Bone complications in cancer patients

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Bone complications are frequently observed in cancer patients. They may be the result of the disease or due to the anticancer treatment. Osteoporosis is seen in up to 30% of cancer patients depending on tumor type and treatment and screening for osteoporosis is indicated in selected patients. It should be prevented by the use of calcium and vitamin D and exercising programs and, if present, should be adequately treated by drugs registered for the treatment of osteoporosis. Bone metastases are observed in up to 75% of metastatic cancer patients depending on the tumor type. Skeletal-related complications, occurring in 50-70% in patients with bone metastases, can be prevented and delayed by the use of bisphosphonates or denosumab. Prevention of the development of bone metastases has been shown by anti-tumor treatment while the role of modification of the micro-environment by bisphosphonates and denosumab needs further study.

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Introduction

Normal bone is composed of different cells (e.g. osteocytes, osteoblasts, osteoclasts, other cells) and an extracellular matrix which consists of organic components (e.g. collagen, osteocalcin, osteonectin, proteoglycans, glycosaminoglycans, lipids) and inorganic hydroxyapatite calcium (65%). Bone is in constant change by bone formation and absorption that is regulated by different hormones (e.g. parathyroid hormone, estrogen/testosterone, glucocorticoids, calcitonin), vitamins (e.g. 1,25-dihydroxyvitamin D3) and cytokines (e.g. fibroblast growth factor, tumor necrosis factor-α,insulin growth factor, interleukin 1, RANKL, osteoprotegerin). The main regulatory mechanism for bone homeostasis is the balance between Receptor activator of nuclear factor kappa-B (RANK) ligand and osteoprotegerin secretion by the osteoblasts. If the ratio is going to RANK ligand dominance, maturation and stimulation of osteoclasts is taking place, resulting in bone absorption (*Figure 1*, page 4).

In oncology patients, different events can lead to bone complications such as osteoporosis and bone metastases. In this review, these events are discussed and the prevention and treatment of bone complications are given.

Osteoporosis

Osteoporosis is a systemic skeletal disease characterized by low bone mass, deterioration of the bone microarchitecture and increased bone fragility, which leads to susceptibility to fracture. It is characterized by a decrease in bone strength and increased risk of vertebral, hip, and other bone fractures.[1]

Osteoporosis is frequently reported in cancer patients; it is observed in 27.2% of breast cancer patients, 18% in patients with prostate cancer on androgen deprivation therapy, 1% in childhood cancer survivors, and 6% after allogeneic stem cell transplantation.[2-5]

Risk factors for the development of osteoporosis are premature menopause due to chemotherapy, hypogonadism due to hormonal therapy (e.g. androgen deprivation therapy, aromatase inhibitors) or pelvic radiotherapy, growth hormone deficiency, childhood/adolescent diag-

