Chapter 13

Intermittent Androgen Suppression Therapy for Prostate Cancer Patients: An Update

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1. Introduction

Prostate cancer is the leading cause of cancer and the second leading cause of cancer-related deaths among men in the Western world [1]. For early stage prostate cancer treatment with surgery and radiation is often curative; however, about 10–20% of men with prostate cancer present with metastatic disease at diagnosis, while 20–30% of patients diagnosed with localized disease will eventually develop metastases [2]. Primary tumor involvement outside the prostatic capsule or relapse following radical prostatectomy results generally in incurability [3,4]. Androgen suppression (AS) is the mainstay of initial therapy in these patients, and orchidectomy or use of LHRH analogs and steroidal or nonsteroidal antiandrogens consistently results in a 90–95% reduction in circulating testosterone levels [5]. However, nearly all patients that respond initially will develop progressive disease, termed castration-resistant prostate cancer (CRPC), after a median duration of 18–24 months. Although CRPC may respond to secondary hormonal manipulations (including antiandrogens, estrogens and ketoconazole) this benefit is usually short-lived.

Although continuous androgen suppression [CAS] therapy has been a cornerstone of the management of prostate cancer for more than 50 years, controversy remains regarding its optimum application. Generally, AS is performed as continuous treatment, resulting in apoptotic regression of the tumor cells in a high percentage of cases. The side-effects of CAS are well described and include anaemia, osteoporosis, impotence, cognitive functional effects, gynaecomastia, muscle atrophy, depression, dyslipidaemia and generalized lethargy [5]. Following failure of the antiandrogenic therapy, chemotherapy is used as secondary treatment. However, responses to cytotoxic therapy are low and only recently several studies revealed a possible benefit of incorporating chemotherapeutic agents in treatment regimen for prostate cancer [6]. In the last years new agents were approved by the U.S. Food

and Drug Administration (FDA), comprising an immunotherapeutic product (sipuleucel-T), the novel taxane, cabazitaxel, which showed a survival advantage over mitoxantrone in docetaxel-pretreated patients and an androgen synthesis inhibitor, abiraterone acetate, which was also reported to improve survival when evaluated against placebo in docetaxel-pretreated patients [3,7].

In order to reduce side effects of the CAS and to prolong the duration of the hormone-responsive state of prostate cancers intermittent androgen suppression (IAS) was introduced as new clinical concept [8]. Stopping CAS has the hypothetical advantage of reducing the selection pressure which favors the clones that have initiated molecular adaptations to achieve androgen-independent growth. If there is a population of androgen-dependent clones left then these will proliferate and repopulate the gland, and androgen dependence will resume. Experimental animal models involving androgen-dependent xenografts supported the hypothesis that during limited regrowth in the antiandrogenic treatment cessation periods tumorigenic cells are residing in an androgen-responsive state. The concept of IAS was experimentally developed using the androgen-dependent Shionogi mouse mammary tumor, investigating regular phases of growth, regression and recurrence of xenograft tumors during serial transplantation [9]. For the androgen-dependent Shionogi carcinoma regular cycles of treatment cessations and castration-induced regressions were successfully repeated four times before tumor growth became androgen-independent during the fifth cycle [10]. The average duration of one cycle was 30 days and progression to androgen-insensitivity was observed after 150 days. Serial determinations of the proportion of stem cells in the Shionogi tumor revealed a constant part during the first three cycles, but a 15-fold increase between the third and fourth cycles [11]. Therefore, it was concluded that independent of intermittent or continuous androgen withdrawal, conversion to hormone-insensitivity occurs when the tumor has accumulated one-third to one-half of the total stem cell compartment with androgen-independent cells. The next step included the switch to a human prostate cancer xenograft model using the LNCaP androgen-dependent prostate cancer cell line, where serum PSA levels correlated well with tumor volume and decreased rapidly following castration, followed by appearance of androgen-independency after 3-4 weeks [12]. IAS therapy prolonged time to androgen-independent PSA production threefold, from an average of 26 days in the CAS group to 77 days in the IAS group. It was concluded that IAS in the LNCaP model delayed the onset of androgen-independent PSA gene regulation markedly, most likely due to androgen-induced differentiation and/or downregulation of androgen-suppressed gene expression. In summary, the animal experimental data indicated that androgen-dependent tumor xenografts can be subjected to several cycles of androgen withdrawal/replacement and revealed prolonged hormone-dependency compared to CAS.

Since induction of androgen independence may occur early after treatment initiation, cessation of antiandrogen therapy prior to this switch is expected to maintain the apoptotic potential of the tumor cells and keep them sensitive to retreatment. Serial serum PSA determinations are used to decide on AS, treatment cessation and reinitiation of therapy [13]. Generally, IAS consists of an initial androgen suppression period of up to nine months combining LHRH antagonists and antiandrogens, which is followed by treatment cessation

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until a certain PSA threshold is reached, then AS is reinitiated for the same time period as the initial suppression phase (Figure 1) In initial pilot trials regrowing tumors of patients undergoing IAS were consistently reported to be sensitive to several cycles of androgen withdrawal [14,15]

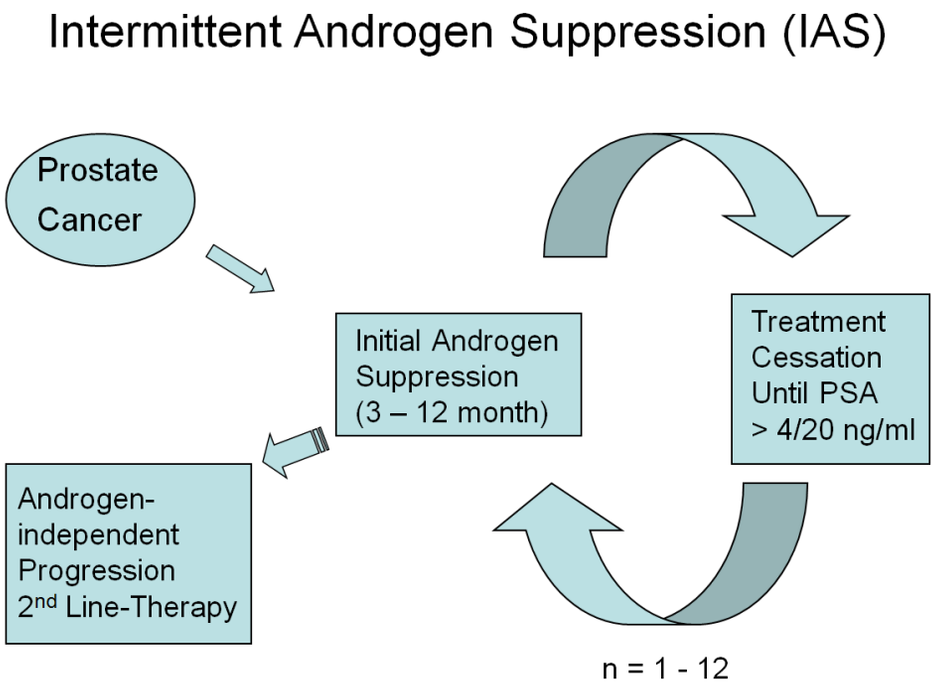

Figure 1. Schematic presentation of IAS. Patients undergo an initial phase of AS. If successful, AS is paused until progression to 4 (localized disease) or 10-20 (metastatic disease) ng/ml PSA. Then AS is resumed and cycles repeated until progression to androgen-independent disease that is treated with diverse regimens second-line.

