

Bone Integrity Affects the Natural History of Prostate Cancer

Much of this issue of *Insights* is devoted to an in-depth discussion of bone integrity. Why so much emphasis on bone? Every so often I come across a topic in PC that rivets my attention. Bone integrity and the factors that relate to growth of PC in bone, why PC spreads to bone, the nature of bone pain from PC and the issue of prevention of bone metastases by changing the micro-environment are important pieces in the puzzle of what we need to solve about PC. Bear with me and read through this issue.

In the last issue of *Insights*, we discussed three concepts relating to bone integrity:

- ❖ **Bone Formation**
- ❖ **Bone Resorption**
- ❖ **Bone Density**

We used the analogy of the bone as a bank account with bone density being the balance, and formation and resorption being deposits and withdrawals, respectively.

When excessive bone resorption persists, a loss in bone mass results. If unchecked, it eventually leads to osteoporosis.

Osteoporosis is a critical health issue in the United States; 1 of 2 women and 1 of 8 men older than 50 years of age are expected to have bone fractures. The cost of osteoporotic related illness in the United States is \$38 million dollars a day or \$14 billion dollars each year. The ratio of bone fractures for men becomes significantly higher when men are subjected to castration since the abrupt decrease in androgens is analogous to what women experience at menopause at the time of abrupt decrease in estrogens. Male menopause is induced by androgen deprivation therapy (ADT), be it from surgical castration, the use of an LHRH agonist like *Lupron*® or *Zoladex*®, or sequential androgen blockade (SAB) using an anti-androgen (*Casodex*®, *Eulexin*®, or *Nilandron*®) with a 5 alpha reductase inhibitor (*Proscar*®).

ADT is an abrupt event. It results in more osteoporosis and related fractures than that observed during natural male menopause. Male menopause induced by castration, from any cause, is an accelerated, compressed, and intensified menopause in contrast to natural menopause,

where a gradual loss of androgens occurs over decades.

In men with prostate cancer undergoing ADT, bone resorption begins immediately. This has been documented in publications looking at the alterations of bone architecture as a result of orchiectomy¹⁻⁵ as well as a side effect of LHRH agonist therapy.⁶⁻⁸

Orchiectomy Causes More Bone Loss Than LHRH Agonists

Compared to orchiectomy, there is a preferential preservation of bone mineralization and less loss of bone osteoid with the use of LHRH agonists. When orchiectomy is performed, the body reacts to the loss of testosterone by stimulating the pituitary to release LH and FSH. The high levels of FSH and LH are also associated with increased levels of ACTH (adrenocorticotrophic hormone) produced by the pituitary with consequent increased levels of cortisol. It is the increased cortisol levels that suppress the osteoblast (the cell that lays down osteoid to initiate new bone formation). These

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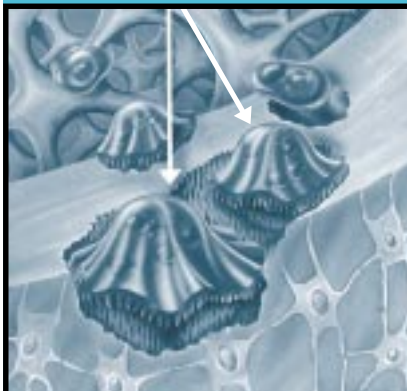
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changes do not occur with LHRH agonist therapy or with treatments involving estrogens. LH and FSH production are decreased by these agents, and there is no reflex stimulation of the pituitary gland.⁹

The Osteoclast Is The Mediator of Bone Resorption

The bone architecture or matrix is essentially a lattice work of collagen fibrils that are mineralized. Bone resorption relates to the disruption of the matrix with loss of minerals and fragmentation of the collagen. Increased bone resorption results from activation of osteoclasts (cells that have the capability of destroying bone matrix by secreting acids and digestive enzymes). Androgens and estrogens stabilize or inhibit the osteoclast as well as stimulate the bone-forming cells, the osteoblasts.¹⁰ A decline or withdrawal of any of these hormones leads to excessive osteoclastic activity and resultant bone resorption. Osteoclastic resorption of bone is charac-

Figure 1: OSTEOCLASTS
Mediators of Bone Resorption



Originate from bone marrow monocytes

Osteoclasts are attracted to bone injury sites and erode bone.

Secrete proteases that degrade collagen into molecular fragments.

Fragments measured in urine as collagen cross-links (Pyrilinks-D) or as peptides (N-telopeptides or Ntx, and C-telopeptides or Ctx).

terized by the development of cavities or lacunae (lakes). In the foreground of Figure 1, two osteoclasts (arrows) are shown lying in their lacunae. In contrast to the bone-eroding osteoclasts, osteoblasts are bone-forming cells. Osteoblasts are derived from precursor cells in the blood. The osteoblasts migrate to areas where bone has been eroded by osteoclasts and lay down collagen and minerals in the cavities. The bone undergoes constant remodeling with osteoclastic activity intimately coupled with osteoblastic activity. There is a close signaling between these cells, both in normal individuals and in those with bone metastases.

We are beginning to understand the roles of androgen and estrogen, as well as various growth factors or cytokines. These include transforming growth factor beta, insulin growth factor-1, parathyroid-hormone related protein, interleukin-1, and interleukin-6, prostaglandins, calcium, vitamin D and analogs of vitamin D. How

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Key Abbreviations

ADT: androgen deprivation therapy is any treatment that decreases the availability of male hormone (androgens) to the prostate cancer cell population. This can occur by decreasing Testosterone (T), by removing the testicles surgically by orchiectomy, or by the use of LHRH agonists such as *Lupron*[®], *Zoladex*[®] or *Triptorelin*[®]. It can also be accomplished by the use of anti-androgens such as *Eulexin*[®], *Casodex*[®] or *Nilandron*[®], either alone or in combination with *Proscar*[®]. Other agents such as *Nizoral*[®], *DES*[®] and *PC spes*[®] are also examples of ADT, with additional anti-tumor effects not mediated by androgen deprivation.

