



National Conference Draws More Than 1,400 People

Prostate Cancer Research Institute's National Conference '99 was the largest doctor-to-patient conference of its kind ever held in this country. Aptly entitled "*Prostate Cancer – Looking Toward 2000*," it drew over 1,400 people from 45 states and seven foreign countries. The attendees were prostate cancer patients and family members, as well as physicians, nurses, pharmacists and other healthcare professionals.

"The conference was extremely successful," said Dr. Stephen Strum, Medical Director of the

PCRI. "We had the world's leading physicians and research scientists present the latest findings in their field of practice including diagnostic techniques, treatment options, nutrition, and new advances in the understanding and treatment of prostate cancer. No one walked away from the conference without being better informed about his disease."

Attendees agreed. For example, attendee and volunteer Liz Derry wrote, "The symposium was

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Overcoming Impotence

By Jim Goyjer

The fear of impotence can have a powerful effect on many men. Too often, men will avoid PSA screening or delay treatment, fearing that they will never be able to have sex again. These decisions can have fatal consequences, but since physicians cannot guarantee that a radical prostatectomy (RP) will not cause impotence, men are sometimes at a loss as to how to overcome what must be regarded as folly. Perhaps they should speak to Bill Whatley.

William Whatley is an active 55-year-old man, an airline captain and Chief Pilot for Polar Air Cargo, one of the largest cargo airlines in the world. He unashamedly admits that making love with his wife has been the greatest joy in his life. However, at the age of 41, Bill Whatley was beset by one of the most virulent cases of prostate cancer I have ever heard of.

No one knows exactly when Bill's PC actually started because PSA levels were not routinely measured in 1985. However, we do know that at diagnosis he had a validated Gleason score of 8. Bill underwent an RP and was found to have extra-capsular extension without apparent nodal spread.

The RP rendered Bill impotent. But not for long. Unlike many men who squeamishly reject even the idea of a penile implant, Bill decided a penile implant was worth trying.

"Why not?" he asks. "A penile implant is placed in the chamber inside your penis. It's there when you want it; you just pump it up. And it's gone when you don't want it; you just bend it down and the fluid flows back into the chamber. I've had nothing but positive experiences with it. I have erections whenever I want them and I can keep it up as long as I like, because it's a mechanical device. I've had three implants now, and I'm going to have another."

(Continued on page 8)

Ipriflavone: A Synthetic Soy Derivative That Corrects Bone Loss and Stimulates Bone Formation

By Stephen B. Strum, M.D.

Ipriflavone (IP) is one of the most intriguing compounds with potential to help men with PC that I have come across in the last year. To date, however, almost all of the studies on IP deal with women. We are currently involved in clinical evaluations of IP in men with prostate cancer (PC). As discussed in detail in Vol. 2, No. 1 of *Insights* (as well as at lectures and the 1999 PCRI Conference), maintaining bone integrity appears to improve the quality of life and prognosis in patients with breast cancer, prostate cancer and multiple myeloma.

Those who have the most to gain from reading this review are (1) men and women

with excessive bone loss determined by elevations in the urine Pyrilinks-D test, (2) those who are already showing evidence of decreases in bone mineral density (BMD), and (3) those with or at high risk for metastatic disease to the bone. Such patients are either not showing full response to the aminobisphosphonate compounds (*Aredia*[®], *Fosamax*[®] or *Actonel*[®]) and/or are having gastrointestinal side effects such as heartburn, difficult swallowing, esophageal spasm, or belching. Other patients find the cost of these agents to be prohibitive, ranging from \$400-800 per month for *Aredia*[®], \$60 to \$120 per month for

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Fosamax® and \$300–\$420 per month for Actonel® compared to the \$24 per month cost of IP. The following is a review of the literature on the clinical and biological actions of IP, a most promising addition to our armamentarium to maintain or improve bone integrity.

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Introduction

And God said, "See, I have given you every herb that yields seed which is on the face of all the earth, and every tree whose fruit yields seed; to you it shall be for food. Also, to every beast of the earth, to every bird of the air, and to everything that creeps on the earth, in which there is life, I have given every green herb for food". Genesis: 1:29-30.

Within this bequest of "herbs and fruits" is the medically important class of *micronutrients* called the flavonoids. Within this category, the soybean sticks out like a noble green thumb. The soybean was such a valuable part of Chinese medicine that the emperor Sheng-nung (c. 2838 BC) designated it as one of the "sacred crops". This appears well-justified considering there are more than 500 peer-reviewed articles on soy protein and its benefits in relation to cancer, heart disease, diabetes, osteoporosis, and renal disease. The PCRI website has a general review of "Soy and Green Tea Polyphenols". The current review focuses on IP.

Carotenoids and Flavonoids

Most of you are familiar with the carotenoids, one of two main families of micronutrients. The carotenoids impart the yellow, orange and red color to fruits and vegetables. The other family, the flavonoids, causes the blues, purples, emerald green and some red coloration of fruits and vegetables. In the plant kingdom, the flavonoids protect the plant DNA from the damaging effects of ionizing ultraviolet light. Of interest is that flavonoids and vitamin C occur together and appear to be mutually protective; this should be simulated in our use of any flavonoid compounds. Flavonoids also enhance vitamin C absorption and stabilize vitamin C. This is why you will often see vitamin C combined with active flavonoids (bioflavonoids). Bioflavonoid is just a term for biologically active flavonoids.

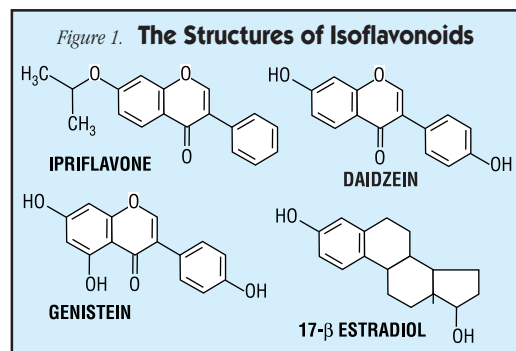
There are approximately 4,000 naturally occurring flavonoids. These compounds are found in fruits, nuts, seeds and vegetables as well as in tea, coffee, cocoa, wine and beer. All flavonoids share a chemical structure called a polyphenolic ring.

FLAVONOIDS & THEIR CLASSIFICATION	
Bioflavonoid Group	Examples & Comments
I. Anthocyanins	Bilberry, Crataegus (found in red-blue fruits e.g. beets, black grapes, red onions, & berries).
II. Minor Flavonoids (Flavanones, Flavan-3-ols)	Epigallocatechin gallate or EGCG (the active ingredient of green tea).
III. Flavones	Baicalin (a major ingredient of PC SPES); (also found in citrus, red grapes, & green beans), Luteolin Quercetin (Rutin) , Kaempferol, Myricetin (found in kale, spinach, onions, apples & green tea)
IV. Isoflavonoids (from legumes)	Genistein, Daidzein, Glycetein
V. Tannins	Proanthocyanidins (the active ingredients in pycnogenol) Gallic acid phenolics (gallic and ellagic acids e.g. raspberries, cranberries, blueberries and strawberries)

Within the flavonoid family are the plant-derived isoflavonoids (also called isoflavones), comprised basically of daidzein, genistein and glycitein. These are the three common natural isoflavonoids found in soybeans. Ipriflavone is simply a *synthetic* derivative of daidzein. The structure of genistein, daidzein and IP are shown in Figure 1. The sole difference between genistein and daidzein rests with the former having an OH (hydroxyl) group on the 4th carbon position of the benzene ring on the left. The difference between daidzein and IP rests in substitutions at the 6th carbon position (uppermost OH group on the left) and at the OH group on the lower right.

Isoflavonoids are Phyto-estrogens

The structure of the isoflavonoids has some like-



ness to that of the estrogen 17-β estradiol. Because of this structural similarity, these compounds are called **phyto-estrogens (plant estrogens)**. In essence, many of the beneficial effects of the isoflavonoids are derived from their interaction at estrogen receptor (ER) sites. The isoflavonoids have the ability to act with different potency at different ER sites found in breast, and bone and in other tissues.

Certain molecules appear to possess the property of **biologic multi-tasking**. They have a stimulatory effect on one receptor while an inhibitory or ambivalent effect or effects on either the same or other receptors. In the realm of estrogen receptors, compounds with this multi-tasking or multi-functional ability are called SERMS or selective estrogen receptor modulators. **The phyto-estrogens interact and occupy estrogen receptor sites with differing degrees of estrogenic effects on breast tissue and uterine tissue while retaining the ability to selectively modulate certain receptors to reduce bone loss.** In this respect, the isoflavonoids are acting as SERMS. Currently, the major compounds in the SERM classification in clinical use are *Nolvadex*® (tamoxifen) which blocks ER and slows down breast cancer growth and *Evista*® (raloxifene) which blocks estrogen receptors in breast tissue and uterine tissue while allowing ER to be stimulated in bone.

Apparently a natural SERM, IP *appears* to have the greatest activity of the isoflavonoids to interact with the bone to reduce bone loss (resorption) and stimulate bone formation. This SERM behavior of the isoflavonoids is the characteristic that makes them attractive as a natural health product. A plant product that occupies an estrogen receptor (or an IP receptor) and stimulates bone formation, while preventing stronger estrogenic compounds from occupying the receptor site within breast tissue and turning on DNA synthesis, it is medically important. This is an example of biologic multi-tasking (not to be confused with pseudo multi-tasking such as what Bill Gates promised us with Windows® 95 and 98). This SERM effect of IP is shared with the other isoflavonoids such as genistein and daidzein. This may play a large role in the decreased incidence of breast cancer in women consuming soy isoflavones on a regular basis (the average Japanese eats over 50

pounds of tofu per year).

Estrogen receptor (ER) structure and function is the subject of intense clinical investigation. There are multiple estrogen receptors. ER alpha and ER beta are two such examples. The ranking of estrogenic potency of phyto-estrogens compared to 17-β estradiol (E2) for both ER subtypes according to the work of Kuiper et al is shown below.¹

- ER alpha subtype (*greatest to lowest affinity for the ER alpha receptor*)
E2 >> zearalenone = coumestrol > **genistein** > **daidzein** > apigenin = phloretin > biochanin A = kaempferol = naringenin > formononetin = **ipriflavone** = quercetin = chrysin
- ER beta subtype (*greatest to lowest affinity for the ER beta receptor*)
E2 >> **genistein** = coumestrol > zearalenone > **daidzein** > biochanin A = apigenin = kaempferol = naringenin > phloretin = quercetin = **ipriflavone** = formononetin = chrysin

IP is a phyto-estrogen, and its interaction at the ER receptor sites, as noted above, may relate, in part, to its ability to reduce bone loss via the same mechanisms involved with 17-β estradiol's effect on reducing bone resorption. This is discussed further in the following section on bone resorption.

