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PCa Commentary

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Special Issue on Intermittent Androgen Deprivation

INTERMITTENT VERSUS CONTINUOUS ANDROGEN DEPRIVATION: TREATMENT FOR MEN WITH RISING PSA'S FOLLOWING PRIMARY TREATMENT OF LOCALIZED PROSTATE CANCER.

The most definitive comparison of IAD versus CAD as treatment of a rising PSA following radiotherapy or prostatectomy was presented by Crook et al., writing for an international collaboration of researchers (*NEJM. Sept 2012).* The study opened in 1999, when the universe of prostate cancer was vastly different from today.

The trial conclusion: the two regimens achieved similar overall survival outcomes.

This finding supports the results of many smaller studies. Since the schema of IAD therapy can vary substantially between different trials, the Crook study must be viewed as analyzing a very specific study-determined scheduling regimen. The findings in this study cannot be safely extrapolated to other regimens where demographics may vary, eligibility criteria and induction durations may be different, and the "off-periods" might be terminated at PSA values as widely different as from 2 ng/ml to 20 ng/ml.

The Trial Regimen:

- The study enrolled 1386 patients (IAD, 690; CAD, 696) whose PSA values had risen to >3 ng/ml after an interval of more than 1 year following surgery or primary or salvage radiotherapy.
- Initial therapy consisted of an 8 month induction with an LHRHa (lutenizing hormone releasing agonist) combined with at least 4 weeks of an antiandrogen.
- Analysis was segregated between those men whose baseline PSA was between 3-15 (77%) v. >15 (23%) ng/ml. In each group 89% had had radiotherapy and 11% a radical prostatectomy.
- Those men randomized to IAD whose PSA dropped to <4ng/ml by the end of induction discontinued androgen suppression. Therapy was restarted for another 8 months period when the PSA exceeded 10ng/ml.
- The development of androgen insensitivity (CRPC) was declared if the PSA rose over three monthly measurements in the presence of castrate levels of testosterone.
- The median follow-up was 6.9 year; median age, 74 years.

Major Findings:

1) The median overall survival for men on IAD was 8.8 years; for CAD, 9.1 years -- not significantly different. For both groups the median 10 year overall survival was ~40%.
2) Measured at a median follow-up of 6.9 years, 268 men on CAD died, 15% from prostate cancer; and on the IAD arm there were 256 deaths, 18% from cancer. In total 58% of men in the study had non-cancer deaths.

INTERMITTENT VERSUS CONTINUOUS ANDROGEN DEPRIVATION continued:

3) 95% of men on IAD completed the first "off-period"; 58% had 2 cycles; and 32% had 3. The maximum number of cycles was 9. The median duration of "off-period" for the first cycle was 20 months; 13.2 months in the second; and 9.1 months in cycle three. "Off-period" in cycles 4 through 7 was 4-5 months.
4) Conversion to androgen insensitivity (CRPC) was ***estimated*** to occur 20% later in men on IAD, a 4 months gain in survival after CRPC developed. However this was not considered a firm finding.
5) Measured at 2 years after cycle #1, 35% of men regained full testosterone recovery to baseline levels, whereas 75% attained a recovery level of >144 ng/ml, the level required for eligibility.
6) Death from prostate cancer occurred twice as frequently in the cohort of men whose entry PSA levels were >15 ng/ml compared to those with lower levels of 3-15 ng/ml.
7) Regarding quality-of-life issues: better performance was seen in certain domains for men on IAD vs. CAD, i.e., significant improvement in the occurrence of hot flashes, urinary symptoms, fatigue, and desire for sexual activity. However, only 29% of men potent at baseline recovered potency. As might be expected, the most notable QOL gains for men on IAD occurred in the first "off-period" of 20 months and diminished in later cycles, in which the periods of testosterone recovery were increasingly shorter.

