

Prostate cancer: What are the news in hormonal therapy? The role of GnRH antagonists

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Summary

The latest EAU guidelines on the evidence based-management of prostate cancer (P.Ca.), with regard to pharmacological androgen deprivation therapy (ADT), reiterate that the primary objective of hormonal therapy is to slow down the progression of the disease to the greatest possible extent. Degarelix a new product for the treatment of hormone-dependent P.Ca. has recently become available in Italy. This product is classified as a GnRH antagonist and provides safe and effective ADT. It completely blocks the synthesis and release of gonadotropins (LH and FSH), thus rapidly reducing the testosterone levels without causing clinical flare. The results of the clinical trials (36 months) demonstrate that degarelix, compared to high-dose leuporelin (7.5 mg), suppresses levels of testosterone and PSA (Prostate-Specific Antigen) more rapidly and reduces levels of FSH and musculoskeletal events associated with treatment (pain, muscle weakness, spasms, oedema/joint stiffness, arthralgia, osteoporosis and osteopenia) to a greater extent. In addition, these results demonstrate a significant increase in the probability of PSA progression-free survival, suggesting a possible delay in the onset of the "castration-resistant" stage. The information available to date supports the use of this new molecule as a valid alternative to GnRH agonists in the treatment of hormone-sensitive P.Ca.

KEY WORDS: Prostate cancer; Androgen deprivation therapy; GnRH antagonists; Degarelix

Submitted 29 March 2012; Accepted 25 July 2012

INTRODUZIONE

The EAU guidelines on the evidence based-management of prostate cancer (P.Ca.) have recently been updated (1). With regard to pharmacological androgen deprivation therapy (ADT), they reiterate that the primary objective of hormonal therapy is to slow down the progress of the disease to the greatest possible extent (1).

ADT is currently based on GnRH agonists (buserelin, goserelin, leuporelin, triptorelin) synthetic GnRH analogues (Gonadotropin-Releasing Hormone). These molecules act on the hypophysis by down-regulating and desensitizing the receptors of this hormone. This suppresses the release of LH and FSH after 2-4 weeks with a consequent reduction in testosterone to levels similar to those that can be obtained by castration (2).

Initially, these products stimulate the hypophyseal GnRH receptors determining an initial increase in testosterone, which may, above all in patients with advanced P.Ca., cause clinical flare (3), which could be the result of acute tumour growth stimulated by testosterone, whose possible clinical consequences (urethral obstruction, bone

pain, obstructive kidney failure, spinal cord compression and cardiovascular events fatal for patients with hypercoagulation disorders) depend on the size of the tumour and the location of the metastases. Attempts may be made to control the clinical flare by administering antiandrogens, which compete with testosterone and dihydrotestosterone at the receptors present in the nucleus of the prostate cells, but this does not completely eliminate the risk of it occurring (4).

It should also be pointed out that at each administration after the first, GnRH agonists may, in about 24% of cases, cause a relative increase in testosterone levels (microsurges) with a risk of exacerbations (miniflares), which have been associated with a negative impact on overall survival (1).

Another disputable clinical aspect of GnRH agonists is the fact that a proportion of patients ranging from 13% to 38% does not reach testosterone levels similar to those that may be obtained by castration (< 20 ng/dL) and that a proportion ranging from 2% to 17% has values of over

50 ng/dL. This value represents the limit of effectiveness laid down by the registration regulations (5-7). This observation has implications on the androgen-independent progression of the tumour, which is correlated with the testosterone levels reached (8). With regard to androgen-independent progression, it should be pointed out that the presence of a large number of receptors for the FSH has been demonstrated in P.Ca. The synthesis of this hormone is little influenced by GnRH agonists, which only reduce the levels by 50% (9). Lastly, receptors for the FSH are functionally active and their stimulation with the hormone induces a significant proliferative response (10).

DEGARELIX

Having been approved by the FDA and EMA for the treatment of hormone-dependent P.Ca., the product degarelix has recently become available also in Italy. This product is classified as a GnRH antagonist and represents a valid pharmacological alternative to the agonists and provides safe and effective ADT (11).

Its mechanism of action differs from that of GnRH agonists in that it rapidly and competitively binds to the GnRH receptors, thus making them unavailable to endogenous GnRH: this completely blocks the synthesis and release of both gonadotropins (FSH and LH), thus rapidly reducing testosterone levels without causing clinical flare (Figure 1). Due to this characteristic, there is no need to associate an anti-androgen with the start of treatment and so hormonal monotherapy may be initiated immediately (1, 12).

