SEATTLE PROSTATE INSTITUTE

PCa Commentary
Vol. 23: August 2004

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BASIC SCIENCE: The Malignant Milieu - "No Man is an Island"

...and no malignant cell arises alone (apology to poet John Dunne, 1684). Although historically the major focus in prostate cancer biogenesis has been on the endocrine effect of testosterone, histologically identifiable "cancer" is spawned in a sea of endocrine, paracrine, and autocrine influences, and is in active reciprocal cross talk with its host speaking the language of growth factors and cytokines. A hook into this all encompassing subject is provided by two studies that illustrate the clinical usefulness of synthetic somatostatin analogs that bind their receptors, which are abundant in prostate cells, benign and malignant. Somatostatin (SST), itself a naturally secreted neuropeptide, functions as a regulator and inhibitor of many cellular processes. "Somatostatin inhibits cell secretion and prevents cell proliferation by inducing cell cycle arrest and apoptosis. These effects are thought to be directly mediated by SST receptors on tumor cells and indirectly on non-tumor cell targets, which inhibit the secretion of tumors and growth factors involved in promoting tumor growth (Hansson). By binding its receptors in the hypothalamus SST downregulates the secretion of growth hormone, another proliferative influence on malignant cells.

After biochemical failure from first line androgen deprivation, chemotherapy is commonly the next therapeutic choice. However, a group of Greek researchers reported (Urology, Jan, 2004) a head to head comparison of chemotherapy (estramustine/Etoposide) with a somatostatin analog in 40 HRPC patients in whom AD was continued.

Somatulane, given intramuscularly every 14 days, was combined with a decreasing dose of dexamethasone tapered to 1 mg/day. The inhibition of pituitary derived growth hormone by the SST analogs effectively suppresses the liver's production of the important prostate cancer stimulating action of insulin-like growth factor-1 (IGF-1).

The outcome of the two treatments was equivalent and both produced a > 50% decrease in PSA of 44-45%; a similar time to progression in the PSA responders in both arms of about 8 months; objective responses in 29-30% of men; and a median overall survival in both arms from protocol entry of 18 months. A clearer test of the somatostatin analog's individual contribution would have a trial schema which added Decadron to the chemotherapy arm, since the corticosteroid alone in a HRPC setting has produced PSA decreased of > 50% in up to 50% of subjects for a disease control of 4-6 months. But the lessor hematologic toxicity, alopecia, and nausea and vomiting in the Somatulane arm makes it appealing.

Further support for prostate cancer suppression by somatotropin analogs comes from a Tulane study (The Prostate 56:pp.183-191,2003) in which the analog, Vapreotide, given alone at the time of relapse from AD suppression produced clinical improvement in 8 of 13 patients with 6 showing a 71% fall in PSA. Supporting basic science studies revealed that "52 out of 80 surgical specimens of prostate cancer (65%) displayed specific binding sites for Vapreotide."

There are five different types of somatostatin receptors on prostate cells, and research is ongoing in an effort to develop somatostatin analogs of greater affinity and specificity to improve the anti-cancer performance of SST analogs.

The second part of this discussion links SST with an analysis of prostatic neuroendocrine cells (NE), which exert a paracrine stimulation of nearby prostate cancer cells, and in the metastatic setting stimulate osteoblasts. Somatostatin analogs function to blunt these adverse relationships. An excellent review of this topic is "Somatostatin receptors: from basic science to clinical approach...", by Mosca (Digestive and Liver Disease 36(Suppl 1) 2004).

NE cells are found in PIN and in all stages of PC. At diagnosis preexisting focal NE cells are present in 30-50% of prostate cancer specimens. NE cells are non-proliferating, and androgen receptor negative, and do not secrete PSA. As pointed up by Dr. Larry True in a January 2004 Journal of Urology editorial, the NE cells are vigorous exporters of a wide variety of growth factors and cytokines, the most relevant for this article being the VEGF (angiogenesis promotion), transforming growth factor-alpha (promoter of tumor proliferation), bombesin (an inducer of tumor invasiveness), and survivin (an anti-apoptotic protein). These "factors stimulate the growth and progression of histologically conventional cancers." (Dr. True) It's important to note that "in an androgen depleted environment, malignant epithelial prostate cells are induced toward NE differentiation, and "hormone-refractory" PCs show increased NE differentiation over time with disease progression. ... Tumors displaying NE phenotype tend to be more aggressive and resistant to hormone-therapy." (Mosca) Chromogranin A (CgA) is a major secretory product of NE cells and studies have shown significant increases in the serum values for CgA 24 months after castration, and to a lessor extent after Casodex therapy. This transition to NE phenotype is especially prominent in bone mestatases where NE cell paracrine factors promote osteoblastic lesions.

The goal for the therapeutic use of SSTs is the development of analogs of high affinity and specificity to effectively inhibit the adverse effects of NE cell derived stimulation of prostate cancer growth. Mosca concludes: "The concept that paracrine factors secreted by NE cells could exert effects on surrounding non-NE cells of PC provide a rationale for the use of somatostatin analogs to counteract these effects."

[An excellent review of this topic is “Neuroendocrine Differentiation in Prostatic Carcinoma”, Jens Hansson, Lund University, Scand J Urol Nephrol 37 (Suppl 212): 28-36, 2003]

Bottom Line: Malignant cells are supported and promoted by cross-talk with their host, and effective therapy requires an interruption of this subversive conversation.

