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Chemotherapy in hormone-refractory prostate cancer can decrease PSA levels and improve quality of life.

The Treatment Challenge of Hormone-Refractory Prostate Cancer

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Background: Both the demographics and treatment of hormone-refractory prostate cancer (HRPC) are changing. Patients are younger and healthier, with fewer comorbidities. The "no treatment until symptoms" approach is disappearing. Chemotherapy is increasingly being utilized.

Methods: The authors review the steps involved in hormone management before chemotherapy is considered. The roles for chemotherapy in current clinical trials are examined.

Results: Effective hormonal management of the prostate cancer patient incorporates an understanding of the stages of hormone sensitivity and prescribing additional interventions beyond simple castration. Once hormone refractoriness is established, the combination of mitoxantrone and prednisone has become a standard chemotherapeutic approach. New agents such as docetaxel are being tested in phase III trials against mitoxantrone plus prednisone.

Conclusions: HRPC is now regarded as a chemotherapy-sensitive tumor. The goals of chemotherapy in HRPC are to decrease PSA level and improve quality of life. New agents and combinations are needed to improve survival.

Introduction

The treatment of hormone-refractory prostate cancer (HRPC) is both challenging and rewarding as new targets are elucidated. As the most common malignancy in men the United States and the second leading cause of cancer death, the large number of patients requiring posthormonal therapy is increasing. In the past, only patients with proven metastatic disease or those with post-local therapy failures received hormonal treatment. Due to the demographic changes in patients treated with hormonal therapy, those now receiving hormonal therapy include not only the

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Submitted: August 6, 2001; accepted: October 9, 2001.

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patients previously mentioned, but also patients with biochemical failures, those on intermittent therapy, those at high risk for recurrence (T3-4, Gleason score ≥ 8 , PSA >20), and patients with locally advanced disease treated with radiation. Thus, the extent of disease at the time of hormonal therapy initiation and ultimate hormone refractoriness may vary considerably. This stage migration may influence treatment outcome.

Despite initial success with hormonal therapy, the durability of this response (median duration <2 years) is inadequate, and subsequent treatment is needed for these patients. With recent advances in the understanding of HRPC, newer treatment targets are being identified. In the past, all treatments including chemotherapy were considered inactive, but newer chemotherapy drugs and drug combinations are now demonstrating improved response rates.¹ The use of PSA as an effective marker of clinical success in the absence of measurable disease has been a boon to the evaluation of therapies. This article outlines an approach to HRPC and examines current trends in chemotherapy and newer targets.

Historical Perspectives

In 1941, Huggins and Hodges² presented their Nobel Prize-winning paper titled *The Effect of Estrogen and Androgen Injection on Serum Phosphatases in Metastatic Prostate Cancer*. Since then, hormonal ablation therapy has remained the mainstay of treatment for patients with advanced prostate carcinoma. Androgen deprivation achieves stabilization or regression of disease in more than 80% of patients,³ but the median duration of response after hormonal therapy in metastatic disease is less than 2 years.^{4,5} Despite castrate levels of testosterone, approximately 80% of patients progress within 12-18 months to an androgen-independent disease that includes hormone-sensitive and -insensitive or hormone-refractory prostate carcinoma tumors with a median survival of approximately 1 year.^{6,7} Therefore, androgen ablation is only a temporizing measure in patients with demonstrable disease.

Chemotherapeutic agents in the management of HRPC were traditionally viewed as having little or no impact on the natural history of the disease. In 1985, Eisenberger et al⁸ reviewed 17 randomized clinical trials with 1,464 patients, and the overall response rate was 4.5%. In a review of 26 cytotoxic chemotherapy trials performed between 1987-1991, the overall response rate was 8.7%.⁹

Two recently published phase III trials that demonstrated the use of mitoxantrone plus a cortico-

