MORE ABOUT DEGARELIX:
New Findings About Its Biological Effects and Two Recent Studies.

There is new understanding about the biology of degarelix (Firmagon) that may explain its superiority over leuprolide (Lupron) when administered to control prostate cancer in men with aggressive disease, i.e. high PSA values (>20 ng/ml) or metastatic disease, the category of patient for which it is FDA approved.

An initial discussion of degarelix was presented in PCa Commentary Vol 78 Nov-Dec 2012 citing that, in comparison with leuprolide, degarelix is associated with a significant lower risk of PSA progression or death in men with advanced disease and a more consistent suppression of testosterone compared to leuprolide. Also cited was data from Crawford's Phase III 27.5 month extension study which showed a statistically significant PSA progression-free survival during a 1 year trial for those men receiving degarelix. The extension study, which followed men for an additional 6 months, found that in the period beyond the first year those men who were progressing on leuprolide who were then switched to degarelix had their rate of progression slowed.

BUT FIRST... New information about the role of the luteinizing hormone releasing hormone receptor (LHRH-R; also termed GnRH-R, i.e. gonadotropin releasing hormone receptor) that may explain the differential clinical responses seen with the two agents that both target this receptor, i.e., degarelix, an LHRH-R antagonist, and leuprolide, an LHRH-R agonist. This subject was reviewed by Tolkach et al. in "Luteinizing hormone-releasing hormone (LHRH) receptor agonists vs antagonists: a matter of the receptors?" (BJU-Int, 2013).

Clinicians are accustomed to thinking about the well-known messaging axis between the hypothalamic/pituitary/testes in the following manner:

1) the hypothalamus sends pulses of signals (Luteinizing Hormonal Releasing Hormone, LHRH) to the nearby pituitary gland and activates a cell-surface receptor, the Luteinizing Hormone Releasing Hormone Receptor (LHRH-R);
2) cells in the anterior pituitary gland dutifully respond by secreting Luteinizing Hormone, LH, and Follicle Stimulating Hormone, FSH, into the blood stream; and
3) the Leydig cells in the testes receive the message and secrete testosterone. Degarelix immediately blocks pituitary LH secretion and testosterone secretion is promptly halted, whereas leuprolide achieves the same result in about one month. Degarelix also suppresses pituitary FSH production and does so more effectively than leuprolide, which may be of clinical significance.

The new finding: Prostate cancer cells themselves express LHRH receptors!

What is the clinical significance of this and how does it relate to the biology of degarelix?

Stimulation of these prostatic LHRH receptors, while not resulting in intraprostastic testosterone production, initiates a cascade of responses involving:

- increased cellular proliferation,
- resistance to apoptosis (cell death),
- increased metastatic potential, and
- increased responsiveness to locally secreted growth factors.

Just as it has been recently learned that prostate cancer cells can generate testosterone by their own intrinsic cellular processes, in a similar fashion prostate cells can activate their own LHRH receptors (autocrine) or receive local stimulation from the surrounding microenvironment (paracrine) from LHRH produced in the prostate itself or nearby.
MORE ABOUT DEGARELIX continued:

Tolkach summarizes: "One of the most important concepts regarding LHRH-receptors in [prostate cells] is that it is part of a local autocrine/paracrine loop which regulates growth and proliferation." Therefore, these receptors have become important additional targets for degarelix and leuprolide.

The reported superiorly of degarelix over leuprolide in advanced disease may be based on several findings:

1) As prostate cancer cells become more aggressive the cell surface density of LHRH-R decreases, but the affinity of those receptors for LHRH increases, and increased affinity for LHRH seems to be the most critical feature;

2) Degarelix accomplishes the blocking of prostatic LHRH-receptors more effectively than leuprolide in the face of more aggressive disease;

3) Leuprolide can induce mutations in the receptor leading to resistance to the drug, whereas degarelix has not been shown to induce mutations. There is a reported 17% response rate by switching to degarelix in the face of resistance to leuprolide; and

4) Degarelix suppresses pituitary FSH production more effectively than leuprolide.

AND NOW … Two recently reported studies comparing degarelix to leuprolide.

At the recent ASCO Genitourinary Cancer Symposium Crawford et al. presented abstract #68 - "Degarelix versus LHRH agonists: Differential skeletal and urinary outcomes from an analysis of six comparative randomized clinical trials."

Their statement: "GnRH antagonists [i.e. degarelix] have a mode of action distinct to that of LHRH agonists and comparative trials have shown differences in efficacy and safety between these two agents." The treatment groups were well balanced with 1491 receiving degarelix and 837 an LHRH agonist.

