What is New in Hormone Therapy for Prostate Cancer in 2007?

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1. Introduction

Since the seminal work of Charles Huggins in the early 1940s, androgen-deprivation therapy (ADT) is the cornerstone strategy for the treatment of advanced prostate cancer (PCa) [1,2]. Huggins showed that depriving PCa cells of androgens by surgical castration or oestrogens induces programmed cell death (i.e., apoptosis), resulting in major shrinkage of the prostate tumour and its metastases. Although the pathophysiology of ADT-induced apoptosis has been extensively studied in human and animal models, the level of testosterone at which apoptosis cell death is triggered is still presently unknown [3].

In 1971, Andrew Schally purified the luteinising hormone-releasing hormone (LHRH) receptor and
synthesised the first LHRH agonists [4,5]. As such, he provided the basis of “medical castration” [6]. LHRH is produced by the hypothalamus and regulates the secretion of luteinising hormone (LH) and follicle-stimulating hormone (FSH) by the anterior pituitary gland, resulting in testosterone synthesis by the Leydig cells of the testes. When using LHRH agonists (ie, synthetic analogues of LHRH) to suppress androgen secretion, the LHRH receptor on the pituitary cells will be activated once, causing an initial surge of LH, FSH, and testosterone and then made unavailable for LHRH. Moreover, a recent study demonstrated that LHRH agonists induce cellular changes in PCa cells [7]. Currently, different LHRH agonists are commercially available including leuprorelin, goserelin, triptorelin, and buserelin.

This paper is based on an interactive discussion on the role of LHRH agonists in ADT held at the Oncoforum summary meeting in Brussels, Belgium in September 2007. The participants’ opinions were assessed via interactive voting and the outcomes of the voting were commented on directly by an expert panel. The participants involved were mainly academic urologists. The discussion focused on new concepts in hormone therapy, including indications for ADT and the potential of the new leuprorelin formulation Eligard® for the management of PCa.

2. Indications for ADT

Although new evidence has emerged to support broader indications for hormone therapy in younger patients with earlier disease, it is still a matter of debate whether it really prolongs survival in all clinical settings [8].

The outcomes of the following question, “Which of these indications is not an evidence-based recognised indication of ADT?” illustrated this relative lack of contemporary evidence (Fig. 1). One of the major issues is the striking difference between the beneficial effect of hormone therapy when it is used alone or when it is prescribed to increase the efficacy of radiation therapy. The European Organization for Research and Treatment of Cancer (EORTC) trial 30891 compared immediate versus deferred ADT in patients with locally advanced PCa not suitable for local treatment. Immediate ADT resulted in only a modest increase in overall survival, with the time to hormone-resistant symptomatic progression and disease-specific survival not increased [9]. The recent update of the Messing trial [10] confirmed that immediate ADT significantly benefits patients with

**Fig. 1 – Outcomes of the voting on the question: “Which of these indications is not an evidence-based recognised indication of androgen deprivation therapy?”**

Answer 1: Immediate treatment of symptomatic patients.
Answer 2: Long-life adjuvant treatment of patients with positive lymph nodes at radical prostatectomy.
Answer 3: Short-term (6 mo) adjuvant treatment to external-beam radiation therapy (EBRT) in patients with locally advanced rapidly progressing prostate cancer.
Answer 4: Long-term (3 yr) adjuvant treatment of patients with positive margins and seminal vesicle invasion after radical prostatectomy.
positive lymph nodes who underwent radical prostatectomy and pelvic lymphadenectomy compared to deferred ADT at a median follow-up of 11.9 yr (Fig. 2). It should be recognised, however, that the patients in this study had high-burden disease (eg, seminal vesicle involvement, positive surgical margins, Gleason score 8–10), which probably does not reflect the majority of patients seen in contemporary series driven by prostate-specific antigen (PSA) levels. These modest results obtained when ADT is used alone contrasts with the super-additive results observed when ADT is combined with external-beam radiation therapy (EBRT), supporting historical in vitro data [11]. In addition to the EORTC 22863 and Radiation Therapy Oncology Group (RTOG) 8531 trials demonstrating that long-term adjuvant ADT improves outcome in locally advanced cancers, evidence now supports similar indications in patients with high-risk localised disease. In a first trial conducted by D’Amico, 206 patients were randomised to receive three-dimensional conformal radiotherapy (3D-CRT) alone or combined with 6-mo of ADT. After a median follow-up of 4.5 yr, patients randomised to receive 3D-CRT + ADT had a significantly higher survival (88% for 3D-CRT + ADT vs. 78% for 3D-CRT alone; \( p = 0.04 \)) [12]. Another retrospective review compiled by the same investigator confirmed the beneficial effect of short-term (6 mo) adjuvant ADT after radiotherapy in men with PCa with a rapidly increasing pretreatment PSA level [13]. Despite the significantly higher proportion of Gleason score 7–10 and advanced clinical T category cancers (T2b–T3), patients treated with radiotherapy and ADT had a significantly longer time to PCa-specific (\( p = 0.005 \)) and overall mortality (\( p < 0.001 \)) compared to patients treated with radiotherapy alone.

