

## Osteoporosis – a partially recognized challenge for oncology

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Osteoporosis is a huge challenge for medicine, especially public health and geriatrics, but also oncology, because it is a chronic disease requiring long-term, sometimes lifelong care. With the ageing of the population, falls are the third most common cause of disability in the elderly and one of the main reasons for admissions to nursing homes. Although there are approximate data on the incidence of osteoporosis worldwide, there are unfortunately no data on the incidence of osteoporosis in cancerous diseases. The incidence of cancer-related osteoporosis is expected to increase as the incidence of cancer in general increases. There are specific problems that concern osteoporosis in cancer patients, including: the mechanisms of development of osteoporosis in cancer diseases, the distinction between cancerous and osteoporotic lesions, undertreatment of patients, the lack of an integrated care system for osteoporosis in cancer patients.

**Key words:** osteoporosis, bone fracture, densitometry, malignant diseases

Osteoporosis is a huge challenge for medicine, especially public health and geriatrics, but also oncology because it is a chronic disease requiring long-term, sometimes lifelong care. Elderly patients often show signs of frailty (reduced mobility, malnutrition, comorbidity, cognitive impairment, polypharmacy, neurosensory deficits, reduced muscular functionality) which are associated with a high risk of falls leading to fracture [1]. Osteoporosis and the fractures caused by it lead to increased mortality. In the case of hip fractures, the increased risk of mortality is particularly pronounced 3–6 months after the fracture. With the ageing of the population, falls are the third most common cause of disability in the elderly, and one of the main reasons for admissions to a nursing home [2, 3].

According to the World Health Organization (WHO), osteoporosis is defined as bone densitometry (DXA) T-scores less than 2.5 at the lumbar spine or femoral neck and microarchitectural deterioration of bone tissue [4, 5]. Osteoporosis is

also defined as a systemic skeletal disease characterised by low bone mass, with a consequent increase in bone fragility and susceptibility to fracture [6, 7]. Despite significant progress in the treatment of cancer, the problem of osteoporosis that accompanies these diseases is often neglected.

While osteoporosis is not a precursor for cancer, many people with oncological diseases develop osteoporosis as a result of the malignant effects of the disease or its treatment. Interestingly, despite the growing problem, osteoporosis issues are generally omitted in oncology textbooks. And yet osteoporosis may be one of the actual side effects of oncological treatment [8].

### Do we have data on the epidemiology of osteoporosis in cancerous diseases?

Unfortunately, there are no detailed data on the epidemiology of osteoporosis in the world. Also, estimates of the incidence

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of osteoporosis vary significantly. Osteoporosis is estimated to affect approximately 200 million people worldwide while osteoporosis fractures are estimated to affect 2.7 million men and women in Europe [6, 9, 10]. At least 40% of postmenopausal women develop osteoporosis and 15–30% of men. According to the National Health Fund data, the estimated number of people suffering from osteoporosis in Poland in 2018 was 2.1 million, of which 1.7 million were women [11]. The incidence of osteoporosis increases with age and particularly affects people who are in their 70s. Population ageing is a global public health challenge. According to WHO figures, the percentage of the population over the age of 60 years will increase from 12% in 2015 to 22% in 2050 [12]. It is estimated that by 2050 this age group will increase to 2 billion. According to the National Health Fund data, the degree of underestimation of osteoporotic patients in Poland in 2018 was 74%. This corresponds to 1.56 million undiagnosed people, of whom almost 500,000 were over 80 years of age [11]. When the inhabitants of the European Union aged 50–80 are stratified into five-year age groups, the highest percentage of women diagnosed with osteoporosis (approximately 3.9 million women) is observed in the 75–79 age group, and among men in the 60–64 age group (about 0.8 million men) [13].

Although there are approximate data on the incidence of osteoporosis worldwide in the general population, there are unfortunately no data on the incidence of osteoporosis in cancerous diseases. The incidence of cancer-related osteoporosis is expected to increase as the incidence of cancer in general increases, including two hormone-dependent cancers in particular: breast cancer in women and prostate cancer in men.