ANDROGEN INSENSITIVE DISEASE: **Duration Of Survival Of Patients Who Developed Hormone Refractory Prostate Cancer**

It would be easy to conclude from a cursory consideration of data from many articles and texts that the median survival for patients with “hormone refractory” prostate cancer (HRPC) is between 12 and 18 months. A recent example to be considered is the ASCO abstract report of the encouraging 18.9 month median survival for “patients with hormone-refractory prostate cancer” treated with Taxotere/Prednisone. It can be misleading to compare results of studies of men with HRPC without having sufficient information about the details of the PSA values of the men in the group being compared from different trials. In this example of the Taxotere/Prednisone study group the median PSA at entry into the chemotherapy programs for the group was 114 ng/mL, and 90% had bone metastases. Hardly early in the “HRPC” phase of their disease!

The article, “Survival of Patients with Hormone Refractory Prostate Cancer in the Prostate Specific Antigen Era” (J UROL, April 1004, by Michael Oefelein et al. addresses the issue of duration of overall survival following the **onset** of hormone refractoriness, defined as the first PSA value above 0.3 ng/mL despite castrate levels of testosterone. The median PSA at which hormone deprivation was initiated in their retrospective study was 204 ng/mL, and the lowest starting PSA was 1.8 ng/mL. However, the survival calculations were based on the date when a man’s PSA exceeded 0.3 ng/mL level, despite the reality that AD was initiated at very different times for men in the course of their rising PSA values. The study examined the records of 131 men, the majority identified in 1999 in the practices at the Cleveland - University Hospitals, Case Medical School. The mean age at diagnosis was 72, the mean Gleason score 8, and the mean duration of androgen deprivation (AD) therapy was 58 months. AD was continued to death. The median overall survival for men studied in this manner was 53 months. The survival was further reported by segregating the duration of survival data into two groups, one for men free of metastatic disease to bone at the onset of AD, and a second composed of men having bone metastases when AD was initiated. The median duration of overall survival for the first group was 68 months, and was 40 months for the second. The study identified 6 “variables adversely associated with survival after a patient enters hormone refractory, androgen independent phase”: higher [pre-AD treatment PSA] nadir, $p = 0.0000001$; advanced age, lower pretreatment testosterone, $p = 0.002$; obstructive uropathy; tobacco history, and higher alkaline phosphatase, $p = 0.02$.

Bottom Line: The data describing the duration of overall survival for men with HRPC measured from a defined point (>.3 ng/mL) marking the onset of “hormone refractoriness” is useful for counseling patients and for evaluation of clinical studies.

PREDICTING OUTCOMES OF PRIMARY TX: Gene Expression Alterations In Prostate Cancer

The article “Gene Expression Alterations in Prostate Cancer Predicting Tumor Aggression and Preceding Development of Malignancy” (July 15, 2004, JCO) by a group of Pittsburgh researchers is a seminal documentation of the genetic basis of prostate malignancy, the

concept of precancerous “field effect”, and the genetic pattern that distinguishes prostate cancer aggressiveness. The basis of this study was the comparative analysis of messenger RNA, the product of gene expression, among prostatectomy specimens of prostate cancer tissue (63), histologically “normal” tissue adjacent to cancer (60), and histologically normal prostate tissue (23) from deceased organ donors. A 671 gene profile correctly distinguished prostate cancer from the normal donor prostate tissue with a 99.9% probability.

The usefulness of gene expression profiling to predict the degree of cancer aggressiveness was evaluated on the basis of a “70-gene” model that retrospectively “correctly predicted 27 of the 29 (93%) aggressive tumors, and 32 of 37 (86.5%) no aggressive tumors, producing 86.5% specificity and 93% sensitivity.” “An aggressive tumor [was] defined by any of the following: cancer invasion into adjacent organs or seminal vesicles, clinical relapse as evidenced by a rising PSA [$\geq$ 4 years follow-up] following radical prostatectomy, or distant metastases.”

A comparison was made between the accuracy of Gleason scoring in predicting aggressiveness. Of 62 cancers, 45 had Gleason scores of $\geq$ 7 and 17 were $\leq$ 6. The “Gleason score has only limited accuracy in predicting true aggressiveness with 33 of 62 (53%) correctly classified.” A second analysis made by adding 23 additional cancer specimens yielded an accuracy for prediction of aggressiveness for the 70 gene model of 78% versus 52% for Gleason scoring. The specificity for the gene expression technique was 82% v. 9% for the Gleason model.

The most thought provocative portion of the study is the evidence that demonstrated the very close similarity between the gene expression profile of apparently histologically benign prostate tissue and the adjacent histologically malignant cells. On the basis of this similarity “ninety percent (54 of 60) of AT [adjacent tissue] tissues were predicted to be tumors with a high ($\geq$ 93%) probability, whereas 10% (6 of 60) were predicted to be tumors with low probability”. The “patterns of gene expression in AT are much more similar to PC [prostate cancer] than to donor prostate, supporting the ‘field effect’ hypothesis”. Further support for the “field effect” derived from the observation that AT shared with PC the same expression pattern for two well recognized PC signature genes, ie. a downregulation of expression of glutathione-S-transferase pi (GSTpi), and an upregulation of alpha-methylacryl-CoA racemase (AMACR) expression.

Bottom Line: “Collectively, these data suggest that genetic alterations in a gland with prostate cancer are not limited to the malignant cells, and these patterns of alteration may predict the population at risk for the disease and for disease progression.”

Acknowledgements:

Once again I would like to enthusiastically thank Ms. Cheryl Goodwin, head librarian at the Swedish Hospital Medical Center library, and her two colleagues, Bob Hollowell and Mike Skully, for their unstinting assistance in facilitating research for these articles. Without their help my work on the Commentary would be vastly more difficult.

I also want to express my sincere appreciation to Charles Heaney, Ph.D., who has been the editor and publisher of this Commentary since its inception. Dr. Heaney is now the Executive Director of the King County Medical Society, but still finds time to continue our collaboration.

And of course, PCa would not arrive on your desk each month were it not for the diligent efforts of Heather Volkers at the Seattle Prostate Institute.