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Comparing testosterone and PSA response for different baseline testosterone concentrations during initiation of degarelix and leuprolide treatment

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INTRODUCTION

Pre-treatment testosterone level has been investigated as a potential prognostic indicator in prostate cancer. In one study in patients with localised prostate cancer treated with radiotherapy, as baseline serum testosterone increased so did the risk of metastatic relapse.[1] A further study suggested that high baseline testosterone was associated with improved response to endocrine therapy in the metastatic disease setting[2]

Demonstrating differences in overall survival between androgen deprivation therapies (ADTs) in patients with metastatic prostate cancer is difficult. However, improved disease-free survival has been linked with low testosterone levels during ADT of non-metastatic disease[3]

Gonadotrophin-releasing hormone (GnRH) receptor blockers induce fast androgen deprivation without the testosterone surge associated with GnRH agonists.[4] A recent phase III trial (CS21) demonstrated that the new GnRH blocker, degarelix, was at least as effective as leuprolide in maintaining testosterone at castrate levels in patients with prostate cancer.[5] Here we report further analyses from CS21 assessing the effects of baseline testosterone on the control of testosterone and prostate-specific antigen (PSA) levels

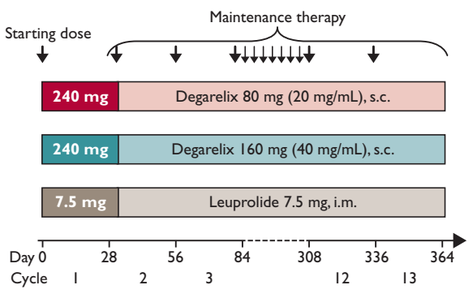
METHODS

Study design

This was a 1-year, multicentre, randomised, open-label, parallel-group trial powered to demonstrate non-inferiority of degarelix vs leuprolide for the primary endpoint (proportion of patients with testosterone ≤0.5 ng/mL at each monthly measurement for 1 year). Patients were randomised to one of three treatment groups (Figure 1)

FIGURE 1

CS21 study design



Patients

Patients with histologically confirmed adenocarcinoma of the prostate (all stages), for whom ADT was indicated, were eligible. This included patients with rising PSA after prostatectomy or radiotherapy of curative intent. Patients requiring neoadjuvant hormonal therapy were not eligible. Patients were also required to have serum testosterone levels >1.5 ng/mL, an Eastern Cooperative Oncology Group performance status ≤2 and PSA ≥2 ng/mL

Baseline testosterone analyses

Median % change and changes in absolute testosterone levels as well as % change in PSA and the achievement of castrate testosterone levels (≤0.5 ng/mL) were compared between degarelix 240/80 mg and leuprolide groups by baseline testosterone subgroups (<3.5; 3.5–5.0; ≥5 ng/mL). Statistical comparisons were performed by Fisher's exact test (% patients with testosterone ≤0.5 ng/mL) and Wilcoxon rank sum test (median % change from baseline in PSA). Results of testosterone analyses for the degarelix 240/80 mg (the FDA/EMEA-approved dose) and leuprolide groups are presented

RESULTS

Patients

In total, 408 patients were randomised to degarelix 240/80 mg and leuprolide 7.5 mg and baseline characteristics were similar between groups (Table 1). Approximately 50% of patients in these two groups had locally advanced (29.2%) or metastatic (20.5%) prostate cancer at baseline

Patients receiving degarelix were fairly evenly distributed between the three baseline testosterone categories

Testosterone effects

By Day 1, testosterone levels had fallen by ≥85% with degarelix treatment (all three subgroups). The testosterone surge induced by leuprolide is shown in Figure 2. The magnitude of the agonist-induced surge was a function of baseline testosterone level

High baseline levels delayed achievement of castrate testosterone in both treatment arms. However, reduction to castrate levels occurred significantly faster with degarelix than with leuprolide for all baseline testosterone subgroups ($p<0.0001$ [Fisher's exact test]). Castrate testosterone levels were achieved by ≥90% (range 90–100%) of degarelix-treated patients by Day 3 (Figure 3). In contrast, only 18% (range 4–31%) of leuprolide-treated patients reached castrate levels by Day 14. All patients had achieved castrate testosterone levels by Day 56

TABLE 1

Baseline characteristics (intent-to treat [ITT] population)

	Degarelix 240/80 mg	Leuprolide 7.5 mg
ITT analysis set, n	207	201
Median age, years (range)	72 (51–89)	74 (52–98)
Median testosterone, ng/mL (P25–P75)	4.11 (3.05–5.32)	3.84 (2.91–5.01)
Testosterone subgroup, n (%)		
<3.5 ng/mL	68 (33)	87 (43)
3.5–5.0 ng/mL	62 (30)	62 (31)
≥5.0 ng/mL	77 (37)	52 (26)
Median PSA, ng/mL (P25–P75)	19.8 (9.4–46)	17.4 (8.4–56)
Stage of disease, n (%)		
Localised[a]	69 (33)	63 (31)
Locally advanced[b]	64 (31)	52 (26)
Metastatic	37 (18)	47 (23)
Incompletely classified[c]	37 (18)	39 (19)
Gleason score, n (%)		
2–4	20 (10)	24 (12)
5–6	68 (33)	63 (32)
7	63 (30)	62 (31)
8–10	56 (27)	51 (26)

