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Enhancement of the Efficacy of Weekly Low-dose Taxotere by the Long Acting Anti-prolactinemic Drug Cabergoline in Pretreated Metastatic Breast Cancer

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Abstract. *In view of its potential action as a growth factor, the evidence of abnormally high blood levels of prolactin (PRL) is associated with a poor prognosis in metastatic breast cancer. Moreover, metastatic breast cancer-related hyperprolactinemia has proven to counteract the efficacy of cancer chemotherapy. The negative influence of high blood levels of PRL on the efficacy of chemotherapy in metastatic breast cancer has been confirmed by previous preliminary studies, showing that the concomitant administration of the anti-prolactinemic dopaminergic agent bromocriptine may enhance the therapeutic effect of chemotherapy. However, the clinical use of bromocriptine is limited by its short duration and gastrointestinal toxicity. Therefore, new anti-prolactinemic drugs, characterized by less toxicity and a longer duration of activity, such as Cabergoline (CBG), could be more appropriated to control PRL secretion in breast cancer. On this basis, a study was planned to evaluate the efficacy and tolerability of a concomitant administration of CBG with weekly low-dose Taxotere (TXT) in pretreated metastatic breast cancer under chemotherapy. The study group comprised 70 metastatic breast cancer patients (females), pretreated with at least one previous chemotherapeutic line containing anthracyclines, who were randomized to be treated with TXT alone or TXT plus CBG. TXT 25 mg/m^2 was given i.v. at weekly intervals for at least 9 consecutive cycles. CBG was given orally at 0.5 mg once per week. Abnormally high pre-treatment levels of PRL were seen in 24/70 (34%) patients, 11 of whom were treated with TXT plus CBG, whereas the other 13 received TXT alone. CBG induced a complete normalization of the PRL levels in all patients within the first two weeks of therapy, whereas no normalization of PRL occurred spontaneously in patients treated with chemotherapy alone. The objective tumor regression rate was significantly higher in patients concomitantly treated with CBG than in those who received chemotherapy alone (31/34 vs 13/36, $p<0.05$), and this difference was particularly evident in patients with high PRL levels prior to therapy (6/11 vs 2/13). No CBG-related toxicity occurred. On the contrary, chemotherapy-induced asthenia was significantly lower in patients concomitantly treated with CBG (5/34 vs 11/36, $p<0.05$). This study shows that the chemoneuroendocrine therapy of weekly low-dose TXT plus the anti-prolactinemic drug CBG is a new, effective and well-tolerated therapy for metastatic breast cancer. It may also be recommended in heavily pretreated patients or in those with poor clinical status.*

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It has been known for more than 30 years that prolactin (PRL), the pituitary hormone responsible for lactation, may also be a growth factor for breast cancer (1). Abnormally high blood levels of PRL have been described in about 30% of women with metastatic breast cancer (2-4). Breast cancer-related hyperprolactinemia has been proven to be associated with poor prognosis and with diminished efficacy of the conventional antitumor therapies, including chemotherapy and endocrine therapy, in women with metastatic breast cancer (2-5). However, despite this evidence, very few clinical studies have been carried out to investigate the therapeutic impact of an anti-prolactinemic pharmacological approach in metastatic breast cancer (6-7).

Under physiological conditions, PRL secretion is inhibited by dopamine and stimulated by the hypothalamic neuro-hormone TRH, corticosteroids, opioids and anti-dopaminergic drugs (8). Therefore, several drugs commonly used in the palliative therapy of advanced cancer patients, namely corticosteroids, morphine and the anti-emetic anti-dopaminergic agents, could negatively influence the clinical course of breast cancer by stimulating PRL secretion. Unfortunately, the measurement of blood PRL is not commonly considered by oncologists in the clinical

Table I. *Clinical characteristics of metastatic breast cancer women treated with taxotere (TXT) alone or TXT plus Cabergoline (CBG).*

Characteristics	TXT	TXT + CBG
n	36	34
Median age (years)	58 (32-73)	60 (31-75)
Median performance status (Karnofsky's score)	90 (80-100)	90 (70-100)
Dominant metastasis site		
Soft tissues	1	1
Bone	5	4
Lung	11	9
Liver	9	9
Liver + Lung	6	7
Serouses	2	1
Bone marrow	2	3
Previous chemotherapy		
One line	9	8
Two lines	26	24
Three lines	1	2
or TXT plus Cabergoline (CBG)		

management of breast cancer patients and, in particular, the possible biological and prognostic significance of PRL receptor expression by breast cancer cells is still unknown.

Preliminary data have shown that concomitant administration of the anti-prolactinemic dopaminergic agent bromocriptine may enhance the efficacy of chemotherapy in metastatic breast cancer (6). However, its administration may further negatively influence the quality of life of cancer patients, because of gastroenteric toxicity. However, normalization of PRL secretion may be obtained by more recent long-acting anti-prolactinemic drugs, such as Cabergoline (CBG), the tolerability of which clearly exceeds that of bromocriptine (6-9).

