SEATTLE PROSTATE INSTITUTE

PCa Commentary

Vol. 22: July 2004

Contents

Your comments and requests for information on a specific topic are welcome at ecweber@nwlink.com

This month's issue plus a compilation of past articles is available online at www.seattleprostateinst.com/pcacommentary.htm

PRIMARY TX UPDATES: Expectant Management Of Localized Prostate Cancer With An Intent To Cure: An Oxymoron?

A thoughtful review of this concept was presented by Kahn, Partin, and Carter in their article, "Expectant Management of Localized Prostate Cancer" (Urology, Nov. 2003). They set the stage for the discussion by stating: "... expectant management with curative intent has recently been described as a rational option for carefully selected men with prostate-specific antigen (PSA) screen-detected cancers thought to be of low volume." In their opinion low volume disease (< .5 cm3) was best predicted by a PSA density of < 0.1/ng/mL/g, stage cTic, Gleason < 6, < 3 biopsy cores positive with none having > 50% cancer. This shift in strategy is away from the concept of "watchful waiting" in which initial therapy is deferred because the patient's predicted life expectancy is considered shorter than the predicted time before symptom onset or death. Recent information detailing emerging prostate cancer demographics has made "expectant management" a relevant issue. What new information have we learned?

As reported by Cooperberg et al. (JCO, June 2004) the CaPSURE data shows that in the period 1999-2001 among patients diagnosed with low-risk disease (PSA $\leq$ 10 ng/mL, Gleason sum $\leq$ 6, clinical stage $\leq$ T2a) nearly two thirds were screen-detected T1c cancers,

compared to 15.2% in 1989-1992; and unilaterally palpable T2a tumors have fallen from nearly three-quarters (1989-1992) to 36% of cases (1999-2001).

It is well known that PSA screening introduces a significant "lead time bias" and this "bias" introduces a confounding factor in comparisons among treatment outcomes. "Lead time" represents the interval between a diagnosis based on PSA screening compared to a diagnosis based on clinical symptoms. Etzioni of the Fred Hutchinson had estimated a mean lead time bias of 3 - 7 years. However, data from Rotterdam (Am J of Urol Rev, April 2004) extends the estimate of lead time on average to 12.3 years, and a Swedish study with 20 years of follow-up presented a median lead time estimate of 12 years.

The large percentage of men who have been recently diagnosed fall into this low risk category, and an even higher proportion will do so in the future. Data based on the 7 year follow-up of 2950 men who were in the untreated cohort in the Prostate Cancer Prevention Trial was reported in the article , "Prevalence of Prostate Cancer among Men with a Prostate-Specific Antigen Level $\leq$ 4 ng per Milliliter" (NEJM, May 27, 2004). Of the 449 men with PSA values of < 4 ng/mL diagnosed as T1c cancers, 302 (67%) had a Gleason score of 6; 47 (10.5%) had Gleason score 5, and 12 (2.6%) Gleason score 4. Gleason scores of 7 or more were found in only 67 (15%) of men. In total 85% of the cancer were Gleason $\leq$ 6. Based on an estimated incidence of prostate cancer in the United States for 2003 of 220,900 men, a rough calculation would suggest that possibly 100,000 of these men would present with low risk, T1c prostate cancer.

The issue of screen-detected low-risk prostate cancer is often linked with a concern of "overdiagnosis", with its implication that treatment in the early stage of prostate cancer is often "overtreatment", or at least treatment rendered unnecessarily early. In contrast, when "early diagnosis" is aligned with the emerging context of "expectant management", a different strategy emerges, namely, postponing treatment - with all its associated side effects - until a later time when intervention can still be predicted to offer the same likelihood of cure as if it had been performed at initial diagnosis.

Jan-Erik Johansson et al. begin their article, "Natural History of Early, Localized Prostate Cancer" (JAMA, June 9,2004) by stating, "Without understanding the natural history of prostate cancer diagnosed at an early, localized stage patient counseling and clinical management are difficult." They point out that few men "diagnosed at an early clinical stage die from prostate cancer within 10 to 15 years following diagnosis." The basis of their article is the mean 21 year follow-up of 223 men with T0-T2 NX M0 prostate cancer, and they observe that "while most cancers had an indolent course for the first 10 to 15 years...local tumor progression and aggressive metastatic disease may develop in the long term. "The prostate cancer mortality rate [for their study group] increased from 15 per 1000 person-years...during the first 15 years to 44 per 1000-person years beyond 15 years of follow-up (P =.01). This cohort was carefully followed with appropriate PSA testing and scans, and during the first 6 years 80% of men were re-biopsied every two years. Their data points up the well known variation Gleason staging that may occur between sequential needle biopsies. Of these 178 re-biopsied patients the subsequent biopsy resulted in upstaging in 17%, downstaging in 18% (from high to moderate differentiation), and downstaging of 13% (from moderate to low). Three percent of men changed from high to low differentiation. When intervention was required hormone deprivation was employed. As expected, disease specific deaths among the 223 men occurred over time: 11 in years 0 - 4; 11 in years 5 - 9; 5 in years 1 - 14; and 8 in $\geq$ 15 years. The cause specific survival for men with T1 and T2 tumors was 80% at 15 years and 56% at 20 years. 168 men died of other causes.

