The remarkable biologic fact about normal cells is that without sufficient survival stimuli from their surroundings - usually in the form of "growth factors" - cells execute their death program and die, that is, undergo apoptosis. Much current biotechnology is focused on exploiting this mechanism in abnormal cells (i.e. cancer cells) by attempting to interrupt signaling via the cellular receptors for these growth factors. "Atrasentan", under development by Abbott (see "Protocol" next section) is a promising drug directed at blocking the Endothelin A receptors on prostate cancer cells. There is good science to support this approach.

Multiple studies illustrate the basis for optimism that an Endothelin A receptor antagonist (Atrasentan) will limit the progression of metastatic prostate cancer.

Carducci (Journal of Clinical Oncology 20:(8);2171-2180,2002) explained that there is a family of Endothelin growth factors, ET-1,-2,and -3. ET-1 is of principle interest because it strongly stimulates the cellular ET(A) receptors on prostate cells thereby promoting cell proliferation, angiogenesis, bone remodeling, and preventing apoptosis. ET-1 was first discovered as a secretion of endothelial cells circulating in plasma where it functioned as a potent vasoconstrictor. However, more importantly, ET-1 is also produced by prostate epithelial cells (normal and neoplastic) and stimulates both the cells producing it and also their neighbors. Plasma ET-1 levels increase in metastatic PC. Interestingly, the cellular expression of the ET-(A) receptor increases in an environment of low testosterone, thereby suggesting usefulness of the ET(A) blocker Atrasentan in association with androgen deprivation therapy.
In an editorial in "The Prostate", Vol.49:91-92,2001, Nelson emphasizes the action of Atrasentan in combating bone metastases. Atrasentan reduces the markers of bone metabolism by silencing the signaling via the ET(A) receptor. Since osteoclasts exhibit ET(A) receptors, Atrasentan, by blocking the receptor, can inhibit the osteoclasts' role in destroying bone and thereby reduce the development or slow the progression of bone metastases. In a study comparing Atrasentan treated patients to those receiving a placebo the Atrasentan treated patients maintained their baseline values (elevated at baseline, as expected) for alkaline and acid phosphatase and N-telopeptides (markers of bone osteolysis) whereas the placebo group showed a dramatic increase in these biomarkers of bone metabolism. A clinical benefit of Atrasentan was less pain from metastatic disease in bone. The editorial conclusion was that Atrasentan limited the progression of metastatic disease in bone.

In the ASCO Abstract #12 (2001) Nelson presented the data showing the inhibition of skeletal metastasis in hormone refractory prostate cancer patients, and in #694 Carducci presented the data from a study of 244 evaluable men with hormone refractory PC showing the increase in median time to both PSA progression and clinical disease progression.

In ASCO Abstract #708 ( May '02) Carducci updated (to June '01) the Phase II data to show a median survival of 583 days for Atrasentan treated patients versus 478 days for placebo patients, and a 196 day versus 129 day median time to clinical progression favoring the patients treated with 10 mg oral Atrasentan. However, as any pharmaceutical company knows... the "proof of the pudding is in the eating", and therefore we await of results of the Phase III studies underway (see below).

**Bottom Line:** The Endothelin A receptor antagonist Atrasentan shows promise in Phase II studies in limiting the progression of metastatic PC.

**PROTOCOL STUDY OF ATRASENTAN** – (Currently open for enrollment)

A pair of PHASE III studies comparing 10 mg oral Atrasentan versus placebo in men with hormone refractory PC have been conducted nationwide. The study for men with metastatic disease is now closed after accruing more then 1000 participants.

The study for PC patients with non-metastatic disease is open and currently has accrued over 700 patients nationwide. The study design is double blinded and compares 10 mg Atrasentan with placebo. Patients may have had either a radical prostatectomy or primary irradiation and must demonstrate a rising PSA while on hormone therapy. Eligibility requires a negative bone scan and CT scan. The PSA must be >1 ng/ml and exhibit three consecutive rises at no less than 2-week intervals. A PSA of >20 by itself is sufficient for entry. Bone scans are repeated at 12-week intervals and newly developed positivity ends the study for that patient. A rising PSA during the study is NOT a reason for study termination. Patients who fail on the placebo arm may then receive Atrasentan.

Questions about entering patients into the study should be directed to Laura Hopper at 215-3373.

**Bottom Line:** This protocol fits into a commonly encountered niche in which there is no standard treatment.

**PALLIATIVE CARE:**

Two major skeletal morbidities plague men undergoing androgen deprivation therapy (ADT) for advanced prostate cancer: osteoporosis and progression of bone metastasis. Both lead to pain and fractures. In the October 2,2002, issue of the Journal of the National Cancer Institute this issue was addressed in an editorial in concert with a study of 643 men on ADT with metastatic bone lesions and rising PSA values. The comparison was between treatment with 4 mg of Zometa at three-week intervals versus placebo over 15 months.
Emerging data is clearly showing that osteoporosis is a significant problem in association with androgen deprivation therapy. Multiple studies show that after one year on ADT men show a 5% to 10% decrease in bone mineral density (BMD) and ADT increases fracture risk 2-fold. 80% of men with advanced prostate cancer develop skeletal metastasis and this group is usually treated with ADT for some number of years.