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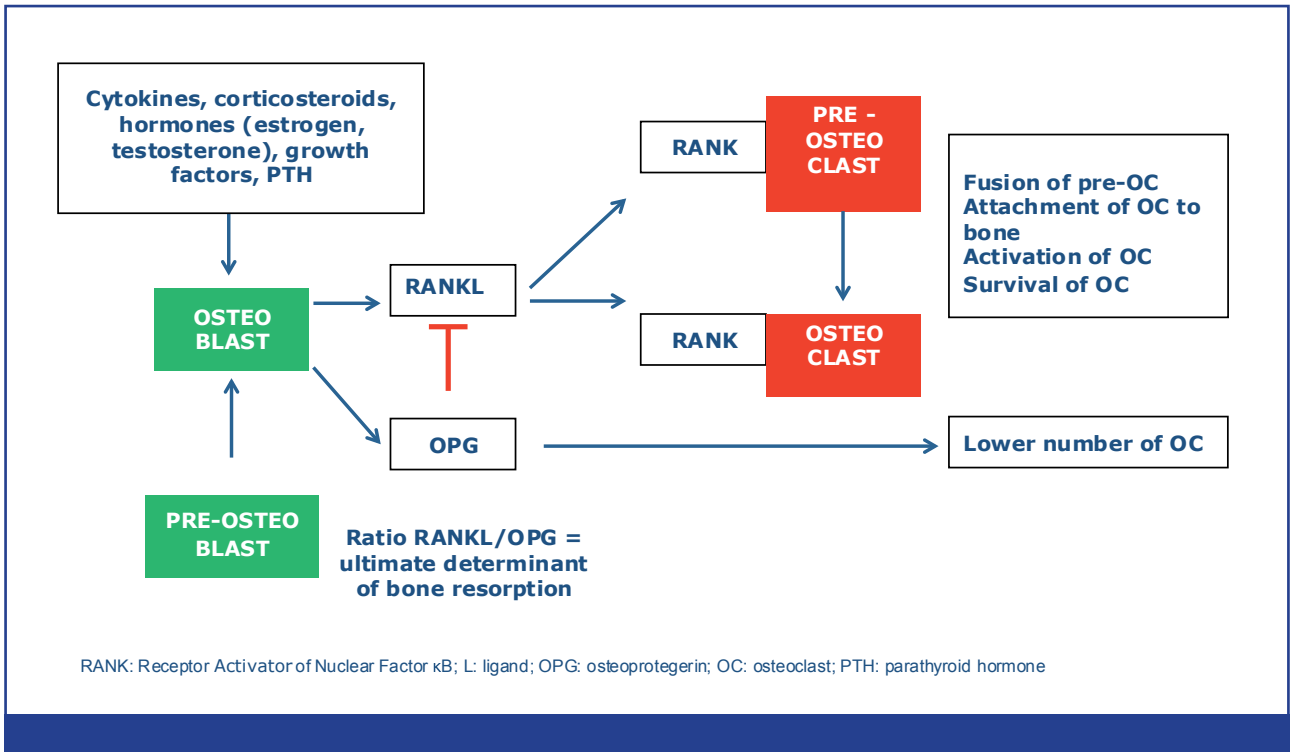

Figure 1. Bone homeostasis: balance between bone resorption (osteoclasts) and bone formation (osteoblasts).

nosis of certain cancers (acute lymphoblastic leukemia, malignant bone tumors, rhabdomyosarcoma, brain tumors) or treatment of these patients with cranial radiotherapy, chemotherapy with ifosfamide or methotrexate, stem cell transplantation or prolonged glucocorticoid therapy.[6]

Cancer patients should be screened for osteoporosis. This can be by a DEXA scan which measures the bone mineral density (BMD) which is the average concentration of mineral in a 2- or 3-dimensional image or in a defined section of bone.[7] Measurements are made at the hip, which best predicts the risk for hip fracture and at other skeletal sites and is used for decision making while spine BMD is the most sensitive parameter to evaluate early bone loss.[8, 9]

Based on the BMD, the T score, which compares the BMD with this of young adults (age 25-50 years) of the same sex, is calculated and used to guide decision making about monitoring and treatment in adults while the Z score, which compares the BMD with this of adults of same sex and same age, is used to guide decision making about monitoring and treatment in children and adolescents.[6] The World Health Organization (WHO) defines a normal BMD as within 1 standard deviation (SD) of a young normal adult or a T-score of ≥ -1.0; osteopenia as a BMD between 1.0 and 2.5 SD below that of a young normal adult or a T-score between -1.0 and -2.5; and osteoporosis as a BMD ≥ 2.5 SD or more below that of a young normal adult or a T-score of ≤ -2.5.[10] BMD should be measured in women older than 65 and men older than 70 years; adults older than 50 years after fracture; adults with a condition (e.g. rheumatoid arthritis) or treatment associated with decreased bone mineral mass and any patient considered for osteoporosis drug treatment.[11] In Belgium, BMD measurement is reimbursed in women older than 65 years with a familial history of osteoporosis and in patients with one or more risk factors such as non-oncologic low impact vertebral fracture, history of peripheral low impact fracture (except fingers, toes, skull, face or cervical vertebra), steroid therapy > 7,5 mg prednisolone during more than 3 months and in cancer patients on anti-hormonal therapy or therapy-induced menopause and some other specific conditions. This examination is repeated every 5 years, or more frequently when osteoporosis therapy is initiated.[12]

