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Urologic Oncology: Seminars and Original Investigations 33 (2015) 7–15

UROLOGIC ONCOLOGY

Review article

Risk of disease flare with LHRH agonist therapy in men with prostate cancer: Myth or fact?

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Received 12 March 2014; received in revised form 18 April 2014; accepted 21 April 2014

Abstract

Objectives: The traditional assumption of a linear relationship between serum testosterone and prostate cancer growth has been seriously challenged, as overwhelming evidence contradicts its basic principles. Luteinizing hormone–releasing hormone (LHRH) agonists are known to cause a peak in serum testosterone level in the initial weeks of treatment, and prevention of the clinical sequelae of testosterone flare by concomitant use of antiandrogens is recommended. Along the present biological concept that there appears to be a limit to the ability of androgens to stimulate prostate cancer growth, termed the *saturation model*, the use of antiandrogens to prevent this disease flare is questioned. The purpose of this review is to gain historical and modern evidence to provide an objective and up-to-date basis for clinical decision making.

Methods and materials: We performed a comprehensive research of the electronic databases PubMed and Embase until April 1, 2014. Studies with the subject of disease flare in men with prostate cancer on LHRH agonist therapy were included, as were studies that assessed the efficacy of antiandrogens to prevent this flare. Case reports were included as well.

Results: Overall, 25 studies considering disease flare were included: 9 randomized clinical trials with an LHRH agonist and an LHRH agonist/antiandrogen arm, 14 observational studies evaluating LHRH agonists only, and 2 case reports. The incidence of disease flare was reported between 0% and 83% owing to a wide set of clinical, biochemical, and radiological factors evaluated. In some of the randomized clinical trials, a statistically significant reduction of the incidence of disease flare by concomitant use of antiandrogens was reported. Most of these historical studies report on subjective worsening of disease symptoms as outcome measure. More objective outcome measures such as the prostate-specific antigen level did not seem to increase to higher than the baseline values.

Conclusions: At present, there is a lack of compelling data showing definite disease progression during the short period of testosterone flare after initiation of LHRH agonist therapy. Based on the *saturation model*, presence of disease flare and the need to prevent this flare by concomitant use of antiandrogens might well be a misconception.

Keywords: Prostate cancer; Antiandrogen; Bicalutamide; Flutamide; Nilutamide; LHRH agonist; Flare

1. Introduction

Testosterone lowering therapy is the mainstay of treatment in advanced and metastatic prostate cancer [1]. In the last 3 decades, luteinizing hormone–releasing hormone (LHRH) agonists have become the "standard of care" in hormonal therapy because they avoid the physical and psychological discomfort associated with bilateral orchiectomy and lack the potential cardiotoxicity associated with diethylstilbestrol [1].

LHRH agonists execute their effect by interfering with the pulsatile release of LHRH from the hypothalamus, thereby down-regulating the secretion of luteinizing hormone in the anterior pituitary gland and reducing serum testosterone to castration level. Owing to the agonistic action of LHRH analogues, serum testosterone may peak to more than 2 times higher than baseline during the first week of treatment, falling to its pretreatment level by day 7 [2]. This so-called testosterone "*flare*" or "*flare-up*" was first described by Faure et al. [3] in 1983. Ever since, concern has been raised that

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http://dx.doi.org/10.1016/j.urolonc.2014.04.016
1078-1439/

this flare may lead to a rapid progression of disease ("*clinical or disease flare*") with excruciating pain, increased voiding symptoms, ureteral obstruction, vertebral collapse with acute spinal cord compression, cardiovascular thromboembolic, or even sudden death [4–8].

