The history of intermittent androgen deprivation therapy — A Canadian story

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Introduction

The luteinizing hormone-releasing hormone (LHRH) agonists and antagonists are a mainstay of treatment for advanced prostate cancer. A key feature of the LHRH analogues is their reversibility. As evidence of the long-term adverse systemic effects of androgen deprivation therapy (ADT) accumulated, this feature has taken on more importance.

Reversibility of ADT offers the potential for intermittent ADT (IADT). This has the potential benefits of improved quality of life (QOL) as testosterone recovers (diminished hot flashes, recovery of libido, return of erectile function, reduction in frailty); reduced morbidity and mortality (less metabolic syndrome, reduced cardiovascular [CV] events, insulin resistance, and bone loss); reduced drug costs; the possibility of improved duration of androgen dependence; and the opportunity for integrated therapy with cell cycle-directed interventions. Although we are in the era of the androgen receptor-axis-targeted therapies (ARATs), which have not been evaluated as intermittent therapy, it is likely that similar principles apply.

The use of lifelong ADT began with the first use of this therapy by Huggins and colleagues for men with advanced metastatic prostate cancer, who had a median survival of three years.[1] In the 90s, when prostate-specific antigen (PSA) failure after local therapy became the commonest indication for ADT, the lifelong ADT approach continued, although these patients had a much longer survival than those with metastatic disease. In fact, other-cause mortality is a more common cause of death than prostate cancer in these patients.

The story

The first use of IADT was in 1980, by Willet Whitmore at Memorial Sloan-Kettering Cancer Center (MSKCC). He had a patient in his 50s with symptomatic metastatic prostate cancer. The patient was an energetic, competitive tennis player. He was started on diethylstilbestrol (DES), the standard of care at the time. His pain improved, but his tennis competitiveness was adversely affected. After a year on DES, he was asymptomatic and demanded that, if possible, his DES be discontinued so that he could resume competitive tennis. There were absolutely no reports of this strategy in the literature, and Whitmore, who was always open to new approaches, said "Let's try it." The DES was stopped, the patient's tennis improved substantially, and he remained off treatment for about 15 months, until his symptoms recurred due to disease progression. He responded to re-treatment, and ultimately was cycled several times before developing castration-resistant prostate cancer (CRPC). This positive experience led to intermittent therapy being adopted as a treatment option at MSKCC in the mid-80s.

I was a fellow at MSKCC at the time, and greatly influenced by Whitmore's approach. I assembled the data on the first 20 patients treated with intermittent DES into a manuscript, which was published in 1986.[2] This was the first report of the clinical use of IADT. It described 20 patients with symptomatic metastatic disease treated with DES, in whom the therapy

was discontinued in those who demonstrated a complete symptomatic response. PSA was not available for disease monitoring, and acid phosphatase considered unreliable. DES was resumed when the bone mets became symptomatic again. The goal was to reduce side effects of therapy and improve QOL. We showed that treatment could be discontinued safely, and patients would respond again upon retreatment. Some patients received four or more cycles of DES over a period of 3–4 years.

Contemporaneously and independently, Nicholas Bruchovsky, an endocrinologist at the BC Cancer Agency, proposed a counter-intuitive hypothesis: that re-exposure of prostate cancer stem cells to androgens could re-induce an apoptotic potential in their progeny, thereby prolonging the time to androgen resistance. In the Shionogi mammary androgen-dependent murine model, his group demonstrated a proof of this concept. Serial re-exposure of these cells to intact mice by transplantation prolonged the time to androgen independence.[3-5]

In 1989, PSA became available, and intermittent therapy became PSA-driven. At that time, the conventional wisdom was that the levels of testosterone were unimportant in men on ADT. In sharp contrast, Dr. Bruchovsky took an obsessive and detailed interest in the response of PSA and testosterone to various forms and durations of hormone therapy, much like one would anticipate an endocrinologist would evaluate the serum glucose in a diabetic patient on insulin.

I met Dr. Bruchovsky in the late 80s, and we immediately established our shared interest in IADT. Under his leadership, together with Juanita Crook, a radiation oncologist in Ottawa, and Larry Goldenberg at the University of British Columbia (UBC), we launched several national phase 2 clinical trials of IADT. These studies led to four pivotal publications in the mid-90s, which documented the clinical, biochemical, and QOL response to initiating and discontinuing ADT.[6-9] Most of what we know today about the time to PSA nadir, predictors for the duration of the off-treatment interval, and the rate of testosterone recovery stems from those articles. Dr. Bruchovsky mentored and inspired a generation of urologists and scientists to take a scientific and analytic approach to ADT (Drs. Goldenberg, Gleave, and Rennie, among others) and laid the seeds for the remarkable Vancouver Prostate Centre.