ACTH: adrenocorticotrophic hormone

ATF: amino terminal fragment (highly active part of uPA molecule)

DES: diethylstilbestrol

EGF: epidermal growth factor

FSH: follicle stimulating hormone

HMW-uPA: high molecular weight uPA

IGF-1: insulin growth factor 1

IGFBPs: insulin growth factor binding proteins

IL-1: interleukin 1

IL-6: interleukin 6

IL1R and IL6R: receptors for IL-1 and IL-6

LH: luteinizing hormone

MMP-2: matrix metalloprotease 2

PDGF: platelet-derived growth factor

PTHrP: parathormone related protein

Resorption: act of removal by absorption

RH: releasing hormone

TGF-b: transforming growth factor beta

TNF-a: tumor necrosis factor-alpha

uPA: urokinase plasminogen activator

Bone Integrity Affects the Natural History of Prostate Cancer...continued

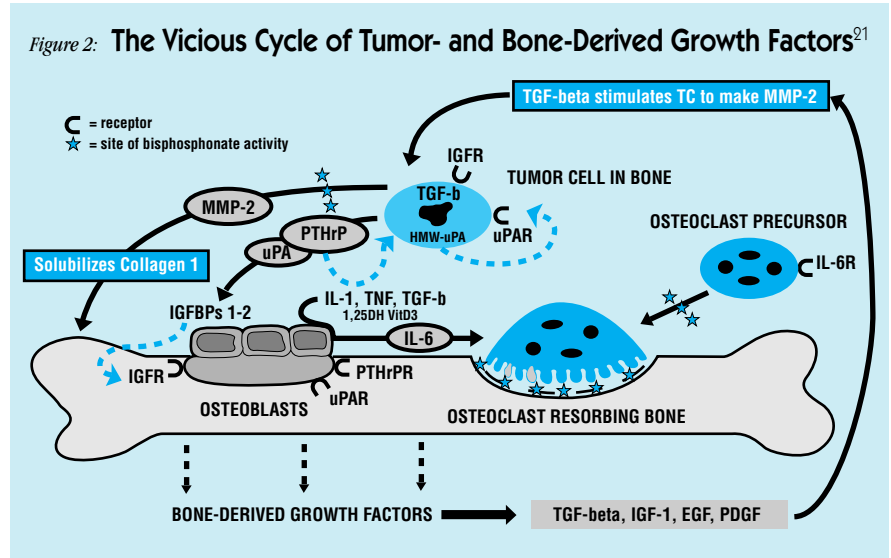
these mediators interact among the tumor cell, the bone matrix, the osteoclast and the osteoblast is just now beginning to be unraveled.¹¹⁻²⁰ This is shown schematically in Figure 2.²¹

Tumor cells try to survive by producing cell products that stimulate the cell's own growth (autocrine loops) or by elaborating proteins or enzymes that affect nearby cells (paracrine loops). For example, uPA (urokinase plasminogen activator) is a key substance made by the tumor cell that is able to self-stimulate both the tumor cell (autocrine loop) and the nearby osteoblast (paracrine loop). PTHrP, elaborated by neuroendocrine cells that make CGA (chromogranin A), is involved with uPA in similar activities.

The uPA also cleaves IGFBPs (insulin growth factor binding proteins) to release IGFs that not only stimulate osteoblast growth, (which in turn makes more IGF-1), but also allows the IGF-1 to turn on uPA production within the tumor cell (paracrine loop). Other interactions are discussed in the following scenario.



A possible scenario: Osteoblastic growth utilizes calcium and causes a drop in serum calcium stimulating osteoclastic bone resorption to lyse (dissolve) bone to maintain serum calcium. This is accompanied by an increase in parathormone (PTH) and vitamin D levels which are also trying to maintain calcium homeostasis. The osteoclastic activity releases bone-derived growth factors such as insulin growth factor-1 (IGF-1) and transforming growth factor beta (TGF-beta). These in turn stimulate the tumor cell population to grow and release PTHrP and uPA. The uPA cleaves insulin growth factor binding proteins 1 & 2 (IGF BPs 1-2) to release IGF-1 and IGF-2. The uPA and the IGFs as well as interleukin-1 (IL-1) also stimulate the osteoblasts to produce IL-6. IL-6 stimulates activity of mature osteoclasts as well as osteoclast



precursor cells which have been shown to have IL-6 receptors (IL-6R).

The tumor cell within the bone also produces TGF-beta which stimulates release of PTHrP and matrix metalloprotease 2 (MMP-2), the latter of which dissolves collagen 1. MMP-2 also cleaves a less active form of uPA (HMW-uPA) into a more active form (ATF) which in turn stimulates osteoblast growth. The tumor cell also has receptors for IGF-1 which in turn stimulates production of uPA, as mentioned previously.

What Are The Implications For Treatment?

The tumor cells survival mechanisms are elaborate. However, as these mechanisms become better understood, they give us new opportunities to block the action of cytokines, proteins and enzymes. *Agouron*[®] 3340, for example, is an investigational agent that blocks MMP-2 (as well as MMP-3, 9 and 13).

