



Clinical Flare: A Crisis That Can Be Avoided

Clinical flare is a drug-induced bodily response that can cause such symptoms as bone pain, compression of a nerve root, spinal cord compression, or blockage of one or both ureters. It is often painful and always dangerous.

A true story always tells so much more than reported material abstracted from everyday life. Here are two case histories obtained by us just recently.

Patient #1 is MF, an 81-year old man who had been following a watchful waiting approach until his PSA rose to 31. He then received a 3-month *Lupron*[®] injection without any regard to possible flare and five days later he developed back pain. Radiologic studies showed hydronephrosis on the right side, and then, a cystoscopy revealed a tumor obstructing the right ureteral orifice. A right percutaneous nephrostomy had to be performed to decompress the kidney. Then, a right ureteral stent was placed requiring a 5 hour operation. The patient suffered a massive heart attack two days later. The patient had not been placed on an anti-androgen anytime during his clinical course.

Patient #2 is MB, a 44-year old man diagnosed with PC when he discovered a lump in his neck and a biopsy showed prostate cancer. His first PSA was 5,700, and a bone scan showed disease in the thoracic spine.

He was treated with simultaneous administration of *Lupron*[®] and *Casodex*[®]. There was no pretreatment with *Casodex*[®] to block the flare response that occurs with initiation of any LHRH agonist, be it *Lupron*[®] or *Zoladex*[®]. Two days after his treatment was started, MB experienced excruciating pain in his thoracic spine and had to be rushed by ambulance to the hospital.

He spent five days in the hospital and received a ten day course of radiation therapy to the thoracic spine. A MRI showed no spinal cord compression, but a nerve root was said to be compressed.

Both patients were inappropriately treated. Major precautions need to be taken if there is a significant tumor burden and a risk of clinical flare upon starting a LHRH agonist. The use of *Nizoral*[®] for 48 hours prior to starting *Lupron*[®] or *Zoladex*[®] or more prolonged use of an anti-androgen (as described in the following article) would have been the safer and more medically sound approach to take. ✚

Prevention of Biochemical and Clinical Flare

Jonathan E. McDermed & Stephen B. Strum

What is flare?

We know that when a luteinizing-hormone releasing-hormone agonist (LHRH-A) is first started, it paradoxically causes a rise in the pituitary hormone LH. This LH rise stimulates the testicles to make more testosterone during the first 5-12 days after *initiation* of the LHRH-A than even the

baseline testosterone. This testosterone rise will stimulate prostate cancer cell growth. This is termed "flare".

Why is it important to prevent flare?

Flare can precipitate severe life-threatening symptoms of disease progression in patients

(Continued on page 2)

Genetics	Philosophical Issues (Pages 7, 10)	Political Activism	Pain Control	PC Address Book	Novel Therapies
Nutritional Adjuncts					
Preclinical Phase	Schematic Approach to Topics in Prostate Cancer Insights Version 1.0				Treatment Side-effects (Page 1)
Diagnostic Phase					Systemic Disease
Risk Assessment	Staging or extent of disease	Local Disease (Page 7)	Hormone Blockade (Page 1)	Bone Integrity (Pages 4, 8)	High-risk PC

In This Issue:

- Clinical Flare** 1
- Prevention of Biochemical and Chemical Flare** 1
- The Importance of Tumor Burden** 4
- Key Abbreviations** 6
- Successful Management of Localized PC** 7
- The Intimate Association of Bone Formation & Destruction** 8
- Doing Your "Homework" Quiz** 10
- Conference Registration Form** 11

Prevention of Biochemical and Clinical Flare...continued from page 1

with prostate cancer having subclinical metastatic disease in critical locations. For example, if the cancer is growing close to a nerve root, flare can result in pain in the distribution of that nerve. More importantly, if the PC is close to the spinal cord, flare can result in spinal cord compression and paralysis. If the prostate cancer involves lymph nodes near the ureters (tubes carrying urine from the kidneys to the bladder), flare can increase the size of nodes and cause compression of one or both ureters. If ureteral compression involves both sides, it leads to kidney failure or uremia. This is manifested by elevations in the BUN and serum creatinine laboratory tests. Flare increasing disease in bone can lead to severe bone pain (Patient #2).

What is clinical flare versus biochemical flare?

When tumor flare causes clinical symptoms such as bone pain, compression of a nerve root, spinal cord compression, or blockage of one or both ureters, we use the term *clinical flare*. If the PSA rises as a result of initiating an LHRH agonist (*Lupron*® or *Zoladex*®), but there is no clinical evidence of disease progression, we call this *biochemical flare*. Even so, we prefer to avoid

an increase in PSA and the potential for PC growth regardless of the presence or absence of clinical symptoms.

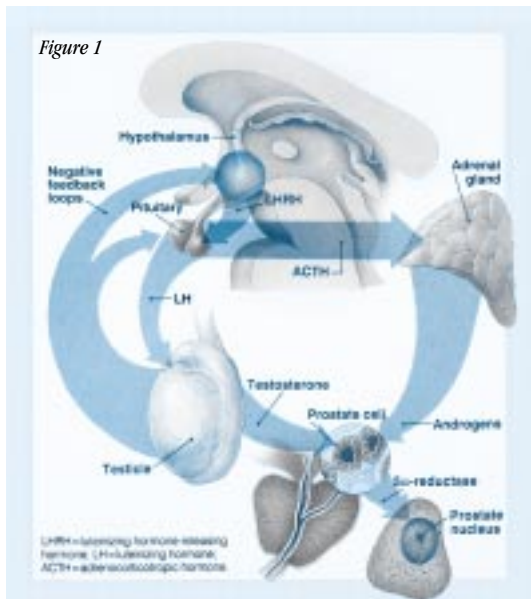
What is the mechanism of flare?

The hypothalamus releases the hormone LHRH which circulates to the pituitary via the hypothalamic-pituitary portal blood system, as shown in Figure 1. The interaction of this *natural* LHRH with the LHRH receptor in the anterior pituitary leads to the production of LH and FSH. This process occurs in the following manner. LHRH binds to the LHRH receptors in the pituitary to form a complex (LHRH_{natural} ↔ LHRH receptor). This complex in turn is broken down by a peptidase-enzyme, releasing LH and at the same time freeing the receptor for more LHRH. This occurs naturally as a result of pulses of LHRH produced by the hypothalamus. This is the process believed to occur with natural LHRH.

One hypothesis as to the mechanism of flare production is that synthetic long-acting LHRH agonists (LHRH-A) such as *Lupron*® or *Zoladex*® bind to the LHRH receptor with a high affinity that is relatively resistant to the action of peptidase. This **binding process results in the release of LH from the receptor leading to biochemical or clinical findings of flare.**

Can we prevent flare?

