SEATTLE PROSTATE INSTITUTE

PCa Commentary

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Your comments and requests for information on a specific topic are welcome at
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INFORMATION SOURCES

National Prostate Cancer Coalition: - E-mail Newsletter: "AWARE": an excellent source of information for patient and doctor alike. As I have learned, cyberspace is stuffed to overflowing with bits of information about prostate cancer. The trick is to click into information that is useful, timely, well-researched, and well-presented. The twice weekly e-mail communication, "AWARE", fits the bill - certainly for patients, and really, for doctors also. It is the production of the research staff of the National Prostate Cancer Coalition, easily subscribed to, and delivered to your e-mail screen Tuesdays and Fridays. Tuesday's edition covers news and patient oriented issues. Friday features more science based data such as clinical trials, new advances, and a very well done section on newly published research. In perusing this area I found I was clicking into links that took me to the same data base, the very abstracts that I consult through PubMed. AWARE's research staff, however, has narrowed the field to ten or twelve pertinent articles. I highly recommend that we do our patients a favor and guide them to this site. (And sneak a look ourselves to be brought up to date ... and know what our patients are learning.)

To subscribe: 1) go to www.pcacoalition.org, the home page; 2) at the upper left of the page click on "Subscribe to Our Newsletter, Aware"; 3) click on "FREE electronic newsletter"; 4) on the following screen, enter your e-mail address. Very simple!

HORMONE INTERVENTION

Prophylactic Breast Irradiation: It is well known that nearly 80% of men with prostate cancer treated with 1 - 3 mg of Diethylstilbesterol (DES) will develop enlargement and tenderness of their breasts. And it is conventional to offer radiation therapy prophylaxis, usually delivered in three fractions *prior* to DES therapy. In UROLOGY 61, Jan, 2003, Widmark reports the results of 12 months follow-up of a large Scandinavian trial evaluating the efficacy of breast irradiation delivered *before* starting Flutamide (250 mg X 3 qd) to prevent gynecomastia and breast tenderness. At the start of Flutamide a single 3-month depot Lupron was given. Serum testosterone measurements were made and 85% of men regained pretreatment levels by 6 months, after which the levels either remained in the normal range or were elevated (as is to be expected in anti-androgen therapy). Proliferation of the glandular portion of the breast is understood to result from increased enzymatic conversion of testosterone to estrogen, and irradiation (RT) blunts or eliminates this response. Most of the units (14 of 16) in the study utilized electron beam therapy (6-9 MeV) delivered in a single 15 Gy dose.

The irradiation was significantly beneficial. 253 men were fully evaluable at 12 months. At the onset of the study the participants were offered a choice of having RT or none, and 174 (69%) opted for treatment. The result: gynecomastia developed in 28% of the RT group versus 71% in the no-RT group; breast tenderness occurred in 43% versus 75%, respectively. As expected, the onset of breast symptoms was delayed until 1- 2 months after the recovery of testosterone levels. (In parallel historical data, 55% of men taking DES developed gynecomastia unless RT was administered.)

Similar unwelcome breast complications develop in men taking Casodex (50 or 150 mg qd), or the Proscar/Antiandrogencombination. The March PCa Commentary reported gynecomastia in 49% and breast tenderness in 40% of men taking 150 mg daily of Casodex. Since it is not possible to predict before antiandrogen therapy which men will be adversely affected or to what extent, it seems prudent to consider offering prior RT, especially if the RT can conveniently be delivered in one fraction.

Bottom Line: Breast RT prior to antiandrogen therapy improves quality-of-life.

CASODEX 50 mg - Where Does It Fit In? Recently I was asked to sit in with a prostate support group and I listened as the men recounted the various treatments they were currently receiving. One man indicated that when his PSA commenced to rise following initial Lupron he was prescribed Casodex, 50 mg daily. This raised in my mind the question of the strength of evidence for that dosage. I have been surprised how little data is available to answer that question.

