The role of intermittent androgen deprivation in prostate cancer

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INTRODUCTION

Hormonal therapy involving LHRH agonists is a widely used systemic treatment for prostate cancer and is recommended in the European Association of Urology guidelines on prostate cancer for use in patients with locally advanced and metastatic disease (www.uroweb.org). LHRH agonists are currently administered to ≈90% of men with prostate cancer who receive hormonal therapy [1]. Nevertheless, the resulting androgen deprivation (AD) is associated with several side-effects, including osteoporosis, hot flashes, loss of libido/erectile dysfunction, fatigue, giaecomasia, cognitive dysfunction, depression, anxiety, loss of muscle mass, glucose intolerance [2–4] and changes in lipid profile [5], which could potentially lead to cardiovascular side-effects. Another issue is the development of androgen-independent prostate cancer. Normal prostate cells are unable to grow and regenerate in an androgen-deprived state, even over several decades of androgen withdrawal. However, prostate cancer cells can become androgen-independent [6]. It has been shown that most patients with metastatic disease under continuous AD (CAD) will have disease progression within 2–3 years [7]. Preclinical evidence suggests that the use of hormonal therapy on an intermittent basis to produce intermittent castration might delay androgen independence and hormonal resistance [8,9].

Additional potential benefits of intermittent AD (IAD) include improved quality of life (QoL) through a reduction in adverse effects during off-treatment phases, and the potential for reduced treatment costs.

QoL AND HORMONAL THERAPY

The principle that IAD is associated with improvements in overall QoL is based on the fact that testosterone levels recover during off-treatment phases [10] and toxicity is reduced in the absence of treatment [11]. The issue of improved QoL with IAD was explored in several studies. Higano et al. [12] examined the effects of IAD on bone mineral density (BMD) in 19 patients with nonmetastatic advanced prostate cancer who were hormonally naïve. During 9 months of hormonal therapy there was a decline in BMD in the lumbar spine or hip, or both. After a median off-treatment phase of 7.9 months there was a degree of recovery of BMD in the lumbar spine, although not to the level before hormonal therapy.

The association between hormonal therapy for prostate cancer and metabolic syndrome was recently reported [5]. This cross-sectional study included 20 men with prostate cancer who had been treated with hormonal therapy for ≥12 months, 18 age-matched men with nonmetastatic prostate cancer who had received local treatment, and 20 age-matched controls. The results showed that men on hormonal therapy had a significantly higher body mass index and lower total and free testosterone levels. The prevalence of metabolic syndrome was significantly higher in the hormonally treated group than in the untreated (P < 0.01) and the control (P = 0.03) groups. As part of the metabolic syndrome, men on hormonal therapy had a higher incidence of abdominal obesity and hyperglycaemia. These androgen-deprived men also had higher triglyceride levels than controls (P = 0.02). The identification of higher rates of metabolic syndrome in men on long-term hormonal therapy puts them at increased risk of cardiovascular disease (CVD).

The risk of CVD in patients with prostate cancer was reported in the Rotterdam section of European Randomized Study of Screening for Prostate Cancer [13]. The risk of cardiovascular death in patients treated with hormonal therapy was lower than in the general population. Cardiovascular mortality risks were also low within each treatment subgroup. At entry to the study, CVD was the most frequently self-reported comorbidity; patients with prostate cancer undergoing radical prostatectomy had the lowest rates. The authors of the report concluded that prostate cancer treatment did not appear to increase the risk of dying as a result of CVD.

The beneficial effects of IAD on cognitive function were studied in hormonal naïve patients with PSA relapse after primary therapy [14]. Patients were treated with 9 months of leuprolide plus flutamide, followed by an off-treatment phase. Cognitive function tests measuring spatial abilities, spatial memory, verbal fluency and memory and selective attention were assessed immediately after hormonal therapy and after 3 months off treatment. The results indicated that hormonal therapy was associated with beneficial effects on verbal memory, but adversely affected spatial ability. IAD had the opposite effect, reducing verbal memory and increasing spatial ability. IAD might also provide benefits in depressed men with prostate cancer. In a study of 40 men receiving CAD or IAD, there was a small but significant positive clinical effect on depression and anxiety scores with IAD [15].

