Bone metastasis in breast cancer is treated by high-dose tamoxifen
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Summary

Purpose: Bone metastases in breast cancer are quite common, and some patients may have no other site of metastasis. An effective treatment is often endocrine agents administration (tamoxifen or antiaromatases), given mainly to postmenopausal women. Radiation treatment is also effective, although difficult to perform in cases of extensive skeletal disease. Chemotherapy does not help.

The purpose of this study was to investigate the effectiveness of high-dose tamoxifen in female patients with breast cancer and bone metastasis.

Methods: 28 patients with breast cancer were treated with high-dose tamoxifen. All of them had been pretreated with hormonal therapy including low-dose tamoxifen.

Results: The results were extremely positive with clinical amelioration and also disappearance of osteolysis in some patients. Twenty six out of 28 patients responded to the treatment, the criteria being mainly pain reduction and body mobilization (an amelioration which lasted 8 months-4 years).

Conclusion: Tamoxifen is efficient when readministered at high dose to breast cancer patient with bone metastasis.

Key words: breast cancer, bone metastasis, high-dose tamoxifen

Introduction

High-dose tamoxifen has been investigated in several trials with doses over 100 mg/m² [1,2] or even higher than 500 mg m² [3,4], but not administered long-term.

The dose of tamoxifen in breast cancer patients has been established to be 20 mg daily. In the past, 30 or 40 mg were used but not continued as long-term administration was suspected to be involved in the development of uterine cancer.

High-dose tamoxifen (200 mg daily) was used for the treatment of recurrent malignant gliomas in order to achieve levels sufficient to inhibit protein kinase C within the tumor cells. A response was reported in 8 patients (25%,4/12) with anaplastic astrocytoma and 4/20 (20%) with glioblastoma [1]. In another published study, high-dose tamoxifen was also given to a small number of patients with malignant gliomas with reported improvement in 3/11 patients [2]. Hepatocellular carcinoma was also treated by high-dose (120 mg per day) tamoxifen in a multicenter randomized controlled trial; it was not found to prolong survival [3]. A phase II study of high-dose (160 mg/m²) tamoxifen was used for patients with hormone-refractory prostate cancer. In 30 patients, one (3.3%) partial response was observed and in 6 (20%) stable disease. Although rapidly reversible grade 3 neurotoxicity was observed in 29% of the patients, other grade 3 toxicities were rare [4]. High-dose tamoxifen was also used in other malignancies such as leukemia and epithelial tumors [5,6].

Breast cancer is a malignancy where endocrine agents are a common, very important and effective treatment. Tamoxifen, at a low dose of 20 mg/day, is one of the endocrine agents commonly administered.

Two previous studies tested a higher dose of tamoxifen in post-menopausal women with advanced breast cancer. One of these studies showed that 20-40 mg of tamoxifen, administered daily in...
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patients with bone disease resulted only in disease stabilization; an increase of the dose to 90 mg daily resulted in partial remission in 2 (7.14%) patients [7]. The second study used tamoxifen 20-40 mg daily in advanced breast cancer with partial response rate of 19.8% [8].

Bone metastases in breast cancer are quite common, and some patients may have no other site of metastasis [9]. An effective treatment is often administration of endocrine agents (tamoxifen or antiaromatases), given mainly to postmenopausal women. Radiation treatment is also effective, although difficult to perform in cases of extensive skeletal disease. When endocrine treatment is ineffective, patients may benefit temporarily from radiation therapy [10]. Chemotherapy does not help.

The purpose of this trial was to investigate the effectiveness of high-dose tamoxifen in female patients with breast cancer and bone metastasis.

Methods

All patients included in the present trial had bone metastases alone and had undergone prior endocrine treatment including low-dose tamoxifen (20 mg) and radiotherapy. Some patients were also given bisphosphonates (either pamidronate or zoledronic acid). On examination, patients showed deterioration of clinical symptoms (pain, fatigue, anorexia). Bone scans were preformed 3 and 8 months after the beginning of treatment.

Treatment

Tamoxifen was administered as monotherapy. The initial dose was 100 mg (5 tablets x 20 mg) daily for two weeks. During this two-week period, pain reduction was the main criterion for determining a response and for treatment continuation. After these two weeks, if there was a response in pain, the dose of tamoxifen was reduced to 80 mg daily for an additional three weeks, followed by 60 mg for 3 weeks and then 40 mg daily for at least two months and eventually 20 mg daily for 1-2 years.

Results

Twenty six out of 28 patients (median age 66 years, range 29-83), were postmenopausal and were included in the study. No patient had metastatic disease in other organs apart from the skeleton. Twenty six out of 28 (92.8%) patients responded to treatment, the criteria being mainly pain reduction, and body mobilization (an amelioration which lasted 8 months-4 years). In 15 patients on treatment for over a year a bone scan showed disappearance of osteolysis of a single bone metastasis (Figures 1 and 2). Four patients who had disease recurrence with pain after 12-18 months, repeated the high-dose tamoxifen treatment with positive results (pain reduction).

Toxicity

No side effects whatsoever were observed provided that the tamoxifen dose was higher than 40 mg daily. The patients’ quality of life improved substantially with the patients resuming almost normal daily activities.

Discussion

To explain the effectiveness of this treatment, we quote from a manuscript published in the New England Journal of Medicine in 1992: “In postmenopausal women, the treatment with tamoxifen is associated with preservation of the bone mineral density of the spine [11].” Similar data have also been reported by other authors [12]. The high dosage of tamoxifen does increase its effectiveness in patients with bone disease. In the aforementioned published trial [11], in women given tamoxifen (even at a low dose) the mean density of the lumbar spine increased by 0.61% per year, whereas in those given a placebo, it decreased by 1.00% per year (p<0.001).
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In vitro studies and studies on animals have shown that the effects of tamoxifen on the bone resemble those of estrogen. Tamoxifen reduces bone resorption and turnover, it stimulates bone formation, and it prevents bone loss after oophorectomy [12-16]. There is some evidence of the preservation of, or increase in bone density. Tamoxifen is not a pure antiestrogen, since it has some estrogen-agonist properties. In particular, does tamoxifen have an antiestrogenic effect on the skeleton and does it minimize bone loss or not [17]. Clinical trials on high-dose tamoxifen (100 mg) especially to treat breast cancer with bone metastases alone have not been reported in the literature. Our data indicate that tamoxifen minimizes bone loss, as it is reported in other studies [18-20].

Conflict of interests
The authors declare no conflict of interests.

References