

Androgen Deprivation and Other Treatments for Advanced Prostate Cancer

Michael K. Brawer, MD,* E. David Crawford, MD,[†] Fernand Labrie, MD,[†] Arturo Mendoza-Valdes, MD,[§] Paul D. Miller, MD,[†] Daniel P. Petrylak, MD^{||}

*Northwest Prostate Institute, Seattle, WA; [†]University of Colorado Health Sciences Center, Denver, CO;

[†]Laval University Medical Center, Quebec, Canada; [§]Médica Sur Hospital, Mexico City, Mexico;

^{||}New York Presbyterian, New York, NY

Among the issues discussed at this year's meeting on prostate cancer in Vail, Colorado, were several that specifically relate to the patient with advanced disease. Dr. E. David Crawford addressed the issue of the timing of hormone therapy, specifically reviewing several important trials that give a glimpse at the potential outcome of aggressive treatment in stage D1.5. The efficacy of antiandrogens, flutamide, bicalutamide, and nilutamide, when combined with chemical or surgical castration, was reviewed. Dr. Arturo Mendoza-Valdes reviewed the rationale behind intermittent (versus continuous) total androgen blockade, especially as related to quality of life. Dr. Paul Miller gave an update on the role of bisphosphonates as adjuvant therapy for prostate cancer. Also discussed was an important new agent for androgen deprivation, Abarelix, a sustained-release GnRH antagonist with low histamine-releasing potential which avoids testosterone and other hormone surge and flare.

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Dr. E. David Crawford presented an enlightening discussion on the role of early versus delayed endocrine therapy. He opened his discussion by noting that although androgen suppression initially results in an extremely positive response, there is almost invariably progression in advanced disease (Table 1). Moreover, the demonstrated improved survival and time to disease progression are not of great amplitude at the late stage of the disease.¹⁻³ Of course, the role of androgen suppression is considerably different from that of even a decade ago

Table 1
Randomized Studies Showing Survival Benefits
Following Androgen Ablation in Localized or
Asymptomatic Metastatic Prostate Cancer

Authors	Benefits
Bolla et al ⁷	45% improved overall survival (<i>P</i> = .001) 77% decrease in cancer-specific death
RTOG trial ⁶⁸	20% improved overall survival for Gleason score 8 to 10 (<i>P</i> = .03)
MRC study ⁶⁹	21% decrease in cancer-specific death (<i>P</i> = .001)
Labrie et al ⁷⁰	69% decrease in cancer-specific death (<i>P</i> < .01)
Messing et al ⁶	81% decrease in cancer-specific death (<i>P</i> = .001)
Granfors et al ⁷¹	39% decrease in cancer-specific death (<i>P</i> = .06)
Hanks et al ⁷²	54% decrease in cancer-specific death for Gleason score 8 to 10 (<i>P</i> = .007)

RTOG, Radiation Therapy Oncology Group; MRC, Medical Research Council.

because of the significant down-staging afforded by early detection. Indeed, the most widely used application for androgen suppression today is so-called stage D1.5 (biochemical) progression following initial therapy with curative intent (radiation or therapy).

The growth of this patient population (D1.5) has resulted in a rethinking of appropriate classification of advanced prostate cancer, as shown in Table 2. Crawford noted that most clinicians believe that progression and indeed death from prostate cancer is inevitable in stage D1.5 if the patient has a significant life expectancy. The question that remains is this: is there any evidence that aggressive intervention in these patients may result in cure? The definitive answer is not apparent. Dr. Crawford reviewed

several important trials that give a glimpse as to the potential outcome of aggressive treatment in this stage.

Studies discussed included the Veterans Administration (VA)

Cooperative group investigations, the Medical Research Council (MRC) study, adjuvant radiation studies, and the Eastern Cooperative Oncology Group (ECOG) Intergroup D1 investigation. In extended analysis of the VA cooperative study reported by Byar,⁴ a nontoxic dose of diethylstilbestrol (DES) 1 mg actually resulted in a survival benefit compared to 0.2 mg, which was found to be ineffective at achieving castrate levels of testosterone, and compared to 5 mg, which resulted in increased cardiovascular toxicity.