IP Stabilizes or Increases Bone Mineral Density (BMD)

IP decreases bone resorption caused by natural menopause, surgical menopause or menopause induced by LHRH agonists (e.g. *Lupron*®) and it maintains bone mineral density. In many studies, IP stabilizes or increases bone mineral density (BMD) in post-menopausal women.²⁻⁵ The standard dose of IP in these studies has been 200 mg three times a day at meal times. Moscarini et al showed that IP increased BMD by 5.8% after 12 months of treatment in 90 women with postmenopausal osteoporosis (PMO). The only adverse effects of IP noted were gastric upset or nausea in 3% of the patients.³ Gennari et al studied IP + 1000 mg of elemental calcium per day vs. calcium alone in PMO. BMD declined in the women taking only calcium by 4.9% +/- 1.1% but in those women receiving IP + calcium, BMD was stable. Urine

hydroxyproline excretion (a bone resorption marker) was diminished in the IP group indicating IP reduces bone resorption.⁵

It is well known that estrogens will stabilize bone loss in post-menopausal women. Estrogens will also prevent bone loss in men with prostate cancer receiving androgen deprivation therapy.^{6,7}

Agnusdei et al, in a multicenter study involving 83 postmenopausal women, showed that the combination of IP and low dose *Premarin*® (0.30 mg/day) **increased** BMD by 5.6% after one year whereas there was a BMD **loss** of 1.4% and 1.7% in the patient groups receiving 0.30 mg of *Premarin*® and placebo, respectively.⁸ It would therefore seem probable that the use of Estriol, an estrogen compound that protects the breast tissue against breast cancer, in combination with IP and calcium, might be an ideal approach to treating PMO. **It is also conceivable that men with PC receiving either *DES*®, *PC SPES*® or *Emcyt*® might derive increasing bone benefit from the combination of such estrogenic compounds with IP along with calcium.**

In women, it is clear that progesterone stimulates bone formation. We therefore suggest an estriol-progesterone combination (2 mg + 100 mg respectively taken twice a day) plus IP along with supplemental calcium for women with documented PMO. Clinical trials to optimize bone integrity using these compounds in women should be undertaken. Studies in men with bone loss are similarly needed, especially

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with the major benefits of the soy isoflavonoids against PC (see *Insights*, Vol. 2, No. 3).

Calcium should be taken in the evening. We recommend two Bone Assure capsules (Life Extension Foundation) at dinner and two at bedtime or all four at bedtime. A spot urine calcium measurement should remain less than 250 mg/ml. Serum calcium levels should be within the 9.2 to 10.5 range. The dose of oral calcium can be increased to six capsules a day or decreased pending these measurements. IP also prevents the bone loss resulting from surgically-induced menopause after the removal of the ovaries. In a randomized study comparing calcium supplementation alone with IP and calcium combined, the combination therapy prevented the increase in urinary hydroxyproline secretion and the associated decrease in BMD ($p < 0.01$) seen in the calcium-only treated group. These results show that administering IP prevents the rapid bone loss that follows ovariectomy. Thus, IP can represent an attractive alternative for the prevention of osteoporosis in postmenopausal women who have contra-

indications to standard estrogen replacement therapy.⁹

Studies in female rats that had undergone surgical menopause not only confirmed that IP inhibited bone resorption on a scale equal to that of estradiol injections but that IP did NOT stimulate uterine tissue. This finding supports IP as a SERM: because it increases its estrogen-like effects in bone tissue but not in uterine tissue.¹⁰

Other studies have evaluated the ability of IP to inhibit the bone loss secondary to LHRH agonist therapy (*Lupron*[®] or *Zoladex*[®]) in female patients with benign gynecological con-

ditions. In Group A, treated with *Lupron*[®] plus IP, a decrease in BMD was not seen, nor were there increases in the products of bone breakdown. In patients not receiving IP, a significant decrease in BMD was noted as was an increase in BRM.¹¹

Another study in women compared IP at 600 mg/day or identical placebo tablets given with 500 mg/day of calcium in patients treated with *Lupron*[®] at 3.75 mg every 30 days for 6 months. This was a double-blinded, placebo controlled study. In the placebo-treated subjects ($n = 39$), urinary hydroxyproline excretion showed a significant ($p < 0.01$) increase, and spinal bone density and total body bone density significantly decreased ($p < 0.001$ and $p < 0.05$, respectively) after 3 and 6 months of *Lupron*[®] administration. Conversely, in the IP-treated group ($n = 39$), no significant difference in bone markers and bone density was seen. These data indicate that IP plus calcium prevent the rapid bone loss that follows medically-induced hypogonadism.¹²

IP Prevents Loss in Bone Mineral Density (BMD) by Decreasing Bone Resorption Markers (BRM)		
Treatment Groups (15 patients/group)	BMD ($p < 0.05$)	BRM ($p < 0.05$)
A: Lupron[®] 3.75/month x 6 + IP 600 mg per day	No Decrease	No Change
B: Lupron[®] 3.75/month x 6 only	Decrease	Increase

KEY ABBREVIATIONS & DEFINITIONS

AA: The usual designation for anti-androgen, but often used also to indicate adrenal androgens or arachidonic acid (therefore be aware of the context of the abbreviation).

ADS: Androgen Deprivation Syndrome; the spectrum of symptoms that may occur as a result of androgen deprivation therapy.

ADT: Androgen deprivation therapy; any treatment that decreases the availability of male hormones to the prostate cell population.

AIPC: Androgen-independent PC; a tumor cell population that grows independently of male hormones.

BMD: Bone mineral density

BRM: Bone resorption marker

CBC: Complete blood count; a test to evaluate your white blood cells, red blood cells and platelets

DHEA: Dehydroepiandrosterone; an adrenal androgen precursor

DHEA-S: Dihydroepiandrosterone sulfate; the sulfated and more stable metabolite of DHEA

DHT: Dihydrotestosterone, the active metabolite of testosterone, 5 times as potent

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.

EMP: A hybrid drug combination of nitrogen mustard and estrogen that disrupts cytoplasmic microtubules

ER: Estrogen receptors

ErMRI: endorectal MRI (magnetic resonance imaging)

IAD: Intermittent androgen deprivation

IGF-1: Insulin growth factor 1: a growth factor that stimulates PC cell growth and osteoblast growth

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 luteinizing hormone (LH). LH stimulates the testicles to make testosterone.

LHRH-A: LHRH agonist: mimics natural LHRH, but then shuts down LH production after continuous exposure

MRS: MR spectroscopy

PAP: Prostatic acid phosphatase: an enzyme that is correlated with extra-prostatic spread of disease and a higher risk of recurrences after RP

PMO: Post-menopausal osteoporosis

PTH: Parathyroid hormone: one of the principal calcium-regulating hormones in the body

PTHrP: Parathyroid hormone related protein

RP: Radical prostatectomy

RT: Radiation therapy that may be external beam radiation therapy or internal radiation with permanent seed implants or temporary wire implants

SERM: Selective estrogen receptor modulators: compounds with multi-tasking capability

T: Testosterone: the major male hormone or androgen, produced mostly by the Leydig cells of the testicles

UDPSA: Undetectable PSA; defined in our research as a PSA of < 0.05 using a hypersensitive assay such as DPC Immulite 3rd generation PSA or Tosoh Assay.

Ipriflavone Decreases Bone Pain

One short-term human study examined the effect of 600 mg/day of IP on accelerated bone loss caused by Paget's disease, a genetically linked bone disease characterized by skeletal deformity and bone pain. Paget's disease of the bone, breast cancer and prostate cancer have many endocrinologic and morphologic features in common. Sixteen patients with active Paget's disease were given either 1,200 mg IP a day in four divided doses for one month and then a month of 600 mg/day of IP in three divided doses, or the reverse, with a 15-day "washout" period in between. Both doses suppressed bone pain and BRM. The 1,200-mg daily dose regimen more significantly reduced bone pain.¹³ **Clinical trials of high dose IP (1200 mg per day) should be considered for treating the bone pain of prostate and breast cancers.**

Ipriflavone Decreases Bone Resorption

We are beginning to understand various cancer growth factors, including transforming growth factor beta, insulin growth factor-1, parathyroid-hormone-related protein, interleukin-1, and interleukin-6. How these factors interact among the tumor cell, the bone matrix, the osteoclast, and the osteoblast is shown schematically in Figure 2.

Tumor cells try to survive by producing cell products that stimulate the cell's own growth or by elaborating proteins or enzymes that affect nearby cells. For example, uPA (urokinase plasminogen activator) is a key substance made

by the tumor cell that is able to stimulate both the tumor cell and the nearby osteoblast. PTHrP (parathyroid hormone related protein) is involved with uPA in similar activities.

Parathyroid hormone (PTH) is one of the two principal calcium-regulating hormones in the body, but it also promotes bone breakdown. PTHrP is also secreted by the prostate's neuroendocrine cells that make CGA (chromogranin A). PTHrP interacts with the osteoblast to release IL-6 and interacts with uPA (urokinase plasminogen activator) to release IGF-1. These factors increase osteoclast activity and recruitment of osteoclast precursor cells. Reread Vol. 2, No. 1 of *Insights* for a review of the important interaction of these cell products.

A study by Mazzuoli et al investigated the effects of IP in men and women with hyperparathyroidism. Nine patients were given 1,200 mg/day IP in three divided doses for 21 days. All the patients exhibited reductions in blood and urinary markers of bone resorption.¹⁴

A study by Tsutsumi et al compared IP to the study drug KCA-098.¹⁵ The latter drug inhibits bone resorption in organ culture. Both KCA-098 and IP inhibited bone resorption PTH, prostaglandin E₂, 1 α ,25-dihydroxyvitamin D₃ and IL-1 beta. The inhibitory activity of KCA-098 was more potent than that of IP by a factor of 10-100 times. Oral administration of KCA-098 (1 and 3 mg/kg) or IP (100 mg/kg) to ovariectomized rats on a low-calcium diet increased the breaking force and bone density of the femora. KCA-098 increased the length and calcium content of nine-day chick embryonic

femora cultured *in vitro*, whereas IP did not, suggesting that KCA-098 had a direct stimulatory effect on bone mineralization. Therefore, KCA-098 is more potent than IP in stimulating bone tissue formation and may thus be expected to become a useful agent for the treatment of osteoporosis and possibly PC.

