Intermittent versus continuous androgen suppression therapy: do we have consensus yet?

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ABSTRACT

Androgen deprivation therapy (ADT) has been a cornerstone in the management of advanced prostate cancer for more than 50 years, but several aspects of the therapy remain controversial. Research since the mid-1980s has looked at the use of intermittent androgen suppression (IAS) as a way to reduce the side effects and costs of continuous androgen suppression. During that same time, testing for prostate-specific antigen resulted in forward stage migration both at diagnosis and at the time of treatment initiation. Earlier treatment has led to prolonged periods of ADT and increasing recognition of the resultant metabolic complications. With preclinical evidence suggesting a potential benefit for IAS in terms of time to androgen independence, with phase II and III studies producing optimistic results, and with the potential for reductions in cost and complications, IAS has become a popular modality of therapy around the globe. Large prospective randomized studies, currently ongoing, will ultimately determine the legitimate place of IAS in the treatment of prostate cancer.

KEY WORDS

Prostate cancer, androgen deprivation therapy, intermittent androgen therapy, continuous androgen deprivation, hormone therapy

1. INTRODUCTION

Huggins and Hodges first established the role of androgen deprivation therapy (ADT) in prostate cancer (PCa) in the early 1940s [1], resulting in the award of the 1966 Nobel Prize in Physiology or Medicine. They demonstrated that, in a patient with advanced PCa, surgical castration delayed tumour progression. Soon thereafter, it was learned that administration of estrogens, with central suppression of luteinizing hormone releasing hormone (LHRH) and peripheral production of testosterone, was an equally effective form of hormonal therapy. A number of topics have been intensely debated within the management of PCa, none more so than the benefits and disadvantages of "early" initiation of ADT.

A strong body of evidence shows that early ADT indeed has a small but significant survival advantage over delayed ADT. Also significant is the delay in time to progression that early ADT provides, allowing PCa patients to avoid complications such as obstructive voiding symptoms, obstructive renal failure, and pain. The "cost" to the patient for the use of early therapy has been the well-established long-term side effects of ADT, including sexual dysfunction, cognitive changes, lethargy, bone demineralization, and metabolic syndrome. Extending the debate, the concept of intermittent androgen suppression (IAS) has arisen as an intriguing means of balancing efficacy with the long-term consequences of continuous androgen suppression (CAS). The disadvantages of ADT have led researchers to search for strategies to reduce negative treatment effects and to improve outcomes. Intermittent androgen suppression seems to be emerging as one such strategy.

The first clinical report of the use of IAS was authored by Klotz *et al.* [2] in 1986. They reported that withdrawal of diethylstilbestrol from patients with metastatic PCa after initial clinical response led to a reduction in the side effects experienced by the patients, without any obvious adverse outcome. Treatment was reinitiated after the patients became symptomatic again, and all patients experienced a rapid clinical response to treatment.

After that initial report, many preclinical and clinical studies—including a number of randomized controlled trials (RCTs)—were completed, and mounting evidence suggests that IAS is not inferior to continuous therapy and has advantages with respect to side effects, quality of life, and economics. In this review paper, we reflect on the key biologic and clinical evidence, and we suggest some practical conclusions that can be drawn from the currently available data and applied to everyday clinical practice. We also outline new research directions associated with the IAS concept.

2. DISCUSSION

2.1 Preclinical Evidence

In androgen-dependent cancers, for reasons that remain unknown, the cell death process induced by androgen ablation fails to eliminate the entire malignant cell population and facilitates progression to an androgen-independent state. The androgen-dependent Shionogi mammary carcinoma responds to androgen ablation in a manner strongly reminiscent of human PCa [3]. In the Shionogi model, So *et al.* demonstrated that progression to androgen independence was proportional to both the initial tumour volume and the delay in time to castration [4], suggesting that early initiation of ADT may be advantageous.

In a preclinical study of IAS in the Shionogi model, Bruchovsky *et al.* quantitated the proportion of androgen-dependent and -independent tumorigenic stem cells present in the pre- and post-castration animals. They demonstrated that castration resulted in a significant enrichment in androgen-independent stem cells, which arose from a small number of pre-existing androgen-dependent stem cells adapting to an altered hormone environment [5]. The concept of IAS was thus based on the hypothesis that the incremental replacement of androgens, even in small amounts, would modulate gene expression in tumour cells surviving androgen withdrawal, driving them into a normal pathway of differentiation (not possible in an androgen-poor milieu) in which the risk of progression is small and apoptotic potential is restored. Thus, the stage would be set for a repeat response to androgen withdrawal, possibly delaying progression to androgen independence.

