

Management of advanced prostate cancer: can we improve on androgen deprivation therapy?

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Gonadotrophin-releasing hormone (GnRH) agonists are currently the mainstay in the management of advanced prostate cancer. Used either as monotherapy or combined with antiandrogens, GnRH agonists suppress serum testosterone levels and thus slow the growth of the tumour cells that depend on testosterone for growth. GnRH agonists have largely replaced orchidectomy in the management of advanced prostate cancer, because patients are reluctant to undergo

surgical castration. However, can we do better in androgen-deprivation therapy? There is some evidence to suggest that GnRH agonists do not achieve the level of testosterone suppression attained with orchidectomy, or as rapidly, factors which could be expected to affect overall survival. Together, these observations highlight the need to develop newer agents that can achieve rapid, profound and sustained testosterone suppression, equivalent to that with

orchidectomy. Preliminary data for the GnRH blocker, degarelix, suggest that this new agent might overcome the shortcomings associated with GnRH agonists. Further clinical data are therefore awaited with much interest.

KEYWORDS

GnRH agonists, orchidectomy, GnRH blockers, testosterone suppression, advanced prostate cancer

INTRODUCTION

The management of patients with metastatic prostate cancer was revolutionized in the 1940s, with the discovery by Huggins and Hodges [1] that testosterone is essential for the growth of prostate cancer cells. They found that in the absence of testosterone, tumour cells undergo apoptosis, resulting in shrinkage of the primary tumour. This led to the development of orchidectomy as the standard treatment for advanced prostate cancer.

As testosterone is largely produced in the testes, orchidectomy achieves effective testosterone suppression. Originally, the level of testosterone suppression achieved with orchidectomy was considered to be ≤ 50 ng/dL, as this was the level of sensitivity of the available assay at the time. The development of the fully automated immunoassay analyser now allows the measurement of testosterone levels down to 0.1 ng/dL [2]. Various studies using this technology have established that orchidectomy suppresses testosterone levels to <20 ng/dL [3–6].

While orchidectomy is highly effective for suppressing testosterone levels, the procedure

is unacceptable to many patients and has now largely been replaced by various forms of medical castration, often referred to as androgen-deprivation therapy (ADT). The most widely used ADT is treatment with GnRH agonists; these agents suppress serum testosterone levels by suppressing the synthesis of testosterone by the testes. Testosterone production is regulated by the peptide hormones GnRH and LH. GnRH, released in the hypothalamus, stimulates the release of LH from the pituitary. LH in turn acts on the Leydig cells of the testes to produce testosterone. GnRH agonists act by binding to the GnRH receptor in the pituitary (Fig. 1). The initial response is the release of LH, followed by inhibition of LH secretion [7]. As a result, GnRH agonists produce an initial increase in testosterone production (lasting 1–2 weeks), known as the testosterone flare, followed by testosterone suppression. First introduced in the 1980s, GnRH agonists now form the mainstay of hormonal treatment of prostate cancer [8,9], although orchidectomy remains the standard against which other therapies are compared [9].

GnRH agonists are widely used in the management of patients with advanced

prostate cancer. In addition, in patients with clinically localized disease who have poor prognostic factors, GnRH agonists are used as neoadjuvant or adjuvant therapy in association with radiotherapy or radical prostatectomy. GnRH agonists are used both alone and combined with antiandrogens, another class of agent which induce apoptosis of prostate cancer cells, this time by inhibiting the binding of testosterone, and its derivative, 5α -dihydrotestosterone, to specific receptors in tumour cells.

At present, ADT is generally administered continuously, but there are theoretical reasons to suggest that intermittent therapy might slow progression of the tumour to an androgen-independent state, and promising data are reported [10,11]. For example, in a large study involving >1000 men with stage D2 prostate cancer, no significant difference in survival was reported for intermittent vs continuous therapy [10], while in a second study, the median time to disease progression and median time to death were greater in patients receiving intermittent than continuous therapy, although the differences between treatment groups were not statistically significant [11]. Intermittent

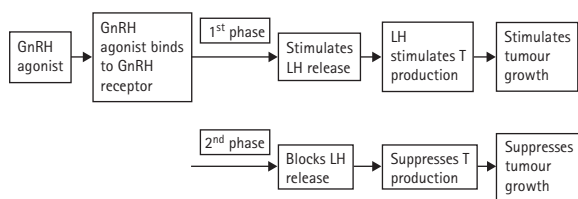


FIG. 1.
The mechanism of action of GnRH agonists.

therapy can also be expected to improve the quality of life for patients during periods without ADT, as reported by Miller *et al.* [11], and to reduce the cost of treatment.

ARE GnRH AGONISTS AS EFFECTIVE AS ORCHIDECTOMY FOR IMPROVING CLINICAL OUTCOME?