In the life and death chess match against the androgen receptor the initial move in response to the first rise of PSA post primary therapy is some form of androgen deprivation. Even the grand chess master Bobby Fisher would open with "Lupron" to "king pawn 3". But other choices are equally acceptable: Zoladex, castration, DES 1 mg/qd, Abarelix (when available and after some additional testing), and Casodex 150 mg/qd. All of these decrease the testosterone level to < 50 ng/dL. Castration usually results in a testosterone value of < 20 ng/dL. The additional options of Casodex 50 mg + Proscar 5-10 mg are also effective despite often raising the testosterone level. Combined androgen blockade (CAB) with an LHRH agonist/antiandrogen was initially reported to provide a survival benefit compared to LHRH monotherapy. Dr. David Crawford's early report indicated a 26% survival advantage for CAB (28.3 vs.35.6 months, P=.35). However, the most recent meta-analyses estimate the benefit at between 1.8% or slightly more. The current National Comprehensive Cancer Network guideline (www.nccn.org) for prostate cancer management makes the interesting suggestion: if monotherapy with an LHRH agonist is initiated, the testosterone level should be checked in several months. If castrate level has not been achieved, then an antiandrogen "may be added".

Casodex (and Flutamide) functions as a competitor to testosterone and dihydrotestosterone for the androgen receptor, and it's effectiveness is *dose dependent*. A 1998 study compared Casodex at doses between 10 and 200 mg daily for 12 weeks in treatment of advanced PC. The median percentage decrease in PSA for the 50 mg, 100 mg, and 200 mg doses were 90%, 93.4%, and 94.8% respectively. Casodex 50 mg/qd is not recommended as primary hormonal intervention based on the data from a 1996 Swedish cooperative study which found an inferior survival for the 50 mg dose of Casodex compared to castration, whereas 150 mg/qd is equivalent to castration in this setting.

The most common point of intervention with second line hormonal therapy, however, is in the setting of a rising PSA post LHRH agonist in patients with either minimal or no evidence of metastases - and this is the situation where the data is skimpy. The best data comes from a SWOG study presented only in abstract form in the ASCO 1997 Proceedings (#116) in which 27 men with rising PSAs received Casodex 50 mg/qd (19 with a positive bone scan, 8 with only a rising PSA). The median time to progression was 53 days (range 8 - 292) with 14 men showing progression within two months.
Because of the minimal benefit of the 50 mg dose, SWOG carried out a second study using a 150 mg/qd dose. This was reported in UROLOGY 2001, July. This trial involved 52 men with advanced PC, 69% with bone metastases and an additional 8% with soft tissue disease only. The means PSA on entry was 107. 20% showed a PSA decrease of > 50%; 32% had stable disease; some experienced palliative benefit; and the median survival was 15 months. One of the hazards

of extrapolating from both the SWOG studies arises from the inclusion in both by large component of men with substantially advanced metastatic disease. If antiandrogen therapy were introduced earlier, there might not have been an improved "response", but the survival times would have been lengthened because of "lead time bias".

Studies have shown that Casodex can effect responses after Flutamide usage. When Casodex 150 mg/qd was used after primary androgen deprivation (CAB) with a LHRH agonist plus **Flutamide** responses occurred in 43%. Casodex therapy was not initiated until there was further PSA failure in the 40% that showed a "flutamide withdrawal response". When Flutamide was used post LHRH/Casodex (50 mg) treatment the response was only 6%. Other studies have recorded responses in the range of 20% to 38% to Casodex after Flutamide usage - especially in instances of Flutamide failure after initial response.

Bottom Line: Casodex 50 mg/qd offers only minimal benefit as second line hormonal intervention.

BASIC SCIENCE AND BIOLOGY

MULTIFOCAL PROSTATE CANCER: The consensus from pathological studies is that PC most times presents as multiple sites within the prostate. This has implications relating to biopsy strategy, and, at a fundamental level, has potential for understanding the genesis of the disease. Studies of glands removed for incidental reasons (such as with a cystectomy) or in the treatment of known prostate cancer find multiple sites of disease in 50% - 76% of specimens. In a study conducted at Stanford and reported by Wise (joined also by Stamey and McNeal: UROLOGY 60;(2)2002,p 264) only 17% of 486 glands had a single foci, 16% had two, and the remaining had from 3 to 12 independent sites. Another study (Miller GJ, J UROL 1994; Nov) reported solitary lesions in 43% of 151 glands, two lesions in 31.1%, and the remaining 25.2% containing 2 to 6 tumors. Djavan in 1999 found multifocality in 66.9% of 308 specimens, with 63% having two lesions, and 37% three or more.

