

Incidence and Outcomes of Bone Metastases. Evaluation of BTAs Therapy, Pain Relief and Quality of Life: Experience from a Single Cancer Center

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Abstract: ***Introduction and objective:** Morbidity and mortality from malignant diseases are usually the result of metastasis. In this study our aim was to demonstrate the importance of BTAs therapy on QoL in bone metastatic patients with "long term survival". **Material and Methods:** This is a retrospective study of patients with metastatic bone disease, conducted between January 2011 and June 2016. A total of 590 patients (51.0% males, 49.0% females) had metastatic bone disease, with the highest incidence between the age range of 60–69 years. **Results:** The commonest primary cancer was breast (34%), followed by prostate (27%), lung (18%), colon (5%), others (16%). The majority (90%) were symptomatic, with pain as the most common symptom and 69% of the patients had manifestations of SRE. **Conclusion:** In our study, breast and prostate cancers were the commonest primary cancers in metastatic bone disease. Most patients had more than one site of involvement and pain at the time of presentation. Well-timed use of Target Therapy (BTAs) allowed us to determine an improvement of clinical benefits and quality of life in these patients, as well as a reduction in the number of hospitalization days related to complications (SREs).*

Keywords: Bone metastases, pain, QoL, BTAs

1. Introduction

The bone is the third most common site of metastasis. In females, the breasts and the lungs are the most common primary disease sites; approximately 80% of cancers that spread to bone arise in these locations.[1-5] In males, cancers of the prostate and the lungs make up 80% of the carcinomas that metastasize to bone.[6] The remaining 20% of primary disease sites in patients of both sexes are the kidney, gut, and thyroid, as well as sites of unknown origin. While any malignancy may metastasize to the bone, it is most prevalent in advanced breast (70–80%), prostate (70–80%), thyroid (60%), lung (10–50%) and renal cancers (30%).[7-11] The consequences of bone metastases include reduced survival, morbidity and pain that negatively affects the patient's quality of life (QOL) as well as skeletal-related events (SREs), [12] including spinal cord compression, bone surgeries, pathological fractures, and severe bone pain requiring palliative radiotherapy.[13,14] In breast and prostate cancers, the symptoms related to metastasis are frequently the first indication of the disease.[15] It is, however, difficult to quantify the prevalence of bone metastases, as the incidence is affected by the sensitivity of diagnostic tools and the duration of patient's survival. Pain from metastases of primitive cancer is the first symptom of disease in 15–20% of patients and remains the most common cause of cancer-related pain[16]. 30–70% of patients have metastases at the time of diagnosis, and 80% of them at the moment of death [17]. One-third of patients with advanced cancer develop chronic pain during the course of the disease. [18] Primitive cancers which most frequently produce bone metastases include breast cancer (stage I: 2%, stage II: 6%, stage III: 15%, at time of first recurrence: 30–70%), kidney cancer (16–40%), lung cancer (10–32%), prostate cancer (stage A: 5–10%, stage B: 10–15%, stage C: 20–30%). [19]

Osseous metastases are most frequently associated with lung and prostate cancer in men and with breast cancer in women. [20] Functional impairment of skeleton, neurologic symptoms, pathological fractures and pain are the most important indications for palliative treatment which should result in tumor regression, relief in cancer-related symptoms and maintenance of functional integrity. Bone metastases are treated with the systemic therapies including radiotherapy, hormonal manipulation, calcitonin, surgical treatment, chemotherapy, and BTAs therapy. Bone oncology requires a multi-disciplinary team approach and a diverse arsenal of cancer therapeutics. The presence of bone metastases is an ominous sign of a disseminated disease and portends a short-term prognosis in cancer patients. Palliation of symptoms, especially pain, prevention of bone complications, and the maintenance of quality of life remain the first aims of any therapeutic approach in the management of bone metastases: a multidisciplinary effort guarantees the best results in improving patients quality of life.

2. Material & Methods

We conducted a retrospective review of cases of metastatic bone disease in Medical Oncology Unit of University of Messina, over a five-year and half period. All patients who were referred to the Oncology Unit for bone metastasis from 1st January 2011 to 30th June 2016 were included in this study. The aim of the study was to create a local profile of patients with bone metastatic disease, with regard to the disease incidence, as well as to study the outcomes and results of management of the disease with BTAs therapy. Quality of life was defined at two levels. Level 1 was defined as the ability to take care of most personal needs (Karnofsky 70%-100%). At level 2, a patient required major

help in self-care (Karnofsky 0 %-70 %). Quality of life was defined as good if most of the patient's life measured from treatment of the first bone metastasis, was in level 1. The presence of debilitating skeletal pain was associated with level 2, in which the patient either spent most of the time in bed or ambulated infrequently with aid. Therefore, the Karnofsky level is an useful index to measure the quality of life, in a patient who has been treated for metastatic bone disease. Data was obtained from the medical records of Medical Oncology Unit, University of Messina. Patients included in this study: Patients who had (a) a histologically proven primary tumor that was presented with metastasis; (b) an unknown primary cancer with histologically proven bone metastasis; or (c) known primary cancer and radiologically proven bone metastasis were included in the study. Patients with primary bone cancers (e.g. osteosarcoma, Ewing's sarcoma and chondrosarcoma), primary hematological tumors (lymphomas, myelomas) and with uncompleted data were excluded.

