

Herrero Vicent C¹, Pascual Pla FJ², Samper Hiraldo JM³, Gavilá Gregori J¹

1 Servicio de Oncología Médica

2 Servicio de Urgencias Médicas

3 Oncología Radioterápica

Fundación Instituto Valenciano de Oncología - Valencia

Multiple skeletal-related events in a patient with breast cancer

Correspondence: Carmen Herrero Vicent - Servicio de Oncología Médica - Fundación Instituto Valenciano de Oncología - Profesor Beltrán Báguena, 8 - 46009 Valencia (Spain)
e-mail: carmendcn@hotmail.com

Date of receipt: 20/06/2013

Date of acceptance: 28/11/2013

Summary

Bone metastases are common in advanced cancer, occurring up to 75% of patients with advanced breast cancer. Complications of bone metastases include bone pain, hypercalcemia and skeletal-related events (SERS), such as fracture, need for radiation or surgery to bone, or spinal cord compression.

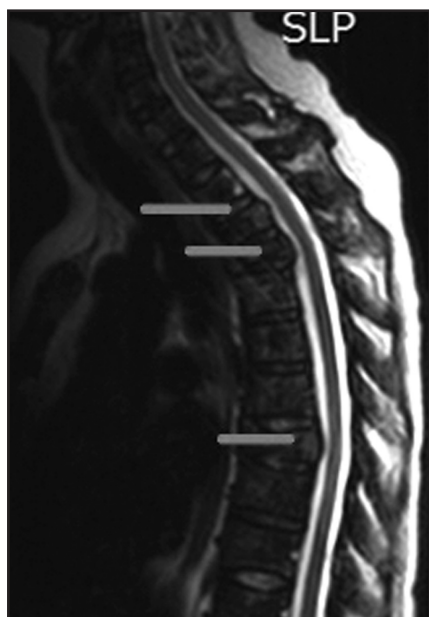
A 50 year-old patient with advanced breast cancer, who has multiple skeletal-related events and poorer overall quality of life.

Key words: *bone metastases, skeletal-related events, cancer, breast.*

Figure 1. (a) X-rays of left humerus, in which are observed a fracture in the middle third and the fixation with an intramedullary nail. (b) X-rays of left femur with lytic metastasis and intramedullary nail



Figure 2. Magnetic resonance of the spine, which evidences medullary compression at the second, third and seventh dorsal vertebrae



Introduction

One of the most aggressive characteristics of cancer in general is its capacity to produce metastases, with the skeleton being one of the most common locations for their development. The activity of osteoclasts produces a local destruction of the bone and, as a consequence, skeletal-related events (SREs) such as pathological fractures and medullary compressions which may require treatment with radiotherapy or surgery, with consequent hospitalisation¹.

Presented here is the case of a patient with advanced breast cancer with multiple SREs with affection of her quality of life, and which required an efficacious treatment based on a multidisciplinary approach.

Clinical case

A patient of 50 years of age diagnosed in December 2002 with infiltrating ductal carcinoma of the left breast, hormonal receptor-positive with the clinical state T3 N0 M0, treated with induction chemotherapy with 4 cycles of fluorouracil-epirubicin-cyclophosphamide, modified radical mastectomy, 4 cycles of docetaxel and adjuvant radiotherapy in the costal wall, left supraclavicular fossa and internal mammary nodes up to 50 Gy. This was followed by hormone therapy with aromatase inhibitors and periodic checks.

In April 2005 the patient reported mechanical lumbalgia which did not recede with WHO first or second level analgesia. A magnetic resonance (MR) scan was carried out in the spine, which found a single metastasis in L4, which was confirmed histologically. An intervention was performed with a fixation followed by radiotherapy on L3-L5 receiving 30 Gy, and chemotherapy initiated with vinorelbine associated with zoledronic acid 4 mg intravenous every 28 days over 2 years (24 doses in total) followed by periodic checks.

In February 2013 the patient complained of pain of a mechanical nature in the upper left limb which developed over a number of hours. A simple radiography of the left humerus was performed which showed a fracture of the inferior third of the diaphysis, which was fixed with an intramedullary nail, along with radiotherapy (Figure 1a). The biopsy was compatible with metastasis originating from the breast. In the axial thoracic-abdominal-pelvic computerised tomography (CT) scan there was evidence of progression in the bone, confirmed by bone tracking (BT).

During admission the patient reported pain in the glenohumeral joint, and after the carrying out of an X-ray a fracture of the right acromion was observed which required fixing.

In April 2013 the patient presented with difficulty walking and acute mechanical pain in the proximal part of the left leg that was not eased with WHO level 3 analgesia. In the X-ray a fracture of the diaphysis of the left femur was found, on which an intramedullary fixation was carried out (Figure 1b).