The MRC study revealed a survival advantage to early versus delayed therapy in locally advanced disease.⁵ Three hundred eighty-seven patients were evaluated. Not only was there a survival advantage with early versus delayed therapy in this cohort, but there was also a significant decrease in major morbidity, including pathologic fractures, cord compression, ureteral obstruction, and extraskeletal metastasis. Although the study has been faulted in a number of regards, the data is certainly provocative (Figure 1).⁵

Another important study was that reported by Messing and associates.⁶ These investigators evaluated D1 (positive lymph node disease). They

Table 2
New Spectrum of Advanced Prostate Cancer

D0	Elevated acid phosphatase
D1	Pelvic lymph nodes
D1.5	Rising PSA after failed local therapy
D2	Metastatic disease in bone and/or other organs
D2.5	Rising PSA after nadir level
D3	HRPC (hormone refractory prostate cancer)
D3S	Hormonally sensitive
D3I	Hormonally insensitive

evaluated immediate versus deferred hormonal therapy in men who had a radical prostatectomy and pelvic lymphadenectomy. This study demonstrated marked improvement in the immediate hormone therapy cohort with respect to both prostate cancer-specific survival (30.8% vs 4.3%) as well as disease progression (75% vs 18.8%).⁶ The big question that remains is whether there is a potentially greater benefit from a combination of surgery and hormonal treatment than from hormonal treatment alone.

Two important studies by radiation oncologists have demonstrated that a combination of hormonal therapy and external beam radiation is superior to radiation alone. Bolla et al⁷ studied patients with T3 prostate cancer. Three years of hormonal therapy in combination with external beam radiation therapy (EBRT) resulted in a significant therapeutic benefit over radiation therapy alone.

Ten-year survival estimates were greater in the combination group (79% vs 62%). Disease-free status was 85% in those patients receiving combination therapy compared to 48% in those receiving EBRT alone.⁷ Again, the question remains as to the importance of the radiation in this cohort. In other words, does radiation add to the beneficial effects of hormone therapy alone? A randomized trial comparing radiation with hormone therapy to hormonal therapy alone is now underway in Canada.

Another important study was that of the Radiation Therapy Oncology Group (8610 trial). In this investigation, 4 months of hormonal therapy with EBRT was demonstrated to improve outcomes over radiation therapy alone for patients with clinical T3 disease. Local control favored the combination (84% vs 71%), and freedom from biochemical failure was achieved in 46% of the combi-

nation cohort versus 21% after radiation therapy alone.⁸ Further analysis demonstrates a survival advantage in the combination group.⁹

Dr. Crawford concluded that these studies demonstrate important survival advantage when androgen suppression is administered early in men with prostate cancer. Similar to other disease sites such as colon and breast, a number of questions remain. Should the hormonal therapy be combined with chemotherapy? What is the role of intermittent therapy? These important questions obviously await more clinical trials.

Benefits of Combined Androgen Blockade in Advanced Disease

An interesting fact is that the demonstration of the benefits of combined androgen blockade has been obtained in the most difficult group of patients to treat, namely in patients suffering from metastatic or advanced disease. The antiandrogens have been shown in prospective and randomized studies to prolong life, to increase the number of complete and partial responses, to delay progression, and to provide pain control (thus improving quality of life) in metastatic prostate cancer when added to surgical or medical castra-

tion compared to castration alone.^{1,10-15} In the first large-scale, randomized study, patients who were treated with flutamide and Lupron (leuprolide acetate) lived, on the average, 7.3 months longer than those who received Lupron plus placebo.¹

Analysis of all the studies performed with flutamide, bicalutamide, or nilutamide associated with medical or surgical castration compared to castration plus placebo shows that overall survival is increased by an average of 3 to 6 months.^{1,3,10-16} Because about 50% of men with prostate cancer die from causes other than prostate cancer, this difference in overall survival translates to an average of 6 to 12 months of life gained for cancer-specific survival, which are obtained by adding an antiandrogen to castration. These data demonstrate the particularly high level of sensitivity of prostate cancer to androgen deprivation, even at the very advanced stage of metastatic disease.

