molecule termed messenger RNA (mRNA). mRNA travels to the cytoplasm of the cell where it is "translated" into amino acids, the basic building blocks of proteins. Cancer, like many diseases, is associated with inadequate or inappropriate production or performance of proteins. Antisense technology involves the use of synthetic segments of DNA or RNA called oligonucleotides to stop the production of such disease-related proteins. Antisense compounds block the transmission of genetic information between the nucleus and the protein production sites within a cell by binding specifically with the messenger RNA and effectively jamming its genetic signal, thereby preventing the production of disease-associated proteins. To do this, scientists synthesize a length of DNA with a sequence of bases complementary to the messenger RNA. The DNA is a mirror image (antisense) of a portion of the messenger RNA (sense). The antisense DNA is taken up by the cell. The DNA binds to the messenger RNA because its sequence is designed to be an exact complement of the target sequence. Once the 2 strands bind, the messenger RNA can no longer dictate the manufacture of disease-associated protein in the ribosome. It is also marked for rapid breakdown by the cell's enzymes, thereby freeing the antisense oligonucleotide to seek and disable another identical messenger strand of RNA.

Blocking Signal Transduction

Signal transduction pathways are the chemical pathways by which messages are transmitted into a cell, through its cytoplasm, to its nucleus. The nucleus then acts on the messages that those signals give it. Research over the past 20 years has reinforced the view that cancer is associated with the damage, loss, or amplification of specific genes. Of the numerous cancer related genes (oncogenes) identified to date, many appear to be abnormal versions of signaling pathway components, such as growth factors, tyrosine kinases (TKs), serine-threonine kinases (STKs), or molecules associated with the ras oncogene. Many scientists are trying to develop drugs and therapies based on blocking the abnormal signal transduction pathways of cancer.

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