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Importance of Rapid and Profound Suppression of Hormone Levels in Prostate Cancer Now Supported by PSA Progression-free Survival

Vienna - Newly released data from an ongoing extension study demonstrate outcome advantages for an antagonist relative to an agonist of gonadotropin-releasing hormone (GnRH) for prostate cancer. Specifically, patients switched to an antagonist after 1 year of agonist treatment experienced a significant improvement in prostate-specific antigen (PSA) progression-free survival (PFS) (lower rate of PSA failure or death). In light of known limitations with GnRH agonists, these data provide insight into the importance of more complete and rapid hormone suppression for preventing prostate cancer progression. Significantly, the data provide additional evidence that it may be valuable to suppress follicle-stimulating hormone as well as to reach and sustain castration levels of testosterone for optimal control of the malignancy. Here at the EAU, long-term follow-up data from a phase III study support the significant PSA PFS benefit of the GnRH antagonist degarelix over the agonist leuprolide and its role as first-line androgen-deprivation therapy.

In the control of prostate cancer, the theoretical advantages of an antagonist over an agonist in suppression of the gonadotropin-releasing hormone (GnRH) pathway are now being corroborated by outcomes. The GnRH agonists initially stimulate before suppressing testosterone and follicle-stimulating hormone (FSH) production. FSH is speculated to play a role in prostate cancer progression. Compared to normal prostate cells, cancer cells contain more FSH receptors and more so in androgen-refractory prostate cancer cells.

Although agonists are highly effective in delaying progression of prostate cancer, the more recently developed GnRH antagonists act immediately. The difference in the speed of testosterone suppression was observed in a phase III trial. New data from the extension crossover phase of the study now show a change in the slope of progression markers when patients are switched from an agonist to an antagonist. This is consistent with their activity.

"It was really something of an accident of history that agonists came before the antagonists. The agonists have an indirect effect, whereas the antagonists block the receptor so they act straightaway," observed Dr. John Anderson, Royal Hallamshire Hospital, Sheffield, UK. One of several experts here at the EAU who addressed the cumulative data regarding the relative effects of GnRH agonists and antagonists, Dr. Anderson stated that the data overwhelmingly support an intervention that provides a rapid and sustained suppression of hormones at the castration level.

Study Findings

The new data were generated from an extension of the registration trial of the GnRH antagonist degarelix. In the initial 12-month trial, known as CS21, 610 patients were randomized to 1 of 2 subcutaneous regimens of the GnRH antagonist (both groups received a starting dose of 240 mg but were differentiated by subsequent monthly doses of either 80 mg or 160 mg) or monthly intramuscular doses of 7.5 mg leuprolide, the GnRH agonist (Klotz et al. *BJU Int* 2008;102:1531-8). The goal of the study was to demonstrate degarelix non-inferiority to leuprolide for maintaining testosterone suppression for 12 months, which it did demonstrate for both doses. Moreover, degarelix provided far more rapid suppression of both testosterone and prostate-specific antigen (PSA) levels. New data from the extension study, CS21a, are now generating evidence that the strategies differ meaningfully in regard to outcomes.

"While there was a significant advantage for PSA progression-free survival (PFS) at 12 months (P=0.05) in the degarelix group, the slope in the hazard of PSA progression changed in the leuprolide group after the crossover to degarelix, which took place at 12 months," reported Dr. Thomas E. Keane, Medical University of South Carolina, Charleston. Specifically, hazard rates for PSA PFS decreased more than 50% from 0.20 events/year in the first year to 0.08 events/year after switching to degarelix (P=0.003). Graphically, the curve of PSA failure or death returned in the more favourable direction seen in the degarelix group. Dr. Keane suggested that this might relate to the consistency of hormone suppression.

"With repeated doses of leuprolide during the randomized phase of the study, there were microsurges in testosterone not seen in patients receiving degarelix, and differences were observed even in those patients who were receiving an antiandrogen therapy with the leuprolide," Dr. Keane told delegates.

