68 Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J. Clin. Oncol.* 2006; **24**: 4448–56.
69 D'Amico AV, Denham JW, Crook J *et al*. Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. *J. Clin. Oncol.* 2007; **25**: 2420–5.
70 Kintzel PE, Chase SL, Schultz LM, O'Rourke TJ. Increased risk of metabolic syndrome, diabetes mellitus, and cardiovascular disease in men receiving androgen deprivation therapy for prostate cancer. *Pharmacotherapy* 2008; **28**: 1511–22.
71 Quyyumi AA. Endothelial function in health and disease: new insights into the genesis of cardiovascular disease. *Am. J. Med.* 1998; **105**: 32S–39S.
72 Tanriverdi F, Gonzalez-Martinez D, Hu Y, Kelestimur F, Bouloux PM. GnRH-I and GnRH-II have differential modulatory effects on human peripheral blood mononuclear cell proliferation and interleukin-2 receptor gamma-chain mRNA expression in healthy males. *Clin. Exp. Immunol.* 2005; **142**: 103–10.
73 Jacobson JD, Nisula BC, Steinberg AD. Modulation of the expression of murine lupus by gonadotropin-releasing hormone analogs. *Endocrinology* 1994; **134**: 2516–23.
74 Chen HF, Jeung EB, Stephenson M, Leung PC. Human peripheral blood mononuclear cells express gonadotropin-releasing hormone (GnRH), GnRH receptor, and interleukin-2 receptor gamma-chain messenger ribonucleic acids that are regulated by GnRH in vitro. *J. Clin. Endocrinol. Metab.* 1999; **84**: 743–50.
75 D'Amico AV, Chen MH, Renshaw AA, Loffredo M, Kantoff PW. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. *JAMA* 2008; **299**: 289–95.
76 Zareba P, Duivenvoorden W, Leong DP, Pinthus JH. Androgen deprivation therapy and cardiovascular disease: what is the linking mechanism? *Ther. Adv. Urol.* 2016; **8**: 118–29.
77 Albertsen PC, Klotz L, Tombal B, Grady J, Olesen TK, Nilsson J. Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. *Eur. Urol.* 2014; **65**: 565–73.
78 National Comprehensive Cancer Network. NCCN treatment guidelines for prostate cancer (v2.2019). [Cited 3 Jul 2020.] Available from URL: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.
79 Koshkin VS, Small EJ. Apalutamide in the treatment of castrate-resistant prostate cancer: evidence from clinical trials. *Ther. Adv. Urol.* 2018; **10**: 445–54.
80 Scher HI, Fizazi K, Saad F *et al*. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N. Engl. J. Med.* 2012; **367**: 1187–97.
81 Beer TM, Armstrong AJ, Rathkopf DE *et al*. Enzalutamide in metastatic prostate cancer before chemotherapy. *N. Engl. J. Med.* 2014; **371**: 424–33.
82 James ND, de Bono JS, Spears MR *et al*. Abiraterone for prostate cancer not previously treated with hormone therapy. *N. Engl. J. Med.* 2017; **377**: 338–51.
83 Fizazi K, Tran N, Fein L *et al*. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N. Engl. J. Med.* 2017; **377**: 352–60.

Editorial Comment

Editorial Comment to Considerations for the use of gonadotropin-releasing hormone agonists and antagonists in patients with prostate cancer

Van Poppel and Abrahamsson comprehensively summarized both gonadotropin-releasing hormone (GnRH) agonist and antagonist drugs, which are available for daily clinical practice.[1] This review allows urologists to understand the differences between various GnRH drugs as one type of androgen deprivation treatment (ADT) for prostate cancer. Despite the recent advancements in prostate cancer drugs, including systemic chemotherapy, second-generation anti-androgen medications and gene mutation-targeting drugs, ADT still plays an important role as a basic treatment for prostate cancer regardless of the stage or degree of hormone sensitivity.

The differences between this report and common Japanese clinical use are that degarelix (12 weeks' continuation) and leuprorelin (24 weeks' continuation) are available for clinical use. Continuation of degarelix for 12 weeks has been available in Japan for clinical use since 2019, and two 240 mg subcutaneous injections are given every 12 weeks based on a confirmed lower testosterone level.[2] Degarelix is associated with a higher rate of injection site reaction than GnRH agonist drugs, including leuprorelin acetate and gosereline acetate, and 12 weeks' continuation of degarelix (2 × 240 mg) is thought to have a higher rate of injection site reaction than 4 weeks' continuation of degarelix (80 mg). Currently, 12 weeks' continuation of degarelix is only available in Japan.

Klotz *et al*. reported the GnRH antagonist, degarelix, was more effective than a GnRH agonist in the treatment of high-risk prostate cancer patients.[3] Sun *et al*. showed the efficacy of degarelix based on a prospective study in an Asian Chinese population.[4] Miller *et al*. reported a case in which changing from leuprorelin acetate to degarelix resulted in improved prostate-specific antigen control.[5] We previously reported a case of a castration-resistant prostate cancer patient in which changing a GnRH agonist to a GnRH antagonist contributed to castration-resistant prostate cancer control. To date, the efficacy of GnRH antagonists in comparison with GnRH analogs is still under investigation. In addition, switching treatment from a luteinizing hormone-releasing hormone agonist to an antagonist is also under consideration as a new treatment strategy.

Continuation of leuprorelin (22.5 mg) for 24 weeks has also been available in Japan since 2015.[6] Leuprorelin (22.5 mg) is used as a muscle injection as 12 weeks' continuation in some countries. In Japan, leuprorelin (22.5 mg) is used as a subcutaneous injection as 24 weeks' continuation treatment.

Nevertheless, patients who undergo ADT tend to be at an advanced stage of prostate cancer. Although some variations exist regarding the injection type and treatment dose differences, a longer duration treatment option for ADT leads to fewer hospital visits and lower medication costs.

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DOI: 10.1111/iju.14346

Conflict of interest

None declared.

References

1 Van Poppel H, Abrahamsson PA. Considerations for the use of gonadotropin-releasing hormone agonists and antagonists in patients with prostate cancer. *Int. J. Urol.* 2020; **27**: 830–7.

2 Ozono S, Tsukamoto T, Naito S *et al*. Efficacy and safety of a 3-month dosing regimen of degarelix in Japanese patients with prostate cancer: a phase II maintenance-dose-finding study. *Jpn J. Clin. Oncol.* 2017; **47**: 438–46.

3 Klotz L, Miller K, Crawford ED *et al*. Disease control outcomes from analysis of pooled individual patient data from five comparative randomised clinical trials of degarelix versus luteinising hormone-releasing hormone agonists. *Eur. Urol.* 2014; **66**: 1101–8.

4 Sun Y, Xie L, Xu T *et al*. Efficacy and safety of degarelix in patients with prostate cancer: Results from a phase III study in China. *Asian J. Urol.* 2020; **7**: 301–8.

5 Miller K, Simson G, Goble S, Persson BE. Efficacy of degarelix in prostate cancer patients following failure on luteinizing hormone-releasing hormone agonist treatment: results from an open-label, multicentre, uncontrolled, phase II trial (CS27). *Ther. Adv. Urol.* 2015; **7**: 105–15.

6 Suzuki K, Namiki M, Fujimoto T, Takabayashi N, Kudou K, Akaza H. Efficacy and safety of leuprorelin acetate 6-month depot in prostate cancer patients: a Phase III, randomized, open-label, parallel-group, comparative study in Japan. *Jpn J. Clin. Oncol.* 2015; **45**: 1168–74.