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Bone fractures in cancer patients

Złamania kości u pacjentów z chorobą nowotworową

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Summary

Bone fractures significantly increase both morbidity and mortality of underlying diseases. Many mechanisms are responsible for bone loss among cancer patients, depending on underlying pathophysiological processes. The mechanisms can be related to the disease itself and the therapies used against cancer. Hormonal treatments used in patients with hormonally-responsive neoplasms can result in hypogonadism and progressive loss of bone mass. Chemotherapy employed in cancer patients causes a decrease in bone mass that is not recovered after discontinuation of the treatment. Patients at increased risk of fragility fractures should begin preventive treatment as soon as possible. The treatment need to assure adequate supplementation of calcium and vitamin D. Bisphosphonates and denosumab are the drugs of choice in patients with neoplastic diseases as they are able to inhibit bone mass loss, reduce the incidence of skeletal fractures and decrease the risk of hypercalcemia and/or hypercalciuria of malignancy.

Streszczenie

Złamania kości w znaczący sposób zwiększają chorobowość i śmiertelność z powodu choroby podstawowej. U pacjentów z nowotworem istnieje wiele mechanizmów przyczyniających się do utraty masy kostnej. Mechanizmy te mogą być związane z chorobą podstawową oraz być następstwem terapii przeciwnowotworowej. Leczenie hormonalne stosowane u pacjentów z nowotworami hormonozależnymi może powodować hipogonadyzm i postępującą utratę masy kostnej. Chemioterapia stosowana u osób z chorobami nowotworowymi powoduje utratę masy kostnej, która nie ulega odbudowaniu po zakończeniu leczenia. Pacjenci z grupy podwyższonego ryzyka złamań osteoporotycznych powinni otrzymać właściwe leczenie tak szybko, jak to możliwe. Leczenie powinno zapewnić właściwą suplementację wapnia i witaminy D. Bisfosfoniary i denosumab są lekami z wyboru u pacjentów z chorobą nowotworową, gdyż są w stanie hamować utratę masy kostnej, zredukować częstość złamań szkieletu i zmniejszać ryzyko wystąpienia hiperkalcemii i/lub hiperkalciurii.

INTRODUCTION

Human skeleton is composed of two structural types of bone tissue: cortical bone, the dense outer layer of the skeleton responsible for supporting the weight of the body, and trabecular bone, the more metabolically active porous matrix located within short bones and ends of long bones. Bone tissue is undergoing continuous dynamic remodeling in a coupled and sequential process of bone resorption and formation, mediated by osteoclasts and osteoblasts respectively.

Many hormones and cytokines are involved in the close cross talk among cells within the bone micro-environment. Osteoclast proliferation and activity are stimulated by interleukin 6 (IL-6), IL-1, prostaglandins,

and colony stimulating factors (CSFs) (1, 2). Activated osteoclasts bind to bone matrix via integrin proteins and secrete acid and lysosomal enzymes that degrade bone. Osteoblasts synthesize the collagenous precursors of bone matrix (osteoid) and regulate its mineralization. They are also involved in the control of osteoclast differentiation through expression of receptor activator of nuclear factor κ B ligand (RANKL), and osteoprotegerin (OPG), a decoy RANK receptor, which inhibits osteoclast formation.

Cancer, after cardiovascular diseases, is the second leading cause of death (30% of total mortality). Its incidence and prevalence are still rising, partly due to aging of the population (2).

PATHOPHYSIOLOGY OF METASTATIC BONE DISEASE

Multiple steps are involved in the development of metastases from a primary tumor to any distant site. These include angiogenesis, which provides nutritional support for tumor growth, local invasion through the basement membrane, adhesion to vessel endothelium in the target organs, and extravasation into the tissue. These events are supported by secretion of e.g. matrix metalloproteinases and cathepsin K by tumor cells (3, 4).

