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. 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. In general, the risk factors for prostate cancer are poorly understood and consequent advice on prevention is not possible. Therefore, the management of prostate cancer focuses on treating the disease, and the hormone dependence of prostate cancer has been recognized for decades. 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. Patients are also categorized into low, high, or intermediate risk of progression according to clinical stage, Gleason score, and prostate-specific antigen (PSA) level. Gleason score and the presence of metastasis were the strongest predictors of prostate cancer-specific mortality in the group with high PSA at presentation. 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%, and avoiding unnecessary treatment is a challenge in these patients. 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.

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)] 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.
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\(^{1}\)) 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 (poly-lactide-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 triptorelinacetate 3-month formulation, with mean (standard deviation) \(C_{\text{max}}\) of 35.7 ng/ml (18.3 ng/ml) and \(C_{\text{min}}\) of 0.063 ng/ml (range 0.021–0.174 ng/ml)\(^{34}\). The IM route of administration may not be suitable for patients receiving anticoagulants for the risk of excessive bleeding or hematomas\(^{35}\), 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)\(^{26}\). 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).

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.\(^{36}\)
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 AEs included, 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 6, 31.

Comparison with Other ADTS

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.

Comparison with degarelix and goserelin: mortality with triptorelin was lower than with degarelix 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’).

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.

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 \(^{20,21,56} \).

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 \(^{5,57} \).

**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.

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