Therefore, the primary goal of IAS was the prolongation of the hormone-sensitivity of the tumors, which in turn was expected to result in increased survival eventually. Furthermore, IAS was expected to reduce the side effects of CAS, comprising reduced sexual activity, cardiovascular problems, metabolic consequences and osteoporosis among others. Based on the available evidence, IAS nowadays represents a valid treatment option for patients with non-metastatic prostate cancer, including those with locally advanced disease, either with or without lymph node involvement, and those who biochemically relapsed following apparently curative treatment. IAS has been researched since the mid-1980s in a number of clinical phase II and III trials in an effort to prolong hormone-dependency and reduce adverse effects and costs of CAS [16]. With preclinical evidence suggesting a potential benefit for IAS in terms of time to androgen independence, with phase II and phase III studies producing optimistic results, and with the potential for decreased costs and complications IAS has now become a popular modality of therapy worldwide. Quite recently, according to results of a Phase III trial presented in a plenary session at the 2012 ASCO Annual Meeting, IAS was shown to be less effective than CAS for a subgroup of patients with hormone-sensitive metastatic prostate cancer, questioning the use of IAS as standard therapy for these patients [17].

2. Clinical evaluation of intermittent androgen suppression

2.1. Introduction

Maximal androgen ablation through combination therapy increases treatment-related side effects and expenses and fails to prolong time to progression to androgen-independence and, furthermore, preliminary evidence indicates that a low androgen milieu is associated with tumor aggressiveness. Transition to androgen-independence is a complex process and involves both selection and outgrowth of preexisting androgen-resistant clones, as well as adaptative upregulation of genes that enable cancer cells to survive and grow after CAS [18]. CAS in men with prostate cancer increases the risk of osteoporotic fractures, type 2 diabetes and, possibly, cardiovascular events [19]. The benefits of CAS in treating non-metastatic prostate cancer need to be carefully weighed against the risks of CAS-induced adverse events. Management of the metabolic sequelae of CAS includes optimal reduction of cardiovascular risk factors, with particular attention to weight, blood pressure, lipid profile, smoking cessation and glycemic control. Supported by preclinical and first clinical IAS results, several centers tested the feasibility of IAS in non-randomized groups of prostate cancer patients with serum PSA as trigger point followed by a number of extended phase II and III trials [16,20]

2.2. Clinical phase II studies of IAS

2.2.1. Comparison of therapeutic efficacies of IAS and CAS

Following apparently successful pilot studies, a number of phase II IAS trials were conducted (Table 1) [16]. Since the end points of most phase II studies were safety and feasibility of IAS, survival data were not reported in general. Out of the 19 studies reviewed by Abrahamsson only five involved more than 100 patients (102, 103, 146, 250 and 566 patients, respectively) and the other smaller studies employed a mean number of 52 patients [16]. Although patients with advanced, metastatic prostate cancer were included in several studies, most patients treated in phase II IAS trials had localized disease or biochemical progression following prostatectomy/radiation therapy. The number of IAS cycles given ranged from 1 to 12, with an average of 2–3 per patient, and the length of time off therapy generally decreased or remained stable with each succeeding cycle. Most of the studies reported off-treatment periods of approximately 50% of the duration of the IAS cycles, dependent on the tumor stage of the respective prostate cancer patients [16]. A metaanalysis by Shaw et al. involving ten phase II trials reported a median number of two cycles per patient and a median time off-therapy of 15.4 months [21]. Time on treatment also varied but was usually in the region of 6–9 months [16]. The proportion of men in whom serum testosterone normalized was generally high following the first cycle (70–90%) but tended to decrease during subsequent cycles [16]. Factors influencing time to delay in testosterone normalization may include advanced age, low baseline testosterone levels, and duration of AS. Testosterone recovery to baseline values was achieved in 79% during the first and in 65% during the sec-

ond IAS cycle, respectively [22]. No significant difference was observed up to 1000 days between IAS and CAS with regard to time to androgen-independent tumor progression.

Authors	#	Endpoint(s)	Tumor stage	Androgen suppression
Calais da Silva et al. [13]	626	Time to subjective or objective progression	Locally advanced or metastatic	GnRH agonist + cyproterone acetate
De Leval et al. [36]	68	Time to androgen-independence	Locally advanced, metastatic or recurrent	Goserelin + flutamide
Miller et al. [37]	335	Time to clinical or biochemical progression	Locally advanced or D1/D2	Goserelin + bicalutamide
Mottet et al. [38]	173	Overall survival	Metastatic PCa (D2)	Leuprorelin + flutamide
TULP [39,40]	290	Time to clinical progression or PSA escape	Advanced or locally advanced	Buserelin depot + nilutamide
Tunn et al [22]	184	Clinical or PSA progression	PSA relapse after radical prostatectomy	Leuprorelin + cyproterone acetate
Verhagen et al. [35]	366	QoL	Metastatic	Cyproterone acetate
Klotz et al.[34]	1386	Survival	PSA recurrence after radical Radiotherapy	All types of AS
Salonen et al. [41,42]	554	Progression/Survival	Advanced or locally advanced	Goserelin + cyproterone acetate
Hussain et al. [17]	1345	Survival	Advanced (D2)	Goserelin + bicalutamide

Table 1. Overview of the published phase II IAS trials

In a study by Bruchovsky et al. men who quickly recovered serum testosterone levels experienced a more rapid rise in PSA levels and a shorter time off therapy [23]. Generally, low levels (2–16%) of progression to hormone-refractory prostate cancer have been reported [16,22]. In a review by Zhu et al. there were 16 trials that compared IAS with CAS with a total of 3264 patients (1624 with IAS and 1640 with CAS) [24]. Pooled effects indicated no significant difference between IAS and CAS groups in terms of death and progression rate (hazard ratio HR=0.99, 95% CI 0.80-1.23, and HR=1.03, 95% CI 0.84-1.26 respectively). Calculated results indicated that quality of live (QoL) on sexual activity was significantly higher in the IAS group (HR=0.24, 95% CI 0.17-0.33, $p<0.00001$). Moreover, IAS could effectively reduce side effects associated with AS. Thus, the therapeutic efficacy was not significantly different between the IAS and CAS groups. However, IAS could effectively preserve the QoL (in particular sexual life) and reduce the side effects.