Degarelix is a new-generation GnRH antagonist developed specifically as hormonal therapy for P.Ca. (1, 11). It is a completely synthetic decapeptide amide containing 7 amino acids not present in nature, 5 of which are D-amino acids (13). Unlike first-generation GnRH antagonists (abarelix), degarelix has a chemical structure that minimizes its ability to induce the release of histamine

(allergic reactions), without this reducing its effectiveness as a GnRH receptor blocker (12, 14).

Preclinical studies have shown that degarelix causes a rapid, dose-dependent and reversible suppression of the hypothalamic-pituitary-gonadal axis, reducing testosterone to levels that inhibit the growth of the tumour to a similar degree as that obtained by surgical castration; unlike GnRH agonists, this effect was obtained without any initial increase in testosterone levels (15).

Clinical trials have demonstrated that, through its direct mechanism of action, degarelix significantly reduces FSH levels with respect to the baseline (-89 %) (16). The functional FSH receptors, as mentioned previously, are also expressed in some forms of prostate cancer (9, 16). For this reason, degarelix reopens the debate on the role of the FSH and its putative direct action in stimulating cancer growth.

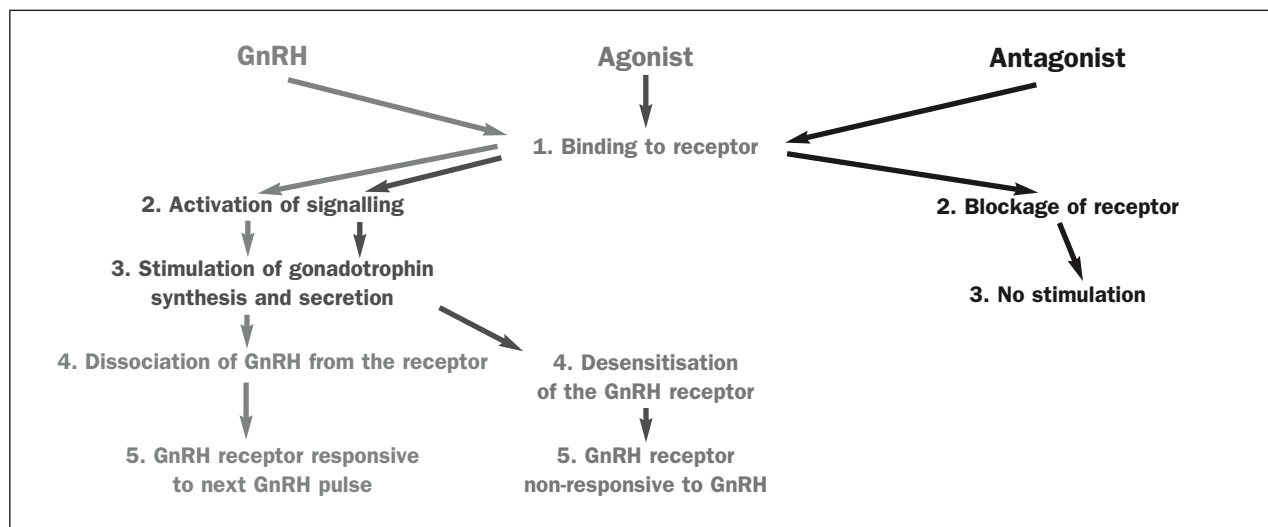
The effectiveness and tolerability of degarelix were assessed in a 12-month phase III comparative study conducted on 610 patients with P.Ca., diagnosed histologically and in all stages, for which there was a clear indication for hormonal therapy (17). The patients enrolled on the trial included those with an indication for first-line hormonal therapy in accordance with the guidelines and those who were candidates for hormonal therapy having undergone treatment with curative intent (biochemical recurrence).

The results demonstrated that degarelix administered via the subcutaneous route is as effective as high-dose leuporelin (7.5 mg), administered via the intramuscular route, in suppressing testosterone and PSA (Prostate-Specific Antigen) levels (17).

Degarelix caused no flare-up in any of the patients treated and gave an earlier onset of action (Figure 2).

