Review

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Radioisotope therapy of bone metastases

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Abstract

Radionuclide therapy has been an integral part of systemic treatment of patients with advanced and disseminated cancer for 50 years. Specific radioisotopes (β- or α-emitters) with selective concentration at sites of bone cancer damage are used in the treatment. Radioisotopes are an important addition to the armamentarium of clinicians who take care of patients with advanced cancer and painful cancer bone metastases (especially osteoblastic and mixed type). They offer a high degree of efficacy with minimal toxicity and simple administration, fulfilling the fundamental criteria for palliative treatment that should combine minimal patient discomfort and toxicity with maximal clinical effect.

Key words: radioisotopes, bone metastases, therapy of pain

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Introduction

Due to constantly increasing neoplastic disease incidence, bone metastases are becoming a more and more serious issue in oncology. As regards the most common tumours, half of them are connected with a high probability of developing metastases to the skeletal system. Bones, next to lungs and liver, are among the top three sites of distant metastases localization. Neoplasms that give metastases to the skeletal system are most frequently cancers of the prostate, breast, kidneys, lungs, and thyroid (Table I).

These metastases are located mainly in the so-called cancellous bones that have good vascularization connected with a large amount of active haematopoietic marrow. This is enhanced by slower blood flow through sinusoid vessels [1]. The scheme of bone metastasis formation is presented in Figure 1 [2].

Bone matrix remodelling occurs as a consequence of neoplastic cell presence. In healthy bone the balance between processes of ossification and resorption is maintained. They always take place in one way that is genetically programmed and modified by particular external and internal factors. A fundamental role in bone

Table 1. Frequency of advanced stage bone metastases

Primary lesion	Frequency of bone metastases occurrence
Prostate	70–80%
Breast	73%
Thyroid	42%
Lungs	36%
Kidneys	35%
Digestive tract	5%

Bone metastasis
Infiltrate of lymphatic or blood vessel walls through primary tumour
↓
Dissemination of neoplastic cells to the bloodstream
↓
Neoplastic cell colonization in bone marrow
↓
Neoplastic cell extravasation:
adherence to endothelium → endothelium spasm → adherence to basement membrane → basement membrane dissolution → neoplastic cell movement to marrow stroma (enhancing factors: large spaces between endothelium cells, fragmentary lack of basement membrane in sinusoid vessels of bone marrow, chemotactic effect of some substances that occur neutrally in bone tissue, e.g. type I collagen, growth factors)
↓
Bone infiltrate with modification of the surroundings
↓
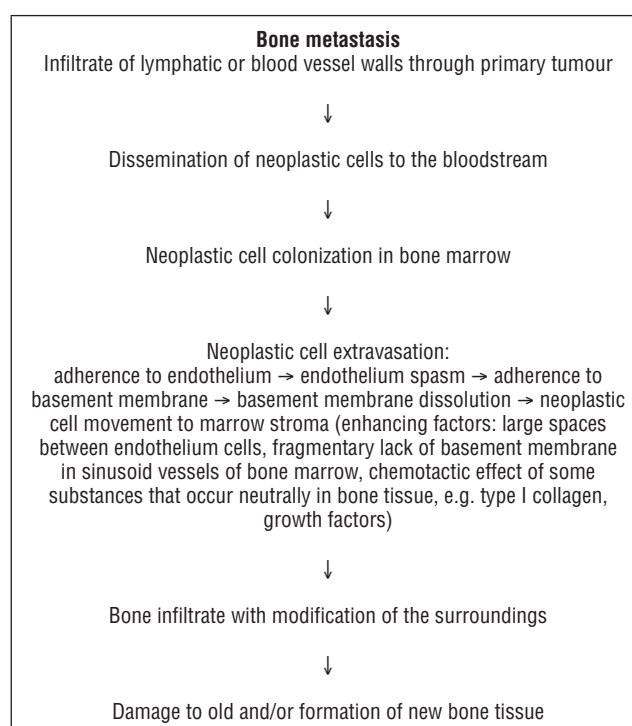Damage to old and/or formation of new bone tissue

Figure 1. Scheme of bone metastasis formation.

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remodelling processes is played by two types of cell that have different functions and origins: osteogenic cells — osteoblasts, and resorption cells — osteoclasts.

Osteoblasts have an approximate life time of 3 months and come from mesenchymoma multipotential matrix cells. They produce type I collagen and proteoglycans that form the organic intracellular structure of the bone which is further calcified. Osteoblasts are also responsible for synthesis of osteonectin, osteopontin, osteocalcin, and various types of proteinase [3, 4].