With this doom scenario in mind, every effort has been made to prevent a disease flare by combining LHRH agonists at the initiation of therapy with a variety of antiandrogenic agents such as steroid antiandrogens [9–11], nonsteroid antiandrogens [4,5,11–15], estrogens [16,17], or ketoconazole [18]. Although "the guidelines on prostate cancer" of the European Association of Urology do not explicitly dictate the use of antiandrogen treatment to prevent clinical flare, they state that "antiandrogens are to be started on the same day as the depot LHRH injection, and should be continued for a 2-week period." The European Association of Urology guidelines further state that combined antiandrogen therapy is especially indicated in the more advanced stages of metastatic disease [1]. The National Comprehensive Cancer Network guidelines recommend that antiandrogen treatment "precede or be co-administered with LHRH agonists and be continued in combination for at least 7 days for patients with overt metastases who are at risk of developing symptoms associated with the flare in testosterone with initial LHRH-agonist alone" [19].

Inspired by the "saturation model" postulated by Morgentaler [20] who demonstrated a nonlinear relationship between testosterone and prostate cancer growth and aggressiveness, we reviewed the literature searching for scientific evidence for the concept of clinical flare induced by LHRH agonists and question the need to prevent this flare by antiandrogens.

2. Patients and methods

2.1. Evidence acquisition

A PubMed and Embase database search was conducted. Predefined search terms were used to identify articles concerning biochemical flare and clinical (disease) flare and reporting on the incidence and prevention of flare in patients with advanced or metastatic prostate cancer in whom LHRH agonist therapy was started. The literature search included papers published until April 1, 2014. Fig. 1 presents the search strategy flowchart. Search terms were LHRH [All Fields] AND "agonist" [All Fields] OR "gonadotropin-releasing hormone" [MeSH Terms] OR "gonadotropin-releasing" [All Fields] AND "hormone" [All Fields] OR "gonadotropin-releasing hormone" [All Fields] AND prostate [All Fields] AND "flare" [MeSH Terms] OR "flare-up" [All Fields]). Then, "LHRH agonist" was replaced by bicalutamide [All Fields], flutamide [All Fields], nilutamide [All Fields], or cyproterone acetate (CPA) [All Fields] to investigate whether additional articles were found. References of all retrieved full-text articles were checked for additional cross-references.

2.2. Inclusion and exclusion criteria

We first limited our search to full-text original articles published in English and available for review. Articles were independently assessed for eligibility using the following predefined criteria:

- *Study population*: patients diagnosed with prostate cancer in whom LHRH agonist therapy was started.
- *Intervention*: the concomitant use of antiandrogen therapy during the initial phase of LHRH agonist treatment.
- *Study outcomes*: studies reporting on clinical progression of disease, radiological progression of disease, and a rise in tumor markers such as prostate-specific antigen (PSA) or phosphate acid phosphatase (PAP) or alkali phosphatase (AP) during the initial phase of LHRH agonist treatment were evaluated. These included studies that investigated the use of concomitant antiandrogen therapy such as bicalutamide, nilutamide, flutamide, or CPA to prevent disease flare.

Studies that only reported on progression or outcome of disease after the initial phase of LHRH agonist treatment, i.e., 4 weeks after the first LHRH agonist injection, were excluded, as were studies reporting on progression of disease on maximum androgen blockade (LHRH agonist therapy with antiandrogens), studies on LHRH agonists reporting on testosterone flare only, studies on LHRH antagonists or estrogens, and studies not related to humans.

2.3. Data extraction

The following data were extracted from full-text articles by the first author: study design, selection and inclusion criteria, study outcome details (clinical progression of disease, radiological progression of disease, and biochemical progression of disease), and type and use of antiandrogens.

3. Results

3.1. Search results and analysis

Our literature search identified 152 original articles, of which 25 were included in the analysis. There were 9 randomized clinical trials (RCTs) directly comparing disease flare in patients on LHRH agonist treatment with those on combined LHRH agonist/antiandrogen treatment, and 14 observational studies that reported on disease flare in men on LHRH agonist therapy only. There were 2 articles that reported on 2 patients only, and these were considered case reports. Differences in study design, type of LHRH agonist and antiandrogen, number of patients, and percentages of reported incidences of disease flare, and outcome measures of disease flare are depicted in the Table.