Editorial Comment:

The primary goal of the trial was to compare overall survival for this specific regimen of IAD to a standard program of CAD. The goal was definitely met: IAD and CAD were conclusively demonstrated to produce similar overall survival outcomes.

One secondary goal was to evaluate if IAD led to a better quality-of-life. Regarding this issues the report concedes: *"Although intermittent androgen-deprivation therapy appears to provide an overall quality-of-life benefit, as compared to continuous androgen-deprivation, the difference is not as profound as one might expect."*

A second goal was to once again investigate whether IAD would meaningfully prolong the development of castrate resistant prostate cancer. Clear evidence that IAD achieves this remains elusive.

Perspective:

The Crook study explored and validated a specific treatment regimen. However, among those assigned to IAD on the basis of achieving a post induction PSA of <4 ng/ml there will be those men whose tumors are exceptionally hormone sensitive and who achieve an induction nadir of <0.1 or even <0.05 ng/ml. One might hope that a follow-up analysis would describe the future clinical course and outcome for this select group. The literature is replete with studies that portend excellent outcomes for men who have a very low nadir after induction. Perhaps, the therapy for this group could be individualized and managed differently with less AD therapy and thereby minimize symptoms of testosterone deficiency.

An editorial by Dr. Oliver Sartor, Medical Director Tulane University Cancer Center in the same NEJM issue was titled "Androgen Deprivation, Intermittent, Continuous or None At All". "It is still unclear which men with rising PSA levels needed treatment." His "none at all" conjecture relates to his acknowledgment that "In addition to knowing little about which men in this population would benefit from treatment as compared with no treatment, we know little regarding the best possible timing of androgen-deprivation therapy for those clearly in need of treatment". Dr. Sartor's citing the uncertainly about the optimal PSA value at which to initiate therapy reflects his awareness that after an initial rise in PSA many men "have a prolonged period (approximately 10 years) of hormone responsiveness". This lengthy interval raises the question of when, and for whom, should IADT be prescribed, since it is now accepted that testosterone lowering therapy carries significant toxicity and the risk/benefit ratio needs to be carefully considered.

BOTTOM LINE: This definitive study lays a sound foundation for further developments toward the nuanced and optimal management of men with a rising PSA following primary therapy.

FINASTERIDE and DUTASTERIDE: Inclusion in Intermittent Androgen Deprivation Prolongs "Off-Time" and Delays Biochemical and Tumor Progression.

The addition of a 5alpha-reductase inhibitor (5a-RI), finasteride or dutasteride, in a regimen of IAD improves its performance. While there have been small research studies supporting the usefulness of adding a 5a-RI, there are no large comparative studies of regimens with and without either of these drugs. If it had been feasible to include a 5a-RI arm in the Crook study (see above) it would have been possible to assess the important goals of IAD: delaying the onset of androgen independence and improving overall survival and quality of life.

However, only two small clinical studies are available for review.

THE DUTKIEWICZ TRIAL:

This trial, reported in *Int Urol Nephrol.* Sept 2011, can be considered as a pilot study as it focused on a limited disease stage: "Comparison of maximal and more maximal intermittent androgen blockade during 5-year treatment of advanced prostate cancer T3NxM1." "More maximal" refers to the addition of finasteride to basic ADT. M1 indicates that the study included men with metastases seen on a bone scan.

The study enrolled 63 men with a median PSA of 17 ng/ml and a mean age of 72. There were two cohorts:

- Group A, which received only the customary ADT (LHRH agonist plus 50 mg bicalutamide).
- Group B was treated with LHRHa plus bicalutamide supplemented with finasteride, which was prescribed during both induction and the "off-periods".

The schema of androgen deprivation induction was somewhat unique. The ADT periods were continued until the PSA was especially low: i.e., reduced to <0.2 ng/ml in Gp A, and to <0.1 in Gp B (taking into account that a 5a-RI halves the PSA value). Androgen suppression was restarted in both groups when the testosterone level rose above the respective target levels of 0.2 and 0.1 ng/ml. Five men in Gp A failed to achieve the required nadir and were excluded.

