Response to degarelix after resistance to luteinizing hormone–releasing hormone agonist therapy for metastatic prostate cancer

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Androgen deprivation with a luteinizing hormone–releasing hormone (LH–RH) agonist is the standard treatment for patients with metastatic prostate cancer who prefer nonsurgical options. Therapy with these agents is usually successful in achieving and maintaining castrate levels (<50 ng/dl) of serum testosterone, but failures have been reported in up to 10% of patients. Traditionally, these patients are offered surgical castration with bilateral orchiectomy. However, the novel LH–RH antagonists may offer a nonsurgical alternative. We describe two patients with advanced prostate cancer who failed to achieve castrate levels of testosterone while on an LH–RH agonist, but subsequently responded to the LH–RH antagonist, degarelix. The first patient is a 63-year-old man who was treated with leuprolide for metastatic prostate cancer. He initially responded with prostate-specific antigen (PSA) that fell to 0.6 ng/ml. However, after 15 months of therapy, his PSA rose to 18.3 ng/ml and his testosterone was noted to be 208 ng/dl. He was switched to degarelix, and 4 weeks later his testosterone was adequately suppressed at 16 ng/dl. The second patient is a 41-year-old man with metastatic prostate cancer who was started on leuprolide, but after 3 months of therapy, was found to have a rising PSA and a testosterone of 96 ng/dl. Four weeks after switching to degarelix, his testosterone was 18 ng/dl and his PSA decreased concordantly. With continued monthly injections of degarelix, his testosterone has consistently remained to be at less than 20 ng/dl over 7 months of follow-up. *Anti-Cancer Drugs* **22:299–302**

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Introduction

The standard of care for the initial treatment of metastatic prostate cancer is androgen deprivation. Historically, this has been accomplished by surgical castration with bilateral orchiectomy. With the availability of long-acting luteinizing hormone–releasing hormone (LH–RH) agonists, pharmacological castration became the treatment chosen by most men, because of the psychological issues surrounding surgical castration. LH–RH agonists are effective in maintaining castrate levels of testosterone in most patients, but many publications have described failures of these agents. We report two cases of patients with metastatic prostate cancer who failed to achieve castrate levels of testosterone while on an LH–RH agonist, but subsequently responded to the LH–RH antagonist, degarelix.

Case 1

A 63-year-old man presented in 2008 with a routine screening prostate-specific antigen (PSA) of 15.4 ng/ml. A prostate needle biopsy showed adenocarcinoma with a Gleason score of 9 (5 + 4). Staging scans had shown numerous sites of bone metastases and retroperitoneal adenopathy. He was started on the LH–RH agonist, leuprolide (Eligard; Sanofi-Aventis, Bridgewater, New Jersey, USA), and over the subsequent 4 months, his PSA fell to 0.6 ng/ml. After 15 months of therapy, his PSA rose to 18.3 ng/ml, prompting the addition of the antiandrogen nilutamide to his regimen. The PSA of the patient fell to 0.5 ng/ml, but he stopped taking nilutamide because of visual disturbances, a known complication of the drug. At this point, the patient was seen at our institution for a second opinion. His testosterone level was found to be 152 ng/dl and on repeat, 208 ng/dl. A bilateral orchiectomy was offered, but the patient declined. He was treated instead with the LH–RH antagonist, degarelix at an initial subcutaneous dose of 240 mg. Four weeks later, his testosterone level had fallen to 16 ng/dl, and his PSA remained 0.4 mg/ml. Degarelix was continued at 80 mg every 4 weeks. After two more injections, the patient was switched to the LH–RH agonist, goserelin given every 3 months because of its more convenient schedule. His testosterone remained at castrate levels over the subsequent 6 months. However, his PSA began to rise again, indicating that he has developed documented castration resistance.