Bone remodeling units involve an overflow of growth factors, cell adhesion molecules, and cytokines that make them attractive sites for metastatic tumor cells. No definitive studies have linked increased bone resorption to increased tumor cell mass, but limiting of bone resorption was found to reduce tumor expansion in bone (5, 6).

Metastatic bone tumors consist of four types of radiographically defined lesions: osteolytic, osteoblastic, osteoporotic and mixed. Osteolytic lesions are characterized by the destruction of bone, recognized as a hole in the cortex on plain radiographic images. Osteoblastic lesions, often referred to as osteosclerotic, are characterized by excess deposition of new bone and appear on X-ray pictures as more dense bone. Osteoporotic lesions create areas of "faded" bone without cortical destruction and mixed lesions comprise a combination of bone destruction and new bone deposition. Mixed lesions often have a central clear area of cortical lysis surrounded by a zone of increased density (sclerosis). Osteolytic damages are most common in patients with breast cancer and multiple myeloma, while osteoblastic lesions in men with prostate cancer (7).

Bone metastases are usually located in the axial skeleton wined by valveless venous plexuses. The highly vascular metaphyseal tissue, composed predominantly of trabecular bone, appears to be the preferred site for bone metastases. The mechanics of its sluggish sinusoidal vascular supply give the invading tumor cells ample opportunity to move in and out of the marrow. The endothelial cells lining the sinusoids express multiple adhesion molecules, including P-selectin, E-selectin, intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion molecule 1 (VCAM-1), that play key roles in extravasation of tumor cells into the marrow. Bone microenvironment contains many bone-stored cytokines and growth factors, such as insulin-like growth factor-1 (IGF-1), transforming growth factor beta (TGF- β), that appear to favor the growth of metastases (8).

In men the most common neoplasm is prostate cancer which develop osseous metastases in 90% of patients with generalized disease (9, 10). Bone metastases typically occur in the axial and/or proximal appendicular skeleton as osteosclerotic lesions, being the result of stimulation of osteoblasts by prostate cancer cells (7, 11).

Multiple myeloma (MM) is a hematological neoplasm characterized by the proliferation of cancerous plasma

cells in the bone marrow and the presence of abnormal monoclonal protein in plasma and/or urine (12). Bone lesions are the result of imbalance between osteoclasts and osteoblasts activities. It was found that suppression of osteoblasts is caused mainly by inhibition of the Wingless/integrase-1 pathway, while an increase in the osteoclasts function is the result of amplification of the RANK/RANKL pathway and the activity of macrophage inflammatory protein 1- α (13, 14).

DIAGNOSIS OF METASTATIC BONE DISEASE

Bone scintigraphy is a nuclear scanning test that allows to diagnose a number of conditions relating to bones, including primary or metastatic neoplastic lesions, bone fractures not visible at traditional plain X-ray images, and damages to bones due to certain infections. The technique used for bone imaging utilizes labeling with Tc^{99m}methylene diphosphonate (Tc^{99m}MDP) that is incorporated into bone tissue during its formation. It means that osteolytic lesions in patients with multiple myeloma are unlikely to be visualized. Metastatic cortical lesions may be best demonstrated on computed tomography, while trabecular lesions with magnetic resonance imaging. The lesions are found mostly at the bones with large quantity of bone marrow, such as cranium, spine, ribs, pelvis and proximal epiphyses of long bones. Increased bone resorption results in accelerated bone mass loss, hypercalcemia, and pathological fractures. Hypercalcemia is found in about 30-40% of patients, and pathological fractures are localized most often at the spine and may cause injury of the medulla (7, 14).

BONE MASS LOSS AND FRACTURE RISK IN CANCER PATIENTS

Various mechanisms responsible for bone loss in patients with neoplasm may exert different impact on the skeleton depending on the characteristics of the disease and therapies used against cancer. Some hormonal treatments employed in patients with breast or prostate cancers cause hypogonadism that accelerates bone mass loss. The chemotherapies, especially those including glucocorticoids, significantly decrease bone mineral density (BMD) and increase the risk of fractures (7, 11).