3. Results

Out of 3047 patients admitted to the Medical Oncology Unit of University of Messina, in the ordinary regimen, Day Hospital / Day Service, for non-hematological malignancies, 590 (19%) had bone metastases, and 2451 (81%) had no bone metastases. Among these 590, 220 (37%) presented the bones as the only site of metastases and the remaining 370 (63%) also the visceral ones. The most commonly encountered type of cancer, in 3047 hospitalized patients in these 54 months, was the colon cancer: 662 cases (22%), followed by lungs: 647 cases (21%), breasts: 466 cases (15%), bladder: 315 cases (10%), prostate: 230 cases (8%), stomach: 156 cases (5%), head and neck: 128 cases (4%), ovaries: 77 cases (3%), biliary tract: 70 cases (2%), liver: 59 cases (2%), kidneys: 45 cases (1%), pancreas: 37 cases (1%), uterus: 37 cases (1%), unknown primary: 37 cases (1%), brain: 30 cases (1%), neuroendocrine: 23 cases (1%), thyroid: 16 cases (0,50%), vulva: 12 cases (0.50%). The other types of metastases (370 cases), in addition to bone, were represented as follows: 358 patients (96%) presented liver metastases, 309 (83%) lymph node metastases, 236 (64%) lung metastases, 48 (13%) pleural metastases, 30 (8%) brain metastases, 18 (5%) cutaneous metastases, and 12 (3%) peritoneal metastases. In 590 patients with bone metastases, the most represented cancer was, however, the breast cancer: 198 cases (34%), followed by prostate: 158 cases (27%), lung: 106 cases (18%), colon: 29 cases (5%), liver: 18 cases (3%), pancreas: 18 cases (3%), bladder: 18 cases (3%), stomach: 9 cases (1.4%), brain: 9 cases (1.4%), uterus: 9 cases (1.4%), neuroendocrine system: 9 cases (1.4%), primitive unknown: 9 cases (1.4%). Of these 590 patients, 341 (58%) had bone localizations at the time of diagnosis, 249 (42%), however, have arisen over time. Of the total of patients, 301 (51%) were males and 289 (49%) females. The mean age was 62.19 years with the range from 32 to 87. The higher incidence of bone metastases was observed in patients between 60 and 69 years. The median time to onset of bone metastases was 6 months (Range 2.3 months-8 months). The median time to onset of the first SRE was 2 months, to second SRE was 4 months, and to the third SRE was 9 months. In patients treated with BTAs, the median time to the onset of first SRE was 4 months versus 2 months

in untreated patients. About the kind of bone injury, 290 patients (49%) had osteolytic lesions, 203 (34%) osteoblastic, and 97 (17%) had mixed lesions. In 183 patients (31%) metastasis was single, in 407 (69%) they were multiple. Regarding the localization of metastases, the main site was the axial bone, with 65% (386 patients) of cases, long bones in 25% of cases (146 patients) and axial and long bones in 10% of cases (58 patients). Of 386 patients with axial bone metastases, in 42% (161 patients) of cases, the localization concerned the ribs, sternum, and skull, and in 58% of cases (225 patients) the dorsal spine. Observing the distribution of SREs, we found that 405 patients (69%) experienced at least one SRE along the course of the disease, while 185 (31%) did not present any SRE. (Figure 1)

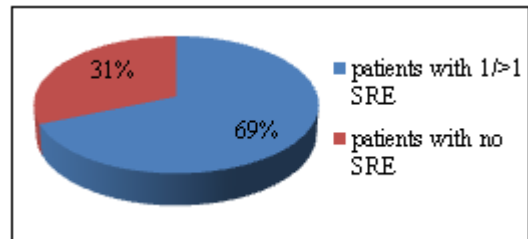


Figure 1: SRE distribution (n 590 patients)

The SREs (405 cases) were distributed as following: 367 patients (90%) required radiation therapy to relieve the pain, 116 patients (29%) underwent orthopedic surgery, 87 patients (21%) experienced pathological fractures, 67 patients (16%) went to cord compression meeting, 48 patients (12%) experienced episodes of malignant hypercalcemia. (Table 1)

Table 1: SRE Types (n= 405 patients)

