Review Article

Androgen Deprivation Therapy for Prostate Cancer an Update on Triptorelin

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ABSTRACT

Prostate cancer is not very common in our country, but the patient usually presented with advanced disease. Androgen deprivation therapy (ADT) is the mainstay palliative treatment for men with locally advanced and metastatic prostate cancer, and aims to reduce testosterone to levels obtained by surgical castration. Gonadotropin-releasing hormone (GnRH) agonists predominantly used among the ADT options. The GnRH agonist, triptorelin is a first-line hormonal therapy that has demonstrated efficacy and safety in clinical trials of patients with locally advanced non-metastatic or metastatic disease in our hospital. Sustained-release 1-, 3- and 6-month formulations of triptorelin, administered intramuscularly or subcutaneously, has been developed to provide improved flexibility and convenience for the patient. Also is state of castration-resistant prostate cancer (CRPC) in patients receiving ADT, continued ADT when introducing one of the various new treatment options for CRPC is beneficial. For improved survival outcomes, there remains a need to tailor ADT treatment regimens, novel hormonal agents and chemotherapy according to the individual patient with advanced prostate cancer.

Keywords: Androgen deprivation therapy, Oncology, Prostate cancer, Sustained-release formulations, Triptorelin.

INTRODUCTION

Cancer is a major public health problem worldwide [1]. In Iraq Cancer of the prostate is the tenth leading cause of cancer death in males. The continued increase in the incidence of prostatic cancer has been attributed to screening with prostate-specific antigen testing[2]. In general, the risk factors for prostate cancer are poorly understood and consequent advice on prevention is not possible[3]. Therefore, the management of prostate cancer focuses on treating the disease, and the hormone dependence of prostate cancer has been recognized for decades[4]. As a consequence, testosterone suppression has been the standard palliative treatment in men with advanced prostate cancer for many years. Orchiectomy is a simple, low-cost surgical procedure that effectively and quickly achieves castration, but because it is irreversible and does not allow intermittent treatment, it replace widely by hormonal therapies.

The selection of appropriate treatment is mainly dependent on the stage of disease and the risk of progression. Prostate cancer is classified using the Tumor-lymph Nodes-Metastasis (TNM) system into localized, locally advanced and metastatic disease [5]. Patients are also categorized into low, high, or intermediate risk of progression according to clinical stage, Gleason score, and prostate-specific antigen (PSA) level[6, 7]. Gleason score and the presence of metastasis were the strongest predictors of prostate cancer-specific mortality in the group with high PSA at presentation [8]. Patients classified as having low or intermediate risk prostate cancer (Gleason score <8 and PSA <20 ng/ml) may have a 10-year prostate cancer-specific mortality of <5% [9, 10], and avoiding unnecessary treatment is a challenge in these patients[11, 12]. Patients with high-risk prostate cancer make up a considerable proportion of our patients and have much higher mortality rates, and therefore, the challenge in these men is to increase overall survival while reducing any adverse effects of treatment[3, 13].

This article reviews the current and ongoing role of the gonadotropin-releasing hormone (GnRH) agonist triptorelin as androgen deprivation therapy (ADT) in the management of locally advanced or metastatic prostate cancer.

The Role of ADT in Prostate Cancer Management

ADT aims to reduce testosterone levels to the levels achieved with surgical castration [defined as <50 ng/dl (<1.7 nmol/l)][3] and is recommended for:

1. patients with locally advanced prostate:
   a. Patients are unwilling or unable to receive any form of local treatment.
   b. Symptomatic patients.
   c. Asymptomatic with a PSA doubling time (PSA-DT) <12 months.
   d. Poorly differentiated tumor.
2. Patients with metastatic prostate cancer.
3. Patients with lymph node positive (N1) prostate cancer whether newly diagnosed or after extended lymph node dissection [3].