In Poland in 2020, the most common cancer in men was prostate cancer (19.6% of all malignant tumours in men) whilst for women that was breast cancer (23.8% of all malignant tumours in women). In the same year, the second leading cause of cancer deaths was prostate cancer in men (10.6% of all malignant tumours in men) and breast cancer in women (15.3% of all malignant tumours in women) [14]. Among men in the oldest age group (the over 65 age group), the most common cancer was prostate (23% of incidences, 13% of deaths) and among women in the same age group, the most prevalent was breast cancer (19% of incidences, 14% of deaths) [14]. Bone changes that lead to osteoporosis in cancer can be caused by cancer itself (cancer-induced bone disease – CIBD) or bone loss caused by oncological treatment (cancer treatment-induced bone loss – CTIBL). Osteoporosis observed in cancer may be the result of the disease itself or the adverse effects of therapy that reduces bone mineral density. The bone microenvironment is a good substrate for the growth of cancer cells.

### **Risk factors for the development of osteoporosis in neoplastic diseases**

Among the factors influencing the development of osteoporosis, are modifiable and non-modifiable factors. The first group of factors includes:

- low calcium intake,
- reduced exposure to sunlight,
- prolonged immobility,
- excessive alcohol intake,
- smoking,
- eating disorders,
- long time immobility,
- low body mass index (BMI),
- low physical activity,
- several medications (glucocorticoids, anticonvulsants, chemotherapy and hormone therapy of breast and prostatic cancer).

The second group of factors includes:

- older age,
- female sex,
- white race,
- personal and parental history of osteoporosis and fractures,
- low body frame size [15].

Virtually all oncological patients are exposed to an increased risk of osteoporosis and associated fractures as a result of an unfavourable combination of factors: cancer, often advanced age, treatment regimens, which all directly or indirectly affect bone cells [16]. Although osteoporosis in oncological patients is usually associated with hormone-dependent cancers (breast cancer, prostate cancer), it can occur during the course of all cancers. As a co-existing disease with cancer, it can significantly worsen the prognosis of cancer patients, because osteoporosis and the fractures caused by it lead to increased mortality. For hip fractures, the increased risk of mortality is particularly exacerbated in the 3–6 months after the fracture. The peak of bone mass formation occurs in most people between the ages of 16 and 25, followed by a slow but steady loss of bone mass of 0.3% per year in men and 0.5% per year in women. But in postmenopausal women, bone loss within 5 years of osteoporosis can be 5–6% per year [17].

### **Specific problems of osteoporosis in cancer patients**

There are specific problems that concern osteoporosis in cancer patients, including:

- the mechanisms of development of osteoporosis in cancer diseases,
- the distinction between cancerous and osteoporotic lesions,
- undertreatment of osteoporosis in cancer patients,
- the lack of an integrated care system for osteoporosis in cancer patients.

Osteoporosis is the end result of various mechanisms leading to its development. The causes of osteoporosis during cancer treatment include:

- therapy-induced hypogonadism,
- use of glucocorticoids in chemotherapy regimens,
- toxic effects of chemotherapy and radiotherapy,

- immobilization,
- eating disorders [18].

In hormone-dependent cancers (breast cancer, prostate cancer), hypogonadism is an intended part of the treatment strategy and substitution treatment cannot be used. The opposite is true in hormone-independent cancers, where hypogonadism is not the intended goal of treatment.

Chemotherapy and hormone therapy cause thinning of the trabecular and cortical bones. The development of osteoporosis is influenced by the type of chemotherapeutic, its dose and duration of use. Drugs used in systemic cancer therapy contribute to the development of osteoporosis, especially: cyclophosphamide, cisplatin, taxanes, aromatase inhibitors, which all reduce calcium levels and lead to bone loss. Steroids that are used in cancer chemotherapy as part of chemotherapy regimens or as an antiemetic cause impaired calcium absorption and bone loss [18].

Similarly, drugs used in bone marrow transplants increase the risk of bone loss. The use of high doses of drugs in bone marrow transplantation is associated with the risk of developing osteoporosis in the first years after transplantation. This is related to the direct and indirect effects of chemotherapy: hypogonadism, increased bone resorption and renal dysfunction, secondary hyperparathyroidism and the use of glucocorticosteroids. The reduction in bone formation is due to malabsorption due to graft-versus-host disease (GVHD), mucositis with reduced absorption of calcium and vitamin D and the direct effect of chemotherapy on osteoblasts [19].