In addition, on the third day of administration, testosterone levels of ≤ 50 ng/dL were recorded in about 96% of patients while, in the leuporelin group, no patients reached this level (17). Unlike the agonist, degarelix did not cause any rise in testosterone (microsurges) after

Figure 1.
Mechanism of action of GnRH agonists and antagonists.



each monthly injection (17). In line with the results observed for testosterone, the PSA levels also dropped more rapidly in patients treated with degarelix (17) (Figure 3).

The tolerability profiles were found to be similar for the two treatments although the injection site reactions (mild or moderate) and chills occurred more frequently with degarelix, while arthralgia and urinary infections were more common with leuprolide (17). The data obtained from the patients in the phase III

study were subjected to further analyses, which gave the following results:

- Degarelix caused a significantly lower risk of a rise in PSA levels (failure) than leuprolide even in the group of patients with a high risk of progression, that is, with PSA > 20 ng/ml at the baseline. In these patients, the time that passes before a PSA failure occurs is greater, that is, 2 consecutive rises in PSA is 50% with respect to the nadir and ≥ 5 ng/ml in 2 consecutive measurements made with a time interval of at least 2 weeks (18) (Figure 4).
- Degarelix reduced serum alkaline phosphatase (s-ALP) levels more rapidly and to a greater degree than leuprolide in patients with skeletal metastases, thus indicating a better control of the latter (19).
- The impact of degarelix on HRQoL (Health Related Quality of Life) was found to be largely comparable to that of leuprolide at 12 months and some statistically significant differences in favour of degarelix emerged from the mental health indexes (MCS - Mental Component Summary) (20).

Figure 2.

The onset of the anti-androgen action of degarelix is earlier than that of leuprolide and this GnRH antagonist causes no initial increase in testosterone levels. Modified from (17).

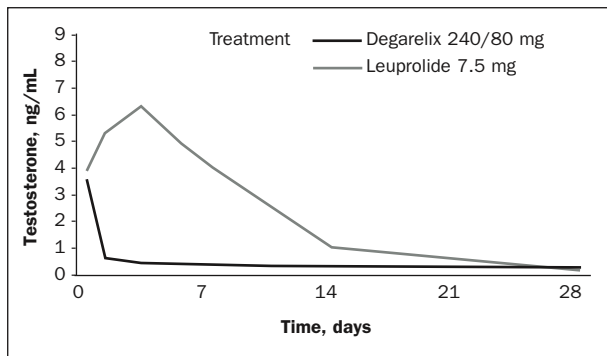
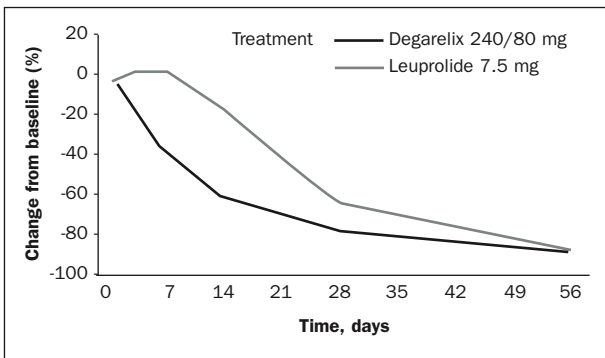


Figure 3.

In patients with prostate cancer degarelix reduces PSA levels more rapidly than leuprolide. Modified from (17).



The data from the extension trial (median follow-up = 27.5 months) of the phase III trial, in which patients in the leuprolide group, whose disease was under control, switched to treatment with degarelix, have recently been published (21).

The results show that these patients recorded a significant increase in their probability of PSA progression free survival (21) (Figure 5).

This could suggest that GnRH antagonists control P.Ca. better than agonists and delay the onset of hormone resistance (21).

The switch from leuprolide to degarelix also revealed greater suppression of FSH levels (21) (Figure 6).

There was also a significant reduction in the musculoskeletal events associated with treatment (pain, muscle weakness, spasms, oedema/joint stiffness, arthralgia, osteoporosis and osteopenia) (21).

