Management of a patient with locally advanced prostate cancer with degarelix: a case report

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RUZHYNSKY V, WHELAN P. Management of a patient with locally advanced prostate cancer with degarelix: a case report. *Can J Urol* 2013;20(3): 6808-6810.

Gonadotropin releasing hormone (GnRH) antagonists, such as degarelix, are emerging as an androgen deprivation therapy primary agents in a treatment of advanced prostate cancer. The role of GnRH antagonists in management of lower urinary tract symptoms associated with prostate cancer has not been clearly established. In this report, we describe the case of a patient with locally advanced prostate cancer who presented with symptoms of urinary retention and renal failure. The use of degarelix in this patient led to a rapid reduction in the prostate-specific antigen level; however, obstructive symptoms persisted despite the use of degarelix and radiation treatment.

Key Words: prostate cancer, urinary obstruction, degarelix, gonadotropin releasing hormone antagonists, androgen deprivation therapy

Introduction

The current standard of care for locally advanced high risk prostate cancer is radiation therapy (RT) combined with long term androgen deprivation therapy (ADT).[1] The available options of ADT are surgical and medical castration. Medical castration has primarily involved the use of gonadotropin releasing hormone (GnRH) agonists. Unfortunately, the use of GnRH agonists for the purpose of medical castration is associated with an undesirable initial surge of testosterone as well as a small risk of therapeutic failure, reviewed in Van Poppel and Klotz.[2] Here we present a case of a patient with locally advanced prostate cancer who presented with symptoms of urinary retention and was treated with GnRH antagonist degarelix (Firmagon, Ferring Pharmaceuticals).

Accepted for publication January 2013

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Case report

An 80-year-old man with known history of benign prostatic hypertrophy (BPH) was urgently referred to the urology service for evaluation of urinary retention and bilateral hydronephrosis. Patient reported a weak urinary stream, nocturnal incontinence and no other urinary symptoms. He had been taking tamsulosin for 2 years for BPH. Physical examination revealed a soft abdomen with a palpable bladder. Digital rectal examination findings were consistent with T3 lesion. Laboratory analyses were as follows: serum prostate specific antigen (PSA) level 151 µg/L, creatinine 323 µmol/L, eGFR 16 mL/min/1.73 m^2, and Hb 100 g/L. Ultrasound showed the presence of bilateral hydroureteronephrosis, a thickened and trabeculated bladder wall, and a 103 mL prostate gland. Urinary retention was urgently managed with an indwelling Foley catheter. Follow up blood work showed resolving obstructive nephropathy (creatinine 194 µmol/L) and rising PSA level (164 µg/L).

Transrectal ultrasound guided prostate biopsy detected the presence of Gleason score (GS) 4 + 3 = 7 multifocal acinar prostatic adenocarcinoma involving

40% of the prostatic tissue (2%-80%). A bone scan showed no evidence of metastatic disease.

The patient received the GnRH antagonist degarelix (Firmagon, 240 mg, intramuscularly). Serum PSA was 73.1 µg/L 1 week later. Degarelix therapy (80 mg) was maintained for 7 months. Repeat serum PSA levels at 7 weeks, 8 months and 10 months since the initiation of the treatment were 22.9, 0.09 and 0.04 µg/L, respectively.

Following a consultation with radiation oncology patient received 45 Gy of external beam radiation to the entire pelvis (lymph nodes, seminal vesicles, prostate) in 25 fractions over 5 weeks followed by a boost of 25 Gy to the prostate only in 13 fractions over 2 1/2 weeks between the 2nd-4th months of degarelix therapy.

Unfortunately, the patient was still unable to void spontaneously after repeated voiding trials. Therefore, transurethral resection of prostate (TURP) was performed 6.5 months after his initial presentation. Even though the prostate gland was still enlarged at that time, pathological analysis showed that only 3% of the resected prostatic tissue involved by GS 4 + 3 = 7/10 adenocarcinoma. The patient was able to void spontaneously following the TURP.

Discussion

The objective of this report was to present a case of degarelix use in a patient with locally advanced prostate cancer. Degarelix administration led to a rapid decrease in the serum PSA level. At the same time, the obstructive symptoms persisted despite continued management with degarelix and radiation treatment.

