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Intermittent androgen deprivation in prostate cancer cases with biochemical progression after radical prostatectomy: Are we ready to treat?

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ABSTRACT

Purpose: To evaluate clinical data from published trials on the use of intermittent androgen deprivation (IAD) therapy in patients with biochemical relapse after radical prostatectomy (RP).
Methods: We searched the Medline and Cochrane Library databases for literature published on IAD and biochemical progression after radical prostatectomy.
Results: To date, we have oncological and functional data from phase 3 studies focused on metastatic and locally advanced stages that confirmed IAD as a valid option treatment. For the aim of this review, only Tunn study, was specifically focused on patients who relapsed after surgery but clear and mature results are still missed.
Conclusions: The use of IAD in cases who relapse after RP is common in the clinical practice. Although specific recommendation on the use of IAD in this setting of patients are not available, we concluded that the real benefit of IAD in terms of long survival and quality of life is mainly for patients treated with surgery.

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1. Introduction

Intermittent Androgen Deprivation (IAD) consists of an alternate androgen blockade (on-phase therapy) with treatment cessation (off-phase therapy), which allows for a restoration of testosterone between treatment periods (Chengalvala et al., 2003; Chen and Petrylak, 2004; Higano, 2006).

IAD has been found to have two purposes: to delay the time to tumor progression due to castration-induced resistance and to reduce the side effects related to androgen deprivation therapy (ADT) (Heidenreich et al., 2013; Bruchovsky et al., 1990).

The rate of diagnosis of prostate cancer (PCa) is increasing in younger men (40–60 years of age) (Siegel et al., 2014) and hormonal therapy is now mainly used as continuous regime in advanced and metastatic cases; thus a great interest has been shown for the hypothesis of IAD. One of the first pieces of evidence of the effects of androgen suppression was derived from a preclinical study by Bruchovsky et al. (1990) who observed a change in stem cell phenotype from an androgen-dependent state to an androgen independent state after androgen suppression. The cessation of androgen deprivation prior to this change seems to be the rationale for IAD. In another preclinical study that used a murine model, Akakura et al. (1993) showed that the time to progression in an androgen-sensitive tumor model was increased 3-fold with IAD compared with continuous androgen deprivation therapy (ADT).

The way in which to design a correct schema of IAD is now more clear: the first cycle of ADT (the "induction" phase), which represents a crucial point in IAD therapy, is continued (mainly 6–9 months in clinical trials) until the prostate specific antigen (PSA) level reaches a nadir (a value that depends on PCa cases); then, this therapy is discontinued (off-phase), which allows the testosterone level to return to normal. The on-phase therapy is resumed when the PSA rises to a predetermined level (a value that depends on PCa characteristics) or when signs of clinical progression are evident. In Table 1, we reviewed the key points on the use of IAD in different populations of patients according to the European Association of Urology guidelines (EAU).

1.1. Clinical trials on IAD

IAD has been recently investigated as a valid alternative to continuous ADT in several phase 2 and 3 studies in different populations of patients: those with locally advanced, metastatic and recurrent prostate cancer after primary treatment (radiotherapy or radical prostatectomy). It is evident that the correct use of IAD and the follow-up depend on the tumor characteristics and the treatment used.

Recent results from randomized phase 3 clinical trials have established that IAD is a valid approach that should be considered as a standard of care in most patients with locally advanced and metastatic disease (Heidenreich et al., 2013). For the subset of metastatic patients, contrasting data are available from randomized studies: Hussain et al. (2013) observed a large cohort of 1535 patients with metastatic disease. This study was inconclusive from a statistical point of view (HR 1.10; 95% CI, 0.97–1.25, $p = 0.25$) and therefore it did not demonstrate the inferiority or non inferiority of IAD to continuous ADT. However, the overall survival results were better in the continuous therapy group (5.8 years in the continuous-therapy group as compared with 5.1 years in the intermittent-therapy group). Salonen et al. (2012) showed no statistically significant differences between IAD and continuous ADT in terms of time to progression (IAD: 34.5 months vs continuous ADT: 30.2 months, HR: 1.08) and overall survival (IAD: 45.2 months vs continuous ADT: 45.7, HR: 1.15) in a cohort of 554 men with locally advanced or metastatic PCa. In the SEUG 9401 trial (Calais da Silva et al., 2009). the analysis of a mixed population of 766 patients with non metastatic and metastatic PCa demonstrated that the time to progression was slightly longer in the continuous arm (HR: 0.81 in favor of continuous ADT, $p = 0.11$) than in the IAD arm with no significant difference in the overall survival (IAD: 54.1% dead vs continuous ADT: 54.2% dead, HR: 0.99, $p = 0.84$). In these studies, patients who were treated with IAD had often a better overall quality of life (QoL) and a reduced frequency of side effects.

For the subset of patients with biochemical relapse (BR) after primary treatment (radiotherapy or radical prostatectomy (RP)), the data are still lacking. Only Crook et al. (2012) enrolled a homogeneous group of 1386 patients with BR after radiotherapy and concluded that IAD was not inferior to continuous therapy with regards to the time to progression and overall survival (HR for death 1.02; 95% CI: 0.86–1.21). Phase 3 trials that have exclusively investigated biochemical recurrence after RP are currently lacking. In Table 2, we briefly present data from all phase 3 trials on the use of IAD in different populations: those with locally advanced, metastatic and recurrent prostate cancer after primary treatment.

1.2. International guidelines and IAD

Table 3 presents a summary of what the international guidelines currently recommend in regard to the use of IAD.

Only EAU guidelines are updated to 2015 for IAD. They consider IAD as a treatment that should be offered to patients with PCa on the basis of phase 3 clinical trials results. Currently, no standardized indications exist about the use of IAD in different populations of patients (i.e., those with metastatic, locally advanced and clinical progression after primary treatment).

2. Aim and methods

In contrast to other available reviews, our review analyzes the oncological and functional results from phase 2 and 3 studies specifically in patients with biochemical recurrence (BR) after radical prostatectomy (RP). This setting most likely has less experimental and clinical trials evidence, but it has a higher use in clinical practice.

2.1. Evidence acquisition

We searched the Medline and Cochrane Library databases (inclusion criteria: primary fields were prostate neoplasm and intermittent androgen deprivation therapy; secondary fields were biochemical recurrence, randomized and nonrandomized trials, and overall survival) for literature published without time limits. We included and reviewed original articles, clinical trials and reviews. In addition, abstracts from trials when the trials were not available online were used to ensure that the information was complete and current. There were no restrictions on the basis of years and language, but we included only clinical trials conducted in humans.

3. IAD for biochemical progression after radical prostatectomy: the rationale

The selection of patients for IAD is considered the crucial point for the utilization of this treatment option. Two systematic reviews (Abrahamsson, 2010; Klotz, 2013) analyzed data regarding the rationale of the use of IAD in patients with different tumor stages. The real benefits that IAD offers to patients involve quality of life (through a reduction in the side-effects and co morbidities related of testosterone reduction during the off-phase treatment periods) and costs (a reduction in the duration of treatment). Based on these considerations, we can hypothesis that the patients who can really