Mini Symposium: Breast Cancer

# What is the best treatment option in postmenopausal, hormone responsive breast cancer patients with isolated bone metastases?

**Turanli S, Oksuzoglu B[1], Bulak H, Cetin A**

Department of General Surgery and [1]Medical Oncology, Ankara Oncology Education and Research Hospital, Demetevler/Ankara Turkey

**Correspondence to:** Dr. Sevim Turanli, E-mail: turanlisevim@hotmail.com

## Abstract

**BACKGROUND:** Bone is the most common metastatic site for breast cancer. **AIM:** To determine the effectiveness of addition of chemotherapy to hormonal therapy in postmenopausal hormone receptor-positive breast cancer patients with isolated bone metastases. **MATERIALS AND METHODS:** Between June 2001 and January 2007, 101 patients were classified into two groups according to initial treatment modalities; patients who received hormonotherapy only (group I) and chemotherapy followed by hormonotherapy (group II). The effect of treatment choice on clinical course, time to progression, and overall survival were evaluated. **RESULTS:** There were 70 patients in group I and 31 patients in group II. Bone metastases in 27 patients (26.7%) were synchronous and the remainder were metachronous. The median follow-up time was 41 months. The two groups showed similar results when patients' tumor characteristics were compared. However, 81% of synchronous cases had upfront chemotherapy following hormonotherapy, whereas this ratio was only 12% in the metachronous group. All patients received systemic antiresorptive bisphosphonates whereas only 24 patients required palliative radiotherapy at some time during the course of their disease. In groups I and II, the median time to progression was 12 and 16 months (*P*: 0.96) and median overall survival was 41 and 40 months (*P*: 0.79), respectively. In HER-2-positive patients, a trend of prolongation of overall survival was observed in group II, but it was not statistically significant (*P*: 0.12). **Conclusions:** Anti-hormonal therapy still seems to be considered as the ideal treatment of choice for postmenapousal breast cancer patients with isolated bone metastases.

**Key words:** Bone metastasis, breast carcinoma, chemotherapy, hormonotherapy, treatment

## Introduction

Bone is the most common metastatic site for breast cancer, and bone metastases develop in 65–75% of patients with metastatic breast cancer.[1] The treatment modalities consist of chemotherapy, hormonal therapy, radiotherapy, orthopedic surgery, and analgesics. Besides, a new approach for the treatment of the metastases is bone-targeted therapy.

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In metastatic setting, patient-related factors (menopausal status, biological age, comorbidities, performance status, adverse effects of prior therapy, socioeconomic and psychological factors, patients preference, and available therapies in the patient's country) and disease-related factors (endocrine responsiveness, human epidermal growth factor receptor 2 (HER-2) status, disease free interval, previous therapies and response obtained, metastatic tumor localization and the number of the metastatic site, need for treatment of rapidly progressive disease, and/or symptom control) affect the choice of treatment modalities.[2,3]

The aim of this study is to determine whether postmenopausal hormone receptor-positive breast cancer patients with isolated bone metastases should initially receive hormonal therapy or whether they might benefit from the addition of chemotherapy.

## Materials and Methods

### Ethical consideration

The data was collected retrospectively and approved by our instutional ethical committee.

### Study population

Between June 2001 and January 2007, the data of the 101 consecutive postmenopausal patients who were diagnosed as hormone receptor positive (estrogen receptor (ER), and/or progesterone receptor (PR)) breast carcinoma with isolated bone metastases at Ankara Oncology Education and Research Hospital were reviewed. None of the patients had synchronous second primary cancer. The median age was 53 (range: 23–81 years). Patients were grouped into two groups according to initial treatment modalities: group I, the patients who received hormonotherapy only (*n*: 70, 69.3%), and group II, the patients who received upfront chemotherapy followed by hormonotherapy (*n*: 31, 30.7%). Twenty-seven patients (26.7%) were found to have isolated bone metastases at the time of or within 6 months after breast cancer diagnosis (synchronous), and the remaining bone metastases developed in the patients only after 6 months of breast cancer surgery (metachronous metastasis).

### Diagnosis of bone metastases and definition of receptor status

All the patients who were diagnosed as breast cancer had been routinely examined with chest X-ray, abdominal ultrasound, and bone scintigraphy. Some of the patients with suspected bone metastasis were further evaluated with magnetic resonance imaging. Bone metastasis had been diagnosed by imaging modalities. Histopathological bone examination had been done only in selected cases with pathological bone fractures. The status of ER, PR, and HER-2/neu proteins were examined by immunohistochemistry. Estrogen and progesterone receptor status were categorized as positive when ≥10% of tumor cells expressed estrogen or progesterone receptor staining. HER-2/neu protein expression was evaluated by immunohistochemistry on a staining pattern (0, 1+, 2+, and 3+) and 3+ values were accepted as positive. Furthermore HER-2/neu 2+ was accepted as positive if fluorescence *in situ* hybridization or silver-enhanced *in situ* hybridization was positive.

