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ORIGINAL ARTICLE

Effect of Bicalutamide Therapy on Prolactin Response to L-dopa in Metastatic Prostate Cancer Patients

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Abstract

OBJECTIVES: The secretion of prolactin (PRL), which is a growth factor for prostate cancer cell proliferation, has been proven to present profound alterations in advanced prostate cancer patients, consisting of abnormally elevated baseline levels and paradoxical response to L-dopa. Moreover, the efficacy of standard therapies for prostate cancer may be mediated at least in part by changes in PRL secretion. The present study was carried out to analyze the effects of the new antiandrogen agent bicalutamide on basal levels of PRL and on its response to L-dopa in metastatic prostate cancer patients.

MATERIAL & METHODS: The study included 10 metastatic prostate cancer patients. They were treated with bicalutamide at a dose of 50 mg/day orally. They were investigated with L-dopa test before therapy and after one month of treatment. L-dopa was given orally at 500 mg, by collecting blood samples before and at 60, 120 and 180 minutes after L-dopa administration. Serum levels of PRL were measured by the RIA method.

RESULTS: Abnormally basal levels of PRL were seen in 4/10 (40%) patients. Mean PRL basal levels decreased after bicalutamide therapy, without, however, significant differences. Before therapy, a paradoxical increase in PRL levels after L-dopa occurred in 4 patients, 3 of them showed basal concentrations of PRL within the normal range. Moreover, bicalutamide therapy significantly reduced PRL increase in response to L-dopa.

CONCLUSIONS: This study would suggest that the measurement of the only basal levels is not sufficient to define as normal the secretion of PRL in advanced prostate cancer, because of the possible existence of altered response to the dynamic tests for PRL secretion. Moreover, the study shows that the antitumor therapy with the new anti-adrogen bicalutamide may reduce PRL secretion and improve its paradoxical secretion in response to L.-Dopa. Further studies will be required to better define the possible prognostic impact of changes in PRL secretion on the efficacy of treatments for metastatic prostate cancer.

Introduction

It is known that prolactin (PRL) is a growth factor for prostate cancer [1]. In particular, PRL has appeared to induce a stimulatory effect independent of testosterone on prostate cancer cells. More in detail, PRL has been shown to modulate the proliferation of androgen-insensitive human prostate cancer cell lines [3]. Moreover, abnormally high levels of PRL have been described in the blood of patients with advanced prostate cancer [4]. Finally, the evidence of high blood concentrations of PRL has been proven to be generally associated with poor prognosis and lack of response to the conventional treatments [4]. However, few studies only have been performed up to now to evaluate the effects of the various oncological therapies on PRL secretion in prostate cancer, in an attempt to establish whether a modulation of PRL production may influence the efficacy of the conventional therapies. Radical prostatectomy has appeared to induce a significant increase in testosterone, estradiol, LH and FSH, and a significant decline in dihydrotestosterone, whereas PRL levels were not influenced [5]. Moreover, blood hormone levels did not correlate with pathological stage or histological grade [5]. LHRH-analogues have appeared to determine controversial results on PRL secretion. In fact, the LHRH analogue buserelin has appeared to enhance PRL levels, even though for a transient period of time, whereas the chronic therapy does not seem to influence PRL levels [6]. In contrast, a small decrease in PRL levels has been described on therapy with another LHRH-analogue, goserelin [7]. These results, even though still preliminary, would suggest that the various LHRH- analogues available up to now for the treatment of prostate cancer may deserve different effects on PRL secretion, which could explain possible differences in their therapeutic efficacy.

Moreover, it has to be remarked that most studies carried out to evaluate PRL secretion in prostate cancer patients have been limited to the analysis of PRL blond levels in baseline conditions, rather than in dynamic conditions by the various endocrine clinical tests, such as L-Dopa test, which represents the main commonly used inhibitory test for PRL secretion. 0ur previous preliminary studies have shown a paradoxical stimulatory response of PRL to L-Dopa in a considerable number of patients with advanced prostate cancer [8]. In contrast, low-dose bromocriptine, a long-acting dopaminergic agonist, has been shown to suppress the abnormally high PRL production in advanced prostate cancer patients [4].

The impact of the association of antiprolactinemic drugs on the therapeutic efficacy of the commonly used endocrine therapies of prostate cancer has-still to be better investigated. The preliminary results available up to now seem to suggest that a combined suppression of PRL by bromocriptine may improve the efficacy of the conventional therapies with respect to orchiectomy alone or orchiectomy plus the antiandrogen flutamide [9], while no clear data are available about the association between antiprolactinemic drugs and LHRH-analogues.

Bicalutamide is a new anti-androgen drug [10], with efficacy superior to that of the most commonly used anti-androgen flutamide in the treatment of advanced prostate cancer, at least in terms of survival time [11]. As far as the endocrine effects of bicalutamide, very few data are available, in particular those concerning PRL secretion. Preliminary results would suggest that PRL secretion may increase on bicalutamide therapy [12]. The present study was performed to evaluate the effect of bicalutamide on PRL secretion, either in baseline conditions, or in response to L-Dopa in advanced prostate cancer.