Bennett et al¹⁵ have performed a meta-analysis of all published peer-reviewed, randomized, controlled trials comparing treatment with flutamide in association with medical (leutinizing hormone-releasing hormone [LHRH] agonist) or surgical castration

Figure 1. Immediate versus deferred treatment for advanced prostate cancer. Adapted from the Medical Research Council, with permission from the publisher, Blackwell Science.⁵

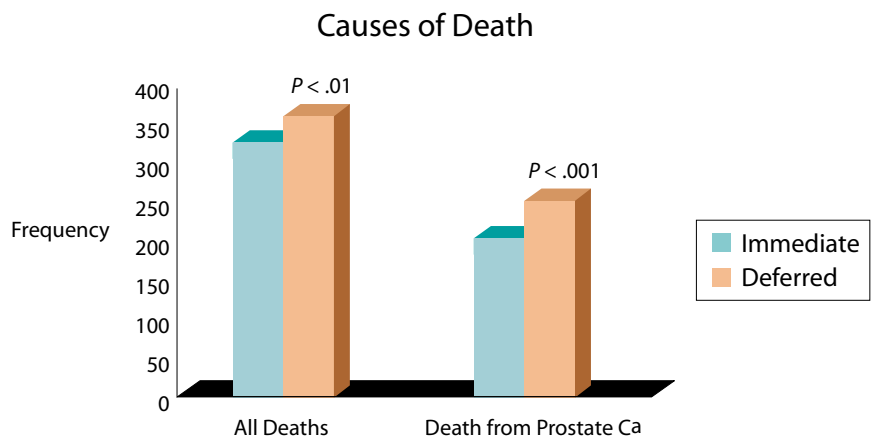


Table 3
Hazard Ratios (RR) and 95% Confidence Intervals (CIs) Using
Alternative Methods for Estimating Hazard Ratios for Survival Data¹⁵
and Comparison with Results from the 2000 PCTCG Analysis

Year of Analysis	Method of Meta-analysis	RR	95% CI	Number of Studies
Bennett et al ¹⁵	Literature-based	0.90	0.79 - 1.00	9
PCTCG ³	Patient-level	0.92	0.89 - 0.95	12

In favor of Flutamide + castration
versus castration alone

PCTCG, Prostate Cancer Trialists' Collaborative Group.

with castration alone in advanced prostate cancer. Nine studies with a total of 4128 patients were included in the analysis, which demonstrated a statistically significant 10% improvement in overall survival with the combination therapy using flutamide compared to castration alone.

As shown in Table 3, similar benefits have been calculated in favor of flutamide plus castration versus castration alone in the meta-analysis of Bennett et al¹⁵ and those of the Prostate Cancer Trialists' Collaborative Group (PCTCG) (Figure 2). As mentioned above and predicted,¹⁸ the difference has also become statistically significant in the most recent PCTCG analysis.³

With the clinical data summarized above, the controversy concerning combined androgen blockade should be part of history, and the addition of a pure antiandrogen should be recognized by all as providing an advantage of 3 to 6 months of life in metastatic disease when no alternative treatment even exists. When considering cancer-specific survival, it has been demonstrated that 6 to 12 months of life are added by adding an antiandrogen.¹³

