SEATTLE PROSTATE INSTITUTE

PCa Commentary

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EDITOR'S NOTE:

This marks the first issue of a communication that I would like to compile on a monthly basis. As most of you know I retired from active clinical practice on July 1st, but my interest in the biology and management of prostate cancer remains strong. This monthly commentary is designed to focus on what is new and interesting in the area of prostate cancer. I hope to cull out and summarize what I think would be relevant to physicians from a wide source of information. I propose to survey clinical journals, basic science journals, conference material, news items, Medscape data - data which a busy practitioner may not have time to cover. I'll try to group the information under categories such as, for example: basic science, outcomes of clinical trials, pathology and diagnostics, nutrition protocols, hormone therapy, and others.

Drs. Grimm, Blasko, and Sylvester have been most gracious in supporting this project, which will be carried out under the auspices of the Seattle Prostate Institute. My hope is that these commentaries will be both brief and useful. I have been given a little time at the October 3 quarterly meeting to talk about this endeavor and will welcome any feedback or ideas you may have that will help make this newsletter a truly valuable one.

Sincerely,

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BASIC SCIENCE

It is appropriate to begin this series by discussing the androgen receptor, the kingpin of the prostate and prostate cancer. As we all know, when we roll an apparent "strike" with an LHrH agonist, the pins frustratingly come back up in less than three years. Why this occurs is not fully known. To change the analogy, we don't know if one bad apple from the start gradually spoils the bushel (clonal selection) or multiple somewhat bad apples learn new tricks and gradually take over (adaptation). We do know that signaling via the AR controls cell growth, survival, and differentiation. And even in the clinical situations we call partial or total "androgen insensitivity", prostate cancer growth and survival is still promoted via AR signaling, albeit, by "abnormal" signals.

In the July 1st 2002 issue of Journal of Clinical Oncology, Vol. 20,3001-3015 Edward Gelmann reports comprehensively on the "Molecular Biology of the Androgen Receptor". I'll quote what, in my opinion, is the most relevant passage for clinicians:

> "However, after hormone deprivation therapy, a number of AR gene alterations have been found. These alterations lead to increased sensitivity of the receptor to low levels of circulating androgens and to the receptor's ability to recognize a broadened spectrum of ligands as potent agonists of AR action. All these findings underscore the general notion that the AR signaling pathway is usually maintained in advanced prostate cancer that progresses after first-line androgen ablative therapy."

Although their exact mechanisms of action are not known, the trio of second-line hormonal agents (Ketoconozole, DES, Dexamethasone) may to some extent function by decreasing the adrenal output of dehydroepiandrosterone (DHEA), which is converted into testosterone (and then to dihydro-testosterone) and thereby further deprive the AR of the agonist by adding to the suppression by the LHrH agent or to the effect of prior castration.

Androgen deprivation, and also high dose anti androgen monotherapy, seem to result in amplification of the AR gene in 25% to 30% of progressing patients (adaptation) and paradoxically may facilitate response to second-line hormone therapy. Androgen deprivation also seems to select for mutations. Clinicians are familiar with the phenomenon of the "anti-androgen withdrawal response" resulting from mutations in the region of the ligand-binding pocket of the AR. Since the AR is located on the X chromosome no paired allele is available to blunt the effect of the mutation.

Once a ligand has mated with the receptor many events occur down the signaling pathway to DNA transcription and beyond. There are co-repressors and co-activators and DNA binding factors and transcription machinery. "The binding of co-repressor molecules are favored when anti-androgens [i.e. Casodex, Eulexin] occupy the ligand binding pocket" (Gelman, ibid) To date, we have mainly focused therapeutically on the ligand binding pocket employing agents that diminish signaling. However, in the future, with a fuller understanding of the entire signaling chain, researchers may be able to provide the clinician with many additional agents to target sites further down the signaling pathway and interrupt the AR's stimulation of growth and survival of prostate cancer cells.

Bottom Line: The AR and its signaling pathway will provide new targets for intervention.

HORMONES AND THERAPY

For the near future, there will be no need to talk to patients about PC-SPES as it's manufacturer, BotanicLab, has stopped production and all grants and studies involving PC-SPES are on hold. The reason: contamination with DES, Indocin and Warfarin in lots manufactured between 1996 and mid-1999. This was reported in an editorial (fascinating reading) and article in the Journal of the National

Cancer Institute, Vol.94, September 4, 2002, 1275-1281. Contamination may have entered at the plants in China. The usual 9 capsules of PC-SPES contained 0.5 mg of DES and 30 mg indomethacin. The study that had been in progress by Dr. Eric Small comparing DES to PC-SPES is currently on hold. There had been good rationale for such a study since the real question was whether PC-SPES had something "extra" that would render it more effective than 1 mg DES. The major herbal ingredients of PC-SPES were biacalin, which inhibits prostate cancer by apotosis and inhibits 5 alpha-reductase and has aromatase inhibitory properties, and a lesser ingredient, licochalocone A (a licorice flavinoid), which has Bcl-2 modulating properties. So legitimate research issues remain, but they need to be carried out with a better regulated product.

