

---

**Contents**

---

|                                         |                                                                                                                   | <u><b>Page</b></u> |
|-----------------------------------------|-------------------------------------------------------------------------------------------------------------------|--------------------|
| <b>HORMONAL INTERVENTION</b>            | <b>Adjuvant Hormone Intervention: Is The Strategy Shifting?</b>                                                   | <b>1</b>           |
| <b>DIAGNOSTICS</b>                      | <b>"Molecular Staging" Assessing The E-Cadherin Gene: When The Loss Of A Gene Can Have Predictive Potential</b>   | <b>3</b>           |
| <b>HORMONAL INTERVENTION</b>            | <b>Intermittent Vs Continuous Androgen-Deprivation Therapy: Two Reports From ASCO 2006</b>                        | <b>4</b>           |
| <b>BONE METASTASES AND OSTEOPOROSIS</b> | <b>Zometa: Once Yearly Dosage Found Effective In Combating Osteoporosis In Men On ADT Without Bone Metastases</b> | <b>5</b>           |

---

Your comments and requests for information on a specific topic are welcome at  
[ecweber@nwlinc.com](mailto:ecweber@nwlinc.com)

This month's issue plus a compilation of past articles is available online at  
[www.seattleprostateinst.com/pcacommentary.htm](http://www.seattleprostateinst.com/pcacommentary.htm)

**HORMONAL INTERVENTION: Adjuvant Hormone Intervention: Is The Strategy Shifting?**

Medical oncologists who have been active in the management of *both* prostate and breast cancer recognize that the basics of the molecular biology of breast cancer are paralleled in prostate cancer, but for their subsequent translation into treatment regimens in the management of prostate cancer there is a lag period of possibly 15 or more years. Adjuvant chemotherapy for node-positive breast cancer was developed in the mid 1960s, and adjuvant tamoxifen for estrogen receptor positive breast cancer emerged in the 1970s.

After Craig Jorden's discovery of tamoxifen, now termed a selective estrogen receptor modifier (SERM), and after appropriate studies, intervention with surgical oophorectomy gave way to tamoxifen. Although not without side effects, the ratio of therapeutic benefit to side effects for tamoxifen is very favorable *and this has made its use acceptable in the earliest asymptomatic stages of breast cancer.*

In prostate cancer management GnRH agonists, e.g. Lupron, have conventionally filled the role of an early adjuvant hormonal intervention, especially in patients at high-risk for

recurrence. But the strategy of androgen depletion is increasingly recognized to carry unwelcome toxic baggage - hot flashes, loss of muscle mass and weakness, weight gain, fatigue, osteoporosis and increased fracture risk, loss of libido and erectile function, lipid abnormalities, mood lability, memory degradation, and now, disorders in glucose metabolism. With the development of inhibitors of androgen receptor function, e.g. bicalutamide, and agents that decrease the delivery of testosterone to the prostate, e.g. 5-alpha reductase inhibitors - neither of which lower serum testosterone levels - prostate cancer management has been provided with effective alternative agents for adjuvant hormonal treatment. As a consequence of their relatively low side effect profiles, these drugs can be deployed with *greater patient acceptance at a much earlier disease stage* compared to standard GnRH agonists. It is now recognized that even in "androgen independent" prostate cancer, signaling through the androgen receptor (AR) continues to play an important role, and bicalutamide, which functions as a co-repressor of AR function, can interfere with alternate pathways of activation commandeering the AR from a variety of growth factors, such as Her 2/neu and the epidermal growth factor.

So where do these considerations lead in the evolution of adjuvant hormonal interventions in early prostate cancer with agents less toxic than GnRH agonists, especially for men at high-risk for recurrence? D'Amico's low- and intermediate-risk groups, based on patterns of PSA, Gleason score, and tumor stage, are in fact heterogeneous in composition, each incorporating a spectrum of risk. There are men in those "favorable" groups who already have occult regional or distant metastases, and others who possess an inherent high-risk to spread at a very early stage. Some examples: about 10% of "low-risk" men at extended lymphadenectomies show lymph node spread; even some "low-risk" cancers lack the metastases suppressing adhesion molecule, E-cadherin and other tumor suppressors; and emerging proteomic, epigenetic, and gene expression analyses have the capacity to identify men harboring high-risk features, who on the basis of conventionally classification would be placed in a lower risk group. If a treatment with a more acceptable side-effect profile than (say) Lupron can be developed and found effective, these men would also benefit early adjuvant hormonal intervention.

