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Review

Intermittent androgen deprivation therapy in patients with prostate cancer: Connecting the dots

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Abstract Intermittent androgen deprivation therapy (IADT) is now being increasingly opted by the treating physicians and patients with prostate cancer. The most common reason driving this is the availability of an off-treatment period to the patients that provides some relief from treatment-related side-effects, and reduced treatment costs. IADT may also delay the progression to castration-resistant prostate cancer. However, the use of IADT in the setting of prostate cancer has not been strongly substantiated by data from clinical trials. Multiple factors seem to contribute towards this inadequacy of supportive data for the use of IADT in patients with prostate cancer, e.g., population characteristics (both demographic and clinical), study design, treatment regimen, on- and off-treatment criteria, duration of active treatment, endpoints, and analysis. The present review article focuses on seven clinical trials that evaluated the efficacy of IADT *vs.* continuous androgen deprivation therapy for the treatment of prostate cancer. The results from these clinical trials have been discussed in light of the factors that may impact the treatment outcomes, especially the disease (tumor) burden. Based on evidence, potential candidate population for IADT has been suggested along with recommendations for the use of IADT in patients with prostate cancer.

1. Introduction

Intermittent androgen deprivation therapy (IADT) has found its way to clinics despite weak evidence of its clear superiority or non-inferiority over continuous androgen deprivation therapy (CADT). The main reasons for preferring IADT over CADT are reduced short- and long-term side-effects of androgen deprivation therapy (ADT) such as compromised sexual functioning, increased risk from cardiovascular diseases and diabetes, osteoporosis, loss of

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muscle mass, weight gain, cognitive decline, fatigue, depression, and hot flushes [1,2]. These side-effects tend to significantly impact the health-related quality of life (HRQoL) in patients undergoing CADT [3–7]. In addition, IADT offers an off-treatment period, which may provide a clinically meaningful relief from these side-effects, thereby improving the HRQoL and treatment compliance [8], and reducing the treatment costs. Most importantly, it is believed that IADT delays the progression to castration-resistant prostate cancer (CRPC), which is thought to begin early after treatment initiation [9,10]. However, stopping ADT prior to progression to CRPC should restore apoptotic potential and retain sensitivity to treatment re-initiation [11–13].

Data from phase 2 and phase 3 studies have shown that IADT may improve the tolerability of the treatment; however, the efficacy may be similar to CADT. Based on these findings, guidelines for the treatment of prostate cancer suggest that IADT may be no longer considered an experimental therapy [14]. Further, it is also noted that not all patients benefit from IADT [15]. Patients with non-metastatic cancer, without bone metastases, with cancer restricted to lymph nodes, and those with local or biochemical failure following radiotherapy are possibly good candidates for IADT [16,17]. On the other hand, patients with large tumors, multiple metastases, and prostate-specific antigen (PSA) levels >100 ng/mL do not have a good prognosis with IADT [18,19], mainly due to a shorter life expectancy and a shorter off-treatment period.

Considering the focus on IADT and data from published studies, it is important to understand different aspects of IADT, mainly, IADT regimen, patients who would benefit from IADT, and the factors governing treatment outcome. Other decision pointers could be the age and medical history of patient. However, studies done until now with IADT constitute mixed populations rather than pure cohorts (non-metastatic, metastatic, and locally advanced), and have variable study designs.

The present systematic review was undertaken to identify these aspects, and weigh the benefits and risks in patients with prostate cancer undergoing IADT. These aspects are discussed in the light of tumor burden, study design, study populations, study endpoints and their analyses, and guidelines for IADT issued by different societies (Table 1).

Table 1 IADT guidelines.

Guideline	Recommendation
AUA 2007 update	• IADT not being discussed
ASCO 2007 update	• More studies with longer follow-up and with larger patient cohorts are needed to determine the impact of IADT
EAU 2015	• IADT could maintain QoL in off-treatment periods and is significantly associated with lower treatment costs • IADT may provide an option for patients in metastatic stage
NCCN 2015	• IADT could reduce side-effects and may improve QoL, however, the benefits are unclear

IADT, intermittent androgen deprivation therapy; QoL, quality of life.

2. Methods

This systematic review includes seven studies, namely JPR.7, SEUG 9401, SEUG 9901, TAP 22, Finn Prostate, TULP, and SWOG 9346 [17,20–25]. All these are phase 3 studies that compared IADT with CADT. The eligibility criteria for studies to be included were a primary endpoint of survival or progression. Retrospective and single arm studies were not included. Besides these seven studies, there were few other studies comparing IADT and CADT for which we have listed the methods/results in Table 2 [16,26–34].

Data for median on- and off-treatment periods, post-treatment PSA levels (progression), overall survival (OS), progression-free survival, quality of life (QoL), adverse events (AEs), and testosterone recovery were presented here in a clear and consistent manner. The results were discussed after considering all the factors that may impact the treatment outcomes, especially the disease (tumor) burden. Based on evidence, potential candidate population for IADT was suggested and suitable recommendations for the use of IADT in patients with prostate cancer have been discussed.

3. Results

3.1. Study designs

Study design is the first challenge in IADT set-up, bringing in a large variability at the very first stage of conceptualization. A non-inferiority design is the best fit for comparing CADT with IADT, considering the ethical challenges with classical placebo-controlled trials in such patients. However, practically it is challenging as non-inferiority designs often require a larger sample size as compared with the superiority studies, putting a huge constraint on enrollment and execution of these studies. Another gap in non-inferiority studies is the lack of consensus on the non-inferiority margin for key outcomes, i.e., OS and progression-free survival.

Of the seven studies included in this review, three were non-inferiority studies (JPR.7 [17], SEUG 9901 [21], and SWOG 9346 [25]), and four were superiority studies (SEUG 9401 [20], Finn Prostate [23], TAP 22 [22], TULP [24]) and all studies compared CADT with IADT. All but one study included patients with metastatic or locally advanced prostate cancer (JPR.7 [17] included non-metastatic patients). All studies except TULP [24], TAP 22 [22], and SWOG 9346 [25] included mixed populations (Table 3).

The PSA eligibility criteria were 3–5 ng/mL for JPR.7 [17], SEUG studies [20,21], and SWOG 9346 [25]. For TAP22 [22], the PSA eligibility criterion was higher (>20 ng/mL), while it was variable in Finn Prostate study [23]. PSA criteria for TULP were not available in the publication [24]. The induction period was also quite variable in these studies: 3 months in SEUG studies [20,21], 6 months in TAP