A phase-2 study of high-dose pineal antitumor hormone melatonin as an adjuvant therapy in triple negative breast cancer.

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Abstract

It is known that triple negative breast cancer (TNBC) is the most prognostically negative mammary tumor, because of its lack of sensitivity to the main growth factors for breast cancer, including estrogens and EGF. However, at least three other hormones would have to be considered, consisting of prolactin (PRL), oxytocin (OT), and the pineal hormone melatonin (MLT). PRL would stimulate TNBC growth, whereas MLT and OT would play an inhibitory action in several tumor histotypes, including TNBC, even though at present only clinical studies with MLT have been performed, by demonstrating that it's in human anticancer activity is a dose-dependent phenomenon. On these bases, a study was planned to evaluate the effects of high-dose MLT chronic administration as an adjuvant therapy on the percent of 3-year progression-free period (PSF) in TNBC after adjuvant chemotherapy. The study included 14 consecutive TNBC patients, who were treated with MLT at 40 mg/day orally in the evening every day without interruption, by comparing the results to those observed in a control group of 16 TNBC patients with comparable clinical characteristics. The 3-year PFS percentage achieved in MLT group was significantly higher than that found in the control group, either in patients with or without node involvement. No MLT-related biological toxicity occurred. On the contrary, most patients referred a mood improvement. These preliminary results justify further randomized study with or without high-dose MLT in TNBC patients, in an attempt to prolong their survival.

Keywords: Breast cancer, Melatonin, Pineal gland, Prolactin, Triple negative breast cancer.

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Introduction

Until few years ago, the endocrine oncological researches have been mainly performed in an attempt to identify possible hormones and growth factors involved in the stimulation of tumor growth, including estrogens for breast cancer and endometrial adenocarcinoma, androgens for prostate cancer, prolactin (PRL) PRL for breast and prostate tumors, and EGF and GH for several tumor histotypes. However, in the last years it has been identified also the existence of endogenous hormones provided by antitumor activity, namely oxytocin (OT) [1] and the pineal hormone melatonin (MLT) [2]. Moreover, it is known that the classical endocrine therapy of breast cancer has no efficacy in triple negative breast cancer (TNBC) because of its lack of sensitivity to hormonal stimulation. On the same way, anti-HER-2 monoclonal antibodies have no therapeutic activity in TNBC [3]. However, it has to be remarked that at least three other hormones would have to be taken into consideration because of their involvement in the control of breast growth, including PRL, OT and the pineal hormone MLT, which have been proven to exert opposite effects, consisting of a stimulatory effect of PRL [4] and an inhibitory action of OT and MLT on breast cancer cell proliferation, including that of TNBC [5]. In more detail, the effects of PRL on TNBC growth are yet controversial, since some authors have also reported an inhibitory action of PRL on TNBC growth [6]. On the same way, the biological and prognostic significance of PRL receptor (PRL-R) expression in TNBC is still unclear, even though most studies have shown that PRL-R expression may be associated with a more biological malignancy [4,6]. Cannabinoid agents have also appeared to inhibit the growth of TNBC expressing cannabinoid receptors [7]. The anticancer effect of OT is still only experimental evidence. On the contrary, all experimental and clinical studies performed up to now have constantly demonstrated the inhibitory activity of the pineal hormone MLT on several tumor histotypes, including breast tumors, including the TNBC. Moreover, it has been shown that tumor expression of MLT receptor (MT-R) may predict a less malignancy and a more favourable prognosis in terms of both response to therapy and survival times [5], even though the antitumor action of MLT is at least in part independent from MT-R expression [8]. The antitumor mechanisms of MLT are multiple and complex [9,10], and however, they include a direct cytotoxic antiproliferative action, a cell differentiating effect, an anti-angiogenic activity, an immuno stimulatory action on the anticancer immunity, namely consisting of stimulation of TH1 lymphocytes (TH1) and dendritic cells, with a consequent enhanced production of the two main antitumor cytokines in humans, consisting of IL-2 and IL-12, respectively [11,12]. Then, MLT would constitute at present the only natural molecule potentially able to counteract the overall phases responsible for cancer progression. Moreover, MLT is the only molecule, which has shown no lethal dose, because of the down-regulation of MT-R exerted by the normal cells, whereas tumor cells are unable to modulate MT-R expression,

then there are exposed to the cytotoxic action of MLT in a dose-dependent manner [13]. On these biological bases, as well as by considering the complete lack of toxicity by MLT, an experimental clinical study was performed in an attempt to evaluate the influence of an adjuvant endocrine therapy with high-dose MLT on 3-year progression-free survival (PFS) in a group of non-metastatic TNBC women after the classical adjuvant chemotherapy.

