



Anita Philyaw. *Daydream*, 2001. Acrylic on canvas, 18" × 24". Courtesy of Stella Jones Gallery, New Orleans, La.

The efficacy of endocrine interventions for patients with prostate cancer is reviewed.

Controversies Surrounding Androgen Deprivation for Prostate Cancer

Stephen G. Patterson, MD, Lodovico Balducci, MD, and Julio M. Pow-Sang, MD

Background: Management of metastatic prostate cancer continues to evolve. The widespread use of the prostate-specific antigen (PSA) assay has led to earlier diagnosis and earlier detection of recurrent disease. Debates continue regarding the proper use and timing of endocrine therapy with orchiectomy, estrogen agonists, luteinizing hormone-releasing hormone (LHRH) analogs, LHRH antagonists, and androgen antagonists.

Methods: The authors reviewed the significant published materials of the last 20 years that have shaped hormonal management of metastatic and progressive prostate cancer. Major areas of controversy were also identified.

Results: The present approach to hormonal management is summarized. Five potential pathways to the development of androgen-independent prostate cancer are described. Controversial topics of hormonal management, including immediate vs delayed hormonal therapy, monotherapy vs maximal androgen blockade (MAB), and intermittent hormonal therapy, are discussed.

Conclusions: Orchiectomy, estrogen agonists, and LHRH analogs have therapeutic equivalence. Patients who have a rising PSA after definitive treatment for prostate cancer and high risk of recurrent disease may warrant early androgen deprivation. MAB does not appear to be significantly better than single-agent LHRH analog therapy. Intermittent therapy may delay emergence of androgen independence and maintain or improve quality of life.

Introduction

Conventional management of non-organ-confined, recurrent or metastatic prostate cancer continues to evolve due to earlier diagnosis of recurrent disease with prostate-specific antigen (PSA) monitoring, new medications such as luteinizing hormone-releasing hormone (LHRH) analogs, LHRH antagonists, and androgen antagonists. This article reviews the evidence supporting current treatment strategies and major con-

From the Genitourinary Oncology Program (SGP, JMP-S) and the Senior Adult Oncology Program (LB) at the H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida.

Submitted April 16, 2002; accepted June 25, 2002.

Address reprint requests to Stephen G. Patterson, MD, Genitourinary Oncology Program, H. Lee Moffitt Cancer Center & Research Institute, 12902 Magnolia Dr, MCC-GUPROG, Tampa, FL 33612. E-mail: pattersg@moffitt.usf.edu

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trouversies related to hormonal manipulations such as immediate vs delayed androgen blockade, monotherapy vs maximal androgen blockade (MAB), and intermittent vs continuous androgen blockade. The thrust of the article is to address which treatment will delay emergence of androgen independence and improve quality of life without sacrificing efficacy.

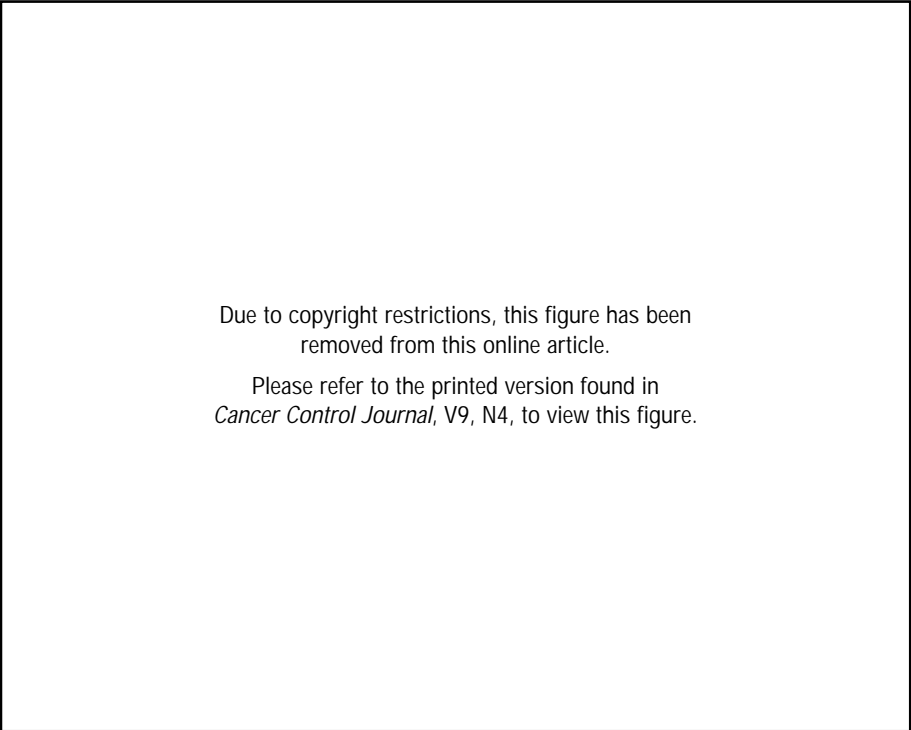
Biological Basis of Androgen Independence

