

## TWENTY-FIVE YEAR EVOLUTION OF MEDICAL HORMONAL THERAPY FOR PROSTATE CANCER Judd W. Moul – Division of

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I was just starting my residency in urology when the first LH-RH agonist agent became available in the United States in 1984 [1,2]. Reflecting back on the last quarter century, it has been an interesting ride! In this issue of *BJU International*, the important paper by Klotz and colleagues introduces the pure LH-RH antagonist, degarelix. To put this new compound in perspective, I will briefly recount where we have come from over the last 25 years.

For the first five years or so after the introduction of LH-RH agonists from 1984 to 1989, the debate was between the efficacy of orchiectomy vs 'medical castration' [3]. In those early days, the LH-RH agonists were only available in daily or monthly dosing and the flare or surge was a real issue. We had many men presenting with advanced disease in this pre-PSA screening era and the risk of clinical adverse events, such as spinal cord compression or urinary retention, were real concerns. In 1989, flutamide was the first pure non-steroidal antiandrogen approved by the US Food and Drug Administration and the debate regarding combined or maximal androgen blockade (CAB/MAB) began and continues to this day [4]! Even though CAB/MAB appears to be associated with a modest survival benefit and is now endorsed by the new American Society for Clinical Oncology practice guidelines, it has never been relied on to block a clinical flare associated with LH-RH agonists [5]. Furthermore, the cost associated with CAB/MAB has been controversial.

From 1989 to about 1999, the decade in hormonal therapy was characterized by incredible growth in medical hormonal use and a general indiscriminate, non-risk stratified zeal to prescribe [6]. This was driven by a number of factors in the US including the screening-induced skyrocketing of patients, the pharmaceutical marketing, the growing PSA recurrence patient population, and the profit margins. In addition, data began to emerge that hormonal therapy added to external radiotherapy for localized and

locally-advanced disease resulted in improved survival [7].

Between 1999 and 2005, many papers began to emerge touting the risk-stratified approach to administration of hormonal therapy. For example, the 1999 'Pound paper' from Johns Hopkins taught us all that PSA recurrence is generally a slow process and that we can use PSA doubling-time (PSADT), Gleason sum, and timing of the recurrence to better assess for metastases and death [8]. As a specific example from my own evolution as a clinician, I remember having no idea when to institute hormonal therapy for PSA recurrence before this landmark study. I am sure I caused more harm than good in some men where I 'pulled the trigger' for hormones in low risk PSA recurrence. In 2004, I was part of a follow up study to Pound *et al.* using the US Department of Defense Center for Prostate Disease Research multi-center database showing that for high risk PSA recurrence (PSADT <12 months or Gleason 8–10) early hormones at least delayed clinical metastases [9].

Now, between approximately 2005 and present, the era is characterized by a sensitized recognition of hormonal therapy side-effects, intermittent hormonal therapy, peripheral androgen blockade (PAD), less reimbursement of LH-RH agonists in the US, and better reimbursement of oral hormonal therapy in the US due to implementation of the Medicare Modernization Act of 2005. It is in this current environment that we are on the brink of a safe and effective pure LH-RH antagonist, degarelix.

In my mind, the highlights of this phase III randomized controlled trial of degarelix vs monthly leuprolide are safety and lack of flare. Unlike the first FDA-approved pure LHRH antagonist, abarelix, this new agent, degarelix, is not associated with significant allergic reactions and anaphylaxis [10]. Furthermore, degarelix does not require the troubling two week dosing in the first cycle that abarelix required. It is my understanding that the chemical compound

of degarelix is also more conducive to longer acting depot formulations, such as 3 to 6 month dosing. With regard to flare, an oral non-steroidal antiandrogen is not needed with degarelix. However, whether adding an oral antiandrogen along with degarelix for long-term survival benefit remains unanswered. While the mechanism of action of a pure LH-RH antagonist is clearly different than the mechanism of action of an LH-RH agonist, it will be intriguing to see how regulatory agencies handle degarelix. In other words, will they lump this novel agent with the LH-RH agonists for reimbursement or will they place this in a separate treatment class?