Agonist and Antagonist Modes of Action

These surges reflect the very different modes of action of agonists and antagonists. The GnRH agonists suppress testosterone only after an initial and sustained surge, according to Dr. Anderson. While testosterone falls to castration levels (<0.7 nmol/L) within about 24 hours after injection of the

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antagonist, the rise in testosterone after injection of an agonist does not even return to baseline for approximately 7 days and then does not reach castration levels for 21 days. It takes 28 days to match the testosterone suppression of degarelix, but repeated injections of leuprolide then produce microsurges in testosterone as well as other sex hormones. The median PSA level in patients on leuprolide did not reach the median level of degarelix for 56 days.

"This difference is certainly important for patients who have symptoms, but I think this difference in PSA control is going to be meaningful for outcome," Dr. Anderson remarked. He also noted that although CS21 was primarily a comparison of degarelix and leuprolide, those on leuprolide were permitted to take antiandrogen therapy to control prostate symptoms. As a result, the study also refutes the assertion that a GnRH agonist can be considered equal to a GnRH antagonist if combined with an antiandrogen. Although this would not be expected to be true from a mechanistic perspective—the antiandrogens only suppress the effects of the testosterone surge, not the surge itself—the difference in the time to PSA suppression in CS21 demonstrates that it is also not true clinically.

One of the issues is not only the consistency of the testosterone suppression but the potential importance of also suppressing FSH and luteinizing hormone (LH). According to Dr. Anderson, who cited several studies supporting this hypothesis, "Evidence is accumulating that FSH may have a direct role in the pathogenesis and the progression of prostate cancer." As "FSH suppression [on degarelix] is more profound and sustained than that achieved with an agonist," this may be a contributing factor to the differences observed.

Testosterone Breakthrough Associated with Poorer Response

Nevertheless, testosterone suppression still appears to be the most important variable affecting outcome. In new data from a study approaching this issue from an entirely different perspective, the effect of testosterone breakthrough was evaluated in prostate cancer patients on continuous GnRH agonists as adjuvant therapy with radiation. The data were drawn from 11,752 patients treated over a 10-year period. Led by Dr. Tom Pickles, Radiation Program, BC Cancer Agency, Vancouver, the study found that the testosterone breakthrough (>0.7 nmol/L) per patient course was 26.8%. Breakthrough was associated with a higher post-radiation PSA nadir (3.0 vs. 0.5 nmol/L; *P*=0.0230), while 5-year biochemical non-evidence of disease was observed in 82% of patients without breakthrough but only 72% of those who did have testosterone breakthrough (*P*=0.03).

"Several groups, including ours, have reported that patients on [GnRH agonists] do not always achieve or maintain castrate levels of testosterone," Dr. Pickles told delegates. "A breakthrough above levels achieved with surgical orchiectomy [<0.7 nmol/L] are associated with a poorer neoadjuvant PSA response, a higher post-radiation PSA nadir and a greater chance of subsequent biochemical relapse." According to Dr. Pickles, testosterone levels should be monitored routinely in patients on GnRH agonists so that the treatment can be switched or an antiandrogen agent can be added when there is a breakthrough.

However, it appears to make more sense to initiate therapy with a GnRH antagonist, which may be more reliable across a broader range of patients. For example, when all patients with a baseline PSA ≥20 ng/mL were considered in a CS21a substudy, the time for 25% of patients to experience PSA failure or death was significantly longer for degarelix vs. leuprolide (514 vs. 303 days; *P*=0.01).

"These data support the durability of the significant PSA PFS benefit of degarelix vs. monthly leuprolide observed during the first year and the use of degarelix as first-line androgen deprivation therapy," reported the author of this analysis, Dr. Bertrand Tombal, Cliniques Universitaires Saint-Luc, Catholic University of Louvain, Belgium.

Summary

GnRH agonists have played an important role in preventing progression of prostate cancer by lowering testosterone levels. However, initial use of agonists causes testosterone to surge while repeated doses cause microsurges. Other sex hormones such as FSH rise initially before falling. A more recently developed GnRH antagonist achieves rapid and profound castration levels with no surge or microsurge and maintains lower FSH levels. These factors may have contributed to the better PSA PFS seen with the antagonist vs. the agonist in a phase III study. Extended follow-up from the same phase III study supports the long-term efficacy of an antagonist, showing favourable trends and even improvements among those switched to the antagonist at the end of 12 months. □

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