Abstract 4573 presented at the 2006 ASCO Annual Meeting by Picus, Small, Vogelzang et al, "Long term efficacy of peripheral androgen blockade on prostate cancer : CALGB 9782", reports the results of a "kinder and gentler" regimen of hormonal intervention: finasteride 5 mg QD/flutamide 250 mg TID. Ninety eight men were evaluable, each experiencing a rising of PSA, above 1 ng/mL, with no detectable evidence of recurrent disease 1 to 10 years after primary treatment. Median follow-up was 59 months. "A >80 PSA decline was seen in 91/94(97%) of the patients", and two others declined 77% and 73%. These nadirs were achieved at a median of 3.2 months. The authors concluded that this regimen "showed excellent activity and produced durable PSA responses." "The median duration of progression-free and overall survival as not been reached, and is likely to be longer than five years." Quality of life data will be reported later. Importantly, of the 22 men who progressed, 15 responded to further hormonal manipulation, (68%).

The CALGB study received favorable comment from Judd Moul, MD, (Fall2006/THE ONCOLOGY REPORT) who indicated that this regimen "has the advantage of not being associated with hot flashes, weight gain, and loss of muscle mass and is less likely than traditional hormone therapy to affect potency and libido". Furthermore, in his experience "the known side effects of gynecomastia and nipple tenderness can be lessened with low-dose breast irradiation or tamoxifen".

The CALGB study was begun in 1998 and, were it to be currently run, it is likely that flutamide would be replaced by 50 mg of bicalutamide, a drug producing less diarrhea and affording the convenience of once daily administration. Wm. Oh, MD, prostate expert at the Dana-Farber Cancer Institute, was unaware of any current protocols testing bicalutamide 50 mg/qd and finasteride 5 mg/qd in the adjuvant setting (personal communication).

However, Dr. Oh was the principle investigator for a report, "Finasteride [5 mg/qd] and bicalutamide [150 mg/qd] as primary hormonal therapy in patients with advanced adenocarcinoma of the prostate", Ann Oncol, June 2004. This study established two important findings: 1) Finasteride added to the effectiveness of bicalutamide. In the study the drugs were used sequentially with bicalutamide first. "At the first nadir, median decrease in PSA from baseline was 96.5%" (median PSA, 0.75 ng/mL; median time to nadir, 3.7 weeks). After the first nadir, finasteride was added, and the median PSA showed a further lowering to 0.35 ng/mL, a 98.5% decrease from baseline. 2) Twelve of 14 (86%) men who subsequently progressed on combined therapy "remained responsive to LH-RH agonists" - a finding roughly similar to the CALGB results. Most men in the Oh study had advanced disease, and the median duration of response was 21.3 months, comparable, in the authors' opinions, to the 18-24 months median duration of response seen with LH-RH agonists in study populations with similar characteristics.

Bottom Line: Early adjuvant hormonal therapy with LH-RH agonists are associated with a delay in disease progression and some prolongation of survival in high-risk prostate cancer patients. However, these testosterone lowering drugs *subject men to the considerable toxicities of extended periods of androgen deprivation*. An alternative, as reported by Pinus, suggests that adjuvant therapy with the androgen blocker bicalutamide combined with finasteride (followed upon failure with an LH-RH agonist) can achieve similar results with far fewer side effects. If randomized studies demonstrate equal effectiveness for a regimen of peripheral androgen blockade, then this therapy could also be acceptably applied to men, who might conventionally be considered at lower risk, but who, in reality, are at high-risk for recurrence as revealed by emerging sophisticated genetic and molecular profiling.

### **DIAGNOSTICS: Molecular Staging" Assessing The E-Cadherin Gene: When The Loss Of A Gene Can Have Predictive Potential**

The gene, *E-Cadherin*, codes for a cell-cell surface adhesion protein involved in the control of cell migration and invasion. It was mentioned in the first article, so some elaboration is in order. Its loss from prostatic tissue has been found to predict a high-risk of metastatic spread, even in presumably low-risk settings. The analysis for the E-cadherin protein, or other biomarkers, might be termed "molecular staging" and is an example how additional refinement and accuracy can be built into our current predictive algorithms.