It has been documented that in women with localized breast cancer the incidence of vertebral fractures was almost five times greater than in healthy patients (odds ratio = 4.7), and in women with soft tissue metastases was over twenty times greater (OR = 22.7). Additional risk factors that increase bone fracture risk include treatment with aromatase inhibitors, low BMD (T-score < -1.5), elderly age > 65 years, low body mass index (< 20 kg/m²), personal history of fragility fracture after the age of 50 years, family history of hip fracture, systemic glucocorticoid use for more than 6 months, and cigarette smoking (15).

In men with advanced prostatic cancer treated with androgen deprivation therapy, who experienced at

least one fracture after their diagnosis overall survival was significantly decreased compared with patients without fractures (median 121 vs 160 months) (16).

HORMONAL THERAPY

Treatments used in women with neoplastic diseases, such as surgical castration, hormonal treatment, radiation therapy and chemotherapy can result in hypogonadism and accelerated loss of bone tissue. Radiation therapy employed in advanced cancer of the uterine cervix and endometrium may contribute to the development of pelvic fractures. It was shown that focal, high dose radiation therapy can induce atrophy of the trabecular bone due to injury of blood vessels.

Estrogen deficiency is the major cause of accelerated bone loss leading to an increased incidence of fractures. In premenopausal women suffering from breast cancer ablation of ovarian function was found to decrease BMD by 8% at the spine and by 4% at the femur (17, 18).

Tamoxifen is a selective estrogen receptor modulator (SERM) currently prescribed for estrogen receptor positive (ER+) breast cancer. The mechanisms of action of SERM class compounds depend on their tissue-selective ER agonist or antagonist activities. SERMs affect bone homeostasis by reducing the activity of osteoclasts in a transforming growth factor- β -dependent manner and decreasing bone resorption. Tamoxifen was suggested to be a viable choice for initial hormonal therapy in women with low probability of carcinoma recurrence and at high risk of skeletal fractures. Tamoxifen acts as an estrogen receptor antagonist on breast tissue, but as an ER agonist in bones and uterus, where it may cause endometrial hyperplasia, polyp production, and possibly increased risk of endometrial cancer. It was found, that in postmenopausal women with breast cancer tamoxifen was able to maintain BMD and to reduce the risk of osteoporotic fractures. Given for five years in premenopausal women, however, the drug diminished bone remodeling and increased the risk of osteoporotic fractures by 32% (15, 18, 19).

Aromatase inhibitors (AI) are used for the treatment of ER+ breast cancer in postmenopausal women. The drugs have been shown to have superior efficacy in reducing the risk of cancer recurrence compared with tamoxifen. In postmenopausal women most of the androgens are converted into estrogens by cytochrome P450 aromatase in the adipose tissue. Currently used the 3rd generation AI, such as anastrozole, letrozole and exemestane inhibit 96-99% of activity of the enzyme, decreasing the levels of endogenous estrogens far below the levels found at natural menopause (20-22).

It was shown that the rate of bone mass loss in patients treated with AI was twice as much as the rate of physiologic BMD loss in postmenopausal women (20). The results of a randomized, placebo-controlled study in postmenopausal women revealed that early administration of exemestane induced significant decrease

in bone mineral density, only partially reversed within a year of follow-up. It was also reported that therapy with AI increased the risk of skeletal fractures (21-23). An indirect comparison of the 3rd generation AIs showed that the use of exemestane was associated with lower incidence of fractures (19.2%) compared with anastrozole and letrozole (21.6 and 22.0%, respectively). It was found, that deleterious effects of letrozole on bones were less pronounced if the therapy was preceded by five-year treatment with tamoxifen (24, 25).

