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Tamoxifen Plus Bromocriptine Versus Tamoxifen Plus Placebo in Advanced Breast Cancer: Results of a Double Blind Multicentre Clinical Trial

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Abstract—*We carried out a double blind multicentre clinical trial in which 171 patients with advanced breast cancer were randomized to receive tamoxifen (30 mg/day) + bromocriptine (5 mg/day) or tamoxifen + placebo. No difference was found in the overall response rates in the two groups (37.5% for placebo; 38% for bromocriptine) or in subgroups (breast tumours, lymph nodes, lung, bone, skin metastases). Tolerability was good in both groups.*

Within the limits of the statistical power of the test (80%), our results do not show any benefit when bromocriptine was added to tamoxifen.

INTRODUCTION

THE ROLE of prolactin in human breast cancer has not yet been clarified. However, prolactin receptors (PRL-R) have been found by several groups and ourselves in about 50% of patients [1]. It has been shown that prolactin (PRL) stimulated the growth of explants of human tumours [2] but the antagonist, bromocriptine, was clinically ineffective when used alone in an EORTC phase two trial [3]. Inconclusive results were obtained when bromocriptine was added to another hormonal treatment [4, 5] but the highly significant correlation between steroid and prolactin receptors [6] prompted us to look for an increase in response rate when the drug was added to tamoxifen treatment in estradiol and/or progesterone receptor positive (or receptor status unknown) patients.

PATIENTS AND METHODS

From September 1984 to September 1986, 171 post-menopausal patients from eight centres with advanced breast cancer entered this double blind randomized trial. None of them had previously received tamoxifen. Only estradiol and/or progesterone receptor positive (R+) or unknown (R?) patients were eligible. All the patients received 30 mg tamoxifen per day. Placebo or bromocriptine (5 mg/day) for 6 months treatment was provided by Sandoz. Tumour response as well as tolerability were evaluated after 45 days, 3 and 6 months according to WHO criteria.

RESULTS

Five patients were found to be ineligible: one R negative, two premenopausal patients, one with a sarcoma and the last one because of a previous treatment with tamoxifen. Seven patients were not evaluable: three for early death due to progressive disease during the first days of treatment, three were lost to follow-up, and one had been given bromocriptine by her physician. Eight patients were evaluable for tolerability only: seven because the treatment was rapidly stopped due to toxicity and one because the metastatic site was not evaluable. Eighty patients were fully evaluable in the placebo group and 71 in the bromocriptine group. Patient clinical characteristics (age, duration and type of menopause, tumour localization, mean number of tumours per patient) were well balanced between the two treatment arms. More patients in the bromocriptine group entered the trial with no prior treatment. Conversely, more patients in the placebo group received tamoxifen as the first treatment for relapse. The response rate was 37.5% in the placebo group and 38% in the bromocriptine group (NS)

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Table 1. Response to treatment

Response	Placebo	Bromocriptine
Complete response (CR)	4	4
Partial response (PR)	26	23
No change	34	34
Progressive disease	16	10
Total (CR + PR)	30/80 (37.5%)	27/71 (38%) NS

Table 2. Response to treatment as a function of the tumor site

	Placebo	Bromocriptine	
Breast	10/20 (50%)	9/23 (39.1%)	NS
Lymph node	14/28 (50%)	13/23 (56.5%)	NS
Lung	4/20 (20%)	9/18 (50%)	NS
Liver	0/2 (0%)	0/2 (0%)	NS
Bone	9/35 (25.7%)	2/26 (7.7%)	NS
Skin	12/23 (52.2%)	6/10 (60%)	NS

(Table 1). No significant difference was observed whatever the tumour site (Table 2). The delay for maximum response was the same in both groups, respectively for placebo and bromocriptine 3.1 ± 2 and 2.7 ± 1.9 months. The tolerability of the two treatments was good; however, seven patients discontinued their treatment because of side-effects, two in the placebo group (digestive symptoms) and five in the bromocriptine group (digestive symptoms in three patients, vertigo in one and confusional state in one). For three other cases, in the bromocriptine group, treatment had to be modified temporarily and a counteractive treatment had to be proposed because of nausea and vomiting, associated in one patient with vertigo.