Radiation therapy has direct and indirect effects on bones. Direct action induces local bone and bone marrow atrophy, leading to bone loss, growth factor deficiency and retardation of bone growth. In turn, the indirect effect of radiotherapy causes vascular changes leading to fractures, especially of the pelvis and ribs [20].

The following factors have an indirect influence on the development of osteoporosis in cancer diseases:

- myelosuppression,
- damage to the gastrointestinal mucosa,
- malabsorption,
- intensification of catabolic processes,
- weakness or fatigue during the course of the cancer,
- weight loss,
- frequent generalised and chronic infections accompanying the underlying disease.

In the development of osteoporosis during the course of breast cancer, a key role is played by the induction of inflammatory stress in osteoblasts, which leads to the synthesis of cytokines acting on osteoclasts, resulting in an increase in bone resorption and a reduction in bone formation. Tamoxifen, used in hormone therapy for breast cancer, has an anti-resorptive effect, but does not affect bone growth. On the other hand, aromatase inhibitors (anastrozole, letrozole and exemestane)

inhibit the production of oestrogens, which leads to a decrease in bone density [18]. In patients with breast cancer:

- bone pain occurs in 40–80%,
- osteoporosis in 40–50%,
- pathological fractures in 10–30%,
- hypercalcaemia 10–30%,
- bone marrow weakness in about 20%,
- spinal cord damage in about 10%.

The risk of developing osteoporosis is 68% higher in women with a history of breast cancer than in healthy women [21]. The risk of developing osteoporosis in women with a history of breast cancer diagnosed  $\leq 50$  years of age is 1.98 times higher than in healthy women.

The risk of developing osteoporosis in breast cancer survivors treated with chemotherapy and hormone therapy is 2.7 times higher than in healthy women. Thus, there is an increased risk of osteoporosis in women with a history of breast cancer who were: younger, had tumours that expressed oestrogen receptors and were treated with hormones or in a combination way (hormone therapy and chemotherapy) [21].

The mechanisms of osteoporosis development in antiandrogenic therapy include: testosterone deficit, decreased aromatization of testosterone to oestrogen. GnRH agonists cause increased activation of osteoclasts dependent on parathyroid hormone. The strongest osteoporotic effect occurs during the first year but persists throughout the therapy. Osteoporosis in hormone-independent tumours mainly affects patients with:

- multiple myeloma,
- lung cancer (glandular),
- kidney cancer (clear cell),
- neuroblastoma,
- Ewing's sarcoma,
- large cell bone tumour,
- tumours of the central nervous system.

Multiple myeloma accounts for 1% of all cancers and 10% of hematologic cancers. The morbidity is estimated at 3/100,000, and the peak of incidence falls in the years 55–75 years. The disease consists in the monoclonal production of plasma cells and their precursors – B lymphocytes.

There are 4 main mechanisms for the development of osteoporosis in multiple myeloma:

1. increased expression of the RANK ligand on multiple myeloma cells, which leads to the stimulation of osteoclasts,
2. other pro-osteoclastic factors: IL-6, IL-11, TGF- $\beta$ , which cause osteoclast activation and bone resorption,
3. protection of multiple myeloma cells from osteoprotegerin by phagocytosis and intracellular lysis,
4. DKK-1 (Dickkopf-related protein 1) synthesis by myeloma cells, which inhibits the differentiation of cells into osteoblasts and thus inhibits the formation of new bone structures.

In patients with multiple myeloma, histological growth type correlates with bone remodelling: paratrabeular/node type leads to a high degree of osteoclastic bone resorption, which is associated with an unfavourable prognosis and is an indication of bisphosphonate therapy. There is no apparent increased osteoclastic resorption in interstitial type and this type of multiple myeloma carries a more favourable prognosis [22].