Intermittent Androgen Ablation
 Dr. Arturo Mendoza-Valdes reported

on intermittent versus continuous total androgen blockade in advanced prostate cancer. Although it is clear that androgen deprivation is the cornerstone of therapy for advanced prostatic carcinoma, this is associated with significant cost both in terms of morbidity as well as economics. Mortality is lower but expense is greater when castration is combined with antiandrogen, so-called total androgen blockade. Morbidity includes decreased libido, erectile dysfunction, decreased lean body mass, fatigue, gynecomastia, breast tenderness, hot flashes, anemia, diarrhea, changes in liver function, and

nausea. Most studies have clearly demonstrated that use of an antiandrogen increases the morbidity over castration alone whether this is performed surgically or with an LHRH agonist. For example, in the Intergroup Trial 0101, 33 patients treated with combined androgen blockade were removed from the study because of drug toxicity compared with only 10 in the placebo arm.¹⁹ The longer life should however be taken into consideration.

Quality of life is an important concern particularly when therapy is primarily of palliative intent. One quality of life study recorded by

Figure 2. Mortality results from the 12 randomized trials of CAB (castration plus flutamide) versus castration alone in advanced prostate cancer. From the Prostate Cancer Trialists' Collaborative Group.³

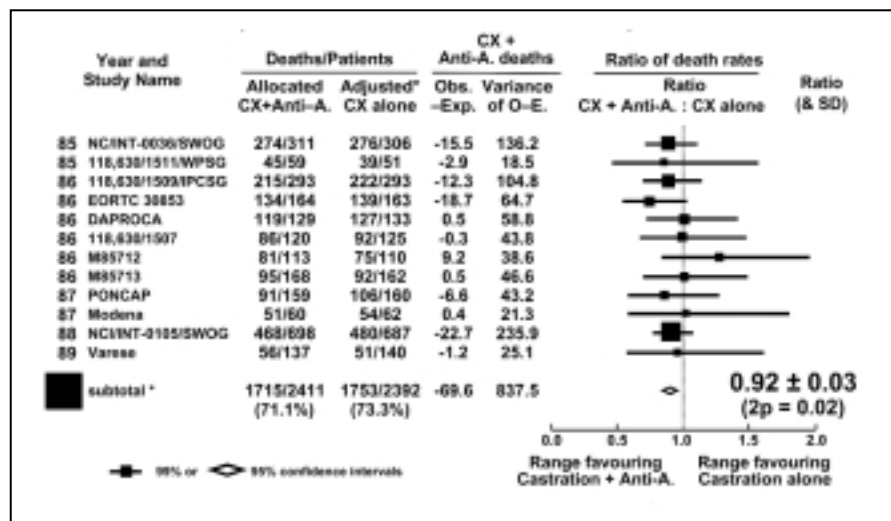


Table 4
Clinical Studies of Intermittent Androgen Suppression

Investigator	Clinical Stage	Mean Follow-Up (Months)	Mean Cycle Length (Months 1,2,3)	Time "Off" Therapy (%)	Mean Time to Nadir PSA	Patients
Goldenberg et al ²³	Local + metastatic	30	18, 18, 16	47	5	47
Gleave et al ²⁴	Local + metastatic	46	18, 18, 16	47	5	60
Higano et al ²⁵	Local + metastatic	26	15, 18	38	3.5	20
Oliver et al ²⁶	Local + metastatic	NA	NA	NA	NA	22
Grossfeld et al ²⁷	Local	24	16, 11, NA	50	4	47
Crook et al ²⁸	Local + metastatic	33	16, 13	46	5	54
Bruchovsky et al ²⁹	Local	NA	9	NA	NA	110
Theyer et al ³⁰	Local + metastatic	NA	8	NA	NA	60
Horwich et al ³¹	Metastatic	NA	5.5	16	NA	16
Kurek et al ³²	Local	48	9	11.6	NA	44
Tunn ³³	Local	48	9	9	NA	20

Moinpour²⁰ as part of the Intergroup 0105 study demonstrated that while quality of life improved in both patient arms, there was less effect in the patients in which an antiandrogen was combined with orchiectomy.