Complete response was defined as → maintaining the target nadirs throughout the 5 year period
Partial response was defined as → achieving only a PSA of <5 ng/ml for Gp A and <2.5 ng/ml in Gp B during the 5 year trial.

Biochemical progression referred to having a PSA of >5ng/ml, Gp A , and >2.5 ng/ml in Gp B.
Total progression meant developing clinical symptoms of progression or death.

What Was Learned?

1) **Men treated with finasteride** enjoyed longer periods of freedom from therapy compared with the LHRHs/antiandrogen only regimen.
2) **The addition of finasteride improved response to therapy.** After 5 years a complete response was seen in 0% in Gp A vs. 53% in Gp B; partial response, 40% Gp A vs. 9% Gp B; biochemical progression, 20% Gp A vs. 19% Gp B; and total progression, 40% Gp A vs. 19% Gp B.
3) Decreasing responsiveness to ADT occurred progressively in both groups as the cycles proceeded.
4) No new symptomatic bone metastases were found in either group during the study.
5) Quality of life was improved in the finasteride group largely as a result of the 53% of men in that arm achieving a complete response which provided those men with longer freedom from testosterone deprivation.

   [Because the restoration of quality-of-life domains is dependent upon the recovery of testosterone levels, restarting androgen suppression at such a low level as >0.2 ng/ml is not as likely to ameliorate T deficiency symptoms as compared to studies restarting ADT at PSA levels of (say) 10 or 20 ng/ml where T levels are considerably higher in the later phases of the "off-periods."]

FINASTERIDE and DUTASTERIDE continued:

THE TRIAL BY STRUM, SCHOLZ, & MCDERMED (*The Oncologist* 2000;5:45-52)

"Intermittent use of testosterone inactivating pharmaceuticals using finasteride prolongs the time off period," (also in *J Urol*. May 2006), reports the experience with IAD over 9 years in 52 men comparing IAD with an LHRHa plus an antiandrogen in one group to another group which received continuous finasteride during induction and during the "off-periods."

IAD was continued until the PSA was <0.05 ng/ml. "Patients were advised to restart IAD if the PSA level reached ≥5 ng/ml during the off-phase".

Excluded from this report were men whose PSA nadir after induction was <0.01 ng/ml. These men, whose cancer was considered especially hormone sensitive, were managed differently. They were not treated with IAD, but instead discontinued LHRHa/bicalutamide after achieving the target PSA nadir and continued finasteride until a PSA rise. At that time ketoconozole 200 mg TID was started. Currently abiraterone or MDV3100 might replace ketoconzole.

Excluded also was another group of men whose T level of did not recover to >150ng/dl during the first 12 months of the "off-period". This exclusion was premised on expectation that without a sufficient T recovery there would likely be no benefit in quality of life.

The characteristics of this study population of 52 men were mixed. It included 46% men with clinical stages ranging from T1c - T2a-c: 37% were treated for PSA recurrence only; and 14% had nodal or bone metastases. The median PSA was 9.1ng/ml; median Gleason score 6; and median baseline testosterone level 412 ng/dl. The median follow-up was 66 months.

The usual regimen carried out by Strum is 12 months of ADT *after* a PSA nadir is achieved, which equated to an median initial induction period of 15.8 months.

What Was Learned:

Finasteride ***doubled*** the time off of "testosterone lowering pharmaceuticals," yielding a median of 31 months in the finasteride arm and 15 months without the drug. For those 28 men who maintained a PSA level of <0.05 ng/ml for one year after induction the median off-phase duration was 29 months (range 7.8 - 87+ months)."

"After a median of 66 months of follow-up, only one (2%) patient developed androgen-independent PC.