A study was planned to evaluate the efficacy and tolerability of a concomitant administration of CBG in metastatic breast cancer patients treated by chemotherapy.

Materials and Methods

The study included 70 consecutive pretreated metastatic breast cancer patients (females, median age 59 years, range 31-75). The eligibility criteria were: histologically proven metastatic breast cancer, measurable lesions, progression after at least one previous chemotherapeutic regimen containing anthracyclines, no brain metastases, no double tumor and no chronic concomitant therapy with drugs stimulating PRL secretion, including corticosteroids, opioids and anti-emetic anti-dopaminergic agents. The experimental protocol was explained to each patient, and written consent was obtained. According to the disease locations and previous chemotherapies, the patients were randomized to receive chemotherapy alone or chemotherapy plus CBG. Chemotherapy consisted of weekly low-dose Taxotere (TXT) (25 mg/m^2 *i.v.*) for 9 consecutive weeks. CBG was give orally at 0.5 mg once per week, without interruption. The clinical response was evaluated according to WHO criteria, based on radiological examination, including CT scan before the onset of chemotherapy and after 9 weekly cycles of chemotherapy. In non-progressing patients, 3 other cycles of chemotherapy were planned. CBG was continued after the interruption of chemotherapy and was administered until disease progression.

To evaluate PRL secretion, venous blood samples were collected in the morning after an overnight fast and before the onset of chemotherapy and at weekly intervals until the end of chemotherapy. Serum levels of PRL were measured by the double-antibody RIA method using commercially available kits. Serum levels of PRL were considered to be abnormally high when they were greater than 23 ng/ml.

The results were statistically analyzed by the Chi-square test, the Student's *t*-test and the analysis of variance, as appropriate. The clinical characteristics of patients treated with chemotherapy or chemotherapy plus CBG are reported in Table I. Patients were considered to be evaluable when they had received at least 6 consecutive weekly cycles of chemotherapy.

Results

All patients were evaluable for clinical response. The two groups of patients were closely comparable in relation to the main prognostic variables, including sites of disease, previous chemotherapies, age and performance status.

Table II. *Clinical response+ (WHO criteria) in metastatic breast cancer women treated with taxotere (TXT) alone or TXT plus Cabergoline (CBG) in relation to pretreatment blood levels of prolactin (PRL).*

Patients	TXT							TXT+CBG						
	n	CR	PR	CR+PR	SD	CR+PR+SD	PD	n	CR	PR	CR+PR	SD	CR+PR+SD	PD
Overall patients	36	0	13	13 (36%)	14	27 (75%9	9	34	1	20	21 (62%)*	8	29 (85%)	5
Normal PRL values	23	0	11	11 (48%)	7	18 (78%)	5	23	1	14	15 (65%)	5	20(87%)	3
High PRL values	13	0	2	2 (15%)**	4	6 (46%)	7	11	0	6	6 (55%)***	3	9 (82%)	2

+ CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease
* $p<0.05$ *vs* TXT alone; ** $p<0.05$ *vs* TXT alone with normal PRL levels; *** $p<0.05$ *vs* TXT alone with high PRL levels

Abnormally high pretreatment serum levels of PRL were observed in 24/70 (34%) patients, without significant differences between the two groups of patients treated with chemotherapy alone (13/36 (36%)) or chemotherapy plus CBG (11/34 (32%)). Even the first CBG administration was sufficient to normalize the PRL levels in 9/11 (82%) patients with high pretreatment PRL values. Moreover, a normalization of PRL concentrations was achieved in all patients within the first two weeks of CBG administration. On the contrary, no normalization of PRL concentrations occurred spontaneously in patients treated with chemotherapy alone.