Osteoclasts, the life time of which amounts to approximately 2 weeks, come from a monocyte-macrofagal line of haematopoietic cells that, after differentiation, connect and build active polynucleated forms. Large amounts of carbonic anhydrase in osteoclast enable separation of H^+ from H_2CO_3 and then its removal directly to the surrounding bone, which initiates the osteolysis process. Osteoclasts have the ability to phagocytise bone and then digest it within its cytoplasm. An important factor for osteoclast function is negative feedback in which apoptosis inducing factors are organic bone matrix degradation products. The products of bone matrix degradation as well as local growth factors (bone morphogenetic protein — BMP), transforming growth factor β (TGFβ), and fibroblast growth factor (FGF) stimulate osteoblast precursor cells for maturation. Osteoprotegerin (OPG) produced by these cells is the main inhibitor of osteoblast maturation and belongs to the RANK/RANKL/OPG system which plays a fundamental role in bone remodelling processes [5, 6].

Classifications and consequences of bone metastases

The most common localization of metastatic lesions is often connected with the site of primary focus and anatomic conditions — direct vascular connections between the main vein systems, portal vein, and pulmonary vein with spinal veins cause frequent metastases to the spine in the course of prostatic and breast cancer. Tumour dissemination to bones typically has a multi-focus nature.

Table 2 presents the most common localization of metastatic lesions out of 100% of patients with diagnosed metastases according to different data [7–10].

A few classifications of stage progress in bone neoplastic dissemination can be found. In orthopaedics, the most commonly used classification is the one by Yamashita presented in Table 3 [11].

As regards nuclear medicine, the Solovay scale or Bone Scan Index (BSI) are used much more frequently [12–15].

The general condition of a patient with bone metastases is typically connected not with the presence of metastases but rather with

Table 2. The most common localization of bone metastatic lesions

The most common metastasis localization	Lesion percentage (%)
Lumbar spine	65–72
Sacral spine	65–68
Pelvis	60–66
Ribs	50–62
Cranial bones	35–44
Femora	30–44
Cervical and thoracic spine	25–40

its consequences — the so-called skeletal-related events (SRE). The latter can be divided into: directly induced by the presence of neoplastic cells in bone (CIBD — cancer-induced bone disease) and related to loss of bone mass as a result of treatment (CTIBL — cancer treatment-induced bone loss), e.g. in antiandrogenic therapy of prostatic cancer. Another significant parameter is the period of time until the moment of occurrence of the first serious bone event — the time to a skeletal-related event (TTSRE) [1].

The most common SREs are: pathologic fracture of vertebrae or other bones (up to 25%), spinal cord compression (up to 8%), hypercalcaemia (up to 25%), and necessary surgical treatment (up to 4%) or radiotherapy (up to 33%) due to clinical symptoms [1, 16, 17].

However, the presence of bone metastases typically causes pain that occurs in over 70% of patients. Bone tissue has rich neuration, mainly from the periosteum, but as it has been recently found that the endings of nerve fibres also reach the medullary cavities in long bones (medullary membrane) and parts of cancellous bones [18].

Pain pathogenesis in metastasis has not been fully understood and in most cases has multiple causes. However, it seems that the following factors are the most significant [18, 19]:

A. Mechanical factors that stimulate bone nociceptors:
   — compression connected with bone remodelling and periosteum damage;
   — increased pressure inside bone;
   — bone deformation due to osteolysis;
   — direct compression of metastatic tissue on nerves or surrounding soft tissue;
   — pathologic fractures that change bone compression distribution (e.g. vertebra compression fractures).

B. Chemical mediators influencing nociceptors:
   — mediators activated or produced by neoplasm (e.g. TGF, TNF, IL);
   — activation of arachidonic acid cascade (prostaglandin E).

C. Other factors:

Table 3. Yamashita classification

Progression stadium	Central skeleton (lumbar and thoracic spine, ribs)	Medial skeleton (pelvis, cranium, cervical spine)	Peripheral skeleton (sternum, scapulae, femoral and humeral bones)
Stadium I	Yes	No	No
Stadium II	Yes	Yes	No
Stadium III	Yes	Yes	Yes

— disturbances in blood supply and outflow.

Symptoms related to bone metastases cause considerable deterioration of the life quality and health condition of the patients and also shorten their life in a statistically significant way.

Bone metastases diagnostics is based on taking history, clinical examination, imaging studies, and biochemical tests. A thorough history completed by a clinical examination allows determination of the location of painful metastatic lesions in 90% of cases. It also allows for the establishment of the nociceptive nature of the pain which in almost 70% of cases accompanies neuropathic pain.