### Follow-up procedure and definition of disease progression

Up to 24 months, tumor response was assessed at baseline every 3 months, and every 6 months thereafter, or until progressive disease. The usual follow-up procedure after the detection of bone metastases at our hospital primarily included physical examination, and laboratory tests, including complete blood count, biochemical tests including calcium, alkaline *phosphatase*, renal and liver function tests, tumor marker (CA 15-3), chest X-ray, breast ultrasonography, and mammography. Bone sintigraphy, magnetic resonance imaging, and positron emission tomography scan were used in selected patients. Progression was defined according to revised Response Evaluation Criteria In Solid Tumors guideline.[4] A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline was considered as a new lesion and indicated disease progression.

### Compared factors

The groups were examined and compared according to the age of metastatic patients, the development time of bone metastases, ER, PR, and HER-2 receptors status. The effect of treatment choice on clinical course, time to progression, and overall survival were evaluated as well.

### Statistical analyses

Patients' and tumor characteristics and trastuzumab availability were compared in the groups by using the chi-square test or Fisher's exact test. The difference in age between the two groups was tested by using the *t* test. Survival was defined as the length of time from the diagnosis of isolated bone metastases till death or last follow-up. Kaplan–Meier curves for overall survival and time to progression were estimated by the systemic therapy and Her-2 status, and compared using the log rank test. These analyses were used to calculate the hazard ratios and 95% confidence intervals (CI). $P$ values $< 0.05$ were considered as statistically significant. All analyses were done with SPSS software (version 16.0; SPSS Inc, Chicago, IL).

## Results

There were 70 patients treated with hormonotherapy (group I) and 31 patients treated with chemotherapy followed by hormonotherapy (group II). The bone metastases in 27 patients (26.7%) were synchronous and the metachronous in 74 patients. Metachronous bone metastases developed at a median of 35.5 months (range; 9–187 months) after surgery for the primary tumor.

According to histopathology, there were 86 patients (85.1%) diagnosed as invasive ductal carcinoma, 13 (12.9%) as invasive lobular carcinoma, 1 (1%) as invasive ductal carcinoma, and 1 (1%) as mucinous carcinoma. Histopathological bone examination was evident only for five patients who had pathological bone fractures. Twenty-four (23.8%) of 101 patients had ER (+) only, 7 (6.9%) had PR (+) only, and 52 (51.5%)

had both ER (+) and PR (+). Eighteen (17.8%) patients had ER (+) but PR was unknown. HER2-neu was positive, negative, and unknown in 20.8%, 62.4%, and 16.8 % of the patients, respectively. The groups and the comparison results are shown in Table 1. The time of diagnosis of bone metastases affected the choice of treatment ($P$ = 0.001). Twenty-two of 27 (81%) synchronous cases had chemotherapy following hormonotherapy, whereas this ratio was only 12% (9/74 patients) in the metachronous group.

### Systemic treatment before and after the bone metastases

Seventy-four breast carcinoma patients with metachronous bone metastases had previously received hormonal and/or cytotoxic therapy after breast surgery on an adjuvant basis. Only six patients (8.1%) received adjuvant tamoxifen alone as hormonal therapy. The remainder received adjuvant chemotherapy followed by tamoxifen. The preferred adjuvant systemic chemotherapy were as follows: cyclophosphamide, methotrexate, and fluorouracil (CMF) in 14 patients; cyclophosphamide, doxorubicin, and 5-fluorouracil (FAC) in 39 patients and anthracycline and taxane-containing regimens in 15 patients. Systemic hormonal and/or cytotoxic therapy was given for the patients after the diagnosis of bone metastases. There were 70 patients treated with hormonotherapy (group I) and 31 patients treated with chemotherapy followed by hormonotherapy (group II).

Thirty-five out of 101 patients received tamoxifen and 66 patients (65.3%) received aromatase inhibitors. In patients who had chemotherapy followed by hormonal therapy (group II), 10 out of 31 received anthracycline-based chemotherapy, 18 patients received anthracycline and taxane-containing regimens and the remainder received taxane-containing regimen. Only two of the HER-2/neu gene amplification-positive patients received trastuzumab as the first line.

All patients received systemic bisphosphonates. Eighty patients (79.3%) were given intravenous monthly zoledronic acid and the remainder were given 1600 mg/day oral clodranate.

