

Metastatic bone disease

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Abstrak

Keganasan tulang sekunder akibat metastases karsinoma merupakan keganasan tulang yang paling sering ditemukan, diperkirakan 70% dari keganasan tulang merupakan keganasan tulang sekunder. Pada pemeriksaan otopsi penderita yang meninggal akibat proses karsinoma ternyata 30 – 85% di antaranya didapatkan metastases di tulang. Tulang merupakan tempat ke 3 yang paling sering disinggahi oleh sel-sel metastatik setelah paru dan hati. 80% dari keganasan tulang sekunder diakibatkan oleh karsinoma payudara, prostat, paru, ginjal dan tiroid. Tulang yang paling sering terkena adalah vertebra torakolumbal, pelvis, iga, tengkorak dan proksimal tulang panjang. Patogenesis dari proses karsinoma metastatik ke tulang diterangkan dengan teori "Seed and Soil" dari Paget dan teori Sirkulasi dari Ewing. Diagnosis keganasan tulang metastatik didapat dengan melakukan anamnesis, pemeriksaan fisik dengan cermat, pemeriksaan laboratorium lengkap, pemeriksaan imaging, sken tulang dan kalau perlu dengan pemeriksaan CT sken torak, abdomen, pelvis dan dikonfirmasi dengan pemeriksaan histopatologis. Tatalaksana penyakit tulang metastatik adalah pemberian kemoterapi, radioterapi, bisphosphonat dan bila ada impending / patologik fraktur dilakukan stabilisasi operatif dengan tujuan untuk menghilangkan rasa nyeri, mempermudah perawatan dan untuk mobilisasi penderita. (*Med J Indones 2004; 13: 127-31*)

Abstract

Metastatic bone disease is the most common malignancy of bone, it is estimated that 70% of all malignant bone tumors are metastatic in origin. At autopsy it has been reported between 30 to 85% of patients who die from cancer show occult skeletal metastases. Bone is the third most common site of metastatic process after lung and liver. 80% of metastatic bone disease arise from Ca of breast, prostate, lung, kidney and thyroid. Typical location are thoracolumbal spine, pelvis, ribs, skull and proximal of femur and humerus. Pathogenesis of metastatic bone disease had been explained by Paget's "Seed and Soil" theory and Ewing's circulatory theory. Diagnostic procedures include complete laboratory examination, diagnostic bone imaging, chest x-ray, total body scan, CT-scan of chest, abdomen and pelvis and confirmed by histopathological examination. Management of metastatic bone disease is palliative that includes : chemotherapy, radiotherapy, bisphosphonates and surgical treatment for impending / established pathologic fracture to alleviate pain, ease nursing and restore functional activity. (*Med J Indones 2004; 13: 127-31*)

Keywords: bone cancer, metastases

Metastatic bone disease is the most common malignancy of bone, it is estimated that 70% of all malignant bone tumors are metastatic in origin.¹ At autopsy it has been reported between 30 to 85% of the patients who die from cancer show occult skeletal metastases, many of those lesions are too small to be detected radiographically.² Bone is the 3rd most common site of metastatic process after lung and liver.³ 80% of metastatic bone disease arise from Ca of breast, prostate, lung, kidney and thyroid. Other primary tumors that cause metastatic bone disease are: gastric and colon cancer.^{1,4} Neuroblastoma is the most common primary tumor that can cause metastatic

bone disease in children.¹ Metastatic lesion are typically multiple and located in the axial and proximal appendicular skeleton. Typical locations are thoracolumbar spine, pelvis, ribs, skull and proximal of femur and humerus.^{2,3} Metastases distal to the knee and elbow (acral metastases) are uncommon, due to rarity of vascular marrow in these areas. Approximately 50% of acral metastases arise from lung carcinomas. Rarely, Ca of the breast, prostate and thyroid may have a distal metastatic pattern.^{2,4,5} Metastases more often go to cancellous bone rather than to cortical bone. However cortical metastases are significant because they affects the integrity of the weight bearing long bone more quickly than does a medullary metastases. Majority of cortical metastases affect the femur and are usually from bronchogenic carcinoma. Carcinomas of the breast, kidney and bladder may also give rise to cortical metastases.¹ Metastases to the

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skeleton can cause substantial morbidity, including pain, pathologic fracture, neurologic deficits, anemia and hypercalcemia secondary to bone lysis.⁶

Biology of bone metastases

Tumor cell movement from the primary organ of involvement to distant sites is not random. Paget's "seed and soil" hypothesis explained that different end organs provided optimal environments for specific cancers. The specific mechanisms involved in determining why certain cancers metastasize to bone are still largely unknown.⁶ Ewing's circulation theory explained the existence of unique features of venous system that account for affinity of certain tumors to metastasize to bone.⁵ The distribution of metastases cells is best appreciated by understanding Batson's vertebral vein plexus. This system is valveless and the blood within the system can freely travel proximally, distally and segmentally into different vertebral bodies, ribs, pelvis and proximal long bones. Ca of breast, lungs, kidneys, thyroid and prostate all drain into Batson's vertebral vein system.^{4,5}

Cell adhesion molecules such as laminin and integrins have been implicated in the process of attachment of the metastases cell to the basement membrane.^{5,6} Once a tumor cell reaches a site of skeletal attachment, it interacts with extracellular matrix and produces certain products.