Materials And Methods

The study included 10 consecutive metastatic prostate cancer patients (median age 71 years, range 64-78), who received bicalutamide therapy after progression on LHRH-analogues plus flutamide. Dominant metastases sites were, as follows: bone: 6; bone plus nodes: 3; bone plus lung: 1. Bicalutamide was given orally at a dose of 50 mg/day, every day. Patients were endocrinologically investigated before the onset of treatment and after the first month of bicalutamide therapy. Patients were analized at 8.00 A.M. after an overnight fast. No patient was under therapy with drugs influencing PRL secretion from at least 10 days prior to study, including opioids, corticosteroids, and dopaminergic agonists and antagonists. L-Dopa was given orally at a dose of 500 mg, and venous blood samples were collected before L-Dopa administration, and at 60, 120 and 180 minutes after L-Dopa administration. L-Dopa test was made before and after one month of bicalutamide therapy.

Serum levels of PRL were measured by the double antibody RIA method, by using commercially available kits. Normal values obtained in our laboratory for male healthy subjects (95% confidence limits) were below 20 ng/ml. Data were reported as mean + SE, and statistically analyzed by the Student's t test and the analysis of variance, as appropriate.

Results

Before the onset of bicalutamide therapy, abnormally high blood levels of PRL were observed in 4/10 (40%) patients. Mean levels of PRL were lower after than before bicalutamide therapy, without, however, statistically significant differences (17,2 +/- 2,9 vs 26,9 +/- 3,8 ng/ml). PRL response to L-Dopa before and after 1 month of bicalutamide therapy is illus-

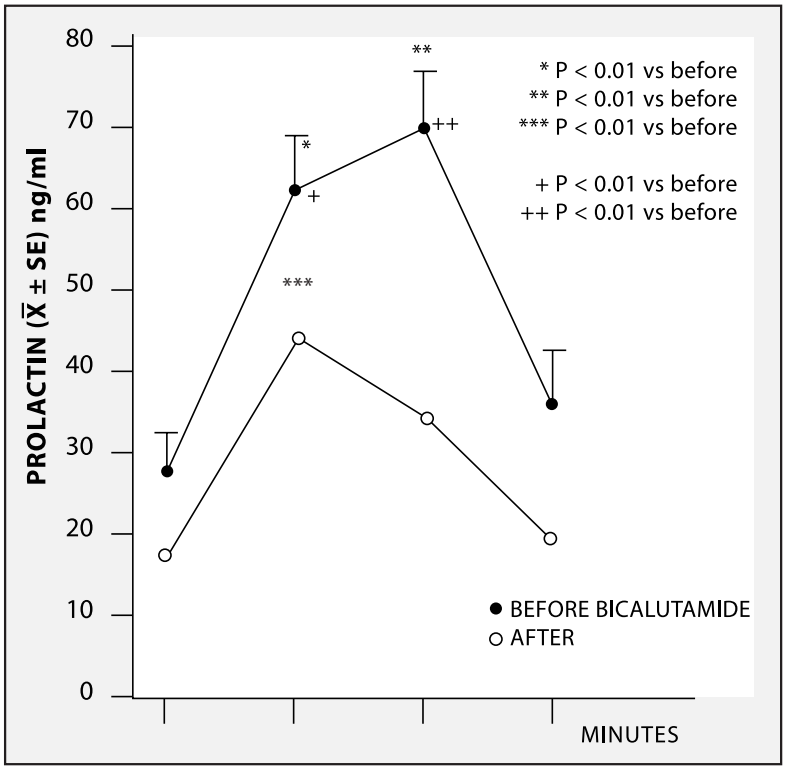

Fig.1. Prolactin response to L-Dopa (500 mg orally) in 10 metastatic prostate cancer patients before and after 1 month of bicalutamide therapy.

trated in Fig.1. Before bicalutamide, a paradoxical increase in PRL levels greater at least than 50% in response to L-Dopa occurred in 4/10 patients, 3 of whom showed basal levels of PRL within the normal range. After bicalutamide therapy, a persistance of the paradoxical response of PRL to L-Dopa occurred in 3/4 patients, whereas the fourth patient showed a complete resolution of the paradoxical response. Mean levels of PRL significantly enhanced in response to L-Dopa either before, or after bicalutamide therapy. However, PRL mean levels in response to L-Dopa were significantly lower after than before bicalutamide therapy.

Discussion

According to previous studies of other authors and ourselves [4, 8], this study confirms that the metastatic prostate cancer is characterized by enhanced PRL secretion and paradoxical response of PRL to the PRL-inhibiting drug L-Dopa. In addition, this study would suggest that the new antiandrogen drug bicalutamide may reduce PRL secretion either in baseline conditions, or in response to dynamic tests. Obviously, these preliminary results do not allow us to draw any define conclusion, but they may only justify further efforts to better investigate and define the endocrine status of prostate cancer patients, rather than to take into consideration the only tumor-related prognostic variables. The evaluation of patient endocrine status could deserve a particular importance during the neoadjuvant therapies, whose aim is the reduction of primary tumor size, in an attempt to enhance the efficacy of surgery or radiotherapy. This statement is justified by the fact that the only clinical stage, whose therapy bas been shown to obtain more benefit from the association of antiprolactinemic drugs, is the locally limited disease [11], whereas there is no evidence of an enhanced efficacy in the metastatic disease.

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