The administration of an anti-androgen such as flutamide (*Eulexin*®), bicalutamide (*Casodex*®), or nilutamide (*Nilandron*®) prior to beginning LHRH-A treatment (e.g., *Lupron*® or *Zoladex*®) will diminish PSA flare and may prevent clinical symptoms. How do we think this occurs? The anti-androgen sits in the androgen receptor and prevents the interaction of testosterone (T) and dihydrotestosterone (DHT) with the androgen receptor. This is shown in Figure 2, from Labrie et al.¹



Combination Therapy with an LHRH Superagonist and a Pure Antiandrogen

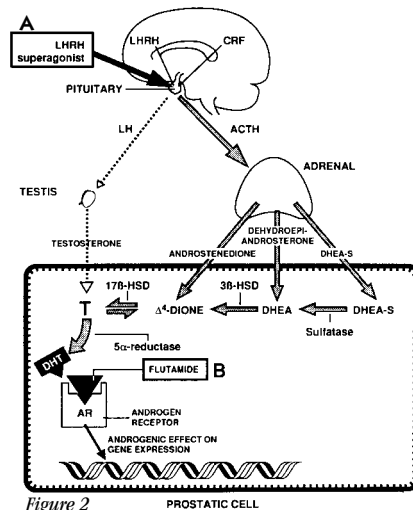


Figure 2

Therefore, *Eulexin*®, *Casodex*® or *Nilandron*® can be used to occupy the androgen receptor in an attempt to block T or DHT from occupying the receptor and initiating DNA synthesis and cell division. The issue is how best to do this. *Eulexin*® has a half-life of less than 8 hours whereas *Casodex*® has a half-life of 6 days. With *Eulexin*®, a steady state or equilibrium is reached in 32 hours (four half-lives) as contrasted to *Casodex*® with which equilibrium is reached in 6 half-lives or 37 days. When these drugs are stopped, it also takes this time to eliminate the respective drug. These considerations must be taken into account in an attempt to prevent flare upon starting the anti-androgen as well as in evaluating the patient for an anti-androgen withdrawal response (AAWR) upon stopping the anti-androgen. In other words, upon stopping *Eulexin*® to observe for an AAWR, it is appropriate to check the PSA 3-7 days later. For *Casodex*®, with its long elimination period, checking would require 6 weeks. No one has studied these agents to see how and when they work to prevent flare. Moreover, little consideration has been given to *Proscar*® to block DHT (which is 4-5 times more potent than T) to further decrease the occurrence of flare.

Other agents can be used successfully to prevent LHRH-A induced flare. These in-

Prevention of Biochemical and Clinical Flare...continued

clude ketoconazole (*Nizoral*®), or DES. Both agents have multiple modes of action. In regard to blocking flare, *Nizoral*® blocks T production whereas DES blocks LH production. There are no modern studies that have reviewed these agents and their effects on PSA production insofar as the prevention of flare.

Can we better understand the flare mechanism?

We propose a study of *Eulexin*® or *Casodex*® in combination with *Proscar*® (finasteride) to understand how best to eliminate biochemical flare. If we eliminate biochemical flare, we eliminate clinical flare. This is our study outline.

Days Before LHRH-A	Blood Levels Obtained	Intervention
Day -7 to -1	baseline PSA, LH, T and daily PSA, LH, T	Give antiandrogen + Proscar®
Day 0 (zero)	LH, T, PSA	Add LHRH agonist
Day +1 to day +14 every 2 days or until PSA, T, LH are stable	LH, testosterone and PSA	Continue antiandrogen + Proscar®
Day +28	Testosterone & PSA levels	Repeat LHRH-A dose

In consenting patients, androgen deprivation therapy will consist of either *Eulexin*® or *Casodex*® plus *Proscar*® starting one week before the first dose of *Lupron*® or *Zoladex*®. Blood levels of LH, testosterone, and PSA will be measured at baseline, on a daily basis prior to LHRH-A, and over the next 14 days following LHRH-A administration. Effective prevention of biochemical flare will be evident if there is no rise in serum PSA. If this study completely prevents biochemical flare, the next logical step would be to determine if this results in a therapeutic advantage for the patient with prostate cancer.

Alternatively, the use of *Nizoral*® to reduce testosterone levels during the first 14 days of ADT could be employed to counteract the increased LH levels normally seen upon initiating an LHRH agonist. Since

Nizoral® works effectively to reduce T within 48 hours, pretreatment with *Nizoral*®, antiandrogen, and *Proscar*®, commencing two days before starting an LHRH agonist, would be reasonable to study as well. In this setting, *Nizoral*® would be continued for two weeks and then discontinued.

In this study we would obtain baseline T, LH and PSA two days before starting the LHRH agonist, commence *Nizoral*®, *Proscar*®, and either *Eulexin*® or *Casodex*® while measuring LH, T and PSA every day. On Day 2, the LHRH agonist is given while continuing to measure LH, T and PSA over the next 14 days or until the PSA and T are consistently falling.

Nizoral for Clinical Flare & its Value in Oncologic Emergencies

In a study by Trachtenberg et al², 13 patients with prostate cancer who initiated high-dose *Nizoral*® treatment had serum hormone levels drawn before and after starting *Nizoral*®. Hormone levels obtained included LH, testosterone, dehydroepiandrosterone (DHEA), androstenedione and progesterone. The results of this study showed that DHEA and androstenedione levels *decreased* while those of progesterone and LH increased by four weeks. No patient sustained an increase in serum testosterone levels.

However, a recent abstract by Wasil et al³ contradicted these observations. In this trial, mild testosterone surges of 11.5% and 17.7% above baseline were noted in 50%

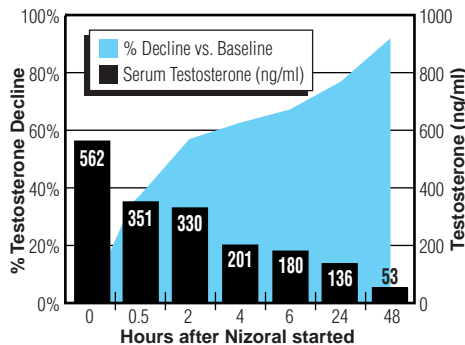
(2/4) of *Nizoral*®-treated patients. The brief rise in testosterone in this small series of patients does not deter us from recommending *Nizoral*® to prevent clinical flare or to acutely lower testosterone levels in an oncologic emergency. Most of such cases were treated by orchiectomy in the past. This achieves castrate levels of testosterone within 3-12 hours (mean 8.6). *Nizoral*® requires 48 hours to reach near castrate levels. [Figure 3, after the work of Trachtenberg et al⁴.]

Summary

The consequences of biochemical flare are unknown, but we cannot imagine that biochemical flare can be good for the patient with PC. Clinical flare can lead to medical emergencies ranging from increased bone pain to ureteral compression and uremia to cord compression and paralysis. The potential to develop any of these problems should be anticipated in men with locally advanced or metastatic bone disease. Measures to prevent biochemical and clinical flare, as outlined above, are mandatory in the proper management of men with PC.

The problems of clinical and biochemical flare are seriously neglected by the majority of physicians initiating treatment with LHRH agonist therapy in the world today. This must be corrected. We urge any patient who has experienced this type of problem to contact the PCRI. We will alert the FDA and request a WARNING label on all LHRH agonists. Alternatively, the use of the new **LHRH antagonists** such as *Abarelix*®^{5,6,7} from Praecis pharmaceuticals may ultimately become the preferred choice of therapy. These agents lower testosterone within 48 hours and reduce testosterone to castrate levels by one week in 76% of patients compared to 0% of patients receiving conventional LHRH agonist therapy.⁸ Unlike LHRH agonists, they do not stimulate LH release with the subsequent increase in testosterone. In the next issue of *Insights*, we will discuss the LHRH antagonists. ❖

Figure 3 Testosterone Decline After Nizoral Administration



The Importance of Tumor Burden as Reflected on Serum PICP, Alkaline Phosphatase and EOD in Relationship to Survival

90% of normal bone matrix is comprised of type I collagen which in essence is the framework of bone. During the formation of type I collagen, type I procollagen is cleaved into type I collagen and PICP. PICP is therefore a bone formation marker. PICP is further broken down or degraded via metabolic pathways in the liver.