With the aid of the WHO FRAX Tool it is possible to calculate the fracture risk based on individual patient factors such as femoral neck BMD and clinical risk factors (e.g. age, race, sex, personal and parental history of fracture, smoking (current) and alcohol use (≥ 3 units/day), body mass index, history of glucocorticoid use, rheumatoid arthritis).[13]

General measures to prevent osteoporosis are to avoid

Table 1. Prevention of skeletal-related complications.[21-23,30]

Tumor type	Medication	Comparator	Endpoint	Effect SRE
Breast	Pamidronate	Placebo	Proportion SRE	PAM > Plac
Prostate	Zoledronic acid	Placebo	Proportion ≥ 1 SRE	ZOL > Plac
Breast	Zoledronic acid	Placebo	SRE rate ratio	ZOL > Plac
Other	Zoledronic acid	Placebo	Proportion ≥ 1 SRE	ZOL > Plac
Breast	Clodronate	Placebo	SRE	CLO > Plac
Prostate	Clodronate	Placebo	Asymp Bone PFS	CLO > Plac
Breast	Ibandronate	Placebo	S Morbidity Period R	IBA > Plac
Other	Ibandronate	Placebo	SRE	IBA > Plac
Other	Clodronate	Placebo	SRE	=
Prostate	Pamidronate	Placebo	Bone pain	=
Breast	Zoledronic acid	Pamidronate	Proportion ≥ 1 SRE	=
Breast	Denosumab	Zoledronic acid	First on-study SRE	DEN > ZOL
Prostate	Denosumab	Zoledronic acid	Time to first on-study SRE	DEN > ZOL
Other	Denosumab	Zoledronic acid	Time to first on-study SRE	=

SRE: skeletal-related event; PAM: pamidronate, PLAC: placebo; ZOL: zoledronic acid; CLO: clodronate; IBA:ibandronate; DEN: denosumab Asymp: asymptomcatic; PFS: progression-free survival; S: skeletal; R: duration,; =: equal

tobacco smoking and excessive alcohol intake; regular weight-bearing and muscle-strengthening exercise to reduce the risk of falls and fractures; and calcium (1,200 mg/day) and vitamin D (800-1,000 IU/day) supplements for persons > 50 years.[11] A recent study showed an increased risk of myocardial infarction with the use of calcium supplements, so this recommendation should be used carefully.[14]

Preventive treatment is indicated in postmenopausal women and men > 50 years with low bone mass (T-score between -1.0 and -2.5, osteopenia) at the femoral neck or spine and a 10-year hip fracture probability ≥ 3% or a 10-year major osteoporosis-related fracture probability ≥ 20% estimate with FRAX.[11] However, preventive treatment is not reimbursed in Belgium.

Indications for treatment of osteoporosis are hip or vertebral (clinical or morphometric) fractures and BMD T-scores ≥ -2.5 at the femoral neck or spine by dual-energy x-ray absorptiometry while reimbursement in Belgium starts from a BMD T score of > 2.5.[11]

Several drugs are registered and reimbursed in the treatment of osteoporosis: bisphosphonates (e.g. alendronate, etidronate, ibandronate, zolendronate), which bind to hydroxyapatite thereby decreasing the number/activity of osteoclasts; raloxifene, a selective estrogen receptor modulator which influences the estrogen receptor in bone and lipids, and acts as an antagonist in breast and uterus, and inhibits osteoclast recruitment and activity; teriparatide, a recombinant form of parathyroid hormone (PTH), which activates osteoblasts more than osteoclasts; strontiumranelate (= calcium analogue) which stimulates calcium-sensing receptors and leads to differentiation of pre-osteoblast to osteoblast and influences osteoclast activation by secretion of osteoprotegerin; and denosumab, a monoclonal antibody against RANK ligand, that inhibits osteoclast maturation and activation.

