

Breast cancer with bone metastasis in south of Tunisia: retrospective review of 225 cases

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Abstract

The aim of our study was to expose clinical characteristics, prognostic factors and outcome of breast cancer bone metastasis. We conducted a retrospective study concerning 332 cases of metastatic breast cancer treated between January 2000 and December 2007. We reviewed patients' clinical records, therapeutic modalities and survival duration.

In our series, bone metastases were the most common metastatic site (67, 7%); they were isolated (with no visceral metastases) in 54% of cases. Spine, ribs and pelvis were more frequently involved with respectively 66%, 31% and 30% of cases. Bony pain was the most frequent symptom (63% of cases), followed by spinal cord compression and pathologic fractures. All patients received systemic anti cancer treatment (chemotherapy and or hormone therapy) associated to Biphosphonates in 41% of cases. Surgery was performed in 8 patients and 78 patients received radiotherapy (52%). Patients with only bone metastases had 23% five-year survival while it was 4% in those with other visceral metastases. Bone metastatic disease in less than 3 sites and loco regional treatment including surgery and/or radiotherapy were associated to a significant better survival rate. Clinical characteristics of breast cancer bone metastasis were not particular in our patients. Survival rate was similar to those of other series in literature. Isolated bone metastasis, reduced number of involved sites and loco regional treatment were significant predictive factors of better survival.

Background

Breast cancer is the first gynaecologic cancer worldwide [1]. According to the three Tunisian cancer registries (North, centre and south), breast cancer is actually in the head of woman malignancies counting for almost 31% of all cancers [2]. Metastases are common in breast cancer as 6-10% of breast cancer patients had metastatic disease at diagnosis (synchronous metastases) and 60-70% of patients with initially localized disease will develop ulterior metastases [3]. The maximum of metastatic replase rate occurs in the 2 to 3 years following the initial breast cancer treatment [3]. Bone represents the most frequent breast

cancer metastatic site. The aim of our study was to assess clinical characteristics of breast cancer bone metastases and to analyze survival prognostic factors according to bone metastases characteristics.

Patients and methods

We conducted a retrospective study throw all registered histologically confirmed metastatic breast cancer patients treated in the medical oncology department of Hbib Bourguiba hospital of Sfax in the south of Tunisia, among a period of eight years (from January 2000 to December 2007), whether patients presented metastases following a previous diagnosis of the disease or presented metastatic disease at the time of initial diagnosis. From 2440 breast cancer patients, 332 had metastatic disease (13%). Two hundred and twenty-five patients (67.7%) had bone metastases. All patients' files had been reviewed by members of medical oncology and radiation therapy departments. We have specified for each patient clinical and radiological characteristics, applied treatments, disease evolution and survival rate. Survival rate was calculated from the diagnosis date of bone metastases to the date of last event. The overall survival was obtained by the Kaplan-Meier method and a comparative analysis of prognostic factors independently contributing to prolonged survival after bone metastases presentation was made by the Log rank test.

Results

1) Clinical, pathological and radiological characteristics

From 332 patients with metastatic breast cancer, two hundred and twenty-five patients (67.7%) had bone metastases. The mean age was 50.5 years. Ductal invasive carcinoma was the most frequent histological type (83.1% of cases) followed by the lobular type (5.7%). Eight patients had mixed type (ductal and lobular).

Bone was the only metastatic site in 116 patients (51.5%); 119 had bony and visceral metastases (liver, lung, brain...). Fifty-three patients (23.5%) had less

than 3 bone metastatic sites, 76.5% had more than three. Metastases occur more frequently in Spine (table 1). Bone metastases were generally symptomatic: 136 patients had bony pain, 38 developed spinal cord compression. Fractures occurred in 8 cases: it concerns femur in 6 cases, humerus in 1 case and ribs in 1 case. Serum calcium levels were not noted in our series.

