Monitoring of Prostate Cancer Patients: Guidelines and Current Practice

Laurent Boccon-Gibod *

Department of Urology, Hôpital Bichat Claude Bernard, 46, Rue Henri Huchard, 75877 Paris Cedex 18, France

Abstract

Objectives: This review paper focuses on monitoring of patients with prostate cancer (PCa) after initiating hormone therapy and discusses the risk of potential side-effects.

Methods: This report is based on a presentation during a satellite symposium held at the European Association of Urology (EAU) 2007 Annual Congress in Berlin, Germany.

Results: The assessment of serum prostate-specific antigen (PSA) levels is still the most widely used practice for PCa screening and remains important for follow-up after hormonal treatment. Serum testosterone levels should be determined to make sure that castrate levels are reached and may help in predicting return of sexual function after cessation of hormone therapy. Other promising markers used for monitoring PCa patients are osteoprotegerin and bone-specific alkaline phosphatase. However, patients receiving long-term hormone therapy are at an increased risk of acute and chronic side-effects, and therefore, careful monitoring is needed. Furthermore, lifestyle changes may be beneficial for preventing bone complications and metabolic syndrome in PCa patients receiving hormone therapy.

Conclusions: These data indicate that PSA is still the most important marker for monitoring PCa patients after they have received hormone therapy. In addition, measuring serum testosterone levels seems to be increasingly important. However, urologists must be aware of the risk of side-effects of long-term hormone therapy and should adequately monitor their patients.

* Tel. +33 (1) 40257100; Fax: +33 (1) 42285320.
E-mail address: Laurent.Boccon-Gibod@bch.ap-hop-paris.fr.

1. Introduction

Hormone therapy was originally introduced as a treatment option for patients diagnosed with metastatic prostate cancer (PCa). Currently, hormone therapy is being increasingly used in earlier stages of PCa, such as for patients with prostate-specific antigen (PSA) relapse after previous radical therapy.
and for patients diagnosed with advanced disease [1]. As a consequence, many patients will receive long-term hormone therapy. Patients receiving hormone therapy are usually followed lifelong or until ageing makes follow-up unnecessary. The main objectives of monitoring patients with PCa receiving hormone therapy are to control treatment efficacy and compliance and to recognise potentially deleterious side-effects.

Although many different types of hormone therapy are available, only a few are recommended by the recently updated European Association of Urology (EAU) guidelines on PCa [2]. Androgen-deprivation therapy (ADT) slows the growth of PCa by lowering the levels of androgens and has been the mainstay of treatment of advanced and metastatic PCa. Androgen deprivation can be achieved either by surgical or medical castration or by inhibiting the action of circulating androgens at the level of their receptor in prostate cells using competing compounds known as antiandrogens. Alternatively, these therapies can be combined. Luteinising hormone-releasing hormone (LHRH) agonists (eg, goserelin, leuprorelin) have become the method of choice for ADT because they have a good efficacy profile, without the physical and psychological discomfort associated with surgical castration, and lack the potential cardiotoxicity associated with oestrogens [2]. In this review, we outline the updated EAU guidelines on monitoring of patients with PCa after they have received different types of hormone therapy: (1) continuous ADT for metastatic (M+) disease, (2) short-/medium-term ADT in conjunction with radiation therapy, (3) intermittent ADT, and (4) nonsteroidal antiandrogen monotherapy. In addition, we put the current guidelines on monitoring of PCa patients into the perspective of clinical practice.

