Abstract

Androgen deprivation therapy is an established therapeutic option for prostate cancer patients, but is associated with serious side effects and quality of life issues. The purpose of this review is to present up-to-date results from randomized trials on intermittent androgen deprivation therapy and to identify those patients that will benefit the most from this approach.

Introduction

Prostate cancer (PCa) constitutes today one of the most severe diseases affecting male population. It is the most common solid neoplasm, outnumbering lung and colon cancer among Europeans and the second cause of death (COD) among all cancers in males. The androgen deprivation therapy (ADT) was first described back in 1941 by Huggins and Hodges and Schally later discovered the LHRH analogues. Continuous androgen deprivation (CAD) has been established as the recommended treatment in a metastatic hormone-sensitive disease. However, despite the high rates in treatment response, gradually acquired treatment resistance demonstrated by most patients results in a mean survival of 2.5 - 3 years.

Cancer cell development is regulated by endogenous androgens (such as testosterone) and any surgical approach or medication inhibiting their development plays an important role in managing the disease. ADT remains one of the most effective palliative treatments in PCa patients. However, its extended and wide administration, gradually led to reports on systemic side effects (SEs) (Table 1). The increased worry over the identification and registry of the SEs contributed to the drawing-up of strategies, aiming to the reduction of the continuous exposure of PCa patients to ADT.

Intermittent androgen deprivation definition - theory - aims

The first intermittent androgen deprivation (IAD) report was made by Klotz et al. in 1981 on 20 metastatic patients. The patients were administered diethylstilbestrol (DES) and the treatment was ceased upon good clinical response.
Intermittent androgen deprivation therapy for prostate cancer: a review of the recent literature and guidelines p. 34 - 41

response, aiming to the reduction of SEs and quality of life (QoL) improvement. The treatment was resumed when the osseous metastases turned symptomatic again, and this first attempt of intermittent medication administration demonstrated its feasible application in clinical practice. The theoretical framework of this model emerged from studies on Shionogi mouse models by Bruchovsky. According to these studies, IAD could retard the development of androgen-resistant cancer cells. Akakura et al. later reported that progression time in androgen-resistant phase was increased by three times when on IAD compared to continuous treatment.

Medication exposure intermission (intervals, off-phase) via the testosterone restoration also aimed to a better QoL with sexual desire and potency preservation and avoidance of the rest known SEs. Despite the fact that most of the trials highlighted the need for regular monitoring of the testosterone levels when on IAD, in clinical practice, only 3% of the patients adhered to the recommendation. The decision for treatment resumption in IAD cases is, in clinical practice, solely based on PSA levels and not on testosterone.

Concluding, from the healthcare system point of view, the cost plays an important role. In a time where healthcare expenses are dramatically increasing in the developed countries and given the economic crisis, any plan that both reduces the expenses up to 50 - 75% and safeguards the therapeutic target is particularly appealing.

### Studies on IAD

From the first IAD description onwards, several studies have been reported in the international literature - more reports on phase II studies and less on phase III.

#### A. Phase II studies

In a recent review of phase II studies of the year 2010, at least 19 studies are reported. Their methodology is quite different regarding patients, PSA limits, treatment cycles duration and therapeutic scheme interruption. The number of patients was small and only five studies comprised more than 100 patients. The stage of the disease was also uncommon, with studies on localized or metastatic disease, combined localized and metastatic disease etc. PSA limit for treatment interruption in the majority of studies was <4 (10 studies) or ≤4 ng/ml. PSA limit for treatment resumption was, in the majority of the studies, ≥10 or >20 ng/ml, although some researchers had set much lower limits. Leuprolide was the medication most commonly administered.