The important point is that the serum level of PICP reflects the short-term formation rate of collagen molecules and hence correlates with bone formation. In the PC patient with bone metastases, there is increased bone formation due to increased osteoblastic stimulation. This is due to activation of androgen receptors, uPA receptors, PTHrP receptors, endothelin-1 receptors, IGF-1 receptors and/or other mediators. See Volume 2, No. 1 of *Insights*.

In a paper by Akimoto et al⁹, the use of androgen deprivation therapy (ADT) in men with D₂ PC was studied to see if any relationship could be found between bone formation and bone resorption markers and survival (cause-specific). Significantly longer cause-specific survival was found with low PICP and low alkaline phosphatase (ALP), but univariate analysis showed no correlation with ICTP or PSA levels. With multivariate analysis, the only significant relationship

found was between extent of disease (EOD) on the bone scan and survival. ICTP is another bone resorption marker. The abbreviation stands for carboxy-terminal telopeptide of type I collagen. ICTP is in the family of bone resorption markers along with Dpd and Pd (see Key Abbreviations on page 6).

PICP and ALP reflect the extent of bone metastases—the very same thing that the bone scan does but with less expense and less difficulty. In addition, the findings of Akimoto et al suggest that PICP and ALP are expressing a tumor population that is to some extent sensitive to ADT. Again, this study supports the use of early endocrine therapy since longer survival is related to treating patients with a smaller tumor burden, as expressed by PICP, ALP and EOD. Akimoto's graphs in Figure 4 for PICP and ALP vs. cause-specific survival are very similar.

Akimoto et al point out that pretreatment PSA levels did not predict survival in patients receiving ADT but the **PSA levels at 3 and 6 months after the start of treatment and the percentage decrease in PSA were significantly correlated with long-term outcome**. We would agree that the response of the biologic marker to treatment is an *in vivo* sensitivity test. The percentage decrease in PSA, the time to

Multiple Biomarkers More Accurately Assess Disease Status & Response

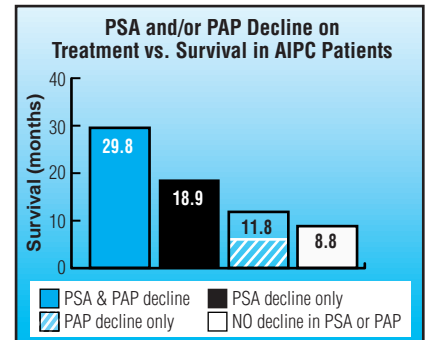


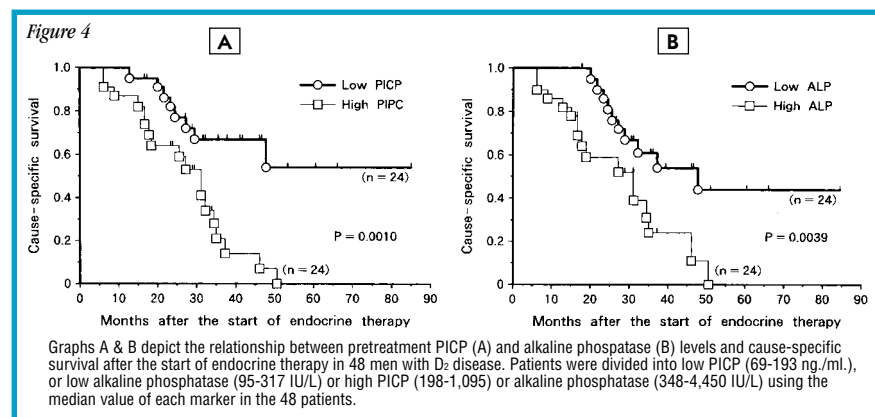
Figure 5

reach an undetectable PSA, and the ability to normalize any other biomarkers should all correlate with the biologic responsiveness of the tumor. In patients with heterogeneous tumor cell populations (multiple clones of tumor cells), the analysis of various biomarkers may provide guidelines to monitor treatment to determine the completeness of response to a particular therapy. This was shown to be the case in the paper by Steineck et al¹⁰ which evaluated PSA and PAP response versus survival in patients with androgen independent PC (AIPC) treated with chemotherapy. The average duration of survival was 29 months in patients with a > 50% decrease to *both* PSA and PAP vs. 19 months if only a PSA response was seen. This is shown in Figure 5.

Extent of disease (EOD), as defined by Soloway et al¹¹ is shown below:

STAGE	DEFINITION
EOD 0	Normal or benign disease only
EOD 1	bone metastases < 6 lesions
EOD 2	bone metastases 6-20 lesions
EOD 3	bone metastases >20 but < super scan
EOD 4	super scan (75% of ribs, vertebrae, pelvic bones have lesions)

A bone lesion is defined as being less than half the size of a vertebral body.



The Importance of Tumor Burden...continued

Labrie et al^{1,12} have also shown a strong correlation between extent of disease and survival in D₂ patients (pts) treated uniformly with an LHRH agonist (*Triptorelin*[®]) and *Eulexin*[®]. Their study showed a 58% survival at eight years with ADT when the pretreatment bone scan showed ≤ 5 bone lesions vs. only a 10-17% survival at eight years if > 5 lesions were found on bone scan. This is shown in Figure 6 and in table format below.

Stage (bone lesions)	# Pts	Rx	Median Survival (years)			
			3	5	8	10
Labrie Flutamide[®] + Lupron[®] vs number of bone lesions on median survival						
D2 (11-40)	50	ADT2 (EL)	45	18	10	
D2 (6-10)	45	ADT2 (EL)	59	30	17	
D2 (1-5)	105	ADT2 (EL)	82	66	58	

(Please also note that we are trying to use a standard nomenclature when describing ADT. ADT refers, of course, to androgen deprivation therapy. ADT₂ refers to two drug combination, and EL refers to the use of *Eulexin*[®] and *Lupron*[®] given in that order. Therefore, this indicates that the physician was cognizant of potential problems with flare and gave the *Eulexin*[®] prior to the *Lupron*[®] or *Zoladex*[®].) We would designate 3-drug ADT as ADT₃ EPL if *Proscar*[®] was the third drug added to this regimen.