Once approved, there are a number of follow-up research questions that will be interesting. For example, in men on peripheral androgen blockade, will response to a pure LH-RH antagonist be superior to using traditional LH-RH agonists? Will oral antiandrogens provide any PSA response or clinical response in men who have progression on LH-RH antagonists? Will there be any differences in response of novel agents or chemotherapy in men on LH-RH agonists vs antagonists? To my knowledge, these types of questions were never adequately addressed with abarelix due to its very short time on the treatment scene.

Overall, this important study on the novel pure LH-RH antagonist, degarelix, adds to our armamentarium of medical hormonal therapies for prostate cancer. It also adds a new chapter to the continuing story of medical management of our patients with prostate cancer.

### CONFLICT OF INTEREST

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and active monitoring, treatments like cryotherapy are largely dependent on site-specific case series.

More fundamentally, the iterative nature of many technologies militates against the collection of long-term data, and can make such data misleading relative to the outcomes achievable with a technology as it has subsequently developed.

Certainly, few would dispute that while the concept had merit, the early technologies for cryotherapy were relatively crude, with the freezing of contiguous tissue around the prostate causing unacceptable levels of morbidity. There is little doubt that these reports blighted the potential of the technology for some clinicians.

Second- and, more particularly, third-generation cryotherapy has seen considerable advances in the sophistication of the technology, with very fine-gauge needles, multipoint thermal sensors and imaging software allowing for much more precise, minimally invasive, focal treatment.

NICE's guidance on cryotherapy for recurrent prostate cancer [4] and as a primary treatment [5] indicated that evidence on safety and efficacy appears to be adequate to support its use, while the effects on quality of life and long-term survival remain uncertain. Both sets of guidance cautioned that 'Clinicians should therefore ensure that patients understand the uncertainties and the alternative treatment options'. At the same time, the overview of salvage cryotherapy for recurrent prostate cancer noted that the technology involved in the procedure was continually developing and as such, earlier studies might have less favourable outcomes, particularly in terms of morbidity, and later studies will have a shorter-term follow-up and perhaps reflect the accumulation of experience.

Among more recent papers, Bjerklund Johansen [6] reported the use of cryosurgical ablation as primary therapy in 27 low-, 37 intermediate- and 26 high-risk patients, with no disease progression at a median of 21 months of follow-up, except in two intermediate-risk patients. No reports were made of bleeding, incontinence or fistula development. All patients in the low- and intermediate-risk groups sexually active before treatment were also sexually active as assessed at the last follow-up. That paper

## NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE GUIDELINE ON PROSTATE CANCER AND THE FUTURE OF CRYOTHERAPY

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### INTRODUCTION

The UK National Institute of Health and Clinical Excellence (NICE) clinical guideline on prostate cancer [1] has been the subject of controversy and heated debate since its publication in February 2008. Among the potential casualties was cryotherapy, a potentially valuable treatment option for prostate cancer, especially for locally recurrent disease. However, NICE has since clarified that the collection of data for national analysis conforms to the guideline [2]. Crucially, this should allow primary-care trusts (PCTs) to continue funding cryotherapy.

Whilst the BAUS has perhaps attracted most attention for its rejection of the clinical guideline on prostate cancer, the extent of criticism was much wider [3]. The comments by Cancer Research UK on the draft guideline

were fairly typical in suggesting that 'the use of consensus rather than evidence has led to an unnecessarily conservative approach to diagnostic prostate biopsy and active treatments. This could potentially worsen 5-year survival rates'. The charity went on to say that 'we need to ensure that flexibility is retained to allow the clinician to work with the patient to reach the treatment option most suitable for them'. Even the Department of Health commented that 'it would be helpful to see much greater emphasis on what is evidence-based and important'. Against that background, newer developing therapies such as cryotherapy were always likely to struggle to find a place in the NICE Guideline Development Group's care pathway for prostate cancer. In a field where Level 1 evidence is still lacking, pending publication of the protracted ProtecT study comparing radical prostatectomy, radical radiotherapy