2.2.2. Comparison of the side effects/QoL of IAS and CAS

Because it became increasingly clear that the time to androgen-independence seems not to be prolonged by IAS, trials focussed on the impact of the intermittent therapy on side effects of AS and QoL. Malone et al estimated that approximately 50% of patients recovered from anaemia during off-therapy periods and that the weight gain normally associated with CAS was prevented [25]. Bouchot et al reported hot flushes in most cases during the on-therapy period, which showed significant improvement during treatment cessation periods and pain

significantly improved during on-therapy periods with no new pain occurring once therapy was withdrawn [26]. Goldenberg et al. observed that all patients tolerated therapy well and responded in a positive physical and psychological manner to the cycling approach [27]. The attenuation of spine and hip bone mineral density (BMD) decline after 3-year IAS compared with those reported for CAS appears to be due to testosterone-driven BMD recovery in the cessation period [28]. Failure of testosterone recovery was associated with worse final BMD. Patients experienced the greatest average change in BMD during early treatment periods of IAS with a smaller average change thereafter and fractures were rare [29]. During the first off-treatment period (median duration 37.4 weeks), BMD recovery at the spine was significant; however, subsequent periods had heterogeneous changes of BMD without significant average changes. By reducing the potential risk for adverse bone complications, intermittent therapy may become an important consideration when the therapeutic ratio is narrow [30]. We examined the effect of IAS on bone metabolism by determinations of CrossLaps levels, a biochemical marker of collagen degradation, in blood samples of prostate cancer patients. Measurements of the CrossLaps concentration in patients under IAS revealed that treatment cessation phases rapidly reversed increased bone degradation, which was associated with the AS phases, in good agreement with the clinical observations of reduced loss of BMD in IAS [31]. Since pretreatment concentrations of CrossLaps were restored within several months of treatment cessation and mean duration of the off-treatment periods ranged from 8–16 months in our patients, this protective effect of IAS is expected to be effective for several treatment cycles. Additionally, procollagen I N-terminal peptide (PINP), a parameter of bone synthesis was increased during off-treatment phases in IAS [32].

Improvement of sexual activity was highlighted in several studies and concerned approximately half of the patients [16]. Sato et al reported significant worsening of potency and physical well-being during AS and significant improvements in potency, lack of energy, social/family well-being, and ability to enjoy life during off-therapy periods [33]. In a study by Spry et al. QoL scores also deteriorated during androgen suppression, but had generally achieved baseline levels by the end of the off-treatment period [28]. In summary, IAS showed benefits in the treatment of prostate cancer with respect to QoL in the majority of trials.

2.2.3. IAS phase II studies – conclusion

In phase II studies there has been considerable variation in the particular approaches in regard to medication, duration of AS phases, target PSA nadir and selection of the PSA value for restarting therapy. At that time preliminary results of the the ongoing randomized controlled trials have generated evidence that the use of IAS in patients with advanced or locally advanced disease was at least as safe as CAS [16,24]. In conclusion, phase II studies of IAS demonstrated that several cycles of IAS were feasible, the duration of response was not worse than historical controls of CAS and well-being was better during treatment cessation periods. Patients with localized disease fared superior under IAS compared to patient with extended disease. The need for randomized phase III trials was stressed in order to get firm

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data on progression-free and overall survival (OS) as well as time to androgen insensitivity for IAS and CAS, respectively.

2.3. Clinical phase III studies of IAS

Nowadays a number of phase III trials have been completed comparing IAS with CAS [16]. Of the ten reported trials, two included patients with relapse after radical prostatectomy or radiation therapy, all others studied locally advanced and metastatic disease [22,34]. The number of patients in these trials varied from 68 to 1386, but only four involved >500 patients; the average age of patients was around 70 years. Full details of trial design are not available for all studies, several reports are available only in abstract form [16]. The treatment regimen in all but one of the trials consisted of a LHRH agonist and an antiandrogen. The exception was Verhagen et al., in which antiandrogen monotherapy (cyproterone acetate/CPA) was the sole regimen studied [35]. Although there was generally consistency in the PSA levels designated for AS discontinuation (0.1/4 ng/ml or 20% of the initial PSA value), the criteria for resuming treatment were less uniform, with 4 ng/ml for biochemical relapses and 10 or 20 ng/ml 20 ng/ml for locally advanced or metastatic disease, respectively. The low PSA nadir and reinitiation values used by Tunn et al. and Klotz et al. are due to the fact that the study involved patients who had relapsed after radical prostatectomy [22,34]. End points in these studies also varied to some degree: whereas the majority had time to progression as the primary end point, three assigned survival and one focussed on QoL outcomes [35]. Average follow-up times in these studies have all been >2 yr, with a maximum of 12 years cited by Calais da Silva et al. [13].

2.3.1. South European uroncological trial [13]

Patients with locally advanced or metastatic with histologically confirmed prostate adenocarcinoma, cT3–cT4 M0, cT3–cT4 M1, PSA >4 ng/ml, were recruited for this study and end point was time to subjective or objective progression. All registered patients had an initial 3-months induction treatment with CPA (200 mg daily for two weeks) followed by monthly depot injections of a LHRH analog plus 200 mg of CPA daily. Patients (n = 626) whose PSA level decreased to <4 ng/ml or by at least 80% of the initial level by the end of the induction were randomized. Time to any progression was slightly longer in the continuous arm, with an HR of progression of 0.81. Both metastatic status and PSA level were independent predictors of progression, with M1 and PSA level > 4 ng/ml associated with a greater hazard of progressing. In the intermittent and continuous arm there was no significant difference in OS ($p = 0.84$) and the HR was 0.99 for CAS compared with IAS. The greater number of cancer deaths in the IAS treatment group was balanced by a greater number of cardiovascular deaths under CAS. Both PSA level and metastatic status at randomization were independently associated with survival. A significant interaction of metastatic status with treatment was almost reached ($p = 0.07$). Among M0 patients, the HR for continuous therapy compared with intermittent therapy was 0.86 (95% CI: 0.65–1.14), favouring continuous; among M1 patients, the HR was 1.26 (95% CI: 0.90–1.78), favouring intermittent. It was concluded that IAS should be considered for use in routine practice because it is associated with no re-

duction in survival, no clinically meaningful impairment in QoL, better sexual activity, and considerable economic benefit to the individual and the community. Since this study used only three months of therapy before stopping treatment in the intermittent arm, without impairing survival, there are significant savings for a patient receiving IAS for one year relative to CAS.