IP has a binding site in an osteoclast precursor cell and appears to partially function by inhibiting release of IL-6, a growth factor known to stimulate growth of osteoclast precursor cells as well as the activity of mature osteoclasts. Benvenuti et al tested IP and its four main metabolites (Metabolites I, II, III, and V) on a clonal population of human osteoclast precursor cells- FLG 29.1. Pharmacological doses of IP and Metabolite III were able to inhibit cell proliferation and interleukin 6 release. Binding studies with radioactive isotope-tagged IP showed the presence of a single specific binding site in the nuclear fraction of osteoclast precursors with a direct effect of IP and Metabolite III on this human osteoclast precursor cell line.^{16,17} **IP reduces bone resorption by inhibiting osteoclast activity.**

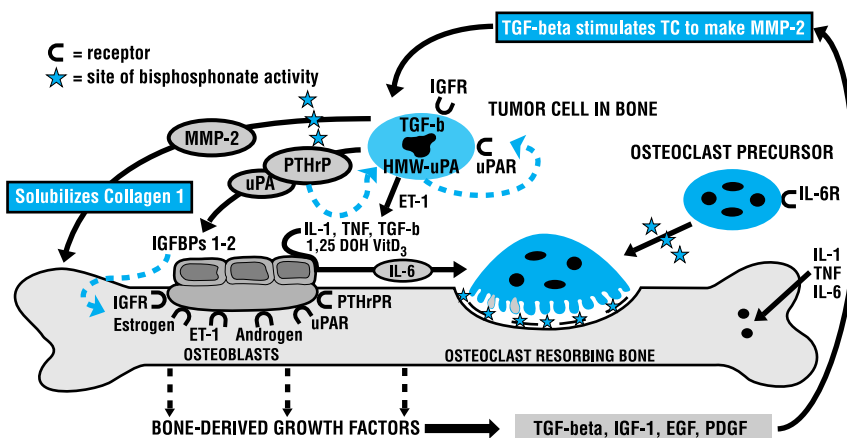
IP also appears to inhibit osteoclasts and osteoclast precursors by increasing calcium influx into these cells via specific IP receptors (two classes), found in both precursor cells and in mature osteoclasts. The fusion of osteoclast precursor cells was significantly inhibited by IP, which led to dose-dependent inhibition of bone resorption and tartrate-resistant acid phosphatase activity. These IP receptors may provide a mechanism to regulate osteoclast differentiation and function.¹⁸ The receptors that accept IP have not yet been identified in human osteoclast cells.

Ipriflavone Increases Bone Formation

IP positively affects bone density in postmenopausal osteoporosis, primarily by inhibiting bone resorption. Using *in vitro* models of human osteoblast differentiation, IP and some of its metabolites stimulated the expression of bone sialoprotein, decorin, and type I collagen, and facilitated the deposition of mineralized matrix. This suggests that IP may stimulate bone formation in addition to its antiresorptive activity.

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Figure 2. The Vicious Cycle of Tumor- and Bone-Related Growth Factors



Androgen Deprivation Therapy: The Basics

By Stephen B. Strum, M.D.

Prostate cancer is an endocrine-related malignancy, and its growth is highly dependent on the availability of male hormones or androgens. Androgen Deprivation Therapy (ADT) is an essential maneuver to kill PC cells, and is a key part of the strategy to reduce tumor volume. Current studies are showing the value of ADT when used to reduce tumor volume in patients receiving radical prostatectomies (RP), external beam radiation therapy (EBRT), or seed implantation.

Treatment with RT is limited by the size of the tumor. To reduce tumor volume, ADT employs drugs that lower the testosterone (T) 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 leuprolide (*Lupron*®) or goserelin (*Zoladex*®). AAs are oral agents given on a daily basis while LHRH-A is given intramuscularly or subcutaneously as long-acting depot injections on a monthly, every three-month or every four-month basis. **It is critical to the proper use of the LHRH-A that the AA be given for at least one week before initiating the LHRH-A to prevent flare.** Flare is a paradoxical reaction that occurs during initial exposure to the LHRH-A and can actually stimulate the production of more testosterone during the first 5-12 days after initiation of the LHRH-A than the baseline testosterone. We routinely use a combination of AA and finasteride (*Proscar*®) to prevent flare.

Rationale for ADT + RT

The rationale for the use of ADT is to reduce tumor volume to allow RT to be more effective. The effectiveness 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 al which employed RT with three years of LHRH agonist therapy to treat high grade Gleason score lesions (GS 8-10) or locally advanced PC (CS T3-4).¹ New studies on the use of ADT by pa-

tients with a lower clinical stage and lower GS appears to validate the use of ADT to allow RT to be more effective.²

Studies are being published that now show the equivalence of RT approaches such as external beam RT or seed implantation when compared to similarly selected patients who undergo RP.³ 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. It is important to realize that the PSA as a reflection of tumor volume becomes less reliable as the Gleason score increases. A decreasing leak of PSA into the blood (serum) most likely reflects a tumor cell population that is more undifferentiated (primitive) and less likely to secrete a mature cell product such as PSA.

Combination Hormone Blockade (ADT₂ or ADT₃)

There is growing evidence that ADT using combined modalities of blockade is more effective than using a single modality of blockade. A recent article, however, showed no benefit of *Eulexin*® when given with orchiectomy (castration) compared to orchiectomy alone in men with advanced PC involving the bone (D₂ disease).⁴ In this study, the patients with minimal bone disease had a 5-year survival of only about 50%. In contrast, Labrie et al reported a 66% 5-year survival in D₂ patients with 1-5 bone lesions receiving combination *Eulexin*® and *Lupron*®.⁵ Moreover, EORTC study 30853 showed improved survival in the group receiving combination *Zoladex*® plus *Eulexin*® vs. orchiectomy. In this 327 patient study, there was a 39% decrease in the death rate in good prognosis patients in the combination group vs. the orchiectomy-only group.⁶

The different outcomes reported need to be resolved, since most men today are still receiving combined hormone blockade using an LHRH-A and an anti-androgen. In addition, clarification of other uses of hormone blockade remains relatively neglected. These include the

use of ADT in earlier stages of PC, inhibition of dihydrotestosterone (DHT) production and the use of prolactin inhibitors. These uses are discussed in the PCRI paper called "Hormone Therapy". In this paper, clinical detailed studies using agents that block additional areas in the hormonal axis are cited. Some of these issues are worth discussing here.

DHT (dihydrotestosterone) is the active metabolite of testosterone, and is five times as potent. Therefore, the use of finasteride (*Proscar*®) to block 5 alpha reductase that converts T to DHT appears reasonable. When we employ three drugs as part of ADT, we indicate this by the designation ADT₃, a terminology that allows us to communicate more clearly. ADT₃ (LEP) indicates three-drug ADT with *Lupron*®, *Eulexin*® and *Proscar*®. There are studies using *Proscar*® in post-RP patients to delay the rise in PSA, as well as studies that have combined *Proscar*® with an anti-androgen (AA).⁷⁻⁸ The latter approach is called sequential androgen blockade (SAB) since it both blocks DHT production and prevents both T and DHT from interacting with the nuclear androgen receptors. The SAB approach maintains a high level of T. In some men, this results in fewer problems with erectile dysfunction, muscle loss and other signs and symptoms associated with testosterone deficiency.

We have used *Proscar*® as part of ADT since 1990, employing a dose of 5 mg twice a day. To date, there are no randomized studies comparing ADT₂ vs. ADT₃. We have published preliminary findings using ADT₃ in the setting of intermittent androgen deprivation (IAD). When such patients are taken off the LHRH-A and the anti-androgen, they are left on *Proscar*® as maintenance therapy. Patients treated with this approach had an average of 13 months additional "off time" from IAD compared to those who received ADT₂ and no *Proscar*® maintenance.⁹

Prolactin is a hormone produced by the pituitary gland that increases the number and sensitivity of androgen receptors. Rana et al used the prolactin-suppressing drug Bromocriptine along with orchiectomy and hydrocortisone (Regimen A) in treating advanced PC. Regimen A was compared to orchiectomy plus *Eulexin*® and to orchiectomy alone. Regimen A resulted in a 61% suppression of primary prostate growth,

compared with only a 48% reduction with orchiectomy and *Eulexin*[®] alone. After 36 months, 40% of the group receiving Regimen A experienced disease progression, compared with 60% in the orchiectomy-only group.¹⁰

PC patients should have their prolactin levels checked via a blood test drawn in the morning. If your prolactin levels are elevated, you should consider one of the following prescription drugs:

- *Bromocriptine*, 5 mg one to two times a day; or
- *Pergolide*, 0.25 mg to 0.5 mg twice a day; or
- *Dostinex*, 0.5 mg twice a week.

You should check your prolactin levels again in 30 days to make sure the drug you choose is, in fact, suppressing prolactin released into your blood from the pituitary gland. *Dostinex*[®] is the newest and easiest drug to use since it has fewer side effects than the older drugs, is more effective in suppressing prolactin, and requires dosing only twice a week.

Many patients use ADT to prepare themselves for local therapies such as RP or RT or Cryosurgery. Others use ADT as a means to extend time before decisions on local therapy, hoping for a new breakthrough that preserves prostatic integrity. Still others are using ADT as primary therapy of PC. **When ADT is used in conjunction with local therapies such as RP, RT (including seed implantation) or Cryosurgery, baseline studies are needed (1) to assess the stage of disease before starting ADT and (2) to coordinate the goals of ADT with the team involved with the local prostate treatment.** For example, the choice of external beam radiation therapy (EBRT) with seed implantation is based on evaluations that include Gleason score, PSA, local extent of disease and gland volume. Studies that involve the latter two items should be done to establish a baseline before ADT is begun. The gland volume should be monitored by digital rectal exams with the goal of lowering the prostate size for optimal implantation. For many brachytherapists, optimal is defined as in the 15-30 cubic centimeter (cc) range.

Biomarkers to Assess Tumor Cell Sensitivity

If tumor cells that make PSA and prolactin (or other biologic markers) are destroyed by anti-cancer therapy of any kind, then the biomarker levels should drop to low or undetectable levels. **The more sensitive the tumor cell population is to the therapy used, the more quickly the biomarker(s) drop and the more sustained is the drop.** It has been our practice to use ADT with the goal of achieving and maintaining an undetectable PSA (UD-PSA) level for at least one year for (1) men using ADT as primary therapy for newly diagnosed PC or (2) men with PSA recurrence (PSAR) following local therapies such as RP or RT. **When we are able to achieve this UD-PSA (<0.05), we feel comfortable that we are not dealing with other mutated tumor cell populations (clones). We believe that these mutated clones are the cell populations that, with continued growth, lead to the clinical expression of androgen-independent PC (AIPC).**

Therefore, our goal is to assess the tumor cell population comprehensively with various biomarkers, treat the tumor cell population with a combination approach such as ADT₃, achieve an UD-PSA and maintain it for approximately one year. We routinely use the three-drug combination of anti-androgen (*Eulexin*[®] or *Casodex*[®]), LHRH agonist (*Lupron*[®] or *Zoladex*[®]), and *Proscar*[®] in our patients. In patients with elevated or high normal prolactin levels, we suggest entry into a trial using *Dostinex*[®] to see if this effects a change in PSA that correlates with prolactin suppression. Our results using *Dostinex*[®] are too preliminary to report at this time.

While our study of the intermittent androgen deprivation (IAD) approach is still investigational, the findings are mature enough to state that **we can report that our average duration of time off-therapy (with UD-PSA achieved and maintained using ADT₂ for >12 months) is currently 29 months.** Moreover, we have found that the use of *Proscar*[®] during induction-ADT and maintenance off ADT extends this time to an average of 42 months. Discontinuation of ADT allows normal T recovery and prevents men on ADT from potential chronic de-

bilitation due to lack of male hormones. Work is needed to refine optimal drug combinations and duration of ADT therapy.