There are other autocrine loops and paracrine loops of importance that are not shown in Figure 2 due to lack of space. PC cell lines express cytokine factors and their receptors for GM-CSF, M-CSF, SCF and G-CSF (autocrine loops).²² These factors are also commonly found in the bone marrow (paracrine loops). Perhaps sampling the

marrow of high-risk patients using micro-metastatic assay approaches as is being done by Impath Labs, and evaluating positive assays by incubating them with these various growth factors would give us ways to manipulate tumor growth as well as to caution us on the use of various growth factors in certain patient subsets.

Endothelin-1[®] (ET-1) is another PC cell product that stimulates osteoblastic growth and may also mediate the pain associated with bone metastases by virtue of its potent vasoconstrictor properties. High-affinity ET-1 receptors were found on osteoblasts and ET-1 increased alkaline phosphatase activity during new bone formation in vivo. Moreover, 58% of men with advanced PC had significantly higher levels of ET-1 than the control group.²³

(Continued on page 4)

Learn from the Experts


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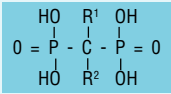
They'll all be at the PCRI National Conference

(see page 12)

The Role Of Bisphosphonates

Overstimulation of the osteoclast cell population, from whatever cause(s), leads to net resorption of bone. Now enter the Bisphosphonates (BPs), a class of agents that fixes this problem and throws in some extras to boot. BPs all contain a P-C-P (phosphorus-carbon-phosphorus) backbone that is structurally an analogue of naturally occurring pyrophosphate P-O-P (O is an oxygen molecule rather than a carbon molecule). See Table 1 below.

TABLE 1: BISPHOSPHONATES: Structure & Relative Potency			
Drug	R ¹	R ²	Relative Potency
Clodronate	Cl	Cl	1
Pamidronate (Aredia)	OH	(CH ₂) ₂ -NH ₂	10
Alendronate (Fosamax)	OH	(CH ₂) ₃ -NH ₂	100
Ibandronate	OH	(CH ₂) ₂ -N-CH ₃ (CH ₂) ₄ -CH ₃	500
Zoledronate	OH	CH ₂ - 	1000

Structure 

BPs are classified as 1st, 2nd and 3rd generation with progressively greater potencies. *Clodronate*® is in the first category, *Pamidronate*® and *Alendronate*® in the second, and *Ibandronate*® and *Zoledronate*® in the third. The cellular action is determined by the side chain on the carbon atom of the P-C-P group- the **R² side chain**.

In other words, **BPs mimic pyrophosphate and bind to the hydroxyapatite crystals in the bone matrix.** In this mineral-bound form, they inhibit attachment of the osteoclasts to the bone matrix and interfere with signaling to osteoclast cell precursors that normally directs them to a point of attachment on the matrix.²⁴⁻²⁵ The proposed cellular actions of BPs and the amino bisphosphonates (ABPs) which include the 2nd and 3rd generation BPs, are represented in Figure 2 by stars. BPs also act directly on the osteoclast to cause programmed cell death or apoptosis.²⁶⁻²⁷

BPs have been shown to interfere with osteoblast-mediated osteoclast activation.²⁸ The actual mechanism of this interaction needs clarification and for this reason, we have not shown this as an area of BP blockade in Figure 2.

Recent excitement has been generated by evidence that amino bisphosphonates (ABPs) also act directly on tumor cells to cause apoptosis²⁹⁻³⁰ and also dose-dependently inhibit the adhesion of tumor cells to bone.³¹ A summary of cellular mechanisms of the BPs is as follows:

- Causes apoptosis (cell death) of the osteoclast
- Interferes with signaling of osteoclast precursor cells attracting them to bone matrix
- Interferes with osteoclast attachment to bone matrix at hydroxyapatite interface
- Inhibits osteoblast-mediated osteoclast activation
- Apoptosis of the tumor cell
- Interferes with adhesion of tumor cell to bone matrix (only the AminoBPs do this).

APBs may turn out to be one of the most critical class of drugs we can employ to prevent bone metastases or to treat established bone metastases to reduce further spread as well as to kill tumor cells. Our April 1996 paper “Bisphosphonates” discussed this potential application of BPs and also their use in reducing bone pain in metastatic PC. Please download this still current paper off our homepage at www.prostatecancer.org.

Areas of clinical importance of BPs are shown as follows:

- Prevention of osteoporosis
- Decreasing fractures, compression of bone
- Decreasing bone pain due to osteoporosis or malignancy
- Decreasing bone metastases
- Treatment of hypercalcemia

- Pushing calcium into bone formation.

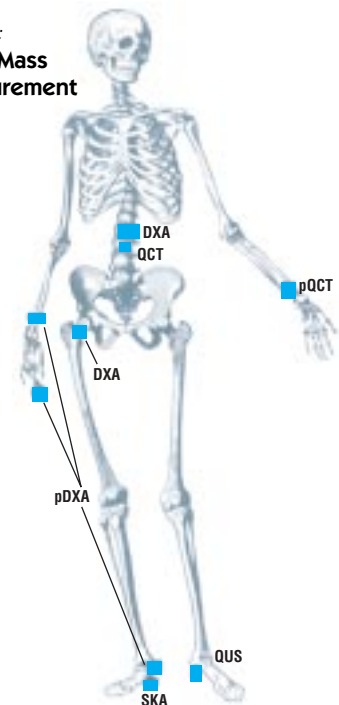
What To Do Next?

Discuss these findings with your doctor and show him the references relating to articles in this exciting field. Determine your bone status with a bone mineral density (BMD) assessment along with a first or second voided urine specimen for *Pyrilinks-D*®. The latter test is one of the measurements of bone breakdown that is increased with excessive bone resorption. Excessive resorption may result from ADT, PC in the bone, the use of steroids or from other factors mentioned in the first issue of *Insights*. Since this a critical issue in the prevention and treatment of bone metastases, a discussion of bone integrity evaluation and management is warranted.