GnRH agonists, the primary agents of medical ADT, has been used for treatment of various stages of prostate cancer, including: localized high-risk, locally advanced, and metastatic prostate cancer.[2] The continuous release of injected GnRH agonists disrupts the physiological pulsatile activity of GnRH in the anterior pituitary. This initially leads to an increase in serum testosterone, but subsequently causes down-regulation of GnRH receptors, a decrease in luteinizing hormone release, and a decline in testosterone concentration, a key factor in preventing the prostate cancer growth.

The initial surge in testosterone levels is one of the major drawbacks of GnRH agonists, as it can cause a flare up of prostate cancer symptoms. Waxman et al showed that 19 out of 46 men (41%) treated with GnRH agonists experienced worsening of their clinical symptoms.[3] In addition, many patients, especially those with localized prostate cancer, will ultimately experience disease progression while being treated with GnRH agonists.[4] Thus, despite being a standard of care for advanced and localized prostate cancer, GnRH agonists have a significant side effect profile, and resistance to these medications can develop after prolonged administration.

GnRH antagonists have mainly been reserved for patients who have failed treatment with GnRH agonists. GnRH antagonists reversibly block GnRH receptors in the anterior pituitary leading to an inhibition of luteinizing hormone and follicle stimulating hormone release, which causes quick and sustained decrease in serum testosterone concentration. Administration of GnRH antagonists is not associated with a flare phenomenon. Therefore, the use of GnRH antagonists as primary agents for ADT has been increasingly advocated in recent years.

Several studies have documented the effectiveness of degarelix, a GnRH antagonist, in the management of prostate cancer. Turner et al found that bony pain was reduced following administration of degarelix to a patient with metastatic prostate cancer.[5] Moreover, the effectiveness of degarelix has also been shown in a phase III randomized control trial (CS21) comparing degarelix and leuprolide.[6] Within 3 days of administration, degarelix produced a rapid decline in testosterone to castrate levels in about 96% of prostate cancer patients. All patients had sustained and comparable testosterone suppression from day 28 until day 364; however, 65% of patients receiving leuprolide experienced an initial surge in testosterone levels. Thus, administration of GnRH antagonists resulted in castrate levels of testosterone and bypassed the initial hormone surge, preventing clinical flare phenomenon. Similar to its effect on testosterone, degarelix administration caused a significant and rapid reduction in PSA levels. Overall, these results indicate that degarelix is more effective then leuprolide in terms of producing a rapid reduction in testosterone and PSA levels, and does not have the adverse effect of a testosterone surge. Degarelix is also at least as effective as monthly leuprolide in the maintenance of testosterone suppression after 28 days.

The activity of degarelix on PSA recurrence-free survival was compared to leuprolide in the extension of the above mentioned CS21 trial.[7] Patients who received degarelix had significantly lower PSA failure rates as well as increased PSA progression free survival. These results were obtained from combined data analysis of patients at different stages of prostate cancer. The subgroup analysis by disease stage showed that PSA failures were observed progressively more frequently in patients with locally advanced and metastatic disease. While degarelix treatment in these subgroups of patients had no significant effect on the disease progression, patients with metastatic prostate cancer who were treated with degarelix had a trend toward delaying PSA recurrence. An additional benefit of degeralix was

evident when degarelix and leuprolide effects were compared in the subgroups of patients with different initial PSA levels. Degarelix treatment significantly reduced the risk of the recurrence in patients whose PSA level was 20 ng/mL-50 ng/mL at the initial presentation. While the number of patients in each subgroup was low, these results suggest that degarelix is more effective then leuprolide in control of PSA levels, particularly in patients with advanced prostate adenocarcinoma.