In lieu of RP, RT or Cryosurgery, PC patients may want to consider protocols that incorporate primary ADT for control of PC. 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 preventive fashion.

Monitoring ADT

Patients receiving ADT need to be monitored for signs of possible toxicity with chemistry panels and CBC levels on a monthly basis. Both *Eulexin*[®] and *Casodex*[®] can cause elevations in the liver enzymes SGOT and SGPT. With monthly monitoring, therapy can be changed, thereby decreasing the risk of significant liver toxicity. Avoidance of alcohol also lessens the chance of liver toxicity. In addition, the use of silymarin (100–200 mg three times a day) or alpha lipoic acid (250–500mg twice a day) will prevent and reduce toxicity to the liver cell (hepatocyte.¹¹) The CBC or complete blood count checks the hematocrit to monitor the anemia of androgen deprivation (AAD) that occurs in 80% of men on ADT.¹² 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.¹³

The Androgen Deprivation Syndrome or ADS

Signs and symptoms resulting from ADT are called the androgen deprivation syndrome or ADS.¹⁴ Androgens are vital to the proper function of most organ systems. For example, blocking androgen in the nervous tissue of the brain may be associated with short-term memory loss whereas blocking androgen receptors in the bone marrow often leads to the anemia of androgen deprivation. Many men on ADT report joint symptoms of aches and pains in their feet, knees and hips and stiffness in their hands. We believe that these symptoms represent the effects of androgen deprivation leading to excessive

(Continued on page 9)

Overcoming Impotence...

continued from page 1

Bill's PC wasn't through with him though. Six years after his RP, Bill had his PSA checked and found that it was 3,552. A bone scan showed uptake in the pelvis consistent with metastatic disease. By March, 1992, his PSA had climbed to 12,600. (That's right: 12,600). He had a second bone scan that showed a significant increase in the number of bony lesions.

Bill was told that he would have to start treatment if he wanted to go on living. Specifically, his physician recommended androgen deprivation therapy, but warned Bill that it would probably reduce his libido so much that it would effectively end his sex life while he was under treatment.

"I gave serious consideration to going ahead and dying rather than live without a sex life with my wife," Bill recalls. "Ultimately, though, I elected to go ahead with the treatment, and it did indeed knock down my libido. My orgasm intensity dropped by about 60%."

Clinically, the ADT was quite effective. He was treated with ADT₂ using *Eulexin*[®] and *Zoladex*[®] beginning in March, 1992. By January, 1994 his PSA had dropped to 156. He reached his PSA nadir two years later in January, 1996 with a PSA of 2.4. During this period, he had been switched from *Eulexin*[®] to *Casodex*[®].

"My sex life became as satisfying as it had ever been," Bill says. "I got a penile implant so that I could perform even if I didn't have an orgasm. Also, I discovered that orgasm is 90% state of mind. If you concentrate on what you are doing and savor the enjoyment during the entire act, you can have an orgasm. You have to quit thinking about whether you should be watering the lawn or other irrelevant thoughts and block out the world. I found that if I focused my mind totally, I would have an orgasm."

Bill's condition deteriorated after the PSA nadir of 2.4 was reached. When his PSA dropped no further and started to rise, *Casodex*[®] was discontinued (November, 1997) in hopes of an anti-androgen withdrawal response. However by the following January 1998, his PSA had risen to 51. At the same time, a pulmonary embolus occurred. By that May, his PSA was up to 122,

Call for Jewish Men

If you are a Jewish man over the age of 50, you can help researchers at the Albert Einstein College of Medicine of Yeshiva University to find the causes and risk factors associated with prostate cancer. The study, called the CLAL Study (short for Cancer, Longevity, Ancestry and Lifestyle Study), is looking at environmental and genetic factors that may be associated with prostate cancer. The long-range goal of the research is to translate the findings into preventative measures and innovative therapies for the disease. By participating in this study you can play an active role in generating new information about this disease.

The scientists, led by Dr. Robert Burk, a Medical Geneticist and Professor of Epidemiology at Einstein, will ask participants to fill out a questionnaire, submit a cell sample easily obtained by rubbing the inside of the cheek with brushes that are provided, sign a consent form and, optionally submit a blood sample. All materials are provided and no travel is required. By submitting these materials, you will help to find environmental exposures as well as genetic factors that may be associated with the development of prostate cancer. Dr. Burk indicates that, "It is likely we will find risk factors which will be directly applicable to other populations, such as their diet, exercise or factors relating to hormones."

Dr. Burk says that there is no evidence that Jewish people have an increased risk of prostate cancer, but there is anecdotal information suggesting a growing incidence. Dr. Burk and the CLAL Research team anticipates that information obtained from the study will benefit those at risk for prostate cancer. As with other types of cancer, it is helpful to study a homogeneous group such as the Jews, who have tended to marry within their community. Thus, there are fewer genetic mutations to sift through in trying to determine which ones may be associated with the development of prostate cancer. If you intend to become part of this study, it is important that both of your biological parents are Jewish for this reason.

Your participation is important for future generations. Prevention and cure start with identification of the causes of prostate cancer. You can obtain more information and register on line at www.ca.aecom.yu.edu/burk or you can join the study by calling (718) 430-3366, toll free (877) 444-2525, or writing to:

Dr. Robert Burk
Albert Einstein College of Medicine
1300 Morris Park Avenue, Ullmann 515
Bronx, NY 10461

The CLAL Research Study team thanks you for your time and effort. ❖

and his bone mineral density showed severe osteoporosis with a T score of -4.4. A bone scan showed metastatic disease in the pelvis and spine.

By December 17, 1998, his baseline PSA was 290 and his PAP was 14.7. At that time, high-dose ketoconazole (*Nizoral*[®]) and hydrocortisone were started. By June 3, 1999, his PSA had dropped to 32.9 with a PAP of 2.6. Since then, unfortunately, the PSA has risen again with his most recent PSA being 109 on October 7, 1999.

However, even with this roller coaster ride, Bill has remained upbeat. When Bill and I talked this summer, he reported that his sex life continues to be rich and fulfilling. When I asked him frankly how this could be, he thought a moment, and then answered this way.

"As I said, an orgasm is 90% psychological. I don't start with a desire to have an orgasm; I start with the desire to seduce my wife whom I love very much. I start hours beforehand, touching, whispering, kissing. We are intimate in every sense of that word. My primary purpose is to please her and I focus on that to the exclusion of everything from the outside world. When she is totally pleased, I am aroused and pleased myself."

I guess the moral of all this is that if a man has a good sex life and a close relationship with his lover, there is no reason that PC must change that. If it does cause a change, it will be a change in attitude, and if you're like Bill Whatley, you simply won't let that happen, whatever the clinical situation may be. ❖



As A Symbol of My Love For You by May Stephens

As the wife of a PC survivor,

I attended the PCRI conference this summer, and heard Harry Pinchot's inspiring message. For those who were not there, I would like to share my reactions to Harry's words.

He opened by crediting April Becker of US TOO with giving him a profound insight into the effect PC has on both partners. "PC is a disease which afflicts not just the man with the prostate, but also his partner. We have come to expect our wives and partners to be there for us in our time of need. We often become fixated with our own problems and the fear of our own mortality, while becoming oblivious to the needs of our spouse."

I identified so well with the partner Harry spoke of, a partner who must not only deal with her husband's "declining health, unusual diets, mood swings, anxiety over PSA test results, doctor visits, insurance, and all the other issues" relating to his disease, but she must also face her own fears. "These are real and pervasive fears which often are not fully shared. She must come to grips with the very real possibility of losing her spouse, her lover, her life partner, her best friend."

The feeling of dread that enters your being when you first learn of your husband's diagnosis never fully leaves you, even when he seems to be recovering from the shock, and even reconciled to it. Harry put it this way: "Recognize her fears and the load she must carry. When your

problems are over, it is she who must pick up the pieces and move on in life's journey without you. Ask yourself what you can do to make her life, now and after you are gone, a better life."

At this point, Harry asked each survivor and his partner to stand. Every man held a rose, and gave it to the woman in his life, repeating Harry's words: "Please accept this rose as a symbol of my love for you, and as an expression of my appreciation and recognition of all you have done for me. For being my partner, for caring for and caring about me, for being there at my darkest moments, for sharing both my victories and my disappointments as we travel down this road together." ❖

Thank you, Harry.

Ipriflavone... continued from page 5

To assess whether these effects translate into an improved bone "quality" *in vivo*, Civetelli et al measured biomechanical properties, mineral composition, and crystallinity of femurs of 12-week-old, male, Sprague-Dawley rats treated with IP for one month. IP-treated bones acquired a higher capacity to withstand dynamic stress, needing 1.5-fold higher energy to fracture femurs of IP-treated rats. IP also increased BMD, assessed by both volume displacement and ash analysis, whereas the relative contents of calcium, phosphorus, and magnesium in the ashes were not affected. Thus, no gross abnormalities in mineral composition of bone occurred after IP administration. Therefore, one-month treatment with IP increased bone density and improved the biomechanical properties of adult male rat bones without altering mineral composition or bone crystallinity.¹⁹

In another study, the effect of IP and its metabolites on the differentiation and function of human osteoblastic cells was investigated. IP and metabolite III stimulated the expression of bone sialoprotein mRNA, a protein involved in cell attachment to the matrix. Only metabolite III increased the steady-state level of decorin mRNA, a collagen fibrillogenesis-regulating

proteoglycan. Metabolites III and V, but not the other isoflavones, increased the expression of type I collagen mRNA. Finally, IP consistently increased the amount of calcium incorporation leading to the stimulation of mineralization.

Thus, IP and its metabolites regulate the differentiation and biosynthetic properties of human bone-forming cells by enhancing the expression of some important matrix proteins and facilitating the mineralization process.²⁰

Summary

IP is a synthetic derivative of daidzein. It has significant properties that relate primarily to decreasing bone resorption. The mechanisms of IP may be related to receptor activation on osteoclasts and their precursors that increase calcium influx and inhibit osteoclastic activity and function. Other IP receptors on osteoclast precursors have been shown to decrease IL-6 production thus affecting osteoclast recruitment and mature osteoclast activity. Studies of IP in men are mandatory to assess effects on bone resorption and formation and PC cell growth as well. It may well be that the

high intake of soy, hence isoflavones, by Asian men not only affects bone integrity in the setting of prostate cancer but alters the natural history in regard to the aggressiveness of PC. ❖

Androgen Deprivation Therapy... continued from page 7

bone resorption. If unchecked, this eventually leads to osteoporosis. How does this happen? Androgen receptors have been found on osteoblasts. Perhaps, the androgen blockade from ADT causes diminished osteoblast growth leading to an uncoupling of osteoblast-osteoclast function with excessive osteoclastic activity and bone resorption.

