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ADJUVANT AND SALVAGE TX FOR PRIMARY TX FAILURE: Adjuvant Androgen Suppression Following Radiotherapy: How Long?

There is no current consensus as to the optimal duration of androgen suppression (AS) for patients at risk for recurrence following primary radiotherapy, and consensus as to who should be treated is evolving. However, clinicians regularly must address this management issue despite lacking guidance from the perfect clinical trial. A case study highlights this question:

Mr. X, now 75, experienced an unimpressive gradual rise of his PSA value from 2.9 ng/mL in 1992 to 4.4 in August 2003 at which time his DRE showed firmness on the right (cT2b,'97). A 6 core biopsy found four right sided cores positive for adenocarcinoma . The Gleason scores were 4 + 5, 4 + 3, 3 + 4, and 3 + 3. Radiotherapy to 74 Gy was given to the prostate and seminal vesicles. Lupron was commenced prior to radiotherapy (along with a short course of Casodex) and has been continued for one year. The current PSA is < 0.1 ng/mL. His question to his radiotherapist is "Is there an advantage to continuing androgen suppression longer, and, if so, for how long?"

Mr. X is at substantial risk for recurrence. The Partin tables and the Kattan nomogram, respectively, give estimates for organ confinement of 28% and 14%; for extracapsular extension, 58% and 46%; for seminal vesicle involvement, 8% and 24%; and for metastases to lymph nodes, 6% and 16%. He has a substantial likelihood of having pT3 prostate cancer.

Multiple trials have compared radiotherapy alone (or with 4 months AS) to XRT with immediate, adjuvant AS delivered for 3 years, or indefinitely. This man's case fits - never exactly - into subsets of most of these trials.

D'Amico's recent JAMA report (Aug.18,2004) of a trial of 6 months of AS with XRT versus no AS for men with clinically localized prostate cancer showed an overall survival benefit at five years for XRT + AS of 88% versus 78%. Androgen suppression was given on relapse in both arms and at five years follow-up freedom from the institution of this salvage AS was seen in 82% of treated men versus 57% who initially received no AS. The study categorized the 206 participants into four disparate groups encompassing intermediate- and high-risk men. Mr. X fits into the study as a member of group 2, ie those men having a Gleason score of $\geq$ 7.

RTOG trial 92-02 (JCO 2003, Nov) studied men with cT2c-T4 disease with PSA values < 150 ng/mL and compared XRT delivered to the prostate and lymph nodes: one group receiving AS for 4 months with XRT, and a second in which an additional 24 months of AS were given. Taken as a whole this study population had more aggressive disease than Mr.X. However, a relevant subset analysis showed a survival advantage at five years for men with Gleason scores of 8 to 10: 81% versus 70.7%, P = .044.

Roach et al (Red Journal, June 2000) authored "Predicting long-term survival, and the need for hormonal therapy: a meta-analysis of RTOG prostate cancer trials". The several studies compared XRT combined with short-term AS to long-term AS. The analysis was categorized into four prognostic risk groups, one of which matched Mr. X, ie (group 3): men with T1-2NX and Gleason scores 8 - 10. Group 3, combined with a higher stage group 4, experienced a 20% higher survival at 8 years. One of these studies, 85-31, had compared immediate, indefinite AS to androgen ablation at relapse in cT1-T2 N1 or cT3 non-metastatic disease. The update (Pileich, [Abstract 381A] ASCO 2003,22) "at 7.3-year mean follow-up demonstrated significant improvement in overall survival, with estimated 10-year survival rates being 53% and 38% in the immediate and deferred treatment groups, respectively." (Messing, reference, see below)

Horwitz et al (Red Journal, Mar. 2001) authored "Subset analysis of RTOG 85-31 and 86-10 indicates an advantage for long-term vs. short-term adjuvant hormones for patients with locally advanced non-metastatic prostate cancer treated with radiation therapy." Statistically significant improvements were found in biochemical disease free survival and freedom from distant metastases for men on long-term AS.

It is usually difficult to find relevant clinical trials that include participants having exactly the characteristics of a single patient of clinical interest, such as Mr.X. However, the trend in these quoted studies and others favor adding long-term AS to primary XRT in cases such as Mr. X as a means of achieving longer freedom from biochemical relapse and longer freedom from distant metastases. These benefits may easily be regarded as clinically desirable even if a survival benefit was not significantly demonstrated in some studies.

he critical issue really is at what price in terms of unwanted "side effects" are these benefits obtained? If an effective and congenial means of long-term androgen suppression were available, the question of duration of treatment may become mute. After all, in the prostate's sister endocrine disease, breast cancer, oncologists have been prescribing Tamoxifen, a medication with a very acceptable side effect profile, for over twenty years to women with estrogen receptor positive disease encompassing a wide spectrum of risk of recurrence. Treatment has resulted in a substantial control of disease progression and a modest survival advantage.

[An excellent review article: “Early Versus Late Hormonal Therapy for Prostate Cancer”, by Miamoto and Messing, in Current Urology Reports 2004, 5:188-186]

Bottom Line: Trends in recent studies would suggest that Mr. X would very likely benefit from long-term - possibly as long as 5 years - suppression especially if a treatment regimen is carefully chosen which has an acceptable “side effect” profile.

ADJUVANT AND SALVAGE TX FOR PRIMARY TX FAILURE: Beginning To Think Out Of The Box: Alternatives To LHRH Agonists As Adjuvant Regimens After Primary Treatment For Prostate Cancer.

