Androgen Deprivation Therapy in Prostate Cancer – Current Status in M1 Patients

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Summary
Androgen deprivation therapy is the cornerstone treatment for metastatic prostate cancer. It can be done either surgically or medically. Luteinizing hormone-releasing hormone agonists and antagonist are the most effective drugs, with different side effects and modes of action, but no clear efficacy differences. Adding a non-steroidal antiandrogen adds a marginal benefit but also significant side effects and costs. Non-steroidal antiandrogens should not be used as monotherapy. In most patients with metastases, immediate castration is the standard of care. The intermittent modality is apparently non-inferior to the continuous one, with some other benefits. Upfront chemotherapy added to castration should be considered as the new standard of care in many metastatic patients. Castration leads to many adverse effects, some potentially life-threatening such as cardiovascular side effects.

Introduction
Prostate cancer (PCa) is the third most common cancer in men in the world, and the most common cancer in men in Europe, North America, and some parts of Africa [1, 2].

Androgen deprivation therapy (ADT) is the standard of care for metastatic PCA [1]. Its action is based on the suppression of testicular androgens or the inhibition of the action of circulating androgens by blocking their receptors. Complete androgen blockade (CAB) is a combination of both methods. Since the publication of Huggins et al. [2] in 1941, the efficacy of ADT in the palliative treatment of symptomatic advanced PCa is well recognized. Nowadays, ADT finds other indications as salvage therapy after biochemical recurrence or as an adjuvant to radiation therapy (RT) for high-risk localized and locally advanced cancers. These indications will not be processed here.

For decades, ADT was based on bilateral orchidectomy and estrogen administration. Since the 1980s, several new compounds have been developed, such as luteinizing hormone-releasing hormone (LHRH) agonists, antiandrogens (AA), and finally LHRH antagonists. More recently, 2 new compounds have been marketed which are considered as a second-line hormonal therapy targeting the androgen axis: abiraterone acetate, a CYP 17 inhibitor leading to the suppression of adrenal androgen synthesis as well as intracrine androgen synthesis, and enzalutamide, a new androgen receptor blocker. A detailed description of their mechanisms of action is beyond this review. Both are only approved for metastatic castration-resistant patients, and have still no place in the androgen-sensitive situations.

Castrate Level
The castrate level of serum testosterone was defined as < 50 ng/dl (1.7 nmol/l) at a time when the lower sensitivity of serum testosterone tests was 50 ng/dl. However, with recent techniques, the average value of serum testosterone after bilateral orchidectomy is recognized to be around 15 ng/dl [3]. Therefore, the redefined castrate level should be < 20 ng/dl (1 nmol/l) with the support of several series that have shown better results with a lower testosterone level [4]. However, the regulatory authorities allow the threshold of 50 ng/dl which is still used in all clinical trials.

Surgical Castration
Bilateral orchidectomy (either total or subcapsular pulpectomy) is a relatively simple, cheap, and safe procedure. It has been gradually almost replaced by medical castration [5, 6].
Estrogen Therapy

Until the introduction of LHRH agonist therapy in the 1980s, estrogen therapy in the form of diethylstilbestrol (DES) was often used for hormonal manipulation of PCa. DES is not associated with bone loss [7]. However, DES is not recommended as first-line treatment based on cardiovascular side effects [1] leading to as much as 20% excess mortality with 5 mg daily [8]. This is mainly due to deep vein thrombosis, transient ischemic attack, and myocardial infarction. Additional studies showed similar therapeutic efficacy with reduced doses of DES (1 and 3 mg/day) but with the persistence of cardiovascular side effects although mortality was reduced [9]. 2 strategies have been tested to reduce cardiovascular morbidity, both proving ineffective: the combination with warfarin or aspirin [10]; the use of parenteral estrogen (polyestradiol phosphate) to bypass the hepatic metabolism [11]. However, DES is no longer registered for PCa treatment in most European countries.

Luteinizing Hormone-Releasing Hormone Agonists

Marketed since 1987, the LHRH agonists are currently the main form of ADT used in industrialized countries [12]. They are obtained by specific modification of the natural LHRH, decapeptide, typically by substitution of an amino acid or by alkylation. Their effect is based on pituitary desensitization following the initial non-pulsed overstimulation of the LHRH receptor resulting in an intense and steady stimulation. This stimulation explains the phenomenon of ‘testosterone surge’ after the first injection. It is constant with a transient increase in serum testosterone 2–3 days after the first injection with a deferred castration achieved around 2–4 weeks later [5]. The achieved testosterone levels are < 20 ng/dl in 85% and < 50 ng/dl in 90% [3] of patients.

This testosterone surge might lead to a clinical flare that usually occurs in patients with a high tumor volume. It can lead to increased bone pain, acute urinary retention, obstructive renal failure, and spinal cord compression. The flare up complications may be limited by short-term administration of an AA [1] or by choosing an antagonist.

