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PCa Commentary

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Contents

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BASIC SCIENCE & BIOLOGY

PSA and Prostate Cancer Tumor Mass: Physicians and patients watch the PSA with an eagle eye: the basic assumption being that as the PSA rises and falls there is a corresponding increase and decrease in the total body tumor burden. Is this correlation unchanging throughout the disease? What is the biological basis of this association? Is the association tight enough so that PSA response to chemotherapy can predict survival?

The clinical aspects of this issue were discussed by Partin in a two part article in ONCOLOGY, September, 2002: "Prostate-Specific Antigen as a Marker of Disease Activity in Prostate Cancer." He indicates that early in the course of the disease there usually is good correspondence between PSA and tumor mass, but Partin points out that PSA reductions from hormonal therapy don't always correlate with survival. He refers to the trial of orchiectomy alone compared to orchiectomy plus flutamide in which the nadir PSA for the combination was significantly lower (P=<.001) but the combined treatment showed no survival advantage. David Crawford provided commentary to this article in which he stated "To date, however, no study has clearly shown a survival relationship between PSA nadir and *survival."* Balk ("Biology of Prostate-Specific Antigen", JCO, January, 2003) did point up the improved *duration of remission* predicted by a PSA nadir of <.4 ng/ml.

A review of the basic biology reveals the complexity of the association of PSA and prostate cancer tumor mass. My interest in this subject arose from the article by Denmeade, PROSTATE, Vol.54, 2003, "Dissociation Between Androgen Responsiveness for Malignant Growth vs. Expression of Prostate Specific Differentiation Markers PSA, HK2, and PSMA in Human Prostate Cancer Models." Analysis of this issues leads to a consideration of the mechanism of activation of the PSA gene. The PSA gene is one of a family that contain

"androgen response elements" (ARE), the very specific points of attachment of the activated androgen receptor (AAR) to its target site within the gene. The most forward portion of the gene contains a "promoter", which in this gene contains two AREs. Four thousand or more base pairs upstream away from the gene lies the "enhancer" containing seven AREs. If only the two AREs in the promoter are occupied by activated AAR, the PSA gene expression is weak. However, if all seven AREs in the enhancer are also engaged, the strength of PSA secretion is increased 1000 to 3000 times. It remains a puzzle how the distant enhancer structurally relates to the promoter to cooperate in the initiation of gene transcription, however, the best explanation is that the DNA, responding the bonding energies, loops back on itself to allow the enhancer to contact the transcription machinery assembled on the promoter and augments the strength of transcription. After transcription is initiated the AAR quickly detaches and is destroyed and another wave of AARs must find its way to the gene to continue stimulation. This complex mechanism for gene expression applies, of course, to all the genes that respond to androgen stimulation - each with its own set of AREs. This family of diverse genes codes for a wide variety of transcripts governing secretion of prostate specific membrane antigen, prostatic acid phosphatase; regulating mitoses and cell cycle progression; controlling tumor suppressors and DNA repair and many others. The total effect is further magnified since some genes that are activated produce transcription factors for yet more genes! The total number of genes controlled by androgen stimulation is unknown. However, preliminary data from DNA microarray analysis suggests that androgen signaling activates 136 genes and silences 215 others! Just this introductory glimpse into the complexity and amazing specificity of this entire process invites speculation that the mutational disarray that results from malignancy could easily uncouple the coordinated expression of this family of genes. And this is the irregularity reported by Denmeade who found in his *in vitro* tests that some prostate cancer cell lines were responsive to androgen for both growth and marker secretion, some negative for both, and others mixed in response. Additionally, he found marked differences in the strength of marker secretion. It would be surprising if these *in vitro* irregularities were not duplicated in real life human prostate cancer.