These intermittent studies generated a great deal of interest and resulted in a flurry of clinical trials, including a pivotal Canadian randomized trial in men with PSA failure, NCIC PR7. We now have the benefit of approximately 17 prospective phase 2 studies and seven randomized phase 3 studies. The publication of the two largest studies, NCIC PR7[10] and SWOG 9346,[11] both in the *New England Journal of Medicine* and both with approximately 1500 patients, provided clarity to the role of intermittent therapy in the management of prostate cancer.

PR7, led by Juanita Crook and myself, was the largest randomized trial undertaken by the NCIC genitourinary site group up to that time. The study randomized patients with PSA failure to eight months of ADT followed by resumption of therapy when PSA reached 10 vs. lifelong ADT, with an overall survival (OS) endpoint. This study received four sources of funding! The National Cancer Institute of Canada (NCIC) paid a modest per-patient stipend. The study mandated two-month Suprefact, a popular LHRH agonist at the time, made by Hoechst Marion Roussel. The company agreed to provide considerable per-patient financial support based on the anticipated increase in the use of Suprefact in this large population. The study became an intergroup trial, supported by the Southwest Oncology Group (SWOG) and the United Kingdom Co-ordinating Committee on Cancer Research (UKCCR), which resulted in additional per-case funding from the U.S. Clinical Trials Evaluative Program. Finally, one of the principal investigators (myself) obtained funding from the NCIC to establish a serum biobank for correlative science studies on the cohort. The 'extra' revenue from this trial was substantial and provided a major financial boost to the nascent Canadian Urologic Oncology Group (CUOG) group.

PR7 opened in 1998. The PSA threshold for patient eligibility was initially set at 6. Initially, Canadian participation was brisk, but SWOG accrual was slow. The American investigators explained that, "Americans insist on treatment for their PSA recurrence; they won't wait until it reaches a level of 6." (There was absolutely no evidence at the time that early initiation of ADT was of benefit.) However, to enhance U.S. participation, the PSA threshold was dropped to 3. In retrospect, what was driving Americans to initiate ADT so early was the huge profits physicians made purchasing the LHRH agonist drugs wholesale and billing Medicare for the retail cost. Congress put a stop to this practice around 2004. Physician profits from administering ADT disappeared, and somehow the insistence by patients that they initiate ADT for barely detectable levels of PSA vanished overnight!

PR7 accrued 1436 patients and reported in the *New England Journal of Medicine* in 2012.[10] It demonstrated non-inferiority of intermittent to continuous ADT therapy for OS survival in the biochemical failure population. There were non-significant trends to more prostate cancer deaths in the intermittent arm and more other-cause deaths in the continuous arm (p=0.23). The difference cancelled each other out with respect to OS. Somewhat disappointingly, no benefit of intermittent therapy in prolonging time to androgen independence (the Bruchovsky hypothesis) was observed.

SWOG 9346, a similar sized trial in men with metastatic prostate cancer, reported about a year later.[11] The results of this study were less clear. There was a 10% difference in mortality favoring the continuous arm, but this did not reach significance. Further, the confidence limits

crossed both unity and the pre-determined non-inferiority margin. Non-inferiority studies whose confidence limits cross both of these lines are, by definition, inconclusive; non-inferiority can not be proved or disproved, nor can superiority of either arm be ruled out.[12] This interpretation was disputed by the authors, and the discussion section of the *New England Journal of Medicine* manuscript reveals this disagreement. Nonetheless, the article states clearly, "Results were inconclusive."

There are three reasons for the ongoing controversy regarding IADT: 1) the benefit is greater in men with non-metastatic disease (i.e., PSA failure), but the use of IADT in metastatic disease is often conflated with non-metastatic patients; 2) the interpretation of non-inferiority trials is confusing and can be counterintuitive (e.g., a trial may fail to disprove non-inferiority, a triple negative); and 3) clinical trials impose an inflexible approach to treatment (for the sake of homogeneity and data interpretation) that does not reflect the reality of an individualized approach to patients (e.g., patients with metastatic disease whose PSA nadirs to <0.2 after six months of ADT enjoy prolonged survival (>6 years) and may benefit from IADT, whereas those with a less vigorous PSA response will not).