The available agonists are leuprorelin, goserelin, and triptorelin. Each has specific characteristics and delivery procedures that must be strictly followed to optimize drug efficacy. They exist in monthly, every 3 months, every 6 months, and yearly formulations. There is no formal direct comparison between these various compounds; they are considered to be equally active [12].

Luteinizing Hormone-Releasing Hormone Antagonists

LHRH antagonists bind competitively and reversibly to LHRH receptors, leading to a rapid decrease in luteinizing hormone and follicle-stimulating hormone release and finally to a decrease in serum testosterone. There is no phenomenon of ‘flare-up’ [13]. 2 compounds have been marketed: abarelix and degarelix, and both use a subcutaneous route.

Abarelix

Abarelix is an LHRH antagonist that has proven its effectiveness compared to agonists in ADT. However, its propensity to induce life-threatening anaphylaxis led to the withdrawal of the authorization initially granted by the FDA [14]. Nevertheless, it retains an indication in symptomatic metastatic PCa with no possibility of another treatment for short-term administration in some European countries [14].

Degarelix

Degarelix is an LHRH antagonist with no associated allergic reaction. The first dose (2 injections of 120 mg) leads to castration from the 3rd day in 95.5% of patients. A randomized control trial (RCT) suggested that this drug is at least non-inferior to monthly leuproreline and achieves a quicker castration. It might even have some benefits [15]. Its side effects are the same as those seen with agonists in addition to a moderately painful injection (40%), mainly after the first injection. In practice, the use of degarelix is limited by a monthly formulation.

Antiandrogens

AA are either steroidal (SAA) or non-steroidal (NSAA) according to their structure. These are peripheral androgen receptor antagonists. In addition to this mechanism, SAA have progestin properties leading to central androgen suppression by crossing the blood-brain barrier [16]. Used as monotherapy, NSAA are not associated with a testosterone level decrease. They could protect against loss of libido, erectile dysfunction, and bone loss.

SAA are still used either in CAB or to treat hot flushes [17]. The NSAA are represented by nilutamide, flutamide, and bicalutamide. Bicalutamide is better tolerated than nilutamide or flutamide. The main NSAA class toxicity is liver toxicity (potentially fatal) requiring monitoring of liver enzymes. NSAA use, especially bicalutamide, is associated with gynecomastia (70%) and breast pain. These side effects can often lead to treatment discontinuation [18].

Androgen Deprivation Therapy in Metastatic PCa

ADT is the standard of care in M1 patients. They represent a heterogeneous group of situations, with survival depending on the location of the metastases (axial bone only, appendicular, or visceral), performance status, Gleason score, initial prostate-specific antigen (PSA) level [19], and alkaline phosphate levels [1]. Another important prognostic factor is the PSA level after 7 months of ADT [20]. In recent reports, the median survival has been 42 months [21] compared to less than 33 months in previous reports [19]. This improvement might be partly explained by the emergence of new compounds, a better treatment policy, as well as a lead-time bias from early diagnosis [22].
Immediate or Deferred Androgen Deprivation Therapy?

Primary ADT is the standard of care for metastatic PCa. There is still some debate regarding the immediate need for ADT in asymptomatic patients. A review of the Cochrane Library on trials conducted in the pre-PSA era found that early implementation of ADT can reduce the risk of developing disease complications such as bone pain, pathologic fractures, and spinal cord compression, but without any overall survival benefit [23]. Nevertheless, ADT was shown to be the most cost-effective modality when used as a deferred treatment [24].

The European Association of Urology guidelines conclude that the only candidates for deferred treatment are asymptomatic patients with a strong will to avoid treatment-related side effects and accepting close follow-up [1].

Which Method of Androgen Deprivation Therapy?

Bilateral Orchidectomy versus Agonists

Despite being a reliable, inexpensive, and very effective modality, orchidectomy has been supplanted by medical methods, largely because of improved patient and physician acceptance [12]. Although agonists do not provide castrate levels as low as those achieved by bilateral orchidectomy in about 15% of cases, and testosterone micro-surges on repeated injection [25] often exist, no differences in disease progression or survival have ever been shown. Therefore, both modalities are considered comparable [6]. However, bilateral orchidectomy is an irreversible method that does not allow intermittent treatment.

Agonists versus Antagonists

Based on a possible clinical flare associated with LHRH agonists, it is accepted that patients with advanced metastatic disease at high risk of complications such as impending spinal cord compression should receive either bilateral orchidectomy or LHRH antagonist as first-line treatment [22]. In other cases, the available data preclude any definitive conclusion regarding formal superiority in the long term of the antagonists compared to the agonists.