The design of phase II studies mainly focused on safety issues and SEs. Mean treatment cycles was 3 - 4 per patient, range 1 - 12 cycles and the duration of each cycle was gradually reducing or, in the best case, remained stable. In a meta-analysis performed by Shaw et al., it was found that the median of treatment cycles was 2 per patient and the intermediate off-phase period was 15.4 months. Data on testosterone levels were available at about 60%: usually, after the first cycle, the values were restored to normal and were gradually reducing over the following cycles. The 5-year overall survival (OS) rates were estimated at 86% in males exhibiting biochemical failure, 68% in metastatic and 90% in localized disease. QoL was improved off-phase, anemia was treated in a significant number of patients and body weight (BW) was steadily preserved in the study of Malone et al. Sexual activity was improved with restoration of sexual potency in 47% of the patients whereas the male subjects studied by Sato et al. reported increased energy and sense of satisfaction in terms of social and family life.

#### B. Phase III studies - Oncologic outcomes

Many phase III studies are currently in progress but not all have published their findings and others have

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Complete androgen deprivation side effects</th>
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</table>
| A. early | -sexual function disorders (↓libido, erectile dysfunction)  
- hot flashes  
- fatigue |
| B. long-term | -anemia  
- osseous mass loss  
- metabolic disorders (↑fat, triglycerides, HDL και LDL, insulin disorders)  
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been presented only as abstracts in conferences. Our search in Medline and Cochrane Library data bases (key words: prostate cancer, intermittent androgen deprivation, randomized trials, survival and quality of life) produced >10 randomized trials. In recent reviews, data from nine\textsuperscript{22} and seven\textsuperscript{23} studies are respectively shown; of these, only five were randomized, phase III, with complete data regarding the findings on OS and QoL\textsuperscript{24-28} - two\textsuperscript{24,25} of these comprised mixed groups of patients. The studies in question included 1320 patients in mixed and 3094 in pure group patients. The initial PSA limit to enter the trial was, in the majority of the patients, >3 or >5 ng/ml and the IAD treatment phase in the trial ranged from 3 to 8 months; in the majority of the cases it was 7 to 8 months. Except for one\textsuperscript{23}, all trials ceased treatment when PSA levels were <4 ng/ml and treatment was reinstituted when PSA levels were >10 or >20 ng/ml. The median monitoring value ranged from 44-108 months. The findings of the studies are briefly depicted in Table 2.

### Table 2

<table>
<thead>
<tr>
<th>Reference (study)</th>
<th>Number of patients (n)</th>
<th>Population</th>
<th>PSA Treatment Cessation</th>
<th>Treatment</th>
<th>Outcomes</th>
</tr>
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<tbody>
<tr>
<td>da Silva et al. (2009) SEUG 9401</td>
<td>766</td>
<td>Locally advanced and M1</td>
<td>&lt;4 or symptomatic. and PSA&gt;10 \leq 80% initial asymptomatic and PSA&gt;20</td>
<td>Triptorelin + Cyproterone Acetate</td>
<td>Progression time HR 0.81, p=0.11 OS HR 0.99, p=0.84</td>
</tr>
<tr>
<td>Salonen et al. (2012) FinnProstate VII</td>
<td>554</td>
<td>Locally advanced and M1</td>
<td>&lt;10 or 50% initial &gt;20 or &gt;initial value</td>
<td>6 months goserelin + Cyproterone Acetate</td>
<td>OS HR 1.15, p=0.17 DSS HR 1.17, p=0.29</td>
</tr>
<tr>
<td>Mottet et al. (2012) TAP 22</td>
<td>554</td>
<td>M1 (bones)</td>
<td>&lt;4</td>
<td>&gt;10 or symptomatic Disease progress</td>
<td>6 months goserelin + flutamide</td>
</tr>
<tr>
<td>Hussain et al. (2013) SWOG 9346</td>
<td>1535</td>
<td>M1 PSA &gt;5</td>
<td>&lt;4</td>
<td>&gt;20 or clinical progress</td>
<td>7 months goserelin + bicalutamide</td>
</tr>
<tr>
<td>Crook et al. (2012) Protocol 7/ NCT 3653</td>
<td>1386</td>
<td>Biochemical recurrence after RT</td>
<td>&lt;4 normal</td>
<td>&gt;10</td>
<td>8 months LHHR analogue + NSID</td>
</tr>
</tbody>
</table>

