Intermittent Hormone Therapy: What Is Its Place in Clinical Practice?

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1. Introduction

Hormone therapy (HT) is the mainstay medical therapy for men with advanced prostate cancer (PCa) (ie, locally advanced and metastatic) and is also increasingly used at earlier disease stages, although there are no specific recommendations for these patients as of yet [1,2]. Although men with PCa may benefit from HT, they will also be subjected to the side-effects of treatment. These side-effects may include hot flushes; sexual problems, such as impotence and decreased libido; fatigue; and psychological effects, such as emotional instability, depression, or cognitive dysfunction [3,4]. It is also becoming increasingly clear that HT induces accelerated bone loss, eventually leading to osteoporosis and, potentially, to fractures as well as to lipid disorders, obesity, loss of muscle mass, and an
increased risk of cardiovascular morbidity and mortality [5–8]. Over the years, intermittent HT (IHT) has garnered interest in the urologic community as a means to minimise the side-effects of HT and to improve the overall quality of life (QoL) of the patient. Additionally, in the early 1990s, preclinical studies showed that androgen replacement restored the apoptotic potential of the androgen-dependent tumour cells that survived HT and delayed the development of androgen independence [9–11]. Moreover, in IHT tumour models, such as androgen-dependent Shionogi carcinomas in mice and lymph node carcinomas of the prostate in human PCA xenografts, a prolongation of androgen independence of up to three times was also reported [9,12–14]. This finding led to the hypothesis that reexposure of PCA cells to androgen would reinduce the androgen-dependent phenotype and that, therefore, IHT could potentially delay the progression to castration-resistant PCA (CRPC). In addition to the reduction of treatment-related side-effects and the potential delay of progression to CRPC, the benefits of IHT could also include reduced health care costs [15,16]. Considering these potential benefits, IHT could be a promising alternative to continuous HT; however, questions remain as to whether the current scientific evidence supports the use of IHT and how IHT should be applied in daily clinical practice. This review discusses clinical phase 2 and 3 trials evaluating IHT and gives practical advice on how to implement IHT in clinical practice.

2. Evidence acquisition

This paper was based on a presentation given at a satellite symposium on PCA that was held March 18, 2009, during the 24th annual meeting of the European Association of Urology (EAU) in Stockholm, Sweden. Data were retrieved from recent review articles and original articles on IHT.

3. Evidence synthesis

3.1. What is the scientific evidence on intermittent hormone therapy?

3.1.1. Phase 2 trials

Over the years, >20 phase 2 trials including >2000 patients have evaluated the feasibility, efficacy, and safety of IHT [15,17]. These studies, however, generally included small numbers of patients with different disease stages (ie, patients with localised disease, locally advanced disease, metastatic disease, prostate-specific antigen [PSA] relapse after local therapy) [15,17,18]. Additionally, they differed in their study design and methodology. A meta-analysis combined 10 phase 2 trials including a total of 1446 patients [18]. In all trials combined, patients spent a mean of 39% of the time off treatment. Fig. 1 displays the overall results regarding the percentage of patients off treatment at 2 yr, overall survival, and the percentage of patients progressing to CRPC for patients with localised disease, patients with a PSA relapse after radical prostatectomy (RP) or radiotherapy (RT), and patients with node-positive or metastatic PCA. Multivariate analysis showed that the initial PSA level and PSA nadir were important predictors of clinical outcome for PCA patients treated with IHT.

The phase 2 trials have limitations, but they do demonstrate that IHT has good acceptance and feasibility. Patients experienced improved QoL, and treatment-related morbidity was reduced during off-treatment periods. Additionally, IHT did not appear to have a negative effect on time to progression or survival. Because these phase 2 studies were of different quality regarding design and the use of small and heterogeneous study populations, these results need to be confirmed in well-designed phase 3 trials. These phase 3 trials also are needed to answer some outstanding questions related to the effect of IHT on time to CRPC and on overall and PCA-specific survival and which patients will benefit most from IHT [3].

3.1.2. Phase 3 trials

Randomised controlled phase 3 trials evaluating IHT are being conducted in Europe, the United States, Canada, and Japan, but unfortunately, most of these trials are not mature yet [3]. Recently, the results of the South European Uroncological Group (SEUG) trial were published, including a total of 626 patients with T3–4 M0–1 PCA receiving no previous treatment [19]. After a 3-mo HT induction period (consisting of maximum androgen blockade [MAB] with cyproterone acetate and a luteinising hormone-releasing hormone [LHRH] agonist), patients whose PSA level decreased to <4 ng/ml or by at least 80% of the initial level were randomised to continuous HT (n = 312) or IHT (n = 314). For patients in the IHT group whose PSA levels had decreased <4 ng/ml, therapy was restarted when PSA levels increased to ≥10 ng/ml for symptomatic patients and to ≥20 ng/ml for asymptomatic patients. For patients whose PSA level had decreased to at least 80% of the initial value, therapy was restarted when PSA levels rose to ≥20% above the nadir. At a median follow-up of 51 mo, 54% of the included patients had died. Median time of treatment for