[a]Localised: T 1/2, NX or N0, and M0; [b]Locally advanced: T 3/4, NX or N0, and M0, or N1 and M0; [c]Includes those who had rising PSA after radical prostatectomy or radiotherapy

FIGURE 2

Median (quartiles) testosterone levels for leuprolide patients between Days 1 and 28

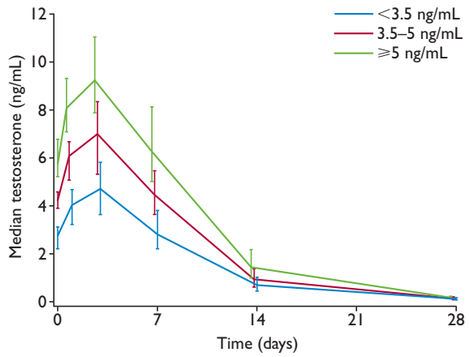
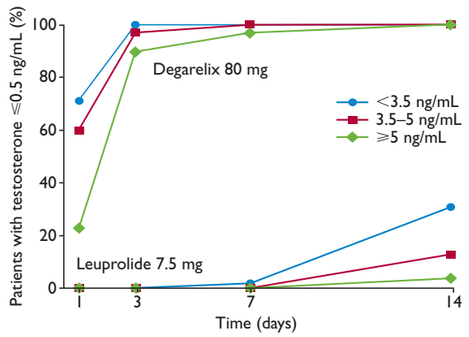


FIGURE 3

Achievement of castrate testosterone levels by baseline testosterone between Days 1 and 14

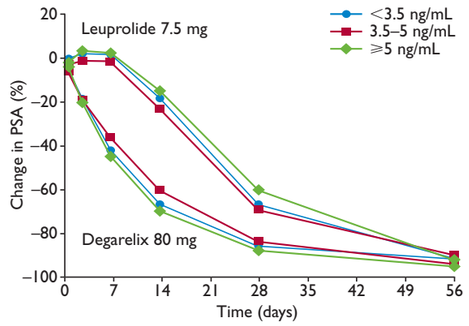


PSA effects

In the degarelix group, a rapid reduction in PSA began on Day 1, with median reductions from baseline of >60% and >84% on Days 14 and 28, respectively (Figure 4). For leuprolide, reductions in PSA ranged between 15–23% at Day 14 and were >60% in all subgroups by Day 28. PSA reductions appeared faster at high baseline testosterone levels in the degarelix group whereas there was a small increase in PSA around Days 3 and 7 in the leuprolide subgroups followed by a somewhat slower reduction in PSA

FIGURE 4

Change from baseline in PSA level between Days 1 and 56 by baseline testosterone



Degarelix was associated with significantly greater median reductions in PSA at Days 3, 14 and 28 compared with leuprolide, irrespective of baseline testosterone level (Table 2). Interestingly, the achievement of PSA control was further delayed the higher the baseline testosterone, such that PSA suppression with degarelix was superior to that of leuprolide even beyond Day 56 in patients with baseline testosterone ≥5 ng/mL

TABLE 2

Significance of treatment differences in median change in PSA between Day 1 and Day 84 by baseline testosterone level

	P-value (degarelix 240/80 mg vs leuprolide 7.5 mg; Wilcoxon Signed-Rank test)		
	<3.5 ng/mL	3.5–5.0 ng/mL	≥5.0 ng/mL
Day 1	0.0007	0.0670	0.1316
Day 3	<0.0001	<0.0001	<0.0001
Day 7	<0.0001	<0.0001	<0.0001
Day 14	<0.0001	<0.0001	<0.0001
Day 28	0.0008	<0.0001	<0.0001
Day 56	0.8862	0.0712	0.0098
Day 84	0.2038	0.5208	0.1074

CONCLUSIONS

- The magnitude of the GnRH agonist-induced testosterone surge was related to baseline plasma testosterone level
- In both treatment arms, higher baseline testosterone led to slower achievement of castrate testosterone levels
- Achievement of castrate testosterone levels occurred significantly faster with degarelix than with leuprolide for all testosterone subgroups
- Degarelix provided faster PSA control than leuprolide, independent of baseline testosterone
- The achievement of PSA control was further delayed in patients with high baseline testosterone
- The importance of these differences in testosterone and PSA response for overall survival is at present unknown

References

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