\textbf{B1. SEUG 9401}\textsuperscript{24}

In the SEUG 9401 study on locally advanced and metastatic disease, the progression time of the disease in the IAD group was slightly shorter compared to CAD (HR 0.81, p=0.11), and OS exhibited no statistically significant difference (HR 0.99, p=0.84). In a non-metastatic disease, OS favored CAD whereas in metastatic patients the data favored IAD. In the recent SEUG 9901\textsuperscript{29} study, the best candidate for IAD is a patient with M0, T3 and pretreatment PSA <100 ng/ml which reduces to <4 ng/ml (and preferably <1 ng/ml) 3 months after the initial treatment.

\textbf{B2. FinnProstate VII}\textsuperscript{25}

In FinnProstate VII, on locally advanced and metastatic disease, no difference occurred both in the number of total deaths in IAD and CAD groups (186 vs 206, p=0.17) and in PCa - related deaths (117 vs. 131, p=0.29).

\textbf{B3. TAP22}\textsuperscript{25}

In the TAP22 study on metastatic Ca, the median OS
(52 vs 42 mo, p= 0.75) and the median OS without disease progression (15.1 vs. 20.7 mo, p= 0.74) had no statistically significant difference between IAD and CAD.

**B4. SWOG 9346**

The SWOG 9346 study recruited the largest number of patients so far (1535) comparing IAD and CAD in patients with metastatic PCa. It included patients with metastases and initial PSA>5 ng/ml in a 7 - month therapy. If PSA was <4 in the 6th month, then, patients were randomized to IAD or CAD. Treatment reinstitution was decided when PSA was >20 ng/ml. The design of the study foreseen that IAD was not inferior to CAD (non-inferiority trial) and the delta coefficient was 1.2. Mean OS was 5.8 against 5.1 years for IAD and CAD, respectively (death HR in IAD 1.10; 90% confidence interval, 0.99 - 1.23) and was not statistically significant. In a further analysis in the course of the study among patients with minimal metastatic disease (spinal column, lymph nodes and pelvis), the mean OS differed by 1.5 year (5.4 years IAD and 6.9 CAD with HR 1.19), whereas in widespread metastatic disease (sides, long bones, skull, intestines) the difference favored IAD by 5 months, 4.9 against 4.4 years (HR 1.02).

The analysis of the SWOG 9346 study presents some contradicting outcomes. The mean OS was shorter on IAD by 7 months, with increase of the relative death risk by 10%. The initial hypothesis of the 20% difference cannot by rejected with 90% certainty. According to the review by Piaggio et al., for the analysis of such studies, when the confidence interval also includes the non-inferiority margin (1.20 in this study) and 1.00, the study produces vague outcomes. Researchers conclude that the outcomes suggest that IAD can affect OS and the following are reported as possible causes in not detecting the difference: a) PSA limits for treatment resumption, b) monitoring period and c) the longer OS (5.8 instead of 3 years) would require a much larger pool of patients in order to establish a 0.15 difference in OS.

**B5. NCT3653 (protocol 7)**

The NCT3653 (protocol 7) study was the first to document that in a certain patient population with localized PCa and radiation therapy (as initial or salvage treatment), IAD is not inferior to CAD in terms of OS. 1386 PSA> 3 ng/ml patients entered the study after a period of more than a year subsequent to external beam radiation therapy. IAD patients were off - treatment for 71% of the total monitoring period (37.6 mo off - phase, 15.4 on - phase). Mean OS was approximately 9 years (8.8 in IAD and 9.1 in CAD) and the difference was not statistically significant (HR 1.02; 95% CI 0.86 - 1.21). p for non-inferiority of IAD against CAD was 0.009 (HR, <1.25).

