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PRIMARY TX UPDATES: Endocrine Treatment, With or Without Radiotherapy, in Locally Advanced Prostate Cancer" - A Randomized Phase III Trial

When the optimal non-surgical management of T3 prostate is considered by clinicians at tumor boards, an undercurrent of concern involves the strength of the data justifying combining radiation therapy with endocrine therapy as opposed to androgen deprivation as single modality. This Lancet report provides that data. Additionally, the report suggests a endocrine regimen that minimizes side effects on quality of life.

The Lancet, January 2009, reported results from this 875 patient trial carried out among 47 centers in Norway, Sweden, and Denmark involving men with locally advanced disease (T3, 78%; T2, 19%; mean PSA, 19 ng/mL; NO; MO). The study is of special interest since as the authors noted that they knew no comparative studies that have assessed radiation combined with antiandrogens versus endocrine treatment alone. The choice of the endocrine regimen may be of interest to clinicians in the USA, since, based on studies showing comparable efficacy, the Scandinavian clinicians largely utilize antiandrogens as their initial choice for sustained androgen suppression in place of LHRH-agonists, the therapy customarily employed in the USA.

In brief, at 7 years the incidence of prostate cancer-specific mortality (PCSM) was 9.9% in the endocrine-alone group versus 6.3% for those receiving combined therapy. By 10 years the benefit of combined treatment had increased to 12% (PCSM for endocrine therapy only, 23.9% vs 11.9% for the combination regimen). "At 7 and 10 years the cumulative incidence of PSA *recurrence* was 71.1% and 74.7% in the endocrine group and 17.6% and 25.9% in the endocrine plus radiotherapy group."

The characteristics of the two groups were very similar: age about 66 years, percentage T2 disease, ~19%; T3, 78%; WHO grade II ~65%, grade III, 19%; and seminal vesicle involvement about 23% in each group. The men whose initial PSA exceeded 11 ng/mL underwent an obdurator fossa targeted lymph node dissection, and those with nodal disease were eliminated from the study.

Androgen suppression was initiated in all subjects with three monthly doses of an LHRH-agonist along with flutamide 250 mg TID, which was then continued until progression or death. After three months, the combination therapy group received 3D conformal radiation therapy (RT) at 50 Gy to the prostate and seminal vesicles, and an additional dose of 20 Gy directed to the prostate, for a total dose of 70 Gy or more. (Current radiation dosage is customarily 78 Gy or more.) If seminal vesicle involvement had been detected by TRUS or palpation an additional 20 Gy was given to that area.

PSA progression during flutamide therapy was seen in 17.5% of men in the endocrine-only group and in 20.2% of the combined treatment group. PSA failure was set a cut-point of $\geq$2 ng/mL above nadir. Men showing progression were switched to bicalutamide at 150 mg/qd. This substitution of antiandrogens for LHRH agonists was based on the finding by Iverson (J Urol 2000; 164) of no difference in efficacy or survival in patients with locally advanced disease between antiandrogens (bicalutamide: 150 mg/qd) and castration at a median follow-up of 6.3 years.

A careful assessment of the side effects of treatment, by both physician reporting and with a standard EORTC quality of life questionnaire, was made at baseline and regularly thereafter. "Our study showed a small but significant increase of moderate to severe late effects related to urinary and sexual function [in the combined group]. At 4 years moderate diarrhea was patient-reported in 9.5% in the endocrine-alone group compared to 11.6% in the combination therapy group."

Physician reporting compared function at baseline with the status at 5 years. At 5 years there were no significant differences between groups for bladder obstruction (2%) or urinary frequency (18%). Differences of statistical significance did favor the endocrine-alone group for moderate or total urinary incontinence 3% v. 7%; urinary urgency, 8% v. 14%; and for erectile impairment, 81% v. 89%. However, at baseline considerable erectile dysfunction was evident in both groups, about 35%.

What are the take-away messages from this study. At 10 years a meaningful benefit of 12% in prostate cancer-specific mortality was found for the combination of a long-term antiandrogen regimen combined with radiotherapy in high-risk T3 locally advanced prostate cancer, and this benefit was gained with a small incidence of side effects. Of special interest is the finding that at 10 years combination therapy also conferred an absolute risk reduction of 16% for PCSM for the T2 cohort, which represented nearly 20% of the patients. This is a group for which the undesirable side effects of long-term LHRH-agoinsts may be unacceptable.

This study is unique in that long-term antiandrogens were employed in place of long-term LHRH agonists. With this regimen of anti-androgens, a survival benefit for a combined

radiation/antiandrogen treatment was achieved, while avoiding the significant toxicity of long-term LHRH-agonists.