THREE FACTS:

1) The two major hormones that drive prostate cancer, testosterone and dihydrotestosterone, have different functions (Eggener, SE et al. *The prostate 66, 2006).* Eggener's studies found that testosterone is the main driver of prostate cell differentiation while DHT promotes cellular proliferation, making DHT the prime target for intervention. On this point of biology, however, some studies differ and have shown that the effect on proliferation and differentiation are equivalent for T and DHT.
   Targeting DHT is additionally pivotal since DHT is 10 - 20 times more potent in activating androgen responsive genes as compared to testosterone.
2) 5alpha-reductase isoenzyme 2 is inhibited by finasteride and in ***non-malignant*** prostate cells is the predominant driver of the conversion of T to DHT. In contrast, in ***prostate cancer*** cells, isoenzyme 1 is the main catalyst for this conversion. Dutasteride, a "dual" 5alpha-reductase inhibitor, inhibits both isoenzymes and therefore has become the preferred agent in treating prostate cancer.
3) Dutasteride at 0.5 mg reduces intraprostatic DHT levels by 95% (a dose of 3.5 mg even more) while causing a slight *increase* in intracellular testosterone. Dutasteride does not lower serum T -- and some studies show a slight increase.

FINASTERIDE and DUTASTERIDE continued:

THE ARTS STUDY: (*Eur Urol.* 2012 Nov, Schroder et al.)

The findings of this study are discussed because the results --for the first time -- demonstrate the effectiveness of dutasteride alone on prostate cancer progression. The observation gives support for inclusion of dutasteride in a regimen of intermittent androgen deprivation.

This recently published study, "Avodart After Radical Therapy for Prostate Cancer Study," evaluated the influence of 24 months of Avodart, 0.5m daily, versus a placebo in the PSA doubling time (PSADT) in 187 men with rising in PSA following primary surgery or radiation.

Details:
Of the study group, 81% had had surgery, 19%, radiation; ~96% had PSA values <10 ng/ml; ~58% had a Gleason score of <7; and 66% were clinical T stage >T1c.
Men with higher baseline PSA values, more rapid PSADTs, higher Gleason scores, and greater T stages gained less from dutasteride therapy.
Breast disorders occurred more frequently in the dutasteride group, 10% vs. 4%.

Their conclusion: "Dutasteride delayed the biochemical progression of PCa in patients with biochemical failure for clinically localized disease." "Dutasteride significantly delayed the time to PSA doubling compared with placebo after 24 mo of treatment," -- a 66% risk reduction ($p<0.001$).

BOTTOM LINE: Clinical studies and basic research have demonstrated a benefit from the inclusion of a 5alpha-reductase inhibitor (preferable dustasteride) in the standard regimen of intermittent androgen deprivation. When added to standard IAD in the setting of a rising PSA after primary therapy for localized prostate cancer, tumor progression is retarded, the "off-period" is prolonged, and a measure of benefit to quality-of-life is gained. Still lacking, however, is convincing data showing a benefit for survival and a delay in the development of androgen insensitivity. The safety of the addition, however, has been established, making the regimen an option for patient management.

INTERMITTENT ANDROGEN DEPRIVATION FOR METASTATIC PROSTATE CANCER

This topic has been sufficiently studied yielding results that discourage the use of this regimen except in carefully selected patients. Although disappointing, the results are not surprising. The outcome of studies for IAD in localized and locally advanced disease, which included some men with distant spread, identified characteristics that predicted poorer outcomes: PSA > 20 ng/ml, induction nadirs > 4 ng/ml, higher Gleason scores, more rapid PDS doubling times, and spread to lymph nodes or bone. The men exhibiting some or all of these features generally experienced shorter "off-periods", fewer successful cycles, and earlier disease progression.

The most definitive data on IAD in metastatic disease was presented at the 2012 ASCO meeting by Dr. Maha Hussain. She presented the results of a 17 year extensive collaboration of international researchers:

"Intermittent (IAD) versus continuous androgen deprivation (CAD) in hormone sensitive metastatic prostate cancer … an international phase III trial (J Clin Oncol 30,2012, supple; abstr 4). ASCO Daily News captured the researchers' overall judgment: "Continuous Androgen-Deprivation Therapy Remains Standard of Care for Metastatic Disease".

