40

Degarelix vs leuprolide in patients with prostate cancer: effect in metastatic patients as assessed by serum alkaline phosphatase

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INTRODUCTION

Bone is the most common site of metastasis in men with prostate cancer.[1] Normal bone remodelling is altered in patients with bone metastases so that bone matrix components are released into the circulation[1,2]

Total serum alkaline phosphatase (S-ALP) is a bone formation marker and is commonly used alongside bone scintigraphy in the diagnosis and follow-up of bone metastases in prostate cancer patients. Elevated S-ALP and bone-specific ALP levels are associated with progression of bone metastases[2] and reduced overall survival[3]

Degarelix is a new gonadotrophin-releasing hormone (GnRH) receptor blocker that induces a fast testosterone suppression, without a surge. In a recent phase III trial (CS21) degarelix was non-inferior to leuprolide at suppressing testosterone to castrate levels over a 1-year treatment period (95–98% response).[4] Although the effects of GnRH agonists on S-ALP levels have been reported,[5,6] the effect of degarelix is not known. Here we report S-ALP analyses from CS21, focussing on the comparison of degarelix 240/80 mg vs leuprolide in line with the recent approvals of this degarelix dose by the FDA and EMEA

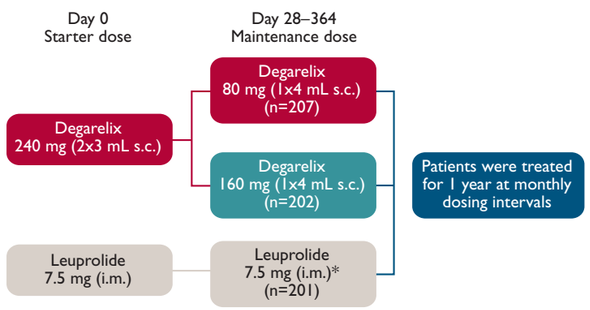
METHODS

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



Patient visits:
Day 0, 1, 3, 7, 14, 28, 56... (+28) ...364
Additional visits occurred after Day 3 and Day 7 following the 9th dose
*Anti-androgen was allowed at the discretion of the investigator

Patients

Patients with histologically confirmed adenocarcinoma of the prostate (all stages), for whom androgen deprivation therapy was indicated were eligible. This included those with rising prostate-specific antigen (PSA) after prostatectomy or radiotherapy with curative intent. 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

S-ALP analyses

S-ALP levels were detected using a standardised colorimetric assay. The normal reference range for S-ALP is 44–147 IU/L. S-ALP was prospectively measured for all patients in CS21 as part of the laboratory tests included in the overall safety analysis. Analysis of S-ALP as a disease marker was not pre-planned; however this would appear to hold little bias given that S-ALP is an objective laboratory measure. An analysis of variance with treatment and day as factors and baseline value as covariate was used to determine between treatment differences at Day 364

RESULTS

Patients

Baseline characteristics were well balanced between groups (Table 1). Approximately half of patients had locally advanced (29.2%) or metastatic (20.5%) disease at baseline and overall, median age was 73 years, median testosterone was 3.93 ng/mL and PSA was 19.0 ng/mL

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)
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)
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)

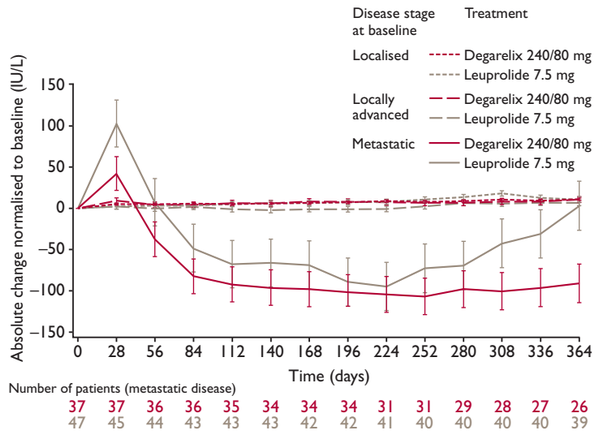
[a]Localised: T 1/2, NX or N0, and M0; [b]Locally advanced: T 3/4, NX or N0, and M0, or N1 and M0

S-ALP by baseline disease stage

Baseline S-ALP levels were high in metastatic patients reflecting the presence of skeletal metastases. After initial peaks in both groups, S-ALP was suppressed below baseline levels with degarelix in patients with metastatic disease, and was also suppressed during leuprolide treatment (Figure 2). The difference in S-ALP suppression in patients with metastatic disease was statistically significant between degarelix 240/80 mg and leuprolide 7.5 mg at Day 364 (p=0.0137). The rise in S-ALP with leuprolide late in the study, suggesting therapy failure, was not observed with degarelix. S-ALP was maintained around baseline levels in patients with localised or locally advanced disease, irrespective of treatment received

FIGURE 2

Mean (± standard error) change from baseline in S-ALP level by baseline disease stage

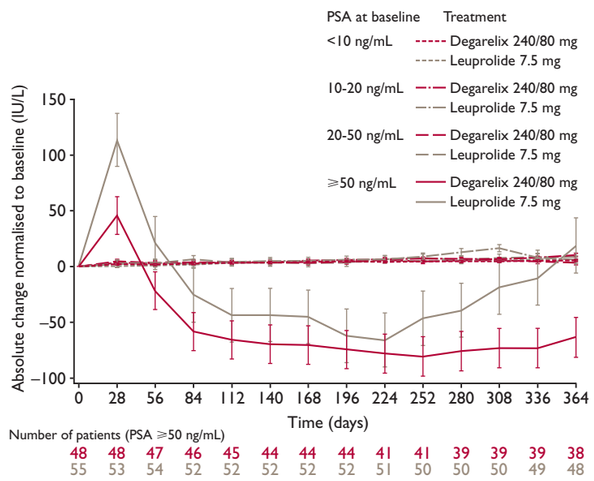


S-ALP by baseline PSA

Baseline S-ALP levels were 3–4-fold higher in those with PSA ≥50 ng/mL than in those with PSA <50 ng/mL. After initial peaks in both groups, patients with baseline PSA levels ≥50 ng/mL experienced greater S-ALP reductions from baseline with degarelix than with leuprolide (Figure 3). The difference in S-ALP suppression in patients with baseline PSA ≥50 ng/mL was statistically significant between degarelix 240/80 mg and leuprolide 7.5 mg at Day 364 (p=0.0073). The late rise in S-ALP observed in the leuprolide group beyond 10 months was not seen during degarelix treatment. In leuprolide patients, S-ALP returned to baseline levels before the end of the 1-year study, whereas S-ALP levels remained below baseline at the end of the study period in the degarelix group. S-ALP was maintained around baseline levels in patients with PSA <50 ng/mL, irrespective of treatment received

FIGURE 3

Mean (± standard error) change from baseline in S-ALP level by baseline PSA



CONCLUSIONS

- Patients with metastatic disease or those with PSA levels ≥50 ng/mL at baseline experienced greater reductions in S-ALP with degarelix 240/80 mg than leuprolide
- Patients in the degarelix 240/80 mg group maintained S-ALP suppression throughout the study and did not display the late rises in S-ALP seen in patients receiving leuprolide
  - The difference in S-ALP suppression between degarelix 240/80 mg and leuprolide was statistically significant at Day 364
- These results indicate better S-ALP control with degarelix than with leuprolide and therefore generate the hypothesis that degarelix may further prolong control of skeletal metastases compared with GnRH agonists

References

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