Smith (N Engl J Med 345;948-955,2001) reported that Pamidronate at 60 mg IV q 12 weeks (trade name "Aredia") (now succeeded by IV Zometa, 100-850 times more potent) protected men from any further loss in bone mineral density at 48 weeks as compared to a loss of 8.5% in the placebo group. It's interesting that 4 mg IV Zometa can prevent progression of osteoporosis in cancer free individuals with dosing as infrequent as once per year. The most efficient dosing schedule for Zometa in cancer patients is under study.

Zometa (as do all bisphosphonates) interferes with bone resorbing action of osteoclasts. Bone lesions in PC are classically considered "osteoblastic", which implies that they are the result of bone build up as opposed to bone loss ("osteolytic"). Clinicians might wonder if a drug that inhibits bone resorption would be useful in a disease that is typically considered to be associated with osteoblastic lesions. However, studies have shown that there is a significant component of osteolysis in PC bone metastases.

The recent study of 643 men reported in the JNCI focused on men with established skeletal metastasis. On average all men had 4.2 skeletal metastases and median PSA was ~80 ng/mL. Zometa prolonged the time to the development of new skeletal events to 420 days versus 321 for placebo (P=.01) and markers of bone resorption were significantly decreased by Zometa.

The accompanying editorial concluded that Zometa was a reasonable option for men at high risk for bone fractures but more data would be required before it becomes standard therapy for all PC men with any degree of skeletal metastases. The issue of what extent of metastatic bone involvement warrants intervention with Zometa is currently up to the clinician's judgment.

The issue of cost is always relevant. 4 mg Zometa is priced at $915 and infusion costs are additional. Perhaps further studies will refine the recommendations regarding the usage of bisphosphonates relative to the aspect of cost effectiveness.

**Bottom Line:** 1) Evaluate BMD in men undergoing ADT and utilize a bisphosphonate to prevent bone loss, and 2) use Zometa in instances of significant bone metastases.

**PATHOLOGY AND DIAGNOSTICS**

Click onto "prostatecalculator.org" and you are immediately into the web site for the "Artificial Neural Networks in Prostate Cancer Project", whose principle investigator is Dr. David Crawford with support from the Veterans Administration and the NCI. The information sources seem very credible to me.

Two of the nomograms that are probably useful to both MDs and patients allow predictions for, 1) the likelihood of PSA rise post primary surgery, and 2) the probability of survival post initiation of androgen ablation therapy. The latter nomogram requires information about pre-treatment PSA, PSA after 8 weeks of ant androgen therapy, and whether the disease is overtly metastatic. This data could very well be encouraging to patients whose PSA falls nicely after ant androgen therapy, which is the majority of patients. Since patients with rising PSA’s, very high PSA’s, or metastatic disease are understandably pessimistic, they will be encouraged, I think, by the data on the nomogram.

Two examples from the nomogram: 1) a patient showing a rising PSA post RP whose PSA has risen to 12 and who achieves a 8 week post Lupron PSA of .2 ng/mL has a 70% likelihood of surviving 37 months. 2) a patient who initially presents with the PSA of 2000 and bone metastases and whose PSA
falls to .2 in 8 weeks has a similar likelihood of surviving 37 months. These estimates do not take into account any current treatments to improve survival.

After exploring this entire web site with its presentation of basic data and useful web links, I decided that this would be a good site to recommend to patients.

The second nomogram of interest was presented by physicians from Memorial Sloan-Kettering Cancer Center, Cornell University, and UCSF-Mount Sinai Cancer Center in the Journal of Clinical Oncology, October 1, 2002:pp 3972-3982. This nomogram takes the next step after the nomogram referenced above and allows prediction of survival of patients with progressive metastatic prostate cancer who have FAILED androgen ablative therapy. The basis of this data is the outcome of 409 patients treated at MSKCC between 1989 and 2000 on 19 different therapeutic protocols utilizing chemotherapy and a wide variety of treatment combinations. These patients exhibited (alone or in combination) rising PSA’s, new bone metastases or increasing soft tissue disease. The usefulness of the nomogram is that it employs data that is routinely available in the clinical setting when treatment options are discussed, i.e. age, Karnofsky performance status, hemoglobin, alkaline phosphatase, LDH, PSA, and albumin. To an experienced clinician the results are fairly intuitive with one exception. As expected, patients do poorly if they are symptomatic because of low performance status, decreased HGB and albumin, or high LDH. The interesting observation is that PSA BY ITSELF is not an independent predictor of survival. A PSA up to 100 contributes only to a small degree in predicting a poor survival and a PSA from 100 to 8450 is virtually insignificant in predicting survival if a patient is free of the other adverse factors. That piece of data by itself can be encouraging to a patient who feels well and exhibits only a rising PSA. The nomogram presents data for probability of median survival and of 1-year, 2-year survival probabilities.

**Bottom Line:** These two nomograms present data on survival probabilities of clinical usefulness, which, in the context of the usual patient pessimism, may be encouraging to many patients with PC.