Mechanism of action of various forms of ADT

Androgen deprivation can be achieved with a number of ways:

1. Bilateral orchiectomy. This terminates testicular androgen.
2. GnRH agonists.these most widely used include triptorelin, goserelin, and leuprolide, stimulate gonadotropins from the anterior pituitary gland and the production of testosterone in men, but continued administration leads to the downregulation of pituitary GnRH receptors, which quickly results in the suppression of gonadotropins [luteinizing hormone (LH) and follicle stimulating hormone (FSH)] followed by a decrease in testosterone levels[14, 15].
3. GnRH antagonists, (e.g., degarelix) competitively bind to the pituitary GnRH receptors and directly inhibit the release of gonadotropins and lead to reduced testosterone levels [16].
4. Estrogens induce pituitary suppression of gonadotropin secretion and inhibit the production of androgens in the testicles but are rarely used due to their side effect profile [17].
5. Anti-androgens,include bicalutamide, flutamide, and the more recently developed enzalutamide which bind to androgen receptors and thereby block the effect of endogenous androgens [18]. Moreover, abiraterone is a novel androgen synthesis inhibitor that has been shown to block androgen synthesis in adrenal glands and prostate cancer cells[19].

Triptorelin as ADT

Triptorelin (Decapeptyl®) is the most widely used GnRH agonist therapy as ADT in clinical practice. It is indicated as the first-line hormonal therapy in patients with locally advanced non-metastatic or metastatic disease as an alternative to surgical castration; and as adjuvant to external-beam radiation therapy.

Triptorelin is administered to patients in the form of acetate or pamoate as a sustained-release 1-month (3 or 3.75 mg), 3-month (11.25 mg), and 6-month (22.5 mg) formulations. (Fig. 1) [20-22]. Sustained-release formulations of triptorelin comprise micro particles of the decapeptide incorporated within a biocompatible and biodegradable copolymer (polylactide-co-glycolide) [23].

Pharmacokinetics

Following intravenous bolus administration, triptorelin is distributed and eliminated by hepatic and renal routes according to a three-compartment model that corresponds to plasma half-lives of 6 min, 45 min, and 3 h. Initially stimulates LH and FSH secretion, with the subsequent increase production of testosterone at around 4 days. Testosterone levels progressively decline after that with continuous exposure to triptorelin [22].

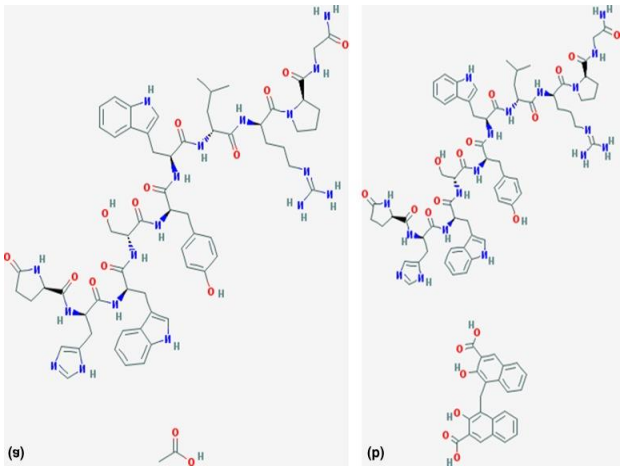

Figure 1: Structure of triptorelin acetate (a) and pamoate (b) [3]

After IM or SC administration of Triptorelin, the mean serum levels of triptorelin are stable at 0.06 ng/ml for approximately 12 weeks after a single IM injection of a triptorelinpamoate 3-month formulation, with mean (standard deviation) C_{max} of 35.7 ng/ml (18.3 ng/ml) and C_{min} of 0.063 ng/ml (range 0.021–0.174 ng/ml) [24].The IM route of administration may not be suitable for patients receiving anticoagulants for the risk of excessive bleeding or hematomas[25], and so SC injections provide an alternative delivery option.

Clinical Efficacy

A significant body of evidence supports the efficacy and safety of sustained-release formulations of triptorelin for the treatment of patients with locally advanced non-metastatic or metastatic prostate cancer.

The biochemical effectiveness of ADT is measured primarily by determining if testosterone levels are reduced by treatment to castrate levels (serum testosterone <50 ng/dl or <1.7 nmol/l) [26, 34-36]. PSA levels are also utilized as a secondary measure of treatment response due to many limitations; for example, there is little precision on the predictive value of PSA levels, there is no consensus on the magnitude or duration of PSA decline that can be used to define response, and PSA kinetics have little value in guiding management decisions, figure (2).

