



Testosterone Recovery Following Prolonged Adjuvant Androgen Ablation for Prostate Carcinoma

Authors: T Pickles, A Agranovich, E Berthelet, et al.

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Background

The use of androgen ablation (AA) has become more common in the treatment of prostate cancer. Androgen ablation has a proven survival benefit in patients with advanced (T3-4, or lymph node positive) disease and in those with high Gleason Score (8-10) disease, via the data of large EORTC and RTOG studies. Furthermore, the use of prolonged hormonal ablation (> 2 years) has been shown to be more efficacious than shorter durations of hormones. With the routine use of hormones in these patients, the number of patients receiving androgen ablation therapy is in the thousands per year. There is concern over the risk of permanent gonadal failure in these patients, with subsequent loss of testosterone production and increased late toxicity. This study investigates the recovery of testosterone production following AA.

Methods

- 267 men treated definitively for prostate cancer with radiation therapy who had normal pretreatment testosterone levels and who were treated with at least 3 months and no more than 3 years of AA.
- These patients were compared to a control group of 517 men who received no AA.
- AA was achieved through cyproterone acetate with stilboestrol (CPA/DES) or 1-month or 3-month LHRH agonists, usually (93%) goserelin ([Zoladex](#)).
- Testosterone levels were measured within 6 weeks of completing radiation, then every 6 months for 3 years.
- If patients achieved a testosterone level of 10 nmol/L at least once, they were scored as recovered. This analysis started at the date the therapeutic agent was meant to cease its action (i.e.-for 1 month and 3 month LHRH agonist preparations, this would be 1 month and 3 months after delivery).
- If the control group's testosterone level dropped below 10 nmol/L, they were scored as testosterone failures.

Results

- 56% were treated with CPA/DES, 18% with 1-month LHRH agonists, and 25% with 3-month LHRH agonists.
- 79% of patients recovered testosterone levels to > 10 nmol/L within 3 years
- 93% of patients recovered testosterone levels to > 5 nmol/L within 3 years
- The control group had a gradual fall off in testosterone levels with 83% maintaining a testosterone level of at least 10 nmol/L at 3 years.
- Factors delaying recovery include increasing age (>75), low pre-treatment testosterone levels, prolonged AA duration, and use of 3 month LHRH agonists.
- Median time to recovery for CPA/DES and 1-month LHRH agonist groups was 7-8 months. For 3 month LHRH group, median time to recovery was 16 months.

Author's Conclusions

- The majority of men treated with androgen ablation will recover to normal testosterone levels.
- The number of patients failing to recover almost matches the natural fall-off of testosterone secretion in healthy men.
- Given the longer time to recovery for the 3-month LHRH agonist preparation, for the last year of an adjuvant program, a switch to a 1-month preparation may be preferable.

Discussion

Hormonal ablation is an essential part of treatment in many patients diagnosed with prostate cancer. However, with more patients being treated with AA, and for longer periods of time, there is concern over the long-term toxicity profiles, mainly dictated by permanent gonadal failure, reflected in testosterone levels. If permanent gonadal failure results, patients would be impotent and at significantly higher risk for osteoporosis, among other things. This study shows that, in the majority of cases this is not a concern, as gonadal function returns within 3 years. In fact, this may simply reflect those patients who would have naturally lost their testosterone production, as shown via the control population. However, though it was stated that longer duration of AA was correlated with less testosterone recovery, there was no data that directly addressing this issue. In fact, only 9 of their patients were treated with over 2 years of AA. As more patients are being treated with 2 to 3 years of AA, this is an important question that needs to be answered. Also, there is no data on symptom recovery (hot flashes, impotence, etc.) as testosterone levels increased after cessation of AA. In addition, patients were scored as recovered if their testosterone rose to normal just once during the analysis period. There is no revision or correction of the data if those patients again dropped below normal. Overall, this study reports encouraging data of testosterone recovery after AA. As long term LHRH agonist therapy has become the standard of care in AA, a prospective study needs to be done to directly address gonadal recovery in these patients.

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