The signs and symptoms relating to the ADS are highly variable from man to man. Some men have few complaints from withdrawal of androgens while others have multiple problems and are miserable. It is our goal to kill as many PC cells as possible while allowing a high quality of life. Volume 2, No. 1 of *Insights* and the PCRI website has articles on ADS and how symptoms can be ameliorated to improve the quality of life of men experiencing such adverse effects from ADT. ❖

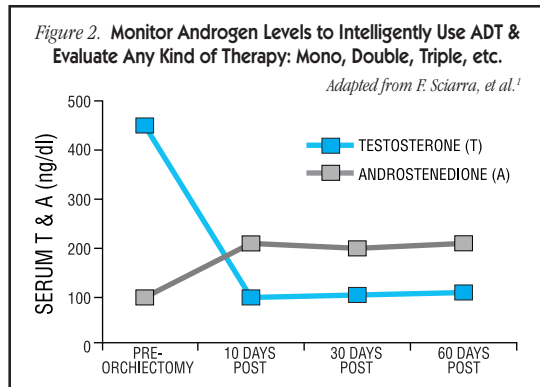
Important Principles in Chemotherapy: Regimens Treating And

One of the greatest problems we face today is how to prevent the emergence of AIPC and how to treat it when it develops. AIPC is defined as disease progression evidenced by a progressively rising PSA (three consecutive rises of at least 10% each or three rises that involve an increase of 50% over the nadir PSA) or an increase in tumor mass on bone scan, X-ray, CT scan or MRI **despite a castrate level of testosterone (T < 20 ng/dl)**. In addition, understanding the endocrinology of PC is essential to accurately defining the patient's status.

For example, if a patient's PSA stops falling and begins to rise on ADT₂ or ADT₃, if the T level is castrate, and if the adrenal androgen precursors are not low, then AIPC is presumed present until proven otherwise. If in this setting, the levels of the adrenal androgen precursors are suppressed, an androgen receptor mutation (ARM) should be excluded. The latter is confirmed by demonstrating a response to anti-androgen withdrawal with falling PSA levels.

As shown in Figure 1, the patient's serum LH level should be checked if T > 20 ng/dL. If LH is not completely suppressed (usually < 1.0), it is reasonable to increase the dosage of the LHRH-A. If the LH level is suppressed, we measure the levels of adrenal androgen precursors DHEA-S and androstenedione. These hormones can be converted to T and may account for T levels of > 20 ng/dl. If such levels were found, we would prescribe drugs to suppress adrenal androgen precursor production such as *Nizoral*[®] (high-dose ketoconazole or HDK) and hydrocortisone.

There are studies to support the concern that adrenal androgen precursors can increase in the setting of PC treatment and that this increase leads to higher T levels which in turn affect a poor clinical outcome, if the condition is not recognized. The elevation in androstenedione and T shown in Figure 2 in 10/27 men undergoing orchiectomy for PC supports our concerns.¹



Defining Key Pharmacological Principles & Supportive Care

Many studies that evaluated the efficacy of various secondary treatments, including chemotherapy of AIPC, predated the days of PSA testing. In these studies, responses were evaluated by improvement in symptoms such as bone pain, or by reduction in tumor size on bone scans or CT scans. Based upon the limited sensitivity of scans to assess tumor response, older studies may have missed patient responses that might have been noted if PSA testing were available. In addition, past studies did not focus on pharmacological principles such as: **Dose Intensity, Exposure Time, Bone Marrow Support and other Supportive Care.**

Treatments that were labeled as ineffective in the past may conceivably turn out to be more effective when given to patients with less tumor volume and under better pharmacological conditions. In a thorough review of the literature,

we have found that long-lasting responses to secondary therapies have been documented. What patient or treatment-related variables were present in such responding patients?

Dose Intensity (DI)

Dose intensity or DI is a term used to compare relative amounts of a drug administered in a given unit of time. For example, compare the relative dose intensities of *Taxotere*[®] regimens A and B. Regi-

men A delivers a dose intensity that averages 93 mg/m² per month. Regimen B delivers a dose intensity that averages 100 mg/m² per month.

REGIMEN A:

- Drug dose:** 70 mg/m² (m is for meters of body surface area calculated using height and weight)
- Frequency:** every three weeks
- Average:** 280 mg/m² in 12 weeks (or 93 mg/m² per month)

REGIMEN B:

- Drug dose:** 25 mg/m²
- Frequency:** every week
- Average:** 300 mg/m² in 12 weeks or 100 mg/m² per month

Regimen B with its more frequent lower doses has less toxicity due to lower peak blood levels than Regimen A with its higher but less frequent dosing. For example, *Taxotere*[®] dosed weekly at 25 mg/m² is associated with far less toxicity in regard to hair loss, bone marrow suppression, and nausea. The doses of premedication (e.g. dexamethasone, benadryl, *Tagamet*[®]) and/or the need for premedications to suppress pulmonary side-effects of *Taxotere*[®] with the weekly regimen are significantly different than with the every-three-week regimen. The efficacies of these different regimens have not been reported in a randomized trial. Low-dose weekly *Taxotere*[®] is unquestionably a more patient-friendly regimen than the higher dose standard *Taxotere*[®] protocol. Our preliminary results appear to confirm similar response rates.

In a study by Chlebowski, et al, *Cytosaxan*[®] at 800-1,000 mg/m² every three weeks intravenously (IV) as a single agent was compared to patients receiving an oral *Cytosaxan*[®] dose of 200

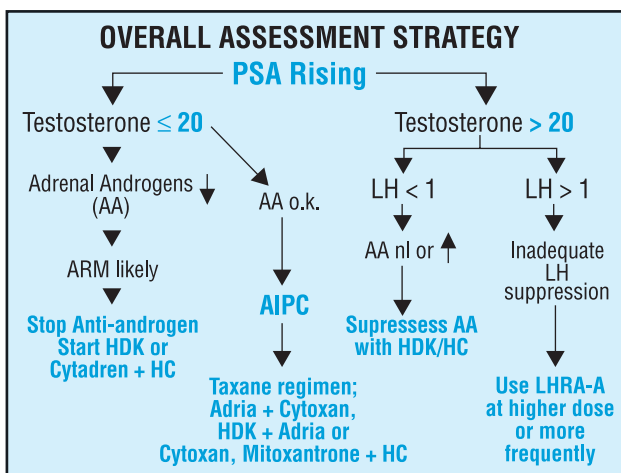


Figure 1. HDK = high dose ketoconazole; HC = hydrocortisone; LH = luteinizing hormone; ARM = androgen receptor mutation

Androgen-Independent Prostate Cancer (AIPC) By Stephen B. Strum, M.D.

mg/m² per day for four days every four weeks as part of a three-drug regimen of *Cytoxan*^{®2}, *Adriamycin*[®] and 5-FU (CAF). Approximately 50% of an oral *Cytoxan*[®] dose is absorbed through the gastrointestinal tract (e.g., its oral bioavailability is only 50%). Therefore, patients receiving oral *Cytoxan*[®] received a “net” dose of 100 mg/m² per day for four days every four weeks. The average weekly *Cytoxan*[®] doses of these regimens would be:

Route	Cytoxan dose/week	Relative DI	Median survival
IV	333 mg/m ²	3.3	18.6 months
Oral	100 mg/m ²		8.1 months

In a more recent trial, Small et al used escalating doses of *Cytoxan*[®] (800-1,200 mg/m²) combined with *Adriamycin*[®] (40 mg/m²)³. Patients were given G-CSF (*Neupogen*[®]) to support their bone marrow in an attempt to prevent a low white blood cell count and possible infection. **There was a greater than 50% reduction in PSA levels in 16/35 (46%) patients, who survived for a median duration of 23 months.** Ten of 35 patients (29%) had a greater than 75% reduction in their serum PSA. The median survival for patients who did not have a PSA response was seven months. Importantly, *Neupogen*[®] support resulted in a significant decrease in white blood cells in only 33% of treatment cycles, and fever developed in only 8% of treatments.

Exposure time

Most chemotherapy agents kill cancer cells that are actively multiplying. PC cells generally grow slowly so they must receive a longer exposure time to the chemotherapy or other anticancer agent. Exposure time can be increased by (1) daily oral therapy, (2) a more frequent schedule of intravenous administration, or (3) use of low-dose continuous intravenous infusions administered by means of a computerized pump given through a venous access device such as a *Port-a-Cath*[®]. Such protracted infusion delivery increases exposure time while decreasing the toxicity of chemotherapy. **Drugs such as *Cytoxan*[®] and *Adriamycin*[®] have a much lower toxicity profile and a higher therapeutic index when given in this way.**

We currently have a protocol in progress that employs *Cytoxan*[®], given as a continuous infusion over 120 hours. In conjunction with another agent, Fluorouracil (during the same pe-

riod of time). This combination has shown high activity in advanced refractory breast cancer in a pilot trial. Since prostate and breast cancer are strikingly similar in so many ways, we have begun this program in advanced PC to utilize a long exposure time of drugs that are known to be active in PC. Moreover, the use of low-dose continuous chemotherapy has another advantage in lowering the toxicity of the drug(s). **Therefore, the therapeutic index, a measurement of efficacy and side-effects is greatly enhanced with protracted chemotherapy administration.** Unfortunately, many oncologists are not familiar with the use of ambulatory infusion pumps or venous access devices such as the *Port-a-Cath*[®].

Two additional studies show this principle of prolonged exposure time. Pavlick et al treated 27 patients with AIPC with high dose ketoconazole (HDK) + hydrocortisone (HC) combined with oral *Cytoxan*[®] at 100 mg/m² per day for 14 days out of each 28 day cycle.⁴ Twenty-one of 27 (78%) of patients had a ≥ 50% drop in PSA with a mean and median PSA decline of 79% and 93%, respectively. The median baseline PSA was 68 and the median nadir PSA was 5.1. The median duration of response was nine months with a range of 3-36 plus months.

Cruciani evaluated 35 patients receiving an oral regimen of *Emcyt*[®] (estramustine phosphate or EMP) and etoposide (VP-16)⁵. **Both drugs were given for 14 days of each 28 day cycle. 30/35 (85.7%) had a ≥ 50% drop in PSA with an actuarial median survival of 32 months for the entire group of patients.**

Bone marrow support

One of the essential factors in the successful management of the cancer patient is adequate supportive care. This involves multiple factors in the medical and surgical management of the patient, and includes psychological support as well. With the advent of agents that can stimulate the bone marrow, we now are able to give chemotherapy at higher doses by supporting and/or preventing such toxicities as low white blood cell counts, anemia, and low platelet counts.

