SEATTLE PROSTATE INSTITUTE

PCa Commentary

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BASIC SCIENCE

With the nearly complete sequencing of the human genome only recently accomplished, the NEXT BIG THING is already well upon us. That is, utilizing the new knowledge and the emerging technology to understand how the genes orchestrate cellular function...and dysfunction. We don't need to understand the mechanics of cDNA arrays, 2 dimension gel electrophoreses, protein chips, mass spectroscopy, laser capture microdissection, etc., but do need to know how to comprehend the direction of this science and how it will advance diagnostics and identify targets for therapeutic intervention. This section will present some of the early findings resulting from the use of complimentary DNA (cDNA) microarrays in the analysis of gene expression.

Being musically inclined, I like to think about gene function using the analogy of a piano with its 88 keys - except the genome has 30,000 or so genes ("keys"). In all cells there is always background "music" playing, the “basso continuo” so to speak, representing the housekeeping genes for the basic operation of the cell. Then, I envision a multitude of pianists, one "playing" in each cell type - a prostate cell pianist, a heart cell pianist, a breast cell pianist.and so on, each playing the unique "chord" of gene expression for that cell type (however, he'll need 100, 200, who knows how many fingers to play the "prostate cell chord"). How the prostate maestro knows *not* to play any inappropriate notes from the breast cell score is still a mystery, now being studied under the heading of "gene silencing." If the prostate musician plays a chord with all the correct notes the result is a normally functioning prostate cell. Play a few clinkers (sour notes resulting, for example, adverse mutations that might give unwelcome growth advantage); while at the same time missing some proper keys (perhaps ones that repair damaged DNA) and the result is a discordant sound. Really mess up, and you have a very malignant cell. Only modern gene expression technology and bioinfomatics can compute the complexity of the simultaneous multiple gains and losses of gene expression suggested by this analogy, and then reduce the candidates to a useful but manageable number. Important information is beginning to emerge from this field of science, but we are only at the beginning. The following are a very few studies selected from the many that resulted from a literature search on PubMed under the query "Prostate cancer AND gene expression.".

1) 63,175 probes evaluated differences between examples of PC that were cured by local treatment versus lesions that had metastasized. 3000 tumor-intrinsic genes were identified that were 3X more expressed in PC vs. normal. They involved functional categories such as cell cycle regulation, DNA replication, and DNA repair
2) 12,600 gene products were evaluated comparing PC vs. normal. The PC cell showed 63 products (mRNAs) that were unique to PC and found that the PC cell lacked 153 normal mRNAs. This study underscored the need to consider the balance between up- and down-regulation of gene expression.
3) Gene expression compared patterns characteristic of various levels of PC aggressiveness (ranging from those that remained local vs. metastatic disease and relating specimens with Gleason sums 4 - 9). 84 genes were identified that were altered significantly in prostate cancer, and 12 were found that were only expressed in aggressive PC as opposed to organ-confined disease.
4) Genes expression differences were sought among 1176 known PC genes to identify patterns that were associated with progression from androgen sensitive to androgen insensitive disease. 34 genes were up-regulated and 8 down-regulated in androgen independent cells.

The data flowing from studies such as these are of such abundance that meta-analyses are being conducted to cross validate findings to identify significant commonalities that would facilitate the manageable use of this type of data for diagnostic and therapy targeting purposes.
Seattle is an important hub for this type of work. Dr. Leroy Hood's Institute for Systems Biology (north shore of Lake Union), the Fred Hutchinson Cancer Research Center, the University of Washington (and in BC the Prostate Centre at the Vancouver General Hospital) share more than $23 million in grants to study the gene expression patterns of PC focusing on issues such as why PC spreads preferentially to bone, the gene expression difference between men who are cured, and those who relapse. Also, a blood test is being sought to identify these tendencies.

Bottom Line: We're in a new era of scientific advancement with much to hope for.

HORMONE THERAPY: Are there alternatives to LHRH agonists (i.e., Lupron and Zoladex) as a primary intervention to achieve androgen deprivation to address a rising PSA?

[This section arose from a question from one of our colleagues who asked about the role of "Casodex", 150 mg daily, as monotherapy. (And I sincerely welcome requests for research topics from the readership.) By coincidence, while I was addressing this topic a patient called for advice. He had had a brief, and biochemical successful exposure to both Lupron and Zoladex, but discontinued therapy because of debilitating side effects. His PSA is rising again. The question: what are his options?]