Evaluation of Bone Integrity & Management

The evaluation of bone integrity involves applying the principles learned in the previous pages. Bone mineral density (BMD) peaks at the age of 25 and ebbs with passing years. How much bone density is left at the time of evaluation is a reflection of the

Figure 3: Bone Mass Measurement Sites



net balance left after formation and resorption. In essence, it is your bone bank balance. BMD is evaluated using either x-ray absorption or ultrasound techniques. The most common device used currently is the *DEXA*[®]. *DXA*[®] or *DEXA*[®] involve dual energy x-ray absorptiometry of the hip, femoral neck and lumbar spine. *DEXA*[®] is the most common of the BMD[®] techniques. This utilizes low level x-rays. *pDXA*[®] or peripheral *DEXA*[®] involves dual energy absorptiometry of peripheral sites such as the finger, forearm and heel. *SXA*[®] indicates single x-ray absorptiometry involving the heel. *QUS*[®] is quantitative ultrasound of the heel. *QCT*[®] involves the use of quantitative CT of the lumbar spine while *pQCT*[®] is a peripheral multiple slice technique involving the wrist.

All of these techniques report BMD for the specific sites they measure as a T score and a Z score. The T score describes the patient's bone mass relative to the average peak bone mass for normal young adult women. No T scores have been established as of yet for men. The patient's findings relative to the normal findings are expressed as the number of standard deviations (SD). For each SD loss in bone density, the risk of fracture doubles. A 1-to-2.5 SD below normal is considered low bone mass or osteopenia, while a > 2.5 SD below normal is defined as osteoporosis. The Z score compares the patient to others of the same age. Since we want comparisons with normal bone, we use the T score, not the Z score.

Excessive Resorption

Excessive bone resorption can occur as part of aging, or it can be secondary to medical diseases e.g. diabetes, alcoholism, hyperthyroidism, hyperparathyroidism, breast and prostate cancers, or the use of medications such as steroids and dilantin. We suggest your bone integrity status be evaluated with a baseline bone mineral density (BMD) to determine your bone mass and also with a first or second morning urine to measure the collagen breakdown prod-

**Figure 4: PYRILINKS-D:
Deoxyypyridinolum
Crosslinks in Urine**

Breakdown product resulting
from osteoclastic degradation
of bone

Cleared by kidneys

Exhibits low day to day
biologic variability

Normal value in men is
up to 5.4



uct deoxyypyridinolum (Dpd) which is commercially available as *Pyrilinks-D*[®] (Figure 4). If either or both of these are abnormal, it would be good medicine to correct this by stopping excessive bone resorption and aiding bone formation. How do you do this?

How To Prevent Excessive Bone Resorption

Calcium supplements help make healthy bone and stop resorption. BPs drive calcium into the bone. If no calcium supplement is given or if calcium is not present during these times, hypocalcemia occurs and poor quality bone is formed. Therefore, when using BPs, start calcium supplements a day or two before initiating BP therapy. Use calcium citrate for better absorption. Calcium by itself has been shown to reduce bone resorption. This is especially true if calcium is administered in the evening, ideally before sleep. Due to the large size of the calcium supplements, we suggest you take 500 mg with dinner and 500 mg at bedtime. Blumsohn et al have described the circadian rhythm of calcium absorption as shown below.

- *Nocturnal increase in parathormone (PTH)*
- *Peak Excretion of Dpd & Ntx at 0300-0700*
- *Calcium taken in evening suppresses nocturnal increase in PTH*

- *Calcium supplements taken in evening suppresses daily excretion of Dpd by 20%, Ntx by 18%.*

Citrical[®] by Mission Pharmaceuticals or *Calcium Citrate*[®] by Solgar are two excellent brands of calcium citrate. If your diet is high in calcium, decrease the calcium supplements accordingly and work with your doctor to optimize calcium administration.

Administering Bisphosphonates

For patients with prostate cancer with evidence of bone metastases detected by bone scan or by bone marrow examination using a monoclonal antibody to detect micro-metastatic disease (*Impath*), we suggest the use of pamidronate (*Aredia*[®]). This is given intravenously. We like to give the first dose at 30 mg over 1.5 hours to minimize the chance of an acute phase response (APR). The APR is usually associated with fever within 28-36 hours of the initial exposure to the ABP. The APR is felt to be due to a first-time reaction of the amino BPs with macrophage-like cells resulting in the release of interleukin-1 (IL-1).³³ Since we have seen two patients in consultation with kidney damage after a high first dose of *Aredia*[®], we routinely give the first dose at 30 mg and then increase to 60-90 mg every two weeks thereafter.

(Continued on page 6)

Synthetic Vitamin D

Not to be confused with ordinary Vitamin D3, synthetic Vitamin D (1,25 DihydroxyCholecalciferol), has many interesting properties for PC. In a recent issue of *The Prostate Forum*, an excellent newsletter published by Snuffy Myers MD and his staff, Vitamin D was reviewed. In the area of bone integrity, synthetic Vitamin D (*Rocaltrol*[®] or *Calcitriol*[®]), can be used to enhance calcium absorption from the gastrointestinal tract. *Rocaltrol*[®] also has anti-proliferative³⁶⁻³⁹ and anti-angiogenesis effects⁴⁰⁻⁴¹ on prostate cancer growth and is able to slow the rate of PSA rise in patients with early recurrent PC.⁴² The limiting factor in this study was the finding of increased urinary excretion of calcium. We would speculate that the administration of calcium at night, as well as the use of BPs to drive calcium into bone formation, would decrease these findings and allow for higher doses of *Rocaltrol*[®]. *Rocaltrol*[®] should also be given at bedtime to decrease urinary calcium excretion.