General health-related QoL (HRQoL) and IAD with maximum androgen blockade (MAB) was studied in 250 men with locally advanced or metastatic disease [16]. Hormonal therapy was stopped after 9 months if the PSA level was <4 ng/mL and restarted when the PSA level rose to >20 ng/mL. QoL was assessed every 3 months for 30 months using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and EORTC QLQ–PR25 module. The results showed...
that testosterone suppression lead to a significant reduction in overall HRQoL and deterioration in most function and symptom scales. During the off-period, there was a trend of progressive improvement in HRQoL, which was in parallel with testosterone recovery. However, the rate of recovery was slower than the rate of deterioration during the treatment phase; the maximum recovery of HRQoL was most often in months 9–12. Notably, testosterone recovery was slower and less complete in older men, and led to concomitant poorer recovery of HRQoL. By contrast, Bouche et al. [17] reported no QoL benefits with IAD in a study of 43 patients with M1b prostate cancer. This prospective non-randomized study involved intermittent therapy with a LHRH agonist with or without an antiandrogen. There was no difference in the EORTC QLQ-C30 between therapy and off-therapy periods, but a rapid decrease in adverse events due to the hormonal deprivation was reported in all patient during the off-therapy period.

It is generally considered that IAD will be advantageous to sexual function. A phase III study by Da Silva et al. [18], comparing IAD with CAD in 874 men with locally advanced or metastatic disease, showed that at 12 months, 29% of patients receiving IAD reported sexual activity in the previous month, compared with 9% of men in the continuous arm.

PHASE II STUDIES OF IAD

Most clinical data on IAD comes from small phase II studies (Table 1) [8,11,19–30]. These population studies include a heterogeneous group of patients with metastatic disease, locally advanced, localized disease or biochemical failure after definitive therapy. Most studies involved the use of an LHRH agonist plus or minus an antiandrogen. The Phase II studies have helped to establish the safety of IAD, as well as to explore how to conduct IAD, i.e. the stop and start values. PSA levels, in general, were in accordance with testosterone increases and decreases, in that PSA followed testosterone but with a delay. In patients with a long off-treatment interval, the PSA level was even more stable at low concentrations, despite normalization of testosterone. The Phase II studies identified no 'flare' of the tumour after stopping androgen suppression.

In all studies, AD treatment continued until a PSA nadir (or most often a predefined PSA level) was attained, and then stopped until an empirically predefined PSA level was reached, which was frequently 10–20 ng/mL. The studies showed the effectiveness of re-instituting hormonal therapy in previous responders. The typical first treatment cycle lasted 7–16 months with a 6–9 month off-treatment period. There was a trend for longer off-treatment intervals in patients treated for localized disease or for PSA-only relapse after definitive local therapy. With increasing treatment cycles, there was a

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease stage, n</th>
<th>Localized PSA relapse</th>
<th>No. of patients</th>
<th>Therapy</th>
<th>Time, months</th>
<th>Off-treatment after 1st cycle</th>
<th>PSA level, ng/mL, to restart therapy</th>
<th>Response to re-treatment</th>
<th>No. of treatment cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>[19]</td>
<td>12</td>
<td>0</td>
<td>8</td>
<td>20</td>
<td>Diethylstilbestrol</td>
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<td>NR</td>
<td>All</td>
</tr>
<tr>
<td>[8]</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>LHRHa</td>
<td>6–9</td>
<td>2–11</td>
<td>NR</td>
<td>All</td>
</tr>
<tr>
<td>[20]</td>
<td>23</td>
<td>0</td>
<td>24</td>
<td>47</td>
<td>LHRHa + AA</td>
<td>6 + until 10</td>
<td>10</td>
<td>10–20</td>
<td>NR</td>
</tr>
<tr>
<td>[21]</td>
<td>2</td>
<td>10</td>
<td>10</td>
<td>22</td>
<td>LHRHa + AA</td>
<td>9–12</td>
<td>6</td>
<td>Varied</td>
<td>NR</td>
</tr>
<tr>
<td>[22]</td>
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<td>20</td>
<td>0</td>
<td>20</td>
<td>LHRHa + AA</td>
<td>9</td>
<td>9</td>
<td>&gt;3</td>
<td>All</td>
</tr>
<tr>
<td>[23]</td>
<td>0</td>
<td>13</td>
<td>7</td>
<td>20</td>
<td>LHRHa + AA</td>
<td>3–48</td>
<td>9–42</td>
<td>Varied</td>
<td>10/13</td>
</tr>
<tr>
<td>[24]</td>
<td>0</td>
<td>19</td>
<td>4</td>
<td>23</td>
<td>LHRHa + AA</td>
<td>9</td>
<td>7</td>
<td>Varied</td>
<td>NR</td>
</tr>
<tr>
<td>[25]</td>
<td>0</td>
<td>0</td>
<td>16</td>
<td>16</td>
<td>LHRHa</td>
<td>5.5</td>
<td>8</td>
<td>Any rise</td>
<td>All</td>
</tr>
<tr>
<td>[26]</td>
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<td>0</td>
<td>110</td>
<td>LHRHa + AA</td>
<td>9</td>
<td>16</td>
<td>&gt;10</td>
<td>All</td>
</tr>
<tr>
<td>[27]</td>
<td>11</td>
<td>4</td>
<td>39</td>
<td>54</td>
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<td>8</td>
<td>8.8</td>
<td>10</td>
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</tr>
<tr>
<td>[28]</td>
<td>24</td>
<td>19</td>
<td>9</td>
<td>52</td>
<td>LHRHa + AA</td>
<td>16 (m)</td>
<td>15.5</td>
<td>5</td>
<td>27 of 30</td>
</tr>
<tr>
<td>[31]</td>
<td>34</td>
<td>27</td>
<td>0</td>
<td>61</td>
<td>LHRHa ± AA</td>
<td>8 (m)</td>
<td>9</td>
<td>Varied</td>
<td>90% of initial responders</td>
</tr>
<tr>
<td>[32]</td>
<td>41</td>
<td>74</td>
<td>31</td>
<td>146</td>
<td>60 LHRHa ± AA; 86 AA alone</td>
<td>14.8 (m)</td>
<td>10.1</td>
<td>&gt;4 for RP; &gt;10 others</td>
<td>NR</td>
</tr>
<tr>
<td>[11]</td>
<td>0</td>
<td>0</td>
<td>107</td>
<td>107</td>
<td>LHRHa + AA</td>
<td>22.9 weeks</td>
<td>14.3 weeks</td>
<td>50% increase over nadir and &gt; 20</td>
<td>49 of 69</td>
</tr>
<tr>
<td>[29]</td>
<td>0</td>
<td>36</td>
<td>13</td>
<td>49</td>
<td>LHRHa + AA</td>
<td>NR</td>
<td>46.1 weeks</td>
<td>15 if pre-treatment level &gt;15, or pre-treat level</td>
<td>6 of 12</td>
</tr>
<tr>
<td>[30]</td>
<td>0</td>
<td>57</td>
<td>0</td>
<td>57</td>
<td>AA or LHRHa</td>
<td>5 or 6 (m)</td>
<td>8 (m)</td>
<td>&gt;4</td>
<td>43 of 51</td>
</tr>
</tbody>
</table>