Genetic mutations play an important role in the development of androgen-independent prostate cancer (AIPC).² Several investigators have offered evidence that androgen ablation provides selective pressure on the androgen signaling pathway for mutation development.^{3,6} Five AIPC mechanisms have been described (Figure).¹ The first three mechanisms (hypersensitive, promiscuous, and outlaw pathways) require the presence of the androgen receptor (AR) and its signaling cascade, the fourth mechanism involves the development of a parallel pathway, and the fifth mechanism involves a separate population of cells.

The “hypersensitive” pathway describes increased sensitivity of the AR to very low serum levels of androgen. Three mechanisms may be involved in the hypersensitive pathway: (1) AR amplification, where prostate cancer cells increase the expression of AR,^{7,8} (2) increased AR sensitivity, where tumor cells are hypersensitive to the growth promoting effects of dihydrotestosterone (DHT) (investigators reported the concentration of DHT required for growth stimulation was 4 orders of magnitude lower than that required for androgen-dependent prostate cancers),⁹ and (3) increased 5-alpha-reductase activity, where enhanced enzyme increases the conversion of testosterone to DHT. AR signaling would continue even in the presence of dramatically reduced serum testosterone.¹⁰

The “promiscuous” pathway involves acquisition of mutations in the AR protein ultimately proceeding to activation of the androgen-signaling axis with ligands other than testosterone.¹¹ In vitro work with the LNCaP model has examined the development of mutations in AR.¹² Molecular analysis and experimentation have shown that hormone ligands such as progestins, estrogens, and antiandrogens bind to mutant AR and function as agonists.¹² The promiscuous pathway may help to explain the clinical observation of the “flutamide withdrawal” syndrome, where patients progressing on therapy improve after flutamide is stopped.¹³

The outlaw pathway provides a mechanism where steroid hormone receptors are activated by mechanisms independent of hormonal ligand.¹⁴ Three growth factors — insulin-like growth factor (IGF-1), keratinocyte growth factor (KGF), and epidermal growth factor (EGF) — have been shown to activate receptor tyrosine kinases (RTKs).⁷ After the RTKs are activated,



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Five possible pathways to androgen independence. (1) In the hypersensitive pathway, more androgen receptor (AR) is produced (usually by gene amplification) or AR has enhanced sensitivity (not shown) to compensate for low levels of androgen, or more testosterone is converted to the more potent androgen, dihydrotestosterone (DHT), by 5 α -reductase. (2) In the promiscuous pathway, the specificity of the AR is broadened so that it can be activated by nonandrogenic molecules normally present in the circulation. (3) In the outlaw pathway, receptor tyrosine kinases (RTKs) are activated, and the AR is phosphorylated by either protein kinase B (AKT) or the mitogen-activated protein kinase (MAPK) pathway, producing a ligand-independent AR. (4) In the bypass pathway, parallel survival pathways, such as that involving the antiapoptotic protein Bcl-2 (B-cell lymphoma 2), obviate the need for AR or its ligand. Finally, (5) in the lurker cell pathway, androgen-independent cancer cells that are present all the time in the prostate — possibly epithelial stem cells — might be selected by therapy. Reprinted by permission from *Nature Reviews Cancer*, Macmillan Magazines Ltd. Feldman BJ, Feldman D. The development of androgen-independent prostate cancer. *Nat Rev Cancer*. 2001;1:34-45.

the AR is phosphorylated by either protein kinase B (AKT) or mitogen-activated protein kinase (MAPK), resulting in a ligand-independent AR.¹ HER-2/neu, a member of the EGF-receptor family of RTKs, deserves special mention. In breast cancer, estrogen independence correlates with HER-2/neu overexpression.¹⁵ It is theorized that HER-2/neu activation indirectly leads to phosphorylation and activation of the estrogen receptor (ER) in the absence of estrogen.¹⁶ Phosphorylation creates an “outlaw ER” in breast cancer cells.¹⁶ Similarly, overexpression of HER-2/neu can activate AR-dependent genes in the absence of AR ligand.^{17,18}

Selective pressure during therapy could upregulate a theorized parallel pathway to provide a substitute survival signal. An effective bypass would facilitate proliferation and inhibit apoptosis.¹ The bcl-2 gene is a bypass candidate that can block apoptosis. Bcl-2 is not expressed in the normal, noncancerous prostate cells,¹⁹ but it is present in AIPC.²⁰

