The current status of intermittent androgen deprivation (IAD) therapy for prostate cancer: putting IAD under the spotlight

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Intermittent androgen deprivation (IAD) is one approach to hormonal therapy for prostate cancer that has been developed with the aim of minimizing the negative effects of therapy while maximizing the clinical benefits and the patient's quality of life (QoL). It can be used in any clinical situation where continuous AD (CAD) treatment could be applied. IAD is a cyclic therapy consisting of on-treatment periods followed by observation periods, known as off-treatment periods or intervals (OTIs), and the response to therapy, or occurrence of disease progression, is monitored by measuring the patient's prostate-specific antigen (PSA) levels. The on-treatment period is generally fixed, normally lasting for 6–9 months or in some protocols until a PSA nadir of <4 ng/mL is reached. By contrast, the OTI is variable and treatment is re-instituted depending on the patient's PSA level; however, the exact trigger point is chosen empirically. The potential advantages of IAD over CAD therapy are an improved QoL, a prolonged period of androgen dependence, a reduced incidence of the side-effects normally associated with AD therapy, and a decrease in the cost of care. Results from phase II clinical studies of IAD have shown that it has good acceptance and feasibility. QoL improves during the OTIs, there is reduced toxicity, and a positive affect on bone density compared with CAD therapy. In these studies IAD appeared to have no negative effects on time to progression or survival. Further investigations of IAD are ongoing in randomized, controlled, phase III trials in the USA, Canada and Europe. Most of these studies are not yet mature and final results are awaited; however, interim analyses from some studies suggest IAD and CAD therapy are equally effective in terms of progression-free survival.

KEYWORDS
prostate cancer, intermittent androgen deprivation therapy

INTRODUCTION

Androgen deprivation (AD) is associated with certain adverse effects with short-term use, including hot flashes, loss of libido/potency, and general fatigue. However, other effects have also been reported to be associated with the longer term use of AD therapy. These include bone demineralization, anaemia, lipid disorders, obesity, muscle wasting, mood changes and neurocognitive decline, and the development of androgen independence within the population of cancerous cells. The benefits and disadvantages of AD therapy therefore need to be carefully balanced, and one approach that aims to minimize the negative effects of therapy and maximize quality of life (QoL) is intermittent AD (IAD). Here I review the current status of IAD for treating patients with prostate cancer.

THE RATIONALE FOR IAD

IAD is a cyclic therapy consisting of on-treatment periods followed by observation periods, known as off-treatment periods or intervals (OTIs). The theory behind IAD was developed by the Vancouver group of Bruchovsky et al. In preclinical studies they found that androgen replacement restored the apoptotic potential of the androgen-dependent tumour cells that had survived AD, and delayed the development of androgen independence [1–3].

In IAD tumour models, such as androgen-dependent Shionogi carcinomas in mice and LNCaP human prostate cancer xenografts, a prolongation of androgen independence of up to three times was reported [2,4–6]. These investigators concluded that IAD can induce multiple apoptotic regressions in these tumours.

In the clinical situation IAD can only be achieved using reversible AD with a LHRI agonist or antiandrogens. The response to therapy and occurrence of disease progression is monitored by measuring the patient's PSA levels.

DEFINITIONS AND CLINICAL APPLICATIONS

A complete IAD cycle comprises both the on-treatment period and OTIs, and is thus the period between initiating AD and re-instituting treatment after an OTI. The on-treatment period is generally fixed, normally lasting for 6–9 months or in some protocols until a PSA nadir of <4 ng/mL is reached. By contrast, the OTI is variable depending on the PSA level. During an OTI, if there is evidence of PSA progression a new treatment cycle is initiated. The optimum treatment duration is at the point of maximum castration-induced apoptosis and treatment should be stopped before the androgen-independent phenotype is produced. This is normally 6–9 months but there has been some discussion of treating for 2–3 months beyond the PSA nadir.

