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SCREENING: Active Surveillance With Elective Delayed Intervention

These title words were followed by ":walking the line between over-treatment for indolent disease and under-treatment for aggressive disease" in Dr. Laurence Klotz's report of the outcome of this management strategy for prostate cancer in 299 men (Canadian Journal of Urology;12 (Supp 1); February 2005). The phrases "active surveillance" (AS) or "expectant management" have replaced the older concept of "watchful waiting", which implied no initial treatment, but instead, palliative intervention when symptoms developed. Serious consideration of a strategy of deferred therapy without sacrificing curative intent is called for as a result of the stage migration resulting from the expanding practice of PSA screening. As cited by Klotz, "PSA screening has increased the ratio of incidence to mortality for prostate cancer from 2.5:1 to 15:1" leading to a lifetime likelihood of a prostate cancer diagnosis in USA males of 1:6, but only a mortality ratio of 1:40. In his editorial in The Journal of Urology, April 2005, "Early Stage Prostate Cancer - Do We Have A Problem With Over-Diagnosis, Over-treatment, Or Both" Peter Carroll called for "identifying better markers of the need for treatment and carefully constructed trials of surveillance in well selected and monitored men". The time is ripe for "unlinking detection and treatment".

Two informative trials have been reported that explore active surveillance. Both reports stress the importance of a careful selection of men who are at low risk for recurrence, and both use the PSA doubling time to trigger intervention. In the staging of candidates for AS the need for a ≥ 12 core biopsy to minimize sampling error was emphasized, as was the importance of good communication between patient and doctor to explain the concept.

n his article Klotz reports an 8 year follow-up of 299 Toronto men with good- or intermediate-risk cancer. Eligibility required PSA < 15, Gleason ≤ 7, cT ≤ 2b. Most men, however, were PSA < 10, Gleason ≤ 6, cT ≤ 2a. Rebiopsy was performed at 1.5 - 2 years. Intervention was triggered by a PSADT < 2 years or developing a PSA >8 ng/mL. At a median of ~ 5 years 60% remained on surveillance. "Of the patients coming off surveillance, 12% of patients came off because of rapid biochemical progression, 8% for clinical progression, 4% for histologic progression, and 16% due to patient preference." At 8 years overall survival was 85%, and disease specific survival 99%. A rapid PSA DT of < 2 years prompted surgery in 24 of the 299. The findings: 10 were pT2; 14, pT3a-c; and 2, N1. Interestingly, "Neither grade, stage, baseline PSA, or age correlated significantly with PDSDT". Reflecting on the trial's outcome, Klotz suggests that the threshold for intervention would best be set at a PSA DT of "around three years", noting that "about 20% of patients will fall into this category."

The Toronto group has initiated a Phase III Intergroup Trial, "Standard Treatment Against Restricted Treatment (START), open to good-risk patients (PSA ≤ 10, Gleason ≤ 6, T1c/T2a) with randomization between active surveillance or definitive therapy with RP, BT, or EBRT. The trial uses a PSA DT of < 3 years, or grade progression to a predominant Gleson pattern of 4 or higher as a trigger for intervention.

The second article, "Early outcome of active surveillance for localized prostate cancer" (BJU Int, **95**, 2005) reports the outcome of 80 men managed at the Royal Marsden Hospital whose disease status was cT1/T2, PSA < 20 ng/mL, Gleason score ≤ 7. Intervention was individualized and based on the relationship of observed PSA DT and the patient's age, or was prompted by an upgrade in biopsy histology. At a median F/U of 42 months, 80% remained on AS. Seven patients had RP and at a median of 20 months all are NED. "The median PSA DT for the group was 12 years, while 25% of patients had a PDS DT of < 4.5 years." A follow-up clinical trial is ongoing at the Marsden in which the PSA eligibility has been narrowed to < 15 ng/mL; and less than half of the cores may be positive. Repeat biopsies are taken every 2 years.

In the "Men & Health" section of the New York Times, June 20, the health columnist, Gina Kolata, presents an up to date summary of issues related to PSA screening, discusses delayed treatment, and highlights the rate of PSA rise as important. This would be an excellent office article for educating men.

