Research Article
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Possible influence of prolactin secretion on the survival time in untreatable metastatic triple negative breast cancer patients

Abstract

Even though there are controversial results, it has been shown than PRL may act as tumor growth factor in the common breast cancer, whereas it remains to be established the role of PRL in the triple negative breast cancer (TNBC). This preliminary study has been performed in an attempt to evaluate PRL blood levels in a group of metastatic TNBC patients, for whom no other effective therapy was available. The study included 21 consecutive patients. PRL serum levels were measured by the IRMA method. Abnormally high PRL levels were seen in 11/21 (52%) patients. Lymphocyte mean count was significantly higher in patients with normal than in those with high PRL values. The percentage of 1-year survival occurring in normo prolactinemic patients was significantly higher than that achieved in the hyperprolactinemic ones (6/10 vs 2/11, P<0.05). The results of this study would suggest that the evidence of abnormally high blood levels of PRL is associated with a lower survival time in metastatic TNBC patients treated by the only pallative care.

Keywords: breast cancer, hyperprolactinemia, prolactin, triple negative breast cancer

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Introduction

It is known since more than 30 years that the pituitary hormone prolactin (PRL) may stimulate breast cancer development and growth in experimental conditions.[1] In contrast, despite the fact that PRL is one of the first identified endogenous factor involved in the stimulation of mammary tumors, as well as despite the evidence that cancer-related hyper-prolactinemia has been proven to be associated with a poor prognosis,[2–4] very few clinical studies have been performed in an attempt to investigate the possible prognostic significance of PRL secretion in human breast cancer and the influence of the inhibition of PRL secretion on the clinical course of breast tumors, and in particular no clinical study of PRL secretion in breast cancer has been carried during the last 20 years. This evidence would be the consequence of the fact that almost all oncological studies performed in the last 20 years have been substantially limited to the investigation of the only biological and genetic characteristics of the different breast cancer sub-types rather than to concomitantly evaluate the biological response of patients, including their endocrinological and immune status, even though preliminary clinical studies had already suggested that the association of anti-prolactinemic agents, such as bromocriptine and cabergoline, may improve the efficacy of the commonly used oncological therapies for the metastatic breast cancer.[5] In any case, it has to be remarked that the relation between PRL and human breast cancer is very complex, and controversial results have been reported in the literature, particularly in the biologically more aggressive triple negative breast cancer (TNBC), which represents about 20% of human mammary tumors, since either a stimulatory[6] or an inhibitory effect[7] has been reported. TNBC is defined as a breast tumor lacking the expression of ER, PgR and epidermal growth factor-2 (HER2). Particularly controversial are the results concerning the physiopathological and prognostic significance of the expression of PRL-receptor (PRL-R) in breastcancer. In mammary carcinomas other than TNBC, PRL-R expression is generally associated with a less malignancy and a better prognosis,[8] whereas its significance in TNBC has still to be better defined, even though preliminary results would suggest that the evidence of PRL-R expression would prevent the onset of TNBC and would be associated with a more favourable prognosis.[7] In any case, the detection of PRL-R expression could allow a novel sub-classifier of TNBC, consisting of TNBC with positivity for PRL-R expression and TNBC without PRL-R expression, which could constitute quadruple negative breast cancer (QNBC) sub-type, being negative also for PRL-R. Preliminary studies would show that PRL-R expressionis down regulated in TNBC.[7] PRL antagonists have been proven to inhibit breast cancer cell proliferation by inducing the apoptosis,[9] whereas no efficacyhas been referred with PRL-R antagonists.[7] Because of the controversial results about the effects of PRL on TNBC growth in vitro and in experimental conditions,[6,8] further informations may be achieved by investigating PRL secretion in TNBC patients, by correlating its behavior with the clinical course of disease. This preliminary study was performed to evaluate PRL bloodlevels in untreatable metastatic TNBC patients, for whom no other standard anticancer therapies were available, then suitable for the only palliative therapy, in an attempt to identify possible differences in the survival time in relation to PRL blood concentrations.