A low white blood cell count (also called *granulocytopenia* or *neutropenia*) is a major dose-limiting factor with chemotherapy and is a cause of infection- the most serious side effect of chemotherapy. *Neupogen*[®] or

Marrow Cell Stimulated	Trade Name	Generic Name
Granulocytes	Neupogen [®]	Filgrastim
Granulocytes & macrophages	Leukine [®]	Sargramostim
Erythrocytes	Procrit [®] , Epogen [®]	Erythropoietin alpha
Platelets	Numega [®]	Oprelvekin

Leukine[®] support reduces or eliminates the number of hospitalizations for infection associated with chemotherapy and reduces other problems such as mouth and throat sores.

Anemia may also be a significant problem for AIPC patients receiving chemotherapy. Usually, a low red blood cell count is already present to some degree in AIPC patients due to their ADT. **Anemia, left untreated, can cause severe weakness, shortness of breath, dizziness, mental status changes and chest pain.** The availability of *Procrit*[®] to stimulate bone marrow red blood cell production can help minimize the adverse effect severe anemia can have upon the AIPC patient. The use of *Procrit*[®] has largely replaced the need for blood transfusions. *Neupogen*[®] and *Procrit*[®] are miracle drugs for the patient receiving chemotherapy. Unfortunately, they are often not used in an attempt by HMO doctors to save money or just plainly out of ignorance.

A low platelet count, also called *thrombocytopenia*, is another dose-limiting factor and is the cause for a serious side effect of chemotherapy, bleeding. Until recently, thrombocytopenia could delay chemotherapy and cause dosage reductions or even changes in drug therapy. ***Neumega*[®] has now become available as a marrow stimulant specific for platelet production and its use will support patients with low platelet counts to prevent hemorrhagic complications.**

Two studies involving marrow supportive agents in patients treated with chemotherapy for AIPC demonstrate the importance of these principles. In a report by Smith et al, high-dose *Cytoxan*[®] was used in 21 PC patients in conjunction with granulocyte-macrophage colony stimulating factor, (GM-CSF or *Leukine*[®]).⁶ *Cytoxan*[®] at a dose of three grams/m² was given intravenously on day one and subcutaneous GM-CSF 5 mcg/kg per day was begun on day three and continued for one week. Patients were given a lower dose of *Cytoxan*[®] if prior pelvic radiation had been given. This study showed a

(Continued on page 16)

Taxotere® (Docetaxel) in the Treatment of Androgen Independent Prostate Cancer

by Robert S. Mocharnuk, M.D.
and Stephen B. Strum, M.D.

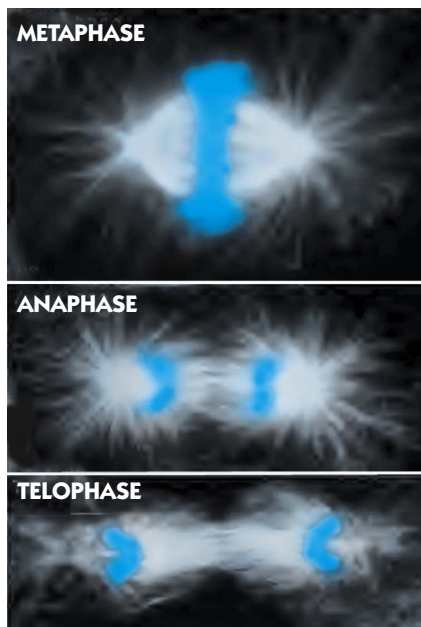
Prostate cancer (PC) poses many clinical challenges when it becomes refractory to androgen deprivation therapy. Fortunately, the use of PSA screening has led to earlier detection and reduction in the number of men first presenting with advanced disease so that definitive treatment can be more frequently offered at the time of diagnosis. But for those who ultimately relapse after local therapy and fail hormone blockade, or those who have AIPC, treatment options must take into account various factors. These include extent of disease, disease symptoms, patient life expectancy, patient performance, pre-existing co-morbid conditions and treatment goals.

Background

Chemotherapy is an important treatment option. However, determining how to gauge response to chemotherapy remains problematic. Reductions in PSA are used commonly to measure tumor response, and indeed, previous multivariate analysis has linked PSA response to prediction of survival. Still, such analyses are retrospective because PSA data was not available for all patients when many of these studies were conducted. Prospective analysis is still needed to confirm that PSA reduction is indeed a marker of response to treatment.

Since the time of these trials, more effective treatments have been developed which utilize advances made in the understanding of the biology of AIPC, including proteins which target apoptosis, peptide growth factors, topoisomerases, the nuclear matrix and cytoplasmic microtubules. Bcl-2, a protein whose expression inhibits cell death, is known to be expressed in 65% of AIPC.¹ Many of the chemotherapy combinations exploit these biologic differences in order to deactivate and eliminate tumor cell lines by different mechanisms. Other combinations seek to eradicate tumor lines synergistically.

Microtubules play a significant role in various cell functions. They maintain cell shape and form the mitotic spindle in the M phase of cell division. Microtubules have been an important target of cancer chemotherapy. Estramustine (*Emcyt*®), a hybrid drug combination of nitrogen mustard and estrogen, disrupts cytoplasmic microtubules by binding to both tubulin and microtubule-associated proteins (MAPs), preventing mitosis.



In the above pictures of cell division (*courtesy of Claire Walczak*), the blue DNA chromosomes are being pulled to opposite ends of the cell by the mitotic spindle.

Unfortunately, gastrointestinal, thrombotic and cardiovascular toxicities from *Emcyt*® can be significant. Chemotherapy combinations of *Emcyt*® with vinca alkaloids (*Velban*®, *Navelbine*®), or with taxanes (*Taxol*®, *Taxotere*®) or the epipodophyllotoxin etoposide (*Vepesid*®) are active in PC. It is known that vinca alkaloids and taxanes inactivate bcl-2 via phosphorylation. Additionally, these agents act on tubulin; the vincas depolymerize microtubules while the taxanes promote polymerization of tubulin, block the disassembly of microtubules and thereby prevent cancer cells from dividing.

While the *Emcyt*® plus *Taxol*® combination appears to be a particularly appropriate one given the affinity of both of these agents for the microtubule complex, *in vitro* studies have shown *Taxotere*® (docetaxel) to be 100 times more powerful than *Taxol*® (paclitaxel) in phosphorylating bcl-2 while achieving similar microtubular inhibition.² The early results of *Taxotere*® used in the treatment of PC indicate a high degree of activity of this agent. *Taxotere*® appears to be the single most active agent in AIPC at this time. This review details the clinical trials using *Taxotere*® alone

or in combination with agents such as *Emcyt*®. Dexamethasone (*Decadron*®) is used to prevent the side-effects of the taxanes.

Recent Clinical Trials

Several clinical trials have looked at the role of *Taxotere*® in the treatment of AIPC (Table 1).

In a Phase I trial of 32 patients, Petrylak et al gave *Emcyt*® and *Taxotere*® both minimally and extensively to pre-treated patients with AIPC.³ This regimen showed the optimal dose levels of *Taxotere*® to be 70 mg/m² for minimally pre-treated patients. PSA decreases $\geq 50\%$ were seen in 70% of minimally pre-treated and 50% of extensively pre-treated patients for an overall response rate of 20/32 or 63%. PSA decreases were $>75\%$ in 40% and 25% of these groups, respectively. The median duration of survival was greater than one year and had not yet been reached. Grade 3 and 4 neutropenia (low white cell count) occurred in 17 patients with one experiencing neutropenic fevers. A *Taxotere*® dose at 60mg/m² was recommended for extensively pre-treated patients.

Because steroids on their own have been shown to be associated with declines in PSA in patients with AIPC, the possibility that *Decadron*® pre-treatment having an effect on PSA could not be excluded. Shelton et al treated 12 patients with *Decadron*® at a dose of 20 mg every 6 hours for three doses every three weeks. If the PSA levels remained stable or declined, the patient was maintained on *Decadron*® alone until disease progression occurred. Patients who progressed were treated with *Taxotere*® plus *Emcyt*® and *Decadron*® as part of a Phase II trial.⁴ Seven of eight (88%) evaluable patients experienced a $\geq 50\%$ PSA reduction and five of eight (63%) patients experienced a PSA decline $\geq 75\%$. This study demonstrated that *Decadron*® did not contribute significantly to the PSA response seen in those patients treated with *Taxotere*® and *Emcyt*®. Grade 3 neutropenia was seen in five patients.

Two Phase I/II trials, Kreis et al and Natale, employed different schedules of *Emcyt*® and *Taxotere*®. Kreis gave *Taxotere*® every 21 days with *Emcyt*® every day for 21 days.⁵ He reported PSA decreases $> 50\%$ in 14 of 17 patients (82%). Natale employed two regimens.⁶ One consisted of *Emcyt*® 420 mg for days 1-4 with escalating

Table 1. Peer-Reviewed Studies of Taxotere® in Androgen-Independent Prostate Cancer (AIPC) 1998-2000

Taxotere® Regimen	Response Rate ≥ 50% PSA Decline (↓) Some data with ≥ 75% PSA Decline (↓)	MDR – median duration of response MDS– median duration of survival	Comments Emcyt® = estramustine Decadron® = dexamethasone bid = twice a day tid = three times a day
Emcyt + Taxotere	20/32 (63%) with ≥50% PSA ↓	MDS > 1yr; not yet reached	Multiple dose levels of Taxotere with optimal dose at 70 mg/m ² on day 2 + Emcyt 280 mg tid days 1-5, Decadron 20 mg midnight, 6 am and just before Taxotere
Petrylak DP, Macarthur RB, O'Connor J, et al: Phase I trial of docetaxel with estramustine in androgen-independent prostate cancer. J Clin Oncol 17:958-67, 1999.			
Emcyt + Taxotere + Decadron after Decadron failure	7/8 (88%) with ≥50% PSA ↓ 5/8(63%) with ≥75% PSA ↓	No data	12 pts who received Decadron first, failed and then treated with Emcyt + Taxotere + Decadron
Shelton G, Gerson H, Zuech N, et al: Activity of docetaxel (D) + estramustine (E) after dexamethasone (Dex) treatment in patients (pts) with androgen insensitive prostate cancer (AIP). Proc Am Soc Clin Oncol 17:343A, 1998.			
Emcyt + Taxotere	10/13 (77%) with ≥50% PSA ↓	No data	Various dose regimens of weekly Taxotere
Natale RB, Zaretsky S: Phase I/II trial of estramustine (E) with taxotere (T) or vinorelbine (V) in patients (pts) with metastatic hormone-refractory prostate cancer (HRPC). Proc Am Soc Clin Oncol 17:338a, 1998.			
Emcyt + Taxotere weekly	14/18 (77.8%) with ≥50% PSA ↓ 9/18 (50%) with ≥75% PSA ↓	No data	Weekly Taxotere at doses ranging 20-35 mg/m ² per week for 6 of 8 weeks. Emcyt dosed tid days 1-3 at 420 mg first 4 doses, 280 mg last 5 doses; Decadron 4 bid day before, of, and day after Taxotere.
Natale RB, Zaretsky SL: Phase I/II trial of estramustine (E) and taxotere (T) in patients with metastatic hormone refractory prostate cancer (HRPC). Proc Am Soc Clin Oncol 18:348A, 1999.			
Emcyt + Taxotere Emcyt 10mg/kg x 5 days + low dose hydrocortisone Chemo naïve	11/19 (57.9%) with >50% PSA ↓ 7/11 (63.6%) with >75% PSA ↓	No data; only 2 cycles of Rx	Taxotere at 70mg/m ² every 3 weeks on day 2
Savarese D, Taplin M, Marchesani B, et al: A phase II study of docetaxel, estramustine, and low dose hydrocortisone in hormone refractory prostate cancer: preliminary results of CALGB 9780, Proc Am Soc Clin Oncol 18:321a, 1999.			
Taxotere Chemo naïve	16/35 (45%) with >50% PSA ↓ 7/35 (20%) with >80% PSA ↓	MDR 9 mos MDS 12 mos	75 mg/m ² every 3 wks No Emcyt used
Picus J, Schultz M, Cochrane J: A phase II trial of docetaxel in patients with hormone refractory prostate cancer(HRPC): long term results. Proc Am Soc Clin Oncol 18:314a, 1999.			
Emcyt + Taxotere Chemo naïve	16/19 (84%) with ≥50% PSA ↓ 13/19 (68%) with ≥80% PSA ↓	MDR if 50% drop 5.5 m (0.75+ -16mos); if 80% or more drop 5 mos (.75-13 mos)	Taxotere at 70 mg/m ² Emcyt 280 tid x 5 days; Decadron 20 po 12 hours, 6 hours and just before chemo every 3 wks
Weitzman A, Shelton G, Zuech C, et al: Phase II study of estramustine (E) combined with Docetaxel (D) in patients with androgen-independent prostate cancer (AIPCA). Proc Am Soc Clin Oncol 18:355a, 1999.			