2.3.2. Study by De Leval et al. [36]

In this trial, a total of 68 evaluable patients with hormone-naive advanced or relapsing prostate cancer were randomized to receive AS (goserelin and flutamide) according to a continuous (n = 33) or intermittent (n = 35) regimen. The outcome variable was time to androgen-independence and mean follow-up was 30.8 months. The estimated 3-year progression rate was significantly lower in the IAS group (7.0%) than in the CAS group (38.9%). It was concluded that IAS treatment may maintain the androgen-dependent state of advanced human prostate cancer, as assessed by PSA measurements, at least as long as CAS treatment. This study may be regarded as underpowered to assess the full impact of IAS and the authors recommended further studies with longer follow-up times and larger patient cohorts to determine the comparative impacts of CAS and IAS with certainty.

2.3.3. Study by Miller et al. [37]

This randomized study compared AS with goserelin + bicalutamide in CAS with IAS. The primary endpoint was time to clinical and/or biochemical progression of the disease and secondary endpoints were survival time, QoL and side effects. Patients had histologically confirmed adenocarcinoma of the prostate in clinical stage T1-4N1-3M0 or T1-4N0-3M1 (D1 or D2). After an induction phase of six months with AS, 335 patients whose PSA decreased under 4 ng/ml or 90% from baseline were randomized. About two-thirds of the patients of both the intermittent and the continuous therapy arm (65% versus 66%, ITT population) experienced a clinical and/or biochemical disease progression. The median time to progression was longer for patients randomised to IAS (16.6 months) compared with patients randomized to CAS (11.5 months; difference not significant). The median time to death from any cause was 51.4 months in the intermittent arm compared and 53.8 months in the continuous therapy arm ($p = 0.658$). There were no differences in the incidence of patients with any safety parameter. Patients' self-assessment of their overall health and of their sexual activity appeared to be favourable in the IAS therapy arm. It was concluded that IAS in D1 and D2 prostate cancer patients seems to be safe and superior in respect to QoL.

2.3.4. TAP22 investigators group trial [38]

This study aimed at comparing CAS to IAS with AS consisting of leuproreline and flutamide in patients with newly diagnosed metastatic prostate cancer with bone metastases (stage D2). All patients had a positive bone or CT scan and a PSA > 20 ng/ml. After a 6 months induction period with AS, they were randomized into two groups if the PSA was < 4 ng/ml. CAS was continued after randomization and in the IAS group treatment was discontinued until PSA > 10 ng/ml or clinical progression. AS was then resumed for

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3 months periods until the PSA became < 4 ng/ml and then treatment was then stopped again until the next progression for a new cycle. 341 patients were selected and received a 6 months induction AS period, and 173 were randomized: 83 to CAS and 86 to IAS. Patients were off-treatment approximately 50% of the first cycle, without decline in succeeding cycles and most had testosterone recovery. A progression occurred in 127 patients (73.4%). The overall QoL did not differ significantly between both arms. Median OS was 52 months for CAS and 42.2 months for IAS (p=0.74) and the median progression-free survial was 15 months for CAS and 20.7 months for IAS (p=0.73). This randomized trial comparing CAS to IAS in metastatic prostate cancer patients suggests that IAS may be as safe as CAS in D2 prostate cancer patients.

2.3.5. Therapy Upgrading Life in Prostate cancer (TULP) study [39,40]

Eligible patients (n = 290) had histologically proven advanced prostate cancer with positive lymph nodes or distant metastases (T2-4N1-3M0 or T2-4NxM1). They received AS with buserelin and nilutamide for 6 months. Patients who had a normalisation of PSA (< 4 ng/ml) after the course, were randomized between IAS (n=97) or CAS (n=96). Median time to clinical progression or PSA escape was 18.0 months in the IAS arm and 24.1 months in the CAS arm. In particular, the 2-year risk of progression for baseline PSA < 50 ng/ml, 50 to <500 ng/ml, and ≥500 ng/ml was 25%, 55%, and 76% (P = 0.03) in CAS, and 38%, 64%, and 85% (p = 0.006) in IAS, respectively. There was no clinically significant difference in QoL scores between patients. Metastatic prostate cancer patients with high baseline PSA, pain, and high PSA nadir, after a 6-months induction course, have a poor prognosis with hormonal therapy. Overall, in this study patients on IAS seem to do worse than CAS patients. Also, patients receiving IAS with low PSA nadir had significantly higher progression rates than CAS patients. In IAS testosterone recovery during the off-treatment phase was incomplete, explaining the missing benefit for QoL, even though more side effects occurred during CAS. Therefore, it was concluded from this study that IAS constitutes not a good treatment option for most metastatic prostate cancer patients.

2.3.6. European trial EC507 [22]

In this multicentre European prospective randomized phase III trial EC507, testosterone serum concentrations under AS were analyzed in prostate cancer patients with PSA progression after radical prostatectomy. Patients were randomized to either CAS or IAS therapy using a 3-months depot with leuprorelin acetate as microcapsule formulation. In 109 patients testosterone recovery to baseline values was achieved in 79% during the first and in 65% during the second IAS cycle, respectively. Median time to testosterone normalization was 100 days in the first and 115 days in the second cycle, respectively. There also appeared to be a QoL benefit during off-treatment intervals owing to the recovery of serum testosterone levels. No significant difference was observed up to 1000 days between IAS and CAS with regard to time to androgen-independent progression. This was the first prospective study of leuprolide, demonstrating normalization of testosterone levels in the off-treatment period in patients undergoing IAS.

2.3.7. Study by Verhagen et al. [35]

This randomized trial compared efficacy and QoL of IAS and CAS treatment by CPA of asymptomatic patients with prostate cancer metastatic to the bone. A total of 366 patients with metastatic prostate cancer received 3 to 6 months CPA (100 mg daily) depending on their PSA response. Patients with a good or moderate response were randomized to continuous or intermittent treatment. Intermittent hormonal therapy of metastatic prostate cancer by CPA has advantages in important QoL domains. However, cognitive function scores appeared reduced in the intermittent group.