Fortunately, there seems to be sufficient linking of a decline in PSA to improved survival exhibited in clinical trials of chemotherapy in hormone refractory PC so that useful conclusions can be drawn. A consensus supports the benchmark that a >50% reduction in PSA achieved after 8 weeks of therapy can serve as an early surrogate for improved survival. It's interesting that the foundation for this consensus rests primarily on one very well done study reported by Smith and Pienta, "Change in Serum Prostatic-Specific Antigen as a Marker of Response to Chemotherapy for Hormone Refractory Prostate Cancer" (JCO, May 1999). The conclusion of this study is especially credible because the study took into account many additional patient factors that potentially could confound the relationship of PSA and survival. The most important of these were performance status, hemoglobin level, measurable disease, alkaline phosphatase, and the relative reduction of PSA at 4 and 8 weeks post initiation of a *uniform therapy,* estramustine/VP-16. Those patients who achieved a >50% reduction of PSA at 8 weeks survived 23 months compared to 9 1/2 months for those who did not (P=.0005). Not surprisingly, performance status was a strong predictor of survival; hemoglobin <10 g/dL was of lesser importance. But when PSA decline was adjusted for performance status and hemoglobin level, PSA retained its independent strength. A second foundation article by Kelly (JCO, April, 1993) used the same criterion for evaluating chemotherapy response in 110 patients and reported a difference in survival of >25 months versus 8.6 months. The strength of their conclusion was weakened because they couldn't take account of performance status since the patients were drawn from disparate studies using a variety of chemotherapy regimens. The consensus for the >50% PSA reduction benchmark was codified by Bubley

(JCO, November 1999) reporting the agreement of 27 respected researchers. It's interesting that for these experts the principle value of this criterion was to guide investigators as to which regimen warranted further study. They cautioned against its use in assuring patients about the likely outcome of their treatment.

Bottom Line: Clinicians and patients are fortunate to have a marker as generally serviceable as PSA to monitor the course of disease. An understanding of the biology of the relationship of PSA to tumor mass, however, can add perspective to PSA interpretation.

ANDROGEN INSENSITIVE DISEASE

Neoadjuvant chemotherapy for "high risk" prostate cancer - ready for prime time? It is routine these days at urology tumor boards for clinicians to ponder whether neoadjuvant therapy would be of benefit to patients presenting with "high risk for recurrence" prostate cancer. Neoadjuvant treatment with hormonal, chemo-hormonal, or chemotherapy, preceding primary therapy (surgery or irradiation) is under widespread active study. And rightly so, since the prospects for sustained freedom from biochemical relapse and ultimate survival are so significantly diminished in this group. Based on an analysis of outcome after radical prostatectomy or radiation therapy, researchers have arrived at a rough consensus that associates "high risk" with a clinical Stage of T2b ('92) or greater, and/or Gleason 8 - 10, and/or PSA usually >l5 or >20 ng/ml. The need for improvement is evident by placing a clinical example with the minimum parameters of this definition into the Kattan outcome nomogram [discussed in PCa Commentary of October 2002]. The result: likelihood of organ confined disease, 7%, and capsular penetration >40%; 5 year likelihood of freedom from PSA recurrence from surgery 30%, or from external beam irradiation (78 Gy) 40%. An excellent recent article that presents a balanced view of the current status of this issue was presented by Hussain in UROLOGY, April 2003: "Neoadjuvant Docetaxel and Estramustine Chemotherapy in High-Risk/Locally Advanced Prostate Cancer."

The initial efforts to improve treatment outcome initially involved the neoadjuvant use of androgen suppression, usually with an LHRH agonist preceding surgery or preceding and concomitant with irradiation. Study strategies have been segregated based on duration of treatment, i.e. 3 months or less versus longer - variously up to 12 months. A substantial consensus of opinion finds that treatment of 3 months or less offers no improvement in outcome over primary therapy alone at the five year benchmark. Meyer (UROLOGY 2001 Aug) reports the Laval University, Quebec, experience in which 756 men were treated between 1991-1998 and PSA failure was set at >.3 ng/ml. Of these, 240 men received androgen suppression for 3 months or less, 129 men for >3 months, and 516 men had RP alone. The $\leq$3 months group gained no benefit. In their study the "longer" treatment group enjoyed a longer disease-free survival (hazard ratio .6) at the median follow-up of 4 years. However, this conclusion was challenged by Dr. Martin Gleeve at the April 2003 AUA meeting reporting the British Columbia study of 502 men who received Lupron and flutamide for either 3 or 8 months prior to RP. At 4 years post surgery the PSA recurrence was similar: 23.6% (8 months) and 25.4% (3 months). The study had no control arm of RP only.