Bottom Line: The increasing relevance of a strategy of active surveillance brings to mind the command of General Putnam at the Battle of Bunker Hill. "Don't fire until you see the whites of their eyes"; with the further advice - unnecessary for clinicans today - "then fire low, take aim at their waistbands" [actually a little lower].

NEW AGENTS FOR TREATMENT: Phenoxodiol - What Is It? Somebody Is Bound To Ask You.

ANSWER: Phenoxodiol is an isoflavone, a more stable synthetic derivative of its cousin genistein, the ingredient of interest in soy products, much studied for its beneficial effect on prostate cancer.

The interest in phenoxodiol results from the November 2004 presentation at the American Association of Cancer Research conference on Translational and Clinical Advances in Prostate Cancer of an Australian Phase Ib/IIa study of this agent in 19 men with late stage, metastatic prostate cancer. At doses of 200 mg and 400 mg q 8 hrs 2 of 4 and 3 of 4 men, respectively, showed no evidence of disease progression at 6 months, and the PSA values in 5 of 6 were below baseline at 6 months. This very encouraging result raised the possibility that phenoxodiol could slow the progression of prostate cancer - and accomplish this with little or no toxicity.

Considerable investigation has been directed at understanding the phenoxodial's mechanism of action, and these findings have provided a sound basic science foundation supporting the expectation that this drug will be clinically useful. In Cancer Research, April 2005, Aguero et al. reported that phenoxodiol induced an inhibitor of cell cycle progression, p21, and achieved its antiproliferative effect by promoting cell cycle arrest at the G1-S phase checkpoint. Other researches have also identified an anti-proliferative effect resulting from interference with a vital cancer cell membrane enzyme and thereby promoting apoptoses. And a report at ASCO 2005 found that phenoxodiol induced increased intracellular levels of ceremide, also a promoter of apopotosis. These researchers concluded "The cytotoxicity of PXD [phenoxodiol] in highly drug-resistant tumor cells suggests its clinical utility in patients with advanced, chemorefractory cancer".

Researchers at Yale have conducted basic science studies in ovarian cancer and determined that phenoxodiol is a potent chemosensitizer of docetaxel and can restore drug sensitivity to doxetaxel-resistant cells. One application of this finding would allow a doxetaxel dose reduction when combined with phenoxodiol. Phenoxodiol is currently under active clinical investigation in ovarian cancer.

Although the drug is not currently available, on the basis of the November report, the FDA has granted the Marshall Edwards Corporation fast track status for wider investigations of phenoxodial in clinical studies of patients with hormone refractory prostate cancer.

A Phase IIB/IIIA multi-center international, clinical trial of phenoxodiol at 400mg q 8 hrs for men with HRPC is planned titled "COMPACT", Comparison of Phenoxodiol Against Conventional Therapy. A company spokesman has indicated that "the COMPACT study is being formulated with a view to commencing later in 2005. It will be conducted in patients with hormone-refractory, doxetaxel-refractory patients, with phenoxodiol being assessed for its ability to reverse chemo-resistance to doxetaxel."

Bottom Line: Encouraging early results suggest clinical usefulness for the newly developed drug, phenoxodiol.

BONE METASTESES AND OSTEOPAROSIS: Painful Bone Metastases: RTOG Trial 9701 Finds Response Rate From 8 Gy Single Fraction Radiotherapy As Effective As A Longer Course

"Randomized Trial of Short- Versus Long-Course Radiotherapy for Palliation of Painful Bone Metastases", JNCI, June 1,2005, reports the findings of a collaboration of 11 major institutions as to "whether 8 Gy delivered in a single treatment fraction provides pain and narcotic relief that is equivalent to that of the standard 30 Gy delivered in 10 treatment over 2 weeks." The study included 898 patients with prostate and breast cancer. The answer to the study query was affirmative. Measured at 3 months "The overall response was 66%. Complete and partial response rates were 15% and 50%, respectively in the 8-Gy arm compared with 18% and 48% in the 30-Gy arm." The criteria for complete response was perhaps unrealistically strict - zero pain and zero narcotic use - since pain from other causes might prompt the need for analgesia. Grade 2-4 toxicity favored the 8-Gy group, 10% versus 17%. Retreatment was employed in 18% of the single fraction group compared to 9% in the 30-Gy arm.