The benefit of intermittent therapy is considerable when the indication for ADT is biochemical failure without bone metastases. These patients have a much longer median survival (10–15 years vs. 3–5 years) and a much more durable response to ADT. They have a longer off-treatment interval. PR7 was the only study confined to patients with non-metastatic disease and showed absolutely no difference in OS. IADT for PSA failure is non-inferior to continuous lifelong therapy with respect to survival, offers significant QOL benefits, and is a standard of care in Canada.

Patients with bone metastases have a shorter life expectancy, a shorter off-treatment duration, and therefore, on average, less benefit of intermittent therapy. Further, in 2020, most of these patients receive an ARAT or chemotherapy. In selected patients, IADT may still have a role. For example, patients treated with the CHAARTED regimen of six months of docetaxel and ADT who have a complete biochemical response (PSA <0.2) may have a prolonged off-treatment interval, and the QOL benefits of discontinuing ADT in these patients is appealing.

Cost reduction is also an attractive component of intermittent therapy. LHRH agonists and antagonists cost $300–400 per month. Because they are widely used compared to most cancer drugs, they represent a major piece of the oncology drug budget in most cancer programs. The appeal of a reduction in drug requirements with attendant cost savings is obvious.[13]

More recently, several national randomized clinical trials testing different nuances of IADT have been carried out in Canada by the Canadian Urology Research Consortium (CURC). The use of a 5-alpha reductase inhibitor (5-ARI) in the off-treatment interval, to modify the impact of recovering dihydrotestosterone (DHT) on disease progression, made perfect theoretical sense. However, a randomized study of dutasteride vs. placebo in the off-treatment interval showed no benefit; in fact, the recovery of PSA occurred more rapidly in the 5-ARI group.[14] Based on current evidence, 5-ARIs should not be used in the off-treatment interval.

The duration of ADT induction in randomized trials varied from three months (SEUG study) to one year. This duration was chosen empirically and had never been tested. A randomized study of 4 vs. 10 months of degarelix showed no difference in the duration of the off-treatment interval or of PSA recovery.[15] The implication is that in men initiating IADT, the ADT should be administered until PSA reaches <0.2 and then discontinued. This may require as little as three months of induction ADT.

Finally, the serum bank established on the PR7 patients has resulted in many correlative science studies, including an analysis of the importance of testosterone levels in men on ADT. This study, on the men in the continuous arm of PR7, clearly showed that men with testosterone below 0.7 nM/dl while on treatment had an improved outcome compared to those with higher levels.[16] Another collaborative study of the predictive value of other androgens and estrogens showed that failure to suppress estradiol also predicted for a more rapid time to progression.[17,18] The observation, now widely accepted,[19] that in men on ADT the testosterone level should be below 0.7 nM presents a potential conundrum; if low testosterone is better, how can IADT be acceptable, since the testosterone rises predictably in the off-treatment interval? The solution, which has many parallels in other areas of cancer therapy, is that while hitting the cells harder (i.e., achieving lower testosterone) results in a better outcome, this does not imply that therapy must be continuous.[20]

What are the implications of all these studies for clinical practice? Patients starting ADT should receive an induction course of 3–9 months (i.e., until PSA <0.2). For maximal effect, this should consist of combined androgen blockade. Those who fail to reduce PSA below 0.2–0.4 should be maintained on treatment. Those who achieve a PSA response to low levels should have a trial of discontinuing therapy. Those who have a short off-treatment interval (<6 months before rise in PSA to >5) should return to continuous therapy. The failure to achieve a low nadir PSA should preclude intermittent therapy. Similarly, patients with bulky tumors, significant burden of nodal and bone metastases, hepatic metastases, PSA >100, rapidly rising PSA (>5 ng/mL per month), or persistent pain from bone metastases are poor candidates for IADT.

This approach will result in most patients with non-metastatic disease being maintained on intermittent treatment,

with the expectation that they will be off therapy about 75% of the time. Some will have very prolonged off-treatment intervals. A subset of patients with metastatic disease will also benefit from a long off-treatment interval.

On a personal note, the IADT story has been a continuous motif throughout my career, from the first IADT publication as a MSKCC fellow in 1986 to an investigator-initiated trial published in 2018 and even more recent correlative science studies. There are still many more studies to do (for example, the role of intermittent ARATs). I've been very fortunate to have this consistent research thread for most of my professional life.

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