It appears that calcium and Vitamin D have a circadian rhythm which obviously affects their biologic function. Perhaps bone formation and resorption occur mostly at night or in the early hours of the morning. This may be the reason for the complaint of growing pains of teenagers occurring at night, and the need to check the *Pyrilinks-D*[®] test with a first or second morning voided urine specimen. ❖

Serum calcium levels should be watched and the patient encouraged to take calcium supplements as discussed previously. In patients without bone metastases, the use of alendronate (*Fosamax*[®]) is encouraged. Since *Fosamax*[®] is poorly absorbed in the small intestine it should be given one hour before breakfast and taken only with water. The patient is advised not to lie down after taking *Fosamax*[®]. If symptoms of gastrointestinal upset such as belching and burping or discomfort in the stomach region occur, *Fosamax*[®] should be stopped and the physician notified.

A key paper on the use of bisphosphonates to reduce new metastases to bone, liver and lung as well as to prolong survival in women with breast cancer was recently published in the *New England Journal of Medicine*.³⁴ Breast cancer and prostate cancer have strong similarities sufficient to warrant extrapolating data from the breast cancer literature and seeing if such approaches are effective in prostate cancer. In this study, the bisphosphonate used was oral *Clodronate*[®] at a dose of 400 mg four times per day. The patients studied included 302 women with breast cancer with tumor cells in the bone marrow. Patients were randomized to *Clodronate*[®] (157) versus control (145). Patients in both groups received standard surgical, hormonal and chemotherapy treatments. The results are shown below.

During the median observation period of 36 months, distant metastases (bone or visceral) were detected in 21 women in the *Clodronate*[®] group as contrasted to 42

women in the control group. In this study, all women had evidence of bone marrow metastases using immuno-histochemical staining of bone marrow aspirates. Details are shown in the table. The results of this paper should prompt a similar study in prostate cancer.

An alternative agent to be used is (*Miacalcin*[®]) nasal spray. *Miacalcin*[®] is a derivative of salmon calcitonin. *Miacalcin*[®] will reduce bone resorption due to prostate cancer³⁵, but there are not as many papers on the use of *Miacalcin*[®] in regard to bone physiology of PC as there are dealing with the bisphosphonates. Randomized studies should be done since *Miacalcin*[®] is so much easier to take than *Fosamax*[®]. *Miacalcin*[®] is dosed as one spray in one nostril per day with the right and left nostrils alternated to prevent nasal irritation. We have seen just one allergic reaction to *Miacalcin*[®] occurring in a patient with a history of fish allergy.

Bone Integrity Concluding Remarks

In my opinion, the institution of bone integrity measures as detailed in this issue of *Insights* should be a routine part of the management of the PC patient. This is true not only to prevent bone metastases, but also to maintain the structural integrity of the bone to avoid fractures and bone pain.

We will continue to watch the literature on bone integrity in PC since it represents an avenue to increased supportive care of the patient and insights into better tumor control. ❖

Outcome	Patients (n=302) (all)	Clodronate group (n=157)	Control group (n=145)	P value
Distant mets	63	21 (13%)	42 (29%)	<0.001
Bony mets	37	12 (8%)	25 (17%)	0.003
Visceral mets	40	13 (18%)	27 (19%)	0.003
Death	28	6 (4%)	22 (15%)	0.001
# Bony mets per patient		3.1	6.3	0.004

The Medical Chart: Your Log

It is important that I share with you my concerns about your medical record. I see much of life as a sailing metaphor. Your life is a passage, a journey through calm and rough waters. Your doctor(s) are your navigators, or in some cases your co-captains. However, this is your passage and no one cares about this as much as you. You need to know what is going on. The consultation reports reflect the rationale, the thinking and the logic of your doctors. You should be the primary recipients of these reports. The secondary recipients are the other doctors involved in your care.

The pathology reports, radiology evaluations and lab results should be kept by you in chronological order. We suggest that you buy a 3-ring binder and tab separators and separate the binder into sections such as: Pathology, Nuclear, X-ray, Laboratory, and Consults. We would also advise that you learn the concept of a "flow sheet". This is a form that contains all your medications in a left hand column, along with basic CBC, chemistry panel results and all tumor biomarker results. Multiple columns allow for input of additional data over time. After a number of entries you can see the trend

or flow of lab entries, including such important items as PSA, other biomarkers, and lab results. If you have internal medicine problems such as hypertension or diabetes, the flow sheet parameters can include blood pressure as well as glucose and glycohemoglobin. A sample flow sheet is shown at our homepage (www.prostate-cancer.org).

The patient should determine which physician will be the chief coordinator of his care. That physician should receive copies of any medical data that relates to the patient. Other physicians involved with the patient can also receive copies. The patient must take responsibility in letting all "involved" doctors know the results of any studies. This includes consultations with other doctors. Failure to do this results in the medical team being less informed as well as causing duplication of laboratory and radiology exams. The latter is not only an inconvenience to the patient, but can also cause harm to the patient as well as generate wasted healthcare expenses. These wasted resources could be used instead to fund research to cure PC. **We waste more healthcare dollars in duplicated or technically inadequate studies than the annual Federal budget for PC research.**

The patient must be responsible for his getting better. This means obtaining the medical reports and sharing them with all the involved crew members. ❖

The PC Digest

We have been asked what course of treatment Tom Harrison decided upon. Readers of Issue 1 of *Insights* will recall that his PC digest (PCD) contained the following data:

- Tom Harrison PCD: age 59
Dx 12/23/97
- bPSA 5.1
- TRUSP volume 44 ccs
- 1/3 cores + on R with GS (3,3)
- 0/3 cores + on L
- Slides reviewed by an expert
- Pathology report available
- CS T1c
- PAP 3.0 (normal to 3.5)
- Ploidy diploid
- Partin: 67,30,2,1
- Narayan: 81,17,3,3
- Bluestein: N
- D'Amico: 84% OCD, 3 YFFR pending erMRI
- Lerner: 5 YFFR if OCD at RP is 85%
- PC calculated volume 0.52 ccs with 80% chance of OCD.

