Obesity and Treatment of Prostate Cancer: What Is the Right Dose of Lupron Depot?

To the Editors: The January 1, 2007, issue of Clinical Cancer Research includes a retrospective analysis by Dr. Smith of two previously reported prospective studies of gonadotropin-releasing hormone agonist treatment in men with locally advanced or recurrent nonmetastatic prostate cancer (1). It was concluded that despite lower pretreatment serum testosterone levels, obese men have higher total and free testosterone levels during treatment with leuprolide than men with normal body mass indices. These results raise the possibility that higher sex steroid levels during gonadotropin-releasing hormone agonist treatment contribute to greater prostate cancer mortality in obese men. It is notable that all the study subjects received the same dose of leuprolide 3-month depot (22.5 mg i.m. every 12 weeks; Lupron Depot, TAP Pharmaceuticals, Inc.) irrespective of their body mass index.

Because of the use of a fixed dose of leuprolide irrespective of the body mass index, the conclusion of a causal relationship between obesity and inferior response to treatment with gonadotropin-releasing hormone agonist is open to debate. Lupron is a synthetic agonist analogue of gonadotropin-releasing hormone. The active form leuprorelin is a peptide and only parenteral forms are biologically active. In the sustained-release depot formulations, the hydrophilic leuprorelin is entrapped in biodegradable highly lipophilic synthetic polymer microspheres. The peptide drug is released from these depot formulations at a functionally constant daily rate for 1, 3, or 4 months, depending on the polymer type, with doses ranging between 3.75 and 30 mg (2). After injection into the intramuscular space, the lipophilic synthetic polymer microspheres are slowly degraded by enzymatic breakdown to release the biologically active hydrophilic peptide. Being hydrophilic, the peptide form remains confined to the extracellular fluid compartment, keeping its volume of distribution ($f_2$ L) almost constant irrespective of the body weight. Hence, a fixed dose of Lupron has been assumed to be adequate for all study subjects.

However, the half-life of a drug in a depot preparation not only depends on the volume of distribution of the active drug, but also on the rate of release of the active drug from its depot formulation. It is possible that the lipophilic depot injection forms a larger area of drug depot in obese subjects due to the increased amounts of adipose tissue in the muscles. This would result in more of the polymer microspheres being exposed to enzymatic breakdown. In this case, the rate of release of leuprorelin peptide from the polymer microspheres will be higher, thereby emptying the depot site of the drug before the 3-month period. In Dr. Smith’s study subjects, the serum testosterone levels were obtained at 3 months, just prior to the end of the depot period. If serum testosterone was found to be elevated, could it have been because the depot preparation in the obese subjects emptied of the active peptide form earlier than in the nonobese subjects, resulting in suboptimal leuprorelin levels?

This concern about body mass index having an effect on the depot preparation of Lupron has been shared by other investigators as evidenced by their use of different doses of Lupron in their patients with respect to the body weight (3–5). As to the effect of obesity on the drug efficacy of gonadotropin-releasing hormone agonists, further studies with simultaneous measurements of serum testosterone and plasma levels of the biologically active peptide form of the drug (leuprorelin) will be needed to clarify this important issue.

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References
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