Antiandrogen Monotherapy

Administration of NSAA (mainly bicalutamide 150 mg/day) as monotherapy in metastatic patients should no longer be considered [1] based on a Cochrane systematic review [25]. The use of NSAA decreased overall survival (OS) (hazard ratio (HR) 1.24, 95% confidence interval (CI) 1.05–1.48), and increased clinical progression and treatment failure. Patients receiving AA were also more likely to stop treatment as the result of side effects (breast pain, enlargement of breast tissue, and symptoms of physical weakness).

Otherwise, bicalutamide monotherapy clearly offers bone protection compared to castration by LHRH agonists [18].

SAA are no longer considered as acceptable monotherapy in metastatic PCa mainly due to the lack of clear efficacy data.

Combined Therapy or Monotherapy?

The results from the many studies comparing CAB with monotherapy are divergent. An overview of the RCTs involving 8,275 patients conducted by the Prostate Cancer Trialists’ Collaborative Group (PCTCG) [26] demonstrated that CAB (orchidectomy or LHRH agonists plus an NSAA) resulted in marginally better OS (27.6 vs. 24.7%; p = 0.005) beyond 5 years, while CAB with an SAA (cyproterone acetate) resulted in worse OS (15.4 vs. 18.1%; p = 0.04). Exclusion of trials in which a short-term AA was not used for disease flare prevention resulted in no difference in survival between CAB and castration even if the AA used was an NSAA [27]. Therefore, CAB is no longer considered as a standard of care [1]. Also, the use of CAB is associated with increased side effects and costs.

Intermittent or Continuous Androgen Deprivation Therapy?

The rationale for intermittent androgen deprivation (IAD) was developed based on animal models and in vitro studies. It represents consecutive cycles of castration and non-castration periods, based on PSA and clinical evolution. It has been suggested that IAD could increase the time to castration resistance, improve quality of life (QoL), prevent complications related to long-term ADT, and reduce treatment costs.

Two systematic reviews were published in 2010 and 2013 [28, 29] summarizing the RCTs comparing IAD and continuous androgen deprivation (CAD) for the treatment of men with relapsing, locally advanced, or metastatic PCa (table 1). IAD is at least non-inferior to the continuous modality. The results of SWOG 9346, which is the largest trial with 1,535 randomized patients, were inconclusive in terms of formal non-inferiority between both modalities [30]. In addition, improvements in QoL are limited regarding sexual function, physical activity, and general wellbeing. Moreover, it seems that IAD reduces bone loss [31] and limits metabolic syndrome effects. Finally, median cost savings with IAD are significant and estimated to be 48% [28].

In practical terms, IAD is reserved for those patients with a major clinical and PSA response 6–7 months after the initial castration. The optimal thresholds to stop and resume ADT have been empirically defined. In metastatic disease, treatment is usually stopped after a clear PSA response (< 4 ng/ml), and resumed if the PSA is greater than 10–20 ng/ml, or upon clinical progression. The patient should be compliant with regard to close follow-up.

Androgen Deprivation Therapy Combined with Upfront Chemotherapy?

On this subject, 3 large RCTs have been conducted; 2 are fully published [32, 33] while the third was presented at the last ASCO meeting [34]. All compared ADT alone as standard treatment with
ADT combined with upfront docetaxel (75 mg/m², every 3 weeks combined with steroid premedication) with the same primary objective (OS). The key findings are summarized in table 2.

In the 2 fully published papers, the results were conflicting, although several differences between both trials might explain the discrepancies: the French trial [32] was clearly underpowered, patients in the Chaarted trial [33] had more advanced disease, and subsequent salvage treatment was different in both trials. In the Chaarted trial, the OS benefit was 13 months (HR 0.61, 95% CI 0.47–0.8) [33]. The final conclusion comes from the STAMPEDE trial [34], although not yet fully published. The results of the 3 trials are summarized in table 2.

In the STAMPEDE trial, parallel arms were conducted at the same time. The reference arm (ADT monotherapy) included 1,184 patients. 1 experimental arm was docetaxel combined with ADT (n = 593 patients), the other was docetaxel combined with zoledronic acid (n = 593 patients). Patients were either M1, or N1, or having 2 criteria out of the following: T3/4 or PSA > 40 ng/ml or Gleason 8–10. They could also be relapsing with 1 of the following criteria: PSA > 4 ng/ml with a PSA doubling time < 6 months, PSA > 20 ng/ml, N1, or M1. No stratification was used regarding metastatic disease volume (high/low). The survival benefit was 10 months for the entire population (HR 0.76, 95% CI 0.63–0.91) and 22 months for the M1 only population (HR 0.73, 95% CI 0.59–0.89).

In the 3 trials, toxicity was mainly hematologic with around 12–15% grade 3–4 neutropenia, and 6–12% grade 3–4 febrile neutropenia. Granulocyte-colony stimulating factor was shown to be helpful, and its use should be based on available guidelines [35].