**SCREENING**

PSA screening has been and remains a controversial issue. Clearly, if early diagnosis and treatment lowers ultimate mortality from PC the debate is over. However, what about overall mortality versus PC specific death rate (PCSD) and the consequences of treatment morbidity in men who then die from other causes? Where does "lead time bias"(the time by which the PSA advances the diagnosis) fit into the picture and how long is it? The five-year survival for patients with PC in 1950 was 40% and now is 95%. Is this real gain or just the consequence of lead-time bias? Some new data sheds some light on this tricky issue.

A much quoted article, "A Randomized Trial Comparing Radical Prostatectomy With Watchful Waiting In Early Prostate Cancer" appeared in the September 12 issue of the N Eng J Med. It reported that the overall mortality in 696 Swedish men at a median follow-up of 6.2 years was not significantly different for the RP group versus the observation group. The men's average was 64 years, PSA's <50 ng/mL, expected future life 10 years or more, and bone scans negative. If nodes were positive at RP the man was excluded from the study. Similar treatment was given to the two groups when local or distant disease developed. Important points for this discussion are: 1) Screening accounted for only 5.2% of diagnoses (the study period began in 1987 at the very beginning of the PSA period) and 40% of men were symptomatic at diagnosis; 2) 12% of men presented with T1C and 12% T1B disease respectively, and 75% were T2, and, 3) 46% of PSA’s were >10 ng/mL, and, 4) 60% of Gleason score were 2-6, 23% 7, and 5% 8-10.

The outcome: at 6.2 year median F/U PCSD was 4.6% in the RP group and 8.9% in the WW group. Early data at eight years showed a PCSD rate of 7.1% for the RP group versus 13.6% for WW.
HOWEVER, at 6.2 years of F/U, the OVERALL mortality was not significantly different. (Editor: This is the point that I fear most lay readers might take away from the study) Interestingly, at only the five year point there was no difference between PCSD in either group. It was only at 8 years that the full survival advantage in PCSD was seen favoring the RP group, i.e. 7.1% versus 13.6%. At 8 years there was a 6% absolute reduction in both overall and disease specific death rate favoring the RP group but this was incomplete data. At 2 years there was no difference in metastatic disease, but by 8 years the RP group showed a 14% comparative reduction. And by 8 years local recurrence developed in 60% for the WW group versus 20% for RP.

**Bottom Line**: The question here is - Is this study really about EARLY prostate cancer?

D'Amico and Ung present the data from a Boston consortium in Urology, September 2002, to show that "early" PC is becoming "earlier" (stage migration) due to PSA screening and current diagnostic techniques. They are among many who report the same trend. They report the preoperative characteristics of 1059 patients with clinically localized PC studied in three time periods, '89-'92, '93-'96, '97-2000 and show a decreasing trend in initial PSA, clinical stage, and biopsy Gleason scores. Of interest to this discussion is the D’Amico data, which may be compared to the findings in the Swedish study in which 75% of men were T2. In contrast, in the D’Amico study 81.7% were T1C and only 17.3% were any T2 stage. Only 31% of PSA’s were >10. It's interesting that the Gleason scores ≤ 6 were similar in the Swedish and D’Amico studies i.e. 60% versus 68%. But with respect to organ confined disease authors such as Catalona has argue that screening doubles the proportion of PCs that are organ confined versus those that are diagnoses by digital rectal exam.

The **Bottom Line** here is that PSA screening finds disease at an earlier stage and this implies greater curability.

So where does "lead time bias" come into this controversy? "Overdiagnosis" (of PCa) in the PSA era was the subject of an editorial in the Journal of the National Cancer Institute, July 3, 2002 and an accompanying article by Etzioni from the Fred Hutchinson Cancer Center. Etzioni contends that PSA screening results in overdiagnosis in 18%-39% of Caucasian men aged 60-84 years and in 20%-40% of African-American men. "Overdiagnosis" for this study implies that the men did not live long enough to have their cancers diagnosed clinically. The basis of this calculation involves an estimate of how many men die with occult PCa. The issue of PCSD cannot be settled completely by retrospective studies and Etzioni acknowledged that many pathologists have found that most cancers found by screening have NOT been insignificant or unimportant. This evolving observation raises the interesting question of whether some cancers are "born" at high Gleason scores or whether the Gleason score for a cancer increases with time. Etzioni’s study suggested that the lead-time bias for PSA screening was about five years for Caucasian men and 7 years for African-Americans.

**Bottom Bottom Line**: The controversy about the utility of PSA screening is still alive and well in academic discussions but the screeners have picked up a few more points. Only the PIVOT trial (Prostate Cancer Intervention Versus Observation Trial), started 1995, will settle the issue in forthcoming years. However, in the clinic the issue is almost uncontroversial. Very few men choose not to be screened when the offer is made.

By the time that the PIVOT trial is fully reported advances in bioscience may have pulled off an "end run" around the issues of screening and the dilemma whether to treat or not. In the December issue we'll touch on developments in micro-array analysis and proteomics and how the data may guide the choices for management of early diagnoses PCa.