2.3.8. NCIC CTG PR.7/SWOG PR.7/CTSU JPR.7/UK trial [34]

This Intergroup randomized phase III trial compared IAS vs. CAS to test for non-inferiority of IAS with respect to OS. Patients had rising PSA > 3.0 ng/ml >1 year post radical radiotherapy (RRT), either initial or salvage, for localized prostate cancer. Stratification factors were time since RRT (>1-3 vs >3 years), initial PSA (<15 vs >15), prior radical prostatectomy and prior AS. IAS was delivered for 8 months in each cycle with restart when PSA reached >10 ng/ml off-treatment. Primary endpoint was OS, secondary endpoints included time to hormone refractory state, QoL, duration of treatment/non-treatment intervals, time to testosterone and potency recovery. The trial was halted after a planned interim analysis demonstrated that a prespecified stopping boundary for non-inferiority was crossed. 1,386 patients were randomized to IAS (690) or CAS (696) arms. IAS patients completed a median of 2 x 8 months cycles (range: 1-9) and median follow-up was 6.9 years. 524 deaths were observed (268 on IAS vs. 256 on CAS). Median OS was 8.8 vs. 9.1 years on IAS and CAS arms, respectively (HR 1.02, 95%CI 0.86-1.21; p for non-inferiority [HR IAS vs CAS ≥ 1.25] = 0.009). The IAS arm had more disease related (122 vs. 97) and fewer unrelated (134 vs. 146) deaths. Time to androgen insensitivity was statistically significantly improved on the IAS arm (HR 0.80, 95%CI 0.67-0.98; p = 0.024). IAS patients had reduced hot flashes, but otherwise there was no evidence of differences in adverse events, including myocardial events or osteoporotic fractures. Thus, in men with PSA recurrence after RRT IAS was non-inferior to CAS with respect to OS.

2.3.9. SWOG 9346 intergroup trial [17]

The largest trial comparing IAS and CAS in metastatic patients was reported by Hussain et al. [17]. Between 1995 and 2008, the study enrolled 3040 men with newly diagnosed metastatic disease and PSA levels ≥ 5 ng/mL. The study population was preselected for hormone sensitivity and when PSA level fell to ≤ 4 ng/mL, patients were randomized to either IAS (n = 770) stopping treatment at that point until a rise in PSA level was observed (an increase to 20 ng/mL, or for those with baseline value < 20 ng/mL, when PSA returned to baseline) or CAS (n = 765). Hormone therapy consisted of goserelin and bicalutamide for 7 months, which was in use in 1995 when the study was launched. At randomization, patients were stratified according to performance status, extent of disease, and prior exposure to hormone therapy.

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At a median follow-up of 9.2 years, median overall survival was 5.1 years with IAS and 5.8 years with CAS, an absolute difference of slightly more than 6 months favoring CAS in the entire study population. The study design specified that survival with IAS would be non-inferior to CAS if the upper 95% confidence bound for the HR did not reach or include 1.2. This specification would rule out with high confidence the possibility of a 20% or greater increase in the relative risk of death with IAS. The difference between the two treatments resulted in a HR of 1.09 in favor of CAS, but the upper boundary of the 95% confidence interval was 1.24, so the conclusion was that the two treatments could not be called equivalent and survival with IAS therapy was regarded inferior to IAS by these authors. For this study, survival in both arms was much better than the expected 3-year median OS. In all examined subgroups, CAS was slightly better than IAS, with exception of extensive disease, where IAS achieved comparable survival (5 years on IAS vs 4.4 years on CAS). In this subgroup analysis, patients with minimal disease had a median overall survival of 5.2 years in the IAS group vs. 7.1 years with CAS, suggesting that the loss of almost two years of life in the intermittent group could not be ruled out. In this study "minimal disease" was defined as disease that had not spread beyond the lymph nodes or the bones of the spine or pelvis and "extensive disease" as disease that had spread beyond the spine pelvis, and lymph nodes or to the lungs or liver.

Trial participants also compared QoL measures across the two study arms during the first 15 months following patient randomization, including measures of sexual function (impotence and libido), physical and emotional function, and energy level. They found improved sexual function in men who received IAS as compared to those on continuous therapy.

2.3.10. FinnProstate study VII [41,42]

The FinnProstate study VII enrolled 852 men with locally advanced or metastatic prostate cancer to receive AS for 24 weeks [41]. Study inclusion criteria were M1 disease at any PSA, M0 disease at PSA 60 ng/ml or greater, or T3-4 M0 prostate cancer at PSA 20 ng/ml or greater, or previously surgically or radiotherapy treated localized prostate cancer and PSA recurrence of 20 ng/ml or greater. Patients in whom PSA decreased to less than 10 ng/ml, or by 50% or more if less than 20 ng/ml at baseline, were randomized to IAS or CAS. In the intermittent therapy arm AS was withdrawn and resumed again for at least 24 weeks based mainly on PSA decrease and increase. Of the 852 men, 554 patients were randomized and observed for a median follow-up of 65.0 months. Of these patients 71% died, including 68% in the intermittent and 74% in the continuous arm ($p = 0.12$). There were 248 prostate cancer deaths, comprised of 43% under IAS and 47% under CAS ($p = 0.29$). Median times to progression were 34.5 and 30.2 months in the intermittent and continuous arms, respectively. Median times to death (all cause) were 45.2 and 45.7 months, to prostate cancer death 45.2 and 44.3 months, and to treatment failure 29.9 and 30.5 months, respectively. Therefore, according to this trial, IAS is a feasible, efficient and safe method to treat advanced prostate cancer compared with CAS. However, the prevalence of adverse events was not significantly lower with IAS [42].

2.3.11. Phase III studies - Summary

In general, the phase III trials comparing IAS with CAS involved a varying number of patients, prostate cancer tumor stages ranging from biochemical relapse to metastatic and recurring disease and widely differing durations of initial AS as well as differing PSA values for the start of treatment cessations and reinitiations. Therefore, conclusions to be drawn are restricted to specific tumor stages and treatment schemes.

2.3.11.1. IAS – phase III – impact on survival

The Miller randomized trial of IAS versus continuous CAS in 335 patients with advanced (lymph node-positive or metastatic) prostate cancer demonstrated equivalent survival [37]. Patients in the intermittent arm were off-treatment >40% of the time. It is important to note that testosterone recovery after discontinuation of the LHRH agonist is often delayed and may depend on treatment duration, age, baseline testosterone, and ethnicity [22,43]. In the TULP trial of IAS versus CAS for advanced prostate cancer, 193 patients were randomized and, after a mean follow-up of 34 months, no difference in survival was observed [40]. The larger de Silva trial randomized 312 men to CAS and 314 men to IAS [13]. With a median follow-up of 51 months from randomization, there were fewer cancer deaths (84 vs. 106), more cardiovascular deaths (52 vs 41), and an equivalent number of total deaths (169 vs. 170) in the continuous versus intermittent arms respectively. Median time off AS was 52 weeks for patients in the intermittent arm [13]. It should be noted that the randomization criteria for all of these trials are a PSA decline of 80–90%, or to <4ng/ml, on initial AS.