If the proposition is accepted that all men presenting with low stage prostate cancer may not require immediate intervention, then the issue becomes who are the men with indolent disease where treatment may safely be deferred, and are there validated guidelines available to help choose the "right" time to initiate treatment so as to preserve the same possibility of cure that existed at initial diagnosis?

This strategy of "expectant management" is a "work in progress", and only partial answers are available. The optimal candidate would be a man with Gleason score < 6, cT1c, and small volume (< .5 cc) cancer. The literature has many reports of delayed treatment in mixed stage and grade populations with higher risk factors, but for the purposes of this discussion these studies are too wide in their focus. However, Carter (J Urol 167: 1231-1235,2002) chose to narrowly define his study group to conform to Epstein's model for predicting small volume cancer: men with cT1c stage, PSA density < 0.15 ng/ml./cm3, Gleason score $\leq$ 6, less than 3 cores positive and none with > 50% cancer. By applying this model 79% of men who had these characteristics had pathologic findings on subsequent RP of a tumor < .5 cc, organ confined disease and not high grade. Carter followed 81 men who initially met the Epstein criteria for small volume cancer. DRE and PSA tests were done twice yearly and biopsies were performed annually. The median initial PSA was 5 ng/ml, median PSA density was 0.1, and median age was about 65 years. During the median follow-up of 23 months 31% had disease progression, defined as having a repeat biopsy containing any Gleason 4 grade tumor, or more than two cores positive or one core with > 50% cancer. 12 of 13 men who underwent prostatectomy had "curable" cancer, "defined as a cancer that was associated with more than a 70% probability of disease-free progression a decade after surgery". These results are the most definitive available to begin to address the issue. The study is ongoing.

The findings on re-biopsy adds an instructive observation that has potential for guiding the decision to continue an "expectant" strategy. Patel et al, "An analysis of men with clinically localized prostate cancer who deferred definitive therapy", J Urol, April 2004, was based on a retrospective study of 88 men diagnosed between 1984 and 2001 all of whom were judged as likely to have small volume cancer. The median follow-up was 44 months (range up to 172). They recommended a re-biopsy at 6 months for all, or at any time "if the patient showed DRE/TRUS or PSA abnormalities consistent with disease progression for any man who developed worrisome findings". Overall, the first repeat biopsy (at a median time after diagnosis of 8 months) was negative in 61%. "Actuarial progression-free probability at 5 and 10 years was 67% and 56%." The actuarial probability of remaining progression free at 5 years was 83% for men whose repeat biopsies were negative, and 43% for those with positive re-biopsy. The study group was not as narrowly defined as in Carter. Interestingly, "Our study failed to show a correlation between short PSA doubling time and progression. In fact, 46% of patients in the study had a negative PSA doubling time, reflecting the limited impact of these low volume cancers on serum PSA." The study acknowledges a critical issue: "Seven of the 31 patients receiving treatment in this study were unable to live with the anxiety of harboring untreated cancer and requested treatment."

Bottom Line: Whether "expectant management with an intent to cure" will become a validated and well-defined option for cT1c, small volume, low grade prostate cancer is yet to be determined, but the issue will increase in importance with increasing PSA screening. Clinicians will need to be compiling a mental file of the emerging data so as to be comfortable with the issues.

NEW AGENTS FOR TREATMENT: Prostate Cancer Vaccines - Where Do We Stand?

The recipe for a successful vaccine against prostate cancer is easy to state: identify one, or preferably several, target proteins that are uniquely expressed only on prostate cancer cells, program the dendritic cells in lymph nodes to present small fragment replicas of those targets, raise up a cadre of properly educated cytotoxic T cells and their associated helper cells, dispatch the T cells to kill the targeted cancer cells, and keep the T cell army re-supplied with new recruits sufficient to wage a long battle. Unfortunately, the "devil is in the details" and accomplishing this difficult feat is keeping many biotech companies working overtime. Articles about cancer vaccines have become popular items in the lay press and clinicians are bound to be asked about this somewhat complicated subject.