Tom had an endorectal MRI with spectroscopy. This showed no evidence of extra-capsular extension. The MRI and spectroscopy both were abnormal at the right base and midgland as well as at the left base. Therefore, Tom elected to have an RP. The microscopic findings from the RP showed no capsular penetration. The surgical margins were clear, and no evidence of extra-prostatic disease was found. The approach used in evaluating Tom was logical, rational and led to an appropriate treatment decision. ❖

Upcoming Events

University of Pittsburgh Cancer Institute & The Johnson Foundation

Marriott City Center,
Pittsburgh, PA, March 19-21, 1999

First Workshop on Properly Staging the Man with Prostate Cancer, and
How to Identify Individuals with High Risk Prostate Cancer

Moderated by Don Coffey and Stephen Strum

Call Maureen Pfeifer at (412) 647-6331 or pfeiferm@msx.upmc.edu



Prostate Cancer Research Institute First Annual Conference '99

Long Beach Convention Center, July 31-August 1, 1999

For details and registration, see pages 11 and 12.

The Androgen Deprivation Syndrome

A myriad of symptoms typically arises in a PC patient who undergoes androgen deprivation therapy (ADT). Some of these occur acutely and many may improve over time, but can still be quite troublesome if not aggravating for the patient. Other symptoms develop more gradually and are subtler, but if not treated in a preventative manner, can have a negative impact upon the PC patient's overall health.

Except for hot flushes and impotency, many ADS symptoms were discounted by physicians and patients as being due to "old age" or other medical problems such as arthritis or heart disease. However, this constellation of clinical and laboratory abnormalities quickly develops in younger men, or older men in otherwise good health, after ADT is initiated. This clearly suggests that these symptoms are not simply attributed to "old age" but are characteristic of what we have termed the Androgen Deprivation Syndrome (ADS).

ADS symptoms are directly or indirectly due to the significant fall in serum testosterone that occurs following orchiectomy or treatment with a LHRH agonist such as *Lupron*[®] or *Zoladex*[®]. In essence, men who are medically or surgically castrated undergo an accelerated and intensified form of "male menopause" which leads to the same types of symptoms in these men that are seen in women who undergo female menopause. Patients treated with combined ADT (LHRH agonists or orchiectomy plus an anti-androgen such as *Eulexin*[®], *Casodex*[®], or *Nilandron*[®]) may have more severe ADS symptoms than those treated with a LHRH agonist or orchiectomy alone. A list the types of acute and chronic ADS symptoms appear in Table 2.

To assess the significance of common ADS symptoms, we questioned 177 hormone-naïve PC patients consecutively treated with a LHRH agonist and an anti-androgen between 1994 and 1997. We asked patients to grade the frequency and severity of ADS as absent (0), occasional (1),

Acute (symptoms in < 2 months)	Chronic (symptoms in > 6 months)
Hot Flashes	Muscle atrophy in chest, arms & legs
Impotence & loss of libido	Atrophy of testicles
Aches & pains in joints	Decreased muscle strength & endurance
Loss of energy & "feeling weak"	Weight gain due to increased body fat
Short-term memory difficulties	Gynecomastia (breast enlargement)
Mood "swings"	Osteoporosis, progressive on CHB
Emotional changes (tearfulness, etc.)	Chronic fatigue-like syndrome
Anemia unrelated to blood loss, iron deficiency or bone marrow involvement	Difficulty controlling blood pressure, often requiring initiation of changes in drug therapy
Loss of blood sugar control in patients with diabetes mellitus (sugar diabetes)	Alzheimer's-like symptoms (severe short-term memory difficulties, inability to concentrate, etc.)
Increase in urinary symptoms (↑ urination or difficulty starting the urinary stream)	Increased serum cholesterol (LDL, or "bad" cholesterol) and/or & triglyceride levels

frequent/bothersome (2) or required drug therapy (3). Other than loss of libido and impotence, Figures 5 and 6 depict the most commonly reported acute and chronic symptoms.

Several patient and treatment-related factors were found to influence the incidence and severity of ADS symptoms. Figures 7a, 7b and 7c depict hot flushes, anemia and osteoporosis when analyzed with

respect to (1) age, (2) choice of ADT and (3) relative duration of ADT, respectively.

Treatment of certain ADS-related symptoms is important as it can help maintain the patient's overall health. The decision as to whether or not treatment is indicated must take into account:

- The goals of ADT (neo-adjuvant, intermittent or continuous treatment)
- The age and overall general health of the patient (active vs. inactive)
- The degree of tolerance by the patient of the various ADT side-effects.

For example, patients who are candidates for potentially curative local therapies, the duration of neo-adjuvant ADT rarely exceeds 1 year. Therefore, such patients suffer the typical acute ADS symptoms, but will not experience chronic ADS symptoms to any significant extent. However, acute ADS symptoms invariably compromise the lifestyles of healthy and active prostate cancer patients, and mandate that certain changes be made in the patients' diet, exercise and/or work habits during ADT.