Patients and Methods

The phase-2 study included 14 consecutive non-metastatic TNBC women (median age 53 years, range 28-68). Eligibility criteria were, as follows: histologically proven TNBC other than the apocrine tumor, measurable lesions, no metastatic location, no double tumor, and previous adjuvant chemotherapy. The experimental protocol after approvation of the Ethical Committee was explained to each patient, and written consent was obtained. Depending on the different oncological Institutions, the adjuvant chemotherapy was consisted of carboplatin plus gemcitabine in 8, carboplatin plus taxolin 4, and 5-fluorouracil, epirubicin and cyclophosphamide in the remaining 2 patients. MLT was given orally at a dose of 40 mg/day during the dark period of the day according to its physiological light/dark circadian rhythm [6]. If we consider that the physiological daily endogenous production of MLT is less than 2 mg, a dosage of 40 mg/day may be retained as a mild pharmacological schedule. MLT was administered every day without interruption until disease recurrence. Patients were monitored for a minimum follow of 3 years. The results were compared with those observed in a control group of 16 non-metastatic TNBC women, who had also received the adjuvant chemotherapy. Data were statistically analyzed by the chi-square test. Moreover, the PFS curves were calculated according to Kaplan Meir method, and analyzed by the log-rank method.

Result

Table 1 shows the clinical characteristics of TNBC women and the 3-year PFS percentage in MLT group and in controls. The two groups of patients were well comparable for the main biological characteristics, including age, menopause status, node involvement and type of adjuvant chemotherapy. The 3-year percentage of PFS achieved in MLT group was significantly higher than that found in the control group, who did not received MLT (10/14 (71%) *vs.* 6/16 (37%), $P<0.05$). The percentage of relapse found in MLT group was significantly lower than that occurring in the control group (4/14 (29%) *vs.* 10/16 (63%), $P<0.05$). The percentage of recurrence was lower in MLT group than in controls also in relation to node involvement (node involvement: 1/6 (17%) *vs.* 3/7 (43%); node involvement: 3/8 (38%) *vs.* 7/9 (78%), $P<0.05$). On the contrary, no significant difference occurred between visceral and non-visceral sites of relapse (visceral recurrence: 3/4 (75%) *vs.* 7/10 (70%). However, the percentage of brain recurrence observed in MLT group was lower than that found in controls (1/14 (7%) *vs.* 3/16 (19%), even though the difference was not statistically significant. Finally the 3-year PFS achieved in MLT group was significantly longer that that found in the control groups ($P<0.05$). No MLT-related toxicity occurred. On the contrary, most patients referred a mood improvement and a more regular sleep quality.

Table 1. *Clinical characteristics of TNBC patients and 3-year progression-free survival (PFS) in MLT group and in controls.*

Characteristics	MLT Group(n=14)	Control Group (n=16)
Median age (years)	53 (28-68)	55 (34-70)
Node involvement	8/14 (57%)	9/16 (56%)
Adjuvant chemotherapy Carboplatin-Gemcitabine Carboplatintaxol FEC	8 4 2	8 5 3
Recurrence ratio Sites of relapse Node Bone Lung Liver Brain	4/14 (29%) ---------- 1 0 1 1 1	10/16 (63%) *P<0.05 ---------- 2 1 1 3 3

Discussion

The results of this preliminary study would seem to *in vivo* confirm the antitumor properties of the pineal hormone MLT also against the TNBC, as suggested by the lower percentage of recurrence in patients chronically treated by MLT as a potential endocrine adjuvant therapy of TNBC. Obviously, further studies in a greater number of patients and with a longer follow up period will be required to confirm the potential efficacy of MLT as an adjuvant endocrine therapy of TNBC. In any case, by also considering the complete lack of MLT toxicity, the results of this study would be already sufficiently promising to justify a randomized study with or without MLT, either alone or in association to the classical adjuvant chemotherapy in the treatment of TNBC women. The typical cancer endocrine therapies on the basis of their action mechanisms are in the reality anti-endocrine treatments, since their action consists of blocking the activity of potential protumoral hormones, such as estrogens for breast cancer and androgens for prostate cancer. On the contrary, the endocrine therapy of MLT, as well that with somatostatin for somatostatin receptor expressing neuroendocrine tumors [14], would represent a direct antiproliferative endocrine therapy of cancer. More predictive clinical information concerning the possible efficacy of MLT as a possible adjuvant endocrine therapy for TNBC may be drawn from the immunochemistry detection of MT-R expression on TNBC cells, since MT-R tumor expression would predict a greater efficacy of MLT itself. Finally, because of the dose-dependency of the antitumor activity of MLT [13], more promising results in reducing the percentage of recurrence in TNBC women could be achieved by a greater dosage of MLT, which has been proven to have no lethal dose [9-12].

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