Tumours of the central nervous system have a complex mechanism at the onset of osteoporosis, which consists of: the use of glucocorticoids, antiepileptic and anticoagulant drugs, chemotherapy and radiotherapy, eating disorders, immobilization and paralysis [8]. In oncology, it is extremely important to distinguish metastatic lesions during the course of cancer from osteoporotic lesions. The clinical picture, as well as radiological and biochemical parameters help to distinguish these changes. In the case of bone metastases, pain is often present clinically, usually in multiple places, while in osteoporosis, the lesions are usually painless unless there are bone fractures [23]. In bone metastases, the radiological picture is rarely normal, while in osteoporosis, unless there are fractures, the radiological picture is usually normal [23]. In biochemical tests, alkaline phosphatase and markers of bone resorption in the urine are usually elevated in bone metastases and hypercalcaemia is common. On the other hand, in osteoporosis, biochemical parameters are usually normal, bone resorption parameters are slightly elevated in the urine and there is no hypercalcaemia [23].

In the treatment of osteoporosis, three key elements should be taken into account:

- pain,
- immobility, and
- as a result of the first two, a complete deterioration of the patients' quality of life.

The main goal of therapy should not only be to control osteoporosis in its active phase (fractures), but also to prevent further fractures. Non-pharmacological measures include a diet, exercise, smoking cessation and reduction of alcohol consumption.

Pharmacological treatment includes the use of bisphosphonates, RANK ligand inhibitor (denosumab), sclerostin inhibitor (romosozumab), recombinant parathyroid hormone (teriparatide) [20]. In the latest recommendations, the American College of Physicians (ACP) recommends that clinicians use bisphosphonates for initial pharmacologic treatment to reduce the risk of fractures in postmenopausal females (strong recommendation; high-certainty evidence) and in males diagnosed with primary osteoporosis (conditional recommendation; low-certainty evidence). Also, ACP suggests that clinicians use the RANK ligand inhibitor (denosumab) as a second-line pharmacologic treatment to reduce the risk of fractures in postmenopausal females (conditional recommendation; low-certainty evidence)

and in males (conditional recommendation; low-certainty evidence) diagnosed with primary osteoporosis who have contraindications to or experience adverse effects of bisphosphonates. Other recommendations apply only to women and ACP suggests that clinicians use the sclerostin inhibitor (romosozumab, moderate-certainty evidence) or recombinant parathyroid hormone (teriparatide, low-certainty evidence), followed by a bisphosphonate, to reduce the risk of fractures only in females with primary osteoporosis with very high risk of fracture (conditional recommendation). Also, ACP suggests that clinicians take an individualised approach regarding whether to start pharmacologic treatment with a bisphosphonate in females over the age of 65 with low bone mass (osteopenia) to reduce the risk of fractures (conditional recommendation; low-certainty evidence) [24].

Bisphosphonates such as risedronate, alendronate, ibandronate, zoledronic acid and pamidronate are a group of drugs that work by slowing bone loss. They are used to treat and prevent osteoporosis. The osteoclast cells absorb the bisphosphonates and their activity is slowed down. Denosumab is a bone anti-resorptive drug used to treat osteoporosis. Denosumab is a total human IgG2 monoclonal antibody that binds to the receptor activator of NF kappa B ligand (RANKL) and competitively inhibits its binding to the receptor activator of NF kappa B (RANK). Denosumab binds to RANKL with high affinity and blocks it from binding to and oligomerizing its receptor RANK, thus inhibiting osteoclast maturation and bone resorption [25]. Abaloparatide is a human parathyroid hormone-related protein (PTHrP) that has been modified in order to potentiate the osteoanabolic effect [26–27]. Teriparatide is a recombinant fragment of the human parathyroid hormone consisting of its first amino(N)-terminal 34 amino acids and a potent osteoanabolic agent. The anabolic effects are mediated by upregulated transcriptional expression of pro-osteoblastogenic growth factors, modulation of the wnt/beta-catenin osteoanabolic signalling pathway by down-regulating the synthesis of the wnt-antagonist sclerostin, and increased expression and activity of Runx2 – a transcription factor essential for differentiation of osteoblasts [28–29]. Romosozumab is the first anabolic medication that both increases bone formation and decreases bone resorption. Data suggest that romosozumab is more effective than oral bisphosphonates in preventing osteoporotic fractures [30].

Raloxifene belongs to a class of drugs called selective oestrogen receptor modulators (SERMs). Raloxifene is a selective oestrogen receptor modulator that produces both oestrogen-agonistic effects on bone and lipid metabolism and oestrogen-antagonistic effects on uterine endometrium and breast tissue. It acts as an antiresorptive, with preservation of both bone mineral density and bone strength [31]. Posology and adverse reactions for osteoporosis according to Qaseem et al. are presented in table I [24].