Their conclusion: Their analysis of these 2328 men showed that, when compared to leuprolide, degarelix treatment was more effective in lowering serum alkaline phosphatase in men with metastatic disease, implying greater control over progression of bone metastases, i.e yielding less muscle and bone pain, 9% v. 12%, and significantly fewer fractures, 1% v. 2%. Urinary tract infections occurred less frequently with degarelix, 5% v. 8%. Men with PSA >50 ng/ml had a lower risk of PSA progression and higher overall survival than patients receiving an LHRH agonist over one year [98.3% v. 98.7%]. In men with no evidence of bone metastases there was no difference in alkaline phosphatase levels between the two drugs.

A second relevant study was also presented at the GU Cancer Symposium in poster form by Peter Albertsen et al. "Lower risk of cardiovascular events and death in patients treated with degarelix compared with LHRH agonists."

The study was based on the same men as in Crawford's trial (see above) and focused on men with advanced prostate cancer. The cardiovascular diseases evaluated were: arterial embolic and thrombotic events, hemorrhagic or ischemic cerebral conditions, myocardial infarctions, or other forms of ischemic heart disease.

Their conclusion: Over a treatment period of one year a cardiovascular (CV) event or death occurred in 3.6% of men taking degarelix as compared 5.7% in those taking an LHRH agonist. The comparison for men experiencing a CV event only was 2.7% v. 4.4%. In men with a history of prior CV events, degarelix was associated with a 50% reduction, i.e. 7% v. 14%, in adverse CV effects or death.

The explanation for this difference is currently unknown, but again the biology of LHRH receptors may be relevant since "In vitro and in vivo experiments have shown that both GnRH and GnRH receptors are expressed outside of the hypothalamic-pituitary-gondala axis including lymphocytes, macrophages, and cardiomyocytes" (Albertsen).

BOTTOM LINE: Biological and clinical studies have demonstrated significant clinical advantages for the use of degarelix as opposed to an LHRH agonist (Lupron and goserelin) in men with advanced prostate cancer.
Currently there are eleven proton beam facilities in the US and a new one is opening every year. The newest is located at Northwest Hospital in Seattle under the aegis of the Seattle Cancer Care Alliance.

Americans are famous for their widespread belief that "new is better." It is timely to consider the known fact(s) about the comparison of this emerging technology to lesser expensive modalities and to try to evaluate if the "emperor" has no clothes, the regular stuff commonly worn, or totally awesome new duds.

What do the most unbiased critics say about the Emperor's "clothes"? A great deal has been written on this subject. However, the result is a frustrating lack of clarity since the efforts to date of necessity have been forced to attempt making informative comparisons based on essentially incomparable data.

A succinct appraisal from the ranking guru on the subject, Dr. Anthony Zietman, Harvard Medical School, captures the current state of affairs:

"Proton therapy is a promising, but costly, treatment for prostate cancer. Theoretical physical advantages exist; yet to date, it has been shown only to be comparably safe and effective when compared with the alternatives and not necessarily superior. If clinically meaningful benefits do exist for patients, more rigorous study will be needed to detect them and society will require this to justify the investment of time and money. New technical advances in proton beam delivery coupled with shortened overall treatment times and declining device costs have the potential to make this a more cost-effective therapy in the years ahead," "Proton beam therapy and localized prostate cancer: current status and controversies," Efstathiou, Gray, and Zietman, Br. J Cancer. 2013 Apr 2.

Fortunately there is an ongoing randomized Phase III National Cancer Institute study, NCT01617161, that is currently recruiting participants to compare proton beam therapy with intensity modulated radiation therapy in men with low or low-intermediate prostate cancer (clinical stages T1c to T2b). The study is justified by the acknowledgment stated in the protocol that "no one knows which of the study options is best." The length of therapy is 8 - 9 weeks. The study is sponsored jointly by Massachusetts General Hospital and the University of Pennsylvania.

There are several outcome measures to be evaluated at 24 months from the start of treatment:

1) Comparison of side effects related to bowel function;
   [This is specifically targeted since there is considerable controversy about treatment differences in this domain with some studies showing that PBT causes greater bowel toxicity.]

2) Cost effectiveness for "alternate treatment delivery and cost scenarios;"

3) Analysis of radiation dose; and evaluation of bowel, urinary and erectile function, and;

4) "Identification and evaluation of biomarkers of PCa behavior."

At 10 years an analysis is planned to "Assess longer-term rates of disease-specific and overall survival as well as development of late effects such as second cancers."

The study is estimated to be completed in January 2016, the final data collection date. The sponsors of the study are well aware that enthusiasm for proton beam therapy might seriously impair recruitment into a randomized trial. However, in a small study of 46 men a slight majority, 58%, stated a willingness to "definitely' or 'probably' participate" (Shah, Int J Radiat Oncol Bio Phys, May 2012). Recognizing this possibility of non-acceptance of randomization, Dr. Zietman indicated that data on those men who participate, but refuse randomization, will be analyzed separately.