Bone metastases

Bone metastases occur frequently in many tumor types: their incidence in patients with breast cancer varies between 65–75%; in prostate cancer between 65–75%; in lung cancer between 30–40% and in bladder cancer it lays around 40%.[15] Bone metastases can lead to complications such as hypercalcemia or other skeletal-related events (SREs) defined as pathological fractures, spinal

Table 2. Prevention of bone metastases development by bone modifying agents in patients with breast cancer.

Author (year)	Control arm	Experimental arm	Bone metastasis control arm (%)	Bone metastasis experimental arm (%)	Disease-free survival	Overall survival
Diel (1998)	No treatment	Clo (1,600 mg/d-2 yrs)	17*	8	Plac < Clo	Plac < Clo*
Saarto (2001)	Plac	Clo (1,600 mg/d-3 yrs)	17	21	Plac > Clo*	Plac > <Clp*
Powles (2006)	Plac	Clo (1,600 mg/d-2 yrs)	9.6*	13.5	NR	Plac > Clo*
Paterson (2012)	Plac	Clo (1,600 mg/d-3 yrs)	4.8	3.7	Plac = Clo&	Plac = Clo
Kristensen (2008)	No treatment	Oral pam (2x150 mg/d-4 yrs)	6.3	7.6		No treat = Pam
Gnant (2009)	No ZA	ZA (4 mg q 6 mo)	23	16	No ZA < ZA*	No ZA = ZA
Coleman (2011)	No ZA	ZA (4 mg q 1 mo x 6 then q 3-6 mo for 5 yrs)	46	40.6	No ZA = ZA	No ZA = ZA
Coleman (2012)	D ZA (4 mg q 6 mo)	IM ZA	24	14	No ZA < ZA*	No ZA = ZA
Möbus (2011)	No ibandronate	Ibandronate (50 mg/d-2 yrs)	=	=	No IBA = IBA	No IBA = IBA

*Treat: treatment; Plac: placebo; Clo: clodronate; Pam: pamidronate; ZA: zoledronic acid; IBA:ibandronate; NR: not reported; *: p<0.05; yrs: years; &: improved in women older than 50 years; mo: months; D: delayed; IM: immediate; yrs: years*

cord compression or need of surgery or radiotherapy to bone.[16] SREs occur in around 50-70% of patients with bone metastases and represents a heavy burden on the quality of life of these patients.

There is a complex interaction between bone and tumor cells. When tumor cells are nested in bone, they secrete different cytokines (e.g. PTH-related protein, prostaglandin E2, interleukin (IL)-1, IL-6, IL-8, IL-11, macrophage-colony stimulating factor, macrophage inflammatory proteins -1α) that influence osteoblast activity. Also, there may be direct interactions between tumor cells and osteoblasts and osteoclasts. When osteoblasts are stimulated to secrete RANK ligand, this cytokine gives rise to osteoclast activation and maturation. There may also be an influence of RANK ligand on the tumor cells itself since RANK is identified on prostate, breast, lung and renal cell carcinoma cells and RANK ligand in prostate, breast and renal cell cancer cells and multiple myeloma.

Osteoclast activation leads to bone breakdown, releasing several factors from bone tissue (e.g. transforming growth factor β, other bone-derived factors), that stimulate tumor cell growth.[17]

Besides the autocrine secretion by tumor and bone cells, the microenvironment can also be influenced by other factors such as hormones. Estrogen and progesterone may induce the production of inhibitory cytokines by fibroblasts in the bone, influencing both osteoblasts and osteoclasts. In postmenopausal women, this inhibition may not be present.[18]

Preventing/delaying skeletal-related events

Several treatment modalities are used to prevent or delay SRE and consists of surgery (e.g. preventive surgery of long bones with osteolytic lesions), external radiotherapy (e.g. preventive or analgesic radiotherapy), radio-isotopes, anticancer drugs and bone-modifying medications (e.g. bisphosphonates, denosumab).