Finally, Isaacs²¹ proposed the existence of a sub-population of androgen-independent tumor cells that are present prior to initial therapy. Epithelial stem cells in the prostate are believed to be androgen independent and their rates of proliferation and death are not affected by androgen ablation.²² Theoretically, the androgen-independent stem cells are thought to be “lurking” in the background until after androgen ablation has eliminated all of the androgen-dependent cells. The malignant epithelial stem cells would then be left to proliferate.¹

Present Approach to Hormonal Treatment

Castration, the time-honored frontline treatment for metastatic prostate cancer, was previously defined by induction of a serum testosterone level of <50 ng/mL.^{23,24} Recent literature redefines this upper limit to <20 ng/mL.²⁵ Testosterone is converted into a more potent compound, DHT. Conversion occurs in the cytoplasm of prostatic cells by the enzyme 5-alpha reductase. In addition to testosterone, adrenal androgens may give origin to DHT.²⁶ According to some studies,²⁷ as much as 40% of DHT is derived from adrenal precursors. This alternative source of DHT may explain in part the progression of some prostate cancers despite castration. Clinical responses still may be observed with adrenal ablation after failure from androgen withdrawal.²⁸ The combination of castration and adrenal ablation is the basis for the MAB approach. The hormonal agents available for treatment of prostate cancer are listed in Table 1.

The first method of permanent castration was bilateral orchiectomy, and the first reversible method was diethylstilbestrol (DES).²⁹⁻³¹ Medical castration may be obtained with estrogen agonists, LHRH agonists, LHRH antagonists, and ketoconazole.

The value of the LHRH analogs is supported by several randomized studies that show equivalent effectiveness between these medications and orchiectomy or DES. When compared to 5 mg of DES, LHRH

Table 1. — Hormonal Agents Used in the Management of Prostate Cancer

Class of Drug	Mechanism	Side Effects
Estrogen Agonists: - Diethylstilbestrol	Suppresses secretion of LHRH (inhibits LH, inhibits testosterone synthesis)	Cardiovascular, pulmonary embolism, cerebrovascular accident
LHRH Analogs: - Leuprolide - Goserelin	Suppress secretion of LHRH (inhibit LH, inhibit testosterone)	Initial symptom exacerbation
LHRH Antagonists: - Abarelix	Directs inhibition of LHRH with no agonist properties	Histamine release
Antiandrogens: Steroidal - Cyproterone acetate - Megestrol acetate Nonsteroidal - Bicalutamide - Flutamide - Nilutamide	Suppress testosterone by feedback effects at the pituitary and hypothalamus Competitively inhibit binding of androgens in target tissue	Weight gain and fluid retention Rare reversible interstitial pneumonitis
Other: - Ketoconazole	Inhibits cytochrome P450 hydroxylase for adrenal and testicular steroidogenesis	Adrenal insufficiency causing increase in corticotropin
LHRH= luteinizing hormone-releasing hormone		

analogs have a more favorable cardiovascular safety profile with a reduced risk of deep vein thrombosis and congestive heart failure.³²⁻³⁴ LHRH analogs are associated with hot flashes and may lead to osteoporosis over several years.³⁵ Potential benefits of estrogen include hot flashes and osteoporosis, as well as preservation of some libido.³⁶ Furthermore, it has never been conclusively demonstrated that DES at 1 mg/day is not as effective and as safe as LHRH analogs. In at least two studies,^{31,37} this dose of DES appeared equivalent to castration.

Two preparations of LHRH agonists are commercially available in the United States: leuprolide acetate (Lupron) and goserelin acetate (Zoladex). Since both of these agents are LHRH agonists, they cause an initial surge in serum testosterone lasting 1 to 2 weeks, which may stimulate tumor growth.^{38,39} For this reason, LHRH analogs are discouraged as initial monotherapy in men with impending spinal cord compression, urinary obstruction, or painful metastatic disease. An antiandrogen (bicalutamide, flutamide, or nilutamide) may be started 2 weeks prior to the administration of an LHRH analog as prophylaxis against these complications.⁴⁰ An alternate form of firstline therapy involves castration with ketoconazole. Like orchiectomy, ketoconazole provides rapid castrate levels of testosterone.⁴¹ Therefore, it may be used for initial temporary treatment in patients who need immediate efficacy and are poor surgical candidates.

