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ORIGINAL ARTICLE

Efficacy of monochemotherapy with docetaxel (taxotere) in relation to prolactin secretion in heavily pretreated metastatic breast cancer

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Abstract

OBJECTIVES: Recent data have suggested that the efficacy of cancer chemotherapy does not depend only on tumor-related characteristics, but also on patient biological status, namely immune and endocrine functions. In particular, it has been shown that prolactin (PRL) is a growth factor for breast cancer, and abnormally high blood levels of PRL have been described in metastatic breast cancer patients. The present study was performed to evaluate the efficacy of chemotherapy with taxanes in relation to PRL blood levels in metastatic breast cancer.

MATERIAL & METHODS: The study included 20 metastatic breast cancer patients, who were treated with taxotere (100 mg/mq I.V. every 21 days) for at least 3 consecutive cycles. Serum levels of PRL were measured by RIA before the onset of treatment and at 21-days intervals.

RESULTS: The clinical response consisted of partial response (PR) in 6, stable disease (SD) in 7 and progressive disease (PD) in the remaining 7 patients. Abnormally high pre-treatment levels of PRL were seen in 7/20 patients. The percent of patients who had PD in response to chemotherapy was significantly high in patients with pre-treatment hyperprolactinemia than in those with normal blood levels of PRL before therapy.

CONCLUSIONS: This study shows that the evidence of abnormally high serum levels of PRL correlates with resistance to chemotherapy with taxanes in metastatic breast cancer. Therefore, a concomitant administration of anti-prolactinemic agents, such as bromocriptine, could enhance the efficacy of chemotherapy itself.

Introduction

Whereas a great advance has been reached in the knowledge of tumor markers and of their prognostic, significance, very few data are available about the possible existence of cancer patient-related biological markers, capable of predicting the efficacy, of anticancer therapies. We could define as bio-markers those parameters, which predict the prognosis of the neoplastic disease on the basis of the endogenous psychobiological status of patients, irrespectively of histological and genetic characteristics of the tumor itself. These potential biological, markers would regard immune and neuroendocrine status of patients. In fact, both immune and neuroendocrine systems have been proven to influence, tumor cell proliferation through the anticancer immune response and the regulation of the endogenous availability of possible tumor growth factors respectively. Blood concentrations of several cytokines, namely IL-2 and IL-12 [1, 2], have appeared to play prognostic significance in both solid and hemopoietic neoplasms. In contrast, very few data are available about the prognostic significance of the neuroendocrine status of patients, and at present they are generally limited to the blood concentrations of prolactin (PRL), whose enhanced secretion has been proven to play an unfavorable prognostic significance in advanced breast cancer [3] and prostate carcinoma [4]. This finding is not surprising, since PRL may be a tumor growth factor for both breast and prostatic carcinomas [3, 4].

Taxotere is a new active chemotherapeutic agent, which may be effective in several tumor histotypes [5], including breast cancer. Previous preliminary clinical studies had already suggested that the evidence of abnormally high concentrations of PRL in the blood was associated with a reduced efficacy of cancer chemotherapy in advanced breast cancer [3]. At present, there are no data about the possible, influence of endogenous biological factors on taxotere efficacy. The present preliminary study was performed to analyze taxotere efficacy in advanced breast cancer in relation to PRL secretion either before or during chemotherapy.

Materials and methods

Eligibility criteria were as follows: histologically proven metastatic breast cancer, measurable lesions at least one previous polychemotherapy containing anthracyclines no chronic concomitant therapy with drugs influencing PRL secretion, including opioids, steroids and anti-dopaminergic agents. Taxotere was given intravenously at a dose of 100 mg/ml every 21 days, for at least three cycles.

Patients were evaluable when they had received at least two cycles. The experimental protocol was explained to each patient and written consent was obtained.

The study included 20 consecutive metastatic breast cancer women (median age: 56 years, range 42–66). Dominant metastasis sites were as follows:

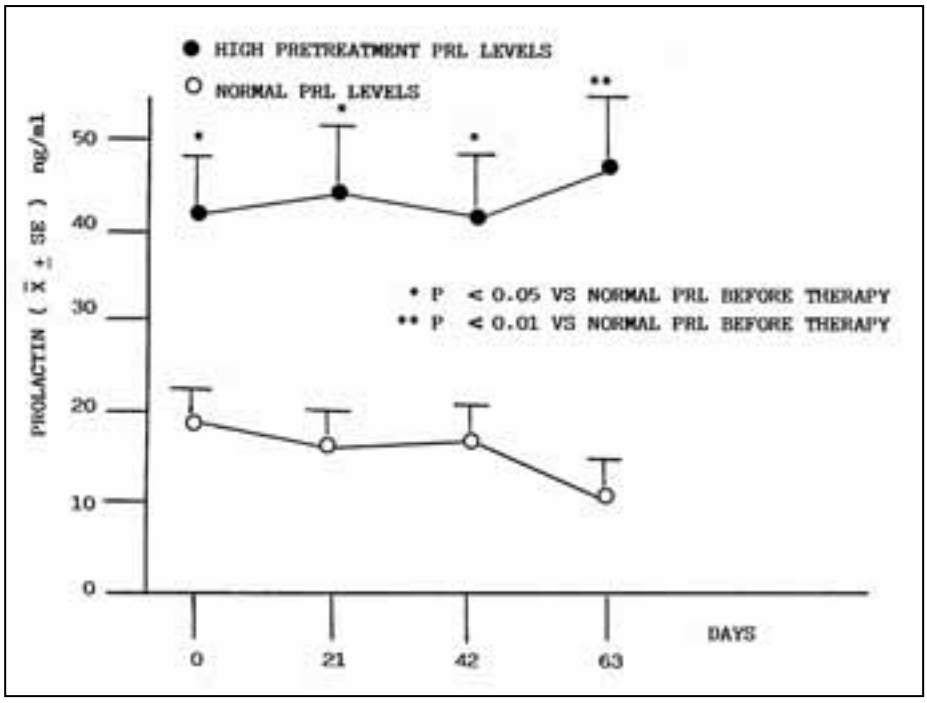

Fig. 1. Changes in mean serum levels of PRL observed on taxotere therapy in metastatic breast cancer women with normal or high pretreatment concentrations of PRL.

bone: 6; lung: 9; liver: 3; liver+lung: 2. The clinical response was assessed according to WHO criteria.

Serum levels of PRL were measured in duplicate by the RIA method and commercially available kits on venous blood samples collected in the morning before the onset of therapy and on the day before the premedication for the successive chemotherapeutic cycle of taxotere. Each cycle consisted of taxotere at 100 mg/ml. Cycles were repeated every 21 days. Serum levels of PRL were considered to be abnormally high when they were greater than 2 SD with respect to those found in age-matched healthy women, corresponding to 25 ng/ml. Data were reported as mean $\pm$ SE, and statistically analyzed by the Student's T-test, the analysis of variance and the chi-square test, as appropriate.

Results

All patients were evaluable for response. No patient had a complete response (CR). A partial response (PR) was achieved in 6/20 (30%) patients, with a median duration of 5 months (range: 3 – 7+). A stable disease (SD) occurred in 7 other patients, whereas the remaining 7 patients had a progressive disease (PD).

Abnormally high pre-treatment serum levels of PRL were found in 7/20 (35%) patients. Moreover, no patient with pre-treatment hyperprolactinemia showed a normalization of PRL blood levels on taxotere therapy. Then, as illustrated in Fig.1, mean serum PRL levels still persisted significantly higher in patients with pre-treatment hyperprolactinemia than in those with normal PRL values before therapy during the whole period of the first 3 chemotherapeutic cycles. Finally, as far as the relation between PRL values and clinical response is concerned, the percent of patients who had PD on therapy was significantly higher in the hyperprolactinemic group than in the group of patients with normal pretreatment concentrations of PRL (6/7 vs. 2/13; $P < 0.05$).

Discussion

According to previous results [3], PRL blood concentrations may be often abnormally elevated in metastatic breast cancer patients, irrespectively of the pharmacological influence of the palliative drugs. Moreover, as previously referred for other anticancer therapies for breast cancer [3], this preliminary study would suggest that taxotere therapy may be also less effective in the presence of breast cancer-related hyperprolactinemia. Recently, it has been suggested that the anti-angiogenic activity may be one of the mechanisms of action of taxane agents [6]. Since PRL or at least some molecular fragments of PRL have been proven to influence the angiogenic processes [7], a diminished anti-angiogenic efficacy could constitute one of the mechanisms responsible for the apparent reduced therapeutic activity of taxotere in metastatic breast cancer. If further studies will confirm these preliminary data, a concomitant administration of anti-prolactinemic agents, such as bromocriptine or its long-acting analogues could be used in an attempt to improve-the efficacy of taxane agents. At present, however, this preliminary study may only suggest the potential prognostic importance of PRL blood levels as a new biomarker to monitor the chemotherapeutic approach of metastatic breast cancer.

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