Patients and methods

The study included 21 consecutive untreatable metastatic TNBC patients (medianage 55 years, range 34-72). Eligibility criteria were, as follows: histologically proven TNBC, metastatic measurable disease, no double tumor, no availability of further standard anticancer therapy. According to the blood levels of PRL, patients were sub-divided into groups, consisting of normo-prolactinemic and hyper-prolectinemic patients. Patients under chronic therapy with anti-dopaminergic agents, corticosteroids, or opioids were not included in the study, because of the potential stimulatory effect of these agents on PRL secretion. The

supportive care was the same in all patients, and it consisted of non-steroid anti-inflammatory agents for pain, corticosteroids and opioids only in the presence of dyspnoea and acute pain, respectively. The clinical characteristics of the two groups of patients are reported in Table 1. For PRL detection, venous blood samples were drawn at 8.00 A.M. after an overnight fast. To exclude possible transient phase of hyper-prolactinemia, venous blood sampling was repeated after 10 days. Serum levels of PRL were measured in duplicate by using an immunoradiometric method (IRMA) and commercially available kits. PRL levels were considered to be within the normal range when they were less than 23 ng/ml (95% confidence limits). Data were reported as mean +/- SE, and statistically analyzed by the chi-square test and the Student's t test, as appropriate.

Results

As shown in Table 1, the two groups of patients with normal or abnormally high PRL levels were well comparable for the main prognostic variables, including dominant metastasis sites, age and performance status (PS). Abnormally high levels of PRL were found in 11/21 (52%) patients, whereas the remaining 10 patients showed normal PRL concentrations. By repeating blood sampling, patients with normal or high PRL levels still persisted to be normoprolactinemic or hyperprolactinemicpatients. After a minimum follow-up of 1 year, the percentage of survival observed in normoprolactinemic patients was significantly higher than that found in the hyper-prolactinemic group (6/10(60%) vs 2/11(18%), P<0.05). From an immune point of view, hyperprolactinemic patients showed a significantly lower lymphocyte mean count that the normoprolactinemic ones(1,946±128 vs 921±287/mm^3, P<0.05), while no difference occurred in monocyte mean count (630±36 vs 557±72/mm^3). Then, lymphocyte-to-monocyte ratio (LMR) observed in normoprolactinemic patients was significantly higher than that found in the group of the hyperprolactinemicpatients(3.2±0.2 vs 1.8±0.3, P < 0.025).

Table1 Clinical characteristics of metastatic TNBC patients in relation to their PRL values

Prl values	Normal prl values	High
N	10	11
Medianage (years)	56 (43-72)	54 (34-70)
Median Performance status (Karnofsky's score)	100 (80-100)	100 (80-100)
Dominant metastasis sites		
- Nodes	2	2
- Bone	1	1
- Lung	2	3
- Liver	3	3
- Brain	2	2

Discussion

The results of this preliminary study would suggest that the evidence of abnormally high PRL blood levels is associated with a reduced survival in untreatable metastatic TNBC. Since the only palliative therapy was given to patients and no other potentially effective anticancer treatment was made, it is probable that the same PRL levels may influence the clinical course of the disease. This finding is not surprising, since most experimental studies have shown a stimulatory role of PRL on breast cancercell proliferation.[1,6] In addition, because of the evidence of significantly lower values of both lymphocyte count and LMR,which has been shown to predict a poor prognosis,[10–12] the more negative prognosis observed in hyperprolactinemic metastatic TNBC patients could depend at least in part on a more severe immunosuppressive status induced by PRL itself, which has been proven to exert immunomodulating effects.[13] Obviously, these preliminary results are not sufficient to justify the use of anti-prolactinemic agents in metastatic TNBC, because of the controversial results reported in the literature,[6,9] since PRL has been shown to either promote, or counteract the generation and growth of TNBC. In particular, there is an apparente opposite prognostic significance between PRL-R expression and PRL blood levels in TNBC patients, since while PRL-R expression would predict a better prognosis, metastatic TNBC-related hyperprolactienemia would be associated with a poor prognosis and a lower survival. This controversial result could be only apparent, since PRL-R expression may simply reflect a major biological differentiation on the basis of the fact that normal breast cancer cells normally express PRL-R,[14] whereas PRL itself could directlystimulate cancer cell proliferation.[1] Moreover, other endocrine and neuroendocrine receptors could be involved in determing the prognosis of the TNBC. In particular, the expression of the receptor for the antitumor pineal hormone melatonin (MLT),[15] as well that for cannabinoid agonists,[16] have been proven to be associated with a more favourable prognosis in the TNBC. In any case, if the negative prognostic significance of metastatic TNBC-related hyperprolactinemia will be confirmed in a greater number of patients, because of their low cost and lack of important toxicity, the anti-prolactinemic agents, such as bromocriptine and cabergoline, could be investigated in the treatment of metastatic TNBC patients, for whom no other standard effective therapy is available, at least in patients with abnormally high blood levels of PRL, either alone, or in association with other potentially anticancer natural agents, such as cannabinoid agonists[17] and the pineal hormone MLT.[18]

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Conflict of interest

The author declares there is no conflict of interest.

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