HORMONE INTERVENTION: Abiraterone - An Update (With contribution and review by Dr. R. Bruce Montgomery)

Abiraterone, the very promising drug for suppression of intratumoral androgen synthesis, is working its way through the clinical trial pipeline and is showing consistently encouraging results. The basic biology and early trial results of abiraterone were reviewed in the PCa Commentary, September 2009, indexed under "Hormone Intervention." As reviewed, this drug effects a selective, irreversible, and continuous inhibition of the enzyme, CYP17, essential for two steps in the de-novo synthesis of testosterone from cholesterol and adrenal androgen precursors within the testes, adrenal glands, and prostate cancer cells. Its clinical advantage results from its effectiveness in further suppressing androgen signaling in the androgen receptor-rich cellular environment of castrate resistant prostate cancer cells that have adapted to low levels of testosterone.

The new information about abiraterone (AA) was presented in Abstract 159 at the 20009 Genitourinary Cancer Symposium by C.J.Ryan, et al.: "Abiraterone acetate plus prednisone in chemotherapy (chemo)-naive castration resistant prostate cancer (CRPC) patients not exposed to ketoconozole: Results of a multicenter phase II study." Thirty-three patients with progressive metastatic disease were treated with AA 1000 mg/qd and prednisone 5 mg/qd; median age 71.5; median PSA at baseline, 24.7 ng/mL; treatment duration - 10.5 months. An LHRH agonist was continued.

Results: Among 21 eligible men 81% showed any PSA decline. "PSA decline of $\geq$30%, $\geq$50%, $\geq$90% were observed in 76%, 76%, 43%. Two patients have achieved undetectable PSA levels."

Comparative results from other studies aid in putting these results into some perspective. Granted that the comparison of results from trials with disparate criteria for eligibility and analysis is a statistical "no-no," non the less, it is helpful to have some overall gestalt regarding PSA responses. The percentage of men showing PSA declines from five studies of AA/prednisone are tabulated below. In all five trials the men had progressive, metastatic CRPC. Trials 2, 3, and 4 were reviewed in the above mentioned PCa Commentary article on abiraterone. For a broader perspective the best PSA declines seen in the two major trials with *chemotherapy alone* in men with CRPC with progressive metastatic disease also are listed (European TAX-327 and the US SWOG-99-16, both employing Taxotere/prednisone). The chemotherapy trials were reviewed and indexed under "Hormone Insensitive Disease" in the archives April 2005 and March 2008.

PSA decline	>30%	>50%	>75%	>90%
1. Ryan, 33 men, no prior chemo (reviewed above)		76%	76%	43%
2. Attard, 21 men, no prior chemo	66%	57%	42%	29%
3. Royal Marsden, 44 men, no prior chemo		61%	50%	25%
4. Danila, 35 men, after chemo failure		45%		
5. Royal Marsden, 34 men, after chemo failure,	65%	47% (ASCO), 2008, (Abstract #5005)		

The range of >50% PSA declines in Tax-329 and SWOG-9916 was between 45% - 50%. For patients who had been previously treated with Taxotere and instead were treated with Mitoxanthrone and a steroid comparable to prednisone, only 15% - 20% showed a PSA decline of >50%.

One caveat must be stated. Most seasoned researchers would maintain that "time to disease progression" is a more informative metric for comparison than PSA decline. This is particularly critical when a drug specifically targets androgens, as PSA is an androgen regulated gene and its decline may not reflect a decrease in disease activity as a whole, but only indicate decreased PSA transcription.

A large Phase III tial: (http://www.clinicaltrials.gov/ct2/show/NCT00638690?term=abiraterone&rank=3.) comparing AA/pred to placebo/pred in CRPC patients who have failed chemotherapy is now closed to enrollment as of April 30. These results are eagerly awaited.

HORMONE INSENSITIVE DISEASE: MDV3100 - A Promising Drug in Early Trials for Castrate Resistant Prostate Cancer. (With contribution and review by Dr. R. Bruce Montgomery, UW)

It is unusual for the Journal SCIENCE (Science Express, April 9, 2009) to judge early trial results and their underlying basic science to be of such merit as to publish the initial study and research findings. The research team was led by Charles Sawyers, Memorial Sloan Kettering Cancer Center, with contributions from the Northwest region by Celestia Higano, UW, and Tomasz Beers, OHSU. MDV3100 can be best understood as a second generation non-steroidal antiandrogen which has been selectively engineered to inhibit signaling via the androgen receptor (AR). The rationale for its development is that recent evidence suggests that prostate cancer cells maintain significant levels of testosterone and dihydrotestosterone (DHT) despite low levels in the blood. Bicalutamide has a 30 fold lower affinity for the androgen receptor than DHT, so the competition for the receptor between these two ligands is fierce and bicalutamide is at a disadvantage. MDV3100 has an affinity for the AR is 5-8 times greater than bicalutamide, and only 2-3 fold less avid than the natural ligand DHT.
The *increased* androgen receptor signaling in CRPC makes its inhibition of AR function a prime target of research.