One of the strategies in improving quality of life and perhaps increasing disease-free survival has been the use of intermittent androgen blockage. A number of investigators have demonstrated both in animal experiments as well as human trials that intermittent androgen suppression may result in improvement in quality of life and potentially increase survival, although the number of patients and duration of follow-up were too small to reach a safe conclusion.²¹⁻³³ The rationale for intermittent approach to androgen suppression is that there appears to be recovery of apoptosis and subsequent slower progression to an androgen independent state.²¹

Intrinsic to the rationale for intermittent androgen suppression is the fact that it is assumed that early androgen ablation is superior to delayed therapy in improving sur-

vival, as suggested by the presentation at this meeting by Dr. Crawford. Moreover, it is assumed that androgen ablation, while helpful, is not curative when started at the advanced stage. Because of the palliative nature of this late-stage ablation, quality of life is an important component of evaluating competing therapies. Finally, the hypothesis that cells surviving androgen withdrawal are forced into alternative pathways of differentiation by androgen replacement and restoration of apoptotic potential may be achievable provides some rationale of biological advantage. An initial report by Klotz and associates in a small number of patients and a short follow-up suggested that an intermittent approach to the use of DES resulted in an improved quality of life and no statistically significant deleterious affect on survival.²² Goldenberg reported on 47 patients treated with medical castration and used prostate-specific antigen (PSA) to decide timing of discontinuing therapy.²³ This small study also suggested an improvement of quality

of life with no negative effect on survival at early follow-up.

Dr. Mendoza-Valdes provided a useful summary of the major intermittent therapy trials, which can be found in Table 4. Major conclusions from these investigations demonstrate that intermittent therapeutic approaches result in improvement in quality of life, sometimes with recovery of libido and potency. An obvious problem is lack of prospective randomized studies comparing intermittent and continuous approaches, the small number of patients in all studies, and the much-too-short follow-up. A major area of controversy is the amount of time for the initial period of castration. Certainly more studies are required before reaching valid conclusions. What does seem to be emerging is that intermittent androgen ablation does not have major negative effect on survival at early time intervals and in general results in less morbidity and potentially improved quality of life, although such conclusions must await large-scale and prospective studies.

Bisphosphonates and Prostate Cancer

Dr. Paul Miller updated the audience on the role of bisphosphonates as adjuvant therapy for prostate cancer. Bisphosphonates have been widely used for the treatment of osteoporosis. Primarily utilized in women, there is increased utilization in men with osteoporosis related to steroid use, hypogonadism, or age-related bone loss, as well as in multiple myeloma. Male osteoporosis is an increasing problem because of increased life expectancy. The changing of the androgen milieu with aging results in decreasing bone density. The only

ment of osteoporosis in women.³⁵⁻³⁸ This agent has been recently shown to result in increased BMD in elderly men. It appears that this agent may have a role in men who are at risk for osteoporosis owing to androgen deprivation because of prostate carcinoma. It seems that these men would be ideal candidates for BMD testing. Bisphosphonates may well be appropriate in patients who either have a low BMD or have already sustained fractures.

Another bisphosphonate, pamidronate, is approved for Paget's disease, the hypercalcemia of malignancy, and in reducing fractures in patients

agonists (leuprolide acetate [Lupron] and goserelin acetate [Zoladex]), have been demonstrated to be as effective as orchiectomy and safer than the hormonal therapy DES.

LHRH agonists stimulate the gonadotropin-releasing hormone (GnRH) receptors in the pituitary before they are able to block the receptors. As a result, LHRH agonists produce an initial surge in androgens (testosterone, dihydrotestosterone) and gonadotropins (luteinizing hormone [LH], follicle-stimulating hormone [FSH]). Therefore, it takes 3 to 4 weeks before testosterone castrate levels (≤ 50 ng/dL) are achieved.⁴⁰ These surges can induce clinical flare (ie, a worsening of symptoms). The acute manifestations of flare include voiding symptoms. In patients with metastatic disease, the surge can exacerbate skeletal pain, ureteral obstruction, and spinal cord compression, and can lead to paralysis and, in rare cases, death. To limit the surge and clinical sequelae, antiandrogens (bicalutamide [Casodex], flutamide [Eulexin]) are often coadministered with LHRH agonists. Antiandrogens, however, do not prevent the surge, and long-term use is associated with increased side effects, noncompliance, and out-of-pocket costs.⁴¹⁻⁴⁴