### 3. Is medical castration comparable to surgical castration?

#### 3.1. LHRH agonists equivalent to orchidectomy?

The conventional urological wisdom supports the equivalence between LHRH agonists and surgical castration in terms of both survival and incidence of side-effects. This postulate, however, relies on a very limited number of trials. Interestingly, a more detailed analysis of these trials highlights the gap between what we have accepted and what is true.

##### 3.1.1. Survival analysis

A direct comparison has been conducted between the LHRH agonist goserelin and orchidectomy in two randomised trials [14,15]. The concluding remark was that overall survival with both treatment options was equivalent [14,15]. An early study conducted by Kaisary et al [14] demonstrated that patients with metastatic PCa had, at a median follow-up of 2 yr, a median survival time of 115 and 104 wk (\( p = 0.33 \)) in the goserelin (\( n = 148 \)) and orchidectomy (\( n = 144 \)) groups, respectively, without differences in causes of death between the treatment groups. Another randomised trial confirmed these results and showed that patients with stage D2 PCa died after a median survival time of 119 wk in the goserelin (\( n = 138 \)) group and 136 wk in the orchidectomy (\( n = 145 \)) group (\( p = 0.42 \)), with a follow-up period of at least 4 yr [15].

But another look at these papers provides other evidence that weakens the commonly held contention that goserelin is equivalent to orchidectomy. Vogelzang et al report in the statistics section of their paper that they stopped the trial early, before their recruitment targets were met, because it had a similar design to the Kaisary trial and they could pool results. Consequently, they were left with a 67% chance to detect a 30% difference. As for the Kaisary trial, although they met the recruitment target of 343 patients, the dropout rate was so high that the number of patients analysed was similar to the Vogelzang trial. Kaisary did not outline the statistics well, but we could hypothesise that they were left with a similarly underpowered study.

Also of interest in this paper is a marked difference in time to progression of 28 wk versus 40 wk in favours of orchidectomy. However, the survival of 90 wk versus 110 wk is not statistically significant with goserelin being the latter. The author notes that at progression, the treating physician was able to do what he considered appropriate. Any additional treatments are not reported on, but based on the difference between time to progression and survival we might conclude that differences could be significant. These data are indeed from the pre-PSA era so that time to progression could have greater significance than what could be generated today from PSA progression.

It may be concluded then, sadly, that we still do not know for sure if LHRH agonists are equivalent to castration.

##### 3.1.2. Side-effects and quality of life

Possible side-effects experienced by patients with PCa due to testosterone withdrawal include hot flushes, loss of libido, erectile dysfunction, gynaecomastia and breast pain, anaemia, decrease in bone mineral density, metabolic syndrome, and
cognitive impairment [8]. According to the multi-centre, randomised trial conducted by Vogelzang et al [15], the most common side-effects after treatment with goserelin and orchidectomy were hot flushes and pain. Although the overall pattern of side-effects was similar for both treatment groups, hot flushes were more frequently reported in the goserelin group than in the orchidectomy group (54% vs. 43%, respectively). In addition, it appears that also the quality of life (QoL) outcomes seem to be different for PCa patients undergoing medical versus surgical castration. Results from the Prostate Cancer Outcomes Study (PCOS) revealed that repeating the injection reawakened the patient’s negative feelings associated with PCa [16]. Patients who received LHRH agonists experienced more physical discomfort and worry about PCa and were more likely to report being in fair or poor health than patients who underwent orchidectomy (Fig. 3).

3.2. What is the reference castration level?

Surgical castration induces rapid, profound, and sustained testosterone suppression. Therefore, levels of testosterone after orchidectomy should be used as benchmarks to compare pharmacological performances of LHRH agonists and antagonists. Because of limitations and poor reproducibility of historical testosterone assays in the 1980s, the Food and Drug Administration (FDA) set castration testosterone levels at ≤50 ng/dl. This is still today the only recognised registration value. Although when using contemporary assays, it appears clearly that surgical castration consistently lowers the level of castration below 20 ng/dL, close, in fact, to an average of 15 ng/dl [14,15,17–20]. This suggests that a limit of 20 ng/dl would be more representative as a reference value of castration to compare the performances of LHRH agonists.