The logical next step has been to evaluate chemotherapy in the neoadjuvant setting. This endeavor is in its infancy. Based on the tentative and hopeful evidence that chemotherapy may have usefulness in the treatment of metastatic PC [see PCa Commentary, February 2003] docetaxel, mitoxanthrone, estramustine (and others) in various combinations have been use neoadjuvantly, sometimes combined with hormone suppression (again for various durations). The rationale underlying the chemo/hormonal therapy is that at the outset PC is

heterogeneous as to cellular sensitivity to androgen deprivation and that chemotherapy might address the androgen insensitive component. It's important for clinicians to realize that when the chemotherapy drug estramustine ("EMCYT") is used, the treatment becomes "chemo-hormonal", since the Hussain article documents that estramustine even at a seemingly low dose of 280 mg TID X 3 days q 3 weeks lowers serum testosterone to castrate levels (<50 ng/dL) by the end of the first three week cycle. And since so many of the current regimens include this drug, an unresolved issue is what contribution chemotherapy may add to the androgen diminishing effect of estramustine. Two trials have used single agent neoadjuvant docetaxel/surgery versus surgery alone and, as also seen in the neoadjuvant hormonal trials, the incidence of positive tumor margins at RP was reduced. The ultimate utility of this reduction awaits further follow-up. In the Hussain study 70% of RP specimens showed negative margins, but no specimen was free of cancer. For comparison, neoadjuvant studies in breast cancer have shown that a survival benefit is achieved only when a complete pathologic remission is effected. At this stage of investigation of neoadjuvant therapy for PC the available early data only relates to the extent of PSA decline and a comparative improvement in negative surgical margins.

A word of caution against premature assumptions of success for neoadjuvant therapy arises from consideration of the experience of neoadjuvant therapy in prostate's sister endocrine sensitive disease, breast cancer. Post- operative adjuvant chemotherapy in breast cancer has been studied since 1965, and neoadjuvant treatment more recently. It's well recognized that chemotherapy in this disease has a success record that far exceeds that for chemotherapy's fledgling role in PC. Postoperative chemotherapy in breast cancer delays disease recurrence by three to four years and confers a small long-term survival benefit. There is no similar body of data for post-operative chemotherapy in PC, although some studies are in progress. Encouraged by success in the use of post-operative adjuvant chemotherapy for breast cancer, study groups moved chemotherapy into the preoperative (neoadjuvant) position and by 2001 were able to report a large experience. The outcome: no overall survival advantage resulted from neoadjuvant chemotherapy compared to the standard post-operative timing. This was the overall outcome despite extensive shrinkage of tumors and a modest numbers of complete pathologic responses. Neoadjuvant treatment in PC, however, is being moved to the front position *without* any convincing positive data from post-operative adjuvant trials.

The motivation to employ neoadjuvant therapy for PC arises from a *very evident need* and a hope based on a hypothesis. No assurance of success can be given to any individual patient to offset the potential toxicities he may experience from treatment. Currently, neoadjuvant (hormonal and/or chemotherapy) treatment can be best justified by incorporation into a well designed clinical trial. Since many or most "high risk" patients are appropriate candidates for irradiation, physicians should consider entering them into clinical trials such as "Phase III Randomized Study of Neoadjuvant Total Androgen Suppression and Radiotherapy in Patients With Intermediate-Risk Adenocarcinoma of the Prostate" (RTOG 9910), or "Phase III Randomized Study of Androgen Suppression and Radiotherapy With or Without Subsequent Paclitaxel, Estramustine, and Etoposide in Patients With Localized High-Risk Prostate Cancer" (RTOG-9902) - or any other appropriately designed trial.

Bottom Line: The benefit of neoadjuvant therapy for PC will need to be clearly established in clinical trials before this type of treatment is accepted as a standard option.