

Bone and cancer: the osteoncology

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Summary

In recent years clinicians have witnessed a radical change in the relationship between bone and cancer, with in particular an increase in bone metastases incidence due to an improvement of patients survival. Bone metastases are responsible for the high morbidity in cancer patients with a strong clinical impact. For all these reasons, efforts have been directed to this important field with the foundation of the osteoncology, a new scientific and clinical branch involved in the management of patients with bone cancer disease, including primary bone tumors and bone metastases. Another innovative and important osteoncology topic is the Cancer Treatment Induced Bone Loss (CTIBL) that is mainly caused by antitumor treatment with bone resorption induction. The diagnostic and therapeutic options are described briefly in order to highlight the importance of the multidisciplinary approach in this new field.

KEY WORDS: bone cancer; bone metastases; CTIBL.

Introduction

The relationship between bone and cancer has undergone profound changes in recent years and oncology has to manage with an increase of bone metastases incidence with a radical change of epidemiological data and a strong clinical impact. For these reasons currently bone metastases are responsible for the high morbidity in cancer patients. This radical change is due mainly to the patients' survival increase due in part to the better understanding of tumor biolo-

gy that led to the development of new available target treatments and in part to the interdisciplinary approach. Furthermore the discovery of the role of bone health in the natural history of cancer had also a great importance in the changes discussed above.

Primitive bone tumors

Primary malignant bone tumors are relatively rare, occurring at a rate of about one to 100,000. As many tumors are asymptomatic until a seemingly trivial insult has serious sequelae, however, it is important to find and categorize bone lesions in the early stages of their development. Proper diagnosis of bone tumors requires careful examination of all available sources of information, including patient history, physical examination, plain films and other imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI). Each imaging option has its own strengths, which must be considered during analysis. The most accurate diagnostic tool available to the clinician is bone biopsy which provides histological evidence, with in an accurate diagnosis of the tumor lesion. However, it provides no evidence as to the progression or aggressiveness of the lesion. Biopsy, therefore, is best used in conjunction with plain films to provide the most complete diagnosis. Primary bone tumors generally present with a specific set of symptoms and radiographic appearances, but other non-neoplastic bone diseases may also present with similar symptoms.

Therefore, the differential diagnosis is not always easy and requires the utmost attention.

Benign tumors are relatively common, and few have either the ability or the tendency toward malignant degeneration. Most benign tumors remain asymptomatic until their presence is indicated by a trivial or accidental injury. The most commonly diagnosed malignant primary bone tumors include: multiple myeloma, osteosarcoma, chondrosarcomas, and Ewing's sarcoma (1).

Bone tumors, as in particular osteosarcomas and members of the *Ewing's sarcoma family of tumors* (ESFTs), are typical malignancies of adolescents and young adults (2), whereas myeloma and chondrosarcoma are frequent in adult and old age. Current diagnostic and therapeutic guidelines for patients of all ages have been developed. The aim of bone sarcoma therapy should be to cure the patient from both the primary tumor and all (micro-) metastatic deposits while maintaining as much (extremity) function and causing as few treatment-specific late effects as possible. Bone sarcoma therapy requires close multidisciplinary cooperation. It usually consists of induction chemotherapy, followed by local therapy of the primary tumor (and, if present, primary metastases) with surgery and further, adjuvant chemotherapy. Surgery is also gaining importance in ESFT, which was long considered a domain of radiotherapy.

Before 1970, amputation was the sole treatment for a high

grade malignant tumor, and 80 % of patients died of metastatic disease, most commonly to the lungs (3). Over the past 3 decades, effective induction (neoadjuvant/preoperative) and adjuvant (postoperative) chemotherapy protocols have improved the ability to perform safe limb-sparing resections, and disease-free and overall survival rates have risen. "Limb-salvage" refers to successful resection of a tumor and reconstruction of a viable, functional extremity. In the setting of induction chemotherapy, limb-sparing resection and reconstruction, rather than amputation, can be safely performed in 90 to 95 per cent of patients (4).

Bone metastases

Metastases from carcinomas are the most common malignant tumors involving bone. Prostate, breast and lung cancer are the most common malignancies in adults and are the most common tumors that metastasize to bone. Moreover, bone metastasis affect more than 60% of advanced stage breast and prostate cancer patients. Carcinoma of kidney, thyroid and melanoma are other common tumors that metastasize to bone (5).

Bone metastases are usually multifocal and have a predilection for the hematopoietic marrow sites in the proximal long bones and axial skeleton (vertebrae, pelvis, ribs and cranium). Continuous and dynamic turnover of the bone matrix and bone marrow provides a fertile ground for tumor cells to utilize the vast available resources (cells, growth factors, cytokines and receptors) for their homing and subsequent proliferation (5). Cancer cells provoke in bone microenvironment a broke in the physiological balance between bone resorption and formation developing lytic, blastic or mixed lesions (6). About 25% of these patients remain asymptomatic, diagnosis is made by exams prescribed for other reasons or during primary tumor stadiation. In the remaining 75% bone metastases are responsible for different clinical complications as pain, pathological fractures, spinal cord compression, bone marrow suppression and decline of Performance Status.

Pain is the most frequent symptoms. Bone pain reduces patient mobility, increase anxiety and depression, lung infection, vein trombosis, cutaneous ulcers, with reduction of life's quality.

The frequency of other major complications depends on the nature of bone lesions, their site, and their treatment (7).

