SEATTLE PROSTATE INSTITUTE

PCa Commentary

Vol. 60: Nov.-Dec. 2009

Contents

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

ecweber@nwlink.com

PROVENGE: Dendreon's Prostate Cancer Vaccine - What's the latest news?

The latest news is found in Cancer, August 15, 2009, in a report by Drs. Higano, Small et al., "Integrated Data From 2 Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trials of Active Cellular Immunotherapy with Sepuleucel-T [Provenge] in Advanced Prostate Cancer."

A discussion of the background of the development of the Provenge vaccine and an explanation of its immunotherapeutic basis and mode of administration is found in the PCa Commentary archives indexed under "New Agents."

This Provenge study integrated the results of 225 men who had objectively demonstrated metastatic prostate cancer, progressing despite Lupron therapy (which was continued during the trial). A serum testosterone of <50ng dL and a life expectancy of at least 3 months were eligibility requirements. Survival data was based on date of death or after all patients had been followed for 36 months. Disease progression was determined by objective measures or clinical events indicative of worsening disease. "PSA was not used as a measurement for progression." Provenge was offered as a "crossover" to men showing progression while on the placebo arm. Ultimately, 60% of men received chemotherapy after disease progression on either of the study arms, and its possible benefit is included in the survival duration calculations.

The integrated data from the two trials (D9901 & D9902A) showed a median survival of 23.2 months for the 147 men receiving Provenge versus 18.9 months for the 78 men in the placebo group (P=.011). The

difference of 4.3 months represents a 33% reduction in the risk of death. Separate analysis of trial D9902, however, only "demonstrated a trend to improved survival, P=.331."

Immune response to the vaccine was evaluated and a favorable immune up-regulation was positively correlated with a reduction in the risk of death.

The median time to disease progression was 11.1 *weeks* for men receiving Provenge and 9.7 *weeks* for placebo treatment - a nonsignificant difference at P=.111. "Many patients had progressed by the time of the first scan, scheduled at 8 weeks." This rather rapid progression in men in *both* arms of the study led the authors to comment, "We have previously demonstrated that the maximal immune response in some patients many not occur until 12 weeks or longer after initiation of therapy;" and hence "overall survival may be a more appropriate end-point for advanced prostate cancer trials."

Dendreon will submit this Provenge data to the U.S.Food and Drug Administration in November, 2009, requesting approval for clinical use.

The strategy of introducing vaccine therapy at an earlier point in the course of prostate cancer was one theme in a July 27, 2009, JCO editorial by Charles Drake, MD, of Johns Hopkins: "Immunotherapy for Prostate Cancer: Walk, Don't run." He regards prostate cancer as an attractive target for immunotherapy because "the slow-growing nature of the disease, allow(s) time for immunologic intervention to overcome immunosuppressive factors in the tumor microenvironment and to mount a clinically meaningful response." His thought: "... it might make more sense to adopt a more considered approach, moving toward studies in patients with a lower disease burden, and carefully exploring combination [ie. combined with chemotherapy] approaches in a randomized phase II setting before moving forward."

Dendreon, in fact, has employed an early vaccine usage strategy in its P-11 trial study of men with non-metastatic prostate cancer and a rising PSA after initial therapy (opened in 2001 but now closed). In this study 176 men have been randomized to receive Provenge or a placebo at the time of PSA rise above 3 ng/mL following a prostatectomy. Early analysis has shown a favorable up-regulation of active immunity in the treatment group. However, results will be several years in coming since the study end-point is time to objective disease progression.

TESTOSTERONE SUPPRESSION: A Word of Caution from a Large Swedish Study

Abstract 0272 presented September 22, 2009 at the joint meeting of the European Cancer Organization and the European Society of Medical Oncology reported an increased risk for various heart diseases related to testosterone suppression. The author of the study was Ms. Van Hemelrijck, a cancer epidemiologist at Kings College, London, who summarized her data at a news briefing.

Many smaller studies have reported an increased risk for adverse cardiac events associated with testosterone suppression, whereas others have reported no increase. This study, the largest and most comprehensive of its kind, analyzed outcomes over three years of 30,642 Swedish men with locally advanced or metastatic prostate cancer who had received hormone treatment as *primary* therapy for their prostate cancer between 1997 and 2006. Treatments included an LHRH agonist +/- an antiandrogen, an antiandrogen alone or surgical castration. The cardiac risk in the men receiving hormone therapy was compared with the prevailing risk seen in the general Swedish population.

"We found that prostate cancer patients treated with hormone therapy had an elevated risk of developing all of the individual types of heart problems and that they were more likely than normal to die from those causes."