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Case 2

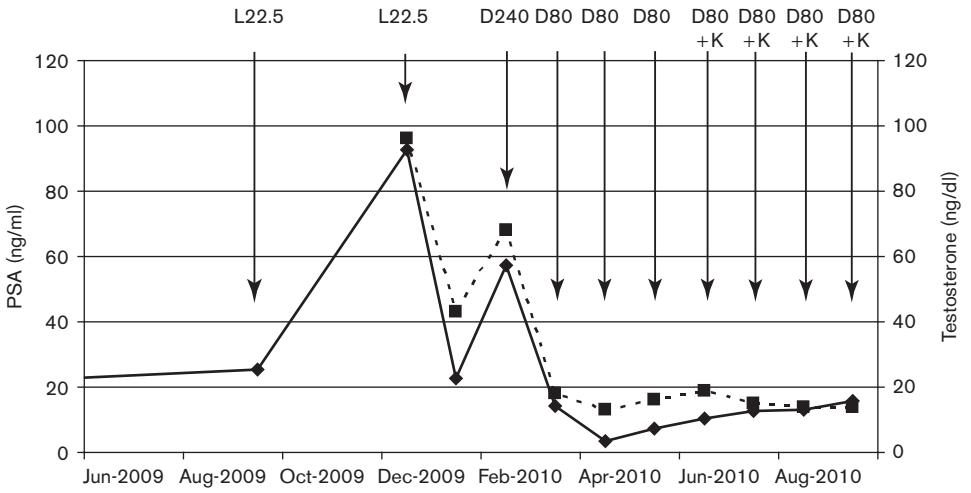
A 41-year-old man presented in 2006 with erectile dysfunction and an elevated PSA of 20 ng/ml. After a positive prostate needle biopsy and negative staging scans, he underwent a robotic-assisted laparoscopic radical prostatectomy with pathology showing Gleason score of 7 (3 + 4), adenocarcinoma involving approximately 50% of the prostate with negative margins and no involved nodes (pT2c N0 M0). His PSA fell to 0.1 ng/ml 1 month after surgery, but he was lost to follow-up until 2009, when he was found to have an elevated PSA of 25.2 ng/ml. A radionuclide bone scan was negative for metastasis, but a computed tomography scan of his abdomen and pelvis showed diffuse retroperitoneal and pelvic lymphadenopathy, measuring up to 1.4 cm in size. He was given an injection of leuprolide intramuscularly (22.5 mg, Lupron Depot; Abbott Laboratories, North Chicago, Illinois, USA), but after 3 months, his PSA had further escalated to 92.8 ng/ml. At this time, his testosterone level was 96 ng/dl, confirming that he had failed to suppress testosterone to castrate levels. He was given another injection of leuprolide. Four weeks later, his testosterone was 43 ng/dl, but subsequently rose to 68 ng/dl. PSA and testosterone levels, shown in Fig. 1, were concordant, suggesting that the PSA rise was because of androgen stimulation rather than development of castration resistance at this time. A bilateral orchiectomy was offered, but the patient declined. He was treated instead with the LH–RH antagonist degarelix at an initial subcutaneous dose of 240 mg. After 4 weeks, his testosterone level had fallen to 18 ng/dl and his PSA had fallen to 14.3 ng/ml. The patient was given a monthly dose of 80 mg of degarelix, and his PSA fell to a nadir of 3.6 ng/ml after 8 weeks of therapy. His testosterone level subsequently remained below 20 ng/dl while on degarelix. However, his PSA started to rise consistently and reached to 13.5 ng/ml 4 months after degarelix was started. For treatment of documented castration resistance, he has been started on secondary hormonal therapy with ketoconazole and hydrocortisone, in addition to continuing monthly degarelix.

Discussion

Pharmacological castration with an LH–RH agonist has been the primary treatment for metastatic prostate cancer in patients who prefer nonsurgical options. Therapy with these agents is usually successful at achieving and maintaining castrate levels of serum testosterone, which is defined as less than 50 ng/dl [1]. However, failures have been reported at rates ranging from 1 to 10%, with some studies supporting the higher end of this spectrum [1–5]. In a phase II study of 56 patients receiving goserelin, Iversen *et al.* [3] report that 9% of the patients failed to achieve castrate levels. Oefelen and Cornum [4] showed similar results, with 5% of 38 men on LH–RH agonist therapy failing to achieve testosterone levels (< 50 ng/dl). In a separate study, Morote *et al.* [5] reported that 10.9% of 144 men receiving LH–RH agonist therapy every 3 months, with or without an antiandrogen, failed to reach castrate levels after a median follow-up of 42 months. These studies and our cases highlight the importance of determining testosterone levels of patients on treatment with an LH–RH agonist, particularly when they develop progressive rise in PSA levels.

