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An Enhanced Medical Approach to Androgen Suppression in Prostate Cancer

Athens - It has been 70 years since investigators first understood that prostate cancer is hormone-sensitive and that medical suppression of testosterone production can control the tumour and affect long-term disease outcomes. Yet there are still questions concerning the best form of androgen-deprivation therapy as well as the specific patient groups who will gain the most benefit from treatment. Gonadotropin-releasing hormone (GnRH) agonists have been extensively used for treatment of prostate cancer in recent decades. These agents are slow-acting and often cause a testosterone "surge" in the initial treatment period, causing a temporary worsening of symptoms that may lead to long-term adverse sequelae. The newly developed GnRH blockers have an immediate onset of action and rapidly reduce testosterone and PSA without flare and are designed to delay progression of prostate tumours upon treatment onset.

Dr. John Anderson, Royal Hallamshire Hospital, Sheffield, UK, noted that the slow onset of action of gonadotropin-releasing hormone (GnRH) agonists results in a two- to three-week delay in achieving castrate testosterone levels. The early testosterone surge that occurs with agonists may well lead to clinical flare, particularly in men with advanced disease. By contrast, no surge and therefore no flare has been observed with the first-in-class GnRH antagonist/blocker degarelix. It produces an immediate onset of action, causing testosterone to drop to castrate levels within a day or two in over 90% of patients (Klotz et al. *BJU Int* 2008;102:1531-8).

"We know that when the agonists stimulate GnRH receptors, it results in a rise in luteinizing hormone (LH) that leads to a surge in testosterone levels, and we see clinical flares. But even when there is no clinical flare, there is surely some subclinical stimulus to the tumour to cause tumour growth. The net effect is that by feedback, a traffic jam eventually occurs at the level of the pituitary and causes a shutdown in LH production," Dr. Anderson explained here at CURy. "In contrast, the GnRH antagonists are more like a road block; they immediately bind with the GnRH receptors and shut things down straight away. This direct mode of action results in a very fast, very profound and sustained drop in testosterone without any evidence of testosterone surges."

Wide Spectrum of Use

According to Dr. Anderson, urologists are already familiar with GnRH analogues so the learning curve for the use of degarelix in advanced prostate cancer will be simple. It is expected to be standard treatment for men with metastasis, particularly those with symptoms and also those with nodal involvement.

This form of medical castration is increasingly being used for the whole spectrum of the disease. "We see it used in the adjuvant setting in patients with locally advanced disease, even in patients with early stage who may not be fit for any radical treatment, but are symptomatic," Dr. Anderson told delegates. "I think we can use GnRH blockers across the full spectrum: metastatic patients, node-positive patients, symptomatic patients with local advanced disease and high-risk localized disease. Patients who have symptomatic advanced disease will benefit from the rapid drop in testosterone. Patients with impending spinal cord compression or urinary obstruction are going to derive significant benefit from this rapid drop in testosterone compared to the analogues which would produce a rise in testosterone and worsening symptoms."

Dr. Anderson suggested GnRH blockers could also be useful in earlier stages of prostate cancer. Patients with short prostate-specific antigen (PSA) doubling time, high PSA levels and high Gleason scores are more likely to have progressive disease which is fatal if not treated effectively. It is clearly in the best interest of these patients to combine an effective GnRH blocker with external beam radiotherapy or surgery for maximum benefit. The advantage of combining androgen deprivation therapy (ADT) with either antagonists or agonists is indisputable, but as degarelix is effectively working sooner and preventing stimulus of tumour growth at its initiation, it may be a better choice for the patient. Neoadjuvant hormone treatment is given with the intention of reducing tumour bulk and treating micro-metastatic disease as well as the primary lesion to better prepare responders for surgery or radiation. Studies have demonstrated that tumour volume reduction in prostate cancer is greater with the GnRH blocker degarelix than with the agonists, so a patient with significant bladder obstruction, for example, may benefit from greater volume reduction, or minimal side effects, ahead of radiotherapy when that drug is used.

Rapid Androgen Suppression

Noting that prostate cancer is the second leading cause of cancer death among men, Dr. Bo-Eric Perrson, Elisabeth Sjukhuset Hospital, Uppsala, Sweden, remarked that optimal therapy remains a subject of debate. But based on more than 20 studies, he believes degarelix presently best meets the needs of prostate cancer patients.

The recent CS21 trial was a pivotal phase III, randomized study that evaluated degarelix and leuprolide (Klotz et al. 2008). The GnRH blocker achieved testosterone and PSA suppression significantly more rapidly than the agonist, a profound suppression that was sustained for the 12 months of

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the trial. The study randomized 610 patients to a starting dose of degarelix 240 mg for a month, then to maintenance doses of 80 mg or 160 mg monthly, or to leuprolide 7.5 mg monthly. The administration of antiandrogens to mitigate clinical flare was left to the discretion of the investigator; 16% of patients receiving leuprolide were given an antiandrogen.