In the study by Miller et al. about two thirds of patients receiving either IAS or CAS experienced clinical and/or biochemical progression, with no significant differences between groups with respect to median time to tumour progression or median time to death [37]. Similarly, Mottet et al. reported no significant difference between patients receiving IAS and CAS with respect to median overall survival (OS; 1265 vs 1560 days) and median progression-free survival (PFS) (620 vs 452 days) [38]. Tunn et al. also reported equivalency between IAS and CAS with respect to PFS (91.7 vs 93.6%) and median time to progression (1.86 vs 2.36 yr), although estimated mean PFS was longer in the IAS group compared with the CAS group (1234 vs 1010 days) [22]. In the TULP study, median time to progression was longer in the CAS arm (24.1 vs 18 months; significance not stated); more recent data from this study show no difference in OS between groups (mean follow-up of 66 months) [39,40]. The Intergroup randomized phase III trial demonstrated non-inferiority of IAS with respect to OS and time to hormone refractory state for patients with biochemical relapses after radical radiotherapy [34]. Similarly, the FinnProstate Study VII, found no significant differences in time to progression and OS, concluding that IAS is an efficient method to treat advanced prostate cancer compared with CAS [41].

However, differences in OS between CAS and IAS have been reported in two studies. De Leval et al. reported that the estimated risk of 3-year progression in CAS patients was significantly higher than in the IAS group (38.9% vs. 7%; $p = 0.0052$) [36]. In patients with a Gleason score >6, 3-year progression rates were significantly higher in CAS than in IAS patients ($p = 0.018$) but not in patients with lower Gleason scores. Compared with CAS, the IAS

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group had better results with respect to the number of deaths from hormone-refractory disease (4 vs. 2), number of patients with disease progression (10 vs. 3), and mean time to progression (21 vs. 28 months) (level of significance not stated for any outcome). In patients without bone metastases at initiation, risk of progression was significantly higher in CAS than IAS patients ($p < 0.001$). The largest trial comparing IAS to CAS is the SWOG 9346 intergroup trial, which included metastatic prostate cancer patients [17]. At a median follow-up of 9.2 years, the median overall survival was six months longer with CAS in the entire study population. This was caused by a comparable survival in extensive disease and an inferior survival in response to IAS in patients with minimal metastatic disease. The results of these two studies point to an inferior clinical results of IAS in metastatic prostate cancer.

2.3.11.2. IAS – phase III – impact on QoL

Early results from the study by Calais da Silva et al. showed no clinically meaningful differences between groups in virtually all QoL parameters and no evidence that IAS carries a significantly higher risk of death [13]. Mottet et al. also reported no significant difference in QoL outcomes in patients receiving either IAS or CAS [38]. However, updated results from a larger cohort of the Calais da Silva study (maximum follow-up of 7 years; median: 2 years) suggest a better tolerability profile for IAS versus CAS, with up to three times as many patients in the CAS arm reporting side effects compared with IAS patients (hot flushes: 23% vs. 7%; gynaecomastia: 33% vs. 10%; headaches: 12% vs. 5%; all $p < 0.0001$) [44]. Levels of sexual activity also increased in the IAS group compared with the CAS group, reported in 28 vs. 10% of patients after 15 months. Similarly, Miller et al. reported that patients' self-assessment of their overall health and sexual activity appeared to favour IAS; however, no differences in incidence of adverse events or other safety parameters were noted in this study [37]. Further evidence of QoL advantages comes from Verhagen et al. who note that EORTC scores on physical and emotional function were significantly better in the IAS group than in the CAS group. Role and social function were equivalent between groups, although cognitive function was surprisingly reduced in the IAS group, but not in the CAS group [35]. AS-related side effects were reported in most patients by de Leval et al., most of which resolved in the IA group on discontinuation of therapy [36]. In the TULP study, 26 preliminary withdrawals were reported due to adverse events, 20 in the CAS group and 6 in the IAS group [39,40]. The FinnProstate Study VII reported no significant difference in the prevalence of adverse with IAS [42]. Improved sexual function in men who received IAS as compared to CAS was confirmed in the SWOG 9346 intergroup trial [17].

2.3.11.3. IAS – phase III trials – Conclusion

Following pilot and phase II clinical trials comparing IAS to CAS, results of phase III studies were awaited eagerly to get a definite judgement of these different regimens of AS. The clinical results, time to progression and OS, seem to be comparable between IAS and CAS for prostate cancer patients with biochemical relapses and localized disease. With the exception of two studies, namely trials performed by the South European Uroncological Group and the SWOG 9346 intergroup, IAS was not inferior to CAS in respect to progression of disease

and OS in metastatic prostate cancer. In the two dissenting studies, patients with limited metastatic disease seem to have an impaired OS under IAS. However, the statement that IAS is possibly inferior to CAS and not standard therapy of all prostate cancer patients is an oversimplification [17]. Improvements in QoL parameters were confirmed by most studies, depending on testosterone recovery and extent of disease.

NCI Trial #	Treatment	End point/Study subject	Start	Status
NCT00283803	Exisulind	Duration of off-treatment period	2006	Unknown
NCT00686036	Zactima (18 mo)	Duration of off-treatment period	2008	Terminated
NCT00553878	Dutasteride	Duration of off-treatment period	2007	Ongoing
NCT00668642	Dutasteride	Androgen-Response Gene Expression	2008	Recruiting
NCT00801242	Degarelix (1 mo)	Duration of off-treatment period	2008	Ongoing
NCT00928434	Degarelix IAS	Duration of off-treatment period /QoL	2009	Ongoing
NCT01512472	Degarelix (4 vs 10 mo)	Duration of off-treatment period	2011	Recruiting
NCT00002651	IAS vs. CAS	Survival/QoL Prostate cancer D2	1999	Recruiting
NCT00223665	IAS	Progression/QoL Localized Prostate Cancer	2005	Recruiting
NCT00378690	ELIGARD	Survival/QoL Metastatic Prostate Cancer	2006	Ongoing

Table 2. Overview of the IAS trials currently under investigation

2.4. IAS trials currently under investigation

Table 2. lists the trials comprising IAS treatment of prostate cancer patients registered in the United States National Institute of Health (NIH) clinical studies site. With exception of a few further trials comparing IAS to CAS in metastatic cancer patients, several drugs are investigated for their potential to prolong the off-treatment phase of IAS. Exisulind (Aptosyn or sulindac sulfone) may be useful as a treatment for men with advanced prostate cancer, achieving disease stabilization. This drug increases the rate of programmed cell death in cancer cells without damaging normal tissue by interfering with cyclic GMP phosphodiesterase in abnormally growing precancerous and cancerous cells [45]. Zactima (vandetanib) is an oral inhibitor of vascular endothelial growth factor receptor 2 (VEGFR-2), epidermal growth factor receptor (EGFR) and Ret tyrosine kinases involved in tumor growth, progression and angiogenesis [46]. Although, as single agent, no significant antitumor activity has been observed for Zactima in small cell lung cancer, advanced ovarian, colorectal, breast, prostate cancer and multiple myeloma. Further drugs target the androgen-stimulated growth by exploiting distinct mechanism or new formulations. Dutasteride is a non-selective inhibitor of steroid 5α-reductase, an enzyme responsible for conversion of testosterone to a more potent androgen dihydrotestosterone (DHT) approved for clinical use in treat-

ment of benign prostate hyperplasia (BPH) and currently tested in clinical trials for prevention and treatment of prostate cancer [47]. Degarelix is a GnRH antagonist, that was found to be at least as effective as leuprolide in the ability to suppress serum testosterone to < or =0.5 ng/mL for up to 1 year in prostate cancer patients in different doses and in depot form [48]. Finally, Eligard constitutes a new leuprorelin acetate formulation that appears to achieve a testosterone suppression of 20 ng/dL in 98% of patients, while maintaining a side effect profile comparable to other products in its class [49]. It remains to be investigated, whether this use of drugs targeting androgen-independent mechanisms or improving AS can prolong the duration of the off-treatment periods of IAS and, possibly, contribute to extended survival compared to CAS.