The equivalence of orchiectomy, estrogen agonists, and LHRH analogs has been well demonstrated in several studies reviewed in a recent meta-analysis by Seidenfeld et al.⁴² Inconclusive results were reported in the comparison of castration and single-agent androgen antagonists. Three of the eight studies in the meta-analysis demonstrated longer survival in the group undergoing castration. This is not surprising because the use of antiandrogen without simultaneous blockage of the hypothalamic-pituitary axis may be associated with increased production of LH, ultimately stimulating the production of testosterone and potentially overwhelming the receptor block. Interestingly, the studies showing equivalence between castration and antiandrogen used cyproterone, a steroidal antiandrogen not available in the United States because of a side effect associated with blockade of pituitary gonadotropin production. The conclusion of the meta-analysis was that monotherapy with steroidal antiandrogens was inferior to castration.⁴² Similar conclusions to those in the meta-analysis were reported in a 1999 publication prepared for the Agency for Health Care Policy and Human Services.⁴³

Boccardo et al⁴⁴ reported the equivalence of bicalutamide and goserelin plus flutamide. The benefits of

monotherapy with antiandrogen included preservation of libido in a number of patients. It is noted that this was a small study with short follow-up and with doses of bicalutamide 3-fold as high as those normally used. Until these results are confirmed by larger trials, castration remains the frontline treatment of metastatic prostate cancer.

LHRH antagonists represent a recently developed class of drug used for androgen deprivation. PPI-149 (Abarelix), a peptide antagonist of the LHRH receptor,⁴⁵ works by directly inhibiting LHRH so there is no initial stimulation of the LHRH receptor.⁴⁶ In contrast, the LHRH analogs leuprolide, buserelin, and goserelin stimulate the LHRH receptor. Thus, there is no initial testosterone flare with administration of Abarelix as occurs with LHRH analogs. Practical shortcomings such as histamine release have limited the use of LHRH antagonists in clinical applications. Several published studies⁴⁶⁻⁴⁹ have concluded that Abarelix as monotherapy achieves castrate levels of testosterone, reduces serum PSA, and avoids the testosterone flare that is characteristic of LHRH analogs. Routine use of LHRH antagonists for advanced prostate cancer may depend on a demonstration of a survival advantage derived from avoiding the testosterone flare.⁴⁶

Immediate vs Delayed Hormonal Therapy

Hormonal therapy involves medical complications, effects on quality of life, and cost. It is reasonable to ask whether this form of treatment should be instituted as soon as the diagnosis of metastatic disease is established or if it should be delayed until symptoms develop. Reports from the Veterans Administration Cooperative Urological Group (VACURG) studies suggested hormonal treatment with DES could be delayed until the development of symptoms.²⁹ Re-examination of those studies, however, may temper these conclusions. In VACURG I, patients with metastatic disease were randomized to 5 mg of DES, 5 mg of DES plus orchiectomy, orchiectomy alone, or placebo.⁵⁰ Patients progressing on observation were eligible for crossover to DES, but their assigned study arm was not changed. No differences in survival were seen between treatment arms. Patients randomized to treatment with DES had a higher incidence of cardiovascular death and lower incidence of prostate cancer death. Lower DES doses were studied in VACURG II. Patients were randomized to 3 different dosages of DES (0.2 mg, 1 mg, and 5 mg) vs placebo.³¹ There was a crossover design. Institutional investigators were concerned about toxicity from high-dose DES treatment as well as the conclusions of VACURG I, and they often withheld crossover therapy too

long, particularly in patients in the 0.2 mg DES arm and in the placebo arm.⁵⁰ Therefore, VACURG II actually studied hormonal treatment vs no treatment.⁵¹ The second study results showed some survival benefit for hormonal treatment.

Five recent randomized, controlled studies have investigated treatment timing. In 1997, the Medical Research Council (MRC) Prostate Cancer Working Party Investigators Group⁵² reported the results of 938 patients with locally advanced or asymptomatic metastatic prostate cancer. Patients were randomized to immediate or delayed treatment with orchiectomy or LHRH analog. The results consistently favored immediate treatment. Progression from M0 to M1 disease ($P < .001$) and development of metastatic pain occurred more rapidly in the deferred-treatment patients. In addition, pathological fracture, spinal cord compression, ureteric obstruction, and development of extra-skeletal metastases were more common in this group. A significant decrement in the death rate from prostate cancer and an improvement in survival was observed. The authors commented that for approximately 10% of patients, treatment does not become necessary during their lifetime. It is unlikely a younger patient will fall into this 10% population who never require treatment. For the elderly man with nonmetastatic disease, deferred treatment probably still remains an option. Because 3% of patients experienced pathologic fracture or spinal cord compression, a major concern with the MRC study was whether patients in the deferred-therapy arm were allowed to progress too far before initiation of hormonal therapy. If patients were allowed to progress too far, it creates the potential for bias that would inflate differences in outcomes between immediate and deferred therapy.