(Continued on next page)

PCRI Conference Questions & Answers

This year's inaugural PCRI Conference stimulated a number of questions from attendees, both when they were at the conference and when they returned home. In this section, Dr. Strum answers some of these questions, both in the area of diagnosis and of on-going treatment.

DIAGNOSIS

Suppose I get a high AMAS test result, confirmed twice and believe it means I'm in the early stage of some cancer, but my PSA stays steady at a low level (.01), so I think I do not have prostate cancer. How shall I proceed to identify what cancer I have?

Dennis Gibson

We don't have answers to many issues and this is one of them. I am still undecided as to the value of the AMAS test. When it can be done anywhere in the U.S. and when the interpretation can be more objective, I will feel more comfortable about this test. Until then, I can only defer back to its originator. If you feel that you might have an occult neoplasm, I would suggest you use your family history, occupational

history and medical findings to organize a search. You might also use colonoscopy to rule out a colonic malignancy, and PET scanning to rule out a cancer elsewhere. If you are or were a significant cigarette smoker (40 or more years of cigarette smoking at 1 ppd), then a spiral CT of the lungs is in order. If you have a family history of stomach cancer, then an upper endoscopy is indicated. These are my thoughts, given the limited information you have presented.

Concerning MRI – what is the value of spectroscopic MRI?

John V. Donovan

The endorectal MRI (erMRI), with or without spectroscopy, is a valuable tool in the assessment of the patient with PC. Many published reports by D'Amico confirm the significance of endorectal MRI findings as a tool to assess organ-confined disease.

One study used the erMRI to predict pathologic organ-confined disease at the time of RP by assessing the endorectal findings before and during ADT. Twenty-one patients had a decrease in the erMRI-determined prostate volume and prostate-specific antigen during androgen

suppression, whereas only 10 of 21 (48%) had a reduction in the erMRI-determined tumor volume. There was a statistically significant increased proportion of patients with a decrease in the erMRI-determined tumor volume ($P = 0.008$) who had pathologic organ-confined disease.¹

D'Amico has also shown that the erMRI is useful in combination with the PSA and percentage core biopsies to predict patients at high risk for PSA failure post-RP. For intermediate risk patients (i.e., either a PSA < 4 and biopsy Gleason sum of 7, a PSA > 4 to 10 ng/mL and biopsy Gleason sum 5 to 7, or a PSA > 10 to 20 ng/mL and biopsy Gleason sum 2 to 7), 50% of patients had pathologic organ-confined disease despite 100% positive biopsies. However, in the subset of intermediate-risk patients with an abnormal erMRI for extracapsular extension (ECE) or seminal vesicle invasion (SVI) and at least 50% positive biopsies, all had extraprostatic disease and failed biochemically by 47 months post-RP. Intermediate-risk patients with < 50% positive biopsies had pathologic organ-confined disease in at least 77% of the cases.² ▶

Taxotere...continued from page 13

doses of Taxotere[®] or Navelbine[®] given weekly. Natale reported 10/13 (77%) PSA response to the Emcyt[®] + Taxotere[®] arm compared to 6/11 (55%) in patients receiving Emcyt[®] + Navelbine[®]. Natale observed no Grade 4 neutropenia in either regimen although significant Grade 4 neutropenia was seen in the higher doses of the Kreis study. The second Natale trial used Emcyt[®] on days 1–3 and Taxotere[®] weekly ranging from 20–35 mg/m². Fourteen of 18 or 77.8% of patients had a PSA decline of ≥50% with 9/18 or 50% having a ≥75% decline in PSA.

Additional trials have attempted to further refine the use of Emcyt[®] to minimize toxicity. Sinibaldi et al administered Taxotere[®] 70mg/m² 12 hours after five oral doses of Emcyt[®] (280mg every six hours).⁷ Of the 22 patients enrolled, 18 were evaluable. A >50% decline in the PSA was observed in seven patients, grade 4 neutropenia occurred in only seven of 98 courses of treatment, and neutropenic fever occurred in only two of 98 courses.

Savarese et al reported on a Phase II trial with Taxotere[®], Emcyt[®] and hydrocortisone.⁸

PSA declines of >50% were seen in 11/19 patients (58%), and 7/11 or 64% had declines greater than 75%. One patient had a complete response with a decline in PSA from 215 to 0.75 after six cycles. The Grade 3 and 4 hematologic toxicity was 50%.

Friedland et al evaluated pain control in a study with single agent Taxotere[®] at 75mg/m² every three weeks.⁹ Seven of eight patients with pain had subjective reduction in bone pain. The overall PSA response rate was 5/12 or 42%.

An additional study from Picus et al also examined single agent Taxotere[®] (75mg/m² every three weeks) as single agent therapy among 35 chemotherapy naïve patients.¹⁰ Seven of 35 patients (20%) had a >80% decline in PSA while 16/35 (45%) had a >50% decline. Combining both PSA and soft tissue responses, one CR and five PRs were observed. The overall median survival was 12 months and the median duration of response was nine months. Toxicities included Grade 4 stomatitis, small bowel obstruction, and gluteal abscess. This trial raises the question of whether reducing Emcyt[®] to one

day's course or omitting it completely may result in fewer side effects yet with equally efficacious results.

Lastly, a study by Weitzman et al looked at Emcyt[®] plus Taxotere[®] in chemotherapy naïve patients. Taxotere[®] was given at a dose of 70 mg/m² with Emcyt[®] for five days and premedication with Decadron[®]. 16/19 or 84% of patients had a PSA decline of ≥ 50% with 13/19 (68%) having an (80% decline in PSA. The median duration of response in the former group was 5.5 months (range 0.75 months to 16 months) and in the latter group five months (range 0.75 to 13 months).¹¹

Conclusions

These studies point out the need for good Phase III data on the use of Emcyt[®] and Taxotere[®], emphasizing the need to enroll patients in clinical trials. Only with larger numbers of patients will the true impact on survival be known. As more is understood about prostate cancer cell biology, it is hoped that more sophisticated combinations of chemo and other multi-modality therapies will be devised with less toxicity and more efficacy. ❖

The erMRI is accurate in these settings. The sensitivity, specificity, positive and negative predictive value, and accuracy to predict established ECE and SVI in clinical Stage T_{1,2} patients was 65%, 100%, 100%, 79%, and 84%, respectively. When the erMRI showed ECE or SVI was present, no patient would have been excluded from surgery on the basis of a falsely positive study. In this study, the percent of patients with pathologic organ-confined disease would have increased from 32% to 61%, and the three-year “no evidence of disease” rate would have increased from 12% to 45% (p = 0.07) if only patients with erMRI stage T₂ disease were selected for surgery.³

Spectroscopy involves the analysis of the amino acids citrate and choline within the prostatic tissue. High citrate to choline ratios are more consistent with benign prostate tissue whereas low ratios are typical of PC. Agreement (concordance) between abnormal findings of MR imaging (MRI) and MR spectroscopy (MRS) increases the accuracy of this tool.⁴ In addition, erMRI evaluation in patients who have had recent prostate (TRUSP) guided biopsies is compromised by hemorrhage resulting from the biopsies. The MRI signal secondary to hemorrhage is of low signal intensity on T-2 weighted images in 80% of patients studied; it is similar to that seen with PC. MRS helps to distinguish post-biopsy hemorrhage from PC.⁵

If the predictive algorithms such as Partin, Narayan, Bluestein, D’Amico and others suggest that there may be extra-prostatic spread, I often use the erMRI with spectroscopy to confirm or refute these concerns. If the endorectal MRI with or without spectroscopy is abnormal in regard to extra-capsular spread in an area, I may consider using external beam RT (3D Conformal) to include that area. Patients who might be referred for seed implantation only would receive either a combination seed plus external beam approach or external beam only. In the same patient, I would not suggest a radical prostatectomy (RP) due to the significant risk of extra-prostatic disease and PSA recurrence post-RP as described above.

ON-GOING TREATMENT

I would like to better understand the various roles of cancer doctors.

1. Does a medical Oncologist utilize chemotherapy in the same manner that a surgeon uses surgery to treat cancer and a radiation doctor uses radiation to treat cancer?

For the most part, the medical oncologist uses chemotherapy to treat systemic disease, i.e. disease that has metastasized or spread beyond the primary site – the prostate gland. Chemotherapy and androgen deprivation therapy are the only two conventional systemic therapies available. The rest of the treatments most often offered to patients are local therapies e.g. RT with seeds and/or external beam, RP, and Cryosurgery.

2. If the answer to the above question is “yes”, how can a prostate cancer patient obtain an optimum and balanced recommendation for treatment if these three types of doctors have different expertise?

The answer is NO. If it were yes, the answer would be to always look for a physician that cares about the patient’s outcome more than the doctor’s income. Outcome > Income is the essential philosophy here.

3. I had a radical prostatectomy six months ago with positive margins and tumor cells out to the capsule. What type of doctor should I be going to for follow-up?