Lytic lesions (more frequent in breast, thyroid, kidney and lung cancer) predispose to severe complications, as pathological fractures and hypercalcemia. The prevalence of osteoblastic lesions, as prostate cancer, predisposes with a minor frequency to these complications. Hypercalcemia is unusual in these patients, instead it is more frequent to observe an hypocalcemia (8). Recently the introduction in clinical practice of bisphosphonates caused a progressive decrease of the frequency of major complications in cancer patients (7, 9).

In two randomized study on breast cancer patients (10) and multiple myeloma (11) treated with chemotherapy, the mean SRE per year rates, without treatment with bisphosphonates, were 3.5 e 2.0, respectively. In a study on 360 patients at the first relapse from breast cancer, hypercalcemia was observed in 79 (19%), pathologic fractures in 68 (19%), and spinal cord compression in 36 (10%) of patients (12). In a study (13) on 254 patients with multiple myeloma, 75% had pains, 54% pathologic fractures, and 33% hypercalcemia.

Furthermore, progress made in understanding the pathophysiology of bone metastases has resulted in the development of new

bone-targeted molecules such as denosumab, and, other molecules are under investigation in various phase I, II and III clinical studies (7). The bone targeted therapy should be combined with specific cancer treatments (chemotherapy, endocrine therapy and biotherapy). Furthermore, a multidisciplinary approach to treatment involving various specialists is essential in the management of patients with bone metastases (14).

Cancer Treatment Induced Bone Loss

The loss of bone mass from cancer treatments is mainly due to the use of drugs (hormone therapy and chemotherapy) that induce bone resorption, leading to a net loss in bone mass, reduced strength and a consequently higher risk of bone fractures in both disease-free and bone metastasis patients. Recent data indicate that this process (loss of bone mass) may play an important role in the implantation of tumor cells aggregates in bone (metastatic niche) from which bone or visceral metastases may be generated. For these reasons bone loss management in cancer patients is important, and identifying those at risk means that the best treatment for the maintenance of bone health can be proposed. Such treatment includes the adoption of a healthier lifestyle, physical activity, cigarettes and alcohol abolition, a diet rich in calcium and in vitamin D. When patients are treated with bisphosphonates or denosumab, calcium and vitamin D3 supplements should always be considered (15).

Bone health is an emerging concern in the early breast cancer setting. Current adjuvant therapies, especially hormonal therapies in premenopausal patients (e.g. goserelin) and aromatase inhibitors in postmenopausal patients, have been associated with substantial decreases in bone mineral density that may place patients at risk for fractures. Bisphosphonates and the recently approved anti-RANKL antibody, denosumab have both demonstrated activity for the treatment of postmenopausal osteoporosis and cancer treatment-induced bone loss (CTIBL) in breast cancer patients, although neither has received widespread approval specifically for CTIBL. However, some bisphosphonates, especially the nitrogen-containing bisphosphonate zoledronic acid, have also demonstrated clinically meaningful anticancer effects in patients receiving adjuvant hormonal therapy for breast cancer and in other oncology settings (16). The effects of denosumab on cancer disease outcomes in the adjuvant setting remain to be established on breast cancer but in recent data (17), induce an increase on Bone Metastasis Free Survival in patients with PSA progression in prostate cancer without evidence of metastatic lesions.

These data highlight the first important point, the bone health maintenance not only in the advanced stage of the disease but also in the adjuvant setting with, as a result, the possible elimination of micrometastases formation that are responsible of failure treatments and of death of our patients.

The second point, from our point of view, is the identification of patient whose primary tumors have a high tropism to bone and that can benefit from bone targeted treatment in adjuvant setting (18, 19).

Conclusion

Advances made in the diagnosis and treatment of tumors, especially multidisciplinary treatments, have increased the can-

cer patients survival of over the last 30 years. As a consequence, bone now represents one of the most common site of metastases after lung and liver. Bone homeostasis is maintained throughout life thanks mainly to the balance due to the activity of two cell types, osteoclasts and osteoblasts. The former resorb bone and the latter move in to fill the void by producing new bone matrix. The break of this balance leads to quality and quantity alterations of the skeleton. Among the many causes of disruption of this balance is the arrival of tumor cells and the induction not only of bone metastases but also of the metastatic niche responsible also of visceral metastases formation. Furthermore bone has an important role in the formation of the premetastatic niche in visceral sites.

All these information are made possible for all recent data on the understanding the molecular mechanisms that underlie the process of metastasis (20-22).

From all this it follows that in recent years the relationship between bone and cancer has changed considerably. From primary tumors, a rare disease to a high incidence disease as bone metastases to bone involvement on the different phases of the natural history of cancer as it is understood by studying the patho-physiology of bone. For this reason on 2000 a new discipline in Oncology was created in Italy called *Osteoncology*; focuses on primary and metastatic bone tumors and also on bone health during antitumor treatment. The main aims of the Osteoncology project are to promote the setting up of multidisciplinary osteoncology centers for the diagnosis, therapy and rehabilitation of cancer-related bone disease, and to carry out active research into this area. Furthermore, multidisciplinary theoretical-practical courses, including those at university level, are being organized in both Italy and abroad to train physicians (Osteoncologists) and other healthcare operators in this new discipline. Our hope is that this new clinical field will spread to all countries in order to relieve the suffering of many patients, increase rates of healing and not less decrease health care costs.

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