The findings: For experiencing testosterone suppression, "The risk of fatal heart attack was increased by 28%, the risk of dying from heart disease 21%, the risk of heart failure death was increased by 26%, and the risk of fatal arrhythmia was increased by 5%. The absolute effect of hormone therapy translates to about "10 extra ischaemic heart disease events a year ... for every 1000 cancer patients."

Two points were of special interest: 1) No increased risk for death from heart disease was seen in the antiandrogen group, and for this group the risk of heart failure was 5% vs 34% for those receiving LHRH agonists; and for the risk of ischemic heart disease, 13% vs 30%.

2) The risk of adverse heart events was "less pronounced in patients who had heart disease before hormone treatment," leading to the speculation that patients with known disease may have already been on medication for heart issues.

Ms. Van Hemelrijck concluded that her findings "may have implications for treatment choice," and that clinicians "need to start considering heart-related side-effects when prescribing endocrine therapy for prostate cancer patients."

DENOSUMAB: Establishing a Role as a Remedy for Suboptimal Bisphosphonate Tx.

Prostate cancer preferentially metastasizes to the skeleton, and the 30 - 40% of men who historically developed rising PSA values despite primary treatment have a 90+% likelihood of experiencing disease in the bones sometime during the course of their illnesses. For men with positive bone scans or a vertebral fractures it has become clinically appropriate to administer a bisphosphonate, *Zometa* or *Aridia*, regimens that repeatedly have been shown to delay further development of bone metastases compared to a placebo.

Once lodged within bone, metastatic prostate cells induce osteoclast activation resulting in excessive bone resorption. A vicious cycle develops in which osteoclast secreted growth factors promote tumor proliferation, which then further stimulate osteoclastic bone destruction. This increase in bone dissolution can be monitored by a variety of bone turnover biomarkers, the most commonly available being the urinary level of the N-terminal telopeptide of type-1 collagen (uNTx). A urinary excretion of greater than 50 units NTx is an accepted indication of excessive bone resorption.

Until recently there has been no alternative to bisphosphonates therapy (Zometa, Aredia, Fosamax) for reducing the occurrence of fractures, or for ameliorating worsening bone disease - including androgen-deprivation related osteoporosis. Therefore monitoring therapeutic effectiveness of these drugs by measuring bone turnover markers had no clinical utility.

Denosumab, under development by Amgen, employs a mechanism of action substantially different compared to bisphosphonates, and as such might be expected to differ in therapeutic effectiveness. Denosumab was discussed in detail in the PCa Commentary (DENOSUMAB - Amgen's Forthcoming Drug, An Inhibitor of Bone Resorption (September 2008).

A study published in the Journal of Clinical Oncology, April 2009, changes the landscape of this issue by presenting convincing evidence supporting the usefulness of monitoring the effectiveness of bisphosphonate therapy with the biomarker, uNTx. The article, "Randomized Phase II Trial of Denosumab in Patients With Bone Metastases From Prostate Cancer, Breast Cancer, or Other Neoplasms After Intravenous Bisphosphonates," was authored by an international consortium of investigators. One hundred eleven patients were studied, 45% with bone metastases from prostate cancer. After 8 weeks of IV bisphosphonate therapy 20% continued to excrete an elevated uNTx (>50 units), indicative of poor control of abnormal bone resorption. At this point in the study 37 patients were allocated to continue bisphosphonate (mainly Zometa 4 mg IV q 4 wks) and 74 were assigned to receive denosumab (optimally, as the study revealed, at 180 mg subcutaneously q 4 wks). Observation was continued for an additional 25 weeks.

"The primary [study] endpoint was the proportion of patients with uNTX lower that 50 [units] at week 13," indicating acceptable control of osteolysis. By 13 weeks 71% of patients in the denosumab arm were within the target range as compared to 29% in the bisphosphonate arm. "A higher proportion of patients treated with denosumab (64%) maintained uNTX excretion lower than 50 units over 25 weeks compared with those treated with IV BP (37%)." During the study, which required evidence of bone metastases at

entry, the incidence of additional "skeletal events" in the denosumab arm was 8% vs. 17% for those continuing IV BP.

Denosumab is not currently approved by the FDA but a ruling by the advisory committee is expected in late October and will apply to prostate cancer patients receiving androgen deprivations therapy and post menopausal women with osteoporosis.

BOTTOM LINE: As a tool in oncologic management, monitoring the effectiveness of bisphosphonate therapy has been off the radar screen. With the likely FDA approval of denosumab, Amgen's candidate drug for inhibiting osteoclast-mediated bone resorption, the measurement of bone turnover with urinary NTx will gain clinical utility in monitoring the effectiveness of bisphosphonate therapy.