**Table 1: Comparison criteria between the groups of postmenopausal breast cancer patients with isolated bone metastasis**

| | | Group I 70 ptsn (%) | Group II 31 ptsn (%) | *P* |
|---|---|---|---|---|
| The age of metastatic patients (mean ± SD) | | 53.4 ± 13.2 | 53.6 ± 10.60 | 0.92 |
| Development time of bone metastases | Synchronous | 5 (7.1) | 22 (71.0) | 0.001 |
| | Metachronous | 65 (92.9) | 9 (29.0) | |
| ER, PR status | Only ER (+) | 17 (24.3) | 7 (22.5) | 0.19 |
| | Only PR (+) | 5 (7.1) | 2 (6.5) | |
| | ER (+), PR (+) | 32 (45.7) | 20 (64.5) | |
| | ER (+), PR (Unknown) | 16 (22.9) | 2 (6.5) | |
| HER-2/neu | (-) | 42 (60.0) | 21 (67.7) | 0.44 |
| | (+) | 14 (20.0) | 7 (22.6) | |
| | Unknown | 14 (20.0) | 3 (9.7) | |

Group I: Patients who received palliative hormonotherapy. Group II: Patients who received palliative chemotherapy followed by hormonotherapy

### Survival analyses

When the data collection was completed in December 2010, the patients were followed-up with a median of 41 months (range; 8–123 months). Clinical or radiological progression was observed in 65 out of 70 patients (92.9%) in group I and in 37 patients (100.0%) in group II, and there was no statistically difference between the groups ($P$ = 0.35). Bone was the most common site of progression (72.3%). While local recurrence in the breast tissue developed in 9 patients, visceral involvement was observed in 35 patients. In progressive setting, a variety of cytotoxic agents, hormonotherapy, and trastuzumab were used. Seven out of 14 patients in group I and 6 out of 7 patients in group II received 2$^{nd}$ or 3$^{rd}$ line trastuzumab therapy (13 out of 21 patients having HER-2 overexpression were given palliative trastuzumab in this series). Twenty-four patients required palliative radiotherapy at some time during the course of their disease.

At the end of the study period, 17 patients (24.3%) in group I and 9 patients in group II (29.0%) were still alive ($P$ = 0.61). The groups were compared for time to progression and overall survival [Figures 1 and 2]. Time to progression was 12 months (95% CI: 10–14 months) and 16 months (95% CI: 13–19 months), ($P$: 0.96) and median overall survival was 41 months (95% CI: 34–48 months) and 40 months (95% CI: 21–59 months), ($P$ = 0.79) in groups I and II, respectively.

Subgroup analysis was carried out in HER-2-positive patients. The outcomes are shown in Figures 3 and 4. The median time to progression was 15 months (95% CI: 6–24 months) and 16 months (95% CI: 6–26 months) and overall survival was 29 months (95% CI: 16–41 months) and 38 months (95% CI: 9–66 months), in groups I and II, respectively. Although, a trend on prolongation of overall survival was observed in group II, time to progression and overall survival were similar in HER-2-positive patients regardless of the treatment they received ($P$ = 0.75 and $P$ = 0.12, respectively).