1. **Intramuscular triptorelin**

IM triptorelin 3.75 mg 1-month and the triptorelin 11.25 mg 3-month formulations are able to achieve castration 3–4 weeks after administration and to maintain it between the injections [24, 28-31]. Castrate levels of testosterone were reached after 28 days in 91.2% of men with locally advanced or metastatic prostate cancer. Triptorelin 22.5 mg 6-month formulation was shown to achieve castrate levels of testosterone in 97.5% of patients after 28 days and in 98.3% after 12 months [15]. Castration is also maintained 3 years after starting ADT [34].

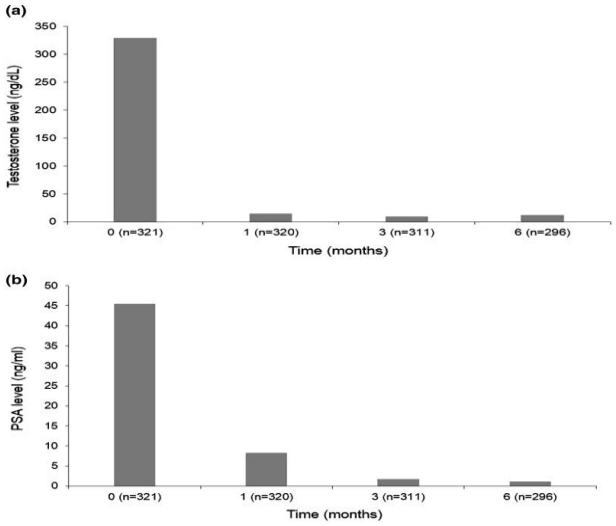

Figure 2: Change in testosterone (**a**) and serum PSA (**b**) levels from baseline with sustained-release 22.5 mg 6-month triptorelin in men with advanced prostate cancer[32]. *PSA* prostate-specific antigen

The sustained suppression of testosterone with these triptorelin formulations leads to reductions in PSA levels from 46.8 ng/ml at baseline to 1.3 ng/ml at 9 months after triptorelin 3.75 mg 1-month formulation[30, 35 and 36]. IMtriptorelin 11.25 mg 3-month formulation reduce median PSA from 112.7 ng/ml at baseline to 10.4 and 11.6 ng/ml at 3 and 6 months, respectively in newly diagnosed locally advanced or metastatic prostate cancer[35]. The longer term Triptocare LT study, showed that median serum PSA reductions were maintained after 3 years of ADT[34].

Subcutaneous triptorelin

Recently, SC administration of triptorelinpamoate 11.25 mg 3-month formulation was shown to achieve castrate levels of testosterone within 4 weeks of the first injection in 97.6% of men with locally advanced or metastatic prostate cancer [25]. Most patients (77.7%) also met the stringent castration definition of testosterone concentration <20 ng/dl at 4 weeks, increasing to 90.8% after 26 weeks. In this study, PSA levels were also reduced from baseline by 64.2% and 96.0% at 4 and 26 weeks after injection, with median PSA levels below 4 ng/ml from week 8 through week 26[25].

These data suggest that both routes of triptorelin administration have a same efficacy.

Effect on Symptoms

Recently, an observational study suggested that treatment with triptorelin 1- and 3-month formulations improved LUTS after 6 and 12 months, as measured by a significant reduction in the International Prostate Symptom Score (IPSS) [37-41]. Interestingly, the improvement in LUTS after triptorelin therapy, correlated with reductions in PSA levels[41]. Similar results were observed with improvement in other clinical symptoms, including bone pain[42].

Tolerability

Triptorelin formulations were generally well tolerated. The most frequently occurring treatment-related adverse events (AEs) with both IM and SC administrations of triptorelin were characteristic of those observed following any GnRH agonist, i.e., castration [15, 31 and 43].

1. IM administration AEs included hot flushes (50% of patients), erectile dysfunction (4%), and decreased libido (3%) [26, 27].
2. SC administration AEsincluded, hot flushes (10.3%) were the most frequently reported followed by increased weight (5.6%) [31].

Despite these AEs, discontinuation rates of triptorelin are infrequent[15, 31].

Comparison with Other ADTS

1. Comparison with leuprolide: Several head-to-head trials demonstrated clinical equivalence in the proportion of men maintaining castrate serum testosterone levels, defined as ≤50 ng/dl, between 2 and 9 months after starting treatment (mean levels maintained below castration limit in 98.8% vs 97.3% of the patients; cumulative maintenance castration rates of 96.2% vs 91.2%, respectively). Changes in the secondary endpoints of LH levels, bone pain, PSA levels, and quality of life were also not significantly different between treatment groups. However, triptorelin was associated with a significantly higher 9-month survival rate than leuprolide (97.0% vs 90.5%; $P = 0.033$) [29-31].
2. Comparison with drgarelix and goserelin: mortality with triptorelin was lower than with drgarelix and goserelin (OR 0.5) [44, 45].