2. Monitoring after continuous ADT for metastatic disease

The key method to follow the course of PCa is to test the serum PSA level at regular intervals. Determination of serum PSA levels together with a clinical evaluation and supplemented with evaluation of standard biologic parameters are recommend as the cornerstones in the follow-up of PCa patients after ADT [2]. The follow-up intervals and which tests are needed are not well studied and often these need to be individualised for each patient. Follow-up visits should be made every 3 and 6 mo after treatment and should at least include a measurement of serum PSA levels. Furthermore, the PSA nadir and time to nadir should be evaluated during treatment. Patients with a PSA nadir ≤ 4 ng/ml need to be followed every 6 mo by assessment of PSA levels, whereas patients with PSA nadir > 4 ng/ml need to be followed every 3 mo to discuss second-line hormone therapy or to recognise transition to hormone-refractory PCa. Data from the Southwest Oncology Group (SWOG) 9346 trial [3] indicated that PSA nadir on ADT is prognostic of survival in new metastatic PCa. A total of 1395 patients with newly diagnosed metastatic disease and a baseline PSA level ≥ 5 ng/ml received a 7-mo induction of ADT (goserelin and bicalutamide). At the end of the induction period, patients achieving a PSA ≤ 4 ng/ml were randomly assigned to intermittent or continuous ADT. A PSA reduction to < 4 ng/ml after 7 mo of ADT was identified as a strong and significant predictor of survival. Median overall survival was 13 mo for patients with a PSA > 4 ng/ml (95% confidence interval [CI], 11–16 mo) and 44 mo for patients with 0.2 < PSA ≤ 4 ng/ml (95% CI, 39–55 mo). Patients with a PSA ≤ 0.2 ng/ml (95% CI, 62–91 mo) had the greatest survival advantage (Fig. 1).

Increased evidence has indicated that not all LHRH agonists are equally effective in achieving castrate testosterone levels. Therefore, serum testosterone levels should be measured in patients with PSA nadir > 4 ng/ml to make sure that castrate levels are reached. Testosterone assays based on chemiluminescence are currently available, making the measurement of testosterone levels in daily clinical practice possible [1].

Additional studies that could be performed to monitor PCa patients after continuous ADT are imaging studies and the detection of bone markers (osteoprotegerin and bone-specific alkaline phosphatase) [2]. Osteoprotegerin is a soluble osteoclastogenesis inhibitor that regulates bone turnover. It has been reported that serum osteoprotegerin levels are significantly increased in patients with

![Fig. 1 – Median overall survival of patients with newly diagnosed metastatic prostate cancer after 7 mo of induction of androgen deprivation therapy [3]. PSA = prostate-specific antigen.](image-url)
advanced PCa [4]. Bone-specific alkaline phosphatase originates from osteoblasts and has a key role in the bone mineralisation process. The measurement of bone-specific alkaline phosphatase was shown to be a sensitive and specific method of determining osteoblastic activity in patients with metastatic PCa [5]. Imaging procedures, however, such as bone scan and cross-sectional imaging (computed tomography, magnetic resonance imaging) are not recommended in stable patients and should be used only in special situations [2].

3. Monitoring after short-/medium-term ADT in conjunction with radiation therapy

Results from randomised, controlled trials indicate that patients with high-risk localised and locally advanced PCa treated with radiation therapy combined with short-term androgen deprivation exhibit a survival advantage compared with patients treated with radiation therapy alone [2]. To monitor PCa patients after short-/medium-term ADT combined with radiation therapy, it is recommended that serum PSA levels should be checked at 3, 6, and 12 mo and then yearly intervals. Measuring serum testosterone levels at 6, 12, and 18 mo after cessation of ADT may help to predict return of sexual function.

4. Monitoring after intermittent ADT

Intermittent ADT is used in the management of patients with low-volume advanced PCa or when PSA levels increase after local therapy. In addition, because continuous ADT is associated with a wide variety of side-effects, intermittent ADT aims to reduce these side-effects. Furthermore, preclinical data suggest that hormonal resistance may be delayed with intermittent ADT [6]. The monitoring of patients who are candidates for intermittent therapy includes PSA measurement at month 6. PSA levels at 6 mo should be undetectable or at least <0.5 ng/ml to allow treatment cessation. In patients receiving intermittent therapy, PSA should be measured every 3 mo to decide date or reinduction of ADT. Measuring of serum testosterone is probably optional in this setting. Currently, urologists are investigating the benefits of intermittent versus continuous ADT using an LHRH agonist for the treatment of patients with relapsing or locally advanced PCa. Approximately 700 patients from 20 different European countries are included in a phase 3, open-label, randomised, controlled, multicentre trial. All patients will receive two Eligard® 22.5 mg 3-mo depot injections for 6 mo as induction therapy. Those men with hormone-responsive PCa will receive either intermittent or continuous Eligard® treatment for 36 mo.