The Intergroup #0036 data showed the effect of tumor burden on the efficacy of ADT₂ vs. monotherapy (*Lupron*[®] or orchiectomy) in D₂ patients. The median survival was almost 20 months greater with ADT₂ over that with monotherapy if minimal disease was seen on scan and the ECOG performance status was 0-2.^{13,14}

The definitions of minimal and maximal disease and the ECOG scale are shown in the following column. The actual median survivals were 61 months with ADT₂ vs. 42 months with monotherapy. The median progression-free survival was 48 months with ADT₂ vs. 19 months on the monotherapy arm with a median follow-up period of greater than five years.¹⁴

Minimal disease = axial skeleton (spine) and/or pelvic bones or nodes

Maximal disease = above + appendicular skeleton (ribs, skull, long bones) or visceral disease (lungs, liver)

ECOG Performance Status

- 0 = asymptomatic
- 1 = restricted in strenuous activity but can do light work
- 2 = up and about more than 50% of the time; unable to do work activities
- 3 = bedridden more than half the time
- 4 = completely disabled, totally confined to bed

It is unfortunate that the EOD used by Soloway or Labrie was not used in the Intergroup trial to confirm the findings of Soloway and/or Labrie et al. To this date, there is no uniform grading of bone scan findings to evaluate response to therapy.

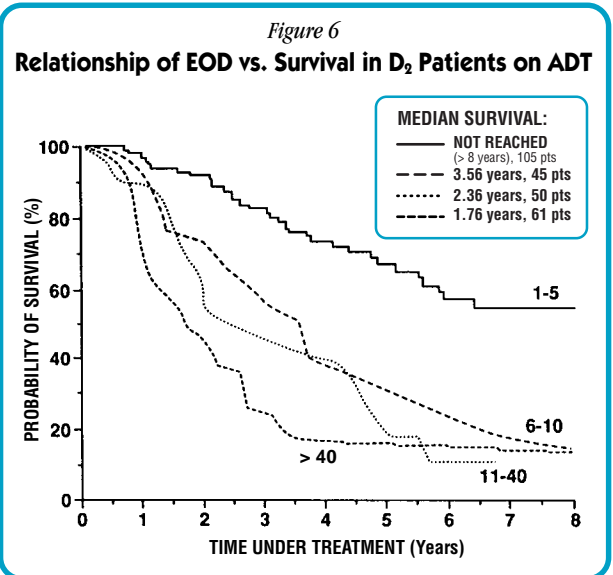
The take-home lessons of this section are the following:

- ❖ *Extent of disease on bone scan is a significant variable that must be accounted for in studies evaluating treatment in men with metastatic bone disease.*
- ❖ *Abnormalities in bone formation markers such as PICP and alkaline phosphatase appear to mimic the findings of EOD on bone scan and should be studied to see if they could replace bone scanning as a staging and response indicator.*
- ❖ *Tumor burden, as seen in the number of osseous metastases, may have a critical threshold that relates to the ability of the patient to respond to ADT or perhaps to the occurrence of androgen independent clones*

of cells that are ex-pressed as tumor volume increases.

- ❖ *We need clues in the form of biomarkers that forecast both the occurrence and the responsiveness of these bone metastases.*
- ❖ *Our studies suggest that the inability to reach an undetectable PSA may indicate either an androgen receptor mutation or more commonly the presence of AIPC. In other words, the response to PSA (and other markers) is an in vivo test evaluating the sensitivity of the tumor cell population to the therapy employed.*
- ❖ *In the presence of multiple biomarker abnormalities (e.g. PSA and PAP), all biomarkers should show evidence of response to result in more durable responses to therapy. We should be looking for a biomarker panel to indicate complete responsiveness of the tumor cell population(s) that we are treating. The other markers represent additional disease populations that may be different in nature and may require different treatment, e.g. chemo-*

(Continued on page 6)



The Importance of Tumor Burden...continued from page 5

therapy or immunotherapy.

- ❖ We have early evidence that suggests that lack of normalization of Dpd in patients on ADT and bisphosphonates such as Aredia® or Fosamax® may indicate PC clones resistant to ADT, suggesting the need for chemotherapeutic intervention. This should not come as a surprise since osteoblastic stimulation is coupled intimately with osteoclastic activity with resultant expression of bone resorption markers such as Dpd. Therefore, high PICP or alkaline phosphatase levels or EOD should be correlated with increased bone resorption activity. This work needs formal confirmation. ❖

PCRInsights

Editor-In-Chief: Stephen Strum, MD
Editor: Charles Bader
Review Board: Stephen Strum, MD
Harry Pinchot
Jon McDermed, PharmD

Publisher: The Prostate Cancer Research Institute

Prostate Cancer Research Institute
5777 Century Boulevard, Suite 885
Los Angeles, CA 90045
Helpline: (310) 743-2110
FAX: (310) 743-2113
Website: www.prostate-cancer.org

Executive Director: Jim Goyjer, MA
Phone: (310) 743-2116
E-mail: pcri_goyjer@earthlink.net

BOARD OF DIRECTORS

Stephen Strum, M.D., Co-Founder,
Healing Touch Oncology

Mark Scholz, M.D., Co-Founder,
Healing Touch Oncology

George Pressler, President,
Planning Decision Resources

Jerome Seliger, Professor of Health Administration,
California State University, Northridge

Chester Swenson, President & CEO, Marketing
& Financial Management Enterprises

This newsletter was made possible through the generous support of Freeman Hospitals Foundation and through an unrestricted educational grant from Amgen Inc.

Key Abbreviations

- AA:** the usual designation for anti-androgens but often used also to indicate adrenal androgens or arachidonic acid (therefore be aware of the context of this abbreviation)
- AAWR:** anti-androgen withdrawal response; a maneuver used to evaluate the presence of an androgen receptor mutation or ARM
- ADT:** androgen deprivation therapy; any treatment that decreases the availability of male hormones to the prostate cancer cell population
- AIPC:** androgen-independent PC; a tumor cell population that grows independently of male hormones
- BPH:** benign prostatic hyperplasia
- CBC:** complete blood count; this includes the white blood cells, red blood cells, and platelets
- DES:** diethylstilbestrol; a synthetic estrogen
- DHEA:** dehydroepiandrosterone; an adrenal androgen precursor
- DHEA-S:** dehydroepiandrosterone sulfate; the sulfated and more stable metabolite of DHEA
- DHT:** dihydrotestosterone; the active metabolite of testosterone, five times as potent
- Dpd:** deoxyypyridinoline (*Pyrilinks-D*®); a bone resorption marker reflecting breakdown of bone collagen
- EBRT:** external beam radiation treatment that can include conventional photons, or use protons, neutrons or electrons. This may be given conventionally or with 3D conformal techniques
- ECOG:** Eastern Cooperative Oncology Group; one of the clinical trials groups
- ET-1:** endothelin-1; a prostate cell product that stimulates osteoblasts, acts as a vasoconstrictor, and may be responsible for bone pain in metastatic prostate cancer
- EOD:** extent of disease; part of what should be a standard approach to staging the bone scan
- FSH:** follicle stimulating hormone; in the male, it stimulates the Sertoli cells of the testicles to make sperm
- ICTP:** carboxy-terminal telopeptide of type 1 collagen; a bone resorption marker like Dpd
- IGF-1:** insulin growth factor 1; a growth factor that stimulates PC cell growth and osteoblast growth
- IL-1:** interleukin 1 (see Vol. 2, No.1 of *Insights*); facilitates osteoblast growth among its many functions
- IL-6:** interleukin 6 (see Vol. 2, No.1 of *Insights*); stimulates osteoclast precursors and mature osteoclasts
- LH:** luteinizing hormone; pituitary hormone that stimulates the Leydig cells of the testicles to make testosterone
- LHRH:** Luteinizing hormone-releasing hormone (also known as GnRH or gonadotrophin releasing hormone); a hormone from the hypothalamus that interacts with the LHRH receptor in the pituitary to release LH
- LHRH-A:** LHRH agonist; mimics natural LHRH but then shuts down LH production after continuous exposure
- MMP-2:** matrix metalloproteinase 2; PC cell product involved in angiogenesis
- Pd:** pyridinoline; a bone resorption marker; a bone collagen breakdown product
- PICP:** carboxy-terminal propeptide of type 1 procollagen; a bone formation marker
- PTHrP:** parathyroid-related protein; a protein involved in osteoblast stimulation; a product also of the PC cell elaborated by neuroendocrine cells that make CGA (chromogranin A)
- RP:** radical prostatectomy
- RT:** radiation therapy which may be external beam with photons, protons, neutrons, electrons, or internal radiation with permanent seed implants, or temporary wire implants (HDR)
- SI:** seed implantation, a form of brachytherapy that uses permanent radioactive iodine or palladium seeds to deliver ionizing radiation
- T:** testosterone; the major male hormone or androgen produced mostly by the Leydig cells of the testicles
- TGF-β:** transforming growth factor beta; a bone-derived growth factor that stimulates the PC cell and osteoblast, among many other functions
- uPA:** urokinase-like plasminogen activator; a protease or digestive enzyme that is made by the PC cell, stimulates PC cell and osteoblast growth, and is involved with invasion and metastasis