The re-institution of treatment in IAD is guided by the patient’s PSA level but the trigger point is chosen empirically. In hormone-naive patients with M0 disease the trigger point is a PSA level of 6–15 ng/mL, whereas in those with M+ disease it is a PSA level of 10–20 ng/mL. In patients with PSA relapse after radical prostatectomy (RP) or radiotherapy (RT) a PSA level of 3–6 ng/mL is used.

The indications for the use of IAD are quite simple, i.e. any clinical situation where
continuous AD (CAD) treatment could be applied. Patients eligible for IAD are those in whom inductive AD produces PSA normalization, i.e. a rapid decline in the PSA level to a ‘normal’ value. In previously untreated patients a normal level is considered to be <4 ng/mL, for PSA relapse after RT it is <1 ng/mL, and for PSA relapse after RP it is <0.5 ng/mL.

The potential advantages of IAD over CAD therapy are an improved QoL, a prolonged period of androgen dependence, a reduced incidence of the side-effects normally associated with AD, and a decrease in the cost of care.

SUMMARY OF PHASE II TRIALS OF IAD

Over the last decade (1995–2006) 22 phase II trials of IAD have been published and these included >1600 patients. These patients were a heterogeneous population representing all tumour stages from A to D2. A multivariate analysis of phase II trials was recently presented at the 2006 International Study of Intermittent Therapy for Cancer of the Prostate meeting in Vancouver, Canada [7]. This analysis included 1653 patients from 11 trials. The authors concluded that the predictors of clinical outcome for patients with prostate cancer treated with IAD included the initial PSA level, the PSA nadir after AD, and the duration of the OTI.

From the results of the phase II studies it can be concluded that IAD shows good acceptance and feasibility. QoL improves during the OTI, there is reduced toxicity, and a positive affect on bone density. In these studies IAD appeared to have no negative effects on time to progression or survival. What remains unknown about IAD is which patients will benefit most, whether PSA is a reliable surrogate marker, what percentage of men will have a useful testosterone recovery, the QoL outcome, and the effect on overall survival. These questions can only be answered in phase III clinical trials.

SUMMARY OF PHASE III TRIALS OF IAD

Randomized, controlled phase III trials evaluating IAD are currently being undertaken in the USA, Canada and Europe, but they are not yet mature, and the final results are awaited.

### NORTH AMERICAN STUDIES

The National Cancer Institute of Canada JPR7/ Southwest Oncology Group JPR7 study is a randomized, multicentre trial including 1386 patients with PSA progression after RT and with no evidence of distant metastases. This study opened in January 1999 and closed in November 2005. Patients were randomized to one of two treatment arms, IAD or CAD with an LHRH agonist plus an antiandrogen. The IAD arm comprised an 8-month on-treatment period which was re-instituted during the OTI if PSA levels increased to >10 ng/mL. The primary endpoints of the study are QoL and overall survival.

The National Cancer Institute of Canada JPR8/ Southwest Oncology Group 9346 is a randomized phase III trial comparing IAD and CAD therapy in men with M+ stage IV prostate cancer. Patients receive combined androgen blockade (CAB) therapy comprising an LHRH agonist plus bicalutamide for 7 months as an induction therapy. They are then randomized to one of two consolidation regimens, continuous CAB (the same regimen as the induction therapy) or intermittent CAB. In the absence of rising PSA levels or clinical symptoms of progressive disease, patients undergo observation only. Patients with rising PSA levels (>20 ng/mL) or evidence of progressive disease resume CAB (the same regimen as the induction therapy). Patients whose PSA levels normalize after 8 months return to observation only. Patients whose PSA levels do not normalize after 8 months continue CAB therapy. To date 1395 men have been randomized and the target is 1512. Primary endpoints of the study are QoL and overall survival.

### EUROPEAN STUDIES

In a South European Urological Group trial, patients with locally advanced prostate cancer with known metastases were randomized to treatment with IAD or CAD. In this trial the duration of AD varied between centres, which might have biased the results. Despite these differing operational variables, to date there are no differences in overall survival between these treatment regimens [8, 9]. The investigators concluded that the use of IAD could become standard clinical practice.