Akakura *et al.* [3] demonstrated that cycling of androgen suppression indeed led to a prolongation of the time to androgen independence in the Shionogi mouse model. Repeated cycles of castration and transplantation to intact mice resulted in a prolongation in the time that it took to observe androgen-independent tumour growth (147 days vs. 51 days). Those results have been observed with other animal tumour systems as well, and taken together, they suggest a delay in the development of androgen independence—and a potential prolongation in survival—with the cycling of androgen withdrawal.

2.2 Clinical Support for IAS

2.2.1 Phase II Studies

A number of phase II trials in IAS have been completed [6–15]. These trials have demonstrated the safety of IAS and have been positive enough to proceed to prospective randomized studies.

In the mid-1980s, the availability of reversible agents for medical castration made it possible to alternate periods of treatment and nontreatment in a patient. Furthermore, serial serum PSA measurements permitted accurate monitoring of disease activity and served as trigger points for stopping and restarting therapy. Those advances prompted Goldenberg and colleagues [9] to proceed with a phase II study of IAS. In their landmark first publication, 47 patients [clinical stages D2 (n = 14), D1 (n = 10), C (n = 19), B2 (n = 2), A2 (n = 2)] were treated with cyproterone acetate and diethylstilbestrol or with LHRH analogues, or both. After at least 6 months of therapy, treatment was interrupted if serum PSA had reached a stable nadir below 4 ng/mL, and therapy was later reintroduced when serum PSA increased to a mean value between 10 ng/mL and 20 ng/mL.

In a follow-up publication of this phase II trial [16], 87 patients were enrolled, 50 of whom had been followed for a minimum of 3 years. The total time on trial ranged from 40 months to 126 months (mean: 65.5 months). During the off-treatment periods, the patients reported improvement in wellbeing and recovery of libido and erectile function. In the patients with lower stages and grades of disease, there was a trend toward faster attainment of PSA nadir and longer periods off therapy. Patients in this group were cycled from 1 to 5 times before androgen independence became apparent, at times ranging from 15 months to 57 months. Of the 87 patients, 23 progressed to androgen independence at a median of 32 months into treatment, and 13 cancer-specific deaths occurred at a median of 48 months. The data for time to progression and overall survival provided by IAS were comparable with (and perhaps even better than) those for historical controls treated with continuous androgen withdrawal. Nevertheless, the fact that 23 patients progressed to androgen-independent cancer states emphasized the point that androgen withdrawal as a single modality, and by any mode of delivery, is unlikely to cure advanced PCa.

A meta-analysis of the phase II trials [17] and a systemic review [18] have been recently published. The meta-analysis by Shaw *et al.* [17] included 1446 men participating in 10 phase II studies from around the world. The stated aims of the analysis were to "develop models predicting the success in IHT [intermittent hormone therapy] and thereby identify features of IHT protocols to be the focus of future prospective trials and to evaluate the use of time off treatment as a surrogate predictor of survival for use in future IHT trials." Factors that were found to have an impact on outcome were the initial PSA level, the PSA nadir reached during the initial cycle, and the type and duration of medication used. Anti-androgen monotherapy appeared to result in inferior outcomes in metastatic cancer, but not in radiotherapy or surgery failures—a finding that is consistent with previous studies. A low PSA nadir was a good predictor of overall outcome in terms both of survival and of time off therapy. The overall percentage of time off therapy in the meta-analysis was 39%. In an excellent systematic review, Abrahamsson concluded that IAS is at least as effective as combined androgen blockade (CAB)

and has improved tolerability over CAB, especially in terms of sexual potency [18]. Abrahamsson made the point that available data cannot support IAS as having impact on quality of life and some of the long-term complications of CAB.