These definitions are not exhaustive descriptions of the above items. They are a concise explanation of what you should know to understand these terms as used in the context of this issue of Insights. ❖

❖ ❖ ❖ The Successful Management of Localized PC ❖ ❖ ❖

The three basic ingredients that relate to the success of any treatment are:

- 1) Selection of the patient,
- 2) Preparation of the patient, and
- 3) Choice of an artist or artists to do the treatment(s).

Selection of the Patient

Selection of the patient in this context involves an accurate assessment of the patient's true status. Knowing where the PC may have spread gives direction to the patient-physician team to perform certain tests to exclude disease at the indicated site(s). For example, if the algorithms show a high risk for lymph node disease, the staging process should include the ProstaScint monoclonal antibody scan. If the risk is negligible for lymph node involvement, this study could be excluded. The same approach is used to evaluate disease at the different stations of involvement. This is shown in Figure 7.

Is there extra-capsular extension (ECE), or seminal vesicle (SV) involvement? Are the lymph nodes (LN) or the bones involved? If one finds a high probability of disease confined to the prostate, then local therapies such as RP, RT (either external beam using 3D conformal techniques, or seed implantation, or a combination of both), or cryosurgery can be used with a greater probability of success. However, there are caveats that relate to the successful use of these therapies as well.

Preparation of the Patient

Preparation of the patient refers to what we can do to increase the likelihood of success with any PC therapy. Treatment with RT is limited by tumor volume. We can reduce tumor volume by using androgen deprivation therapy. ADT employs drugs that lower the testosterone level as well as other androgens such as dihydrotestosterone (DHT)

and adrenal androgen precursors such as DHEA-S and androstenedione. Most commonly, ADT involves the use of anti-androgens (AA) coupled with LHRH agonists (LHRH-A). Examples of AA include Flutamide (*Eulexin*®), Bicalutamide (*Casodex*®) and Nilutamide (*Nilandron*®). Examples of LHRH-A include *Lupron*® or *Zoladex*®. AAs are oral agents given on a daily basis while LHRH-As are given intramuscularly or subcutaneously as long-acting depot injections on a monthly, or every 3-to-4 month basis. It is critical to the proper use of the LHRH-A that the AA is given for one week before initiating the LHRH-A to prevent flare. Flare is characterized by an initial increase in release of LH from the LHRH receptor that is eventually blocked by the LHRH-A. This is described in the article on Clinical and Biochemical Flare (beginning on page 1). We believe that finasteride (*Proscar*®) is an important addition to ADT.¹⁵

Monitoring of ADT

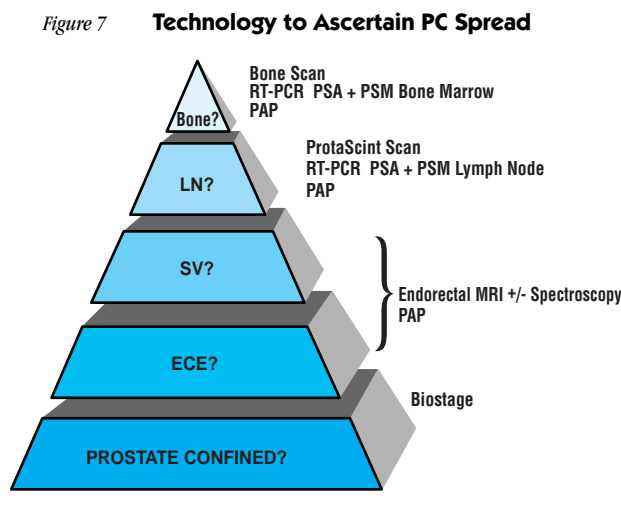
Patients receiving combination hormone blockade using the above drugs need to be monitored with chemistry panels, complete blood count (CBC), testosterone, and PSA levels on a monthly basis. Both *Eulexin*®

and *Casodex*® can cause elevations in the liver enzymes SGOT and SGPT. With monthly monitoring, the risk of significant liver toxicity is minimized. In addition, the avoidance of alcohol and the use of silymarin (100-200 mg three times a day) will prevent toxicity to the liver cell or hepatocyte. The CBC checks the hematocrit to monitor the anemia of androgen deprivation that occurs in 80% of men on ADT.¹⁶ In cases where the anemia is severe, the use of erythropoietin (*Procrit*®) will correct this problem and alleviate symptoms of fatigue, shortness of breath and possibly angina.¹⁷

Rationale for ADT

The rationale for the use of ADT is to reduce tumor volume to allow RT to be more effective. The efficacy of RT is compromised when the PC volume is too great to allow RT to effectively eradicate the total tumor cell population. ADT reduces the tumor volume, synergizes with RT, and decreases angiogenesis to allow for a better outcome with RT. This has already been reported in the landmark paper by Bolla et al¹⁸ which employed RT with 3 years of LHRH agonist therapy to treat high grade Gleason score lesions (GS 8-10) or locally advanced PC (CS T3-4).

The literature on the use of ADT in patients with a lower clinical stage and lower GS is currently being written and appears to validate the use of ADT to allow RT to be more effective.¹⁹ Studies are being published that now show the equivalence of RT techniques



(Continued on page 10)

The Intimate Association of Bone Formation and Destruction: Osteoblast And Osteoclast Functions Are Closely Linked

Pyrilinks-*D*[®] (deoxypyridinoline, or Dpd, collagen cross-link excretion levels) was discussed in Volume 2, No. 1 of *Insights* as an important marker of bone breakdown. Takeuchi et al²⁰ studied Dpd and pyridinoline (Pd) cross-links as well as osteocalcin (a bone formation marker) and alkaline phosphatase in three groups of patients. Group I had 28 BPH patients, Group II had 19 clinically localized PC patients and Group III had 28 patients with bone metastases.