DISCUSSION

This trial shows that bromocriptine (5 mg/day) associated with tamoxifen (30 mg/day) does not improve the response rate observed with tamoxifen alone. Given this study design, it is unfortunately not possible to obtain any information on response duration and survival. Another reason for the absence of difference between the two treatment arms may be the lack of compliance by the patients. This cannot be excluded as plasma prolactin was not measured in all patients. A lack of effectiveness due to the absence of PRL-R is possible too since they were not determined. An interaction between tamoxifen and bromocriptine seems unlikely. In our experience bromocriptine, given before surgery, does not modify ER positivity rate at least in postmenopausal patients [7]. We are not aware of any study on PRL-R in patients receiving tamoxifen nor of an interaction between tamoxifen and bromocriptine at the plasma level. The effect of tamoxifen on prolactin levels has been extensively studied and tamoxifen was generally found either to have no effect or to lower prolactin plasma levels [8]. We used 5 mg bromocriptine as it has been shown that this dosage was sufficient to lower prolactin plasma levels in controls. In 58 patients, randomized in the bromocriptine group, prolactin levels were always found in the normal range; in 34 cases they were below the limit of detection of the method. The secretion of prolactin remaining during bromocriptine treatment could be enough to stimulate tumour growth. Another reason why we have not obtained any difference between the two treatments is probably that a total antilactogenic effect could not have been obtained by an antiprolactinic drug used alone. It has been shown that human growth hormone is as lactogenic as human prolactin [9] and it is known that bromocriptine has an effect on growth hormone secretion only in acromegaly. It would be desirable in future to study the effect of an association of an antiprolactin and anti-growth hormone like somatostatin in advanced breast cancer.

A few studies have been published on the effect of antiprolactin drugs in association with other hormonal treatments in advanced breast cancer. Ward [4] gave tamoxifen with levodopa and obtained eight responses out of 19 patients; with carbidopa, he obtained five responses from 13 patients and with bromocriptine three out of 13; this was not a comparative trial and response rates were about the same as those obtained with tamoxifen alone. More recently, Robustelli Della Cuna *et al.* [5] have presented updated results of an Italian trial, comparing bromocriptine (10 mg/day) and medroxyprogesterone acetate (MPA) (1 g i.m./day × 4 weeks and then 500 mg i.m. twice a week) versus the same dose of MPA used alone. Response rates were 43% for MPA and bromocriptine ($n = 51$) and 35% for MPA ($n = 41$). Median durations of response were 8 and 9 months respectively. These results and ours show that bromocriptine, even at high doses [5], cannot improve the response rate of another hormonal treatment in patients with advanced breast cancer.

REFERENCES

1. Bonneterre J, Peyrat JP, Vandewalle B *et al.* Prolactin receptors in human breast cancer. *Eur J Cancer Clin Oncol* 1982, **18**, 1157–1162.
2. Peyrat JP, Djiane J, Bonneterre J *et al.* Stimulation of DNA synthesis by prolactin in human breast tumor explants. Relation to prolactin receptors. *Anticancer Res* 1984, **4**, 257–262.

3. European Breast Cancer Group. Clinical trial of 2-Br-ergocriptine (CB154) in advanced breast cancer. *Eur J Cancer* 1972, **8**, 155–156.
4. Ward HWC. Combined antiprolactin and anti-estrogen therapy for breast cancer. *Clin Oncol* 1977, **3**, 91–95.
5. Robustelli Della Cuna G, Dogliotti L, Di Carlo F. High dose medroxyprogesterone acetate (HD-MPA) vs. HD-MPA + bromocriptine (BR) in metastatic breast cancer; a randomized multicentric clinical trial. 14th Int Cancer Congress, Budapest, 27 August 1986, No. 3391 (abstr).
6. Bonneterre J, Peyrat JP, Beuscart R, Demaille A. Correlation between prolactin receptors (PRL-R), estradiol (ER) and progesterone receptors (PgR) in human breast cancer. *Eur J Cancer Clin Oncol* 1986, **22**, 1331–1336.
7. Peyrat JP, Vennin Ph, Bonneterre J *et al.* Effect of bromocriptine treatment on prolactin and steroid receptor levels in human breast cancer. *Eur J Cancer Clin Oncol* 1984, **20**, 1363–1367.
8. Patterson AG, Turkes A, Groom GV *et al.* The effect of tamoxifen on plasma growth hormone and prolactin in post-menopausal women with advanced breast cancer. *Eur J Cancer Clin Oncol* 1983, **19**, 919–922.
9. Kleinberg DL, Todd J. Evidence that human growth hormone is a potent lactogen in primates. *J Clin Endocrinol Metab* 1980, **51**, 1009–1013.