Androgens deprivation therapy (ADT) has become an established form of treatment for men with disseminated prostate cancer. ADT used in older men with advanced prostate cancer resulted, however, in high bone turnover, significantly accelerated decrease in BMD, and increased risk of bone fractures (26, 27). It was found that 53% of men with prostate cancer treated with ADT suffered from osteoporosis. A recent meta-analysis showed, however, that even in patients with hormone-naive prostate cancer the prevalence of osteoporosis varied from 4 to 38%, with higher percentage in men with more advanced disease. It suggests that all men with prostate cancer should have regular monitoring of bone health, regardless of the start of ADT (28).

TREATMENT OF METASTATIC BONE DISEASE

Over the last two decades bisphosphonates and denosumab have become significant elements of current therapies in cancer patients.

Bisphosphonates (BPs) are the analogues of pyrophosphates which decrease bone resorption and increase mineralization of bone tissue. BPs are embedded in bone, primarily at the active remodeling sites, released in the acidic environment of the resorption lacunae under osteoclasts and taken up by them. BPs inhibit osteoclast differentiation and maturation, diminish their adhesion to bone matrix and activity, and induce osteoclast apoptosis. These effects were suggested to be partly mediated via decreasing IL-6 secretion by bone marrow cells and inducing expansion of gamma/delta T cells, possibly contributing to a direct anti-tumor activity of BPs (29, 30).

Many double-blind, placebo-controlled trials showed effectiveness of BPs in reducing skeletal morbidity from metastatic cancers (30). It has been shown that BPs were strong inhibitors of osteolysis and limited the invasion and survival of tumor cells in the bone marrow. Contributing to apoptosis of malignant cells BPs were found to act synergistically with anti-neoplastic medications. This was confirmed in the case of chemotherapy given together with clodronate, ibandronate and zoledronic acid as well as with ablative therapy given together with clodronate and zoledronic acid. Clinical benefits were also observed in combined treatment with BPs and radiotherapy that resulted in increased bone mineral density and improved re-calcification of involved area (2, 18, 30).

Bisphosphonates were supposed to have direct anti-tumour and anti-angiogenic effects, but it still remains

a controversial issue. It was found that BPs relieve pain caused by the metastases itself or by radiotherapy, reduce the need to take opioids and improve the quality of life.

BP can prevent complications of bone metastases, such as vertebral wedge-shaped fractures with compression of medulla and fractures of weight bearing bones of lower extremities resulting in long-term immobilization (31-33).

It has been shown that bisphosphonates can inactivate the receptor of the human epidermal growth factor (HER) family of receptor tyrosine kinases (RTK), reducing cell viability in HER-driven lung, breast, and colon cancers (34, 35). The demonstration of this mode of action of BPs, could explain the reduced spread of cancer cells, the increase in disease-free survival (36, 37) and a lower incidence of colon cancer and breast cancer in patients taking oral BPs for the treatment of osteoporosis (38, 39). In women with breast cancer treated with anastrozole, the use of clodronate, pamidronate, and zoledronic acid were found to reduce osteopenia related to anti-neoplastic therapy. Current guidelines recommend dual energy absorptiometry (DXA) measurements for all women beginning therapy with AI. BPs should be started simultaneously with AI therapy for patients with T scores less than -2.5 or a history of fragility fracture. The UK Expert Group recommends BPs for women treated with AIs who are over 75 years old and have one or more risk factors independent of BMD. For younger women with osteopenia, it recommends starting therapy with BP at a T score of less than -2.0 or even at a T score of less than -1.0 in younger women receiving ovarian suppression (18, 33).

In patients with prostate cancer treated with androgen deprivation therapy the use of clodronate, pamidronate or zoledronic acid can prevent ADT-induced bone loss. Current recommendations suggest assessment of BMD with the method of DXA in men beginning ADT. Bisphosphonates are indicated if their T score is less than -2.5, or between -1.0 and -2.5 if other risk factors exist. Zoledronic acid was also proved for the treatment of bone metastases in patients with prostate cancer (18, 33).