2.2.2 Phase III Studies

A large RCT from the Southern European Uroncological Group [19] enrolled 766 patients and randomized 626 with locally advanced or metastatic PCa. The induction phase of the trial was only 3 months, after which patients were randomized either to continuous LHRH and cyproterone acetate treatment or to intermittent therapy. Patients who did not achieve a PSA nadir below 4 ng/mL or an 80% reduction in pre-treatment PSA were not randomized. In the IAS arm, retreatment triggers depended on the PSA responses. For men who achieved a PSA below 4 ng/mL, the next cycle began when PSA rose to more than 10 ng/mL (for symptomatic patients) or more than 20 ng/mL (for asymptomatic patients). There was no difference in overall survival between CAS and IAS. Side effects such as gynecomastia, hot flashes, headaches, and skin complaints were reported less frequently in the intermittent group. There were significantly fewer problems with, and higher reported frequency of, sexual activity in the intermittent group. At 15 months after randomization, 28% in the intermittent arm and 10% in the continuous arm reported sexual activity in the preceding month.

In 2007, the Cochrane group reported a systematic review of five RCTs [20]. Limited survival data made it difficult for the authors to draw conclusions about the role of IAS in the treatment of PCa, and they recommended further research. Currently, two ongoing large phase III trials have completed accrual. The RCT PR7 by the National Cancer Institute of Canada (NCIC) is being conducted in the setting of biochemical recurrence after radiotherapy for localized PCa. Patients (n = 1386) were randomized to continuous androgen suppression or to IAS. The primary endpoint is overall survival, but secondary endpoints include quality of life, time to androgen independence, time off therapy, and time to testosterone recovery. The Southwest Oncology Group (SWOG) 9346 trial (NCIC PR8) is a large RCT involving 1500 patients with newly diagnosed metastatic PCa randomized to either continuous or intermittent androgen ablation after an induction course of combined androgen deprivation for 7 months. The primary endpoints of that study are survival rates and quality of life. The results of these definitive studies are keenly awaited and, hopefully, will provide further evidence to define treatment strategies for patients with PCa.

2.3 Future Directions in IAS

In a limited pilot experience in patients treated on an intermittent protocol, Bruchovsky *et al.* [21] used finasteride during the off-treatment interval to prolong the time off treatment. Those authors reported that the duration of the off-treatment interval was approximately doubled in patients treated with finasteride after discontinuation of LHRH analogue. In this small series, non-adjusted PSA was used as the trigger for re-treatment. Patients being re-treated after biochemical progression on finasteride continued to respond to LHRH analogue during the next treatment cycle.

Retrospective data from Scholz *et al.* [22] in 2006 showed that the use of finasteride doubled the length of the off-treatment period. The hypothesis that 5α-reductase inhibitors may prolong the "off cycle" of IAS and therefore improve quality of life is being tested in a Canadian RCT (AVIAS/DUT 104923). This multicentre double-blinded study is comparing dutasteride 0.5 mg daily with placebo in men receiving intermittent androgen ablation therapy for PCa.

3. SUMMARY

As a treatment option, IAS has been embraced by urologists, oncologists, and the general public. There is ample phase II evidence that IAS is "non-inferior" to continuous androgen ablation in terms of time to progression and overall survival, and evidence is accumulating to suggest that IAS offers significant quality-of-life benefits, particularly with regard to sexual function during the off-treatment phase. In the current climate of health care cost containment, IAS represents significant savings, in terms both of reduced medication needs and of reduced costs for managing the complications of prolonged CAS.

Current evidence has led to the endorsement of IAS by a few professional bodies. The European Association of Urology 2009 guidelines on PCa state that "IAD [intermittent androgen deprivation] is currently widely offered to patients with PCa in various clinical settings, and its status should no longer be regarded as investigational" [23]. The U.K. National Institute for Health and Clinical Excellence recommends that IAS be offered as a first-line hormonal therapy option to men with newly diagnosed or relapsing metastatic cancer, provided they are aware of the therapy's unproven status [24]. The American Urological Association has yet to acknowledge IAS in its treatment guidelines.

In the near future, data from the two ongoing multicentre RCTs (NCIC PR7 and SWOG 9346) will provide answers to some of the questions that remain, particularly with regard to the quality-of-life benefits of IAS over continuous ADT and whether IAS has a role in the prevention of the long-term complications of continuous ADT. Unless data suggest otherwise, IAS has earned its place as a treatment strategy in the management of PCa, particularly in men with locally advanced disease and those with recurrence after definitive therapy in whom quality of life is a priority.

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