An exemplar case in point is the data reported in J.Urol., Oct. 2006, from the University of Michigan: "E-Cadherin Protein Expression Predicts Prostate Cancer Salvage Radiotherapy Outcomes". Twenty-five of 37 prostate specimens showed, low E-cadherin expression. Quoting liberally from their results: "At a median clinical follow-up of 40 months univariate analysis demonstrated that E-cadherin staining was not associated with Gleason score, extracapsular extension, surgical margin status, pre-prostatectomy or pre-radiotherapy prostate specific antigen, complete biochemical response after radiotherapy or adjunctive hormonal therapy, but it was associated with seminal vesicle invasion. Two year failure-free survival was 55% in patients with aberrant [low] E-cadherin expression compared with 92% in patients with normal E-cadherin expression (p=0.02)".

Sophisticated analyses now combine the assessment of biomarkers such as E-cadherin expression with other recognized predictors of adverse outcome: bcl-2, an inhibitor of apoptosis; CD44v6, whose overexpression is associated with malignant transformation and invasion; the proinvasive matrix metalloproteinases (MMP), which facilitate cell movement through the extracellular matrix; and the tumor suppressor, p53. Combinations have the potential of additional predictive leverage, but Judd Moul, MD, has pointed out the need for a careful evaluation of the reliability of these bioassays when performed on core biopsies, since data from small samples may be misleading. The Michigan report cited above relating low E-cadherin expression with an adverse outcome needs further confirmation to be confidently used in clinical practice. However, this article's highlighting of E-cadherin is a heads-up to suggest forthcoming analytic aids that may have useful clinical application.

### **HORMONAL INTERVENTION: Intermittent Vs Continuous Androgen-Deprivation Therapy: Two Reports From Asco 2006**

Numerous studies in recent years have compared intermittent androgen deprivation (IAD) with continuous treatment, and generally suggest that IAD is *not inferior* in terms of disease progression and survival, but have found that IAD does provide substantial therapy "off-periods" during which the side effects of androgen suppression lessen, albeit "off-periods" of decreasing lengths. Although basic science studies suggest that there may be benefits at the molecular level associated with IAD that forestall transition into androgen refractoriness, clinical evidence supporting this potential advantage has as yet not been identified.

Two abstracts presented at ASCO 2006 addressed intermittent treatment. In abstract 4513 Da Silva presented results based on 626 study participants (31% metastatic, 69% stage T3 or T4; baseline PSA > 4 ng/mL) who achieved a PSA drop to < 4ng/mL or 80% below baseline after initial treatment for 3 months with a regimen of cyproterone and a GnRH agonist, at which time they were randomized to continuous CAB or IAD with CAB. An overall observation was that the amount of time off therapy was determined by the nadir value of the post-induction PSA decrease.

Of the 312 men in the IAD arm 50% were able to be off treatment for at least 52 weeks following the induction period, and 29% of them had an initial off-therapy time of >36 months. The initial off-treatment period for the 197 men who achieved a nadir PSA of <2 ng/mL was a median of 74 weeks, and this group experienced a median of 82% of their total study time off of therapy. The abstract did not detail the protocol instructions for re-starting treatment after an "off" period.

"In the intermittent arm, 41% were sexually active at 9 months, 40% at 15 months, and 35% at 21 months".

Conclusion: "Estimated 5-year survival for the IAD cohort was 53.8%, and 51% in the continuous group."

The second abstract, 4517 (Southwest Oncology Group Trial 9346), was a interim report on 1134 men who achieved a PSA of  $\leq 4$  ng/mL after an induction period of 7 months of ADT and then were randomized to IAD or continuous therapy. Eligibility required D2 disease and baseline PSA  $\geq 5$  ng/mL. The median baseline PSA for the group was 76.1 ng/mL, 38% with bone pain, and 47% with Gleason sum >7.