Strategies of ADT in Prostate Cancer Management

Two important topics on the role of ADT in prostate cancer management continue to be debated. First, whether tolerance and side effects of ADT can be diminished by altering the regimens used, for example, with intermittent ADT. Second, with the introduction of newer treatment options, mainly indicated for metastatic CRPC, there is a concern among clinical experts that some physicians may disregard the need for continued ADT (i.e., 'backbone ADT')[46].

1. ADT using GnRH agonists should be combined at treatment initiation with the short-term administration of anti-androgens to prevent flare-up of symptoms due to the initial pituitary stimulation and increase in testosterone levels[3].
2. Intermittent ADT: The feasibility of intermittent ADT for management of newly diagnosed metastatic hormone-sensitive prostate cancer was found to be inferior to continuous ADT on survival outcomes[47]. However, intermittent ADT may still have a role in none metastatic disease as the patient profile fits this strategy, or because of the strong belief that toxicity is reduced. The analysis of intermittent versus continuous ADT suggested that the 10-year

cumulative incidence of ischemic and thrombotic events was significantly higher with intermittent ADT (33%) versus continuous ADT (24%, *P* = 0.02). In conclusion, older men with metastatic prostate cancer who received intermittent ADT had no reduction in bone, endocrine or cognitive events, but ischemic and thrombotic events were more frequent compared with continuous ADT [48], in addition to the trend for improved HRQoL and reduce cost with intermittent versus continuous ADT [49]. The aspect of treatment cost reduction is of very important in our patient due to economical state of our country.

3. Delayed ADT: Another strategy for the management of asymptomatic disease is to defer ADT until the development of symptoms. A Cochrane review of studies from the pre-PSA era suggested that early ADT in a metastatic population significantly reduced disease progression and associated complications [50]. However, the EAU guidelines highlight the difficulties in making any recommendations due to the lack of quality data [3].
4. Backbone ADT (triptorelin +abiraterone): On the issue of backbone ADT, the need to eliminate or suppress as many parts of the androgen receptor signaling pathway as possible provides a rationale for continuing androgen deprivation while inhibiting androgen biosynthesis with abiraterone [46]. Data suggest that the combination of abiraterone and ADT provides more sustained suppression of testosterone than abiraterone monotherapy. Specifically, the use of abiraterone alone is not able to maintain decreased levels of testosterone in men who have not achieved castration, whereas the addition of abiraterone to backbone ADT results in sustained suppression of testosterone to low levels[51-53].
5. ADT with chemotherapy: The rationale for continuing ADT when starting chemotherapy in metastatic CRPC (mCRPC) is that cessation of ADT may cause renewed testosterone release and stimulation of the remaining androgen-sensitive elements of the tumor [46]. Although survival benefits of lowered testosterone in the setting of metastatic prostate cancer have not been conclusively demonstrated, improved overall survival by 13.6 months was shown with the inclusion of ADT during chemotherapy initiation compared with ADT alone in men with metastatic prostate [54]. In addition, an 8.5 month increase in median time to biochemical, symptomatic or radiographic progression with the addition of chemotherapy has been gained. However, the incidence of Grade 3–5 AEs was considerably higher in this strategy[55]. Thus, it seems the combination of ADT and chemotherapy should be initiated earlier in the treatment algorithm for high-risk disease. [20, 21 and 56].
6. ADT after radical prostatectomy: the use of adjuvant ADT after radical prostatectomy when nodal involvement is detected continues to have an important role [3].
7. ADT plus radiotherapy: adjuvant or neo-adjuvant ADT plus radiotherapy is established as standard practice for locally advance prostate cancer, especially when disease is classified as high risk [3,57].

