Editorial Comment on: Degarelix: a Novel Gonadotropin-Releasing Hormone (GnRH) Receptor Blocker—Results from a 1-yr, Multicentre, Randomised, Phase 2 Dose-Finding Study in the Treatment of Prostate Cancer

Patrick J. Bastian
Urologische Klinik und Poliklinik, Ludwig-Maximilians-Universität München, Klinikum Großhadern, Marchioninistr. 15, 81377 München
patrick.bastian@med.uni-muenchen.de

The Nobel prize-winning discovery of the importance of androgenic influences on the growth of prostate cells by Charles B. Huggins and C.V. Hodges in 1941 established androgen-deprivation therapy (ADT) as a treatment for metastatic prostate cancer. As known from the literature, androgen-deprivation therapy reduces bone pain in 80–90% of cases, leads to objective responses in soft tissue and bone, and normalizes serum prostate-specific antigen (PSA) in over 90% of patients [1,4,5].

However, ADT results in erectile dysfunction, loss of libido, fatigue, hot flashes, and loss of muscle and bone mass, all of which adversely impact quality of life.

Various forms of ADT exist today, including bilateral orchiectomy, GnRH agonists, estrogen therapy, ketokonazole to block adrenal androgens, and combined androgen blockage, where a GnRH agonist or orchiectomy is combined with an antiandrogen.

The study of van Poppel et al describes a multicentre, randomised phase 2 dose-finding trial of the novel GnRH antagonist degarelix [2]. A faster and more profound testosterone suppression can be achieved using this novel agent compared to other GnRH antagonists.

The authors defined the castration levels as $\leq$50 ng/dl. Due to novel, more sensitive assays — such as the radioimmunoassay technique and the chemiluminescent technique—levels as low as 20 ng/dl can be detected. There is limited clinical basis for reducing castrate levels, and no studies have shown that by lowering the level of testosterone to $\leq$20 ng/dl survival is statistically improved. It would be interesting to see what the response rate in this lower castration level group may be.

However, it must be recognized that 2–13% of patients fail to achieve <50 ng/dl testosterone following LHRH therapy and 13–37% fail to reach <20 ng/dl [3].

Another interesting point that warrants discussion is the rate of withdrawals. Fifteen percent of the enrolled patients withdrew due to adverse events or insufficient castration level. This level seems very high and needs additional corroboration.

Nevertheless, this is an interesting and important study to mark the emerging role of GnRH antagonists in the treatment of prostate cancer.

References

[1] Heidenreich A, Aus G, Bolla M, et al. EAU guidelines on prostate cancer. Eur Urol 2008;53:68–80.
[2] Van Poppel H, Tombal B, de la Rosette JJ, Persson B-E, Jensen J-K, Kold Olesen T. Degarelix: a novel gonadotropin-releasing hormone (GnRH) receptor blocker—results from a 1-yr, multicentre, randomised, phase 2 dose-finding study in the treatment of prostate cancer. Eur Urol 2008;54:805–15.
[3] Tombal B. Appropriate castration with luteinising hormone releasing hormone (LHRH) agonists: what is the optimal level of testosterone? Eur Urol Suppl 2005;4(5):14–9.
[4] Clarke NW. Management of the spectrum of hormone refractory prostate cancer. Eur Urol 2006;50:428–39.
[5] Wirth MP, Hakenberg OW, Froehner M. Antiandrogens in the treatment of prostate cancer. Eur Urol 2007;51:306–14.

DOI: 10.1016/j.eururo.2008.04.066
DOI of original article: 10.1016/j.eururo.2008.04.065