The increasing utilization of androgen suppression in men with prostate cancer has resulted in an ever-increasing population at risk for osteoporosis.

reliable method to diagnose osteoporosis before a fracture has occurred is by measuring bone mineral density (BMD). Diagnostic criteria (absolute BMD or standard deviation scores, the "T-score" established for postmenopausal women by the World Health Organization) are not clearly defined for men, yet it seems from preliminary data that men may fracture at similar BMD as women. Hence, asymptomatic men 65 years of age or older should be provided counseling on risk of osteoporosis and treatment with bisphosphonates when BMD thresholds similar to those that exist for women are reached.³⁴

The increasing utilization of androgen suppression in men with prostate cancer has resulted in an ever-increasing population at risk for osteoporosis. The bisphosphonate alendronate is U.S. Food and Drug Administration (FDA) registered for the treatment of osteoporosis in postmenopausal women; and, based on similar increases in BMD in men, has been FDA approved for the treat-

with known metastatic skeletal disease and multiple myeloma.³⁹

The bisphosphonates are currently being investigated with a therapeutic intent owing to their preclinical evidence of reducing establishment of bony metastasis. Bisphosphonates have been shown to inhibit tumor cell adherence to bone matrix in both breast and prostate cancer models. In addition, they have been shown to induce apoptosis in tumor cells. Large phase III trials are currently underway to examine the potential role of zoledronate to prevent skeletal metastasis in men with nonmetastatic prostate cancer.

In conclusion, male osteoporosis is increasing. Men with prostate cancer are at particular risk. Bone BMD testing and bisphosphonate in men with prostate cancer who are at risk for osteoporosis may be an important part of our future treatment regimens.

Abarelix, a Gonadotropin-Releasing Hormone Antagonist
Introduced in the mid-1980s, LHRH

Abarelix, a Pure GnRH Antagonist with a Different Mechanism of Action

GnRH antagonists have a different mechanism of action than LHRH agonists. Unlike LHRH agonists, which cause an initial up-regulation before a down-regulation of the GnRH receptor, GnRH antagonists act by directly blocking the GnRH receptor in the pituitary.

The clinical development of GnRH antagonists was hampered by problems, including insufficient potency, lack of solubility, and unacceptable histamine release. Abarelix (Plenaxis)

is the first GnRH antagonist formulated as a sustained-release product. In vitro data show that abarelix has low histamine-releasing potential at doses that cause rapid testosterone suppression without the initial androgen and gonadotropin surge.⁴⁵

Data from several clinical trials have been reported in abstract form, and several studies (McLeod; Trachtenberg and colleagues, manuscripts in preparation) are underway. One phase 2, open-label study con-

evaluations, and endocrinologic evaluations during the first 12 weeks of the study. The Tomera et al paper⁴⁶ reported the results through the first 27 days of the study.

No man treated with abarelix experienced a testosterone flare (defined as an increase in testosterone level by $\geq 10\%$ above baseline value on any two of days 2, 4, or 8) during the first week of study, compared with 82% of men treated with LHRH agonists. Seventy-five percent

depot on FSH is of great interest in light of in vitro studies with metastatic prostate cancer cell lines. One study suggested that FSH may play a role in the progression of prostate cancer.⁴⁸ Further studies are being conducted to better understand the role of FSH in the etiology of prostate cancer.