EFFECTS ON SURVIVAL

While GnRH agonists are widely used and are readily accepted by patients in preference to orchidectomy, the question remains as to whether they are as effective. Many studies have compared the efficacy of GnRH agonists and orchidectomy. Seidenfeld *et al.* [12] identified five large randomized studies that compared GnRH agonists with orchidectomy. While none of the five studies showed a statistically significant difference in overall survival among the treatments, three of the studies reported better survival for orchidectomy, and a fourth reported identical survival for both treatment groups. These authors also performed a meta-analysis of data from 12 studies (involving 1539 patients in all) comparing GnRH agonists and orchidectomy. The hazard ratio for GnRH agonists relative to orchidectomy was 1.262 (95% CI, 0.915–1.386), indicating an insignificant survival advantage for orchidectomy. These data suggest that GnRH agonists are largely used rather than orchidectomy because of patient preference and acceptability, rather than better clinical efficacy, as the overall survival achieved with GnRH agonists is at best comparable to that achieved with orchidectomy.

Detecting differences in overall survival between treatments for metastatic prostate cancer is necessarily difficult, given the long median survival for such patients and that the survival outcome is also likely to be influenced by treatments given once the tumour becomes refractory to hormone therapy. Another way of comparing the efficacy of different approaches to ADT is to compare their efficacy for achieving testosterone

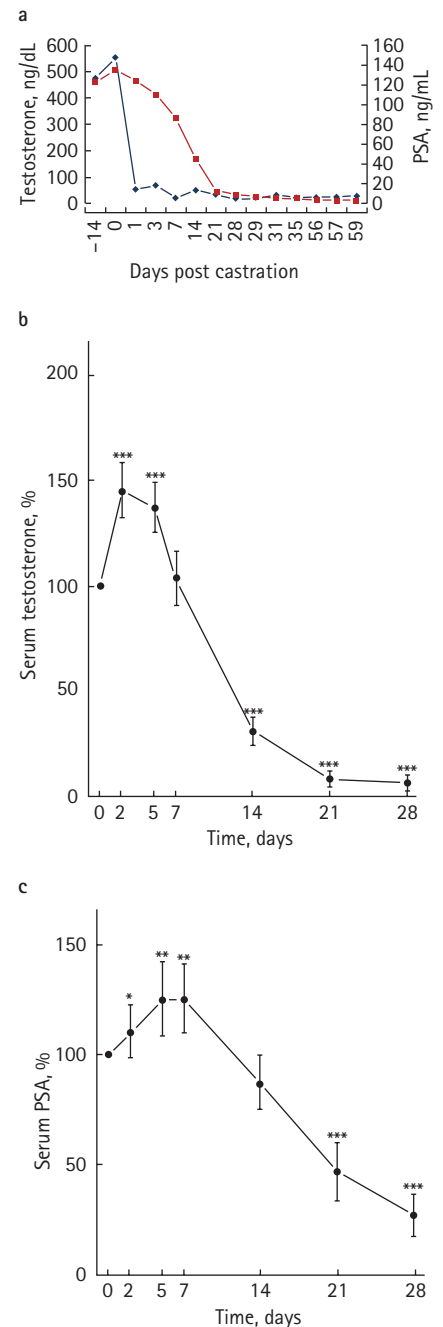
suppression. Given that orchidectomy and GnRH agonists both exert their effects by suppressing testosterone, this is likely to be an informative surrogate marker for efficacy. Indeed, Morote *et al.* [13] recently reported that disease-free survival (defined as the duration of survival free of androgen-independent progression) was significantly related to testosterone levels ($>$ or $<$ 32 ng/dL) during ADT in patients with nonmetastatic prostate cancer (mean disease-free survival 88 vs 137 months, $P < 0.03$).

TIME TO SUPPRESSION OF TESTOSTERONE

After orchidectomy, patients achieve rapid suppression of serum testosterone levels, followed by decreases in levels of the tumour marker PSA (Fig. 2a) [14]. For example, Lin *et al.* [6] found that testosterone levels of $<$ 20 ng/dL were achieved at 3–12 h (mean 8.6 h) after orchidectomy. This is accompanied by a decrease in PSA levels to $<$ 10 ng/mL by 21 days after orchidectomy [15]. By contrast, after administering a GnRH agonist, serum testosterone levels initially rise to a peak 1.5–2 times greater than the initial testosterone levels (Fig. 2b) [16]. Testosterone levels then remain above baseline levels for $\approx$ 7 days and do not reach castrate levels until $\approx$ 3 weeks after administration of the GnRH agonist. As a result, serum PSA levels are not effectively suppressed until at least 4 weeks after administering the GnRH agonist (Fig. 2c).