The subject of this report was not a mature comparison of survival between the intermittent and continuous cohorts, but rather an examination of whether the duration of survival was related to the nadir of the PSA achieved at the end of the 7 month induction period. The

answer: a resounding "yes". "After adjusting for significant independent risk factors", the median survival for those who achieved a post-induction PSA  $\leq 0.2$  ng/mL was 75 months; for a PSA between 0.2 and 4.0, 44 months; and for PSA  $\geq 4$  ng/mL, 13 months. Commenting in ONCOLOGY, OCT 2006, Drs. Kantoff and Appleman cautioned that until the final results of this important study are known, IAD should be considered investigational in metastatic disease.

Of note is a small study reported In J. Urol, 2006 May, "Intermittent use of testosterone inactivating pharmaceutical [IAD] using finasteride prolongs the time off period". This strategy builds on the fact that even when serum testosterone is in the castrate range ( $< 50$  ng/mL), the intratumoral levels of DHT and testosterone are sufficient to drive the androgen receptor. Their schema randomized 60 men to received 5 mg of finasteride during the time-off periods, and 41 received none. Their findings were suggestive of usefulness of 5-alpha reductase inhibition: the median time-off therapy for the finasteride group was 31 months compared to 15 months without finasteride.

**Bottom Line:** Study results are converging to suggest equivalency between IAD and continuous ADT therapy with the duration of time-off treatment in the IAD regimen determined by the PSA nadir after induction therapy. There is suggestive evidence that finasteride administered during IAD off-periods can increase their duration.

### **BONE METASTASES AND OSTEOPOROSIS: Zometa: Once Yearly Dosage Found Effective In Combating Osteoporosis In Men On ADT Without Bone Metastases.**

Once again prostate cancer management parallels developments in breast cancer treatment, but again with a slight lag. Immediately following the female menopause, bone mineral density in women rapidly decreases as the level of bone-building estrogen drops. The bisphosphonate, Zometa, is effective in reversing this loss of bone density. The minimal effective dosage to counteract this fall was the subject of a Feb 28, 2002 report in the NEJM which somewhat surprisingly found that a single 4 mg dose of Zometa administered annually in cancer-free women resulted in an increase in spine bone mineral density (BMD) of 4.3% - 5.1%, and at the femoral neck of 3.1% - 3.5%, as compared a placebo.

Multiple studies of prostate cancer patients with bone metastases have established a consensus that the standard of care for these men is 4 mg Zometa administered every 3 weeks. This regimen has repeatedly resulted in a significant reduction of additional "skeletal events", e.g. mainly fractures, as compared to men not receiving the drug. And this regimen has largely been adopted by inference for asymptomatic men with positive bone scans. The open question has been whether to, and how to, use a bisphosphonate in men with no indication of bone metastases in whom the use of ADT predictably leads to an approximately 5% loss of bone mineral density in the first year of treatment. This loss can be even greater in men who already have low BMD (T score  $> 2.5$ ), or are at increased risk for low BMD, e.g. due to high alcohol or tobacco usage, low body weight, corticosteroid therapy, or significant co-morbidities. For these men a pre-ADT bone density study (DEXA) is appropriate.

The answer to the question "whether to use and how frequently to dose" zoledronic acid (Zometa) in the large population of asymptomatic men receiving ADT is suggested in Abstract 4515, ASCO 2006: "Annual Zoledronic Acid to Prevent Gonadotropin-Releasing Hormone Against-Induced Bone Loss in Men with Prostate Cancer: A Randomized Placebo-Controlled Trial". Forty-four men with non-metastatic prostate cancer were treated with one dose of 5 mg Zometa or placebo. Pretreatment DEXA studies of the lumbar spine and hips were done, and follow-up testing took place at one year. Results: Mean BMD of the postanterior lumbar spine

increased by  $4.0\% \pm 0.9\%$  with zoledronic acid and decreased by  $3.1\% \pm 0.9\%$  with placebo. In the hips the difference was  $-0.7\% \pm 0.6\%$  for Zometa, vs  $-1.9\% \pm 0.7\%$ , placebo. Their conclusion: "An annual zoledronic acid dose may be a convenient, effective prophylactic treatment for bone loss in hypogonadal men". Measurement of N-telopeptides indicated a confirmatory decrease of bone turnover in the treatment group.

Bottom Line: A single annual dose of 5 mg Zometa can not only reverse the approximately 5% first-year bone loss from ADT in men without bone metastases, but can increase bone density in the lumbar spine by 4%.