In summary, abarelix rapidly induces medical castration without the initial testosterone surge characteristic of LHRH agonists administered with or without an antiandrogen. Abarelix represents the first sustained-release GnRH antagonist that may be an alternative to both medical and surgical methods of androgen ablation in the treatment of all stages of prostate cancer. The physiologic results of rapid reduction of androgens and gonadotropins with abarelix could be clinically beneficial neoadjuvant hormonal therapy to rapidly reduce prostate gland volume reduction. Abarelix may also have clinical utility as an intermittent hormonal therapy, as treatment for metastatic prostate cancer, or in other situations requiring immediate or reversible medical castration.

Chemotherapy for Hormone-Refractory Prostate Cancer

Dr. Daniel Petrylak reviewed chemotherapy for advanced hormone-refractory prostate cancer at

In vitro data show that abarelix has low histamine-releasing potential at doses that cause rapid testosterone suppression without the initial androgen and gonadotropin surge.

trasted the endocrinologic and biochemical efficacy of abarelix with LHRH agonists, administered with or without an antiandrogen.⁴⁶ Abarelix 100 mg was given as an intramuscular injection to 209 men every 28 days with an additional injection on day 15. Thirty-three men received either Lupron (3- or 4-month depot formulation) or Zoladex (as a 1- or 3-month depot formulation) administered according to package labeling for the product. Men in the LHRH agonist group could also have received flutamide or bicalutamide. All men had the same baseline screening examinations, laboratory

of men treated with abarelix achieved medical castration (defined as testosterone ≤ 50 ng/dL), compared with 0% of men treated with LHRH agonists. Abarelix was well tolerated, with a safety profile comparable to LHRH agonists with or without a concomitant antiandrogen.

An additional new observation of this clinical investigation was the differential effect of abarelix on FSH. Compared with treatment with leuprolide with or without bicalutamide, abarelix reduced FSH levels more rapidly, to a greater level, and for longer than the comparator agents did.⁴⁷ The effect of abarelix

Main Points

- Studies demonstrate important survival advantage when androgen suppression is administered early in men with prostate cancer.
- Analysis of all the studies performed with flutamide and nilutamide associated with medical or surgical castration compared to castration plus placebo shows that overall survival is increased by an average of 3 to 6 months.
- Conclusions from major intermittent therapy trials demonstrate that intermittent therapeutic approaches result in improvement in quality of life, sometimes with recovery of libido and potency.
- Bone mineral density testing and bisphosphonate in men with prostate cancer who are at risk for osteoporosis may be an important part of future treatment regimens.
- Abarelix, a sustained-release GnRH antagonist, rapidly induces medical castration without the initial testosterone surge characteristic of LHRH agonists administered with or without an antiandrogen.
- A number of therapeutic targets for hormone-refractory prostate cancer are being investigated, including proteins that modulate apoptosis, cytoplasmic microtubules, the nuclear matrix, peptide growth factors, and topoisomerases.

the Vail meeting. He opened his comments by noting that although androgen ablation in advanced prostate cancer is most commonly associated with dramatic improvement by both objective and subjective criteria, it is relatively short-lived, with median responses of 12 to 18 months, and virtually all patients succumb to their disease. Once prostate cancer becomes androgen-insensitive, the median survival is only 9 to 12 months. In a historical review by Yagoda and Petrylak of 26 studies performed between 1988 and 1991, the overall response rate

to androgen deprivation.⁵¹ However, bcl-2 decreases the cytotoxic effect of doxorubicin in the Dunning model.⁵² Agents that inactivate bcl-2, for example the taxanes and vinca alkaloids, are under investigation to capitalize on this mechanism.

The Fas ligand has been proposed as a class of agents that would overcome an apoptotic block that the mutant form of p53 creates.

In his presentation, Dr. Petrylak highlighted the difficulty in assessing the anti-cancer drug activity in hormone-refractory prostate cancer. The fact that most of these men have

causing cell death. Retinoids may actually increase PSA expression.