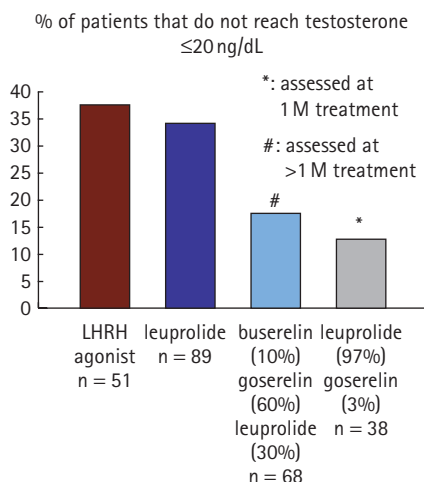
This phenomenon, which is related to the mechanism of action of GnRH agonists, is known as the 'testosterone flare' and might have important clinical implications. In patients with extensive disease, the testosterone flare can be accompanied by a worsening in clinical status, known as a 'clinical flare'; this is a result of the tumour-promoting effect of the increased testosterone levels. The main symptoms include bone pain, BOO, ureteric obstruction and spinal cord compression [17]. Increased bone pain occurs at the site of skeletal metastases and often requires increased

FIG. 2. Changes in serum testosterone and PSA levels (a) after orchidectomy [14]; and (b) and (c) PSA levels after administration of leuprolide. Pretreatment values are considered to be 100%. The vertical bar represents the SEM. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs value before the administration. Reproduced with permission from [16].



analgesic use to control the pain. In patients with vertebral metastases and/or urinary obstruction or haematuria, the increased tumour growth can cause ureteric

FIG. 3. The percentage of patients failing to achieve testosterone levels of ≤ 20 ng/dL during therapy with GnRH agonists [3,24–27].



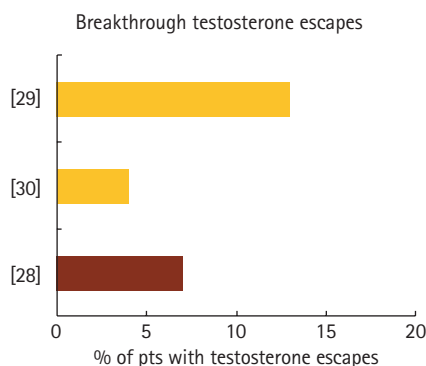
obstruction and/or spinal cord compression that can lead to paralysis. As a result, GnRH agonists are contraindicated in such patients [9], or such patients should be monitored closely during the first few weeks of therapy. Many studies of GnRH agonists have therefore excluded such patients.

To avoid the clinical flare associated with GnRH agonists in patients with advanced symptomatic disease, it is now routine practice in many countries to give 'flare protection' therapy before administering the first dose of GnRH agonist therapy in such patients, or in all patients. Indeed, a recent survey found that in five European countries, 75–95% of all patients are given flare protection therapy on starting continuous GnRH agonist therapy [18].

Flare protection involves treatment with an antiandrogen for ≥ 2 weeks, often starting on the same day as the depot injection of the GnRH agonist [9]. Co-administration of an antiandrogen inhibits the consequences of the testosterone flare, preventing the increase in PSA levels [19,20]. Flare protection reduces the incidence of clinical flare, as reported in one study which found that daily treatment with nilutamide during the first 2 weeks of treatment with buserelin reduced the incidence of worsening bone pain compared with treatment with buserelin alone [21].

While flare protection is generally given to at-risk patients before their first dose of a GnRH

FIG. 4. The percentage of patients with breakthroughs in testosterone suppression (i.e. increases to >50 ng/dL) during therapy with GnRH agonists. From [28–30], with permission. [Correction added after online publication 29–4–2008: Company's name and logo removed.]



agonist, it is not generally offered before subsequent injections. This reflects the fact that the increase in testosterone levels after subsequent injections is much lower than after the first injection in patients receiving continuous therapy. However, several authors have reported that testosterone levels can increase after the second and subsequent injections. For example, Zinner *et al.* [22] reported that 22% of patients receiving goserelin at 28-day intervals had an increase in serum testosterone to greater than castrate level (defined as 18.5 ng/dL) after one or more injections (excluding the first injection). Such 'microflares', while insufficient to exacerbate symptoms, might be expected to promote tumour growth to some extent and might therefore adversely affect survival.

Clinical flare generally occurs in patients with advanced disease, but the absence of clinical flare in those with less advanced disease does not necessarily imply that the testosterone flare has no clinical effects in such patients. The absence of clinical flare probably reflects the fact that the tumour is smaller, rather than the absence of testosterone-stimulated growth in these patients. Stimulation of growth of smaller tumours might not produce clinical symptoms, but might adversely affect long-term outcome. This suggests that the testosterone flare is a concern in the management of patients with less advanced disease, as well as those who are clearly at risk of clinical flare.