CONCLUSION

In our hospital ADT remains the mainstay of treatment for advanced prostate cancer, with GnRH agonists predominating as a hormonal therapy of choice. Triptorelin is a GnRH agonist that is indicated as the first-line hormonal therapy in patients with locally advanced non-metastatic or metastatic disease. The availability of sustained-release 1-, 3- and 6-month formulations of triptorelin delivered via IM or SC routes offers the potential for improved flexibility and convenience for the patient with advanced prostate cancer. Moreover, sustained-release triptorelin treatment has a proven efficacy and safety profile in clinical trials, with observations from routine practice indicating patient satisfaction lending credence to clinical trial data. The only drawback is the high cost of this drug which is unsuitable to some patient with low socioeconomical status. It is imperative that the emergence of new treatment options for castration-resistant prostate cancer does not lead physicians to overlook the benefits of continuing ADT in their patients. However, it is also clear that optimum treatment sequencing of ADT, novel hormonal agents, and chemotherapy needs to be defined and individualized for men with advanced prostate cancer.

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Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies performed by the author.

REFERENCES

1. Ahmed in Jemal, Rebecca Siegel, Elizabeth Ward, Taylor Murray, Jiaquan Xu. Michael J. Thun. Cancer Statistics, 2007. CA Cancer J Clin 2007, 57, 43-66.
2. Jemal A, Clegg LX, Ward E. Annual report to the nation on the status of cancer, 1975– 2001, with a special feature regarding survival. Cancer 2004, 101, 3–27.
3. Mottet N, Bellmunt J, Briers E. Guidelines on prostate cancer. 2016. Available at: https://uroweb.org/guideline/prostate-cancer/.
4. Huggins C, Hodges CV. Studies on prostatic cancer 1: the effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res. 1941, 19, 293–297.
5. Sobin LH, Gospodarowicz MK, Wittlekind C. TNM classification of malignant tumors. 7. Oxford: Wiley-Blackwell; 1999.