Tumor cells produce various products such as:⁶

- 1). Metalloproteinases (MMPs) which are involved in bone matrix turn over and stimulate proliferation of tumor cells.
- 2). Urokinase plasminogen activator (uPA) system is believed to be an important pathway in the development of metastases of breast, lung and prostate.
- 3). Cytokines such as interleukins (IL-1, IL-6, IL-8) and tumor necrosis factor – alpha (TNF- α) which are involved in the stimulation of osteoclastic bone resorption.

The result of increased osteoclastic activity in radiographic examination could be seen as an osteolytic lesion. The biology of osteoblastic bone metastases is less well understood. In animal models extracts from certain prostate cancer cell lines have induced mitogenesis in osteoblast type cells and proliferation in fibroblast.⁶ The lytic, blastic or mixed

appearance of a metastatic lesion on X-ray depends on the relative rates of osteoclast and osteoblast activity and the degree of coupled bone turn over at that site. Only in the latter stage of bone destruction, does direct tumor cell mediated osteolysis occur.² The mechanisms that encourage osteoclast mediated bone destruction are: (1) Stimulation of osteoclast binding to bone, (2) Stimulation of osteoclastic bone resorption, (3) Prolongation of osteoclast survival and (4) Acceleration of osteoclast formation by influences in post mitotic osteoclast precursor cells.⁵

The effect of metastatic lesion in the bone are disturbance to:

- 1). Structural support
- 2). Hematopoietic system
- 3). Mineral metabolism

Osteolytic lesion in the structural support may give rise to an impending fracture. Impending fracture may be defined as a fracture that will likely to occur with physiologic loading such as walking, turning over in bed or other activities of daily living.

Pathologic fracture in weight bearing bone could be predicted (impending fracture) if there is more than 50% cortical destruction and if there is a long lytic permeative lesion in the diaphysis of a long bone.^{5,7} A detailed study of CT features of an osteolytic lesion can also be used to predict pathologic fracture.⁷

Overall, pathologic fracture occurs in approximately 10% of skeletal metastases. Over 60% of all pathologic fracture secondary to metastatic disease occur in patients with Ca of the breast because they have the longest survival after the onset of skeletal metastases.²

Patients with metastatic bone disease may have significant hematologic abnormalities. Anemia is a common problem secondary to marrow replacement by tumor cells, cytotoxic chemotherapy and radiation.⁵ Hypercalcemia is a manifestation of disturbance of mineral metabolism in cancer patients with metastatic bone disease and could be found in patient with cancer of the lung and breast.⁸ The presentation may be very subtle. Early symptoms include fatigue, anorexia, nausea, constipation and polyuria. These symptoms may appear to be flu like and thus can deceive the examiner.⁵ Hypercalcemia affects 10% to 40% of cancer patients at some time in the course of their disease.³

Diagnosis

Pain is the most frequent symptom associated with skeletal metastases. It has an insidious onset, becoming gradually more severe over the course of weeks to months. At early stage of a metastatic process, the underlying lesion may not be evident in plain films.

The clinician should be suspicious of osseous metastases when a patient with a known malignancy complains of pain.²

A comprehensive history and physical examination must be performed to determine the overall state of the patient and to detect the presence of associated conditions that may require treatment.

The evaluation of metastatic bone disease should include a complete laboratory examinations, diagnostic bone imaging, chest X-ray, total body scan, if necessary CT of the chest, abdomen and pelvis could also be performed to detect the primary site.^{2,5}

There have been improvement to detect metastatic disease with the use of advanced, functional radiographic techniques such as positron emission tomography (PET) scanning.^{6,8} Currently there are no reliable markers to predict which tumor will spread to bone.⁶ New studies evaluating biochemical markers of bone turnover such as N-telopeptide (NTX) and C-telopeptide (ICTP) have revealed promising data.⁶

The differential diagnosis of a solitary destructive lesion of bone in adult (age > 40 years) are : metastatic bone disease, chondrosarcoma, malignant fibrous histiocytoma, myeloma and lymphoma.⁵ Needle biopsy is an excellent method to confirm the diagnosis of bone metastases. CT guided fine needle aspiration or core needle biopsy are both very accurate and easy to perform.⁵