**Table I.** The posology and most common adverse reactions for osteoporosis therapy

Drug	Dose	Side effects
alendronate (bisphosphonate)	10 mg orally, once a day or 70 mg once a week	upper gastrointestinal disturbances, osteonecrosis of the jaw, atypical femur fractures, severe bone, joint and muscle pain
risedronate (bisphosphonate)	35 mg orally, once a week	upper gastrointestinal disturbances, osteonecrosis of the jaw, atypical femur fractures, severe bone, joint and muscle pain
zoledronate (bisphosphonate)	usually 5 mg/100 ml by intravenous injection once a year	osteonecrosis of the jaw, atypical femur fractures, severe bone, joint and muscle pain
denosumab (RANK ligand inhibitor)	60 mg by subcutaneous injection every 6 months	joint and muscle pain, constipation, dermatologic reactions and serious infections, including skin infections, osteonecrosis of the jaw, atypical fractures, delayed fracture healing
abaloparatide (parathyroid hormone-related protein)	80 µg per day by subcutaneous injection	hypercalcaemia and hypercalciuria, dizziness, headache, back, joint and muscle pain, nausea, hypertension, palpitations, hypersensitivity reactions
teriparatide (recombinant human parathyroid hormone)	20 µg per day by subcutaneous injection	confusion, constipation, depression, dry mouth, headache, incoherent speech, increased urination, loss of appetite, metallic taste, muscle weakness, nausea, stomach pain, thirst, tiredness, vomiting, weight loss, arm, back or jaw pain, chest pain, fast or irregular heartbeat, fever or chills, sweating
romosozumab (sclerostin inhibitor)	210 mg once a month for 12 months (two consecutive 105 mg injections at different injection sites) supplemented with calcium and vitamin D	arthralgia, headache, hypersensitivity, increased risk of infection, muscle spasms, neck pain, skin reactions, cataract, hypocalcaemia, myocardial infarction, stroke, angioedema
raloxifene (selective oestrogen receptor modulator)	60 mg orally, once a day	hot flashes, action, abdominal pain, indigestion, flu-like symptoms, blood pressure, headache (including migraine), bulging, leg muscle spasms, breast pain, enlargement and tenderness, peripheral circumference, thrombocytopenia, stroke, thromboembolic event in the venous system, including deep vein thrombosis, pulmonary embolism, thrombosis of the yellow vein, superficial thrombophlebitis, circulatory thromboembolism

### Undertreatment of osteoporosis

The probable causes of insufficient treatment of osteoporosis are: fear of adverse effects of treatment, low awareness of the problem of osteoporosis among both medical staff and patients, problems with reimbursement of treatment and poor coordination of health care – especially in patients suffering from co-existing diseases such as cancer [32]. In addition, treatment of osteoporosis is hampered by poor patient compliance, which is particularly evident with the use of bisphosphonates [33–35]. This is made worse by the fact that the prescription of bone-protective drugs is declining worldwide [34].

Between 2001 and 2011, the number of prescriptions for bone-protective drugs in the United States fell from 40% to 21% [35]. A similar decline was observed in other countries [36–39]. Treatment of osteoporosis in cancer patients can be initiated in patients at risk of bone fractures, even in old age, and continued as long as evidence indicates the effectiveness of this treatment.

### The need for an integrated care system

An opportunity to improve the fate of oncology patients diagnosed with osteoporosis is the creation of an integrated care

system such as Fracture Liaison Services (FLS). Such a system would not only ensure effective and safe care, but also improve the correct intake of the drug [40, 41]. As opposed to England and Wales, where only 51% of NHS trusts have an FLS, there is a 100% coverage of FLS in Scotland and Northern Ireland.

### Conclusions

1. Osteoporosis can occur in virtually all cancerous diseases.
2. In order to assess the scale of the osteoporosis and its therapeutic procedures, there is a need to create a registry of osteoporosis, especially in malignant diseases.
3. In order to provide optimal care for oncological patients diagnosed with osteoporosis, integrated care centres should be established.

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