![Fig. 1 – Results of a meta-analysis of 10 phase 2 studies on intermittent hormone therapy (IHT) showing the percentage of patients off treatment at 2 yr, overall survival, and the percentage of patients progressing to castration-resistant prostate cancer (CRPC) separately for patients with localised prostate cancer (PCa), patients with a prostate-specific antigen (PSA) relapse after radical prostatectomy (RP) or radiotherapy (RT), and patients with node-positive (N+) or metastatic (M+) PCa [18].](image-url)
patients in the IHT arm was 13 mo, with 50% of patients being off therapy for ≥13 mo and 29% of patients being off therapy for ≥36 mo. There was no difference in overall survival between both groups (170 deaths in the IHT arm vs 169 deaths in the continuous HT arm; Table 1). Time to objective progression and/or subjective progression was slightly longer for patients treated with continuous HT compared to IHT (Table 1). The slightly greater number of cancer deaths in the IHT arm (106 vs 84) was balanced by a greater number of cardiovascular deaths in the continuous HT arm (52 vs 41). Side-effects were more pronounced in the continuous HT arm compared to the IHT arm (Fig. 2). Both PSA level and metastatic status at randomisation were independently associated with survival. It was concluded that although further randomised studies are needed, IHT should be considered for use in routine practice because it seems to be associated with no reduction in survival, with better QoL, and with a considerable economic benefit to the individual and community.

Another phase 3 randomised trial evaluating IHT versus continuous HT is the Southwest Oncology Group (SWOG) 9346 trial. This trial included 1395 patients with newly diagnosed metastatic stage IV PCas and a baseline PSA level of at least 5 ng/ml [20]. These patients received MAB (LHRH agonist plus bicalutamide) for 7 mo as an induction therapy; those with a PSA level <4 ng/ml were then randomised to either continuous HT or IHT. The patients in the IHT group remained untreated (off-treatment period) in the absence of rising PSA levels or clinical symptoms of progressive disease. The SWOG 9346 trial has not closed yet, and final results are awaited. In a preliminary analysis, Hussain et al have evaluated whether the PSA level after the 7-mo induction period is a prognostic factor for survival for patients with metastatic stage IV PCAs treated with HT [20]. At the end of the induction period, 965 patients (71%) had a PSA level of <4 ng/ml and 604 patients (45%) had a PSA level of ≤0.2 ng/ml. Median survival was 13 mo for patients with a PSA level >4 ng/ml, 44 mo for patients with a PSA level 0.2–4.0 ng/ml, and 75 mo for patients with a PSA level <0.2 ng/ml. A PSA level ≤4 ng/ml after 7 mo of HT was a significant predictor of risk of death (hazard ratio [HR]: 0.26; 95% confidence interval [CI], 0.22–0.31; p < 0.0001), indicating that these patients had one-fourth the risk of dying relative to those who did not have a PSA level of ≤4 ng/ml. A PSA level of ≤0.2 ng/ml was also a significant predictor of longer survival (HR: 0.34; 95% CI, 0.29–0.40; p < 0.0001). It was concluded that a PSA level of ≤4 ng/ml after 7 mo of MAB induction therapy is a strong predictor of survival. Patients with a PSA level of ≤0.2 ng/ml have the greatest survival advantage.

Contrary to the previous trials that evaluated IHT in patients with advanced or metastatic PCas, the randomised, multicentre, European phase 3 trial EC507 evaluated IHT in PCa patients in whom a relapse in PSA level after radical prostatectomy had occurred [3,17,21]. Patients received 6 mo induction therapy with MAB; if the PSA level decreased <0.5 ng/ml, the patient was randomised to either IHT (n = 109) or continuous HT (n = 92). In the off-treatment period, treatment was reinstated when the PSA level increased >3 ng/ml or when there was clinical progression. The 2-yr results were presented at the 2007 annual meeting of the American Urological Association (AUA) [22]. Patients spent a median of 57% of the total time in the first cycle off treatment and 53% of the total time in the second cycle off treatment [3]. Kaplan-Meier analysis showed no statistically significant difference in progression-free survival between the IHT and the continuous HT arms (p = 0.883). Patients in the IHT group experienced fewer days with side-effects such as hot flushes than patients in the continuous HT group. Additionally, there was less bone degradation in patients treated with IHT versus continuous HT [15]. Early results from a European phase 3 trial comparing IHT monotherapy (n = 460) with continuous HT consisting of MAB (n = 454) in patients with advanced PCAs also showed that IHT monotherapy was associated with fewer side-effects and better sexual activity than continuous combined HT [23].

