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Platinum Priority – Collaborative Review – Prostate Cancer

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Intermittent Androgen-deprivation Therapy in Prostate Cancer: A Critical Review Focused on Phase 3 Trials

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Abstract

Context: Intermittent androgen deprivation (IAD) in prostate cancer (PCa) patients has been proposed to delay development of castration resistance and to reduce the side effects and costs of androgen deprivation therapy (ADT).
Objective: This review analyzes (1) the oncologic and quality of life (QoL) results from randomized phase 3 trials comparing IAD and continuous ADT and (2) the prognostic parameters for IAD.
Evidence acquisition: We searched the Medline and Cochrane Library databases (primary fields: *prostate neoplasm* and *intermittent androgen deprivation*; secondary fields: *randomized trials, survival, quality of life, predictors*) without language restriction.
Evidence synthesis: We found seven extensively described phase 3 trials randomizing 4675 patients to IAD versus continuous ADT. Other randomized trials investigating IAD have been performed, but available data are limited and have been published only in preliminary fashion. In all seven trials, patients spent most of their time on, rather than off, ADT. The induction periods ranged from 3 mo to 8 mo; in all but one trial, the PSA level designated for ADT discontinuation was <4 ng/ml. Mean follow-up ranged from 40–108 mo. Collectively, these trials support the concept that, mainly in metastatic cases, IAD can produce oncologic results similar to continuous ADT. In terms of overall survival, the hazard ratios for IAD and continuous ADT were very similar (range: 0.98–1.08). The QoL benefit of IAD appears to be modest at best. With IAD, QoL is likely influenced by the duration of the off-treatment periods and by the rate of testosterone recovery.
Conclusions: The evidence indicates that IAD is not inferior to continuous ADT. Data are insufficient to determine whether IAD is able to prevent the long-term complications of ADT. More comparative analysis focused on QoL is warranted.

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1. Introduction

1.1. Definition and rationale

The definition and strategy of intermittent androgen deprivation (IAD) is to alternate androgen blockade (*on* phases) with treatment cessation (*off* phases), allowing androgen recovery between treatment periods [1]. The first clinical report of IAD was in a group of patients treated with diethylstilbestrol in the era before prostate-specific antigen (PSA) screening, with re-emergence of bone pain as the indication for resuming treatment [2]. IAD was subsequently hypothesized to delay the time to tumor progression due to castration-induced resistance and to reduce side effects related to androgen deprivation therapy (ADT) [3,4]. The concept has been supported by experimental models (Shionogi model, LNCaP cell lines) based on a different castration effect on immature stem cells or mature PCa cells [4,5]. In a murine mammary model, Akakura et al. [6] showed that time to progression in an androgen-sensitive tumor model was increased three-fold with IAD when compared with continuous ADT. In human patients with advanced PCa, a single-center randomized clinical trial showed that the intermittent administration of ADT can significantly reduce the increase in serum chromogranin A as a marker of neuroendocrine differentiation when compared with continuous administration of ADT [7].

A possible benefit of IAD is the preservation of quality of life (QoL) in off-treatment periods through the intermittent regulation of testosterone [1,3]. An appealing advantage of IAD is decreased treatment cost for both the patient and the health care system [1].

1.2. Indications and modalities

IAD has been investigated as an alternative to continuous ADT in several phase 2 and randomized phase 3 studies in patients with locally advanced or metastatic PCa [8–15]. IAD has been also tested in men with biochemical failure after radical prostatectomy (RP) or radiation therapy (RT) [13,16]. Table 1 shows some key points from the European Association of Urology (EAU) guidelines [17] that must be considered.

The majority of IAD clinical studies have emphasized the need to monitor testosterone levels of patients using IAD [18]. However, surveys have demonstrated that a minority of clinicians regularly monitor serum testosterone in clinical practice [19]: In one study, only 3% of subjects always measured serum testosterone, 21% did so at least once, 50% measured testosterone only in the event of a PSA rise, and 26% never measured testosterone level. The decision to resume therapy during IAD is based on PSA levels rather than on testosterone levels [20].

Some studies proposed to analyze the duration of the off-treatment interval using agents during the off-treatment interval including finasteride, cyclooxygenase inhibitors, and thalidomide [21–23]. None of these studies was designed to demonstrate a survival advantage.

1.3. Aim

In this review, we analyzed the oncologic and QoL results from randomized multicenter studies comparing IAD with continuous ADT and the prognostic parameters for IAD from clinical trials.

2. Evidence acquisition

We searched the Medline and Cochrane Library databases (inclusion criteria: primary fields were *prostate neoplasm* and *intermittent androgen deprivation*; secondary fields were *randomized trials, survival, quality of life, predictors*) for the literature of the last 10 yr. Original articles were included and reviewed; review articles, editorials, and letters to the editor have been included only if deemed to contain relevant information; and abstracts from trials (2010–2012) were used to complete and ensure current information. We started with 102 articles and ultimately selected 39 articles. For the studies, we critically evaluated the level of evidence (LOE) according to the grade of evidence from the Oxford Center for Evidence-based Medicine [24].

3. Evidence synthesis

3.1. Oncologic results in randomized trials

Several phase 2 trials demonstrated the feasibility of IAD in metastatic or biochemically recurrent disease [1,25]. However, as also stated by international guidelines,

Table 1 – Key points on the use of intermittent androgen deprivation from the European Association of Urology guidelines [17]

Key point	Suggestion
Drugs	IAD is based on the concept of intermittent castration; therefore, only drugs leading to castration should be considered.
Induction period	The duration of the initial (induction) cycle of ADT is a crucial point, and it must last between 3 mo and 9 mo.
On phase stopped	The on phase with ADT is stopped only if patients have no evidence of clinical progression and a clear PSA response, empirically defined as a PSA level <4 ng/ml in advanced PCa cases or 0.5 ng/ml in biochemically relapsing patients.
On phase resumed	The on cycle with ADT is resumed when there is either clinical progression (imaging studies) or PSA progression over a predetermined empirical cut-off value (mainly, 4–10 ng/ml in nonmetastatic PCa and 10–15 ng/ml in metastatic PCa). The new on cycle is continued as the induction cycle for at least 3–6 mo, depending on the time to reach a new PSA nadir.
Follow-up	Patients under IAD should be strictly followed (more than cases under continuous ADT and particularly during the off phases) with clinical examinations every 3–6 mo and with PSA and testosterone measurements.

IAD = intermittent androgen deprivation; ADT = androgen-deprivation therapy; PSA = prostate-specific antigen; PCa = prostate cancer.