steroid in HRPC have changed the philosophy of treating HRPC.^{10,11} These studies led to US Food and Drug Administration approval of mitoxantrone plus corticosteroids for the treatment of HRPC. A study by Tannock et al¹⁰ compared mitoxantrone plus prednisone to prednisone alone. The study was based on the null hypothesis that chemotherapy would not produce benefit for HRPC. In the mitoxantrone/prednisone arm, pain relief was significantly improved and a longer duration of palliation was obtained. Quality-of-life scores improved with mitoxantrone/prednisone, and the treatment was well tolerated with minimal side effects. The median time to disease progression was 131 days in the combination arm vs 69 days in the prednisone only arm. Median survival was not improved, however, with a survival of 11.3 months in the combination group and 10.8 months in the prednisone only group. Kantoff et al⁶ performed a similar randomized trial in 1999 comparing mitoxantrone plus hydrocortisone to hydrocortisone alone. Median survival was 12.3 vs 12.6 months, respectively. Although there was no survival advantage between the two treatment groups, those who had a PSA response of $\geq 50\%$ or a decline from baseline of $\geq 80\%$ had a survival of 20.5 months vs 10.3 months for those who did not, regardless of treatment ($P < .001$). In addition to a slightly longer time to progression, there was an indication of better quality of life in the mitoxantrone/hydrocortisone group. These trials have demonstrated that there are options beyond hormonal manipulation in patients with HRPC who previously had no other alternatives.¹¹

Diagnosis

The hormone sensitivity of prostate cancer cannot be measured in absolute terms but rather should be viewed as a continuum with varying levels of hormone sensitivity. Most prostate cancer cells are hormone dependent and therefore have normal expression of androgen receptors. These receptors bind to dihydrotestosterone, and the complex migrates to the nucleus and binds to the androgen response element, resulting in cell growth. Androgen ablation causes the death of androgen-sensitive cells by apoptosis. Androgen-resistant clones, however, can survive in most patients supported by mitogenic growth factors, particularly in bone marrow stroma.¹² These cells eventually predominate and contribute to hormonal failure. It is at this point that chemotherapeutic agents are indicated.

The next level of hormone sensitivity in the progression to the hormone-refractory state is hormone independence. As previously described, the cells of the androgen-dependent tumor are initially similar to the

cells of the normal prostate epithelium, and they regress in the absence of androgen. However, some tumor cells proliferate despite castrate levels of testosterone. Tumors that grow despite initial surgical or chemical castration are considered hormone-sensitive, androgen-independent tumors. Substantial recent data have demonstrated that the androgen receptor may be activated in the absence of androgen by protein kinase A and other nonhormonal growth factors.^{13,14} This activation occurs in the transcriptional activation domain. Protein kinase A activation is blocked by some nonsteroidal antiandrogens (eg, bicalutamide) and not by others (eg, flutamide). It is conceivable that, in the androgen-depleted state, the inhibition of protein kinase A activation may be important. Thus, hormone-independent prostate cancer may respond to additional hormonal maneuvers.¹⁵⁻¹⁷ Ultimately, progression leads to hormone-insensitive, androgen-independent cells (HRPC) that are truly unresponsive to further hormonal manipulation. At this point, treatment with chemotherapy^{8,18,19} or newer approaches such as growth factor inhibitors²⁰ is indicated. An understanding of the phases of hormone sensitivity is crucial in evaluating response in clinical trials.

Management of Hormone-Independent Prostate Cancer

In a patient with rising PSA where castrate testosterone levels have been achieved, prostate tumors still may be susceptible to hormonal maneuvers. If testosterone levels are not at castrate levels on adequate

luteinizing hormone-releasing hormone (LHRH) agonist, then orchiectomy should be considered. The management approach to such a patient should be tailored to the level of sensitivity to androgen (Table 1). If the patient is not taking an antiandrogen, then one should be prescribed. If the patient is already taking an antiandrogen, it should be withdrawn. If flutamide was the initial antiandrogen used and a response was seen, then bicalutamide could be tried. In addition, the toxicity profile of bicalutamide is superior to that of flutamide. Furthermore, high-dose bicalutamide can also be used as an additional hormonal maneuver.²¹ Current practice dictates the continuation of the LHRH agonist.¹

Studies in tumor biology have led to the understanding that withdrawal of antiandrogen may elicit a fall in PSA level, termed "antiandrogen withdrawal syndrome." Some patients have a mutant androgen receptor in which flutamide was thought to actually stimulate cell growth.²² Taplin et al²³ reported a small number of patients and suggested that androgen receptor mutations are not responsible for the antiandrogen withdrawal response. In their retrospective review of three reports, Small and Srinivas¹⁷ noted that 29 (21%) of 138 patients had a 50% or greater decline of serum PSA after antiandrogen withdrawal. Thus, when a rise in PSA level occurs in a patient taking an antiandrogen, the antiandrogen use should be discontinued and his PSA level should be followed.