The study accrued 3040 men, PSA ≥5 ng/ml, who were treated for 6 - 7 months with an induction regimen of an LHRHa plus bicalutamide. Only 1535 men, 50.2%, achieved the required PSA response of 4 ng/ml or less. Patients were stratified between "minimal" disease (disease that had not spread beyond the pelvic lymph nodes or the bones of the spine and pelvis) and "extensive" disease (disease spread further to bones beyond the spine and pelvis, and to non-pelvic lymph nodes, lungs, or liver). This occurred in 48%.

INTERMITTENT ANDROGEN DEPRIVATION continued:

This distinction, now considered inappropriate, was in use, however, at the time the study was designed 20 years ago and related to the work of Crawford and Labrie which showed that men with only 1-5 bone metastases did far better under treatment than those with increasingly more extensive disease. Randomization assigned 765 men to CAD and 770 to IAD. The median follow-up was 9.2 years.

The trial schema for IAD specified induction cycles of 7 months of treatment. If a post induction PSA nadir of <4 ng/ml was reached, ADT was stopped and an observation period ensued. This ended when the PSA reached >20 ng/ml (or reached the baseline PSA for those men whose PSA had been less than 20 ng/ml at study entry). If the nadir value after induction was not met, the man continued on CAD until progression.

Over the course of the trial 56% of men on CAD died and 64% on IAD.

Results:

Measured from the time of randomization the median overall survival for men in the CAD group was 5.8 years, 25% of whom lived for 10 years. For the IAD group, the median overall survival was 5.1 years, with 23% living 10 years. The appraisal by Dr. Hussain was this represented an inferior outcome for IAD. It represents a 9% increase in relative risk of death. She termed this "clinically concerning".

When analysis was directed to subsets, the only group in which IAD was (slightly) favored were the men with "extensive" disease -- a vexing outcome for many clinicians. Continuous androgen deprivation was favored for all other subgroups: men with "minimal" disease, bone pain, and especially men with no bone pain.

The outcome of those men who had met the randomization requirement of a PSA ≤4 ng/ml was analyzed in two groups: i.e. one showing a post induction nadir PSA of ≤0.2 ng/ml and another whose PSA nadir was between 0.3 and 4.0 ng/ml. The 2-year risk of PSA progression within this low nadir group was 53% for IAD vs 31% for CAD.

However over the course of the study, continuous androgen deprivation and IAD were favored to approximately the same extent. This represents an important observation since intuitively it might be expected that the men in whom induction yielded a very low PSA nadir (in this case ≤0.2 ng/ml) would do comparatively better.

No major quality-of-life differences were seen between the two groups, although low grade side effects were seen more in the CAD group.

In a regimen of IAD in this more aggressive setting of metastatic disease the 'off-treatment" periods are relatively short compared to studies of IAD in lower grade, localized prostate cancer. Dr. Charles Myers estimated the average duration of "off-time" in the Hussain study as about 6 months.

A recently reported European study (Mottet et al. *BJU Int. 2012 Nov)* also studied IAD vs.CAD in patients with metastases and employed a roughly similar schema. The "off-periods" for cycle #1 was about 5 months, and was ~4 months in the next few cycles, then decreased in additional cycles.

BOTTOM LINE:

In Hussain's most definitive study to date of intermittent versus continuous androgen deprivation for the treatment of metastatic prostate cancer, continuous hormone suppression produced a superior overall survival.

However, this trial tested a specific regimen. It is possible that future treatment regimens may succeed in achieving the as yet unrealized goals of intermittent androgen suppression: to prolong survival, delay the conversion to hormone insensitivity, and to improve quality of life. Compared current therapies using continuous ADT, a successful IAD regimen might avoid the unwelcome toxicities of long-term testosterone deficiency.

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