Considering the efficacy of degarelix in the rapid suppression and control of testosterone and PSA, it is plausible to hypothesize that this class of medications would be effective in controlling lower urinary tract symptoms (LUTS) associated with advanced prostate cancer. Unfortunately, evidence supporting this hypothesis is scarce at the present time. Anderson and colleagues compared the effects of degarelix to goserelin (a GnRH agonist) plus bicalutamide (an anti-androgen) on LUTS in a small group of prostate cancer patients.[8] The results of their analysis showed that degarelix was not inferior to the GnRH agonist and antiandrogen combination treatment in reducing the International Prostate Symptom Score (IPSS) after 12 weeks of treatment. Degarelix treated patients had greater reductions in prostate size, as well as statistically significant improvements in IPSS scores and quality of life (QoL). Interestingly, the IPSS subscore for "straining" was the least improved parameter, although the significance of this finding was not addressed. Early termination of this trial due to low participant accrual precluded further data collection and analyses. In another RCT Axcrona et al evaluated the efficacy of degarelix and the GnRH agonist goserelin on prostate volume as well as improvement of LUTS and QoL.[9] They demonstrated that degarelix was not inferior to goserelin plus bicalutamide in reducing prostate volume, and it was equally effective in improving patients' QoL after 12 weeks of treatment. Moreover, degarelix treated patients with IPSS scores greater than 13 at initial presentation had significant improvement of their LUTS scores. These results further support the efficacy of the GnRH antagonist degarelix in improving LUTS in patients with advanced prostate cancer.

Similar to the results of the aforementioned studies, degarelix treatment in this case was associated with a rapid drop in PSA at 7 weeks (by 86%) which is similar to previously observed data.[6] Despite the PSA drop obstructive symptoms persisted, requiring surgical intervention. One possible explanation for these findings could be that more time was required for the prostate to shrink since the initial PSA was so high. Moreover, BPH component of the prostate might be less responsive to anti-cancer therapy. Toxic and inflammatory effects of radiation therapy could also have prolonged the symptoms of bladder outlet obstruction. Interestingly, while it is conceivable that not all of the prostatic tissue was resected during the operation, the pathologist's report indicated that the amount of tissue involved by prostate cancer was only 3%. A decrease of cancerous prostatic tissue from an average of 40% to 3% provides pathological evidence supporting the combined efficacy of the GnRH antagonist and radiation. Moreover, to our knowledge this is the first report describing the use of degarelix as a neoadjuvant medication prior to radiation therapy.

In summary, degarelix lead to a rapid and sustained decrease in the serum PSA concentration of a patient with locally advanced high risk prostate cancer presenting with obstructive LUTS. Despite a positive biochemical response, the obstructive symptoms did not improve and surgical intervention was required. Further investigations are required to elucidate the exact effects of GnRH antagonists on storage and voiding LUTS and their role as neoadjuvant agents. □

References

1. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Prostate Cancer. National Comprehensive Cancer Network: Fort Washington, PA, Version 3.2012. Available from: http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed July 2012.
2. Van Poppel H, Klotz L. Gonadotropin-releasing hormone: An update review of the antagonists versus agonists. *Int J Urol* 2012;19(7):594-601.
3. Waxman J, Man A, Hendry WF et al. Importance of early tumour exacerbation in patients treated with long acting analogues of gonadotrophin releasing hormone for advanced prostatic cancer. *Br Med J (Clin Res Ed)* 1985;291(6506):1387-1388.
4. Janoff DM, Peterson C, Mongoue-Tchokote S et al. Clinical outcomes of androgen deprivation as the sole therapy for localized and locally advanced prostate cancer. *BJU Int* 2005; 96(4):503-507.
5. Turner B, Drudge-Coates L, Pati J. 'Nurse: My back hurts!': case study review of degarelix in metastatic prostate cancer. *Int J Urol Nurs* 2011;5(2):90-94.
6. Klotz L, Boccon-Gibod L, Shore ND et al. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. *BJU Int* 2008;102(11):1531-1538.
7. Tombal B, Miller K, Boccon-Gibod L et al. Additional analysis of the secondary end point of biochemical recurrence rate in a phase 3 trial (CS21) comparing degarelix 80 mg versus leuprolide in prostate cancer patients segmented by baseline characteristics. *Eur Urol* 2010;57(5):836-842.
8. Anderson J, Al-Ali G, Wirth M et al. Improved relief of lower urinary tract symptoms (LUTS) with a gonadotrophin-releasing hormone (GnRH) blocker compared with an agonist + antiandrogen (AA) in an open-label, randomised study (CS28). Eur Multidisciplinary Meeting on Urol Cancers 2011.
9. Axcrona K, Aaltomaa S, da Silva CM et al. Androgen deprivation therapy for volume reduction, lower urinary tract symptom relief and quality of life improvement in patients with prostate cancer: degarelix vs goserelin plus bicalutamide. *BJU Int* 2012; 110(11):1721-1728.