Bolla et al⁵³ reported results of 415 patients with locally advanced prostate cancer. Patients were randomized to receive radiation therapy alone or radiotherapy plus immediate treatment with goserelin for 3 years. The median follow-up was 45 months. Kaplan-Meier estimates of overall survival at 5 years were 79% in the combined-treatment group and 62% in the radiotherapy group ($P = .001$). The proportion of surviving patients who were free of disease at 5 years was 85% in the combined-treatment group and 48% in the radiotherapy-alone group ($P < .001$). The authors concluded adjuvant treatment with goserelin when started simultaneously with external-beam radiation improved local control and survival in patients who had locally advanced prostate cancer.

In 1997, the Radiation Therapy Oncology Group (RTOG) Protocol 85-31⁵⁴ published the results of 977 patients enrolled in a randomized phase III study inves-

tigating the benefit of adjuvant goserelin in definitively radiated patients with locally advanced prostate cancer. The actuarial projections showed at 5 years, 84% of patients on the adjuvant goserelin arm and 71% on the observation arm had no evidence of local recurrence ($P < .0001$). The corresponding figures for freedom from distant metastases and disease-free survival were 83% vs 70% ($P < .001$) and 60% vs 44% ($P < .0001$). If a PSA level greater than 1.5 ng/mL is included as a failure (after >1 year), the 5-year disease-free survival rate on the adjuvant goserelin arm was 53% vs 20% on the observation arm ($P < .0001$). The 5-year survival rate (for the entire population) was 75% on the adjuvant arm vs 71% on the observation arm ($P = .52$). However, in patients who had tumors with a Gleason score of 8 to 10, the difference in actuarial 5-year survival (66% on the adjuvant goserelin arm vs 55% on the observation arm) reached statistical significance ($P = .03$). The authors concluded that application of androgen suppression as an adjuvant to definitive radiotherapy has been associated with a significant improvement in local control and freedom from disease progression. With a median follow-up of 4.5 years, a significant improvement in survival was observed only in patients with centrally reviewed tumors with a Gleason score of 8 to 10.

There are differences between the Bolla study and the RTOG 85-31 study. In the Bolla study, which reported a survival advantage for patients who received early hormonal therapy, the LHRH analog was started on the first day of radiation, while in the RTOG 85-31 study, which reported no overall survival advantage for early hormonal therapy, the LHRH analog was started during the last week of radiation. A possibility exists, therefore, that either by downsizing the prostate or through some other unidentified beneficial or synergistic effect of hormonal therapy, the radiation was more effective on the localized or regional tumor in the study by Bolla and colleagues than it was in the RTOG 85-31 study where radiation was initiated without any influence of hormonal therapy.

Granfors et al⁵⁵ reported the results of 91 patients with clinically localized prostate cancer who were treated for pelvic-confined prostate cancer. Patients had surgical lymph node staging and were then randomized to receive definitive external-beam radiotherapy or combined orchiectomy and radiotherapy. Patients who received radiation alone without hormonal treatment were treated with androgen ablation at clinical evidence of disease progression. Results were reported at a median follow-up of 9.3 years. Clinical progression was observed in 61% of patients treated with radiotherapy alone and in 31% of patients who received combined treatment ($P = .005$). Mortality was 61% and 38%, respectively, and cause-specific mortality

was 44% and 27%, respectively ($P=.06$), in groups 1 and 2. Differences in favor of combined treatment were mainly seen in lymph node positive tumors. Node-negative tumors showed no significant difference in survival rates. The authors concluded the progression-free, disease-specific, and overall survival rates for patients with prostate cancer and pelvic lymph node involvement are significantly better after combined androgen ablation and radiotherapy than after radiotherapy alone. These results strongly suggest that early androgen deprivation is better than deferred endocrine treatment for these patients.⁵⁵

In 1999, Messing et al⁵⁶ published the results on 98 men with prostate cancer who underwent radical prostatectomy and pelvic lymphadenectomy and were found to have nodal metastases. These men were randomized to receive immediate antiandrogen therapy with goserelin or bilateral orchiectomy or to be followed without further therapy until disease progression. After a median of 7.1 years of follow-up, 7 (15%) of the 47 men who received immediate antiandrogen treatment died compared with 18 (35%) of 51 men in the observation group ($P<.02$). The authors concluded that immediate antiandrogen therapy after radical prostatectomy and pelvic lymphadenectomy improved survival and reduced the risk of recurrence in patients with node-positive prostate cancer.