Sre Types	N. Patients	(%)
Radiotherapy	367	90
Orthopedic Surgery	116	29
Pathological Fractures	87	21
Medullary Compression	67	16
Malignant Hypercalcemia	48	12

We evaluated the Visual Rating Scale (VRS) pain severity, and found that of 590 patients, 194 (33%) reported, at the time of presentation, some soreness (mild pain), 198 (33%) moderate pain, 139 (24%) severe (strong) pain, 59 (10%) did not complain about any pain. (Figure 2)

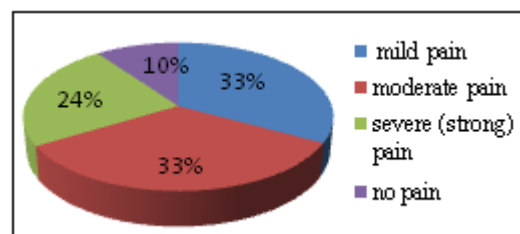


Figure 2: Severity of pain (evaluated with VRS) before treatment with BTAs (n =590 patients)

Therefore, 346 (58%) patients received BTA (Zoledronic acid, Denosumab): 231 (39%) patients received zoledronic acid, while 115 patients (20%) Denosumab; 244 patients (41%) did not receive any of the two treatments. (Figure 3)

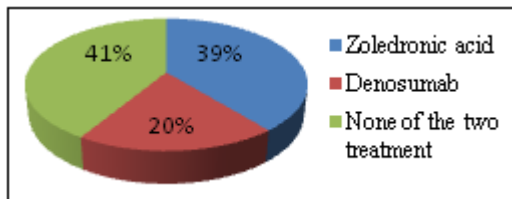


Figure 3: Treatment with Biphosphonates/Denosumab (n = 590 patients)

Treatment was discontinued in 115 patients (33%) due to: deterioration and/or death: 62 patients (54%), progressive bone metastases: 25 patients (22%), side effects: 6 patients (5%), progressive disease: 2 patients (2%), patient's preference: 2 cases (2%) and physician's preference: 2 cases (2%), contraindications: 1 case (1%) and reason was unknown in 15 patients (10%). (Figure 4)

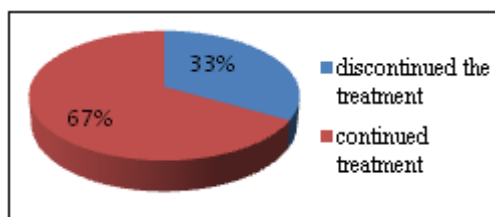


Figure 4: Patients continued the treatment with BTAs vs Patients discontinued the treatment with BTAs (n = 346 patients)

The 231 patients who underwent regular treatment with Denosumab and Zoledronic acid, demonstrated a reduction in the severity of pain: in fact 77 patients (33%) did not report any more pain, 115 (50%) reported mild pain, 31 (13%) moderate pain, and only 8 patients (4%) reported severe (strong) pain. (Figure 5)

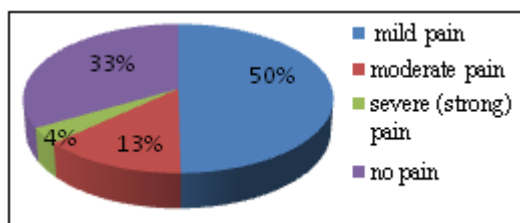


Figure 5: Severity of pain (Evaluated with VRS scale) after regular and continuous treatment with BTAs (n = 231 patients)

Quality of life was good (Level 1) in 83% (192 patients) of the 231 patients (treated with BTAs). These patients achieved a relatively pain-free status wherein they could ambulate. Quality of life was Level 2 in 17% (39 patients) of the 231 patients (treated with BTAs). (Table 2)

Table 2: Overall Quality of Life after BTAs

Primary Site	N. Patients	Karnofsky Level 1 More than Half of Remaining life		Karnofsky Level 2 More than Half of Remaining life	
		(n pz)	(%)	(n pz)	(%)
Breast	98	88	89	10	10
Prostate	39	31	79	8	20
Lung	19	10	52	9	47
Other	75	63	84	12	16
Total	231	192	83	39	17