Alkaline Phosphatase as a Marker of Osteoblastic Activity

Takeuchi et al showed positive correlations between metastatic PC and abnormal alkaline phosphatase and a similar correlation between Pd and Dpd and bone metastases. No such relationship was seen with osteocalcin. **Patients with BPH or clinically localized PC had no elevation of Pd or Dpd.**

Alkaline phosphatase is normally elevated during adolescence during the period of rapid bone growth. Most scientists therefore regard alkaline phosphatase as a marker of osteoblastic activity. We now know that the PC cell makes various substances that stimulate the osteoblast, e.g. uPA, PTHrP, Endothelin-1, TGF β . Therefore, it is not surprising to see bone changes that reflect this increase in osteoblastic activity. Examples are increased uptake on the bone scan and the appearance of dense (sclerotic) bone metastases. **Elevations of alkaline phosphatase, in the setting of PC, are due to osteoblastic metastases stimulated by PC cell products and by bone-derived growth factors until proven otherwise.**

Coupling of Osteoblastic and Osteoclastic Activities

Normally, osteoblastic and osteoclastic activities are intimately linked. Where there is bone erosion at specific remodeling sites, there are osteoblasts laying down new bone as part of the repair mechanism. When osteoclastic activity exceeds osteoblastic bone formation, excessive bone resorption or solubilization (dissolution of bone) results in bone loss. If this is moderate bone loss (>1 but < 2.5 standard deviations below normal), then osteopenia is present. If it is >2.5 standard deviations below normal, then osteoporosis is present. In PC, the increased osteoblastic activity results in increased osteoclastic activity since the osteoblast makes or utilizes various cell products that stimulate the osteoclast. These include interleukin-6 (IL-6) and interleukin-1 (IL-1). The increase in osteoclast activity is also manifested by increased bone collagen breakdown products, namely Pd and Dpd. **In fact, at diagnosis, the only patients with elevated Pd or Dpd were those with bone metastases.** No patients with BPH and only 1 patient with clinically localized PC had an elevated Dpd or Pd. In this patient, the result was just above the upper limit of normal.

In other words, if you were a newly diagnosed patient with PC and were found to have an elevated Pd or Dpd, there would be greater concern about the presence of bone metastases than if the Pd or Dpd were normal.

This statement is true in the setting of a newly diagnosed and untreated patient. Patients undergoing ADT will frequently have elevated Dpd as a reflection of excessive bone resorption due to androgen deprivation.

Of the 28 patients with bone metastases (Group III), 25 or 89.3% had urinary Pd levels that exceeded two standard deviations above the mean urinary Pd (41.9 pmol/ μ mol. creatinine).

If these relationships are operative, the extent of the bone metastases should correlate with these markers: alkaline phosphatase, Pd and Dpd. Takeuchi et al have shown this to be true. As shown in Figure 8 (page 9), modified from Takeuchi et al, **there are statistically significant correlations between the extent of metastatic bone disease (EOD) per Soloway¹¹ (see page 4) and Pd, Dpd, and alkaline phosphatase. No such correlation was found with osteocalcin or with PSA.**

In this study, serum alkaline phosphatase, urinary Pd and Dpd were correlated with EOD with p values of p<0.0008, p< 0.0001, and p< 0.0001, respectively.

As the EOD increased from 1 to 4, the urinary breakdown products of bone increased likewise, as did alkaline phosphatase. Perhaps the sequence of events here is increased tumor cell activity leading to high levels of uPA, PTHrP, and ET-1 that leads to stimulation of the osteoblast followed by production of IL-6 that recruits new osteoclasts and also increases mature osteoclast activity.

In 20 of 28 patients who had a clinical response to endocrine therapy in this study, there was an upward trend in alkaline phosphatase, Dpd, and Pd at one month. This

The Intimate Association of Bone Formation and Destruction... *continued*

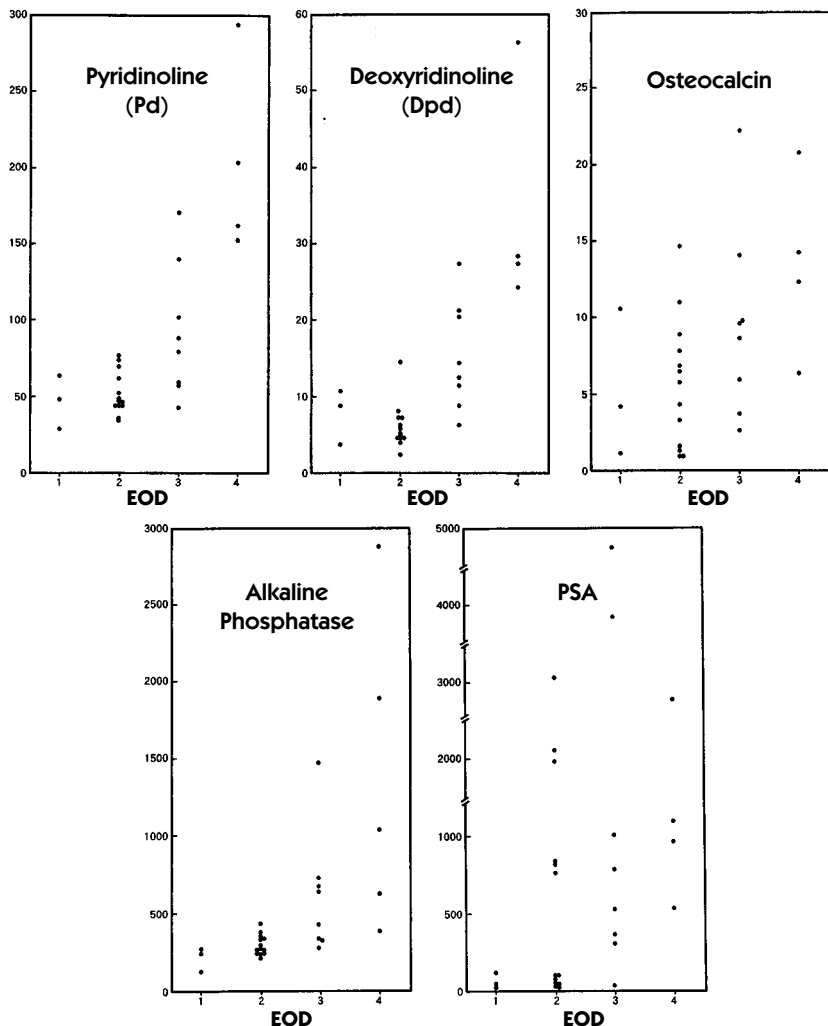
was followed by a downward trend thereafter. In eight patients with progressive disease, there was no paradoxical increase in these markers at approximately one month. The increase in alkaline phosphatase and other bone markers such as PIGP have been reported elsewhere. In a review of our patients presenting with bone metastases and responding to ADT, we find fluctuations in alkaline phosphatase up and down in the first 3-4 months of therapy followed by a persistent downward trend in alkaline phosphatase that may take years to finally reach a new low steady state. Since osteoblastic and osteoclastic activity are coupled, it would not

be surprising to see elevations or declines in alkaline phosphatase mirrored by similar changes in Dpd and Pd in patients receiving endocrine therapy.