The observation that ADT could increase the cardiovascular risk, above all when GnRH agonists are combined with anti-androgens (22), induced researchers to assess this risk in patients treated with degarelix: a broad analysis conducted on 1704 men treated with degarelix for about

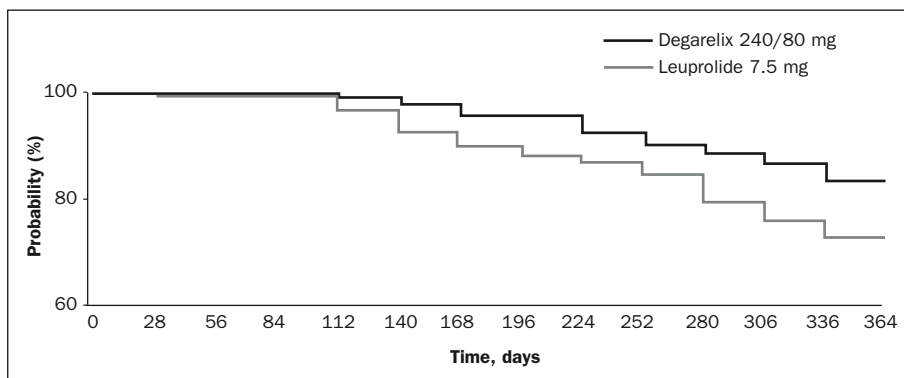


Figure 4.

In patients with prostate cancer and PSA > 20 ng/mL at the baseline degarelix reduces PSA failures more than leuprolide ($p = 0.04$). Modified from (18).

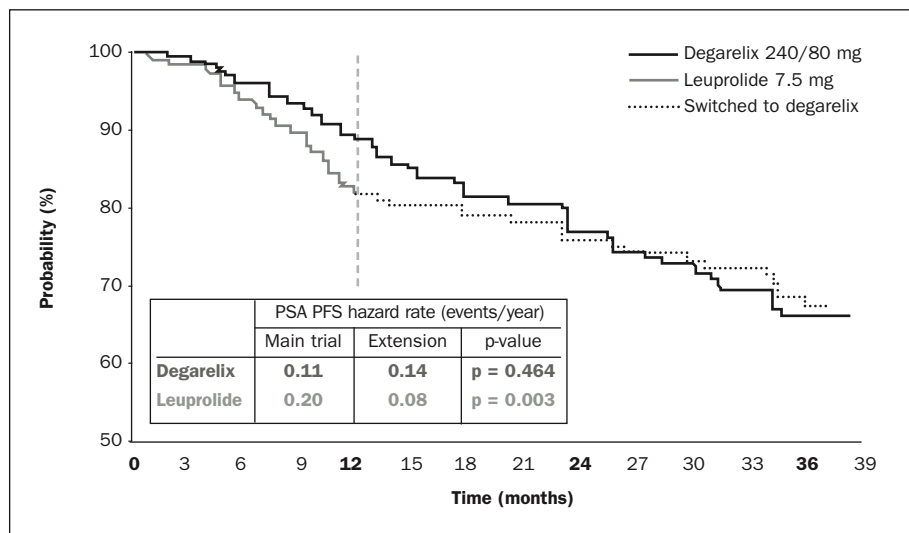


Figure 5.

In the long term (36 months) degarelix reduces the risk of biochemical recurrence or death to a greater degree even in patients treated previously with leuprolide. Modified from (21).

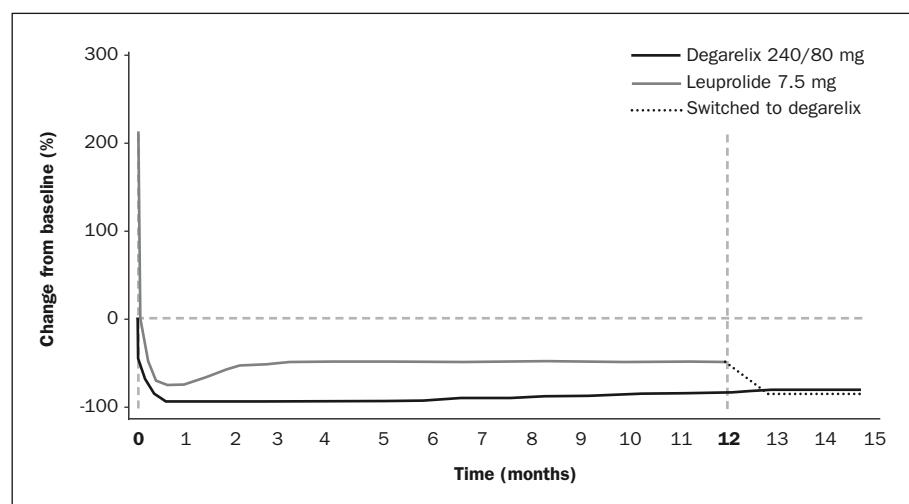


Figure 6.