Figure 5: Incidence & Severity of Common Acute ADS Symptoms

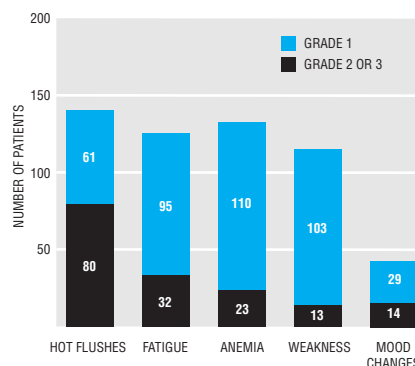


Figure 6: Incidence & Severity of Common Chronic ADS Symptoms

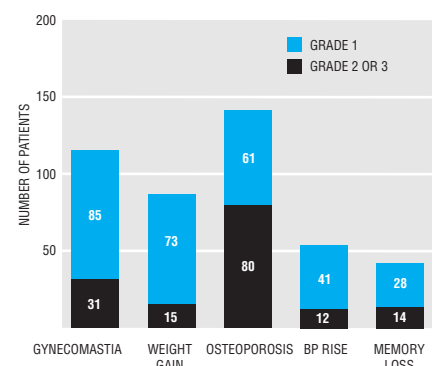


Figure 7a: Incidence & Severity of Hot Flashes With Age

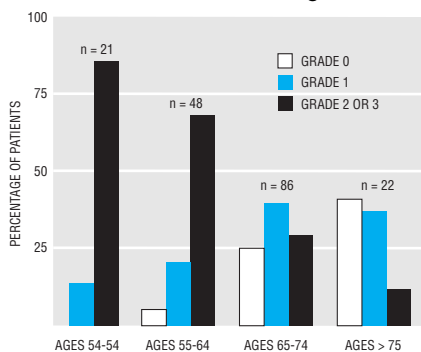


Figure 7b: Incidence & Severity of Anemia by ADT Used

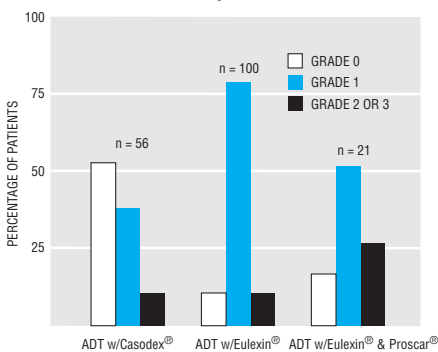
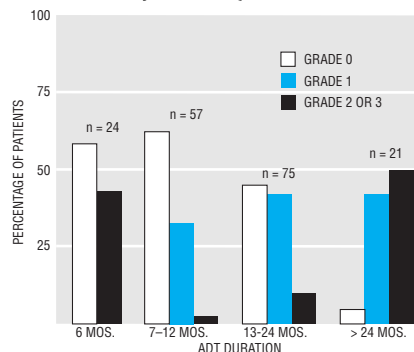


Figure 7c: Incidence & Severity of Osteoporosis by ADT Duration



Chronic ADS symptoms are much more prevalent in PC patients treated with ADT than is currently recognized, and some are nearly inevitable in patients treated longer than a year. For such patients, specific treatment strategies must be implemented to minimize or prevent the development of chronic ADS. Left untreated, chronic ADS is progressive with ongoing ADT and often lead to other medical complications.

Summary

In the past, patients who were not candidates for local therapy were typically treated with some form of androgen blockade indefinitely. Armed with our current knowledge of acute and chronic ADS symptoms, we treat such patients with one or more of the therapies listed in Tables 3a and 3b to prevent and/or treat acute ADS (Table 3a) and chronic ADS (Table 3b).⁴³ Another means to avoid chronic ADS is to offer Intermittent Androgen Deprivation (IAD). Depending upon the required duration of ADT individually determined for patients, IAD may be a viable alternative for patients meeting specific response criteria.⁴⁴ ❖

Key to Table 3a and 3b Footnotes:

* Doctor's prescription is required to obtain medication

** Available from nutrition or health food stores

TABLE 3a: Preventative & Active Treatments for Acute ADS

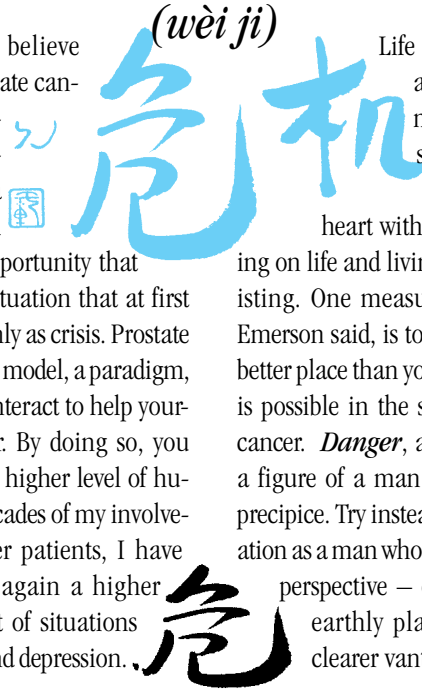
Acute ADS Symptom	Preventive Treatment Strategy
Hot flushes	Soy**, genistein**, Megace®, Depo-provera®, DES*, Effexor®*
Aches & pains in muscles and joints	Acetaminophen, ibuprofen, Fosamax®, Aredia®, plus calcium, vitamin D, aerobic exercise, walking
Fatigue & feeling weak	Aerobic exercises, muscle stretching
Memory difficulties	Ginkgo**, Eldepryl®, memory excises
Mood & emotional swings	Depo-provera®, patience (may improve on its own)
Symptomatic anemia (shortness of breath, dizziness, severe weakness)	Injections of human erythropoietin (Procrit®)*
Urinary frequency	Hytrin®, Cardura®, Flomax®*
Impotence, loss of libido	Viagra®, Muse®, Caverject®*