### 3.2. Intermittent hormone therapy in daily clinical practice

#### 3.2.1. How should intermittent hormone therapy be applied?

IHT is a cyclic therapy consisting of on-treatment periods followed by off-treatment periods. A complete IHT cycle comprises both the on- and off-treatment periods and is thus the period between initiating HT and reinstituting treatment after an off-treatment period [3]. In most clinical trials, an induction therapy of 6–9 mo is applied; however, there is no clinical evidence supporting one duration over another. Treatment can consist of MAB or LHRH agonist monotherapy and should ideally be continued until castration-induced apoptosis is maximal and tumour regression is induced, but it should be stopped before the androgen-independent phenotype is developed [15,16]. Generally, a fixed, on-treatment period is used, lasting for

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**Table 1 – Intermittent hormone therapy versus continuous hormone therapy: results from the South European Uroncological Group (SEUG) trial [19]**

<table>
<thead>
<tr>
<th>Overall survival</th>
<th>HR: 0.99 (95% CI, 0.80–1.23; p = 0.84)</th>
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<tr>
<td>Subjective/objective progression</td>
<td>HR: 0.81 (95% CI, 0.63–1.05; p = 0.11)</td>
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HR = hazard ratio; CI = confidence interval.
6–9 mo. In some protocols, however, this period lasts until a PSA nadir of <4 ng/ml is reached [15]. The off-treatment period is variable and depends on local progression and/or progression of PSA. Trigger points for restarting therapy should be individualised and should depend on the pretreatment PSA level, clinical stage, PSA velocity, presence of symptoms, and tolerance of HT [16]. Gleave et al suggest that in patients with metastatic disease and high pretreatment PSA levels, therapy should be restarted when the PSA level increases to 20 ng/ml [16]. In patients with locally recurrent disease and moderately elevated pretreatment PSA levels, therapy should be restarted when the PSA level reaches 6–15 ng/ml [24], and HT should be started earlier than this for patients with relapses after RP. It should be noted, however, that these PSA-threshold levels for reinstituting therapy are currently chosen empirically and are based on the ongoing phase 3 trials [3].

During the IHT cycles, patients should be monitored with testosterone and PSA measurements at the start of therapy and every 2–3 mo during the off-treatment interval [24]. A clinical evaluation should take place every 6 mo.

### 3.2.2. Who can be treated with intermittent hormone therapy?

IHT can be considered in patients who respond to HT with a decline in PSA levels to normal values (<4 ng/ml). In previously untreated patients, a normal value is considered to be <4 ng/ml; for patients who have had a relapse in PSA level after RP or RT, the level should be <0.5 ng/ml [15].

Caution is warranted in patients with high pretreatment PSA levels or low PSA doubling times, patients with a high clinical stage or high-grade disease, or patients with a high metastatic burden [16,17]. In a Finnish multicentre study comparing IHT with continuous HT, it was shown that patients with advanced PCa with a high baseline PSA level, high alkaline phosphatase level, high proportion of T4 tumours, poorly differentiated tumours, metastatic disease, and those with more than five skeletal hot spots did not show an adequate PSA response to HT [25]. According to the authors, these patients should not be candidates for IHT. IHT, however, does seem to be a feasible treatment option for patients with locally advanced hormone-sensitive PCa.

### Conclusions

IHT aims to minimise side-effects of treatment, to improve overall QoL, to reduce costs of therapy, and possibly to delay the progression to CRPC. Over the years, IHT has been evaluated in several phase 2 and 3 trials. From these trials, it can be concluded that IHT appears to have a beneficial effect on the incidence of side-effects and on QoL. Additionally, IHT appears to have no negative impact compared to continuous HT in terms of overall survival or progression-free survival. It could not yet be demonstrated that IHT prolongs the time to CRPC. It should be noted that most phase 3 studies are not yet mature, and definite results regarding overall and PCa-specific survival, time to CRPC, and QoL benefits are awaited. It also is not yet clear whether minor increases in testosterone levels during off-treatment intervals may induce or delay progression of PCa [26]. Further studies are needed to provide guidance on how to implement IHT in daily clinical practice. The optimal duration of induction therapy, the optimal triggers for restarting therapy during off-treatment periods, the use of MAB versus LHRH monotherapy during the induction period, and the issue whether some patients derive a cancer-survival benefit from reexposure to endogenous androgens should be further evaluated. For now, the EAU guidelines conclude that it is possible to offer IHT to selected patients, but results from clinical trials are still lacking. A minimum therapy induction period of 6–7 mo and PSA response to a level of <4 ng/ml in previously untreated patients are recommended for use in clinical practice [1].

### Conflicts of interest

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