Once antiandrogen therapy and withdrawal have been utilized, there are several points at which the syn-

Table 1. — Classification of Prostate Tumors Based on Hormone Sensitivity

Category	Tumor Factors	Host Factors	
1) Androgen-dependent:	Hormone-naive, ie, no prior hormone therapy	Decrease in proliferation if: 1) antiandrogens are withdrawn 2) antiandrogens are administered	Physiologic levels of androgens in the blood
	Hormone-sensitive: 1) relapse after neoadjuvant therapy 2) intermittent therapy-planned discontinuation of hormones 3) relapse while on antiandrogens alone	Decrease in proliferation if: 1) androgens are withdrawn 2) antiandrogens are administered (except for situation 3)	Noncastrate levels of androgens in the blood
2) Androgen-independent:	Hormone-sensitive	Decrease in proliferation in response to: 1) adrenal androgen blockade 2) corticosteroids 3) withdrawal of agents that bind steroid hormone receptors 4) other hormonal manipulations	Castrate levels of testosterone
3) Hormone-independent:	Androgen-independent and hormone-insensitive	Insensitive to all hormonal manipulation(s)	Castrate levels of testosterone

From Scher HI, Steineck G, Kelly WK. Hormone-refractory (D3) prostate cancer: refining the concept. *Urology*. 1995;46:142-148. Adapted with permission.

thesis of adrenal hormones can be suppressed. Aminoglutethimide, ketoconazole, and hydrocortisone are agents that can suppress this production, which can account for 10% of circulating testosterone. Aminoglutethimide inhibits adrenal steroidogenesis by blocking P450 mediated by hydroxylation. Ketoconazole inhibits P450 in the adrenals and testes. In a study of 48 patients treated with ketoconazole plus hydrocortisone, Small et al²⁴ found a >50% decrease in PSA in 30 patients. Hydrocortisone suppresses the pituitary adrenal axis by suppressing corticotropin (ACTH).²⁵ In a recent study of 37 patients, Nishimura et al²⁶ examined the efficacy of low-dose dexamethasone, a potent glucocorticoid, and found that 62% of patients had a decline in serum PSA of more than 50% in 4 weeks. Median time to progression in this study was 9 months. In 18 patients who had bone pain, 61% had improvement of symptoms. In patients who experienced a decrease in PSA of at least 50%, median survival was increased to 22 months compared with 9 months in those who did not experience this decline in PSA. In summary, in the setting of hormone independence, manipulation of the adrenal hormonal axis may lead to a decline in PSA and fewer symptoms.

Management of Hormone-Refractory Prostate Cancer

Prostate cancer should be considered as hormonal refractory only when all of the above maneuvers have failed. Chemotherapy should then be considered, particularly if the patient has good prognostic factors (eg, performance status and hemoglobin level), ideally in a clinical trial. The unique dilemma in treating a patient on a clinical trial is deciding on the appropriate time to commence therapy. The Prostate-Specific Antigen Working

Group has recommended that two consecutive increases in serum PSA be documented.²⁷ Furthermore, the value should be at least 5 ng/mL prior to entering a patient in a clinical trial; changes are difficult to interpret at a lower level.²⁷ Patients with clinically evident disease need assessment by appropriate radiologic studies.

Based on their mechanism of action, active chemotherapeutic agents can be divided into several groups including microtubule agents, alkylating agents, and topoisomerase inhibitors.

The “standard” chemotherapy for HRPC, based on data from Tannock et al,¹⁰ is mitoxantrone plus prednisone. Mitoxantrone, a topoisomerase II inhibitor, is administered at a dose of 10-14 mg/m² intravenously every 3-4 weeks.

Estramustine is an oral microtubule active agent that interferes with mitosis.²⁸ It was initially synthesized as a conjugate of nitrogen mustard and estradiol. It has been used as a single agent for many years and was originally used in a chemotherapeutic approach to prostate cancer. Benson and Hartley-Asp²⁹ reviewed 18 phase II clinical trials involving patients with HRPC and found an objective measurable response in 19%. However, Small et al³⁰ in 1999 summarized the results of several trials in which estramustine was combined with various other agents showing improved response rates. These other agents included vinblastine, etoposide, paclitaxel, docetaxel, and carboplatinum (Table 2).