3. Discussion

In many patients with prostate cancer, androgen deprivation therapy is administered over prolonged periods of time. The benefits of long-term AS in patients with advanced disease are well established, nevertheless, because this therapy has potential long-term side effects strategies should be applied that manage or prevent long-term complications [50]. One such strategy is IAS, in which patients receive regular cycles of AS, the duration of which is usually determined by PSA levels [51]. Canadian prostate cancer researchers have led the field of androgen withdrawal therapy for many years, from Nobel prize winner (Halifax born) Charles Huggins in 1940 to Nicholas Bruchovsky's Vancouver team's preclinical and clinical work on intermittent therapy in the early 1990s [52]. The basic premise of IAS is that periods (or cycles) on androgen deprivation for cancer control are followed by periods off therapy for testosterone recovery and improvements in quality of life parameters (such as libido, sexual function, energy, cognition and sense of masculinity). Preclinical studies suggest that the reintroduction of testosterone into the cellular milieu during the off-treatment period keeps the remaining cancer cells androgen-dependent, allowing for the next successful round of AS and delaying progression to hormone-resistant prostate cancer [51]. Accumulating data indicate that this approach improves the tolerability of AS and patients' QoL, without compromising clinical outcomes.

Consequently, the latest European Association of Urology guidelines state that IAS should no longer be considered investigational. Furthermore, given the adverse effects of CAS, there may be beneficial effects and potential cost savings in time off therapy with intermittent treatment, particularly if suppressive effects on prostate cancer are equivalent to CAS [53,54]. Seruga and Tannock, reviewing >1000 randomised patients, concluded that compelling data indicate that IAS should be regarded as standard therapy [54]. Likewise, Spendlove and Crawford put forward a strong argument that IAS has now demonstrated that it is no less effective than CAS and that it clearly reduces the impact of the side effects of hormone therapy on patient QoL [55]. Although current evidence suggests that IAS may be reasonable for some patients with hormone-sensitive prostate cancer, there are still questions about patient selection, timing, and methodology of IAS [56].

Results of the IAS phase III trials were expected to finally give some answers in regard to the clinical applicability and feasibility of this novel form of AS in prostate cancer patients. Phase II trials pointed to a non-inferiority of IAS as compared to CAS and improved tolerability of AS; however, these findings were only partially confirmed in phase III studies. According to the part of these trials involving patients with biochemical progression and confined disease, IAS can be regarded as non-inferior to CAS and superior in respect to QoL. For metastatic prostate cancer patients the situation seems to be different: whereas in patients with extended disease the intermittent and continuous form of AS were equivalent in respect to disease progression and OS, patients with limited metastatic disease fare worse, according to preliminary data stemming from the South European Uroncological Group trial and to definitive data from the SWOG 9346 intergroup trial [13,17]. The latter study could not exclude the loss of two years in OS in patients in which the disease that had not spread beyond the lymph nodes or the bones of the spine or pelvis. The results of Hussain et al. did not apply to men without metastases, who constitute a much larger group getting hormonal therapy. For those men IAS remain a reasonable option and even men with metastatic cancer might still opt for IAS to give their years more live instead of giving their live more years. It should be noted that the metastatic prostate cancer patients in this study had an unusual mean OS and AS consisted of a 7 months course, that may be short of the minimum of 8 months requested by Bruchovsky et al. for full downstaging [57].

The question that needs to be discussed is the selection of the prostate cancer patients who will get an optimal benefit from IAS instead of CAS. Men with local or biochemical failures after radiotherapy would benefit from IAS because they are treatment-free for longer periods of time and so are less likely to develop hormone-refractory disease [58]. De la Taille et al. identified patients >70 years of age with localised prostate cancer, a Gleason score of < 7, and a first off-therapy period of >1 year as the best candidates for IAS [59]. Grossfeld et al. recommend investigation of IAS in patients with clinically localised cancer who are not appropriate for definitive local treatment, but have significant risk of tumour progression, patients who refuse all local treatment options despite risk of progression, and those who have failed prior local therapy [60]. Poor candidates for IAS have been described as those with initial bulky tumors, with numerous lymph nodes or bone metastases, PSA doubling time <9 months, and initial serum PSA >100 ng/ml or severe pain [61]. Gleave et al. suggest that patients who fail to achieve a PSA nadir of <4 ng/ml after 6 months of therapy and most men with TxNxM1 disease should not be offered IAS, whereas those with TxN1-3M0 who are sexually active, compliant, or intolerant of AS side effects make good candidates, as long as they are informed of its investigational status [62]. Patients most likely to benefit are those with locally advanced prostate cancer with or without lymph node metastases but without any evidence of bone metastases. Also, those patients with biochemical failure following radiologic or surgical therapy for prostate cancer, those who cannot tolerate side effects of CAS, and those who wish to remain sexually active would appear to be good candidates. However, treatment should be restricted to those who can comply with close follow-up. Clearly, IAS is impossible in a significant fraction of men who do not respond to an initial course of AS.

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Although the American Urological Association has not yet included IAS in its treatment guidelines for prostate cancer, the European Association of Urology acknowledged that IAS is at present widely offered to patients with prostate cancer in various clinical settings and states that its status should no longer be regarded as investigational [63,64]. This is in contrast to the American Society of Clinical Oncology practice guidelines, which state that there are currently insufficient data to support the use of IAS outside of clinical trials [65]. The 2008 UK National Institute for Health and Clinical Excellence (NICE) 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 its unproven status [66]. They also note that results from uncontrolled studies have shown satisfactory outcomes and that IAS will probably be more cost effective than CAS, despite the need for close monitoring. Irrespective of official guideline recommendations, IAS is a treatment option used worldwide by both urologists and oncologists outside of clinical trials. Based on available evidence and general clinical opinion, IAS is a valid treatment option in non-metastatic prostate cancer cases, that is, patients with locally advanced disease with or without lymph node involvement and those experiencing relapse following curative treatment. These patients have a higher chance of survival than those with more advanced disease, making QoL a key consideration.