6. Lukka H, Warde P, Pickles T. Controversies in prostate cancer radiotherapy: consensus development. Can J Urol. 8, 2001, 1314–1322.
7. Delahunt B, Egevad L, Grignon DJ, Srigley JR, Samaratunga H. Prostate cancer grading: recent developments and future directions. BJU Int. 117(Suppl 4), 2016, 7-8.
8. Ang M, Rajcic B, Foreman D, Moretti K, O'Callaghan ME. Men presenting with prostate-specific antigen (PSA) values of over 100 ng/mL. BJU Int. 117(Suppl 4), 2016, 68–75.
9. Bill-Axelson A, Holmberg L, Garmo H. Radical prostatectomy or watchful waiting in early prostate cancer. N Engl J Med. 370, 2014, 932–942.
10. Wilt TJ, Brawer MK, and Jones KM. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med. 367, 2012, 203–213.
11. Hoffman KE, Niu J, Shen Y. Physician variation in management of low-risk prostate cancer: a population-based cohort study. JAMA Intern Med. 174, 2014; 1450–1459.
12. Aizer AA, Paly JJ, Michaelson MD. Medical oncology consultation and minimization of overtreatment in men with low-risk prostate cancer. J OncolPract. 10, 2014, 107–112.
13. Gravis G, Boher JM, Fizazi K. Prognostic factors for survival in noncastrate metastatic prostate cancer: validation of the glass model and development of a novel simplified prognostic model. Eur Urol. 68, 2015, 196–204.
14. Tunn UW, Wiedey K. Safety and clinical efficacy of a new 6-month depot formulation of leuprorelin acetate in patients with prostate cancer in Europe. Prostate Cancer Prostatic Dis. 2009; 12:83–87.
15. Lundstrom EA, Rencken RK, van Wyk JH. Triptorelin 6-month formulation in the management of patients with locally advanced and metastatic prostate cancer: an open-label, non-comparative, multicentre, phase III study. Clin Drug Investig. 2009; 29:757–765.
16. Klotz L, Boccon-Gibod L, Shore ND. 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; 102:1531–1538.
17. Ockrim J, el Lalani N, Abel P. Therapy Insight: parenteral estrogen treatment for prostate cancer—a new dawn for an old therapy. Nat ClinPractOncol. 2006; 3:552–563.
18. Akaza H, Hinotsu S, Usami M. Combined androgen blockade with bicalutamide for advanced prostate cancer: long-term follow-up of a phase 3, double-blind, randomized study for survival. Cancer. 2009; 115:3437–3445.
19. Merseburger AS, Scher HI, Bellmunt J. Enzalutamide in European and North American men participating in the AFFIRM trial. BJU Int. 2015; 115:41–49.
20. Ipsen Ltd. Decapeptyl SR. 3 mg. Summary of product characteristics. 2015. Available at: https://www.medicines.org.uk/emc/medicine/868.
21. Ipsen Ltd. Decapeptyl SR. 11.25 mg. Summary of product characteristics. 2015. Available at: https://www.medicines.org.uk/emc/medicine/13851.
22. Ipsen Ltd. Decapeptyl SR. 22.5 mg. Summary of product characteristics. 2015. Available at: https://www.medicines.org.uk/emc/medicine/24154.
23. Ploussard G, Mongiat-Artus P. Triptorelin in the management of prostate cancer. Future Oncol. 2013; 9:93–102.
24. Bouchot O, Soret JY, Jacqmin D, Lahlou N, Roger M, Blumberg J. Three-month sustained-release form of triptorelin in patients with advanced prostatic adenocarcinoma: results of an open pharmacodynamic and pharmacokinetic multicenter study. Horm Res. 1998; 50:89–93.
25. Lebret T, Rouanne M, Hublarov O. Efficacy of triptorelinpamoate 11.25 mg administered subcutaneously for achieving medical castration levels of testosterone in patients with locally advanced or metastatic prostate cancer. Ther. Adv Urol. 2015; 7:125–134.
26. Lee CR. Thrombosis and anti-thrombotic therapy. In: Lee GR, Bithell TC, Foerster J, Athens JW, Lukens JN, editors. Wintrobe's clinical hematology. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1993. p. 1533.
27. Boccardo F, Decensi A, Guarneri D. Long-acting (depot) D-TRP-6 LH-RH (Decapeptyl) in prostate cancer. An Italian multicentric trial. Am J ClinOncol. 1988; 11(Suppl 2):S129–S131.
28. Minkov NK, Zozikov BI, Yaneva Z, Uldry PA. A phase II trial with new triptorelin sustained release formulations in prostatic carcinoma. IntUrolNephrol. 2001; 33:379–383.
29. Kuhn JM, Abourachid H, Brucher P. A randomized comparison of the clinical and hormonal effects of two GnRH agonists in patients with prostate cancer. Eur Urol. 1997; 32:397–403.
30. Heyns CF, Simonin MP, Grosgurin P, Schall R, Porchet HC. Comparative efficacy of triptorelin pamoate and leuprolide acetate in men with advanced prostate cancer. BJU Int. 2003; 92:226–231.
31. Abbou CC, Lucas C, Leblanc V. Tolerance and clinical and biological responses during the first 6 months of treatment with 1-month sustained release LHRH agonists leuprolerin and triptorelin in patients with metastatic prostate cancer. Prog Urol. 1997; 7:984–995.
32. Martinez-Pineiro L, Schalken JA, Cabri P, Maisonobe P, de la Taille A, Triptocare Study Group Evaluation of urinary prostate cancer antigen-3 (PCA3) and TMPRSS2-ERG score changes when starting androgen-deprivation therapy with triptorelin 6-month formulation in patients with locally advanced and metastatic prostate cancer. BJU Int. 2014; 114:608–616.
33. Botto H, Roupret M, Mathieu F, and Richard F. Multicenter randomized trial comparing triptorelin medical castration versus surgical castration in the treatment of locally advanced or metastatic prostate cancer. Prog Urol. 2007; 17:235–239.
34. de la Taille A, Martinez-Pineiro L, Cabri P, Houchard A, Schalken J. Factors predicting progression to castrate-resistant prostate cancer in patients with advanced prostate cancer receiving long-term androgen deprivation therapy. BJU Int. 2016.
35. Kao CC, Chang YH, Wu T. Open, multi-center, phase IV study to assess the efficacy and tolerability of triptorelin in Taiwanese patients with advanced prostate cancer. J Chin Med Assoc. 2012; 75:255–261.
36. Teillac P, Heyns CF, Kaisary AV, Bouchot O, Blumberg J. Pharmacodynamic equivalence of a decapeptyl 3-month SR formulation with the 28-day SR formulation in patients with advanced prostate cancer. Horm Res. 2004; 62:252–258.
37. Lehrer S, Stone NN, Droller MJ, Stock RG. Association between American Urologic Association (AUA) urinary symptom score and disease stage in men with localized prostate cancer. UrolOncol. 2002; 7:73–76.
38. Axcrona K, Aaltomaa S, da Silva CM. Androgen deprivation therapy for volume reduction, lower urinary tract symptom relief and quality of life improvement in patients with prostate cancer:

degarelixvsgoserelin plus bicalutamide. BJU Int. 2012; 110:1721–1728.