Mitoxantrone, a topoisomerase II inhibitor combined with prednisone, demonstrated a 36% palliative response.⁵⁶ Other studies have confirmed these findings. The Tannock investigation demonstrated significant improvement in palliation of 29% in men receiving mitoxantrone and prednisone, compared to 10% in prednisone alone.⁵⁷ The Cancer and Leukemia Group B study has shown improvement in time to treatment failure and disease progression, although no benefit on survival was demonstrated.⁵⁸ Dr. Petrylak noted that in many organ systems other than prostate, chemotherapy in advanced disease (as with the patients treated with mitoxantrone in the above-mentioned studies) rarely shows survival benefit and suggests the possibility that these agents may have a more effective role in earlier stage disease. Following this logic, the Southwest Oncology Group is currently comparing a combination of 2 years of combined androgen blockade with 6 cycles of mitoxantrone and prednisone to 2 years of combined blockade alone in men with poor prognosis following radical prostatectomy.

Estramustine, a combination of an estrogen with nitrogen mustard strobecytin microtubules, inhibits assembly of the nuclear matrix and inhibits a multidrug resistance transporter p-glycoprotein.⁵⁹ The combination of estramustine with vinblastine or other agents is commonly used in practice and demonstrates PSA decline of greater than 50% in 45% to 52% of patients coupled with objective responses in 26% to 33% of men.

Taxane-based therapy has been extensively evaluated in prostate cancer. It has been felt that these agents affect microtubules. Recent data demonstrate that both docetaxel

Mitoxantrone, a topoisomerase II inhibitor combined with prednisone, demonstrated a 36% palliative response. Other studies have confirmed these findings.

to chemotherapy was only 8.7%.⁴⁹ There was no evidence of a trend toward improvement in survival. Over the past 5 years, more effective regimens have been developed.

A number of therapeutic targets for hormone-refractory prostate cancer are being investigated. These include proteins that modulate apoptosis, cytoplasmic microtubules, the nuclear matrix, peptide growth factors, and topoisomerases. Petrylak cited the recent approval of the mitoxantrone/prednisone combination for palliation of bone pain as an example that chemotherapy is becoming increasingly effective. Two of the major strategies for increasing effectiveness of chemotherapy in prostate cancer have been mechanisms to overcome classical drug resistance mechanisms, such as p-glycoprotein, as well as agents to increase apoptosis. Anti-apoptotic protein bcl-2 is found in approximately 65% of androgen-independent human prostate cancer specimens.⁵⁰ Transfection of this protein into the LNCaP creates resistance

disease limited to bone renders standard measurement criteria of soft tissue masses invalid. He noted that although PSA decline appears to correlate with survival, this is considered at best a surrogate endpoint, which is not accepted by the regulatory agency as an indication of effectiveness of agents. This is counter-intuitive in a sense, given the fact that a multivariate analysis by Kelly et al⁵³ of 110 patients with hormone-refractory prostate cancer demonstrated that PSA declines of >50% and a decline in the natural log of lactose dehydrogenase were the most important prognostic factors for survival. Smith et al⁵⁴ demonstrated that a >50% decrease in PSA level 8 weeks following initiation of therapy with estramustine and etoposide was predictive of prolonged survival. Dr. Petrylak noted, however, that caution must be exercised, as some chemotherapeutic agents may modulate PSA expression.⁵⁵ Suramin has been demonstrated to decrease expression of PSA messenger RNA without

and paclitaxel inhibit the antiapoptotic effects of bcl-2. Such studies with these agents appear promising.^{60,61} Combination studies with estramustine and taxanes have shown even greater efficacy.⁶²⁻⁶⁵ A major toxic effect of taxanes has been neutropenia. Studies are underway with weekly administration of taxanes, which obviates the significant side effects.^{66,67}

Phase III studies utilizing this regimen have been introduced by the Southwest Oncology Group. Patients with metastatic hormone-refractory prostate cancer are randomized to the control arm of mitoxantrone combined with prednisone versus estramustine, docetaxel, and dexamethasone. Accrual has been rapid and we anticipate early results from this study. ■

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