INTERMITTENT ANDROGEN DEPRIVATION (IAD) FOR ADVANCE PROSTATE CANCER. WHY NOT THE STANDARD OF THERAPY?

Dominique Prapotnich, Rafael Sanchez-Salas, Xavier Cathelineau, Oleksandr Stakhovskyi, José EA Rocha Jr and Guy Vallancien.


Summary.- OBJECTIVES: To review the literature and present a contemporary image of androgen deprivation for prostate cancer.

METHODS: We conducted a PubMed search on intermittent androgen deprivation. Articles obtained on intermittent androgen deprivation (IAD) and the experiences at Institut Montsouris were used for the review.

RESULTS: IAD is an approach to hormonal deprivation that holds effective cancer control while preventing the morbidity associated with continuous androgen blockade. IAD nuances have been assessed by urological community teams in order to verify its possible potential benefits. Evidence based approach supports the idea of IAD as a standard of therapy for advanced prostate cancer requiring hormone deprivation. Variation among medical teams’ criteria for the treatment and surveillance await standardization.

CONCLUSIONS: Reassessing the gold standard of hormonal blockade in advanced prostate cancer is mandatory. The undeniable evolution of IAD needs to be embraced by the urological community.

Keywords: Intermittent hormone treatment. Prostate cancer. Androgen blockade. Castration. Androgen antagonists.

Correspondence
Dominique Prapotnich
Urology Department
Institut Mutualiste Montsouris
Université Paris Descartes
42 boulevard Jourdan
75014 Paris cedex France
dominique.prapotnich@imm.fr
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INTRODUCTION

Intermittent androgen therapy (IAD) has been extensively proven as feasible by several clinical groups around the world; although, published series are difficult to evaluate due to their heterogeneity in terms of inclusion criteria. Interestingly, almost every study has shown three interesting facts:

First, IAD is at least equal to continuous androgen deprivation in terms of cancer control.

Second, there is at least one single benefit (sexual function) for the patient in terms of testosterone recovery and

Third, IAD treatment is less expensive than CAD for obvious reasons. Based on these premises and in our own experience, we remain objectively enthusiastic towards IAD. Herein, we present a right to the point revision that aims to support IAD as a potential standard of therapy for the same indications that have been deployed for CAD thus far.

The benefits of hormonal blockade for metastatic prostate cancer (HBMPC) have been demonstrated for 68 years by Huggings & Hodges (1). HBMPC remains a palliative treatment as the disease would eventually evolve towards hormonal resistance. HBMPC also harbors several immediate and delayed secondary effects (Immediate: hot flashes, fatigue, sexual impotence, loss of libido. Delayed: bone demineralization (2), fracture risk, muscle wasting, depression, increased insulin resistance, anemia, malaise, lipid disorders, and fat accumulation in the tissues). The aim of the intermittent androgen suppression is to decrease the undesirable effects of HBMPC while still benefiting from hormonal blockade.

The initial experience with intermittent androgen suppression was published by Klotz et al in 1986 (3). This pioneer experience settled the concept of a tailored hormonal intervention and it was performed by the deployment of stilbestrol in an ON phase treatment followed by an OFF phase (no treatment at all), depending on testosterone and PSA levels.

Several experimental studies on intermittent androgen deprivation (IAD) have been presented. In 1990, Bruchowsky (4) demonstrated the feasibility of intermittent hormonal blockade in Shionogi mouse breast tumors, by performing ON phase treatment and OFF phase (surveillance phase). This procedure permitted a 3-fold time delay to hormonal resistance when compared with the continuous treatment models. Sato (5) verified the mentioned effects of IAD in his preliminary experience with LNCaP implantation in a mouse model.

These experimental results supported the deployment of IAD in clinical protocols. The original idea was to control the clone selection pressure, which in continuous androgen deprivation (CAD) ends in hormonal resistance, by periodically exposing cancer cells to androgens. A mathematical non linear model by Shimada (6) tried to explain why IAD can be effective.

In summary, competitive effect plays an important role between androgen-dependant and independent cancer cells and it is assumed to be essential for the decrease of androgen independent cells under a normal androgen level.

Nowadays several phase II studies (7-8) have proven feasibility, lower toxicity and good tolerance of IAD, which improves the quality of life by diminishing secondary effects of androgen blockage during OFF phases.