LHRHa, LHRH agonist; AA, antiandrogen; RP, radical prostatectomy; NR, not reported; (m), median.
suggestion that the off-treatment period became progressively smaller, until androgen independence emerged [31,32]. However, a decrease in the off-treatment interval only indicates decreasing androgen responsiveness if all of the patients complete each of the cycles [33]. If this is not the case, then later cycles will only include those patients who had a shorter off-treatment interval in the initial cycles. To correct for this is it necessary to make individual off-treatment comparisons. In one Canadian study, the individual duration was expressed as a percentage of the first off-treatment interval, and as such it appeared to be fairly stable over five cycles [33].

The first study on IAD was reported by Klotz et al. [19], who treated 20 patients with advanced prostate cancer with an IAD protocol involving resumption of treatment with diethylstilbestrol on symptomatic clinical progression. The disease progressed after a median period of 8 months. Notably, sexual activity was restored during the off-treatment phase in nine of 10 patients rendered impotent during treatment. All patients had a rapid clinical response when treatment was restored.

The definition of optimal trigger points for stopping and starting treatment was developed by Goldenberg et al. [20]. Patients were treated with combined androgen blockade until a PSA nadir in the normal range (≤4 ng/mL) had been reached. Treatment was then stopped until the PSA level increased to a mean of 10–20 ng/mL. Serum testosterone was normalized within 8 weeks of stopping treatment. The mean and median overall survival times in this group of 47 patients were 210 and 166 weeks, respectively. Again, the off-treatment phase was associated with a recovery of libido and potency, as well as an increased sense of well-being.

A multivariate analysis was conducted on the 22 phase II studies published, including >1600 patients [34]. Of 1643 patients, the 5-year overall survival reported was: 86% in those with PSA relapse after radiotherapy or radical prostatectomy (563 men); 68% in patients with metastatic disease (366); and 90% in patients with localized disease (714). Predictors for outcome with IAD were shown to be initial PSA level, PSA nadir after hormonal therapy and length of off-treatment phase.