There have been a number of published reports describing individual cases of LH–RH agonist resistance

Fig. 1



Prostate-specific antigen (PSA) and total serum testosterone over time in the patient described in case 2. Solid line with diamond represents PSA, and dashed line with square represents testosterone. 'L 22.5' indicates leuprolide (22.5 mg); 'D 240' indicates degarelix (240 mg); 'D 80' indicates degarelix (80 mg); and 'K' indicates ketoconazole.

[6–11]. Several mechanisms for this phenomenon have been postulated, and they fall into two broad categories. First, there may be inadequate systemic delivery of the LH–RH agonist. Some reports describe patients who developed sterile abscesses at the site of their depot injections and subsequently went on to develop resistance [7,10]. In these cases, investigators have suggested that the abscess may be sequestering the drug, or that the local inflammation may be releasing the depot. Some have additionally hypothesized that an anti-LH–RH agonist antibody may be the culprit. Another potential mechanism is resistance of the pituitary cells to the LH–RH agonist. One case report describes a patient who ultimately was found to have a pituitary adenoma that was oversecreting LH and follicle stimulation hormone (FSH) [9]. Another hypothesis is that mutations in the LH–RH receptor may result in a decreased affinity for the drug. These theories remain unproven, and in the majority of published cases, the cause of resistance is unknown.

The standard treatment for patients with resistance to the LH–RH agonists is surgical castration with bilateral orchiectomy. However, with the introduction of LH–RH antagonists, there may be an efficacious nonsurgical alternative. These agents bind to and block LH–RH receptors in the pituitary gland, leading directly to decreased secretion of LH and FSH, which induces a rapid reduction in testicular testosterone production [12]. This is in contrast to the function of LH–RH agonists, which are synthetic analogs of LH–RH that bind to and activate pituitary receptors, leading to receptor desensitization and a delayed reduction in levels of LH, FSH, and testosterone [12]. By taking advantage of this alternative mechanism of action, the resistance occasionally seen with the LH–RH agonists may be circumvented.

Abarelix was the first LH–RH antagonist approved by the United States Food and Drug Administration in 2004. Abarelix was compared with leuprolide in 255 men with prostate cancer who were candidates for androgen-ablation therapy. Patients were randomized to either abarelix depot (100 mg, intramuscularly) or leuprolide (7.5 mg, intramuscularly) every 28 days for 24 weeks. Patients receiving abarelix also received an additional injection on day 15 and those receiving leuprolide also received bicalutamide (50 mg daily) to prevent testosterone flare. The primary endpoints were avoidance of testosterone surge (defined as a >10% increase) within 7 days of the first treatment and achieving castrate levels of testosterone on day 8. Testosterone surge was avoided in 100% of patients treated with abarelix compared with 14% of those receiving leuprolide and bicalutamide. Castrate levels of testosterone were achieved on day 8 by 68% of patients receiving abarelix compared with zero patients on leuprolide and bicalutamide [13]. Though allergic reactions were infrequent in this study, immediate onset allergic reactions have been reported in 1.1–3.7% of patients receiving abarelix [12]. Abarelix was suspended from the USA market in 2005 because of limited sales and economic costs related to allergic reactions caused by the drug. Degarelix was developed from modifications in the peptide structure of the abarelix molecule and is associated with fewer allergic reactions [12].

Degarelix was approved by the United States Food and Drug Administration in December 2008 after showing noninferiority to leuprolide in 610 patients with any stage of prostate adenocarcinoma. Patients were randomized to one of two degarelix-dosing regimens (either 240 mg subcutaneously × 1 dose followed by 80 mg subcutaneously monthly or 240 mg subcutaneously × 1 followed by 160 mg subcutaneously monthly) or leuprolide (7.5 mg, intramuscularly) monthly. Patients in the leuprolide group could receive bicalutamide (50 mg, orally) once daily for prevention of flare, at the discretion of the investigator, which was done in 11% of the patients. The primary endpoint was suppression of testosterone (< 50 ng/dl) at all monthly measurements for 1 year. This was achieved in 97.2, 98.3, and 96.4% of the patients receiving degarelix (240/80), degarelix (240/160), and leuprolide, respectively. After 3 days of the treatment, approximately 96% of the degarelix patients had achieved castrate levels of testosterone compared with zero patients on leuprolide. In contrast with abarelix, no allergic reactions were seen [14].

In summary, patients with resistance to the LH–RH agonists have traditionally been offered surgical castration with bilateral orchiectomy. However, our cases show that the novel LH–RH antagonist may offer nonsurgical alternatives.

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