Two very acceptable options are: 1) Bicalutamide ("Casodex") 150 mg daily and 2) finasteride ("Proscar") 5 mg once or twice daily combined with and either flutamide ("Eulexin") 125-250 mg TID or bicalutamide 50 mg daily. Both of these regimens result in an *increase* in testosterone while at the same time depriving the PC cell the key stimulating molecule dihydrotestosterone. Bicalutamide as monotherapy at 50 mg daily is insufficient to achieve the desired result. As a consequence of this elevation of serum testosterone physical capacity, sexual interest, and bone density are preserved.

The most recent and comprehensive discussion of bicalutamide therapy appears in UROLOGY Vol.60 (Supplement 3A) pp.64-71 by Dr. Peter Iverson, University of Copenhagen, Denmark: "Antiandrogen Monotherapy: Indication and Results." There is an extensive literature on this subject mostly coming from Europe where this regimen is extensive used. Mature data is available combining results from two large randomized trials (480 patients) studying men with locally advanced, nonmetastatic disease (stage M0). The comparison regimens were LHRH agonists or castration or bicalutamide, 150 mg daily. In studies of the M0 group, bicalutamide, 150 mg daily, and castration shared an essentially similar in survival outcome yielding a 46% survival for both with a median follow up of 6.3 years. (By checking "*Prostatecalculator.org",* which shows the outcome of "Zoladex" in the non-metastatic situation, it can be seen that the "Casodex" 150 mg regimen is similar.) The outcome of this comparison for M1 (metastatic) disease favored castration. At a median follow up of 1.9 years the mortality was 43% with a 6-week advantage for castration. However, in patients with PSAs <400 the outcome was equivalent. Quality of life issues favored bicalutamide with libido maintained 40% vs. 15% and in men sexually active before treatment erectile function was preserved 31% vs. 7%, and hot flashes occurred in 13% vs. 50%. The unwelcome side effects of bicalutamide were gynecomastia 49.4% and breast pain 40.1%. Studies are in progress to evaluate if pretreatment breast irradiation can lessen these consequences. (flutamide and nilutamide have not been sufficiently studied to allow comparable evaluation to bicalutamide) Cost can be an issue; "Casodex" runs about $13per 50 mg pill, hence 90 pills per months costs roughly $1200.

The second applicable option is the finasteride/antiandrogen regimen. This regimen has been less well studied and the supporting literature is older. The rationale is based on the combined physiologic actions of both agents. The initial step in androgen activation of prostate cells is the inward diffusion of testosterone. At this point testosterone is converted into the 20X more potent form, 5alpha-dihydrotestosterone by the enzyme 5alpha-reductace. Finasteride inhibits this enzyme. The antiandrogen (flutamide or bicalutamide) upregulates the corepressor mechanism restraining signaling via the androgen receptor thereby further reducing the androgen stimulation. The serum testosterone rises >50%, the serum dihydrotestosterone falls by 74%. In a study of 13 men (UROLOGY 1996 Dec; 48:901-5) the PSA fell 91% with 85% of men showing a nadir of PSA >4 and 46% achieving levels .2 ng/mL or less. In another study the PSA drop was 97.6%. In a small group followed for more than 2 years the antineoplastic effect was sustained. The patients treated with this regimen experienced the same benefits in quality of life as mentioned for bicalutamide monotherapy. The regimen I have preferred uses finasteride 5 mg BID and bicalutamide 50 mg daily. (The serum half-life of bicalutamide is 7 days allowing once-a-day dosing, whereas with a half-life of 5-6 hours flutamide requires TID dosing, and flutamide induces more diarrhea). I've heard Dr. David Crawford favorably refer to this regimen. He was at that time unsure if an LHRH agonist could be successfully used as a rescue when the combined regimen faltered."Proscar", 5 mg, runs about $3 each. At two pills daily per month the cost is roughly $175. By adding the cost of "Casodex", 50 mg daily, at roughly $400, the monthly total for the regimen rises to about $575.

Bottom Line: Several useful options are available for primary androgen suppression and clinicians may choose among them to best meet the individual requirements of patients.