The possible effect of the testosterone flare on tumour growth might be even more

important in the context of intermittent therapy. In this context, each initiation of GnRH agonist therapy would be associated with a testosterone flare that could stimulate tumour growth. The accumulating effects of multiple testosterone flares might have an appreciable adverse effect on survival, unless flare protection therapy was given with each initiation of therapy. Thus the testosterone flare associated with GnRH agonist therapy could be a significant shortcoming of this therapy, especially in the context of intermittent therapy.

LEVEL OF TESTOSTERONE SUPPRESSION ACHIEVED

Another consideration is the degree of testosterone suppression achieved. A threshold of 20 ng/dL is now recognized as the level of suppression that is achieved with orchidectomy and is the target for GnRH agonist therapy [23]. However, data from various studies suggest that a significant proportion of patients receiving GnRH agonists do not achieve this level of suppression (Fig. 3) [3,24–27]. For example, in one study in which patients received leuprolide acetate, measurement of serum testosterone at 29 days after administration showed that 34% of patients had testosterone levels of ≥ 20 ng/dL [25], while Morote *et al.* [26] assessed serum testosterone levels in patients treated with 3-monthly GnRH agonist injections and found that 37.5% of patients had testosterone levels of ≥ 20 ng/dL. This would appear to be a significant shortcoming of many GnRH agonist preparations and might be expected to affect the long-term outcome.

A further consideration is whether testosterone suppression is maintained during therapy. Several authors have reported 'breakthroughs' in testosterone suppression in some patients [28–30] (Fig. 4). For example, in a long-term follow-up of 62 patients who had received a 3-month leuprolide depot, Jocham [28] reported increases in testosterone to >50 ng/dL in four (6.5%), while in a larger study (120 men), there were 'breakthroughs' in five (4%) of patients receiving a 3-month goserelin acetate depot [30]. These studies all used 50 ng/dL as a definition for 'breakthrough'. It seems likely that if the threshold had been defined as 20 ng/dL, the rate of breakthrough would have been considerably higher. These data therefore suggest that GnRH agonists might fail to

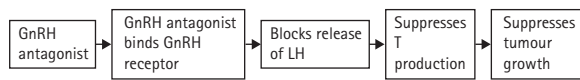


FIG. 5.
Mechanism of action of GnRH antagonists (e.g. degarelix).

achieve sustained testosterone suppression in significantly many patients.

Taken together, these data suggest that there might be significant shortcomings associated with current GnRH agonists, which could affect the long-term outcome of therapy.

WHAT ARE THE ALTERNATIVES?

Faced with the shortcomings of current GnRH agonists, there is a need to develop agents that produce rapid, profound and sustained suppression of testosterone without a testosterone flare. A promising class of agents that might address these shortcomings is the GnRH blockers. GnRH blockers, like GnRH agonists, bind to the GnRH receptor, but produce immediate LH and testosterone suppression (i.e. with no initial testosterone flare; Fig. 5), as has been reported for degarelix, the most promising agent in this class to date. The results of phase II studies showed that ≈90% of patients receiving degarelix at a dose of 240 mg achieve suppression of testosterone to ≤50 ng/dL by day 3, with no testosterone flare, and that up to 96% of patients achieving this level of suppression by 28 days achieved sustained suppression over a year of monthly maintenance therapy [31]. Preclinical data from a study in rats suggest that the rapid, profound and sustained testosterone suppression achieved with degarelix might result in greater suppression of tumour growth than is achieved with GnRH agonists [32], but this has yet to be confirmed in clinical studies. An ongoing phase III study is comparing the efficacy of degarelix with GnRH agonists in the treatment of patients with metastatic prostate cancer, and should help to clarify the possible advantages of degarelix over GnRH agonists.

CONCLUSIONS

The unacceptability of orchidectomy to many patients means that ADT is the mainstay for managing advanced prostate cancer, especially now that many patients are diagnosed and treated earlier in the course of their disease. While GnRH agonists are the

treatment of choice for most patients, these agents might not provide the level of suppression achieved with orchidectomy. Accumulating data suggest that a significant proportion of patients do not achieve castrate levels of testosterone (i.e. <20 ng/dL) and in some patients suppression is not sustained. Given that testosterone levels of >32 ng/dL have been shown to be associated with a shorter time to androgen-independent progression, this suggests that failure to achieve optimal suppression might adversely affect overall survival. In addition, that the initial injection is accompanied by a flare in testosterone levels, and that it takes up to 28 days to achieve maximum suppression after the first injection, could have important implications, especially if therapy is to be given intermittently. These observations therefore suggest that there is a need for new agents that can achieve more rapid, profound and sustained testosterone suppression. Preliminary data for degarelix, a GnRH blocker, suggest that this agent might address these shortcomings. Further clinical data are therefore awaited with interest.

CONFLICT OF INTEREST

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Abbreviation: ADT, androgen-deprivation therapy.