Estramustine in combination with other agents has been studied since the early 1990s. Hudes et al³¹ reported the first results in 1992 in their evaluation of estramustine and vinblastine. In a similar series,³² PSA

Table 2. — Selected Estramustine-Based Chemotherapy Trials in Hormone-Refractory Prostate Cancer

Source	Treatment	No. of Patients	50% PSA Response	Measurable Disease Response
Hudes et al ³¹	E + V	25	61	14
Pienta et al ⁵⁷	E + VP-16	42	57	14
Dimopoulos et al ⁵⁸	E + VP-16	56	58	45
Hudes et al ⁵⁹	E + P	32	58	44
Petrylak et al ³⁶	E + D	21	62	28
Kelly et al ⁶⁰	E + P + C	26	73	64
Smith et al ⁶¹	E + VP-16 + P	37	65	45
Savarese et al ⁶²	E + D + Dex	47	69	-

E = estramustine V = vinblastine
 VP-16 = etoposide P = paclitaxel
 D = docetaxel C = carboplatin
 Dex = dexamethasone

From Small EJ, Reese DM, Vogelzang NJ. Hormone-refractory prostate cancer: an evolving standard of care. *Semin Oncol.* 1999;26:61-67. Reprinted with permission.

responses were obtained in 42% of 83 patients, with objective responses in 31% of 19 patients. Various combinations have since been studied and summarized.³⁰ When evaluating which combination provided the highest rate of PSA response, the combination of estramustine and docetaxel was superior; however, all of the response rates were clustered at approximately 60%. When the response of measurable disease was evaluated, the combination of estramustine, etoposide, and carboplatinum was the most successful, with estramustine plus docetaxel second in efficacy. More interestingly, the majority of combinations fell far below the 60% mark. Thus, while most agents were able to provide a PSA response, most combinations did not fare as well when evaluating response of measurable disease. In conclusion, a combination of estramustine plus taxanes appears to provide the highest benefit in the treatment of HRPC. Toxicities associated with estramustine use include nausea, vomiting, and deep venous thrombosis. Current treatment protocols with estramustine are requiring some form of anticoagulation such as warfarin (Coumadin). In addition, lower doses have been used to limit gastrointestinal toxicity.

Docetaxel, now a commonly used chemotherapeutic agent in the treatment of HRPC, acts by inhibiting microtubule function (Fig 1).³³ It is possible that prostate cancer cells can concentrate this drug intracellularly, permitting a low-dose extracellular concentration. In addition, docetaxel can bind to Bcl-2, an anti-apoptotic protein overexpressed in prostate cancer cells. Bcl-X_L, another anti-apoptotic molecule, is also downregulated by docetaxel.³³

With the ever-increasing presence of docetaxel in clinical trials, an understanding of the pharmaceutical and pharmacokinetic properties of this agent is important. First, the kinetics of docetaxel are linear with dose independent of schedule of administration. Second, docetaxel is cleared via hepatic metabolism, and therefore toxicity is associated with impairment in hepatic function.³⁴ Prostate cancer with bony metastasis will lead to an elevation in alkaline phosphatase, so no dosage adjustment is required in this situation. Hepatic function needs to be assessed independently of alkaline phosphatase. The dose-limiting toxicity for docetaxel is neutropenia, which is usually brief in