Meta-analysis

A meta-analysis published in 2006 (9) combined the results of the 10 available protocols covering more than 50 patients. Our institution collaborated with data from 411 patients out of the 1446 incorporated for final analysis in this work. The highlight of this meta-analysis was the criteria heterogeneity for the ON and OFF phases of IAD treatment among the different groups in different continents. Phase OFF treatment of IAD tends to be longer in the USA and shorter in Europe. No differences in survival were verified in the locally advanced cases with treatment less than 4 months and those longer than 8 months.

On the other hand, in patients with important metastatic disease, an androgen blockade longer than 8 months was proven as beneficial. In this analysis 366 patients had node involvement or bone metastatic disease. 1080 patients did not harbor metastasis (517 had IAD as primary treatment and 563 received initial primary treatment and were indicated for IAD at the time of biochemical recurrence (BCR).
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The initial PSA level and PSA nadir were clearly identified as strong predictors of disease free survival (Initial PSA < 10 ng/ml, better than > 10, and the lower the nadir, the better it is).

The recommended approach for IAD was complete androgen blockade which was achieved by combining LH-RH analog and non-steroidal anti-androgens. A PSA level of 15 ng/ml was identified as the restarting point for treatment in order to obtain the lowest ratio for ON/OFF treatment. A level of PSA less than 4 ng/ml is widely considered as the threshold to start surveillance.

This timely work has demonstrated the feasibility and safety of IAD in a large group of patients. IAD was verified as a logical treatment option for any patient previously considered for continuous hormonal blockade.

The Montsouris IAD experience

The results and recommendations presented in the above mentioned meta-analysis reflect those of our series in terms of outcomes and cutting points for treatment and surveillance. In our experience which began in 1992, 566 patients have received IAD at IMM. Initial and updated reports have been previously published (10,11). In summary, our PSA criteria for ON phase and OFF phase are 20 ng/ml and 4 ng/ml, respectively (Figure 1). Patients with important metastatic disease are poor candidates for IAD. Out of the 566 patients treated, 218 patients received IAD after primary therapy and subsequent BCR and 348 patients had micro or macro metastatic disease and underwent IAD without another previous therapeutic approach. We have treated patients with a median age of 74.7 with a median PSA of 17 ng/ml and the median follow-up for our series is as long as 81 months. The oldest patients in our experience have received 13 cycles (ON phase + OFF phase) and we observed a difference of median cycle duration (23 months vs 10 month) when comparing the induction cycle vs. the 6th cycle. Median cycle duration stabilized and reach a plateau after the 6th cycle. 32% of the patients developed hormone resistant disease during follow-up. Cancer specific mortality was 13%. A 12-year median cancer specific survival was confirmed for the entire series (Figure 2). Initial PSA, initial Gleason score and age were identified as predicting factors for survival.

FIGURE 1. Graphic example of an IAD patient follow-up at IMM.

FIGURE 2. Cancer specific survival probability for the series at IMM.
(The arrow indicates the median survival time).
Randomized studies

The timely studies by Goldenberg et al. (12) defined the optimal triggers for IAD using PSA level and laid the foundations for the desired phase III clinical trials.

Several randomized studies comparing IAD and CAD have been performed and their results are available. Salonen et al. (13) conducted The Finn Prostate Study VII to identify patients who could benefit from IAD. A total of 856 men with locally advanced or metastatic prostate cancer were enrolled and given induction ADT for 24 weeks. ADT responders were randomized, one by one, for either continuous androgen depriviation or intermittent androgen deprivation. The randomization criteria were a decrease of PSA by less than 10 ng/ml or by more than 50% if less than 20 ng/ml at baseline. 564 patients (66%) were randomized for IAD or CAD. The group of patients not meeting the randomization had significantly higher PSA, alkaline phosphatases, proportion of T4 tumors, poorly differentiated cancers, metastatic disease and a great number of skeletal hot spots in M1 disease. These patients with more advanced disease are likely poor candidates for IAD.