Based on these data, upfront docetaxel combined with ADT should be considered as a new standard in newly diagnosed metastatic patients, at least in the high-volume situations, provided patients are fit enough and accept to receive the drug.

### Androgen Deprivation Therapy-Associated Side Effects

ADT is associated with multiple known side effects. A detailed review is far beyond this text [36]. Apart from the well-known hot flushes, changes in libido, erectile dysfunction, and bone and mus-

<table>
<thead>
<tr>
<th>Study [ref.]</th>
<th>Patients, n</th>
<th>T stage</th>
<th>PSA threshold to stop, ng/ml</th>
<th>PSA threshold to resume, ng/ml</th>
<th>Median follow-up, months</th>
<th>Time to progression</th>
<th>Specific survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calais da Silva [41]</td>
<td>766</td>
<td>locally advanced/metastatic</td>
<td>&lt; 4</td>
<td>&gt; 10 for symptomatic and &gt; 20 for asymptomatic</td>
<td>50</td>
<td>HR 0.81 in favor of the continuous arm; p = 0.11</td>
<td>IAD 23.6% dead, continuous 20.8% dead HR 0.88</td>
<td>IAD 54.1% dead, continuous 54.2% dead HR 0.99; p = 0.84</td>
</tr>
<tr>
<td>Salonen [42]</td>
<td>554</td>
<td>locally advanced/metastatic</td>
<td>&lt; 10</td>
<td>&gt; 20</td>
<td>65</td>
<td>IAD 34.5 mo., continuous 30.2 mo. HR 1.08; p = 0.43</td>
<td>IAD 43% dead; 45.2 mo. continuous 47% dead; 44.3 mo. HR 1.17; p = 0.29</td>
<td>IAD 45.2 mo., continuous 45.7 mo. HR 1.15; p = 0.17</td>
</tr>
<tr>
<td>Hussain [30]</td>
<td>1,535</td>
<td>metastatic</td>
<td>&lt; 4</td>
<td>&gt; 20</td>
<td>108</td>
<td>IAD 16.6 mo., continuous 11.5 mo.; p = 0.17</td>
<td>IAD 64% dead, continuous 56% dead</td>
<td>IAD 5.1 years, continuous 5.8 years HR 1.09</td>
</tr>
<tr>
<td>Langenhuijsen [43]</td>
<td>193</td>
<td>metastatic</td>
<td>&lt; 4</td>
<td>&gt; 10 for not metastatic and &gt; 20 for metastatic</td>
<td>31</td>
<td>IAD 18.0 mo., continuous 24.1 mo.</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mottet [44]</td>
<td>173</td>
<td>metastatic</td>
<td>&lt; 4</td>
<td>&gt; 10</td>
<td>44</td>
<td>IAD 20.7 mo., continuous 15.1 mo. p = 0.74</td>
<td>–</td>
<td>IAD 56.9% dead; 42.2 mo. continuous 54.2% dead; 5 20 mo. p = 0.75</td>
</tr>
<tr>
<td>De Leval [45]</td>
<td>68</td>
<td>locally advanced/metastatic/BCR</td>
<td>&lt; 4</td>
<td>&gt; 10</td>
<td>31</td>
<td>IAD 28 mo., continuous 21 mo.</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

HR = Hazard ratio; CAD = complete androgen deprivation; mo. = months; PSA = prostate-specific antigen; BCR = biochemical recurrence.

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Table 1. Key findings of intermittent androgen deprivation (IAD) compared to continuous treatment in locally advanced/metastatic situations

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The first is characterized by the presence of 3 of the following factors: waist circumference > 102 cm, serum triglyceride > 1.7 mmol/l, blood pressure > 130/80 mm Hg or use of medication for hypertension, high-density lipoprotein cholesterol < 1 mmol/l, and glycermia > 5.6 mmol/l or the use of medication for hyperglyceremia. The prevalence of metabolic syndrome is increased with ADT [37], and it can occur as early as in the first 3 months of treatment. The syndrome has an association with cardiovascular risk factors.

Cardiovascular mortality is now the most common cause of death in PCa patients. The increased cardiovascular morbidity and mortality risks are clear even after 6 months of ADT [38]. The mortality risk is especially important in patients with a previous history of cardiovascular morbidity, or with a metabolic syndrome [39, 40]. Different castration modalities might be associated with different cardiovascular risk, even if no clear evidence is available so far. Preventive advice includes non-specific measures: weight loss, increased exercise, improved nutrition, and smoking cessation.

**Conclusion**

Progress is being made in the treatment of M1 patients. ADT still represent the major treatment modality, associated with significant side effects to consider. The testosterone level must be monitored and kept as low as possible. The early introduction of docetaxel combined with ADT in hormone-sensitive patients represent a major improvement in the treatment policy of these patients, with a median survival benefit close to 1 year.

**Disclosure Statement**

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