What else do these studies reveal? The Wise study found that when multifocality exists the size of the largest tumor decreases as the number of additional sites increases. After contemplating this

relationship the authors were led to consider whether tumors might enlarge by accretion, "swallowing up" the surrounding smaller tumor sites, particularly in the small confines of the peripheral zones. The secondary tumors were mostly small, >.5 cm3 in 58% of the observations. (Another study found 80% of the secondary lesions < .5 cm3). Wise's follow-up results indicated that the risk of biochemical relapse, however, was related to the size and grade of the largest tumor. Their follow-up results led them to speculate that multiplicity was in some way protective since patients with multifocal disease had better outcomes than patients with solitary lesions when those patients' largest tumors were of similar size.2) The Miller study found "that tumors need not acquired either large volume or high grade before they" invade through the prostatic capsule. Among capsule invading tumors of less than 3 cm3 there was an equal division between those with Gleason sums of 2,3, and 4 and those of 5,6, and 7. Contrary to Wise (above) Miller's opinion was that multifocality adversely affected prognosis. 70% of the organ confined tumors less than 1 cm3 had a Gleason sum of 4 or less.

Several thoughts arise from the fact of frequent multifocality. Considering the relatively small size of a biopsy specimen, sampling error is lessened by more probes into a potentially multifocal tumor field. Currently there is a worthwhile effort to try to relate the risk of treatment failure to the "number of positive biopsy cores", but the randomness of hitting or missing additional tumor sites will challenge the statistical strength of this association. (Dr. Kattan is currently attempting to include this factor in the Partin Tables). A study by Mazal (Eur Urol, 2001, June) addressed the issue of spacial distribution of multiple prostate cancers. Prostatectomy specimens from men whose initial biopsies were negative revealed biopsy-undetected tumor most frequently in the apical region ($p<0.001$) and the the dorsal region ($p<0.01$).

Ruijter (J Pathol 1996 Nov, and 1999 July) probed the issue of multifocality deeper by studying the histological relationship among a prostate's various tumors. In the 1996 study whole mount prostatectomy specimens for 61 T2 prostate cancers were mapped for histological grade heterogeneity and tumor multifocality. Multiple tumors occurred in 72% and only 16% showed a single histologic grade. Extracapsular invasion was often associated with tumors of small volume and low histological grade. Variability of histological grade was directly proportional to the total tumor volume. The 1999 study attempted to further the analysis by using sophisticated molecular biological techniques to examine for clonal concordance among tumors. This proved to be a very challenging effort. Some individual tumors contained several distinct clones, and among tumors in a single prostate specimen the various tumor sites often showed a mixture of clonal similarity and difference. Their conclusion was that "no clear evidence was obtained for either a clonal or a non-clonal origin of multiple lesions in a given prostate".

Since there is strong support for the hypotheses that high-grade prostatic intraepithelial neoplasia (HGPIN) is a precursor to cancer, it's possible that the study of this lesion may provide clues to the "first three minutes" of the genesis of small emerging galaxies of early cancer in the multi-billion cell universe of the prostate gland. Bostwick, by studying chromosome regularity (karyometry) among the nuclei of a single HGPIN lesion found evidence that even at this stage there were differences in chromosome numbers. A Spanish researcher compared chromosome features between HGPIN and PC in a single prostate and found that in 75% the two lesions shared abnormalities of chromosome 7 and 8, common know abnormalities. And to make the analysis even more complicated an Italian pathologist found nuclear abnormalities in normal-looking cells adjacent to and distant from sites of HGPIN and PC.

Bottom Line: Application of advanced analytic techniques to the study of tumor multifocality will move us closer to an understanding the genesis of prostate cancer.