CHEMOTHERAPY PLUS VITAMIN D EQUALS BETTER OUTCOME - POSSIBLY

The outcome of many recent chemotherapy trials has in general produced quite similar results. However, in the January 2003 issue of the Journal of Clinical Oncology, pp 123-128, Dr. Beer and colleagues from the Oregon Health & Sciences University report results of their efforts to improve outcome in their article:

"Weekly High Dose Calcitriol and Doxetaxel in Metastatic Androgen-Independent Prostate Cancer". Their study involved 37 men with progressive PC (increasing metastatic disease or rising PSA or worsening pain) treated with standard dose doxetaxel ("Taxotere") at 36 mg/m2 weekly six times in an eight week cycle accompanied by standard Decadron supplement. The novel feature was the addition of one day of calcitriol (Roche,"Rocaltrol") at the high dose of 0.5 micrograms/ kilogram body weight divided into four doses on the day prior to chemotherapy. Results: 81% of men achieved a >50% decrease in PSA and in 27 the fall was greater than 75%. Eight of 15 men with measurable disease had partial responses; the median time to progression was 11.4 months; and the median survival was l9.5 months. Survival at one year was 89%.

Why Vitamin D? Calcitriol is 1,25-dihydroxyvitamin D3 (not standard vitamin pill vitamin D). It is the active form of the vitamin. The kidney is the site where other forms of oral vitamin D and the vitamin D that is generated in our skin by sunlight are activated into the functional molecule. Nephrologists are familiar with this agent and supplement kidney dialysis patients with 0.25 - 0.50 micrograms *daily* to maintain calcium balance and bone density. "High dose" in this study meant that a man of 160 pounds would get 35 micrograms once every weekly cycle. Underlying the design of the Beer study is the emerging body of evidence that signaling through the vitamin D receptor (the natural ligand for calcitriol) retards proliferation of PC cells, enhances chemotherapy cytotoxicity, and facilitates apoptosis (programmed cell death). There is considerable evidence mounting that variations in the gene (polymorphisms) that codes for the vitamin D receptor confer different degrees of susceptibility to PC, and that this consequence may be operative in individual cases or even on the racial level. The administered calcitriol remains in the blood for several days and is therefore present during the highest period of doxetaxol serum concentration. The side effect of calcitriol in this study was three instances of mild, transient hypercalcemia.

Do the docetaxol-high dose calcitriol study results represent an improvement over prior chemotherapies? The conclusion of the report calls the results "promising" and indicates that a placebo-controlled, double-blinded, randomized comparison of their regimen vs. doxetaxol alone is already underway.

However, what are the reported results of "standard" chemotherapy - that is: mitoxanthrone/prednisone, a taxane (either Taxol or Taxotere) with or without estramustine ("Emcyt")? In his article Dr. Beer references results of his own prior study of docetaxol (36 mg/m2, 6 weeks out of 8/cycle) and results of a second similar study and two others dosing the chemotherapy at 75 mg/m2 every 3 weeks. Collectively, they show a median fall of PSA of 42%, 28% partial responses, time to progression of 4.6-5.1 months, and survival of 9.0-9.2 months. Other studies report somewhat better results. The article that ushered in the recent era of PC chemotherapy, "Hydrocortisone with or without mitoxanthrone in men with hormone-refractory prostate cancer" (Journal of Clinical Oncology 1999 Aug; 17(8):2506-13) showed an overall survival of 12.3 months of M+H vs. 12.6 months for hydrocortisone alone. Quality of life issues favoring M+H was the basis for the FDA's approval of mitoxanthrone in the treatment of PC. In CANCER 2002 March:1457-65 Carducci reported a docetaxol/estramustine trial that showed that 45% of men had a >50% fall in PSA, a median duration of response of 4 months, and a median survival of 13.5 months. At this time there is no consensus regarding the dose of estramustine, and some researcher question whether it’s a necessary ingredient considering its toxcitities. If the 12.6 months survival in the hydrocortisone alone arm of the M+H vs. H study is taken as a baseline, then all current varieties of chemotherapy treatments fail to show a significant survival advantage compared to H alone. That is why Dr. Beer and his group find "promise" in the median survival of l9.5 month in their study and hope that it can be confirmed in a larger study.

Bottom Line: The search for more effective chemotherapies in PC is being actively pursued.