The clinical response observed in patients treated with chemotherapy alone or chemotherapy plus CBG is shown in Table II. A complete response (CR) was achieved in 1/34 (3%) patients treated with chemotherapy plus CBG, but in none of the patients who received chemotherapy alone. A partial response (PR) was obtained in 20/34 (59%) patients treated with chemotherapy plus CBG, but in only 13/36 (36%) patients who received TXT alone. Therefore, the objective tumor response rate (CR + PR) achieved in patients concomitantly treated with CBG was significantly higher than that observed in patients treated with chemotherapy alone (21/34 (62%) *vs* 13/36 (36%), $p<0.05$). A stable disease (SD) was obtained in 8 and in 14 patients treated with TXT plus CBG or with TXT alone, respectively. The percent of disease control (CR + PR + SD) obtained in patients concomitantly treated with CBG was higher as compared to that observed in patients treated with chemotherapy alone, even though the difference was not statistically significant (29/34 (85%) *vs* 27/36 (75%)). The remaining 5 patients treated with TXT plus CBG and the remaining 9 patients treated with TXT alone had progressive disease (PD). As far as the clinical response in relation to the pretreatment concentrations of PRL is concerned, the objective tumor response rate observed in hyperprolactinemic patients concomitantly treated with CBG was statistically significantly higher than that achieved in hyperprolactinemic patients, who received chemotherapy alone (6/11 (55%) *vs* 2/13 (15%), $p<0.05$). The tumor response rate was higher in the group concomitantly treated with CBG and also in patients with normal pretreatment values of PRL with respect to those treated with chemotherapy alone, even though the difference did not reach statistical significance (15/23 (61%) *vs* 11/23 (48%)). Moreover, the concomitant administration of CBG negated the difference in the percent of objective tumor responses between patients with normal or high pretreatment levels of PRL (15/23 (65%) *vs* 6/11 (55%)). In contrast, within the group treated with chemotherapy alone, the tumor response rate was statistically significantly higher in patients with normal pretreatment concentrations of PRL than in hyperprolactinemic patients (11/23 (48%) *vs* 2/13 (15%), $p<0.05$). Finally, the mean time to progression observed in patients concomitantly treated with CBG was statistically significantly longer with respect to that obtained in patients treated with chemotherapy alone (9.7±0.6 *vs* 6.1±0.8 months, mean±SE, $p<0.025$).

The chemotherapy was well-tolerated in both groups of patients. No CBG-related toxicity occurred and, in particular, no gastroenteric side-effects were observed. Rather CBG improved the tolerability of chemotherapy, since the percent of asthenia observed in patients concomitantly treated with CBG was significantly lower than in the chemotherapy alone group (5/34 *vs* 11/36, $p<0.05$). In addition, 6/34 (18%) patients referred to an improvement in their mood under CBG administration.

Discussion

As previously described for bromocriptine (6), this study shows that the concomitant administration of the long-acting anti-prolactinemic dopaminergic agent CBG is also able to enhance the efficacy of chemotherapy in metastatic breast cancer. The mechanism of action of CBG may involve the proneoplastic activity of PRL as a growth factor for breast cancer (1). In fact, CBG-induced enhanced efficacy of chemotherapy was particularly evident in patients with abnormally elevated pretreatment blood PRL, clearly confirming the negative influence of abnormally high blood levels of PRL on the clinical course of metastatic breast cancer and on the efficacy of cancer chemotherapy. However, the greater efficacy of chemotherapy induced by CBG concomitant administration also in patients with PRL pretreatment levels substantially within the normal range would suggest that mechanisms other than an anti-prolactinemic action may be involved in the CBG-induced enhancement of chemotherapy efficacy.

Dopaminergic agents have been shown to play a direct anti-proliferative effect on cancer cell lines under experimental condition (10). Moreover, experimental studies have shown that the carcinogenic process is characterized by a progressive decline in dopamine brain content, which does not simply represent an epiphenomenon, since the pharmacological correction of diminished brain dopaminergic tone by dopaminergic agents appeared to counteract carcinogen-induced tumor development and progression (11).

Finally, because of the fundamental role of brain dopamine in the neurobiochemestry of well-being and pleasure perception (12), the dopaminergic activity of CBG could explain the diminished chemotherapy-induced asthenia in cancer patients concomitantly treated by CBG.

Therefore, the results of this study would suggest that CBG is a more appropriate drug to control PRL secretion in breast cancer as compared to other dopaminergic agents,

such as bromocriptine, which is less active and more toxic in terms of gastroenteric symptomatology. CBG may be recommended in breast cancer to abrogate the stimulatory influence of PRL on breast cancer cell proliferation.

At present, CBG is commonly used for the therapy of hyperprolactinemia due to PRL-secreting pituitary adenoma (13). This study, by showing a greater efficacy of chemotherapy in metastatic breast cancer patients concomitantly treated with CBG, namely in those with elevated pretreatment levels of PRL, would suggest a possible use of CBG in the treatment of metastatic breast cancer. Therefore, the results of this study justify further clinical investigations on the interaction between anti-prolactinemic dopaminergic agents and cancer chemotherapy, particularly to establish whether chemotherapeutic drugs other than taxanes may have benefits from an association with dopaminergic agents, such as CBG. Moreover, further studies are necessary to investigate the relationship between blood levels of PRL and PRL-receptor expression by cancer cells, in order to better define the importance of PRL in influencing the clinical history of breast cancer. Finally, because of the potential immunomodulatory effects of PRL (14), further studies are required to analyze the influence of a normalization of PRL secretion on the immune status of metastatic breast cancer patients.

In conclusion, this study suggests that chemoneuroendocrine therapy of weekly low-dose TXT plus the long-acting dopaminergic drug CBG is a new, effective and well-tolerated therapy for metastatic breast cancer, which may be recommended particularly in heavily pretreated patients.

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