available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Prostate Cancer

Additional Analysis of the Secondary End Point of Biochemical Recurrence Rate in a Phase 3 Trial (CS21) Comparing Degarelix 80 mg Versus Leuprolide in Prostate Cancer Patients Segmented by Baseline Characteristics

Bertrand Tombal[a,*], *Kurt Miller*[b], *Laurent Boccon-Gibod*[c], *Fritz Schröder*[d], *Neal Shore*[e], *E. David Crawford*[f], *Judd Moul*[g], *Jens-Kristian Jensen*[h], *Tine Kold Olesen*[i], *Bo-Eric Persson*[j]

[a] *Cliniques Universitaires Saint Luc/Université Catholique de Louvain, Brussels, Belgium*
[b] *Charité Universitätsmedizin Berlin, Berlin, Germany*
[c] *CHU Hôpital Bichat-Claude Bernard, Paris, France*
[d] *Erasmus MC, Rotterdam, The Netherlands*
[e] *Carolina Urologic Research Center, Myrtle Beach, SC, USA*
[f] *University of Colorado Denver, Aurora, CO, USA*
[g] *Duke University Medical Center, Durham, NC, USA*
[h] *Ferring Phamaceuticals, Copenhagen, Denmark*
[i] *Ferring Pharmaceuticals Inc, Parsippany, NJ, USA*
[j] *Ferring Pharmaceuticals, Saint-Prex, Switzerland*

Article info

Article history:
Accepted November 10, 2009
Published online ahead of print on November 20, 2009

Keywords:
Degarelix
GnRH receptor antagonist
GnRH receptor blocker
Leuprolide
Prostate cancer
PSA

Abstract

Background: Recent data suggest prostate-specific antigen (PSA) progression may predict overall survival in prostate cancer patients.
Objective: To compare the activity of degarelix and leuprolide regarding PSA recurrence-free survival.
Design, setting, and participants: Phase 3, 1-yr, multicentre, randomised, open-label trial comparing the efficacy and safety of degarelix at 240 mg for 1 mo, and then 80 mg monthly (240/80 mg); degarelix at 240 mg for 1 mo, and then 160 mg monthly; and leuprolide at 7.5 mg/mo. Overall, 610 patients with histologically confirmed prostate cancer (all stages), for whom androgen deprivation therapy was indicated, were included. The primary end point of this trial has been reported previously; the protocolled and exploratory subgroup analyses reported in this paper focus on degarelix at 240/80 mg (dose approved by the US Food and Drug Administration and the European Medicine Evaluation Association for the treatment of patients with hormone-naive advanced prostate cancer).
Measurements: PSA progression-free survival (two consecutive increases in PSA of 50% compared with nadir and $\geq$5 ng/ml on two consecutive measurements at least 2 wk apart or death) and change in PSA were reviewed. Effects of baseline disease stage (localised, locally advanced, and metastatic) and PSA level ($<$10, 10–20, $>$20–50, and $>$50 ng/ml) were analysed.

* Corresponding author. Cliniques Universitaires Saint Luc/Université Catholique de Louvain, 10 Avenue Hippocrate, 1200 Brussels, Belgium. Tel. +32 2 764 5540; Fax: +32 2 764 5580.
E-mail address: bertrand.tombal@uclouvain.be (B. Tombal).

0302-2838/$ – see back matter doi:10.1016/j.eururo.2009.11.029

Results and limitations: Patients receiving degarelix showed a significantly lower risk of PSA progression or death compared with leuprolide ($p = 0.05$). PSA recurrences occurred mainly in patients with advanced disease and exclusively in those with baseline PSA >20 ng/ml. Patients with PSA >20 ng/ml had a significantly longer time to PSA recurrence with degarelix ($p = 0.04$). The relatively low number of patients in each subgroup is a limitation of this study.

Conclusions: These results generate the hypothesis that degarelix at 240/80 mg offers improved PSA control compared with leuprolide. PSA recurrences occurred almost exclusively in patients with metastatic prostate cancer or high baseline PSA during this 1-yr study. Further studies are warranted to confirm these findings.