### PHASE III STUDIES

Several large-scale phase III studies are currently ongoing, comparing IAD with CAD, and these are summarized in Table 2. Preliminary results are available from the following studies: SEUG; Japanese study (only published trial of preliminary results); SWOG 9347; and EC 507. The SEUG study examined IAD with MAB vs continuous MAB and the primary outcome was efficacy (overall survival) and QoL (QLQ C30). In all, 766 patients with T3N0M0 or M1 prostate cancer and no previous treatment (including radiotherapy) were recruited. The mean follow-up in the 626 patients randomized (based on a PSA decrease to <4 ng/mL or to 80% below the initial value) is currently 2.5 years. Initial results indicate that IAD was associated with fewer side-effects (half of that with CAD) and better sexual activity (about three times that with CAD). In 20% of patients, treatment was resumed in <1 year; in 79%, the off-treatment period was >1 year and in 56% it was >2 years. Furthermore, there was no significant difference in the survival and, specifically, no early induced hormone-refractory status. The PSA level at randomization appeared to be a major factor for time off treatment [35].

The Japanese trial is the only study examining the effectiveness of adjuvant IAD after neoadjuvant endocrine therapy and external beam radiation therapy in men with locally advanced prostate cancer [36]. The primary objective is progression-free survival and the secondary objectives are overall survival, cancer-specific survival and QoL. To date, 215 of the required 300 patients with T3N0M0 or T4N0M0 disease have been registered; randomization is based on attaining a PSA level of <10 ng/mL and less than the pretreatment value. In all, 82 patients have been randomized to CAD and 80 to IAD after an initial hormonal treatment period of 14 months (the longest of all the IAD phase III trials). At a mean follow-up of 17.3 months, a progression-free survival of 97.5% has been reported and 41 patients in the IAD group have had three cycles of treatment.

Limited data were released from the SWOG 9346 study, which enrolled patients with metastatic stage IV disease for IAD or CAD with MAB [37]. The main objective is survival, and 1395 patients have been recruited from

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population (N)</th>
<th>Status</th>
<th>PSA nadir, ng/mL, when treatment stopped</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCIC-PR7</td>
<td>PSA relapse (radiotherapy) (M0); Target: 1340</td>
<td>Closed</td>
<td>≤10 and no CP</td>
</tr>
<tr>
<td>(NCIC-JPR7,</td>
<td></td>
<td></td>
<td>2.5 or CP</td>
</tr>
<tr>
<td>SWOG JPR 7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EC 507</td>
<td>PSA relapse after RP (201)</td>
<td>Closed</td>
<td>&lt;1.0 and no CP</td>
</tr>
<tr>
<td>ICELAND</td>
<td>PSA relapse/locally advanced (700)</td>
<td>Open</td>
<td>&gt;10 (or 20 or +20% nadir)</td>
</tr>
<tr>
<td>SEUG</td>
<td>Advanced prostate cancer (766)</td>
<td>Closed</td>
<td>&gt;10 or CP</td>
</tr>
<tr>
<td>Japan</td>
<td>Locally advanced (300)</td>
<td>Closed (?)</td>
<td>&gt;20 or CP</td>
</tr>
<tr>
<td>SWOG 9346*</td>
<td>M + (PSA &gt; 5 ng/mL)</td>
<td>Open</td>
<td>&gt;10 or CP</td>
</tr>
<tr>
<td>Target: 1500</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EC 210</td>
<td>M + (PSA &gt; 20 ng/mL)</td>
<td>Closed</td>
<td>&lt;0.5 and no CP</td>
</tr>
</tbody>
</table>

RP, radical prostatectomy; CP, clinical progression. *(NCIC-JPR8, INT-0162, CALGB-9594, NCIC-PR8, ECOG-S9346, EORTC-30985).
the 1500 patients included. Patients were randomized after 8 months of MAB based on achieving a PSA level of ≤4 ng/mL and with no signs of clinical progression. To date, the PSA level at 7 months after randomization appears to be a strong predictor of survival. For a PSA level of 4 ng/mL, ≤4 ng/mL and <0.2 ng/mL, the median survival was 13, 44 and 74 months, respectively.

The EC210 study is a Phase Ib/2 randomized study of intermittent vs continuous MAB therapy (leuprorelin 11.25 mg plus flutamide) in patients with metastatic stage IV prostate cancer (PSA ≥20 ng/mL and a life-expectancy of >9 months). The primary objective of the study is survival of patients responsive to MAB (median overall and progression-free survival) and the secondary objectives are comparison of side-effects, overall QoL and overall tolerance. Patients undergo 6 months of MAB therapy and are then randomized based on obtaining a PSA level of ≤4 ng/mL and no signs of clinical progression. To date, 387 patients have been included and of these, 194 were randomized to intermittent therapy or CAB (96). The planned analysis of overall survival is due at the end of 2007.