4. Discussion

The number of patients who present with metastatic bone disease has been increasing. This could be attributed to longer duration of survival due to advancements in cancer treatment, greater awareness among patients and better detection of metastatic disease. The skeletal system is the most commonly affected organ in metastatic disease, and it is also known to be the site of metastasis that incurs the highest morbidity. [14] Multiple bone metastases, presence of bone metastases for more than two years, and occurrence of previous SREs are associated with a risk of occurring further SREs. [21-23] There are cancer patients whose disease progresses to a stage where cure is no longer feasible, treatment options referred to as "palliative care" must then be considered. The objective of palliative care is to maximize survival time, or to decrease pain and suffering, thereby enhancing the remainder of the patient's life. We wanted to focus our work on the pain and suffering. Palliative care may involve surgery, chemotherapy, radiation therapy or other approaches to manage advanced cancer. The objective of our study was twofold: 1) to estimate the incidence of bone metastases from solid tumors and 2) to describe trends in the use of BTA in our Unit, and the results that the use of BTA had on our patients with bone metastases (outcomes), in terms of quality of life and clinical benefits. [24] In this study we included 590 eligible patients who were diagnosed with metastatic bone disease from 1st of January 2011 to 30th June 2016. All cases were retrospectively reviewed and the outcomes were analyzed. The gender distribution in our study population was almost equal (51% males, 49% females). Among female patients, breast cancer was the most prevalent primary cancer, while that of male patients were prostate and lung cancers. The age distribution of our cohort was largely based on the type of primary tumor of the patients. The highest incidence of metastatic bone disease was observed in patients aged 60-69 years, followed by patients aged 70-79 years. In our study, the primary cancers with the lowest incidence of metastatic bone disease were brain cancer, uterus cancer, stomach cancer, and primary unknown cancer. Metastasis is more prevalent in the axial skeleton compared to the appendicular skeleton. We have registered the intensity of pain through VRS: 194 (32.8%) of patients had little/mild pain, 198 (33.6%) moderate pain, 139 (23.6%) severe (strong) pain, and 59 (10%) had no pain. After therapy with BTAs, in 231 patients that underwent regular therapy, there was a marked reduction of the severity of pain: 77 (33%) of patients did not refer any pain, 115 (50%) referred mild pain, 31 (13%) moderate pain, 8 (4%) severe (strong) pain. The origin of pain associated with bone metastasis can be biological or mechanical. [25] Biological pain is caused by the local release of cytokines and chemical mediators by tumor cells, periosteal irritation, or stimulation of the intra-osseous nerves. Mechanical pain is due to pressure or mass effect of the tumor tissue within the bone, with the weakening of bone strength giving rise to activity-related pain. Although mechanical pain is common in osteolytic lesions, it is also present in osteoblastic lesions. This is due to the structural compromise of the affected bone. [25] On radiography, metastatic bone disease can appear osteolytic, osteoblastic, or both. While a majority of spinal metastatic lesions are osteolytic, up to 50% of the bone must be eroded

before a conspicuous change can be noted on plain radiographs. Osteoblastic or osteosclerotic lesions are commonly seen in carcinomas of the prostate and breast.[26] Pathological fractures are commonly seen in patients with breast cancer due to the mainly lytic nature of the lesions. They are, however, infrequently seen in patients with lung and prostate cancers, as the survival rate is short in the former and the lesions are mainly osteoblastic in the latter. On plain radiographs, lytic lesions must be at least 1 cm across and affecting 30%–50% of bone density to be clinically detectable.[27] Breast and lung cancers usually present with osteolytic lesions, while prostate cancers frequently present with sclerotic lesions. The majority (49.2%) of our patients had lesions that were osteolytic in nature. Sclerotic lesions accounted for 34.4 % of the observed lesions, while 16.4 % of the lesions were a mixture of osteolytic and sclerotic densities. With the ongoing advancements in cancer treatment, patients with metastatic bone disease are surviving longer, thus making them more susceptible to bone-related complications, and the pain secondary to bone metastasis, when uncontrolled, seriously impacts a patient's quality of life. Without systematic monitoring of pain using validated patient-reported outcome assessments, patients' pain is often under-reported and inadequately managed.[28] Indeed, under-treatment of bone pain is common, in up to 55 % of patients with advanced cancer, which further adds to the burden of disease. [29,30] Bone-targeting agents such as bisphosphonates and Denosumab have been shown to reduce skeletal complications and the worsening of pain associated with bone metastases in patients with advanced solid tumors [31-39] and are recommended for patients with or without pain due to bone metastases from solid tumors.[40]. In our center, a systematic multidisciplinary approach to the diagnostic and therapeutic management of these patients is resulted in cost-effective, adequate pain control in the majority of the cases. The interference of pain with other aspects of life including activity, affect (mood), and overall (activity, mood, walking ability, normal work, relations with others, sleep, and enjoyment of life) was evaluated as part of study and we arrived to the conclusion that, in these patients treated with BTA, we could see a net improvement of these aspects.

5. Conclusion

Therefore, we can conclude that the use of BTAs in patients treated in our Medical Oncology Unit, has brought a net improvement of the conditions and the quality of life in those that received a continuous and regular therapy, determining the reduction of SREs and of support therapy related to their management and to the number of hospitalization in terms of reduction of number of recoveries and days of hospitalization. BTA therapy has offered a significant and sustained relief from bone pain and also improves quality of life in patients with metastatic cancer.

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