Since the introduction of PSA screening in the late 1980s, more prostate cancers have been detected, and at an earlier stage that are low grade and slow growing and will not need aggressive therapy [67,68]. With this long natural history and a median survival without treatment that often approaches at least 15 to 20 years many patients will die rather with than of prostate cancer. Approximately one-third of patients who undergo radical prostatectomy will develop a detectable PSA level within 10 years [69]. Management of PSA recurrence is controversial, as prostate cancer may take an indolent course, or it may develop aggressively into metastatic disease. Prostate cancer is over-treated at present but a short course of AS might identify those patients for whom the outcome would be good with IAS by identifying those with a good PSA response. Multivariate models show the power of the initial PSA level and PSA nadir, and type of treatment and the PSA threshold for restarting treatment, in predicting outcome [21]. In those patients who rapidly achieve a good PSA nadir it is safe to shorten treatment to < 4 months. In the presence of evidence of metastasis, treatment must be protracted to ≥ 8 months. Restarting treatment when the PSA level approaches 15 ng/mL is associated with improved survival in patients with metastases, indicating the need for a more aggressive treatment strategy in these patients. Maximum androgen blockade or LHRH analog should be the standard for patients treated with IAS. The duration of biochemical remission after a period of IAS is a durable early indicator of how rapidly progression and death will occur, and will make a useful endpoint in future trials. The initial PSA level and PSA nadir allow the identification of patients with prostate cancer in whom it might be possible to avoid radical therapy.

Twenty years ago it was expected that the IAS regimen would be associated with extended survival, mainly through postponing the castration-resistant status [70]. The expected associated benefits were a decrease in the adverse effects of castration, such as hot flushes, decreased libido and erection, bone and muscle problems, depression, and metabolic

syndrome (Table 3). Regarding the expected QoL and adverse effects benefits, few prospective data from randomized trials are available comparing IAS to CAS treatment. The report from Salonen et al. shows some benefit in QoL for activity limitation, physical capacity, and sexual functioning [41,42]. Surprisingly, no difference was observed in drug-induced adverse effects, such as hot flushes or night sweats. This lack of a clear sexual benefit is disappointing and a little different from what is observed in other trials, especially the South European Urooncological Group or the Miller trial [13,37]. The different questionnaires might partly explain this difference, as might the different treatment modalities, such as varied duration of treatment cycles and combined treatments or monotherapy. It was also hoped that IAS would decrease the treatment adverse effects; this decrease, at best, has been marginally obtained as the claimed QoL benefit. The thresholds, which were different from trial to trial, were only empirically chosen. The lower the PSA level after the AS induction period, the longer the survival. Therefore, the threshold of 4 ng/ml to stop the treatment in most metastatic trials might be too high and the threshold of 20 ng/ml to resume treatment might also be too high; however, it allows a longer off-treatment period, although not long enough to lead to a clear large QoL benefit [70]. Mottet concludes that apart from treatment cost, IAS does not hold to its promises and should probably be considered with caution in the most advanced situations, even in patients with a clear PSA response.

Initial goals of IAS

- Prolongation of androgen dependence and survival
- Therapy working in most stages of prostate cancer
- Reduction of the side effects of CAS
- Reduction of adverse events associated with CAS
- Reduction of the costs of prostate cancer treatment
-

Current status of IAS

- Survival under IAS not inferior to CAS?
- Prolongation of androgen-dependence of tumor not confirmed
- Most suitable for relapse after prostatectomy/radiation therapy
- Reduction of side effects of AS in most studies?
- Improved quality of life during off treatment dependent on testosterone recovery
- No consistent and optimal scheme for the implementation of IAS?
- Reduced costs of IAS compared to CAS

Table 3. Summary of the achievements and shortcomings of IAS

These findings for IAS are far from what was initially expected, and the presented SWOG 9346 trial added even more questions regarding IAS [17]. It has long been said that IAS does not appear to be inferior to CAS. Those results were obtained from under-powered trials or large trials including heterogeneous patients, such as the FinnProstate Study VII [41] or even the large, recently presented SWOG JPR7 [17] trial in postradiotherapy relapsing patients. None of the trials even suggested increased overall or specific survival. IAS was expected to postpone androgen independence; this finding, however, as well as an increase in OS has never been obtained in any trial. Thus, the marked elongation of hormone-dependency in the Shionogi mouse model could not be materialized in patients, which may be most likely due to increased cycle length of several months in humans compared to one month these animals, allowing for better adaptation to hormone deprivation. Furthermore, the Shionogi study was done on androgen-dependent mouse mammary carcinoma. This animal model may be insufficient to explain homeostasis of human stem cells and their progenies in relation to human prostate cancer. Miki et al. reported that human prostate cancer stem cells had no androgen receptors or PSA [71]. Guzmán-Ramírez and coworkers presented a similar protein expression pattern of prostate cancer stem cells [72]. There is a high probability that human prostate cancer stem cells are really androgen-independent. Another possibility is that two populations of stem cells exist within human prostate cancer and that the first population is androgen-sensitive and the second is androgen-independent. Our knowledge of prostate cancer stem cells is still too immature to support the rational approach for IAS therapy. Furthermore, Pfeiffer and Schalken reported difficulties in finding stem cells within established prostate cell lines in vitro, reflecting their limited use in such research [73].

In the world of medicine it has been estimated that it takes an average of 17 years for practice changing evidence to reach the bedside [52]. The first phase II study of IAS was published in 1995 and after 17 years it was advised to accept that multiple randomized controlled trials have supported its use as a non-inferior option to CAS in defined populations and to reintroduce suitable men with prostate cancer intermittently to the pleasure of their androgens [52]. High-risk patients seem to be poor candidates for any type of androgen suppression. In summary, it can be concluded from the trials that IAS is neither inferior nor superior to CAS with respect to clinical end points, namely the time period until hormone-resistance as well as cancer-specific survival, but offers significant advantages in terms of adverse effects, quality of life and costs. The off-treatment periods particularly offer the possibility to apply drugs, such as finasteride, or chemotherapeutics in order to delay disease progression [74]. However, the clinical lack of prolongation of the hormone-sensitive state of prostate cancers by IAS raises doubts about the underlying hypothesis of keeping the prostate cancer cell in an androgen responsive state by cycling between AS and off-treatment periods. Fundamental tumor biology studies in patients would be needed to clarify this issue. Otherwise IAS may be regarded as treatment regimen aiming simple for AS reduction to a level that does not permit efficient tumor growth and simultaneously lowers the side effects of AS. Patients that respond well to a first cycle of AS may go on off-treatment for years [75]. Clearly, IAS is not standard therapy for all prostate cancer patients, but a valid and favourable regimen for a significant part of selected patients.

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