Bone metastatic lesion imaging and determination of bone remodelling type

In imaging diagnostics of bone metastases, plain X-ray of a particular skeletal element is used as well as computed tomography (CT), magnetic resonance (MRI), positron emission tomography (PET), and tests with the use of nuclear medicine techniques (SPECT planar scintigraphy). Basic radiologic classification of bone metastases differentiates osteolytic and osteoblastic types. In practice, bone metastases are never of uniform nature. It is more accurate to describe them as metastases with a dominant osteolytic process and a dominant process of osteosclerosis, while in the case of no dominance — mixed metastases (osteolytic-osteoblastic) (Table 4) [1, 20].

Determination of bone remodelling type is extremely significant in making decisions connected with patient qualification for

Table 4. Most commonly observed variants of bone metastases depending on primary focus site

Primary focus	Metastases properties
Prostate	Osteoblastic (75%) mixed and osteolytic (25%)
Breast	Osteolytic (65%) mixed and osteoblastic (35%)
Lung, kidney, pancreas, oesophagus, melanoma	Osteolytic
Stomach	Osteoblastic/mixed
Large intestine	Osteolytic/mixed/osteoblastic

metastases treatment. Bone metastases from various organs are different in terms of their effect on osteoclast and osteoblast function. Increased pathologic stimulation of an osteoclast leads to intensification of osteolysis with concurrent tendency for hypercalcaemia. Increased osteoblast stimulation causes overproduction of bone matrix with secondary hypercalcification and is very rarely accompanied by a tendency for hypercalcaemia. In these patients calcium concentration is much more frequently close to the lower limit and is accompanied by increased levels of alkaline phosphatase. However, both described situations occur at the same time in a large group of patients (Figure 2) [7–10, 21].

Plain radiograms have considerably low sensitivity in detecting early changes in bone matrix density caused by the presence of neoplastic cells. In the past, limit values of detecting metastatic focus in X-rays were lesions with a diameter over 10 mm and change in bone matrix density of 40–50% compared with surrounding healthy tissue. Currently, as X-ray apparatus have increasingly better quality (digital techniques) which allows a precise computer analysis of the obtained image, detection sensitivity is evidently rising. It is extremely important from a clinical standpoint as in the case of prostatic cancer approximately 40% of spine metastases is detected during pain syndrome diagnostics treatment based on initial diagnosis of degenerative spinal disease [22].

Currently, computed tomography seems to be a sufficient study for clear diagnosis of bone metastases. It allows, especially with the use of multi-row detector CT, precise evaluation of both the extent and nature of the lesion. In exceptional cases, most commonly of single lesions, the necessity of additional differential diagnostics between neoplastic and inflammatory osteolysis or neoplastic and degenerative osteosclerotic process might arise.

Magnetic resonance, similarly to CT, shows high sensitivity (over 70%) and specificity (almost 100%) in detecting metastatic lesions and allows for differentiation of osteoblastic and osteolytic foci. Low focus intensity in T1 weighted time, and increased in T2 weighted, suggests osteolysis, while reduction of signal in T1 and T2 weighted indicates osteoblastic nature of metastasis. Whole body MRI (MR-WBS) in T1 and T2 weighted sequences, including STIR, with application of paramagnetic contract appears to be particularly useful — sensitivity over 90%. Apart from revealing bone metastases, it also allows for evaluation of neoplasm invasiveness in bone marrow [23].
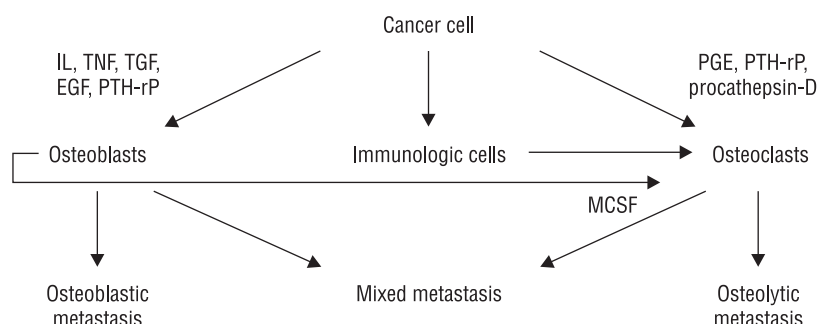

Figure 2. Mechanisms inducing bone remodelling in bone metastatic focus. IL — interleukin; TNF — tumor necrosis factor; TGF — tumor growth factor; EGF — epidermal growth factor; PTH-rP — parathyroid hormone-related protein; PGE — prostaglandin E; MCSF — macrophage colony-stimulating factor.

PET study is not a target method for bone metastases diagnostics (due to economically unfavourable ratio of test effectiveness to test cost). Also, in order to obtain the best diagnostic outcomes, 18-NaF ought to be applied (high affinity to hydroxyapatite) and not 18-fluorodezoxyglucose (18-FDG), which is a typical metabolic tracer and provides a number of additional diagnostic data in most neoplastic patients [24].