TABLE 3b: Preventive & Active Treatments for Chronic ADS

Chronic ADS Symptom	Preventive Treatment Strategy
Loss of muscle bulk & strength, worse in pectoral, biceps and quadriceps	Regular exercise of pectoral, biceps & quadriceps muscles with light weights, electrical muscle stimulation?
Weight gain and fat redistribution	Low fat diet, regular exercise routine
Chronic fatigue syndrome	Walking, regular exercise, avoid inactivity
Gynecomastia	Breast radiation or Arimidex® to prevent occurrence; liposuction or surgery to treat severe cases
Osteoporosis	Fosamax®, Aredia®* or Evista®, plus calcium & vitamin D, aerobics, walking
Alzheimer's-like symptoms	Ginkgo**, Aricept®, reading or other mind-stimulating activities
Increased serum cholesterol & triglyceride levels	Low fat diet, regular exercise, if no help, Lipitor®, Pravacol®, Zocor®, Mevacor®*

CRISIS AS OPPORTUNITY

You may not believe this, but prostate cancer is an opportunity. As the Chinese say, there is a seemingly small but important opportunity that comes out of a situation that at first glance appears only as crisis. Prostate cancer is a path, a model, a paradigm, of how you can interact to help yourself, and another. By doing so, you evolve to a much higher level of humanity. In the decades of my involvement with cancer patients, I have seen again and again a higher spirit emerge out of situations laden with fear and depression.



Life is more than the accumulation of material possessions. It is the sharing of one's heart with others, of focusing on life and living rather than existing. One measure of success, as Emerson said, is to leave the world a better place than you found it. All this is possible in the setting of prostate cancer. *Danger*, as shown below, is a figure of a man on the edge of a precipice. Try instead to see your situation as a man who has a newly found perspective – one who sees the earthly plain below from a clearer vantage point. ❖

Thanks For Your Help

I want to acknowledge the support of the Freeman Hospitals Foundation in being vital to the survival of the Prostate Cancer Research Institute during these formative years. I wish to express my heartfelt thanks to Linda Moore and the library staff at the Daniel Freeman Marina Hospital for their tireless efforts in securing the many references cited in these issues of Insights. I want to sincerely thank those of you who have shown support of our organization. We are hoping that as a result of our research efforts we can secure funding for the PCRI that will make our survival more certain.

Clinical Trials of Interest Conducted at The PCRI via Healing Touch Oncology

Taxotere® + Estramustine Phosphate (Emcyt)

- Patients with hormone refractory PC
- Men with progressive PC despite castrate levels of testosterone
- Exclusions are severe low blood counts, liver disease or pre-existing nerve damage
- Total of 20 patients to be enrolled
- Supported by Rhone-Poulenc-Rôrer

Dostinex® in Hormone Blockade

- Men on ADT who fail to reach undetectable PSA and have borderline or elevated prolactin levels
- Exclusions are concurrent investigational trial
- *Dostinex*® is a new prolactin-lowering agent that is much better tolerated than Bromocriptine. Note that prolactin increases the number of androgen receptors and facilitates androgen entry into the PC cell
- Total of 12 patients to be enrolled
- Supported by Pharmacia Upjohn

OncoVax® in Prostate Cancer (1)

- Men with progressive PC despite castrate levels of testosterone; D-2 stage
- Exclusions are concurrent investigational trials
- *OncoVax*® is a bioengineered PSA vaccine
- Study is placebo controlled but if PSA rises on placebo, patient is crossed over to *OncoVax*®
- Total of 60 patients in 4 research centers
- Supported by Jenner Technologies

OncoVax® in Prostate Cancer (2)

- Patients with recurrent disease after RP, or RT
- Exclusion includes previous androgen deprivation therapy, cryosurgery
- If patient randomized to placebo and disease increase seen, then switch over to *OncoVax*®
- Total of 60 are planned at 5 research centers
- Supported by Jenner Technologies

High Dose Cytosax® , 5 Fu and Dexamethasone® + Neupogen® in AIPC

- Men with AIPC who have already undergone anti-androgen withdrawal
- Exclusions are WHO performance status of < 2, and life expectancy < 3 months
- *Cytosax*® is one of the most active agents in PC, yet the studies using high dose regimens have not been done with supportive measures
- Total of 54 patients
- Supported by Amgen

Modified Citrus Pectin

- Men who are currently involved with watchful waiting but who have a persistent rise in their PSA; men who are post RP, RT, Seeds, or Cryosurgery with a slow but persistent rise in PSA
- Exclusions are patients on other active trials
- Total of 20 patients
- Supported by EcoNugenics.

❖ ❖ ❖ ❖ For Further Information call the **Prostate Cancer Research Institute at (310) 827-2366 PST** ❖ ❖ ❖ ❖

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Internationally recognized prostate cancer research and treatment pioneer Dr. Stephen Strum has assembled top prostate cancer specialists from around the country for a 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 with experts that will provide information on leading-edge developments in the field.

***Don't miss this conference.* You'll 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.**

Fees for the two-day conference are just \$50 for those who register on or before March 1, 1999 (\$40 for spouses). After March 1, the fees will increase by \$25, so use the registration form on page 11 and register now.

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