However, as noted, in one or two years following the completion of treatment, near-term side effects on urinary, bowel, and erectile function will have become analyzable. Although in choosing initial treatment men are understandably ultimately concerned with survival outcome, when outcomes of therapy appear to be similar, decisions are most times made based on the consequences of side effects, so that solid information in this area will be very useful for decision making.
PROTON BEAM THERAPY continued:

What is known about side effects at this time?

Both proton beam therapy and IMRT result in low toxicity. Reported results vary considerably, but late (> 5 years) grade 3 GI and GU toxicity seems to be less than 3% for both. There may be some transient “potential early short-term, though time limited, improvement in bowel and urinary symptoms with PBT vs IMRT (Zietman).” But overall, Zietman summarizes: “… despite the theoretical physical advantages of proton therapy, studies have yet to show any clear clinical benefit to proton beam over IMRT in terms of morbidity in the treatment for prostate cancer.”

Communities should be pleased with the availability of proton beam therapy. Proton beam therapy has an established and useful role in treatment of the tumors of the skull base and eye and for targeting the rather rare pediatric tumors of the brain stem, spinal cord, or any tissue in a developing child. However, it is feared that proton beam centers will be required to predominantly treat men with prostate cancer in order to recoup the high expense of the proton facility, with costs ranging from $150 - 200 million for a 3-4 room cyclotron facility. "New single gantry facilities are being developed with a $15-25 million price tag," (Zietman).

This cost differential between proton and photons is substantial. The fact that proton therapy is 2 Xs, maybe ultimately 3 or 4 Xs more costly than IMRT seems to have hit a raw nerve in the health care community and is viewed with great concern. Although anyone familiar with the arcane intricacies of pricing for medical services knows that it is nearly impossible to "know" the actually billed "cost," none the less, as an example, the Medicare reimbursement for proton therapy is $32,428 and for IMRT, $18,575 (Yu et al, 2013). The Center for Medicare and Medicaid Services has no general policy covering reimbursement and leaves the decision of coverage and reimbursement up to the privately contracted insurance providers responsible for the men in these groups.

At root, this is a "value added" issue. The important question is whether this price differential can be justified considering that the best credible evidence to date shows no substantial outcome differences between treatments.

BOTTOM LINE: The evidence to date finds proton beam therapy safe and effective for treatment of localized prostate cancer, but not superior to other currently modalities.

ANDROGEN DEPRIVATION THERAPY AND DIABETES:
Awareness of the association is essential for comprehensive clinical management

[This article was inspired by my hearing of the experience of Jerry, a prostate group member, who was on ADT and reported how the therapy was worsening his diabetic control, threatening his eyesight, and aggravating a peripheral neuropathy.]

Androgen deprivation therapy decreases insulin sensitivity in non-diabetic men and unmasks latent glucose intolerance, and worsens glucose control in men already diagnosed with diabetes ADT. It’s as straightforward as that.

This adverse effect from ADT occurs in 25-60% of patients within as little as three months after ADT initiation, and long-term ADT is associated with a higher incidence of diabetes (Hara, Exp Diabetes Res. 2012). There is insufficient awareness of this important relationship which should be considered in decisions of clinical management.

Background for this discussion:
A landmark study by Keating, Smith, et al, (Boston - Massachusetts General Hospital and Brigham and Women’s Hospital) "Androgen-deprivation Therapy and Diabetes control Among Diabetic Men with Prostate Cancer," (Eur Urol. 2013, Feb) provides background information.

Their 2-year study analyzed diabetic control data in men with both diabetes and prostate cancer all of whom were already taking antidiabetic medications. There were 3156 men treated with ADT and 4437 receiving no ADT. Key observations included glucose levels, Hemoglobin A1c (HbA1c) levels, and the frequency of requiring additional medication to control diabetes.
ANDROGEN DEPRIVATION AND DIABETES continued:

[HbA1c is a standard test for monitoring glucose control and summarizes the glucose levels for the prior 3 months. A value of <5.7 is considered normal, 5.7 - 6.4 represents "pre-diabetes"; and >6.5 is diagnostic of overt diabetes.

Values of < 7 are the goal of treatment. In the Keating study the HbA1c baseline for both groups was 7.24 and all were under treatment with antidiabetic medication.]

The Keating findings:

Men on ADT had a 18.2% rise in HbA1 to 7.38 over 1 year compared to a slight fall to 7.14 in those not receiving ADT-- a net difference of 0.24. There was a 20% increase in fasting glucose is those on ADT; and 20% of those men required an intensification of anti-diabetic medication.