The most important protocol in terms of methodology is the SEUG study by Calais da Silva et al. (14) which deployed the same rational criteria as used at our institution (IMM). They presented 766 patients with locally advanced or metastatic prostatic carcinoma who received a 3-months induction treatment. Patients with a prostate-specific antigen (PSA) decreased by < 4ng/ml or by 80% below the initial value (626) were included in the study. Cyproterone acetate and luteinising hormone-releasing hormone (LHRH) were used for induction. Complete androgen blockade was deployed in the continuous arm. There was no difference in survival between IAD vs. CAD. Although there were a greater number of cancer deaths in IAD arm; cardiovascular deaths were higher in CAD arm. Side-effects were more significant in the continuous arm. Patients who received IAD showed better sexual function. These authors did not find any differences between IAD and CAD in terms of disease progression and overall survival after an 8-year follow-up. We can expect that these results will probably favor IAD in future analysis during follow-up.

A report by de Leval (15) had also found a lower progression rate in the IAD arm vs. CAD (7% vs. 38.9%). They reported a clinical trial that randomized 68 patients with advanced prostate cancer to intermittent or continuous AD therapy with goserelin acetate and flutamide. After a median follow-up of 30.8 months, the 3-year androgen-independent progression rate was significantly lower in the intermittent arm than in the continuous arm (7% vs. 38.9%). Patients receiving intermittent therapy were off treatment 59% of the time.

The randomized protocol by Mottet (16) did not find any significant differences in survival and the quality of life when comparing CAD with IAD; however, this study included patients with important metastatic disease (Median PSA : 663 ng/ml) and a short overall survival (between 3 and 4 years), which precludes a comparison. Our experience agrees with that of Salonen et al. (13), regarding the inadequacy of IAD in important metastatic prostate carcinoma.

Irani et al. (17) have also published their results that do not state any difference between the two approaches. Results from this study are based on a comparison of 6 months of treatment and 6 months of surveillance, without any individual PSA control. This approach does not profit from the potential benefits of IAD, as there is an important ON phase treatment delivered in the supposedly IAD arm of the study. Testosterone recovery is essential in IAD, and the latter implies a clearly dynamic treatment delivery in order to benefit from a limited hormonal blockade exposure. Gulley (18) showed that a preconceived ON phase treatment might compromise testosterone recovery. In their study, after 6 months of GnRH-A therapy in 80 patients, dihydrotestosterone and testosterone levels did not return to normal for a median of 14.9 and 16.6 weeks. Other factors associated with multivariate analysis with delayed testosterone recovery included advanced age, low pre-treatment testosterone level and the use of 3-month GnRH preparations vs 1-month GnRH preparations (19). Off phase treatment is the cornerstone of IAD and it has been shown that use of a cyclooxygenase-2 inhibitor during the off-phases of IAD may increase the effectiveness and off-therapy time (20). The overall message supported by literature with substantial evidence, is that IAD when compared to its continuous counterpart, has never produced lesser outcomes (While having better results in several manuscripts).

DISCUSSION

All the available data motivated the urological community to host a plenary session on this subject at AUA Chicago 2009. The panel question was whether intermittent or continuous androgen therapy
should be a standard of care. In addition, the task of the panel discussion was to verify the rationale, evolution and outcomes of IAD. Based on these elements, it was clearly established that IAD can be considered as a potential gold standard treatment for advanced prostate carcinoma in regards to cost and effectiveness. It was also considered as a less deleterious approach with equivalent cancer control (two definitive international trials are under way attempting to answer the question of whether intermittent or continuous therapy should be definitively the standard of care). In the past, Tannock (21) has the well deserved honor of questioning CAD vs a potential novel standard re-presented by IAD. We are at the beginning of change in hormonal treatment for prostate cancer and the birth of a new paradigm, our patients must become the natural benefit recipients of this evolution. It must be said that we still need to refine and standardize inclusion criteria and follow-up for IAD, which remains a hard task due to the fact that treatment has to be tailored to every patient based on the particular aggressiveness of the disease, and this is the only way to obtain the best outcome.

CONCLUSION

IAD must now be regarded as a safe and reliable treatment option of care for advanced prostate cancer (except for patients with important metastatic disease or PSA level > 100 ng/ml) based on evidence provided by several institutions. Survival rate and precise patient selection remain unresolved issues that should be developed in the future.

REFERENCES AND RECOMMENDED READINGS

(*of special interest, **of outstanding interest)