The effectiveness of IAD compared with CAD is being compared in an ongoing, randomized, multicentre trial being undertaken in Germany and Italy (EC507 trial) in patients with PSA relapse after RP. Many of the patients recruited to the trial have unfavourable prognostic factors, e.g. T3 disease (64% of patients), node-positive disease (30%), or a PSA level of >20 ng/mL before RP (36%). All patients initially receive AD therapy with leuprolarin 3-month depot for 6 months plus cyproterone acetate for the first 4 weeks. They are then randomized to receive either intermittent or continuous therapy. The on-treatment period is 6 months and the treatment resumes during the OTI when the PSA level increases to >3 nmL/mL. The current status is that 240 patients are now randomized.

An interim analysis showed that OTI, when expressed as a percentage of the duration of the whole treatment cycle, appears to decrease with subsequent cycles (Table 1) [10]. Initially this might suggest a decrease in androgen responsiveness of the tumour, but an OTI decrease only indicates decreasing androgen responsiveness if all patients complete each of the cycles. If not, later cycles will only include those patients who had a shorter OTI in the initial cycles [11]. To correct for this it is necessary to make individual OTI comparisons, such as has been done in a phase II study undertaken in Ottawa, Canada.

<table>
<thead>
<tr>
<th>Completed cycle number</th>
<th>Number of patients</th>
<th>Duration of cycle, months</th>
<th>OTI, %</th>
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<tbody>
<tr>
<td>1</td>
<td>77</td>
<td>16.0</td>
<td>62.5</td>
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<tr>
<td>2</td>
<td>37</td>
<td>12.1</td>
<td>50.5</td>
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<tr>
<td>3</td>
<td>3</td>
<td>9.6</td>
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of IAD therapy with leuprorelin plus nilutamide in patients with recurrent or metastatic prostate cancer [11,12]. In that study the number of patients completing a cycle of therapy decreased with subsequent cycles (Fig. 1). To allow for this, the individual duration of the OTI was expressed as a percentage of the duration of the first OTI. Using this analysis, OTI in the Canadian phase II study appeared to be fairly stable (±10%) across all cycles (Fig. 2).

A realistic IAD concept assumes the recovery of testosterone levels during the OTI. In the EC507 study testosteronone was normalized after ≈3 months off-treatment [10]. It was normalized (a level of >2.3 ng/mL) in 90% of patients in cycle 1 and 81% in cycle 2, while baseline testosterone levels were reached in 75% of patients in cycle 1 and 60% in cycle 2. Bone degradation was found to be worse in CAD-treated patients (Fig. 3). However, IAD treatment was associated with a better QoL than CAD therapy, as assessed by the European Organization for Research and Treatment of Cancer quality-of-life questionnaire C30. The investigators have to date concluded that IAD and CAD are equally effective in terms of progression-free survival, with no difference between treatment arms (Fig. 4).

CONCLUSIONS

In recent years the concept of IAD has passed from hypothesis to laboratory experiments and is now being investigated in randomized, controlled clinical trials. The potential benefits of IAD are an improvement in the AD adverse-event profile normally associated with CAD therapy, an increase in the patient’s overall QoL, and a prolongation of the time taken for the tumour to become androgen-independent. A range of phase II studies have shown the feasibility and acceptance of IAD, and the beneficial effects in terms of QoL and a reduction in morbidity. The randomized phase III trials that are currently underway will answer the question as to whether these potential benefits can be realized in full. Until then, IAD should be considered only in carefully selected patients with prostate cancer who are closely monitored and well-informed.

CONFLICT OF INTEREST

None declared.

REFERENCES


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Abbreviations: (I)(C)AD, (intermittent) (continuous) androgen deprivation; QoL, quality of life; OTI, off-treatment interval; RP, radical prostatectomy; RT, radiotherapy; CAB, combined androgen blockade.