The EC507 trial is a large-scale phase III European study measuring the comparative effect of IAD and CAD in patients with PSA progression after radical prostatectomy over a 2-year period [38]. In all, 201 patients were randomized; 92 in the CAD group and 109 in the IAD group. A similar number of patients in both groups had androgen-independent tumour progression. There was no significant difference in time to progression in the two treatment groups after a mean follow up of 31 months. IAD led to significantly fewer days per quarter with specific side-effects than CAD, at a mean (SD) of 23 (28) vs 47 (40) days, respectively (P < 0.001).

PROPOSAL FOR THE USE OF IAD

There is a clear need for guidance on the use of IAD in patients, as the various studies that have been conducted use a range of PSA values for stopping and starting treatment, as well as different treatment regimens. None of the current prostate cancer guidelines provide detailed guidance on how to use this form of therapy. There is also confusion amongst urologists on which patients are eligible for IAD. A survey of 135 urologists conducted in three European countries (France, Italy and Germany) explored the current use of IAD (Takeda, data on file). This showed that 10–25% of LHRH agonists used was for IAD. In terms of the future use of IAD, i.e. in the 3 years after the survey, respondents stated that the use of IAD would increase in patients who were not suitable candidates for surgery, and in those with late-stage nonmetastatic disease and relapsing disease after radical surgery or radiotherapy.

One factor to consider is the duration of androgen suppression and the side-effects, which is particularly important in localized and locally advanced disease if patients are asymptomatic. This patient group is likely to undergo hormonal therapy for a prolonged period, due to their longer life-expectancy, even though there is no indication, as in the case of localized disease. In metastatic disease, the issue of side-effects is probably less important, even if a significant decrease of side-effects would be of interest. Patients who are considered suitable for immediate hormonal therapy and consequently IAD are:

- Localized disease: Unfit for local curative treatment; PSA ≥ 50 ng/mL; PSA doubling time <12 months; Gleason score ≥8; age <70 years [39].
- Locally advanced: N+ at radical prostatectomy [40] Locally advanced but not candidates for adjuvant radiotherapy: Gleason score >8; positive margins; positive seminal vesicles; PSA relapse after definitive therapy; short PSA doubling time of <12 months;
- Metastatic disease;

It is suggested that IAD should not be considered in patients who are eligible for hormonal therapy unless: (i) There was an excellent response during a 6–9 month induction phase (PSA level ≤4 ng/mL in metastatic patients or <0.5 ng/mL if the patient had previously received local therapy, e.g. radical prostatectomy or radiotherapy); (ii) The patient was motivated and well-informed; (iii) There was close follow-up of the patient by the physician (clinical monitoring and PSA measurement at 3- or 6-month intervals); (iv) Re-induction therapy if there was any sign of progression, either local or defined by a PSA level above a predefined level (>10–20 ng/mL in metastatic patients; >4 ng/mL in relapsing patients). The cost-effectiveness of IAD also needs to be considered, as there is a reduction in drug costs, but an increase in costs due to more physician visits and PSA testing. In patients with localized and locally advanced disease, long-term metabolic symptoms should be monitored. At present there is insufficient evidence to specify both the PSA nadir and the PSA levels for re-starting therapy, although an induction phase of ≥6 months is considered necessary. The predefined proposed thresholds to stop and resume the treatment are based only on the current and published trials. Specific trials should clarify those thresholds.

IAD should be conducted with agents that suppress androgen secretion (LHRH agonists, cyproterone acetate or diethylstilbestrol); excluded are nonsteroidal antiandrogens except for preventing ‘flare’, as there are currently no trials using these agents alone. Concern has been expressed about the increased testosterone level with this drug used as monotherapy.

CONCLUSIONS

IAD is a safe treatment option for patients with locally advanced and metastatic prostate cancer. It can be used in patients eligible for hormonal therapy, provided they meet certain criteria.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

L. Boccon-Gibod is an Advisor to, and N. Mottet and U. Tunn are Study Investigators for the sponsor.

REFERENCES


33 Tunn U. The current status of intermittent androgen deprivation (IAD) therapy for prostate cancer: putting IAD under the spotlight. BJU Int 2007; 99 (Suppl. 1): 19–22


39 Collette L, Studer UE, Whelan P et al. Is the degree of PSA decline after immediate androgen deprivation a prognostic factor for outcome in patients with T0–4, N0, M0 prostate cancer not suitable for local treatment with curative intent? (Results from the EORTC 30891 trial). Eur Urol 2006; 5: 288, Abstract 1062


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Abbreviations: (C)(I)AD, (continuous) (intermittent) androgen deprivation; (HR)QoL, (health-related) quality of life; BMD, bone mineral density; CVD, cardiovascular disease; MAB, maximum androgen blockade; EORTC, European Organization for Research and Treatment of Cancer.