Granfors et al⁵⁵ and Messing et al⁵⁶ have published the only randomized data with pelvic lymph node dissections and definitive treatment to the prostate in which early hormonal therapy was compared with late hormonal therapy. Survival advantages were documented in both studies with the early administration of hormonal therapy in patients who had nodal metastases. Based on these data, immediate hormonal therapy could be justified in patients who have pathologically positive lymph nodes and undergo definitive treatment to the prostate.

Patients who have undergone primary treatment (prostatectomy, radiation therapy, or brachytherapy) and experience a PSA recurrence (D1.5 disease) present a difficult management issue. A recent structured debate recommended delayed androgen deprivation over immediate treatment for men with nonmetastatic disease and biochemical relapse.⁵¹ A review from the Cochrane Foundation noted a small increase in overall survival at 10 years for men treated in this fashion.⁵⁷ The natural history of disease in this patient population is unknown, and reasonable concerns about complications and cost of hormonal treatment have been raised. A series of 1,997 men who underwent radical prostatectomy for clinically localized prostate cancer at the Johns Hopkins Hospital between April 1982 and

April 1997 was reported.⁵⁸ The actuarial metastasis-free survival rate of all 1,997 men was 82% at 15 years after surgery. Of these men, 315 (15%) developed biochemical PSA elevation. One third of the patients with PSA elevation developed detectable metastatic disease, and the remaining two third had no other evidence of disease. The median actuarial time to metastases was 8 years from the time of PSA elevation. In survival analysis, the time to biochemical progression ($P<.001$), Gleason score ($P<.001$), and PSA doubling time ($P<.001$) were predictive of the probability and time to the development of metastatic disease. An algorithm combining these parameters was constructed to stratify men into risk groups. Once men developed metastatic disease, the median actuarial time to death was 5 years.⁵⁸ The issue of how early and what to do with the D1.5 patient has not been resolved, and further clinical trials need to be performed.

It appears that starting hormonal therapy at first evidence of PSA elevation after prostatectomy, radiation therapy, or brachytherapy delays the development of overt metastatic disease. A survival advantage with early therapy may be seen only in those patients who at diagnosis had a Gleason score of 8 to 10. One conclusion that could be drawn is for patients at high risk of recurrent disease, it is reasonable to consider initiating hormone treatment early. For the remaining majority of men with standard risk of recurrent disease, early therapy should be done in the setting of a randomized clinical trial.

Monotherapy vs Maximal Androgen Blockade

The basis of MAB is concomitant neutralization of both testicular and adrenal sources of androgen. The question of whether MAB is advantageous over castration has been debated for 15 years. The rationale of MAB is eliminating the influence of adrenal generated androgens by adding one of the antiandrogens to castration. Several large trials have evaluated the efficacy of MAB. Three large trials suggested that MAB conferred an important survival advantage.⁵⁹⁻⁶¹ More recently, Eisenberger and colleagues⁶² published results of 1,387 men with metastatic prostate cancer treated with orchiectomy and either flutamide or placebo. The addition of flutamide was not associated with a meaningful improvement in survival. It should be noted that patients treated with orchiectomy in this study had similar survival to those treated with MAB in previous studies, suggesting either that enrolled patients had less advanced disease or castration might not have been as complete with LHRH analogs as it was with orchiectomy. In the Intergroup study,⁵⁹ cas-

tration was obtained with daily injection of leuprolide. It is reasonable to assume compliance with daily injections was inconsistent.

The Prostate Cancer Trialists' Collaborative Group⁶³ performed a meta-analysis of 27 randomized trials involving 8,275 men with metastatic (88% of subjects) or locally advanced (12% of subjects) prostate cancer. Half were over 70 years of age, and follow-up was typically for 5 years. At the time of meta-analysis, 5,932 men (72%) had died; of the deaths for which causes were provided, approximately 80% were attributed to prostate cancer. The 5-year survival rate was 25.4% with MAB vs 23.6% with androgen suppression alone. The difference was not statistically significant (SE = 1.3; log-rank 2p = 0.11). There was no significant heterogeneity in the treatment effect (MAB vs androgen suppression) with respect to age or disease stage. The results for cyproterone acetate, which accounted for only one fifth of the evidence, appeared slightly unfavorable to MAB (SE = 2.4; log-rank 2p = 0.04 adverse); whereas those for nilutamide and flutamide appeared slightly favorable (SE = 1.3; log-rank 2p = 0.005). Non-prostate cancer deaths accounted for some of the apparently adverse effects of cyproterone acetate. The analysis concluded that in advanced prostate cancer, the addition of antiandrogen to androgen suppression improved the 5-year survival rate by approximately 2% to 3% (depending on whether the analysis includes or excludes the cyproterone acetate trials), but the range of uncertainty as to the true size of this benefit is approximately 0% to 5%.⁶³ It is not clear from these studies whether the small benefits of the antiandrogen might have arisen from offsetting tumor growth stimulation caused by the initial spike of testosterone following LHRH analog initiation.

