LHRH Antagonists vs LHRH Agonists: Which Is More Beneficial in Prostate Cancer Therapy?

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Crawford and Hou[1] review the data on luteinizing hormone-releasing hormone (LHRH) antagonists in prostate cancer. They describe the results of a phase III trial comparing monthly degarelix to monthly leuprolide in men with advanced prostate cancer. Degarelix treatment was associated with a more rapid decline of serum testosterone, and was not associated with an initial surge of serum testosterone seen during the first few days of treatment with leuprolide. They discuss the role of this new form of medical gonadal suppression for the treatment of prostate cancer.

Androgen-Deprivation Therapy

Androgen-deprivation therapy (ADT) is an effective treatment for patients with prostate cancer. Most patients with metastatic prostate cancer treated with ADT demonstrate major declines of the serum levels of prostate-specific antigen (PSA), and objective tumor responses, evident clinically or by imaging tests. In patients with metastatic disease, ADT reduces bone pain and other serious and debilitating disease-related complications (ie, pathologic fractures, spinal cord compression, and urethral obstruction).[2]

Suppression of gonadal testosterone by medical (LHRH agonists) or surgical castration is considered the central mechanism of ADT for prostate cancer.[3] Prospectively randomized clinical trials in patients with metastatic disease assessing medical vs surgical castration have resulted in comparable rates of clinical benefits and similar distributions in time to disease progression and survival.[4] Over the years, LHRH agonists virtually replaced the use of surgical castration in the Western world.

Key Study Findings

Treatment with short- and long-acting preparations of LHRH agonists is associated with an initial release of luteinizing hormone, and consequently, an initial surge of serum testosterone that occurs during the initial 72 hours of treatment. With continuous exposure, gonadal luteinizing hormone receptors are downregulated, and testosterone levels decline to the castration range after 1 month. Initial studies of LHRH agonists reported that a number of patients with bone metastasis and bone pain at baseline had transient worsening of their symptoms (ie, flare phenomenon) during the initial few weeks of treatment. Symptomatic management was the recommended approach, and most patients eventually improved without the need for major changes in therapy.[5] Special caution has been suggested for patients at risk for serious disease-related complications such as spinal cord compression and urinary obstruction. However, a clear-cut association has not been shown between the development of spinal cord compression or bladder outlet obstruction and the initial rise in serum testosterone during LHRH agonist therapy. While the concerns are legitimate, the association remains primarily a plausible (and reasonable) concern.

Subsequent studies suggested that a short course of steroidal antiandrogens (eg, cyproterone acetate [Androcur]) could significantly reduce the incidence and magnitude of initial testosterone flare, and studies combining nonsteroidal antiandrogens with LHRH agonists in patients with advanced disease suggest a change in the trend for deterioration of signs and symptoms associated with the disease.[6] The latter could represent either a more rapid response to treatment or simply a
counteraction of the disease flare by the nonsteroidal antiandrogen.[6]
LHRH antagonists bind to the LHRH receptors on pituitary gonadotropin-producing cells. They do not cause an initial release of luteinizing hormone or follicle-stimulating hormone, and thus avoiding the flare phenomenon of LHRH agonists. Abarelix was the first US Food and Drug Administration (FDA)-approved LHRH antagonist for advanced prostate cancer. However, it was withdrawn from the market because of a high incidence of anaphylaxis. Degarelix was approved by the FDA in December 2008, based on the phase III trial in 610 men randomized to degarelix or leuprolide,[7] as described by Crawford and Hou. Degarelix was associated with a more rapid (within 3 days) decrease of testosterone levels in 96% of patients. This serum testosterone suppression was maintained for the duration of this 1-year trial. Although local injection site reactions were occurred more frequently with degarelix (40% vs < 1% with leuprolide), no systemic allergic reactions were reported.

**Benefits and Limitations**

Crawford and Hou provide a concise review of the current data on LHRH antagonists in the treatment of prostate cancer, focusing on their experience with degarelix. The data suggest that degarelix is a reasonable alternative for gonadal androgen deprivation treatment for prostate cancer. Long-term suppression of serum testosterone can be achieved with either approach, and the testosterone suppression is faster with degarelix than with LHRH agonists. While one can argue that these results are from a single trial and that follow-up time is relatively short, it is likely that the benefits are comparable to those of LHRH agonists. The issue to consider, however, is whether there is additional benefit associated with a more rapid decline of testosterone.

At the present time, most patients with metastatic prostate cancer have no symptoms at presentation, and the majority have less extensive disease compared to more than 2 decades ago, when LHRH agonists were approved. The short-term advantage is limited to the rare patient at risk for disease flare or in need of rapid symptom control,[5] and even in this situation the concerns may be minimized by employing a short-term combined regimen with an LHRH agonist plus an antiandrogen. The advantage of using LHRH antagonists over LHRH agonists is even more obscure for patients with no evidence of metastatic disease.

Finally, patient compliance with treatment and cost-effectiveness are important issues, especially when ADT is administered for long periods of time. In its current formulation, degarelix is administered monthly, as opposed to the longer and more convenient depot formulation of LHRH agonists. This is certainly one of the major limitations of the newer agent, since most patients treated with LHRH agonists are treated on an every-3-month basis, which improves patient compliance and cost by reducing the number of injections to four per year.[8]

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**References:**