1. Introduction

Gonadotrophin-releasing hormone (GnRH) agonists are the mainstay of androgen deprivation therapy for prostate cancer. These agents initially overstimulate GnRH receptors, and eventually, this results in suppression of luteinising hormone (LH) release through desensitisation of the pituitary–gonadal axis. This mechanism of action results in an initial testosterone surge, which in patients with advanced disease can stimulate tumour growth and exacerbate clinical symptoms (*clinical flare*) [1]. Treatment with GnRH agonists can also result in testosterone microsurges on repeat injections [2]. With chronic administration, testosterone release is suppressed and castrate levels (≤0.5 ng/ml) are achieved in 90–100% of patients after 7–21 d [3]. GnRH blockers (antagonists) are a new class of hormonal therapy that immediately block GnRH receptors, resulting in fast testosterone suppression without the surge, clinical flare, or microsurges associated with GnRH agonists [4,5].

Prostate-specific antigen (PSA) is a commonly used marker in prostate cancer screening. It can monitor response to treatment, disease recurrence, and potentially provide evidence of progression [6,7]. Absolute PSA level is also a marker of disease stage and extent of disease in prostate cancer patients. PSA control is associated with improved overall survival [8–10] and routinely used to monitor patients under therapy and assess response in most clinical settings. A recent phase 3 trial (CS21) demonstrated that degarelix, a new GnRH blocker, was associated with significantly faster LH, follicle-stimulating hormone (FSH), testosterone, and PSA suppression, and it was as effective as leuprolide in suppressing testosterone to castrate levels in prostate cancer patients over the 12-mo study period [11]. In this paper, we report exploratory subgroup analyses of PSA data from the CS21 trial.

2. Methods

2.1. Study design and patients

The methodology and results for this study have been reported previously [11]. Briefly, CS21 was a phase 3, multicentre, randomised, open-label trial powered to demonstrate the noninferiority of degarelix versus leuprolide for the primary end point (probability of patients having testosterone ≤0.5 ng/ml at each monthly measurement for 1 yr). Patients were randomised either to a degarelix starting dose of 240 mg for 1 mo and thereafter monthly doses of 80 mg (240/80 mg) or 160 mg (240/160 mg) or to leuprolide at 7.5 mg/mo. Concomitant antiandrogen could be given as flare protection to patients in the leuprolide group at the discretion of the investigator. Patients with histologically confirmed prostate cancer (all stages), for whom androgen deprivation therapy was indicated, were eligible (including patients with rising PSA after prostatectomy/radiotherapy). Patients were also required to have testosterone >1.5 ng/ml, an Eastern Cooperative Oncology Group performance status ≤2, and PSA ≥2 ng/ml.

This trial was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Independent ethics committees and institutional review boards were utilised for participating sites.

2.2. Prostate-specific antigen analyses

Blood samples for PSA analyses were taken at screening and before dosing (day 0), and at days 1, 3, 7 (±2 d), and 14 (±2 d) after the initial dose. Subsequent blood samples were taken on day 28 (±2 d), then once every 28 d (±7 d) before dosing and at final study visit. PSA analyses were performed at a central laboratory by Esoterix Inc using a validated immunoassay. PSA recurrence (a secondary end point) was defined as two consecutive increases in PSA of 50% compared with nadir and ≥5 ng/ml on two consecutive measurements at least 2 wk apart, with the end point recorded on the date of the second measurement. Analyses of PSA recurrence over time and percentage change in PSA from baseline to 14–28 d were preplanned and included in the CS21 statistical analysis plan; the remaining analyses were of an exploratory post hoc nature. PSA progression-free survival was analysed using the Kaplan-Meier method, and *time to event* was defined as the number of days from first dosing to the first of PSA recurrence or death. Overall survival was analysed using similar methodology. PSA recurrences were analysed by baseline disease stage (localised, locally advanced, metastatic) and PSA level (<10, >10–20, >20–50, and >50 ng/ml). Median percentage change in PSA level from baseline was also analysed by baseline disease stage. Statistical comparisons were performed using a Cox proportional hazards analysis adjusted for baseline disease stage and PSA level, and the log-rank test (unadjusted analysis).

These exploratory subgroup analyses focus on the comparison of leuprolide 7.5 mg/mo with degarelix 240/80 mg, in line with recent approvals of this dose for the treatment of advanced prostate cancer by the US Food and Drug Administration and the European Medicine Evaluation Association.