

SHORT COMMUNICATION

High-dose tamoxifen in breast cancer bone metastasis

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Summary

High-dose tamoxifen was used as a treatment for bone metastasis in 16 patients with breast cancer. All of them had been pretreated with hormonal therapy, including low-dose tamoxifen. The results were extremely positive with

clinical amelioration and also disappearance of osteolysis in 5 patients.

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

Introduction

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 as a strong causative factor in the development of uterine cancer. 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.

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) patients with anaplastic astrocytoma and 4/20 (20%) with glioblastoma multiforme [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 tamoxifen (160 mg/m²) 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 toxic-

ities 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 daily, is one of the endocrine agents commonly administered.

Two past 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 to patients with bone metastases resulted only in disease stabilisation; an increase of the dose to 90 mg daily resulted in a 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. 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. When endocrine treatment is ineffective, patients may benefit temporarily from radiation therapy. 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 biphosphonates (either pamidronate or zoledronic acid). On examination, patients showed deterioration of clinical symptoms (pain, fatigue, anorexia). Bone scans were performed 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 2 weeks. During this 2-week period, pain reduction was the main criterion for determining a response and for treatment continuation. After these 2 weeks, if there was a response in pain, the dose of tamoxifen was reduced to 80 mg daily for an additional 3 weeks, followed by 60 mg for 3 weeks and then 40 mg daily for at least 2 months and eventually 20 mg daily for 1-2 years.

Results

Sixteen patients (median age 66 years, range 29-83), all postmenopausal except one, were recruited. No patient had metastatic disease in other organs apart from the skeleton.

Fifteen out of 16 (93.75%) patients responded to the treatment, the criteria being mainly pain reduction and body mobilization (an amelioration which lasted from 8 months to 4 years). On CT scan, 5 patients on treatment for over a year showed disappearance of osteolysis of a single bone metastasis. Four patients who had disease recurrence with pain after 12-18 months, repeated the high-dose tamoxifen treatment with positive result.

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 placebo it decreased by 1.00% per year ($p < 0.001$).

In vitro studies and studies on animals have shown that the effects of tamoxifen on the bone, resemble those of estrogens. Tamoxifen reduces resorption and turnover and stimulates bone formation, and prevents bone loss after oophorectomy [12-16]. There is some evidence of 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 with 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 presented in other studies [18-20].

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