Jerry Boldra

Look for the doctor that knows this disease well. If your PSA is >0.07 post-RP, you have persistent PC. If the PSA is climbing with sequential PSA testing, you have evidence of increasing PC necessitating therapy. Depending on the findings at RP (Gleason score, presence or absence of nodal disease, and the PSA velocity post-RP) you can determine your risk of local vs. systemic PC. If the risk of systemic PC is high, you would best be treated with ADT (androgen deprivation therapy). If your risk of local disease is high, then RT to the prostate bed is recommended. We would also want a ProstaScint scan to show ONLY uptake in the prostate bed before proceeding with RT. We do not want to use RT if the chance of success is slim. ❖

Videos are available from
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VIDEO 1

Evaluating PC: Important Concepts

Stephen B. Strum MD,
Alan W. Partin MD, PhD

PC My Story

Charles “Snuffy” Myers MD

VIDEO 2

Nutritional Factors in PC:

Myth or Reality

Mark Moyad MPH

PC SPES in PC: Results of the UCSF Trial

Eric Small MD

VIDEO 3

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Stephen B. Strum MD

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Mark C. Scholz MD

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Important Principles in Chemotherapy... *continued from page 11*

greater than 90% reduction in PSA levels of 6/21 (29%) patients, but gave no survival information.

Another study used the novel agent DPPE (a histamine antagonist) to potentiate chemotherapy cytotoxicity and thereby protect bone marrow integrity, minimize gastrointestinal toxicity, and prevent hair loss⁷. In this study, 20 patients with AIPC were treated with *Cytosaxan*[®] 600-800 mg/m² intravenously once per week for four weeks. A 50% reduction in soft tissue measurements in five of the seven patients (71%) who had measurable soft tissue tumor was observed. A greater than 50% drop in PSA was seen in 9/18 (50%) patients. **Eleven of the 13 patients (85%) with bone pain had a partial or complete response.**

Other supportive care

A medical oncologist should offer the most effective medications or other approaches to maximize the level of supportive care for the AIPC patient receiving chemotherapy, in order to minimize side effects such as those shown in the following table.

Potential side effect	Supportive care options
Loss of appetite	Megace [®] (megestrol acetate)
Nausea and/or vomiting	Zofran [®] (ondansetron), Kytril [®] (granisetron), Anzemet [®] (dolasetron), Reglan [®] (metoclopramide), Decadron [®] (dexamethasone)
Diarrhea	Imodium-AD [®] (loperamide), Lomotil [®]
Constipation	Colace [®] (docusate sodium), milk of magnesia
Dry skin, hair loss	Emollients, vitamin E, zinc supplements
Heart injury	Zinecard [®] (dexrazoxane)
Bladder injury	Mesnex [®] (mesna)
Nerve injury	Ethylol [®] (amifostine)
Extravasation injury to soft tissue	DMSO topically (70% solution)
Kidney injury	Sodium thiosulfate injection

Unfortunately, there are no medications or approaches available that will prevent loss of hair from chemotherapy. However, hair will grow back in the weeks after therapy is stopped, and may actually begin to grow back during continued chemotherapy treatments.

Certain intravenous chemotherapy drugs can cause significant tissue damage called “extravasation injury” if they accidentally leak out

of the vein into surrounding tissues. Drugs that can cause extravasation injuries are known as vesicant chemotherapy agents. Patients receiving vesicant chemotherapy through a peripheral (hand, arm or leg) vein should inspect the chemotherapy injection site for several days after each treatment.

To prevent potential extravasation injuries, vesicant chemotherapy should be given with caution to patients with poor quality veins, or patients who are to receive a drug or drugs as a protracted infusion over several days. For such patients, it may be preferable to place a central venous catheter or vascular access device, e.g. *Port-A-Cath*[®], prior to therapy. This not only lessens the chance for potential extravasation injury, but also provides access to a patient’s veins to draw blood and/or to give blood products, intravenous fluids or any kind of drug. If chemotherapy extravasation does occur, 70% DMSO applied topically prevents tissue injury and should be administered at least 4-6 times a day until the site of extravasation is fully healed. If stinging occurs with DMSO application, the patient should wipe off the remaining DMSO and apply aloe vera gel to the skin.

It is very important that a patient promptly report any unusual symptoms or side effects during chemotherapy treatment to his physician to be sure that it is not, or does not become a major problem.

Summary

It is important to properly identify AIPC and not confuse it with an androgen receptor mutation (ARM) or with inadequate suppression of testosterone by an LHRH agonist (Lupron[®] or Zoladex[®]). Once AIPC is properly identified, it is equally important to understand essential principles in the pharmacology of the agents employed in treating and supporting patients with AIPC. As there is a need for artistry in doing a radical prostatectomy, seed implantation, external beam RT or cryosurgery, there is also artistry needed in the medical oncologic care of the PC patient, especially those with AIPC. ❖

National Conference... *continued from page 1*

spectacular. I attended with my brother and his wife, my husband and my father-in-law, a retired surgeon, and we all agreed that we learned a great deal. All of the doctors were excellent speakers, technical, but not too technical. They were interesting, spoke to the point and were passionate about their work. All the guys at PCRI really pulled it off and I know how difficult it was.”

All of the speakers came from prominent medical institutions including Johns Hopkins, Harvard Medical School, Josephine Ford Cancer Center, Stanley Scott Cancer Center and the Universities of Virginia, California, Michigan, and Washington.

Some attendees followed up after the conference was over. Mike Korek not only made a donation to PCRI, he also wrote on P2P, “I attended the conference last week and was very impressed with the depth, breadth, and dedication of all involved, especially Dr. Strum. I was glad that I could help by making a donation, and I encourage others to do the same.”

Dr. Strum moderated the conference. The

co-founder and Medical Director of PCRI and the founder of Healing Touch Oncology, Dr. Strum is an internationally recognized medical oncologist who has specialized exclusively in the treatment of prostate cancer for the last 15 years. His humanistic approach to prostate cancer treatment is well known by patients and his peers. Mark Scholz, MD, the other co-founder of PCRI, was also one of the speakers.

The Conference was underwritten by the attendees and by the generous contributions from the event’s sponsors. Among the sponsors were Daniel Freeman Hospitals, Freeman Hospitals Foundation, Amgen, Bristol-Myers Squibb, Immunex, Rhone-Poulenc Rorer, TAP Pharmaceuticals, cancerfacts.com, Life Extension, Schering, SmithKline Beecham, Ortho Biotech, Inc., Econugenics, and the American Cancer Society. *(A complete list is on page 20)*

Because of the Conference’s success, the PCRI Board of Directors approved holding another conference in the year 2000. Once again, it will be held at the Long Beach (CA) Convention Center on October 14 and 15. ❖

Communication & Balance: From Microcosm to Macrocosm

by Stephen B. Strum, M.D.

Life (bios) is a series of mysteries that man links together through thought and concept. Using a conceptual approach facilitates the understanding of information that is presented to us and allows us to apply concepts elsewhere in life. Data are then no longer countless bits of information but instead are threads of a woven blanket that take on substance and meaning.

In my 37 years as a scientist and physician, I have seen the importance of communication and balance in all aspects of “life” surface time and time again. The word “life”, as used here, is not to be taken glibly. Life is the miraculous expression of creation. Life, in all its glory, should be seen with curiosity, wonder, and respect. We are here to enjoy life. This life process is a continuum; it is at a cellular level as well as at an individual, global and cosmic level. This continuum is in constant flux with cellular interactions affecting individual, global and cosmic states and vice-versa. From my perspective, so much of what I have seen at a cellular level also has parallel meanings using individual, global, or cosmic perspectives. I contend that communication and balance are the pivotal concepts that apply to the individual-global-cosmic realities. This concept can be viewed from different points of perspective.

At a cellular level:

Communication and balance = health.

Virtually all health disorders are results of miscommunication at a cellular level. These are disruptions in the balance (homeostasis) of cells. Even at a genetic level, abnormal genes do not communicate the proper signals; they often send out messages that prompt too much or too little response. Telomeres, which are part of each gene, are built-in time clocks that influence the rapidity of aging. Individuals with small telomeres prematurely age, as seen in progeria, the disease where children age rapidly.

Malignant disorders are frequently associated with p53 and p21 mutations. Deficiencies in natural (wild type) p53 and p21 genes are adverse prognostic findings in regard to survival in many types of cancer, including PC. Genes like p53 and p21 and other genes like p27 increase cell cycle time and affect the growth rates

of malignant cells. Both synthetic vitamin D (Rocaltrol) and milkweed (Silymarin) upregulate (increase) p27. The gene for p27 (kip1) is activated by both of these products. Dietary excess, smoking and excessive alcohol consumption all lead to the generation of free radicals that cause oxidative damage that in turn damages DNA, thereby interfering with cellular communication and leading to aging.

However, aging also results from hormonal imbalance. Hormones are chemical messengers within cells, between cells and between tissue. In youth, we do not understand or accept our mortality, or for that matter our susceptibility to age itself. If medicine is to advance, it must look at these concepts and study hormonal imbalance and the need to protect our cells from the effects of oxidation, not when we are 62, but when we are 26 or perhaps younger.

**At an individual level:
Communication and balance = love.**

The health within our cells and tissues as a reflection of communication and balance has its counterpart in the individual's ability to understand his or her nature and learn what is needed to bring harmony into his or her life. All of us have felt those times that we were most happy. I can recall my year as an Intern when I both had the sense of accomplishment of being a doctor, and the time to exercise my body coupled with the exuberance of youth.

Many great writers have written about the importance of knowing thyself (Socrates) and being true to thyself (Shakespeare). Through the ages, there have been great writings about balance, yin-yang, harmony, and the need for self-reflection and meditation. Communication and balance at a personal level must lead to self-love. The personal love that we feel when we are in tune trickles down to a cellular level to affect our health, and vice-versa.

**At a global level:
Communication and balance = world peace.**

In 1985, after the Chernobyl accident, I was part of a delegation of 48 American children and



their chaperones who visited the Soviet Union. The mission was entitled Children as Teachers of Peace and was headed by Gerald Jampolsky and Diane Cirincione. The Soviet people were able to see the love surrounding these children diplomats. This began to dissolve the barrier to communication, and eventually allowed both Soviets and Americans, young and old, to dispel their misconceptions about each other. Boundaries were shattered and replaced with Glasnost, and the bell tolled for the Cold War. People are all the same the world over.

We need to communicate with each other. We need to help each other in our individual struggles. We need to achieve balance within the world as it relates to people, governments, and nature. Harmony at a global level is our only chance for world peace, and for preservation of this beautiful planet. What peace we would bring to this planet if we showed our ability to hear the plight of others by lending a helping hand to those in need. What opportunities are lost at times of national or global disasters when there is no reaching out to touch someone, thereby manifesting communication and our desire to help others restore balance to their lives. Our leaders should learn to lead.

**At a cosmic level:
Communication and balance = rapture.**

At a universal or cosmic level, communication and balance must lead to our ultimate evolution. Whatever you call it, Nirvana, Heaven, or Rapture, it is all the same. If we are to evolve at a cellular level, at an individual level, at a global level, or at a universal level, we must strive for harmony and balance. The key to such a goal rests within communication and balance. ❖

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