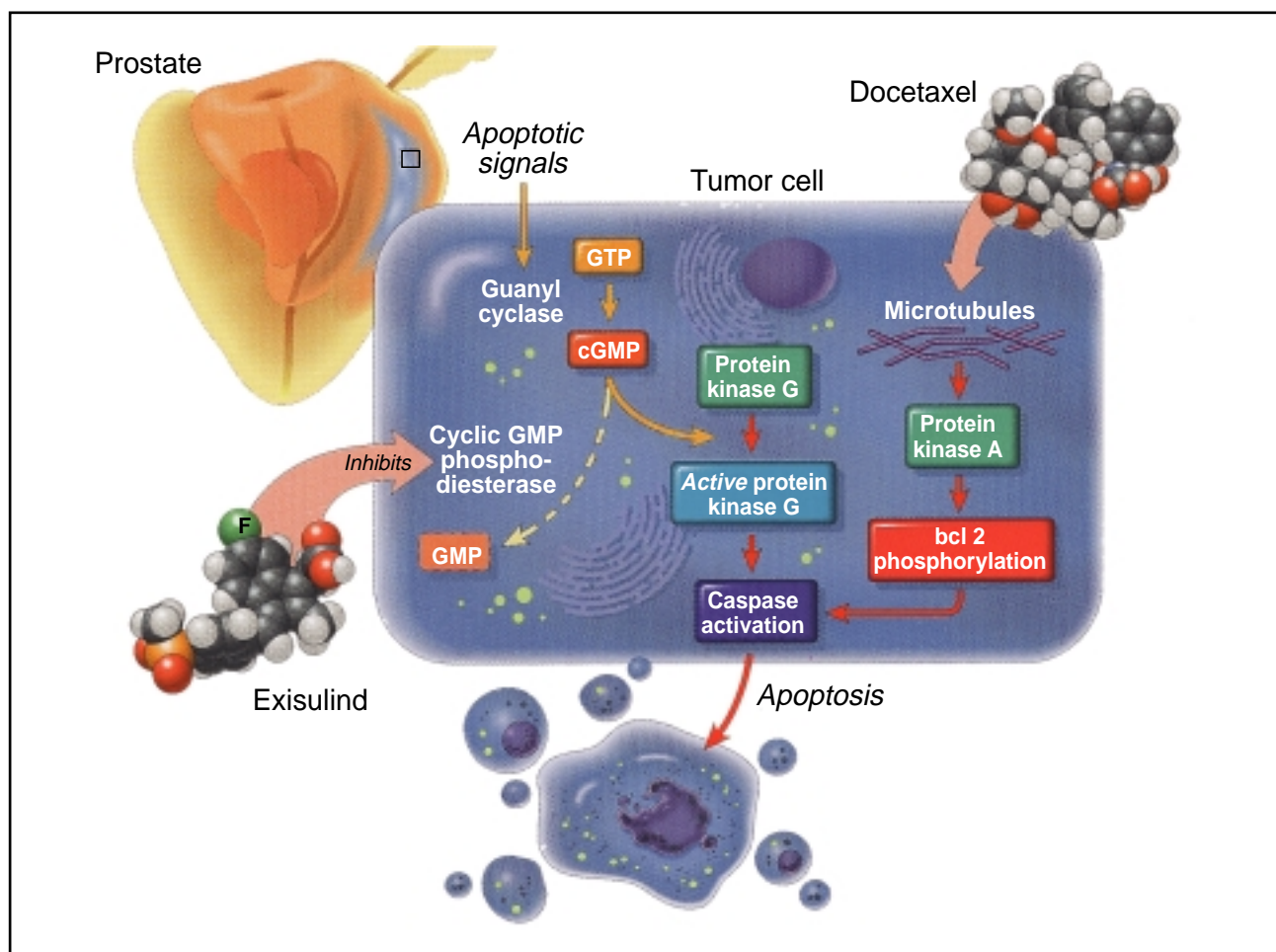


Fig 1. — Proposed mechanism of action of exisulind and docetaxel. From Ryan CW, Vogelzang NJ, Stadler NJ. Rationale for docetaxel and exisulind in hormone refractory prostate cancer. *Adv Prostate Cancer*. 2001;5:5-7. Reprinted with permission from Physicians' Education Resource.

duration. The initial dose as a single agent in most non-prostate clinical trials was 75-100 mg/m² given every 3 weeks. In this dose range, 75% of patients will develop grade 4 neutropenia. Lower doses are usually used with prostate cancer. Other significant toxicities include rash, stomatitis, and diarrhea.

The initial studies of docetaxel were done in combination with estramustine.^{35,36} Kreis and colleagues³⁵ examined this combination and found that the maximum tolerated dose of docetaxel was 70 mg/m² every 3 weeks. Furthermore, at the high-dose level, there was a significant decrease in PSA in 80% of patients. The overall response rate in this series was 63% as measured by PSA response.

Since estramustine has significant gastrointestinal toxicity, namely nausea, attempts have been made to decrease and even eliminate this agent in clinical trials. Petrylak and colleagues³⁶ attempted to decrease the amount of estramustine from the schedule utilized by Kreis et al³⁵ and found that there was no change in the response rates. Some investigators are successfully utilizing weekly taxanes as monotherapy. Picus and Shultz³⁷ examined docetaxel monotherapy and achieved a 45% PSA response rate in patients treated with 75 mg/m² every 3 weeks. However, in a recent abstract, Berry et al³⁸ examined paclitaxel, another taxane, with or without estramustine in patients with HRPc. The PSA response was 48% for the combination vs 25% for paclitaxel alone. It appears from this more recent study that estramustine may be a requisite for effective chemotherapy in the treatment of HRPc. The Southwest Oncology Group is currently conducting a phase III randomized trial of mitoxantrone plus prednisone vs docetaxel plus estramustine.