> “Because of increased awareness of prostate cancer and improved detection methods, patients are presenting with earlier-staged disease and at a younger age than before. Drug therapy for prostate cancer therefore needs to consider patients’ QOL as well as survival endpoints.”

This quote comes in the conclusion of the excellent review “An Evaluation of Bicalutamide in the Treatment of Prostate Cancer” by Schellhammer and Davis, Clinical Prostate Cancer, March 2004. Bicalutamide - “Casodex” - is being extensively studied as adjuvant therapy in stages T1-T2 and locally advanced PC in the 8113 man Early Prostate Cancer (EPC) trial, a composite of separate trials in the USA, and Scandinavia, and collectively in Europe, Israel, South Africa, Mexico, and Australia.

The schema for these trials is the comparison of Casodex 150 mg/day with a placebo. The USA trial continued treatment for 2 years, and the others for ≥ 5 years. “The primary endpoints of the trial are time to *objective* progression and overall survival.” Since the PSA values for the placebo group would be expected to rise, PSA progression was *not* an endpoint in itself, but time to PSA doubling over baseline was noted. 55% of participants had undergone radical prostatectomy. The patients “were scheduled to have bone scans at two years, or earlier if clinically indicated”. Although survival data is immature, 3 year follow-up data (Iverson, J UROL Dec. 2003) found that 150 mg Casodex was associated with a superior outcome compared to placebo in the following categories.

1) Casodex reduced the overall risk of *objective disease progression* by 42%. Data from the USA trial is still immature since determining the outcome of its relatively better stage patients, who mostly had cT1c-T2a and pathologic T2 disease, will require longer follow-up. The risk reduction at 3 years for localized prostate cancer was 28%, and for locally advanced PC, 54%. For men with Gleason scores 5-6 the reduction was 47%, and for those with Gleason 7-10, 43%. Risk reduction occurred irrespective of nodal status. In node positive patients the reduction was 71% and in node negative men, 41%, and in NX, 40% (UROL, May 2004)- i.e., the greatest benefit was seen in the patients with the poorest prognosis.

2) Casodex reduced the risk of time to PSA doubling from baseline by 59%.

3) At 48 weeks some sexual function was retained in 75% of men in the Casodex arm versus 85%, placebo; and sexual frequency was retained in 63.5% vs.78% for the placebo arm.

4) The EPC trial reported that Casodex was associated with gynecomastia in 66% of men and breast pain in 73%, although these events were mild to moderate in > 90% of patients. Other studies have shown that 1 or 2 prophylactic electron beam treatments prior to starting Casodex reduces gynecomastia by 33%. In Casodex patients hot flashes occurred in 13%, impotence in 9% and physical capacity was better maintained. [Note: Casodex accentuates the action of Coumadin]

Two large earlier studies compared 150 mg/day Casodex to castration or a LHRH agoinst in 480 men with locally advanced M0 disease. With a median follow-up of 6.3 years, these studies established there was no significant difference in outcome between the two treatments in M0 disease. The median survival was approximately 5 3/4 years for both arms. In M1 disease survival in the castration arm was superior only by a median of 42 days.

Casodex, a nonsteroidal antiandrogen, blocks access of testosterone to the androgen receptor thus decreasing proliferative stimulation of cancer cells, but serum testosterone levels are maintained, unlike the fall to castrate levels of testosterone which follows Lupron, for example. This biologic difference explains the important contrasting side effect profiles between the two medications. In these two Casodex vs. castration trials bone density in the lumbar spine, evaluated at two years, *increased* by 2.4% in the Casodex arm but *decreased* by 5.4% in patients undergoing medical castration.

A 12 month study of 51 men with M0 disease evaluating Casodex (C) vs. Lupron (L) (Smith, JCO July 1, 2004) with respect to changes in bone mineral density and body composition reported results in the following categories:

1) trabecular bone mineral density in the lumber spine, C = +4.7%, L = -7.6%;
2) lower extremity strength, C = +3.7%, L = -1.2%;
3) fat mass, C = +2.4%, L = +3.6%;
4) breast enlargement/breast tenderness C = 100%/100%, L = 54%/ 8%
5) loss of sexual interest, C = 40%, L = 81%.

Dr. Iverson (J UROL, Dec. 2003) in the discussion portion of the article pointed out that “there is a growing amount of experience from previous bicalutamide trials that from 30% to 50% of patients [who fail 150 mg Casodex] will respond favorably to second line LHRH or castration.” This contention is strengthened by a recent article from the Dana-Farber Cancer Institute, Boston, (Annals of Oncology 15, 974-978, 2004): “Finasteride [5 mg/day] and bicalutamide [150 mg/day] as primary hormonal therapy in patients with advanced adenocarcinoma of the prostate”. These patients had metastatic disease. The relevant point to be made apropos of the issue of subsequent salvage by Lupron is that of 14 patients who experienced PSA failure during the course of the Casodex regimen 12 responded again to medical castration for a median of an additional 9.8 months until further PSA progression.

A strategy could be emerging of exploiting the QOL advantages of adjuvant Casodex as initial therapy, while reserving Lupron for salvage when, and if, needed.

The application for approval of use of the 150 mg dose of Casodex in the USA was denied by the FDA in 2002. However, much new favorable data has accumulated since that time and one might expect an approval on the next application.

Bottom Line: Data is accumulating establishing the efficacy of 150 mg/day of Casodex as adjuvant therapy following primary treatment for men with higher-risk prostate cancer.