ACTIVE SURVEILLANCE: Supplying the "Missing Link"

Those of us who recommend PSA screening have been forced onto the defensive by the blitz of media and academic articles that reverberate with the pejorative words "overdiagnosis" and "overtreatment." A factually credible and well-researched study published online August 31st in the *Journal of the National Cancer Institute* by the Dartmouth Institute for Health Policy & Clinical Practice reported that since the beginning of widespread PSA screening 1.3 million men have been diagnosed whose cancer would likely not have been otherwise discovered, and that with one million additional men treated "most of this excess incidence must represent overdiagnosis."

In an accompanying editorial Otis Brawley, M.D., Chief Medical Officer, American Cancer Society, emphasized a salient point: "We desperately need the ability to predict which patient has localized cancer that is going to metastasize and cause suffering and death and which patient has a cancer that is destined to stay in the patient's prostate for the remainder of his life."

The "missing link" between "overdiagnosis" and "overtreatment" is an *informed management decision* regarding whom to treat and who should be offered active surveillance. With active surveillance as an option "overdiagnosis" can become an opportunity, - an opportunity to select those men who would benefit from treatment from a much expanded pool of potential candidates.

In current clinical practice many urologists are already counseling active surveillance based on clinical and biopsy characteristics suggestive of low-risk, low-volume prostate cancer. But the inherent sampling error associated with a biopsy diagnosis renders all management decisions vulnerable to cancer grade underestimation. And furthermore, even well-selected "low-risk" cancers based on clinical features may mask underlying molecular biologic elements that portend aggressive disease.

A locally available national protocol, "PASS", is designed to gather information that in the future that will fortify the strength of a decision between active surveillance or immediate treatment. Dan Lin, M.D., urologist at the University of Washington, is the principle investigator of the PASS protocol in the Pacific Northwest region and has kindly offered this summary:

The Prostate Active Surveillance Study (PASS) is a research study for men who have chosen active surveillance as a management plan for their prostate cancer. PASS, sponsored by the Canary Foundation and coordinated by the National Cancer Institute's Early Detection Research Network (EDRN), is a multicenter study and biorepository that will discover and confirm biomarkers of aggressive disease as defined by histologic, PSA, or clinical criteria. To be eligible for the study, men must have previously untreated, clinically localized prostate cancer. Participants will be evaluated on a routine schedule of physical exams, PSA measurements, and prostate biopsies. Biospecimens (blood, urine, tissue) will be collected and stored for use in biomarker studies. During the past year PASS has enrolled over 250 participants at 6 sites in the western United States and Canada, including over 50 patients at the University of Washington. For more information or to refer patients to this important study, please contact the UW study coordinator, Leslie Butler, RN, at 206-626-7416 or the lead study PI, Dan Lin, MD, at dlin@u.washington.edu. The study anticipates opening at 3 new sites in the eastern US in the near future.

For more information about PASS, including contact information for each study site, please visit http://clinicaltrials.gov/ct2/show/NCT00756665http://clinicaltrials.gov/ct2/show/NCT00756665 or http://www.canaryfoundation.org/prostate-clinical-studies.cfm%22 %5Co %22blocked::http:/www.canaryfoundation.org/prostate-clinical-studies.cfmhttp://www.canaryfoundation.org/prostate-clinical-studies.cfm.

We clinicians who recommend PSA screening should support this protocol to assist in filling in the "missing link."

ABIRATERONE THERAPY: Available on Protocol through the University of Washington and the Seattle Cancer Care Alliance.

Abiraterone, an endocrine therapy under development for prostate cancer, has shown a promising ability to reclaim control of disease progression in men who have developed "castrate resistant prostate cancer (CRPC)" while on hormone suppression. Its usefulness additionally extends to men with CRPC whose cancer has progressed after chemotherapy. For a discussion of the drug see: ABIRATERONE: A Hormone Therapy for "Hormone Refractory" Prostate Cancer - An Introduction (September 2008), indexed under "New Agents."

Dr. Evan Yu, Division of Oncology, University of Washington, is the principle investigator of Protocol COU 302 which makes abiraterone available to appropriate candidates with CRPC. The administration of the protocol is site specific so that Dr. Yu would need to direct patient management during the course of treatment.

The protocol details: COU-302 - Eligibility is restricted to men with metastatic, CRPC who have not received chemotherapy. This is open at the SCCA. Patients cannot have received prior ketoconazole and have to have mild or no symptoms (meaning no pain medications, no opiates, no radiation). Patients are randomized 1:1 to prednisone with placebo or abiraterone. The study is placebo-controlled, blinded and randomized, and is open at a very large number of US and international sites.

For information regarding registration contact the research coordinator, Teresa Gambol, at 206-288-6452 or via pager, 206-541-1547.