Alkylating agents such as cyclophosphamide have been used with some limited success. Regimens incorporating cyclophosphamide with doxorubicin have demonstrated a 46% PSA response.³⁹ In initial preclinical trials, temozolomide, an oral alkylating agent, also showed antitumor activity. In a report by van Brussel et al⁴⁰ that examined the efficacy of temozolomide in 16 patients with HRPc, all patients developed progressive disease within 2 cycles, and they did not benefit from a quality-of-life standpoint. Therefore, the use of this alkylating agent is not recommended in the treatment of HRPc.

Several new phase II trials of agents have been studied for HRPc. Suramin, an antiparasitic drug, showed preliminary evidence of antitumor activity against prostate cancer with inhibition of binding of growth factors to their receptors. Small et al⁴¹ compared hydrocortisone alone with suramin plus hydrocortisone and found a durable improvement in pain as well as PSA response. A subsequent phase III trial demonstrated that dose escalation of suramin produced increased PSA response but did not prolong survival.⁴²

Thalidomide has caused angiogenesis inhibition in prostate cancer. Phase II trials of thalidomide plus docetaxel are currently in progress.⁴³ Exisulind is a metabolite of sulindac, a nonsteroidal anti-inflammatory drug. Exisulind was initially developed for the treatment of familial adenomatous polyposis. It inhibits cGMP phosphodiesterase isoforms PDE5 and PDE2, leading to an induction of cGMP-dependent protein kinase G. In addition, β-catenin is degraded. The cumulative effect is apoptosis. The combination of exisulind and docetaxel (Fig 1) is currently under trial at the University of Chicago.⁴⁴

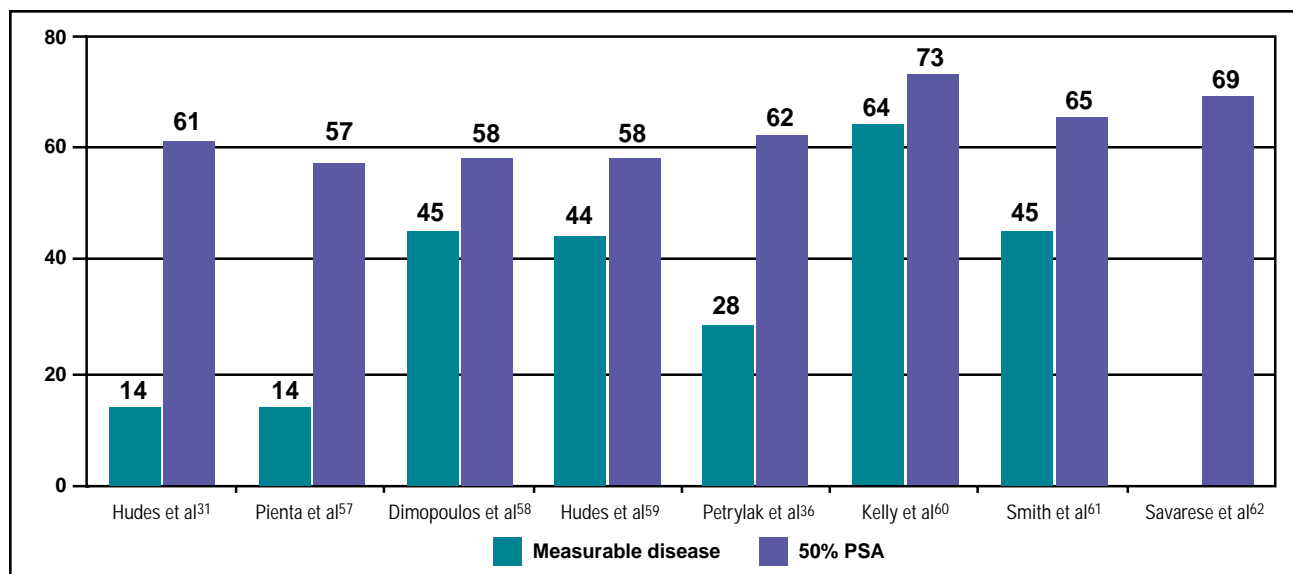


Fig 2. — Summary of measurable disease response and 50% PSA response using estramustine plus other agents. Data from Small et al.³⁰