Dr. Perrson reported that both degarelix doses were at least as effective as leuprolide at inducing and sustaining testosterone suppression to levels of ≤0.5 ng/mL but achieved it more rapidly. By day 3, testosterone levels were ≤0.5 ng/mL in 96% of degarelix patients compared to none of those receiving leuprolide. The first median castrate levels of testosterone in the latter group were not observed until day 28. None of the degarelix-treated patients experienced a testosterone surge, as opposed to 81% in the leuprolide group. Additionally, degarelix provided a significantly faster drop in PSA than leuprolide, indicating more rapid control of disease.

In CS21, degarelix achieved a significantly more rapid reduction from baseline in PSA levels at 14 days, declining by 64% vs. 18% in the leuprolide group. Those figures were 85% and 68% at 28 days. PSA suppression was maintained throughout the study period in both treatment groups.

Influence of Baseline Testosterone Levels

A subgroup analysis of the CS21 trial sought to determine if baseline testosterone levels influence the outcome of testosterone and PSA suppression by GnRH agonists and GnRH blockers. Groups were divided according to baseline testosterone levels of <3.5 ng/mL, 3.5-5 ng/mL and ≥5 ng/mL.

According to Dr. Bertrand Tombal, University Clinic Saint-Luc, Brussels, Belgium, data suggest that few clinicians measure baseline testosterone levels before initiating ADT for prostate cancer. "It is clear," he said, "that the higher testosterone concentrations are at baseline, the longer it will take to induce castration levels in patients. This was true for degarelix in a recent comparative trial, but was most clearly observed with leuprolide. The difference in time to castration between the two drugs at various time points was highly statistically significant in favour of degarelix from days 3 to 28 in all categories according to high, intermediate or low baseline testosterone levels (<3.5 ng/mL, 3.5-5 ng/mL and ≥5 ng/mL), and remained significant in the high baseline testosterone patients through day 56, with additional non-significant benefits extending to day 84."

Dr. Tombal added, "Using PSA progression-free survival that incorporates time to PSA failure in the intent-to-treat population, there is a clear difference in PSA progression-free survival between patients receiving degarelix or leuprolide. PSA progression-free survival was significantly longer with degarelix."

Dr. Jan-Erik Damber, Gothenburg University, Sweden, reported that by day 1, testosterone levels fell by at least 85% with degarelix treatment compared with rises of 36% to 55% with leuprolide. The magnitude of agonist-induced testosterone surge was found to be a function of baseline testosterone. The rate at which castrate testosterone levels were achieved slowed with increasing baseline testosterone in both groups. Between days 1 and 14, achievement of castrate levels occurred significantly faster with degarelix than with leuprolide in all baseline testosterone subgroups studied. Only leuprolide-treated men showed testosterone microsurges 7 days following their ninth injection. Men with higher baseline testosterone values experienced larger testosterone microsurges during leuprolide treatment.

Regarding PSA values, a rapid reduction from baseline began with degarelix on day 1 (median reductions of >60% and >84% on days 14 and 28). In contrast, there was a small increase in PSA on days 3 and 7 in the leuprolide group, which was greatest in patients with baseline testosterone >5 ng/mL. By day 14, reductions in PSA ranged from 15% to 23% and reached >60% in all subgroups by day 28.

Dr. Damber also noted that patients with high baseline testosterone levels receiving leuprolide may experience a greater magnitude of GnRH agonist-induced testosterone surge, a delay in PSA suppression of up to 3 months and a greater magnitude of GnRH agonist-induced microsurges.

He told delegates, "degarelix induced significantly greater PSA reductions at days 3, 14 and 28 than leuprolide regardless of baseline testosterone level. PSA suppression with degarelix was superior to that of leuprolide even beyond day 56 in patients with baseline testosterone ≥5 ng/mL." Dr. Damber concluded that these data suggest that degarelix provides faster disease control in terms of testosterone and PSA reductions, no GnRH-induced testosterone surges and no microsurges.

Summary

Unlike the GnRH agonists, the GnRH blocker degarelix has shown an immediate onset of action, providing a rapid fall in LH, FSH and testosterone without testosterone surge, clinical flare or testosterone microsurges. Regardless of higher baseline testosterone levels, there is a profound and sustained reduction in testosterone similar to orchidectomy with the GnRH blockers, thereby overcoming a limitation of GnRH agonists. These data support the rationale for baseline and ongoing testosterone monitoring to ensure optimal management of the patient's prostate cancer. □

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