The question had always been whether PC-SPES was just a very much more expensive way to give an estrogen - such as DES. (Thirty 1 mg tabs of DES are available at Kelly Ross pharmacy for $30 - phone number: 622-3565). Many articles report the temporary effectiveness of 1 mg DES. An illustrative article is "Stilbesterol Effective As Salvage Therapy For Refractory Prostate Cancer" in Br J Urol Int 2000;85:1069-1073. In this study, 1 mg DES was combined with hydrocortisone (not required, as reported elsewhere -editor's note). Among 29 patients, they report a median drop of PSA of 84% (292 ng/mL to a nadir of 66 ng/mL). The nadir occurred at 4 months and the response persisted a median of 6 months, but some responses lasted considerably longer. Interestingly, 9 capsules of PC-SPES reduced PSA by 54% in hormone resistant patients for a median duration of four months. Finally, in other studies, 0.5 mg DES was used with similar results, which links us back to the PC-SPES story.

Bottom Line: Availability of PC-SPES halted, but 1 mg DES probably has equal effect.

PATHOLOGY AND DIAGNOSTICS

A nomogram suitable for the Palm Pilot (or PC) that presents good data on the outcomes of primary treatments for prostate cancer is available through Memorial Sloan Kettering Cancer Center. The nomogram addresses pretreatment and post-op data and gives comparative outcomes for surgery, external beam radiotherapy and brachytherapy after you have entered your patient's data for PSA, Stage, and Gleason Sum. It throws in a calculator for PSA doubling time calculation just for good measure. I think many physicians who deal with prostate cancer would enjoy having it on their Palm. Patients were always impressed when I pulled out the Palm, entered their data, and gave them a rough idea of 5-year bPFS prognosis. This is data pulled together by Dr. Kattan and colleagues.

You too can have this nomogram on your Palm! Here's how: 1) Go to www.mskcc.org and select "Medical Professionals" 2) Then select "Professional Resources", and on that page select "Nomograms" 3) Then you will be offered "Select a Nomogram Topic". Choose Prostate Cancer and then from the offered menu choose "Request Nomogram Software" You will have to register. The nomogram is free. If you have trouble accomplishing all this, I'll be glad to help.

Bottom Line: You too can be a Palm Pilot expert.

RESULTS OF CLINICAL STUDIES

EBRT vs RP (51 mos. FU): Kupelian, in the August 15, 2002, issue of the Journal of Clinical Oncology, presented a study comparing the efficacy of radiotherapy versus radical prostatectomy involving 1682 Cleveland Clinic patients. 1054 patients had surgery and 628 had radiotherapy with a median follow up of 51 months. The patients were stratified by pretreatment PSA, stage, Gleason score and age. Numerically, the RT group was slightly older and had slightly less favorable clinical characteristics. An important finding was the clear superiority of RT > 72 Gy versus less. The 8-year bRFS rates of RP versus RT (all doses) were 72% v.70%. RT when delivered at >72 Gy was slightly

superior to RP (p=0.004). For both treatment modalities the 5 year bRFS for T1-T2A was 90% and for T2B-T2C 60%. (An editorial reviews the study and refers to the utility and validity of the Kattan nomogram referred to elsewhere in this commentary)

Bottom Line: On an apples to apples comparison, RT = RP reminding us that consideration of a patient's other clinical factors is key in selecting treatment.

PSA Doubling Time Predicts Distant Failure: In an editorial (JCO, August 1,2002) Dr. D'Amico discusses the issue of predicting prostate cancer specific death (PCSD) when the PSA rises post treatment. A rapid rise (PSA Doubling Time: 6-12 months) significantly predicts distant failure. A post-RT PSA DT <1 year was associated with PCSD of 52% v. 10% for DT >1 year (p=.007). D'Amico briefly refers to data from his institution showing PSA DT < 1 year also is associated with an overall all-cause death rate of 53%. This fact will lead in a later commentary to a discussion of the recently published Scandanavian study comparing rates of PCSD with all-cause death.

Bottom Line: Post treatment PSA DT predicts for distant failure and death and can therefore guide treatment decisions.

THE FUTURE FILE

Free PSA Update: Coming soon: further analysis of serum PSA. In the June 2002 issue of Urology Mikolajczyk presents a review, "Free Prostate-Speficic Antigen In Serum Is Becoming More Complex." As we know, serum PSA is a serine protease that circulates in the serum bound by alpha-1-antichymotrypsin, which renders PSA inactive. Unbound PSA also circulates, and the new analysis finds that the "free PSA" has three components. Precursor PSA (pPSA) is associated with cancer; BPSA is a degraded PSA largely associated with BPH; and the third is a form that is a varient of PSA but similar to active PSA.

Bottom Line: Further analysis of pPSA amd BPSA will advance the understanding of prostate diseases

New Drug in the Pipeline: A promising new concept for a drug to treat PSA-producing prostate cancers: Denmneade from Johns Hopkins (Abstract #205.AACR,April 2002) is working toward a prodrug that links Thapsigargin, an extract from a Mediterranean plant in the carrot family,to a peptide that is a specific target for cleavage by the protolytic action of PSA. The concept is that once inside a PSA producing prostate cancer cell, the compound will be hydrolyzed thereby releasing the toxic Thapsigargin to kill the androgen-independent cell.

Bottom Line: Restrict your intake of seeds from Mediterranean carrots. [Editor's Note: Will systemic toxicity result from "free-PSA",(see Free-PSA update)]