Unlike leuprolide, degarelix further reduces FSH levels. Modified from (21).

2 years did not reveal any increase in their cardiovascular risk (HR 1.10, 95% CI 0.85-1.42, p = 0.45) due to this new GnRH antagonist with respect to the baseline. The frequency of cardiovascular events was 5.5% before administering degarelix compared to 6.1% after treatment with degarelix (23).

Finally, new information on the reduction in size of the prostate has become available (24). In monotherapy, degarelix was found to reduce prostate volume at three months in patients with cancer as much as a treatment with monthly goserelin combined with an agent for the protection flare (50 mg bicalutamide) for the first month.

In terms of relief from lower urinary tract symptoms (LUTS) in clinically symptomatic patients (IPSS score > 13) degarelix was found to be significantly superior to the reference treatment; on the basis of recent data from animal experiments (25), the authors believe that degarelix may also act on the peripheral GnRH receptors (bladder/prostate) reducing the prostate size as much as the GnRH agonist.

EAU GUIDELINES: INDICATIONS ON HORMONAL THERAPY

In the latest EAU guidelines on P.Ca. (1), the indications for ADT are divided roughly between:

- First-line hormonal therapy
- Hormonal therapy after treatment with curative intent.

The indications for first-line hormonal therapy, like the other therapeutic options, took into account the stage of progression of the cancer as indicated in Table 1.

The guidelines indicate that ADT may be beneficial for patients with locally advanced cancer, as monotherapy in symptomatic patients, in combination with radiotherapy (neoadjuvant and adjuvant) and in combination with radical prostatectomy (adjuvant), particularly when lymph node involvement is observed after surgery (1).

ADT is the standard treatment for cancer with local lymph node involvement and in the presence of metastases (1) (Table 1).

Table 1.

EAU guidelines on prostate cancer: indications for first-line ADT. Modified from (1).

Stage	Treatment	Comment	GR
T1a	Hormonal	Not an option.	A
	Combination	Not an option.	C
T1a-T2c	Hormonal	Symptomatic patients, who need palliation of symptoms, unfit for curative treatment.	C
		Anti-androgens are associated with a poorer outcome compared to 'active surveillance' and are not recommended.	A
	Combination	For high-risk patients, neoadjuvant hormonal treatment and concomitant hormonal therapy plus radiotherapy results in increased overall survival.	A
T3-T4	Hormonal	Symptomatic patients, extensive T3-T4, high PSA level (> 25-50 ng/mL), PSA-Doubling Time (DT) < 1 year.	A
		Patient-driven, unfit patients.	
		Hormone monotherapy is not an option for patients who are fit enough for radiotherapy.	
	Combination	Overall survival is improved by concomitant and adjuvant hormonal therapy (3 years) combined with external beam radiation.	A
		NHT plus radical prostatectomy: no indication.	B
N+, M0	Hormonal	Standard adjuvant therapy in more than 2 positive nodes to radiation therapy or radical prostatectomy as primary local therapy.	A
		Hormonal therapy should only be used as monotherapy in patients who are unfit for any type of local therapy.	
	Combination	No standard option. Patient-driven.	B
M+	Hormonal	Standard option. Mandatory in symptomatic patients.	A

After treatment with curative intent, the EAU guidelines recommend ADT in case of biochemical recurrence or as a second-line approach:

- after radical prostatectomy in that it reduces the frequency of clinical metastases;
- after radiotherapy, in patients with presumed systemic relapses (1) (Table 2).

In the clinical trials conducted to date, degarelix has been found to be effective at all stages of hormone-sensitive P.Ca. The results obtained, according to Crawford, the author of the most recent publication, support its use as an alternative to GnRH agonists (21).

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Table 2.

EAU guidelines on prostate cancer: indications for ADT as an approach treatment with curative intent. Modified from (1).

Management of (PSA) relapse after RP	
Recommendations	GR
PSA recurrence indicative of systemic relapse is best treated by early ADT resulting in decreased frequency of clinical metastases.	B
Luteinising hormone releasing hormone (LHRH) analogues/antagonists/orchiectomy or bicalutamide, 150 mg/day, can both be used when there is an indication for hormonal therapy.	A

Management of (PSA) relapse after radiation therapy	
Recommendations	GR
In patients with presumed systemic relapse, ADT may offered.	B

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