This seemingly modest net difference begs some background. "In the United Kingdom Prospective Diabetes Study, each 1% decrease in the updated mean Hb1c was associated with a 21% lower risk of death related to diabetes and a 37% lower risk of microvascular complications. When applied to the Keating study the small worsening documented in the analysis "could lead to a 2.5% increase in risk of death from diabetes and a 4.5% increase in microvascular complications."

KEATING CONCLUSIONS: "Men with diabetes who start ADT should be counseled about the potential need for intensification of diabetes therapy and should have their HbA1c levels monitored during therapy, especially if they continue on long-term continuous ADT."

METFORMIN, PROSTATE CANCER, AND DIABETES -- What's the Connection?

Metformin is a standard drug used for the control of blood sugar levels in people with Type 2 Diabetes. Nearly 30% of men analyzed in the Keating study (see above) were taking this agent. Metformin is now being viewed as an important drug in prostate cancer control, in part through actions that are different from its mechanism in controlling blood sugar.

Studies of metformin in this new role have already suggested it can slow disease progression and delay the transition to castrate resistant prostate cancer (CRPC). More studies are planned to try to confirm these early findings. There are 40 open studies of metformin in all types of cancer, and Clinicaltrials.gov lists eight studies of this agent in various phases of prostate cancer.

One about to open is (NCT01733836), "to determine whether the use of metformin in patients with low-risk prostate can delay progression to clinically significant prostate cancer," and another planned to further explore whether metformin can reduce hyperinsulinemia and diabetes resulting from ADT. These trials build on the existing studies suggesting a "decreased incidence of cancer in diabetic patients taking metformin as well as improved survival with metformin" (Spratt, referenced below).

How might metformin function to inhibit the growth of prostate cancer?

Three likely possibilities are foremost.

1) metformin increases the availability of an enzyme (adenosine monophosphate kinase), which when insufficient, facilitates cell proliferation; and

2) it suppresses the gene expression of multiple inflammatory cytokines, notably the ubiquitous nuclear factor kappa B (NFKB). Suppression of the NFKB pathway reduces the inflammatory response thought to play an important role in the genesis and progression of prostate cancer.

3) metformin lowers the increase in insulin resulting from suppressed testosterone, thus limiting the effect of an overabundance of insulin in promoting cellular growth.
METAFORMIN continued:

A favorable safety profile plays to the advantage of this drug -- it does not reduce blood sugar levels in non-diabetics. But in the face of cellular insulin resistance, characteristic of Type 2 diabetics, metformin does decrease insulin resistance and reduces blood sugar levels.

A major contribution to understanding of metformin's role in prostate cancer control is a recent article by Spratt, Zhang, Zelefsky, et al, (Columbia University Medical Center and Memorial Sloan-Kettering Cancer Center), "Metformin and Prostate Cancer: Reduced Development of Castration-resistant Disease and Prostate Cancer Mortality," *European Urology*, Dec 2012.

The research was based on a retrospective analysis of 2901 consecutive patients with prostate cancer -- 157 men with diabetes taking metformin, 162 diabetics not taking metformin, and 2582 non-diabetic patients serving as the control group. All of the men had received external beam radiotherapy for localized prostate cancer. ADT was used at the discretion of the treating physician and employed as salvage treatment for PSA failure.

The objective was "To determine whether the use of metformin would be associated with improved clinical outcomes and a reduction in the development of CRPC." The men were well matched as to important disease characteristics.

**The findings - Summary:** "... metformin decreased the risk of PSA recurrence, distant metastases, and PCSM [prostate cancer specific mortality] compared with diabetic non-metformin patients."

**Details** for comparison between diabetics taking metformin v. non-metformin diabetics v. non-diabetic controls:

1) PSA recurrence: 16.5% v. 32.7% v. 25.89%;
2) Development of distant metastases while on study: 5.7% v. 24.1% v. 11.5%;
3) 10-year actuarial PCSM: 2.7% v. 21.9% v. 8.2%;
4) 10-year actuarial overall survival: 81.5% v. 55.4% v. 71.8%;
5) Development of CRPC: 4% v. 43% v. 26%.

**BOTTOM LINE:** The Spratt study, by providing "the first clinical evidence that metformin may improve cancer-specific survival outcome in prostate cancer," gives strong reason to believe that metformin is likely to have an important future role in the treatment of prostate cancer.

Ed Weber, M.D., Editor

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*I want to thank Dawn Scott, Staffperson, Seattle Prostate Institute, and Mike Scully, Librarian, Swedish Medical Center for their unfailing, timely, and resourceful support of the Commentary project. Without their help this Commentary would not be possible.*