Bisphosphonates have become the crucial part of the standard treatment of the multiple myeloma. The results of large meta-analysis that compared efficacy of different bisphosphonates vs. placebo in patients with MM revealed that clodronate, pamidronate, and zoledronic acid reduced the number of pathological fractures, bone lesions and other skeletal related events. A survival benefit has recently been reported in zoledronate-treated patients with newly diagnosed disease (13, 14, 40).

Denosumab (DSB) is a fully human, monoclonal antibody that binds to RANKL with high affinity and prevents its interaction with RANK in a way similar to the natural endogenous inhibitor – osteoprotegerin. It was documented that DSB, even after a single subcutaneous dose, caused rapid and profound suppression of

bone turnover in patients with multiple myeloma and breast cancer. Much greater reduction in serum concentration of biochemical marker of osteoclast activity (tartrate-resistant acid phosphatase) caused by DSB compared with BPs may suggest that in patients treated with BPs significant number of osteoclasts remain active leading to inadequate answer to anti-resorptive therapy. The switch to treatment with DSB could help to suppress the residual activity of osteoclasts (41-44).

It was confirmed that BPs and DSB prevented bone loss in women with suppressed ovarian function and/or given AIs due to breast cancer as well as in men treated with ADT because of prostate cancer. Pamidronate, zoledronic acid and DSB were shown to be effective, compared with placebo, in reducing the number of skeleton related events (SREs), such as progression of bone metastases, bone fractures and hypercalcemia of malignancy. It was found that zoledronic acid was superior to other bisphosphonates in preventing SREs and revealed an antitumor effect which led to 16% reduction in the risk of mortality within the first year of treatment. Denosumab was shown to be the most effective of the bone-targeted agents in reduction of the incidence of SREs and mortality (18, 45).

Therapy with high doses of potent antiresorptive medications, such as nitrogen-containing bisphosphonates and denosumab may result in development of rare but serious complications: osteonecrosis of the jaw and atypical femoral fractures. Most of the reports on those complications refer the association with high frequency of intravenous doses of pamidronate and zoledronic acid used in patients with breast cancer or multiple myeloma. Many of these patients had been previously and/or concurrently treated with chemotherapy and/or radiotherapy. In a retrospective review of medical records of "Cancer MD Anderson Center" of 4000 cancer patients receiving pamidronate, zoledronic acid or both osteonecrosis of the jaw has been described in 0.825% of the cases (18, 46).

It needs to be remembered that the key component of the therapy in the prevention of bone fractures is to ensure the adequate vitamin D and calcium supplementation. Practical guidelines for the supplementation of vitamin D and the treatment of deficits in Central Europe published in 2013 recommend 25(OH) vitamin D testing in patients with different types of cancer. Individuals with diagnosed vitamin D deficiency should be given higher doses of vitamin D up to 10,000 IU/day. Other persons require daily supplementation of 800-2,000 (4,000) IU/day, depending on age and body weight, between September and April or throughout the whole year, if sufficient skin synthesis of vitamin D is not ensured (47).

Daily calcium intake of approximately 1000-1300 mg/d is usually essential. In cancer patients, however, calcium supplementation has to be used with caution. It may be necessary in men with osteoblastic lesions due to prostatic cancer, but even dangerous in persons

with osteolytic metastases and hypercalcemia and/or hypercalciuria of malignancy (18, 48).

CONCLUSIONS

Multidisciplinary management integrating experts in systemic treatments, radiation therapy, orthopedic surgery, radiology and supportive care including palliative medicine is required for effective treatment of metastatic bone disease. Radiotherapy is the treatment of choice for palliation of localized bone pain. Single fractions seem to be

as effective as fractionated radiotherapy for relief of pain.

The bisphosphonates and denosumab are important agents for the treatment of metastatic bone disease, as they are able to decrease the rate of disease progression, delay complications, relieve symptoms and improve quality of life. Zoledronic acid seems to be the most effective bisphosphonate for prevention of morbidity from metastatic bone disease, while denosumab seems to be the currently most effective of the bone-targeted agents.

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