Treatment

It is imperative that management of metastatic bone lesion needs a multidisciplinary approach that consisted of medical oncologist, radiotherapist, orthopaedic surgeons and rehabilitation medical officer.² Once a cancer metastasizes to bone, the prognosis for the patient is poor. Treatment priorities for patient with metastatic bone disease are directed toward pain control, maintenance of function,

ambulatory ability and at palliating symptoms.^{3,5,6} For cancer patients with bone metastases, a combined therapeutic approach involving the use of standard chemotherapy to decrease spread of tumor cells and bisphosphonates to inhibit osteoclastic bone resorption should be employed.^{6,9,10,11} Bisphosphonate have demonstrated some degree of antitumor activity in a number of clinical settings. There is some evidence that oral clodronate may reduce the occurrence of bone metastases patients with no distant metastases at study entry, studies in patients with established bone metastases suggest a reduction of tumor burden or improved survival associated with bisphosphonate therapy.¹¹

Endocrine therapy is the initial treatment of choice for hormone receptor positive breast cancer in patients with metastatic bone disease; except when extensive or aggressive visceral disease coexist, in these situation, cytotoxic chemotherapy is the initial treatment of choice.¹⁰ For hypercalcemic patients are treated with saline diuresis and bisphosphonate. Bisphosphonate therapy⁷ is the mainstay of anti hypercalcemic treatment.⁷

External Beam Radiation Therapy (EBRT) is the treatment of choice for patients with metastatic bone disease when there are painful or progressing osteolytic lesions that do not meet the criteria for impending fracture. Pain control is excellent and can be achieved reliably in greater than 80 to 90% patients.^{4,9} EBRT is more effective for preventing progression of disease in patient with breast or lung cancer than in patients with renal cell carcinoma. New technology has allowed more focused radiation to be delivered with a variety of dose fractioning methods and less damage to the surrounding soft tissue. Depending on their location, early radiation treatment of painful lytic lesions may allow the patients to avoid surgical intervention. The most common metastatic carcinoma are radiosensitive and palliative effects are seen in 80% of these patients for up to 1 year.² EBRT and intravenous bisphosphonates are bone specific treatment that oftenly used to treat patients with skeletal metastases and considered as the cornerstone of treating symptomatic bone metastases.¹²

Another non-operative option that has been used to decrease pain in patients with metastatic bone disease is the administration of radioisotopes such as Strontium -89 and Samarium -153. The use of these radiopharmaceuticals has been associated with improved mobility, decreased used of narcotic analgesic,

improved performance status and quality of life, and in some reports, improved survival.⁶

Radiofrequency electrocautery, which induces ionic agitation in surrounding tissues and results in frictional heating has also been used for treatment of musculoskeletal metastatic lesions, and its use currently has been approved in the United States.¹³ In selected anatomy locations it is used to treat bone metastases measuring as large as 7 cm.⁶

The indications for operative treatment are directed to stabilized an established pathologic fracture and in impending fracture (prophylactic internal fixation). Criteria for proceeding with prophylactic internal fixation are as follows :

- A destructive lesion that comprises greater than 50% of the cortex
- A long permeative that is entirely lytic
- A lesion that is in a high risk area, such as trochanteric region of the femur, midshaft of long bones.⁴

Intramedullary devices is the most used implant for lesion in the upper and lower extremities. For lesion in the proximal femur, prosthetic replacement (standard or long stemmed) is the therapy of choice.

The goals of surgical stabilization of a impending / pathologic fracture are to alleviate pain, ease nursing care and restore functional activity.² To achieve these goals, it is imperative to secure a sound a stable fixation; bone cement is extremely useful adjunct for fixation enhancement.⁶ After surgical stabilization, the patient is given local irradiation. External beam irradiation is generally begun 2 to 4 weeks after surgery.⁵

Prognosis

Virtually all patients with metastatic bone disease will eventually succumb to their disease with median survival from 6 to 48 months. In general metastatic bone disease in patients with breast and prostate cancer live longer than patient with lung cancer.⁵

Carcinoma of unknown origin

After a complete evaluation and biopsy proven carcinoma metastatic to bone there are a minority of cases (15%) that the primary site is still unknown.

These cases typically have a rapidly declining clinical course in the absence effective therapy. The primary site of disease may never be identified.¹⁴

In patients in whom no primary tumor is detectable, the results for the use of chemotherapy have been disappointing and therefore chemotherapy may not indicated.⁸

Future consideration of these patients may include a different approach such as cDNA, molecular markers, serum markers, DNA staining of body fluids and stool, and PET studies.¹⁴

Future directions

With advances in earlier diagnosis and treatment of cancer, patients will survive longer with their disease. In the future there will be more patients living with bone metastases.⁶

The future of treatment of osseous metastatic disease is exiting. Improvement in surgical implants, less invasive techniques and ability to treat and prevent the many complications common to these patients improved, these patients hopefully will continue to realize increasing quality of life despite of their diagnosis.¹³

New treatments are needed for patients known to have bone metastases and those who are at high risk for having bone metastases to develop. Enzyme pro drug gene therapy treatment strategies currently are being explored for their potential benefit in designing novel therapies for bone cancer.¹²

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