Osteolytic lesion was the most common radiological presentation. They were diagnosed on standard radiographs, CT scan or MRI. In 96 cases, standard radiographs did not show any abnormal images and the diagnosis of bone metastases was based on scintigraphy (table 2).

2) Treatment modalities and disease evolution

All patients received systemic therapy (chemotherapy and/or hormone therapy). The choice between chemotherapy and hormone therapy was made according to the type of metastases (bone metastases only or associated to visceral ones), anterior therapies, hormone receptor status and time to relapse. Ninety-four patients (41.7%) received biphosphonates therapy (Pamidronate, Zoledronate or Ibandronate). Patients received biphosphonates during a mean period of 18.6 months (1-96 months).

Fractures and spine cord compression occurred in 46 patients. These events occurred less frequently in biphosphonates treated patients compared to those not receiving it, but this did not reach statistical significance ($p=0.5$). From the 8 cases of pathological fractures, six had surgery. Seventy-eight patients (34.6%) received radiation therapy which was for analgesic purpose in 33 cases (42%), décompressive in 32 cases (41%) and curative in 6 cases (8%). Radiation therapy was successful in 69% of patients suffering from spine cord compression resulting on bony pain control and compression neurologic symptoms improvement. The mean time to radiation therapy effect was 26 weeks with as result an important reduction in analgesic drugs consumption.

3) Survival analysis

Five-year overall survival was 23% in patients with only bone metastases while it was 4% in those with visceral and bone ones. Survival was analyzed according to number of bone metastatic sites (less or more than 3 sites) and to whether a loco regional treatment (by surgery and/or radiation therapy) was associated or not to systemic therapy. Patients with less than 3 bone metastatic sites and those who had undergone a loco regional treatment had significantly a better survival (table 3).

Discussion

Bone is the most common metastatic site in breast cancer. In our series, 67.7% of patients had bone metastases which is comparable to the literature as bone metastases prevalence in breast cancer is between 66% and 77% [4,5,6,7]. In breast cancer, bone metastases involve most frequently spine, pelvis and ribs [8,9], which is concordant with our series. These metastases can have different radiological presentations: osteolytic lesions are the most frequent (65-75% of cases); condensing or mixed lesions are rare [9]. In our series, 77.5% of metastatic lesions were osteolytic.

Bone metastases can be painful so that major analgesic drugs and even analgesic radiation therapy can be needs. They can be also complicated fractures, spine cord compression and hypercalcemia. These events can deeply alter patients' life quality. The data shows that these events occur in 35 to 79.9% of cases [10,11,12,13,14,15]. They occurred in 63.2% of our patients.

Bone metastases in breast cancer are treated as metastatic disease using chemotherapy, hormone therapy and targeted therapies. The choice between these

therapies depends on disease characteristics: associated visceral metastases, time to relapse, anterior treatments, hormone receptors and Her2 neu status.

In many series, biphosphonates have shown benefit in metastatic breast cancer by reducing bone events morbidity and by improving life quality [10]. Randomized trials comparing systemic therapy (chemotherapy or hormone therapy) plus biphosphonates versus systemic therapy plus placebo in bone metastatic breast cancer have shown a significant decrease in bone skeleton events [10]. In our series, forty-six patients experienced bone events; there was less events in the group of patients receiving biphosphonates than in the group not receiving it but this did not reach significance ($p=0.5$).

Bone metastases surgery is indicated in case of pathological fracture or if there is an important risk of ulterior fracture [16]. In case of pathological fracture, patients eligible for surgery are those who have life expectancy more than 6 months, good performance status, expected good surgical results and finally patients in which surgical treatment looks to have superior results than medical treatment alone.

In case of menacing osteolytic metastases, surgery is indicated if lesions concern bearing bones (femur and pelvis mainly), if the lesion measures more than 2 cm and if bone cortical destruction exceed 50% [16]. After surgery, bone metastatic sites should be irradiated to consolidate them [17]. In our series, 8 patients had pathological fractures and 6 of them had undergone surgery followed in all cases by radiation therapy.