An up to date example of this developing science was reported in the June issue of the Journal of Clinical Oncology by the Eastern Cooperative Oncology Group: "Phase II Randomized Study of Vaccine Treatment of Advanced Prostate Cancer...". Their results illustrate that progress in this area will be soberingly slow, requiring sequential, small carefully made steps.

The study was conducted on 65 men with rising PSA values above 2 ng/mL after primary therapy (surgery or irradiation). The study focused on the evaluation of the immune response to a PSA based vaccine, with a secondary interest in PSA response. Probably the most interesting aspects of their work were: 1) the method of constructing the vaccine, and, 2) the biology underlying the vaccine's mechanism of action. Vaccinia and fowlpox viruses were genetically engineered to express a full-length complementary copy of the human PSA gene. The vaccinia virus has an acceptable safety record for local intra-dermal administration; and the fowlpox virus, which was given by intramuscular injection, lacks the ability to replicate in human tissue and has the additional favorable characteristic of expressing its PSA antigen payload for long periods. Four vaccinations at 6 week intervals were given.

The biologic response to the administered vaccine is intriguing. The blood mononuclear cells, precursors of the antigen presenting dendritic cells, are "infected" by the viruses, and the viruses (now within the cytoplasm of the cell) begin to manufacture PSA using the PSA gene as the template. But PSA, instead of being secreted into the serum as occurs in prostate cells, is digested into a multitude of small 10 amino acid fragments, and these fragments are moved to the surface of the now mature dendritic cell. Cradled within surface portion of the major histocompatibility complexes, the protein fragments are "presented" to T cells, thus sensitizing them to recognize the counterpart target PSA fragments which appear on the surface of prostate cancer cells. The consequence of this T cell recognition is a potential death blow to the cancer cell.

Now the sobering part from the study! No PSA responses nor clinical responses were observed. However, the small but important step forward was the observation that 46% of the patients demonstrated sensitization of their T cells to PSA fragments, indicating a successful immune response to vaccination. The subsequent planned trial will be a Phase III randomized trial to further evaluate whether this PSA directed/viral vaccination can exert control over a rising PSA, and in this trial the vaccine will be combined with the immunologic stimulant, granulocyte-macrophage colony stimulating factor (GM-CSF).

The Dendreon Corporation currently has two prostate cancer vaccine trials underway. The February 2004 PCa Commentary featured a discussion of these two vaccine trials, both applicable for men post prostatectomy. PII is open for men with a rising PSA post primary surgery; and protocol D9902B is currently open for men with metastatic hormone refractory

whose Gleason sum is ≤ 7. D9902B is the follow-up trial to the initial protocol D9901 in which men with the full range of Gleason sums had been eligible, and which showed, in its Gleason ≤ 7 subset, a significant difference in time to objective progression of 16 weeks for vaccinated men versus 9 weeks for the control group. The Dendreon vaccine employs an immunologic boost from GM-CSF, which is incorporated into their prostatic acid phosphatase (PAP) based vaccine, "Provenge". Unfortunately, the method of administration (leukophereses, ex vivo incubation, and subsequent IV infusion X3 q 2 wks) for this product is cumbersome, and my candid editorial opinion is that, if an effective vaccine can be developed that can be administered by the intra-dermal, subcutaneous, or intramuscular route, an injectable vaccine of this sort will become the preferred method for widespread useage.

Cell Genesys Corporation with its GVAC vaccine product has taken yet another approach to the formulation of an anti-prostate cancer vaccine. Drs. Corman (VMMC) and Higano (U of W) have been active participants in the 80 man trial reported in abstract form at the June ASCO meeting. The study group was comprised of men with metastatic hormone refractory disease. The vaccine is comprised of cultured allogenic human prostate cancer cell lines that have been irradiated and genetically modified to secrete the human cytokine, granulocyte-macrophage stimulating factor (GM-CSF), the potent stimulator of immune response. The vaccine is given by injection. The mechanism underlying this type of vaccine is dependent upon the ingestion of these cell by the subject's phagocytes. These modified human prostate cells exhibit the fullest range of prostate cancer cell antigens, and ultimately result in the dendritic cell exhibiting a wide variety of protein fragments exhibited by the target cancer cells. This is a different strategy than arbitrarily choosing fragments of, for example, PSA, PMSA, or PAP for T cell sensitization. The GVAC vaccinations were given twice monthly for 24 weeks. Results at a median of 5.4 months were reported. Of 19 patients who received the highest dose, 32% showed decline in PSA, and 82% of men in this group developed an antibody response to at least one cell line. Activity against bony metastases was evaluated by measuring a selected biologic marker of osteoclast activity, which is proportional to the amount of destruction of bone by metastatic cells. This marker was decreased in 62% of men. This Phase II study is now closed, and a follow-up Phase III is planned to open in several months and will compare GVAC to a standard chemotherapy treatment in HRPC men with bone metastases. This Phase III protocol will be available locally in Seattle, and clinicians should keep this option in mind for eligible patients.