Bicalutamide currently sets the bench mark for antiandrogen effect. MDV3100 (and the companion drug, RD162, also under development) are superior inhibitors of AR function than bicalutamide by virtue of several important mechanisms resulting from their enhanced AR binding. Clinicians are aware that over time due to AR adaptation the current antiandrogens can become agonists (evidenced in practice as the "antiandrogen withdrawal response"), but MDV3100 does not elicit this adverse transformation which develops in AR-overexpressing cells. MDV3100 interrupts the AR translocation into the nucleus and prevents the DNA binding and consequent gene expression that promotes cancer cell growth, a binding not blocked by bicalutamide.

Results of testing in mice showed that the "Median time to tumor progression in the RD162-treated group was 186 days versus 35 days in the bicalutamide-treated group." MDV3100 showed similar results in mice. Due to its "favorable drug-like properties" MDV3100 was chosen for human studies. "In an ongoing phase I/II clinical trial, of 30 men with CRPC who have progressed on first-line antiandrogens, 12 of whom had also failed taxane-based

therapy," 22 showed a sustained PSA decline for at least 12 weeks and a greater than 50% PSA reduction for 13 men. Additional results in 110 men treated at a higher dose is forthcoming.

The clinical results with MDV3100 and abiraterone, the inhibitor of tissue androgen synthesis, suggest that more effective hormone ablation is in sight. An interesting speculation is that the combination of MDV3100 and abiraterone might become a uniquely effective "cocktail" for men who have progressed to the recalcitrant phase of castrate resistant prostate cancer.

BONE METASTASES & OSTEOPOROSIS: Of Bones and Drugs: New Trial Results Regarding Zometa and Denosumab

ZOMETA: The administration of an LHRH-agoinst has consistently led to a loss of bone mineral density (BMD), with losses in the lumbar spine roughly estimated in a year at about a 5% decrease. Abstract #4515, ASCO 2006, (reviewed in the PCa Commentary Nov. 2006) was first to report that a single yearly 5 mg dose of Zometa in men on ADT *without bone metastasis* showed a 4% increase in BMD at the lumbar spine versus a 3.1% decreased in BMD for the placebo.

At the April 2009 AUA meeting, an abstract also reported results a of single infusion of zoledronic acid [Zometa, 4 mg] in this case in 40 men with *metastatic prostate cancer*. At the start of LHRH therapy these men either received the Zometa or no therapy. Current practice employs Zometa at the same dose at various intervals ranging from monthly to every four months in men with metastatic disease. This abstract reported that at 6 months the men receiving Zometa showed a 5.1% increase in BMD at the lumbar spine versus a 4.6% decline for the non-treatment group, and this significant difference was maintained at 12 months. Urinary N-telopeptide, a marker of bone metabolism that measures the rate of bone destruction, was "significantly decreased in the zoledronate group compared with controls at 6 mo, but returned to pretreatment levels at 12 mo in the zoledronate group."

These finding will allow reducing the frequency of Zometa dosing while maintaining effectiveness, very likely decreasing the incidence of osteonecrosis of the jaw, the incidence of which increases with longer Zometa usage.

DENOSUMAB: Another 2009 AUA abstract evaluated the effects of a twice-yearly subcutaneous 60 mg dose of denosumab in 1468 men who had variable periods of prior androgen deprivation therapy. BMD was measured at the lumbar spine, hip, and distal radius at 24 months. "Compared to placebo, denosumab significantly and consistently increased BMD at all measured skeletal sites in every subgroup ($p<0.0001$).

"A Randomized Phase II Trial of Denosumab ..." (JCO April 1, 2009) links denosumab with Zometa in a informative way, i.e. by comparing the effectiveness of the two drugs in lowering urinary N-telopeptides (uNTz) levels to below 50 units. The study evaluated men with metastatic prostate cancer and other tumor types who had $\geq$1 bone lesion. An entry requirement was a baseline uNTz level of $\geq$50 units despite Zometa therapy for the preceding $\geq$8 weeks. The subjects were randomly assigned to either continue IV Zometa or receive subcutaneous denosumab. In the initial 13 weeks of the trial denosumab lowered the uNTz levels to <50 units in 71% of patients. Only 29% of men continuing on Zometa achieved that low level. The authors point out that men with elevated uNTz levels (>50 units - moderate; >100 units - high) experience "excessive bone resorption, [and] are at increased risk for skeletal-related events (SRE), cancer progression, and death." Other studies have shown that 20% of men on Zometa therapy continue to have uNTz levels above 50 units. In this JCO

study at 6 months 64% in the denosumab arm maintained levels below the 50 unit mark versus 37% in the Zometa arm. Additional SREs developed in 8% in the denosumab group verses 17% in the Zometa arm. Adverse events in the two arm were similar.

The authors concluded that denosumab could effectively suppress osteolysis in men for whom Zomata was not adequately controlling bone loss.

The basic biology of denosumab was reviewed in the PCa Commentary in September 2008. Amgen filed with the FDA for marketing approval in December 2008.