The accompanying editorial put the results of the RTOG study into perspective and asked "How Much More Evidence Is Needed?" There is no current consensus as to the optimal fractionation schedule. 20 Gy in five treatments is common in Canada, and single fraction treatment with 8 Gy is most common in European countries. All told there are 40 variations.

The editorial reviews the Dutch Bone Metastases Study (1171 patients)and the Bone Pain Trial Working Group trial (765 patients) both of which found an equivalent response efficacy for an 8-Gy schedule compared to a multifraction schema. Overall response in the Dutch study was 71% with 35% CRs; and for the BPTWG trial overall response was 78% and CR 57%. The retreatment rate for the single fraction vs multifraction in the Dutch study was 24% vs 6%, and in the BPTWG, 23% vs. 10%.

Athough the editorial acknowledges that the retreatment rate "may be of concern to some oncologists", it points out that in the RTOG study there was "no statistically significant difference in the treatment failure rate in the two arms" and speculated that the ease of a single fraction retreatment may have favored its use. In the Dutch study "Retreatment for nonresponders was successful in 66% of the single-fraction group but in only 33% of the multiple-fraction group (P=.24)".

Bottom Line: In three very large randomized trials 8-Gy radiation therapy delivered in a single fraction "is sufficient to achieve palliation of painful bone metastases." [Editorial, above]

CLINICAL TRIALS AND PROTOCOLS

FROM ASCO 2005: Interim Results Of High-Dose Calcitriol/Docetaxel (C/D) Versus Docetaxel (D) In Men With HRPC.

Dr. Beers, Oregon Health Sciences University, has pioneered the investigation of high-dose calcitriol because of preclinical evidence that "it enhance[s] the anti-tumor activity of multiple classes of chemotherapy". At ASCO he reported on the combination C/D vs. docetaxel alone in a study of 250 men with metastatic AIPC and rising PSA levels despite androgen suppression (testosterone levels < 50 ng/mL). The interim analysis at 6 months - median F/U 9 months - favored C/D over D with a $\geq$ 50% decline in PSA in 58% vs. 49% of men, and an objective response in 28% vs. 20%, respectively. Toxicity was less in the C/D arm. Neither difference was at a level of significance. A later report of overall survival and PFS will be forthcoming.

FROM ASCO 2005: Final Results Of Dendreon Vaccine Trial D9901 In 127 Men With Metastatic, Asymptomatic AIPC.

At a median F/U of 36 months 82 men receiving the PAP/GM-CSF vaccine ("Provenge") as compared to 45 men on a placebo experienced a median survival of 25.9 months vs. 22.0 months (P=0.020). At 36 months from the start of the study 33% of the vaccine patients were alive vs. 11% for the men in the placebo arm (P=.003).

In the evaluation of time to objective disease progression it was noted that during the first 3 months of the study a large number of men on both arms progressed. The ASCO presenter, Dr. Eric Small, postulated that immunotherapy requires sufficient time to "kick in", but noted that at 8 weeks a T-Cell proliferation test evaluating immunologic response showed an 8 fold superiority in the vaccine treated group. Dr. Small cautioned against comparing the median survival figure in the D9901 trial with the two month prolongation of median survival achieved in the recently reported Docetaxel/Emcyt vs. Mitoxanthrone/Prednisone trial since the men in these chemotherapy study arms had more advanced disease. His suggested strategy for vaccine usage in the AIPC setting (should the vaccine be approved for general use) would be to initially employ the vaccine while reserving chemotherapy for vaccine failures.

A pilot study of 22 men with AIPC combining Provenge with Avastin has been reported and showed a prolongation of PSA DT from a pretreatment value of 6.7 months to 12.7 months. Trials combining Provenge with chemotherapy are planned.

The current Dendreon trial D9902B for men, post prostatectomy, with AIPC and Gleason scores $\leq$ 7 is accessible at the Virginia Mason Medical Center and the Seattle Caner Care Alliance. Details at Dendreon.com.