Bottom Line: Slow but steady progress is being made in developing an effective vaccine against prostate cancer.

CLINICAL TRIALS & PROTOCOLS: Chemotherapy News From The June 2004 Asco Meeting: Results Of Two Important Chemotherapy Trials In Men With Metastatic Hormone Refractory Prostate Cancer

>> Oncologists have been eagerly awaiting the report of "A multicenter phase III comparison of docetaxol (D) [Taxotere] + prednisone (P) and mitoxanthrone (MTZ) [Novantrone] + prednisone in patients with hormone-refractorty prostate cancer (HRPC)." Mitoxantrone was the first chemotherapy drug approved for use in HRPC based on the superior, but modest, effectiveness of this combination in controlling pain from bone metastases compared to prednisone alone. No survival difference, however, was demonstrated between the two arms. Promising results of the newer drug, Taxotere, had been recently demonstrated in several Phase II trials and there was an emerging expectation that Taxotere might be a superior drug

for HRPC than Mitoxanthrone. In the reported Phase III trial MTZ+P was administered to 337 men in standard fashion, 12 mg/M2 q 3 wk X 10 cycles with continuous P 5 mg BID. Taxotere was also combined with P 5mg BID and given in tworegimens: D 75mg/M2 q 3 wk X 10 cycles (335 men), or D 30mg/wk X 5 of6 wks X 5 cycles (334 men). The patients had histologically proven metatatatic disease, and testosterone levels were maintained at < 50 ng/ml. The study end points were survival, PSA response, pain response and toxicity. Overall grade 3/4 toxicities were greater in the two D arms versus MTX, 45%-43% for D and 34% for MTZ. The weekly D arm showed only 1.5% high grade neutropenia, whereas D/q 3 wk was 32% and MTZ was 22%. Results for median survival: D/q 3 wk - 18.9 mo.; D/q wk - 17.4 mo.; and MTZ - 16.5 mo. Results for a PSA decrease of > 50% for at least 4 weeks: D/q 3 wk - 45%; D q wk - 48%; and MTZ-32%. Pain response: D/q 3 wk - 35%; D/q wk - 31%; MTZ - 22%. Conclusion: D/q 3 wk + P showed improved overall survival and better PSA and pain responses than MTZ+P. The abstract concludes "This is the first phase II trial to show a significant survival benefit in HRPC."

Complementing the above trial was the report of the SWOG trial 99-16, "Randomized phase III trial of docetaxel (D)/estramustine (E) [EMCYT] versus mitoxantrone (M)/prednisone (P) in men with androgen-independent prostate cancer", which studied 770 men with progressive metastatic disease. EMCYT was dosed at 280 mg PO D1-5 q 3 wks (332 men). The alternative arm was D given at 60 mg/M2 on day 2 (after 60 mg premedication of Decadron on day 1) and repeated in 3 wks (334 men). D was increased to 70 mg/m2 and M to 14 mg/M2 if toxicity permitted. Results: median survival D/E - 18 mo; M+P - 15 mo. (P =.008). Objective disease response for D/E was 17% and for M+P 10%. Grade 3/4 toxicity overall in D/E was 54% versus 34% in M+P; and this included high grade gastrointestinal toxicity of 18% in D/E versus 6% in M+P and high grade cardiovascular toxicity of 14% in D/E versus 6% in M+P, the higher toxicities in D/E likely due to side effects from EMCYT. This trial could also claim a position as the first trial to show a survival advantage in HRPC. For perspective in evaluating these encouraging Taxotere results it can be cited that in the earlier 1999 pivotal trial, "Hydrocortisone with or without Mitoxanthrone in men with HRPC, results of the CALGB 9281 study" (Kantoff,P, JCO 1999;17;2506), the median survival of M/H was 12.6 months versus 12.3 months for H alone and no significant difference in survival was seen between the two study arms. It would be a fair statement (although not strictly methodologically acceptable) in counseling patients who are considering chemotherapy to use the12.3 months survival of Hydrocortisone alone as a baseline comparison to the ~18 months median survival of these two Taxotere studies, even though corticosteroids alone have shown some small benefit in controlling prostate cancer progression.

Bottom Line: Survival advantage for Taxotere chemotherapy regimens in two Phase III trials can has now been documented as compared to the prior standard of Mitoxantrone/Prednisone. The Taxotere/Prednisone combinations yielded an ~18 month median survival comparable the Taxotere/Emcyt regimen, but did so with lesser toxicity.