During admission she presented with pain in the upper dorsal zone with a positive spinal apophysis percussion test, due to which a CT scan was requested, which showed a bulge in the posterior wall of D3 and D7, which was confirmed through MR (Figure 2). After evaluation for radiotherapy it was decided to administer 20 Gy to D2-D3 and D7, and 20 Gy to the left femur. At the time of producing this work (June 2013) the patient was in treatment with capecitabine, despite presenting a score of 3 on the Performance Status scale, secondary to the multiple skeletal-related events which resulted in dependency for the activities of daily living.

Discussion

Physiologically, there is a balance between bone formation and resorption. The osteoblast line cells are involved in oste-

oblast function and differentiation by means of the RANK factor (Ligand Receptor of the Activator of Nuclear Kappa-B factor) present in their membrane. The bonding of RANK to its ligand (RANKL) stimulates differentiation, the survival of the osteoclast precursor cells and the activity of the mature osteoclasts, thus increasing the expansion of the osteoclast mass and bone resorption².

On the other hand, osteoprotegerin (OPG) has been identified as a protein which inhibits the development of osteoclasts. When there is sufficient OPG in the environment this protein bonds with the RANKL of the osteoclasts, impeding their interaction with the osteoclast precursors, which slows the process of bone resorption. Changes in the RANKL/OPG quotient are decisive in the pathogeny of bone loss, from osteoporosis to bone metastasis.

Bone is a target tissue for metastasis in breast cancer. This is due, in part, to the irrigation of the bone itself, and to growth factors IGF-1, FGF and PDGF, which exert an attraction on cancerous cells and are a suitable medium for cell growth³.

The bone balance is altered by the arrival of the tumorous cells. It is necessary that the neoplastic cells are retained in the sinusoids of the bone medulla, that they migrate, that they pass through the vascular wall and adhere to the extracellular matrix of the bone surface of the periosteum in order to be able to stimulate the osteoblasts and osteoclasts. In breast cancer there may be an increase in bone resorption over formation, favouring the formation of osteolytic bone metastases. This imbalance is related to an increase in markers for bone resorption such as urinary N-terminal telopeptide of collagen type 1 (uNTX), C-terminal telopeptide of collagen type 1 (CTX), the alkaline phosphatases, (AFs), the amino-terminal propeptide of procollagen type 1 (PINP) or tartrate-resistant acid phosphatase (TRAP-5b)⁴.

Clinical trials have shown that the bisphosphonates inhibit the resorption of bone mediated by the osteoclasts, which means that it could be a therapeutic option for the prevention of bone loss induced by oncological treatment secondary to hormonal deprivation, especially if the patient has a low bone mineral density or has risk factors for the development of fractures from minimal traumas. In the initial stages of non-metastatic breast cancer, zoledronic acid administered every 6 weeks, oral ibandronate monthly and weekly risenedronate have been shown to prevent bone loss associated with the use of aromatase inhibitors in breast cancer in postmenopausal women. On the other hand, SRES occur in 64% of patients with breast cancer who are not treated with bisphosphonates, which is why the American Society for Clinical Oncology (ASCO) recommends treatment with intravenous bisphosphonates in patients with pain or destruction of bone evidenced by radiography⁵⁻⁷.

Other, more recent treatments are those monoclonal antibodies such as denosumab, which have a great affinity with RANKL, impeding the RANKL/RANK interaction on the surface of the

osteoclasts, thus diminishing bone resorption. In a phase II clinical trial carried out in patients with breast cancer and bone metastasis in which were compared 120 mg subcutaneous denosumab, plus an intravenous placebo, and 4 mg intravenous zoledronic acid, adjusted for renal function, plus a subcutaneous placebo every 4 weeks, it was shown that denosumab reduced the time until the first bone event by up to 23% (HR 0.82; CI 95%, 0.71-0.95; p=0.1 superiority) and the risk of multiple events by up to 18% (HR 0.77; CI 95%, 0.66-0.89; p=0.001), compared with the zoledronic acid [8]. These data translate into a greater quality of life for the patient^{9,10}. In addition, unlike zoledronic acid, denosumab is not nephrotoxic, which means that there is no requirement to adjust according to creatinine clearance, it is administered subcutaneously and has lower toxicity.

The better understanding of bone metabolism, advances in molecular biology and a better characterisation of the signaling systems of the RANK/RANKL/OPG pathways represent an advance in the treatment of bone metastases, as well as in the prevention of states of osteopenia and osteoporosis secondary to oncology treatment, given that these negatively influence the morbimortality of our patients.

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