Why, however, do we see the upward trend in these markers in the first 3-4 months of treatment in patients who are responding to treatment? This latter puzzle needs to be solved. In our patients, we have avoided flare secondary to institution of an LHRH agonist by pretreating patients for one week with an anti-androgen. Therefore, flare is not the explanation. Does anyone have a reference that answers this puzzle? Let us know and we will publish the findings. ❖

Figure 8

Bone Markers vs. EOD at Diagnosis²⁰



Learn from the Experts

Israel Barken • Donald Coffey
 Anthony D'Amico • Tia Higano
 Mark Moyad • Snuffy Myers
 Robert Nagourney • Alan Partin
 Oliver Sartor • Mark Scholz
 Stephen Strum • Eric Small
 Ash Tewari

**They'll all be at the
 PCRI National Conference**
(see page 12)

Upcoming Events

Midwest Prostate Symposium
 Somerset Inn
 Troy, Michigan
May 22-23, 1999
 To Register, call:
 (248) 652-5611

❖ ❖ ❖ ❖ ❖

**UCSF Cancer Center
 Annual Symposium
 Focusing on Prostate Cancer**
 Cole Hall – UCSF Main Campus
 San Francisco, California
May 25, 1999
 To Register, contact:
 MJ Norman (415) 502-5190 or
 Amy Barach (415) 476-8790

❖ ❖ ❖ ❖ ❖

**2nd International
 Prostate Cancer
 Symposium for the Patient**
 University of Michigan
 Ann Arbor, Michigan
July 17-July 18, 1999
 To Register, call:
 (800) 949-3434

The Successful Management of Localized PC...continued from page 7

such as external beam RT or seed implantation when compared to similarly selected patients who undergo RP. In such good risk patients, the 10 year actuarial disease-free survival rates are about 80%. This means that there is no evidence of biochemical relapse as seen by a rising PSA in 80% of these patients at an actuarial time of 10 years. It is not surprising that this equivalence to RP is being seen with RT when the tumor volume is being controlled by selecting patients with low levels of PSA and Gleason scores that reflect a lower tumor burden.

There are many fine points that relate to the above discussion. Limitations of space do not allow for all of these to be dealt with in this overview. Vol.1, No. 1 and Vol.2, No.1 of *Insights* have examples of how a patient can proceed in a step-wise fashion in the evaluation of his disease; *Insights* can be printed off our homepage.

In lieu of immediate RP, RT or cryosurgery, PC patients may want to consider protocols that incorporate combined androgen deprivation for temporary control of most prostate cancers. In essence, this is the primary use of hormone manipulations to control PC growth. Innovative natural adjunctive therapies are also implemented immediately upon the initiation of ADT or any anti-cancer therapy. Ideally, many of these adjunctive therapies should be utilized in a preventative fashion.

Choice of an Artist to do the Treatment

All treatments in cancer medicine are associated with a skill factor. In this respect, a treatment should be regarded as the “message” with the physician performing them regarded as the “messenger” for that specific treatment or therapy. Not all urologists can do a radical prostatectomy with an equal degree of excellence nor do all radiation or

medical oncologists have equivalent skills.

When we became super-selective in our choice of consultants for RP, SI & EBRT, the incidence of adverse side-effects changed drastically. For example, the 40-50% incontinence rates that we had previously seen after RP became <1% when we directed patients to the very best urologists.

Newer procedures, such as cryosurgery, have even fewer highly skilled physicians able to perform this treatment without a significant risk of leaving the patient with serious complications.

We have heard physicians make derisive remarks about cryosurgery when in our experience with this modality it is usually the ill-talented physician that causes the complications and the lack of efficacy, not the procedure.

Never get the message and the messenger confused. ❖

Doing Your “Homework”

One ingredient, not often mentioned, in the successful evaluation and treatment of prostate cancer involves the co-partnership of the patient and doctor teams. On the patient side, co-partnership responsibilities include: understanding the illness, maintaining your medical records, enhancing communication between everyone involved in your care and being involved in all activities that improve your understanding of prostate cancer so that prostate cancer will not be a threat to any man's life. The physician and patient must do their “homework”. Let us see if you understood some of the important points that were presented in this issue of *Insights*. The answers are on page 11.

1. There is no difference in survival if you treat patients with D₂ disease early or late because there is no correlation between tumor burden and response to ADT. **True or False?**
2. Abnormalities in bone formation markers such as PICP and alkaline phosphatase mimic the findings of EOD on bone scan and should be studied to see if they could replace bone scanning as a staging and response indicator. **True or False?**
3. The inability to reach an undetectable PSA may act as a test to evaluate the tumor cells' sensitivity to the therapy employed. **True or False?**
4. In the presence of multiple biomarker abnormalities such as PSA and PAP, both biomarkers should show evidence of response to result in a more durable response to therapy. **True or False?**
5. A newly diagnosed untreated patient with PC found to have an elevated Pd or Dpd should not be worried about bone metastases. **True or False?**
6. The EOD (extent of disease) seen on bone scan does correlate with Dpd, Pd and alkaline phosphatase. **True or False?**
7. An increase in alkaline phosphatase and/or Dpd or Pd at 1-3 months after starting ADT in patients with D₂ disease indicates treatment failure. **True or False?**
8. Flare can be prevented by all of the following means: pretreatment with an anti-androgen for at least one week prior to starting the LHRH agonist, use of an LHRH antagonist, use of Nizoral starting 48 hours prior to the LHRH agonist, or use of saw palmetto. **True or False?**
9. Clinical flare is best treated with radiation therapy. **True or False?**
10. Concerns for severe flare reactions are of more concern when the baseline tumor burden is high. **True or False?**

References:

1. Labrie F, Belanger A, Dupont A, et al: Science behind total androgen blockade: from gene to combination therapy. *Clin Invest Med* 16:475-492, 1993.
2. Trachtenberg J: Ketoconazole therapy in advanced prostatic cancer. *J Urol* 132:61-4, 1984.
3. Wasil T, Kreis W, Budman D et al: Rapid fall in serum testosterone levels with oral ketoconazole. *Proc Am Soc Clin Oncol* 16:347a, 1997.
4. Trachtenberg J, Halpern N, Pont A: Ketoconazole: a novel and rapid treatment for advanced prostate cancer. *J. Urol* 130:152-153, 1983.
5. Menon M, Glode LM, Martin K, et al: Abarelix (PPI-149), a novel and potent GnRH antagonist, induces a rapid and profound reduction in testosterone and PSA in advanced prostate cancer patients. *J Urol* 159:334A, 1998.
6. Garnick MB, Gittelman M, Steidel C, et al: Abarelix (PPI-149), a novel and potent GnRH antagonist, induces a rapid and profound reduction in prostate gland volume (pgv) and androgen levels before brachytherapy (BT) or radiation therapy (XRT). *J Urol* 159:220A, 1998.
7. Garnick MB, Campin M, Kuca B, Tomera K: PSA kinetics: rates of decline are significantly more rapid following therapy with the GnRH antagonist Abarelix-Depot (A-D), compared to superagonists Lupron® (L) and Zoladex® (Z) in prostate cancer (PrCa) patients (pts). *J Urol* 161:98, 1999.
8. Garnick MB, Tomera K, Campion M, Kuca B: Abarelix-Depot (A-D), a sustained-release (SR) formulation of a potent GnRH pure antagonist in patients (pts) with prostate cancer (PrCa): phase II clinical results and endocrine comparison with superagonists Lupron® (L) and Zoladex® (Z). *J Urol* 161:340, 1999.
9. Akimoto S, Furiya Y, Akakura K, et al: Inability of bone turnover marker as a strong prognostic indicator in prostate cancer patients with bone metastasis: comparison with the extent of disease (EOD) grade. *Prostate* 38:28-34, 1999.
10. Steineck G, Kelly WK, Mazumdar M, Viamis V, Schwartz M, Scher HI: Acid phosphatase: defining a role in androgen-independent prostate cancer. *Urology* 47(5):719-26, 1996.
11. Soloway MS, Hardeman SW, Hickey D, Raymond J, Todd B, Soloway S, Moinuddin M: Stratification of patients with metastatic prostate cancer based on extent of disease on initial bone scan. *Cancer* 1988;61:195-202.
12. Labrie F, Dupont A, Cusan L, Gomez J & Diamond P: Major advantages of "early" administration of endocrine combination therapy in advanced prostate cancer. *Clin. Invest. Med.* 16:6493498, 1993.
13. Crawford ED, Eisenberger MA, McLeod DG, et al: A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. *N Engl J Med* 321:419-424, 1989.
14. Eisenberger MA, Crawford ED, Wolf M, et al: Prognostic factors in stage D2 prostate cancer; important implications for future trials: results of a cooperative Intergroup study (INT.0036), *Sem Oncol* 21:613-619, 1994.
15. Scholz M, Strum S, McDermed J: Intermittent androgen deprivation (IAD) with finasteride (F) during induction and maintenance permits prolonged time off IAD in localized prostate cancer (LPC). *J Urol* 161:156A, 1999.
16. Strum SB, McDermed JE, Scholz MC, et al: Anemia associated with androgen deprivation (AAD) due to combination hormone blockade (CHB) responds to recombinant human erythropoietin (r hu-EPO). *J Urol* 157:232 1997. (abstract).
17. Strum SB, McDermed JE, Scholz MC, et al: Anaemia associated with androgen deprivation in patients with prostate cancer receiving combined hormone blockade. *Br J Urol*; 79(6): 933-41, 1997.
18. Bolla M, Gonzalez D, Warde P et al: Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med* Vol 337: 295-300 1997.
19. Zelefsky MJ, Lyass O, Fuks Z, et al: Predictors of improved outcome for patients with localized prostate cancer treated with neoadjuvant androgen ablation therapy and three-dimensional conformal radiotherapy. *J Clin Oncol* 16:3380-3385, 1998.
20. Takeuchi S, Arai K, Saitoh H, et al: Urinary pyridinolone and deoxy pyridinolone as potential markers of bone metastasis in patients with prostate cancer. *J Urol* 156:1691-1695, 1996.

Answers to Quiz "Doing Your Homework"

on page 10:

1. **False.** Labrie
2. **True.** Akimoto
3. **True.** Strum, Scholz
4. **True.** Steineck
5. **False.** Takeuchi
6. **True.** Takeuchi
7. **False.** Takeuchi
8. **False.** McDermed & Strum
9. **False.** McDermed & Strum
10. **True.** McDermed & Strum

PCRI NATIONAL CONFERENCE REGISTRATION FORM

Name _____ Spouse/Significant Other Name: _____

Street Address: _____

City: _____ State: _____ Zip: _____

Phone: () _____ Fax: () _____ E-mail: _____

Registration Payment: \$75.00 Attendee \$65.00 Spouse

Saturday Evening Dinner: \$20.00 per person additional

Please Register me for the PCRI National Conference '99: My check is enclosed (payable to PCRI)

Please Bill me for the PCRI National Conference '99: American Express MasterCard VISA

Account Number: _____ Expiration Date: _____

Cardholder Name: _____ Cardholder Signature: _____

Total Amount: _____

Mail your completed registration form and your check to:

Prostate Cancer Research Institute

5777 W. Century Blvd., Suite 885

Los Angeles, CA 90045

Or Fax your completed registration form to:

FAX (800) 370-5370

Telephone registration with credit card:

(800) 370-4370

❖ ❖ PLEASE RETURN THIS FORM ON OR BEFORE JUNE 1, 1999 ❖ ❖

IF YOU NEED ANOTHER REGISTRATION FORM, SEE OUR WEB PAGE AT: www.prostate-cancer.org

PCRI Moves To New Quarters

Due to increased demand for PCRI's services, the Institute has moved to larger offices. PCRI is now located conveniently near Los Angeles International Airport. Our research staff, our Helpline, and our administration can now be reached at:

5777 W. Century Boulevard, Suite 885
Los Angeles, CA 90045



The new **Helpline** number is 310-743-2110
our **FAX** number is 310-743-2113

and you can reach **Executive Director Jim Goyjer** at 310-743-2116



So direct your requests for information or service
and any donations to our new quarters.

You'll find us most responsive.

*Thank you Daniel Freeman Hospital for your generous
donation of office furniture to the PCRI.*

“ *The goal of the PCRI is to end
the threat of prostate cancer
to any man's life.* ”

Companies as well as individuals share that goal and have made their support tangible through donations. Among the companies have been Amgen, Pfizer, and the Freeman Hospitals Foundation, as well as many, many individuals.

If you would like to help us in our work toward this goal, send your tax-deductible donation payable to “PCRI” to:

Prostate Cancer Research Institute
5777 W. Century Boulevard, Suite 885
Los Angeles, CA 90045

PCRI is also accepting property donations from interested donors throughout the U.S. If you wish to make a tax-deductible donation of jewelry, art, real estate, or other property, call toll-free 1-800-203-2940.

If you live in Southern California, consider donating an automobile. You may well find that your tax savings may approach your car's trade-in value and relieve you of the bother of selling it. We offer free towing for donated cars anywhere in Southern California. Free appraisals are included. Just call toll-free 1-800-203-2940.

DON'T MISS PCRI'S PROSTATE CANCER CONFERENCE

The millennium is coming closer and so is **PCRI'S PROSTATE CANCER CONFERENCE OF THE MILLENNIUM**. Reservations for this important national conference have surpassed all our projections at this time. Patients with prostate cancer, their spouses, physicians and researchers, and other healthcare professionals are demonstrating keen interest in this unique conference.

Internationally recognized prostate cancer research and treatment pioneer Dr. Stephen Strum has assembled top prostate cancer specialists from around the country for this two-day conference at the Long Beach (CA) Convention Center on **July 31 and August 1, 1999**.

The two days will be filled with seminars led by experts who will provide information on leading-edge developments in the field.



This is your conference. Learn new facts about diagnostic techniques, treatment options, nutrition, quality of life, and other advances in the understanding of prostate cancer that can affect your life.

Attendance is limited, so use the registration form on page 11 and register now.

PCRIInsights

is published by:

The Prostate Cancer Research Institute
5777 W. Century Boulevard, Suite 885
Los Angeles, CA 90045

Non Profit Org.
U.S. Postage
PAID
Inglewood, CA 90311
Permit No. 166