5. Monitoring after nonsteroidal antiandrogen monotherapy

The EAU guidelines advise nonsteroidal antiandrogen monotherapy (eg, bicalutamide) as an effective alternative to castration for those patients with locally advanced (T3–T4 M0) PCa, with or without radiation therapy. Measuring serum PSA levels is still a key marker to determine treatment efficacy. Nonsteroidal antiandrogens do not suppress testosterone levels, which remain normal, or conversely, slightly elevated. As a consequence, monitoring serum testosterone may be important for these patients to determine the percentage increase over baseline levels [2].

6. Side-effects of hormone therapy

Patients receiving long-term hormone therapy are increasingly vulnerable to the side-effects of this therapy. The most frequently reported side-effects include hot flushes, loss of libido, erectile dysfunction, gynaecomastia and breast pain, anaemia, decrease in bone mineral density, metabolic syndrome, and cognitive impairment [2,7,8]. In this paper, we will mainly focus on reduction in bone mineral density and development of metabolic syndrome and will discuss these side-effects in more detail.

6.1. Decrease in bone mineral density

It has been described previously that ADT causes a 3–5% annual reduction in bone mineral density with an increased risk of fractures, which occur mainly in the spine and hip [7]. Bone mineral density can be measured by ultrasound, computed tomography, or dual energy x-ray scan [9]. Initially, patients should be encouraged to adopt lifestyle changes (more physical activity, decrease in alcohol consumption) to reduce their fracture risk. Although no approved treatments are available for preventing or treating osteoporosis in men, bisphosphonates markedly reduce bone resorption in PCa and represent an attractive treatment strategy. Furthermore, the use of calcium and vitamin D supplementation is recommended [7].
6.2. Metabolic syndrome

In a recently published paper, Braga-Basaria et al.[8] demonstrated that men with PCa undergoing long-term ADT have an increased risk of metabolic syndrome. In this cross-sectional study, they evaluated 58 men with recurrent or metastatic PCa, including 20 patients with PCa undergoing ADT for at least 12 mo (ADT group), 18 patients with nonmetastatic PCa who had received local treatment (non-ADT group), and 20 patients with a normal PSA (control group). Metabolic syndrome was defined according to the Adult Treatment Panel III criteria. Different parameters including plasma glucose levels, serum triglyceride levels, serum high-density lipoprotein levels, waist circumference, and blood pressure were measured. Men were classified as having metabolic syndrome if three of the five criteria were met [8].

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Table 1 – Definition of metabolic syndrome according to the Adult Treatment Panel III criteria

| Definition metabolic syndrome
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<tr>
<td>Plasma glucose level &gt; 110 mg/dl</td>
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<td>Serum triglyceride level &gt; 150 mg/dl</td>
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<td>Serum high-density lipoprotein level &lt; 40 mg/dl</td>
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<tr>
<td>Waist circumference &gt; 102 cm</td>
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<td>Blood pressure &gt; 130/85 mm Hg</td>
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A participant was classified as having metabolic syndrome if three of the five criteria were met [8].

Fig. 2 – Prevalence of metabolic syndrome in patients with prostate cancer undergoing long-term androgen deprivation therapy [8]. ADT = androgen deprivation therapy.

7. Conclusions

The importance of optimal monitoring of patients receiving long-term hormone therapy has already been demonstrated. Recommended tests during follow-up visits include measurement of serum PSA levels, determination of osteoprotegerin and bone-specific alkaline phosphatase, clinical evaluation, and assessment of serum testosterone levels. All these assessments will improve the overall management of PCa patients receiving hormone therapy. However, practicing urologists must be aware of the risk of potential side-effects after patients have received long-term hormone therapy and, therefore, patients need to be carefully monitored.

Conflicts of interest

The author has no conflicts of interest to report.

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