Radiation therapy has an important analgesic effect for bone metastases as it contributes to bony pain control in 80% of metastatic patients [18,19]. Ninety percent of our patients had their pain controlled due to radiation therapy. Single doses of 6 to 8 Grays radiation are as efficient as 25 to 40 Grays of fractioned radiation therapy. Radiation therapy of 30 Grays in 10 fractions permitted pain control in 82% of our patients. The mean time for analgesic effect of radiation therapy is usually 11 to 24 weeks. It was 26 weeks in our series.

Vertebral metastases have worst outcome compared to other bone metastatic sites as 5% of them develop spine cord compression. In a randomized trial, Patchell at al. [6] concluded that decompressive surgery followed by radiation therapy should be preferred to exclusive radiation therapy in case of spine cord compression. Exclusive radiation therapy should be performed in case of surgical contraindication: poor performance status or irreversible neurological deficit.

From all osteophilic cancers, thyroid and prostatic carcinomas have best survival in case of bone metastases (with 60% and 40% 5-year survival respectively) [20,21] followed by breast cancer with 20% 5-year survival [22,23,24]. In our series, it was 23%.

In opposite, renal and lung carcinomas have worst outcome with survival rate less than 5-10% [21,25].

In our study, the absence of visceral metastases (liver, lung, brain...) was significantly correlated to a better survival. In addition, better survival was correlated with limited bone metastases (less than 3 sites) and it was improved when loco regional treatments (surgery and/or radiation therapy) were associated to systemic therapy; these findings are concordant to literature [20,25,26].

Our study showed the importance of a multi disciplinary management of breast cancer between medical oncologists, radiotherapists and orthopedic surgeons as only-bone metastatic breast cancer has significantly better survival than with visceral metastases so that we can reach a 5-year survival up to 20%. In our series, we have demonstrated that, in metastatic settings, not only systemic therapies (chemotherapy and hormone therapy) have impact on survival but also loco regional treatment of bone metastases was significantly associated to better survival.

Conclusion

Metastatic breast cancer is a heterogeneous disease with survival rate depending on many factors (RH status, HER over expression, metastatic sites...). Bone represents the most frequent breast cancer metastatic site. Only-bone metastatic patients have better outcome and should be treated with curative intent mainly if there is few metastatic lesions in which local treatment is possible. Surgery and radiotherapy had a major role like systemic therapies and biphosphonates in the management of bone metastatic breast cancer as they are associated to better survival and quality of life.

Conflicts of interest: no conflict of interest

Tables

Table 1: Bone metastatic sites distribution

Metastatic bone site	Number	Frequency (%)
Spine	148	66%
Ribs	70	31,2%
Pelvis	68	30,5%
Head	40	17,7%
Femur	39	17,4%
Sternum	31	13,8%
Humerus	25	11%
Scapula	24	10,6%
Clavicles	18	8%

Table 2: Radiological presentation of bone metastases in standard Rx, CT scan and MRI

Bone metastases characteristics		Number	Frequency (%)
Osteolytic lesions	Standard Rx	26	77.5 %
	CT scan	16	
	MRI	56	
Condensing	Standard Rx	2	7.8 %
	CT scan	4	
	MRI	4	
Mixed	Standard Rx	3	14.7 %
	CT scan	10	
	MRI	6	

Rx: Radiography, CT scan: computed tomography scan, MRI: magnetic resonance imaging

Table 3: Survival factors according to bone metastases presentation and treatment

Prognostic factors	5-year survival	p
Only bone metastases Vs Visceral and bone metastases	23%	0,001
Less than 3 bone metastatic sites Vs More than 3 bone metastatic sites	20%	0,037
	13%	

Loco regional treatment of bone metastases	21%	0,013
Vs No loco regional treatment	11%	

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