Another meta-analysis published in 2001 by Schmitt et al⁶⁴ concluded that there was a 5% improvement in survival at 5 years (30% vs 25%) with MAB, as well as an improvement in progression-free survival at 1 year. It is noted that only 7 of the 20 randomized studies evaluated would, however, be considered high-quality studies. If the meta-analysis is limited to these 7 studies, there was no improvement from MAB. Also, only 3 of these 7 studies reported a positive survival advantage for MAB, and this may have skewed the results of the meta-analysis. The necessary interpretations of this closer inspection of the recent meta-analysis are that a minor improvement in survival may be seen with MAB and that if 20 trials have not conclusively demonstrated benefit from MAB over monotherapy, it is doubtful further trials will do so.

Quality-of-life (QOL) parameters in patients receiving monotherapy compared with MAB have been eval-

uated.⁶⁵ Data were collected on five primary QOL parameters including treatment-specific symptoms (diarrhea, gas pain, body image), physical functioning, and emotional functioning. Cross-sectional analyses reported statistically significant differences favoring monotherapy in two of the five parameters: increased diarrhea ($P=.001$) and worse emotional functioning ($P<.003$). The longitudinal analyses were reported to replicate these findings. The remaining 3 QOL parameters (gas pain, body image, and physical functioning) favored the group receiving monotherapy; however, the results were not statistically significant. The authors also reported that there was a consistent pattern of better QOL outcomes at each follow-up assessment during the first 6 months of treatment for patients receiving monotherapy, and improvement over time was observed in both treatment groups but more so for the monotherapy patients.

In summary, MAB does not appear significantly better than single-agent LHRH analog therapy. At present, it appears reasonable to prescribe an antiandrogen during the first month of treatment with an LHRH analog. Prolonged treatment beyond 1 month with MAB is not superior to monotherapy with an LHRH analog.

Physiological Changes Associated With Castration

Gonadal steroids influence growth rate and body composition. Adult males of most mammalian species are heavier and have a larger skeleton, more protein, a lower amount of body fat, and a higher resting energy expenditure than female or castrated animals.⁶⁶ Castration has been observed to have cumulative detrimental effects on the musculoskeletal system, endocrine system, and cardiovascular system, as well as the more commonly considered effects on libido and potency. Testosterone is connected with the maintenance of lean body mass and body fat distribution. Reduction in serum testosterone to castrate levels frequently results in weight loss and an increase in fat gain. Animal studies have been performed examining the metabolic effects of medical castration. Studies have objectively shown castration to induce body fat, and whole body protein content has been shown to be unchanged or decreased secondary to medical castration in animals.^{67,68}

An animal study performed examining the relationship of castration and cortical bone formation revealed that castration slowed the rate of bone formation and accelerated the rate of bone resorption.⁶⁹ Castration was found to affect the composition and the quality of cortical bone as well. The quantity of cortical bone was observed to have progressive reduction with longer

time after castration. Inhibited rate of bone formation and accelerated rate of bone resorption were found to be the etiology. Compared with intact animals, castrated animals had reduced their bone mass between 12% and 29%. The reduction in bone mass after castration has also been reported by other groups.⁷⁰⁻⁷² It was concluded that castration produced marked osteoporosis or osteopenia of the cortical bone as a result of changed rates of both bone formation and bone resorption.⁶⁹ Observations documenting an increase in frequency of osteoporotic fractures in men receiving androgen deprivation therapy have been made⁷³ as well as diminished bone mineral density with increasing duration of androgen deprivation therapy.⁷⁴

A study examining 10 men who had prostate cancer and were treated with buserelin over a 12-month period evaluated the effects of the LHRH agonist on protein and glucose metabolism. Treatment with buserelin was associated with a reduction in cortisol, an increase in triiodothyronine (T3) and free triiodothyronine (free T3), and a 17% increase in serum cholesterol. Basal energy expenditure was not changed over time. Increases in body weight, triceps skin fold, cholesterol, and fat mass were noted in the subjects.⁷⁵

Intermittent vs Continuous Hormonal Therapy

Intermittent hormonal therapy only became feasible when medical castration became available. Advan-

tages include reduction of side effects from therapy such as the physiological changes associated with castration, reduction of cost, and potentially delayed emergence of hormone refractoriness. Some studies have investigated the use of intermittent rather than continuous hormonal suppression. The intended goals include prolonging the initial hormone-sensitive period, achieving suppression of tumor growth at testosterone levels above those achieved by castration, and allowing sexual function during the interval between active androgen suppression. Experiments involving hormone-dependent breast cancer in the Noble rat model revealed that with a moderate reduction of the hormone level, tumor growth diminished and emergence of the hormone-independent state was delayed. Castration in the same rat model actually accelerated the progression to the hormone-independent state and hastened the death of the animal.⁷⁶ The results suggested that a delay in progression to hormone independence can be achieved using intermittent androgen suppression.⁷⁷