Bisphosphonates bind to bone sites of active remodelling and inhibit osteoclast-mediated osteolysis. Bisphosphonate treatment has shown to reduce the risk of SREs in patients with metastatic bone disease (*Table 1*, page 5), increase the time to first and subsequent SREs and reduce the proportion of patients suffering from SREs by 30% - 50%.[19] They also have a beneficial effect on skeletal-related pain.[20]

Side effect of intravenously administered bisphosphonates are fatigue, nausea and vomiting , bone pain and myalgia, headache, fever, hypocalcaemia, increased serum PTH, subtrochanteric fractures, transient leukopenia/anemia, renal insufficiency and osteonecrosis of the jaw, while oral preparations can, in addition to the previous side effects, give rise to gastrointestinal disturbances such as pyrosis, oesophageal irritation

Key messages for clinical practice

1. Bone complications are frequent in cancer patients.
2. Osteoporosis should be screened for in selected patients and should be adequately treated.
3. Skeletal-related events can be prevented and postponed by the use of bisphosphonates and denosumab.
4. Prevention of the development of bone metastases can be done by anticancer treatment while the use of bone-modifying agents needs further study.

and ulceration. However, in general these side effects are mild and easily manageable.

Recently, studies comparing zoledronic acid, a bisphosphonate, with denosumab, a monoclonal antibody against RANK ligand in patients with breast and prostate cancer and other tumor types including multiple myeloma have shown that the latter was not inferior to zoledronic acid and increased the time to first SRE with 8.2 months, reduced the number of SRE both in patients with a first and subsequent SRE and delayed pain progression and the need for strong opioids (*Table 1*).[21-23] There was no difference in progression-free and overall survival. The toxicity profile of denosumab is similar to that of zoledronic acid although there is no need to adapt for renal function since it has no known renal toxicity. More acute phase reactions and hypocalcaemia are observed in patients treated with denosumab.[24]
Both zoledronic acid and denosumab are registered and reimbursed in Belgium in the prevention of SREs in cancer patients with bone metastasis.

Preventing/delaying bone metastases
Since bone metastases are such an invalidating complication of cancer, prevention of the development of bone metastases is of importance. This can be done by treatments aiming at the cancer cell itself or at the microenvironment.
In patients with hormone-sensitive breast cancer, adjuvant treatment with hormones (e.g. tamoxifen, letrozole) is able to decrease the incidence of bone metastasis around 4% compared to placebo.[25,26] Also targeted therapy has been shown to decrease the incidence of bone metastases in patients with HER2 overexpressing breast cancer and treated with trastuzumab compared with placebo by 0.8-4.3%.[27,28]
Targeting the microenvironment has also been tested in the prevention of bone metastases. Conflicting results have been reported with older bisphosphonates such as clodronate or oral pamidronate in relation to their bone metastasis protective effect in patients with breast cancer and treated in adjuvant setting (*Table 2*). Most of these studies could not show a survival benefit. Similar results were obtained for zoledronic acid and ibandronate (*Table 2*) with no overall survival benefit, although subgroup analysis showed a beneficial effect in postmenopausal women, showing the importance of hormones on the microenvironment. However, most of these latter findings were by retrospective analysis and their validity remains to be proven.
Denosumab was compared to placebo in patients with castration-resistant prostate cancer to improve bone metastasis-free survival. There was an improvement of this primary endpoint but not in overall survival. More patients experienced hypocalcemia and osteonecrosis of the jaw in the denosumab arm.[29]

Other studies are examining the effect of these bone-modifying agents in different tumor types and settings. At the moment there is no registration for this indication with any of the medication mentioned.

Conclusion

Bone complications are frequent in cancer patients. Osteoporosis should be detected and treated adequately to prevent osteoporotic fractures. Also bone-modifying agents should be used in patients with bone metastases to prevent and delay SREs. However, at the moment there is no place to use these agents in the prevention of bone metastasis development.

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