With new insights into tumor immunology, dendritic cells have been used to treat HRPC. One product that has reached the market is Provenge, which consists of autologous dendritic cells that are loaded ex vivo with recombinant fusion protein consisting of prostatic acid phosphatase and granulocyte-macrophage colony-stimulating factor (GM-CSF). In a trial of 31 patients, all patients developed immune responses to the recombinant protein, and 38% developed response to prostatic acid phosphatase.⁴⁵ Randomized trials are currently ongoing. The concept that the immune system can be conditioned to bring about a response against HRPC is enticing.

In a patient with a limited number of metastatic sites, external-beam radiation therapy may be effective in palliation.⁴⁶ However, in a patient with numerous metastatic sites, radiopharmaceuticals that target bone metabolism (eg, strontium-89, samarium-153, and phosphorous-32) may be more appropriate. These agents are approved only for palliation of painful bony metastasis; they are not effective in managing soft tissue metastasis or in the setting of myelosuppression or spinal cord compression. Furthermore, some may have irreversible granulocytopenia, and the ability to administer chemotherapy at a later time is compromised.

Biphosphonates are another option in the management of painful bone metastasis. Pamidronate has shown promise in this situation. In a pilot study, improvement in bone pain in 30%-90% of patients was noted.⁴⁷ Most attractive is the fact that biphosphonates are nonmyelosuppressive and have minimal other toxicities. New biphosphonates are being tested, and a phase III trial will compare pamidronate vs placebo.

Evaluation of Response

Measuring response is a complex issues in assessing the potential benefits of different forms of therapy in HRPC.⁴⁸ Between 80%-90% of patients with HRPC do not have bi-dimensionally measurable disease.⁴⁹ The majority of patients have bone metastases that are difficult to quantify accurately.⁵⁰ Many studies have suggested a correlation between the magnitude of post-therapy PSA decline (50% or greater vs less than 50% decline) and survival.^{10,51-54} The Prostate-Specific Antigen Working Group recently recommended a standardized method for reporting PSA response in phase II trials.²⁷ These studies formed the foundation for the consensus report of the PSA Working Group in assessing clinical trials in HRPC. The benchmark was set at a minimum 50% decline in PSA level. This standard is based on the findings of several authors including Kelly et al,⁵² who reported that a posttherapy decline of at least

50% was associated with survival advantage in a study of 110 patients. In 1999, Scher et al⁵⁴ reported that a PSA decline of greater than 50% achieved at 8 weeks and 12 weeks was a statistically significant factor associated with survival. It is therefore appropriate that PSA level may be used as a marker of success and a predictor of survival in the appropriate setting (Fig 2, Table 2). There are caveats to this statement, as several drugs can cause a decrease in PSA independent of their effect on cell death. In addition, since many patients with HRPC experience significant bone pain and cancer-related decreases in quality of life, subjective benefits such as quality of life and pain scores represent important measures of the effectiveness of therapy. Quality-of-life scores are useful in clinical trials of chemotherapy for HRPC.¹⁶ In summary, the current recommended standard for clinical trials is to report PSA data, palliative endpoints, and changes in measurable disease independently in each treatment report.¹

Conclusions

The use of chemotherapeutic agents is beneficial to patients with HRPC. These patients should be enrolled in clinical trials if possible. The use of prognostic factors can give some insight into predictive factors for response. In a recent review, nine studies contained sufficient numbers of patients to perform multivariate analysis.⁵⁵ The most important factors that affected prognosis were performance status and hemoglobin level. Other factors of importance appeared to be serum levels of lactate dehydrogenase and alkaline phosphatase.

In the era of routine PSA screening, 92% of prostate cancer is still detected while localized.⁵⁶ However, since the management of localized prostate cancer is not perfect, many patients will eventually present with metastatic disease and/or PSA progression. Unfortunately, hormonal ablation is not curative in the patient with either local failure or metastatic disease. Chemotherapy posthormonal treatment is now commonly used. Thus, there is now new hope that chemotherapeutic agents may provide palliation and ultimately improve survival. Randomized trials must continue in order to identify new agents for the treatment of HRPC. While PSA responses are a starting point for trial design, patient survival is ultimately the goal. With new agents and targets and with improved understanding of tumor biology, this goal can be reached.

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