3.3. Pharmacology of LHRH agonists

Medical castration is different from surgical castration because LHRH agonists initially stimulate LHRH receptors in the pituitary. This induces a transient elevation of testosterone above physiological levels within 2–3 d, known as the testosterone surge. The testosterone surge can cause or aggravate urinary symptoms or bone pain, and even lead to severe neurological complications in case of preexisting bone metastasis and should therefore be associated with an antiandrogen during 2 wk [8]. The second drawback of LHRH agonists is the fact that castration is delayed, with lower levels of testosterone being obtained within 2–4 wk following the first injection. Most LHRH agonists formulations are delivered as depots, the drug being released over a 1–3-mo period. In case the depot formula does not cover the entire delivery period, there will be unoccupied LHRH receptors, so that a new testosterone surge will occur after repeat injection. These rises are commonly called mini-flares. The clinical significance of mini-flares is unknown. Mini-flares are different from late breakthrough escapes, which are persistent elevations of testosterone above the limit of 50 ng/dl despite continuous administration of the LHRH agonist. It is important to recognise this phenomenon and not to consider the cancer as hormone resistant. Late breakthrough escapes can simply be managed by switching to another agonist or doing an orchidectomy.

3.4. Are conventional LHRH agonists equivalent to orchidectomy in terms of testosterone control?

Although LHRH agonists have replaced surgical castration [21], most LHRH agonists are not equivalent to surgical castration in terms of testosterone
Several studies have demonstrated that conventional LHRH agonists fail to achieve testosterone levels \( \leq 50 \text{ ng/dl} \) in 2–12.5% of patients [22–27], whereas testosterone levels comparable to surgical castration (\( \leq 20 \text{ ng/dl} \)) are not reached in 13–46.4% of patients [20,22,24,25,28,29]. In addition, repeat injection of conventional LHRH agonists is associated with late breakthrough escapes [27,30,31] and mini-flares [23,32] in 4–12.5% and approximately 10% of patients, respectively.

### 4. Pharmacological performances of Eligard

The delivery system of synthetic LHRH agonists is important to achieve optimal concentration of the agonist and therefore improve testosterone control. Conventional leuprorelin acetate depot is embedded in microspheres injected intramuscularly. In contrast, Eligard uses a unique Atrigel delivery system, in which leuprorelin acetate is combined with a biodegradable polymer and a liquid carrier. When Eligard is subcutaneously injected as a liquid, it solidifies in the body and biodegrades over time, providing a sustained and controlled release of leuprorelin acetate [33]. Eligard is currently available in several European countries as a 1- or 3-mo formulation. In addition, this improved delivery system has made it possible to develop a 6-mo formulation.

Similar to other LHRH agonists, testosterone castrate levels are usually obtained within 2–4 wk after injection with Eligard [30,32,34]. A serum testosterone level \( \leq 50 \text{ ng/dl} \) is obtained in all patients with Eligard 1- and 3-mo depot formulations [35,36] and in 99% of patients receiving a 6-mo depot injection [34]. In only 2.5%, 6%, and 12% of patients receiving 1-, 3-, and 6-mo Eligard formulations, respectively, was a serum testosterone level \( \leq 20 \text{ ng/dl} \) not achieved [34–36]. None of the patients on all three Eligard formulations had mini-flares, whereas late breakthrough escapes did occur in only 1% of patients on Eligard 3- and 6-mo formulations [30–32].

It is certainly too premature to know whether Eligard will improve survival and QoL outcomes. The ability to develop a 6-mo formula, though, is of immediate benefit for patients looking at greater flexibility in their treatment regimen. A survey conducted in 200 patients with PCa from five European countries demonstrated that 68% of patients would, if available, prefer a 6-mo depot formulation to increase the interval between two injections [37]. Nearly half of all patients believe that a 6-mo injection would significantly improve their QoL. The main advantages they reported were fewer visits to the doctor, less reminder of the disease, and more convenience. Furthermore, 86% of patients felt that having one product available in a 1-, 3-, and 6-month formulation would be advantageous. However, patients receiving long-term hormone therapy are at an increased risk of side-effects. Mild to moderate hot flushes were the most frequently reported side-effects with Eligard [34].

### 5. Conclusions

Until now, the appropriate timing and duration of ADT is still a matter of debate. Surgical castration induces rapid, profound, and sustained testosterone suppression. Medical castration with conventional LHRH agonists does not reach the same testosterone level as surgical castration. In addition, the maintenance of low testosterone levels is not consistently accomplished because late breakthrough escapes and mini-flares are observed. Eligard 1-, 3-, and 6-mo formulations may achieve optimal testosterone control. Although it is too early to know whether Eligard will improve survival and QoL outcomes, an Eligard 6-mo formulation may offer some benefits for men with PCa.

### Conflicts of interest

Prof. Tombal is a paid consultant for Astellas, AstraZeneca, Ferring, Pfizer, Ipsen, and sanofi-aventis.

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