Laboratory evidence suggests that intermittent androgen blockade improves outcome by delaying the onset of hormonal resistance,⁷⁸ but currently there are no clinical data available to verify this hypothesis. Serial serum PSA determinations make intermittent androgen suppression possible by providing an easy method for early determination of tumor growth during periods of no treatment. The important question of whether intermittent hormonal therapy improves survival can be accurately addressed only in a randomized trial.

Table 2. — Selected Trials Investigating Intermittent Hormonal Therapy for Prostate Cancer

Investigator	Year	No. of Patients	Hormone Therapy Used	No. of Responders to 1st Tx	Length 1st Hormone Tx	PSA Level to Restart Tx	Mean 1st Time Off Tx	No. of Patients Responding to Re-treatment
Klotz et al ⁷⁹	1986	20	DES	12	10 mos (median)	NR	7.8 mos	All initial responders
Goldenberg et al ⁸⁰	1995	47	MAB	30	6 mos and until PSA nadir	Between 10 to 20	10 mos	NR
Higano et al ⁸³	1996	22	MAB	15	9 to 12 mos	Varied	6 mos	NR
Horwich et al ⁸¹	1998	16	LHRH analog	11	5.5 mos (mean)	Any rise in PSA	8 mos	All 10 patients who reinitiated
Crook et al ⁸²	1999	54	MAB	41	8 mos	10	35 wks	20 of 35
Grossfeld et al ⁸⁴	2001	61	MAB or LHRH analog	52	8 mos (median)	Varied	9 mos	90% initial responders

DES = diethylstilbestrol
MAB = maximal androgen blockade
LHRH = luteinizing hormone-releasing hormone
NR = not reported
Tx = treatment

Intermittent hormonal therapy consists of an initial active androgen suppression period, usually between 6 and 9 months, followed by a corresponding length of time where no active therapy is undertaken. Patients are then followed at regular intervals off therapy, and when laboratory values meet threshold criteria for reactivation of disease, active androgen suppression is reinitiated until maximal effect is again observed. Each period of active treatment followed by treatment cessation is referred to as one cycle of treatment. Ordinarily, patients who respond to an initial cycle will be observed to respond by objective criteria to a second initiation of androgen suppression. The key results of five trials investigating intermittent hormonal therapy are summarized in Table 2. A variety of reversible medical modalities have been used to induce testosterone suppression intermittently.⁷⁹⁻⁸⁴ Most of the reported phase II clinical trials have utilized approximately 8 months of androgen blockade followed by a period of no treatment when serial PSA is followed. Treatment is usually restarted after the PSA crosses a threshold of approximately 10 ng/mL. There are some anecdotal observations in the reported trials that the inability of a patient to reach normal levels of PSA with initiation of therapy could be considered a poor prognostic indicator.

Significant findings consistent among all five studies were recovery of libido during time off treatment in men who had normal libido prior to initial antihormonal therapy, effectiveness of reinstatement of hormonal suppression in prior responders, and subjective improvement in overall sense of well-being during time between active hormonal suppression. SWOG 9346, a multicenter randomized trial, is currently underway comparing intermittent vs continuous suppression. Assessed endpoints include quality of life and survival.

Intermittent androgen suppression may not only allow a reduction of the harmful side effects observed in patients who are treated with continuous androgen suppression, but also provide intervals of potency and regained libido during the intervals without androgen suppression. Investigators have theorized improved outcomes with intermittent hormonal therapy. To date, no randomized trial results have been reported that support such theory.

Conclusions

Orchiectomy, estrogen agonists, and LHRH analogs produce equivalent clinical responses in advanced prostate cancer. Castration remains the frontline treatment for metastatic prostate cancer. Patients who have undergone definitive local treatment for prostate cancer

but have a rising PSA are candidates for initiation of hormonal therapy. For the majority of men with a standard risk of recurrent disease, early hormone treatment should be performed only in the setting of a randomized clinical trial. MAB does not appear to be significantly more effective than single-agent LHRH analog. Prescription of an antiandrogen during the first month of treatment with an LHRH analog should be considered, but prolonged MAB beyond 1 month is not superior to LHRH analog monotherapy. Castration produces detrimental effects on the musculoskeletal, endocrine, cardiovascular systems, libido, and potency. Intermittent hormonal therapy may delay progression to the hormone refractory state and lengthen survival.

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