39. Mason M, Maldonado Pijoan X, Steidle C. Neoadjuvant androgen deprivation therapy for prostate volume reduction, lower urinary tract symptom relief and quality of life improvement in men with intermediate- to high-risk prostate cancer: a randomised non-inferiority trial of degarelix versus goserelin plus bicalutamide. ClinOncol (R CollRadiol). 2013; 25:190–196.
40. Anderson J, Al-Ali G, and Wirth M. Degarelix versus goserelin (+ antiandrogen flare protection) in the relief of lower urinary tract symptoms secondary to prostate cancer: results from a phase IIIb study (NCT00831233) Urol Int. 2013; 90:321–328.
41. Gil T, Aoun F, Cabri P, Maisonobe P, van Velthoven R. A prospective, observational grouped analysis to evaluate the effect of triptorelin on lower urinary tract symptoms in patients with advanced prostate cancer. TherAdv Urol. 2015; 7:116–124.
42. Peltier A, Aoun F, De Ruyter V, Cabri P, Van Velthoven R. Triptorelin in the relief of lower urinary tract symptoms in advanced prostate cancer patients: the result study. Prostate Cancer. 2015; 2015:978194.
43. Shore ND, Sieber P, Schimke L, Perzin A, Olsen S. Comparison of tolerability and adverse events following treatment with two GnRH agonists in patients with advanced prostate cancer. UrolNurs. 2013; 33(236–44):48.
44. Crawford ED, Phillips JM. Six-month gonadotropin releasing hormone (GnRH) agonist depots provide efficacy, safety, convenience, and comfort. Cancer Manag Res. 2011; 3:201–209.
45. Uttley L, Whyte S, Gomersall T. Degarelix for treating advanced hormone-dependent prostate cancer: a single technology appraisal. Sheffield, UK: ScHARR, University of Sheffield; 2013.
46. Merseburger AS, Hammerer P, Rozet F. Androgen deprivation therapy in castrate-resistant prostate cancer: how important is GnRH agonist backbone therapy? World J Urol. 2015; 33:1079–1085.
47. Hussain M, Tangen CM, Berry DL. Intermittent versus continuous androgen deprivation in prostate cancer. N Engl J Med. 2013; 368:1314–1325.
48. Hershman DL, Unger JM, Wright JD. Adverse health events following intermittent and continuous androgen deprivation in patients with metastatic prostate cancer. JAMA Oncol. 2016; 2:453–461.
49. Brungs D, Chen J, Masson P, Epstein RJ. Intermittent androgen deprivation is a rational standard-of-care treatment for all stages of progressive prostate cancer: results from a systematic review and meta-analysis. Prostate Cancer Prostatic Dis. 2014; 17:105–111.
50. Kunath F, Grobe HR, Rucker G. Non-steroidal antiandrogen monotherapy compared with luteinizing hormone-releasing hormone agonists or surgical castration monotherapy for advanced prostate cancer. Cochrane Database Syst Rev. 2014; 6:CD009266.
51. O'Donnell A, Judson I, Dowsett M. Hormonal impact of the 17alpha-hydroxylase/C (17, 20)-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer. Br J Cancer. 2004; 90:2317–2325.
52. Ryan CJ, Peng W, Kheoh T. Androgen dynamics and serum PSA in patients treated with abiraterone acetate. Prostate Cancer Prostatic Dis. 2014; 17:192–198.
53. Sonpavde G, Attard G, Bellmunt J. The role of abiraterone acetate in the management of prostate cancer: a critical analysis of the literature. Eur Urol. 2011; 60:270–278.
54. Sweeney CJ, Chen YH, Carducci M. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med. 2015; 373:737–746.
55. James ND, Sydes MR, Clarke NW. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomized controlled trial. Lancet. 2016; 387:1163–1177.
56. Scher HI, Fizazi K, Saad F. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012; 367:1187–1197.
57. Bolla M, Van Tienhoven G, Warde P. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. Lancet Oncol. 2010; 11:1066–1073.

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