C. Comparative analysis of randomized trials findings

The discussed randomized trials demonstrate that they pertain to different patient populations, a small pool of male subjects, although the two most recent ones (SWOG9346 and NCT3653) comprised a large number of men. In terms of evidence-based medicine (EBM), the outcomes were all la and lb class (LoE) - they were however based on specific - inhomogenous-populations thusly rendering the formulation of a broad spectrum of outcomes difficult. In the SWOG9346 study, in patients with metastatic disease, the design of a non - inferiority trial with a set delta coefficient, led to a statistically vague outcome. In the NCT3653 study, a non - statistically significant difference was found both in OS and in disease-specific survival.

The studies in question, along with their reported limitations, illustrate that IAD treatment does not result in significant OS shortening compared to CAD. Combined with QoL results and cost reduction, IAD seems to play an important role in certain patient groups and consequently it bears a particular value in defining the patients to benefit the most from it.

D. Quality of Life on IAD

The main reason behind IAD studies is the preservation of the patients’ better QoL which is considered to be
a result of the testosterone recovery to normal levels when off-treatment. Recovery pace is multi-factor dependent (age, IAD treatment duration and number of cycles, pretreatment testosterone levels, nationality). In the five randomized studies reported presenting OS and QoL data, different comparative methods were followed: the EORTC QLQ-C30 questionnaire in three studies, Cleary’s 30-question health-related quality of life (HRQoL) domains and scores in one and SWOG’s special questionnaire in another. Of the available data in a summary, deterioration in cognitive functions when on IAD is reported, which is an unexplainable finding and further investigation is suggested.

In TAP22, even though small differences were observed in QoL in both groups, these were not deemed significant. On IAD, less SEs were encountered (p = 0.042), and lower rates of headaches and hot flashes were reported. In SEUG9401, SEs were more frequent in the CAD group. Statistically significant differences were found in the affective domain (p = 0.01), in nausea and vomiting (p = 0.03) and in insomnia (p = 0.03). In the FinnProstate VII study, the IAD group exhibited lower reduction rates in activity, physical ability and sexual function. On the contrary, sexuality was higher in the CAD group. Regarding SEs, no statistically significant difference was reported.

In NCT3653, in terms of QoL, the IAD group patients demonstrated slightly better outcomes in body functions and overall health status (non-statistically significant) whereas the differences were greater in terms of symptoms related to androgen deprivation such as hot flashes, desire for sexual activity and urinary system symptoms (p < 0.001, < 0.001 and = 0.006, respectively). 29% of patients with good pretreatment erectile function reported its restoration. In their discussion, the researchers report that they did not observe great differences in QoL, maybe due to the fact that the analysis in question was not related to the treatment phase from the outset.

In SWOG 9346, better preservation of the erectile function, higher libido and physical function is reported 9 months after randomization and better mental health preservation in the IAD group only in the first trimester.

E. IAD-induced Side Effects

In a recent review of the literature by Gruca et al., 13 studies were chosen for the analysis of the patients’ safety on and tolerability to ADT, 8 of which were randomized. SEs are categorized into early and late. The first category includes hot flashes and erectile function and desire disorders. The effect of hot flashes was analyzed in 5 trials and a statistically significant difference was found in favor of IAD. For the erectile dysfunction, studied in 6 of the trials, libido and erectile function were lower on IAD whereas the study conducted by de Leval reported that sexual function was restored off-phase in 47% of the men. In the study performed by da Silva, the difference was 28 vs. 10% (p ≤0.01), however, the reduction of the erectile function was greater on CAD (0.9 vs 5.5%, p ≤0.01).

In the aforementioned complications, osseous density and mass reduction, anemia, obesity and cardiovascular diseases incidences are reported. Regarding the comparison between IAD and CAD, only one study compared the incidence of osteoporotic fractures with no difference detected. Anemia was investigated in one study in absence of group comparison. Obesity was studied in three trials; BW increase was identified during therapy and BW reduction upon treatment cessation, without comparative studies. Concluding, cardiovascular complications were investigated in three studies. The acute myocardial infarction (AMI) incidence increased on CAD (4.6 vs 2.8%, p = 0.4), cerebrovascular accidents (CVA) on IAD (5.5 vs 0.9, p = 0.6%), and deep vein thrombosis (DVT) also on IAD (3.7 vs 1.8%, p = 0.3).