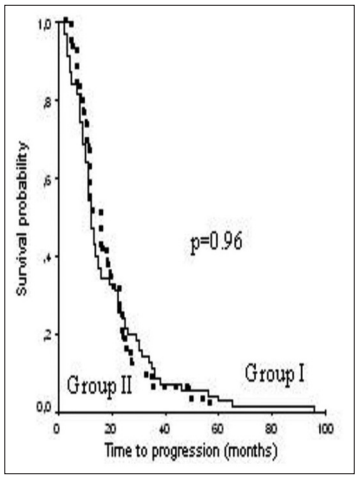


**Figure 1: After the diagnosis of bone metastasis, the effect of treatment options on time to progression**

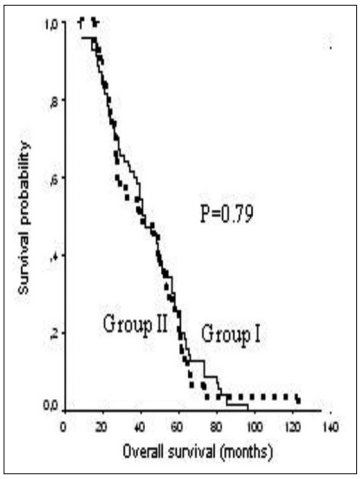


**Figure 2: After the diagnosis of bone metastasis the effect of treatment options on overall survival**

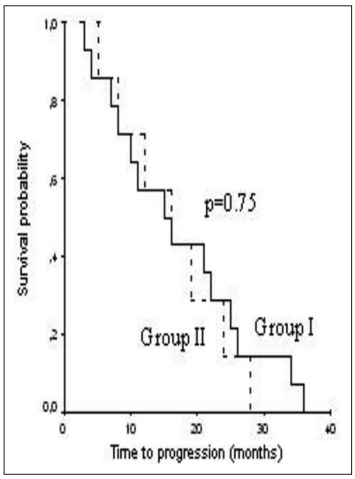


**Figure 3: The effect of treatment options on time to progression in HER-2 receptor-positive patient subgroup**

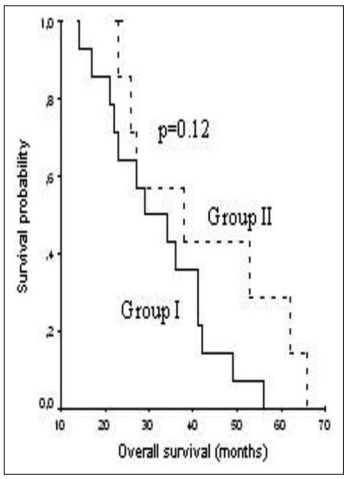


**Figure 4: The effect of treatment options on overall survival in HER-2 receptor-positive patient subgroup**

## Discussion

The aims of the treatment of metastatic breast cancer are to improve quality of life and to prolong survival with a treatment regimen that balances efficacy and toxicity. Most factors influence treatment decision, including patients' and tumors' characteristics, previous treatment, and tumor burden.

A number of new and effective agents are available. Clinical investigations have been progressing on clarifying the roles of endocrine therapy, chemotherapy, and biologic therapy in metastatic setting. In the management of ER-positive, advanced breast cancer, conventional wisdom dictates the use of endocrine therapy for patients with good prognostic features, whereas chemotherapy is recommended for the treatment of visceral crisis.[5] The patients with visceral crisis, frequently defined as the presence of lymphangitic lung metastases, bone marrow involvement, carcinomatous meningitis, or significant liver metastases, are recommended to be treated with chemotherapy, even in the case of ER-positive disease for rapid response.[6-8] In addition to the reported literature, guidelines may not always dictate the routine practical decisions in clinics. In this study, we have seen that in hormone responsive breast carcinoma patients who was admitted to the clinics with bone metastasis (synchronous cases), the approach is more aggressive including chemotherapy (81% of synchronous cases). In this study, development time of bone metastases was found to affect the choice of treatment. This may be related to difficulties in predicting the natural course of disease and limited knowledge in those selected subgroup of patients. Besides that, about 72% of the patients with metachronous bone metastasis (group II) had received adjuvant chemotherapy previously. This may be the reason of choosing palliative hormonotherapy as the first line of treatment in 88% of the cases.

In the whole cohort, HER-2 was positive in approximately 20% of the cases which was compatible with the literature.[9-11] HER-2 positivity was associated with a significant risk of endocrine therapy failure.[9] Endocrine responsive tumors overexpressing HER-2 require the blockage of the HER-2 pathway in addition to estrogen deprivation. Combination of trastuzumab with anastrozole in this subset of triple-positive metastatic breast cancer led to doubling of progression- free survival and significant improvements in clinical benefit rate, time to progression, and overall risk ratio compared to treatment with anastrozole alone.[11] Phase III trials of first-line trastuzumab with various chemotherapy regimens compared to chemotherapy alone demonstrated a significant improvement in survival.[12-14] On the other hand, other studies demonstrated that single agent trastuzumab was active and an important treatment option in HER-2-positive metastatic breast cancer after progression on chemotherapy. [15,16] Combination chemotherapy with anti-HER-2 therapy should be the first-line treatment option in patients with good performance status, visceral crisis, or rapidly progressive disease in patients with HER-2/ hormone receptor co-positive cases. Patients with poor performance status, slowly progressive tumors, and non-visceral disease who did not receive previous endocrine treatment could be considered for up-front treatment with first-line hormonal therapy in combination with anti-HER-2 therapy.[10] In our study, 13 over 21 (61.9%) HER-2 (+) patients had the chance of having trastuzumab on progression. The median time to progression was 15 months and 16 months and overall survival was 29 months and 38 months, in groups I and II, respectively. When HER-2-positive patients who received palliative chemotherapy followed by hormonotherapy compared with HER-2-positive patients who received palliative hormonotherapy alone, prolongation of overall survival trend was observed in the former group. For patients with HER-2 negative hormone positive breast cancer endocrine therapy was considered for the treatment of choice.

Also, bone-targeted therapy for metastatic breast cancer is under investigation. Bisphosphonates reduces the risk of skeletal-related events and skeletal morbidity rate, while increasing the time of first skeletal-related events.[17] Adjuvant bisphosphonate treatments, especially zoledronic acid, may have antitumor effects that both prevent and treat bone metastasis, as well as improving survival.[18] In this series, all the patients received bisphosphonates. Denosumab is one of the principal regulators of osteoclast differentiation, function, and survival.[19] In addition to denosumab, Src kinase inhibitors are promising agents under development for the treatment of bone metastases from breast cancer; however, none of the patients of this study had such a treatment option.

Although new chemotheurapeutic agents have been arising in the market, anti-hormonal therapy still seems to be considered as the ideal treatment of choice for postmenapousal breast cancer patients with isolated bone metastases.

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