IAD eligibility criteria

Subsequent to the confirmation of biochemical failure in PCa patients who underwent therapy, the androgen deprivation is usually advised. In patients with no osseous metastases (M0), IAD treatment may as well be applied, on condition that the possibility to recourse to salvage therapy has been examined. Based on the recent data found in the SWOG9346 study in metastatic patients (M+), we should be cautious with intermitted treatment. In these cases, the PSA nadir could be considered in assessing which patients will respond, as it has been suggested by some researchers. In practice, this means that the patients eligible for androgen deprivation proceed with the treatment and are assessed after the end of the first treatment cycle with PSA nadir and clinical response to the treatment.
be tested; otherwise, CAD is a better option, especially when the off-phase period is short. In patients with advanced PCa who are primarily interested in preserving their QoL, IAD may also be recommended in patients demonstrating CAD therapy-induced serious SEs. Finally, in patients with biochemical failure after radiation therapy for localized disease, as it was shown in the NCT3653 study, no statistically significant difference was found in OS and consequently, IAD is not a good option.

**Prognostic factors**

The most common prognostic factor following IAD treatment is PSA nadir\(^{24,39,40}\). On IAD, the PSA nadir is indicative of the respective risk: in the study performed by Sciarra et al. PSA nadir < 0.1ng/ml was considered a good prognostic factor whereas PSA levels > 0.4 ng/ml were accompanied by double or triple the risk\(^{37}\). In the same study, the preparation’s Gleason score and the duration of the first off-phase period (≤24 or >48 mo, p= 0.01) were also very significant. Gleave et al. demonstrated that when PSA nadir is not <4 ng/ml, IAD is not indicated\(^{35}\). In Keizman et al.’s study, apart from PSA nadir, PSADT was also measured prior to therapy (≥6 or <6 mo, p= 0.047) and after the end of the first cycle (≥3 or <3 mo, p= 0.05)\(^{36}\). Yu et al., in a phase II study, report that the off-phase period > 40 wks after the first cycle (p= 0.03) was a critical and independent factor related to the transition to castration-resistant PCa\(^{38}\).

**International guidelines on IAD**

The review of the recent guidelines on IAD delivers several recommendations. The European Association of Urology (EAU), in its revised guidelines of 2013, reports that IAD is advised as a therapeutic option in a large number of PCa patients and should now be considered a method under investigation (LoE:2)\(^{41}\). It is also pointed out that even though the eligibility framework remains to be set, it will probably include males with locally advanced disease or after a local recurrence, on condition that complete response is achieved. The American Urological Association (AUA) has not published any revised guidelines from 2007 onwards on PCa and IAD is not included\(^{42}\). The guidelines of the American Society of Clinical Oncology (ASCO), also dated 2007, report the lack of sufficient evidence on IAD application outside the clinical trials framework\(^{43}\). To conclude, in the recent review of the National Comprehensive Cancer Network (NCCN) guidelines in 2014, it is reported that IAD is widely applied aiming to the reduction of SEs and the results of the NCT3653 study in patients with biochemical failure after radiation therapy (non-metastatic disease) are cited\(^{44}\). No clear suggestions are included on metastatic diseases since the findings of the SWOG 9346 and NCI Canada PR7 studies on advanced disease have not been included; however, certain categories of patients are suggested where IAD is applicable due to serious SEs or desire for better QoL.

**Conclusions**

IAD, as it is shown in recent studies, can result in similar oncological outcomes with continuous therapy and better treatment tolerability by patients. Yet, more comparative studies are required on QoL issues, prevention of long-term complications of the intermittent therapy compared to CAD and certainly a determination of the applicable prognostic factors on treatment response.
Intermittent androgen deprivation therapy for prostate cancer: a review of the recent literature and guidelines p. 34 - 41

References

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