Commonly used PET-CT with 18-FDG in the case of high differentiation of neoplastic cells, low metabolism of primary lesion and metastatic lesions might give false negative results, especially in skeletal system foci.

Currently, the fundamental study in bone metastases diagnostics is still scintigraphy. In the skeletal system this study confirms neoplastic dissemination to bone but also provides additional data on the extent and localization of the lesions. Scintigraphy sensitivity in detecting metastatic lesions might even be a few times higher compared to plain X-ray. It detects foci of abnormal bone metabolism (mainly neoplastic metastases) even of 1–2 mm in size and bone matrix density change of approximately 10%. Unfortunately, scintigraphy clearly loses its value compared to MR-WBS [25–28]. However, scintigraphy sensitivity might be increased from 70% to over 80% by using SPECT technique. A further considerable increase in sensitivity is possible by conducting studies with SPECT-CT. Introduction of new informatics technology, which has been suggested by recent reports, might increase scintigraphy sensitivity to as much as 89% [29, 30]. According to many opinions, no dominance of the MR-WBS method over classic scintigraphy can be found in clinical practice. Both studies performed concurrently complete each other perfectly. Low specificity remains a crucial issue in scintigraphy. Routinely applied carriers in isotopic diagnostics are ^{99m}Tc labelled phosphonate compounds (the most commonly used is methylene diphosphonate — MDP) which accumulate in all the sites of increased bone metabolism within a newly-formed bone due to chemiabsorption and phosphonate complex exchange. In certain cases, only a thorough history and the said additional imaging tests are sufficient to differentiate potentially metastatic lesions with post-trauma, inflammatory, and necrotic lesions. Based on scintigraphic study (in contrast to the imaging studies described above) it is not possible to clearly determine the type of metastasis and fracture presence.

A number of cases in bone metastases diagnostics require "overlaying" diagnostic images with the use of at least two techniques. In clinical practice it is recommended to combine isotopic studies and radiology (X-ray, CT, MRI), which is partly possible due to modern gamma cameras. This is critical in the case of qualification for isotopic treatment — foci lesions, like bone metastases that are not always visible in MRI or CT, must intensely accumulate phosphonate derivatives used in diagnostic and therapeutic isotope techniques (Figure 3). This works the other way round as well — intense accumulation of MDP-Tc[99m] in scintigraphy that qualifies patients for treatment does not exclude the presence of unstable pathologic fractures or a large lytic focus which carries the risk of fracture and requires urgent orthopaedic and neurosurgical attendance in the first place (Figures 4–6).

Biochemical diagnostics of bone metastases has been the subject of numerous discussions on the possibilities of using bone turnover markers in oncology. The American Society of Clinical Oncology suggests labelling calcium concentration and potential
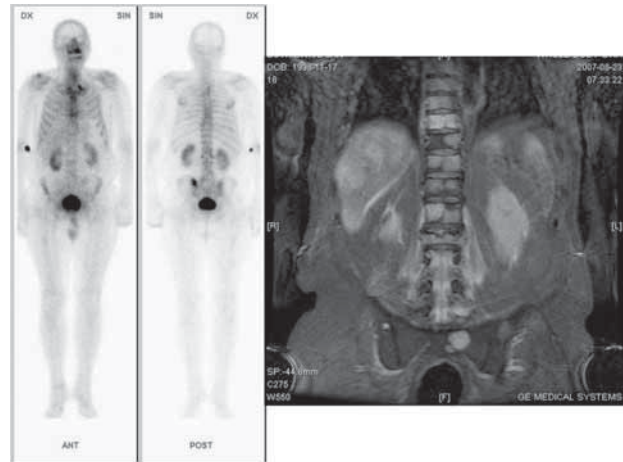

Figure 3. Disseminated metastatic lesions in the bone with pathologic vertebra fracture clearly visible only in MRI (70-year-old man with palatine tonsil cancer and prostate cancer).

Figure 4. Osteolytic lesions in the femur with subsequent pathologic fracture in a 67-year-old woman with kidney cancer.

bone alkaline phosphatase (BALP) and also indicates that routine labelling of bone turnover markers in monitoring the course of treatment should not be recommended, despite its usefulness in certain cases [31–33].

To conclude all the above data, the following course of action might be suggested in cases of suspected bone metastasis in order to chose proper treatment, including isotopic therapy:

1. Confirmation of the presence and stage of metastases (bone scintigraphy, X-ray, CT, MRI, PET).
2. Evaluation of bone metastasis nature — osteolytic, osteosclerotic, or mixed (typically in the case of larger foci X-ray is sufficient) and exclusion of the presence of especially unstable pathologic fractures as well as evaluation of potential risk of spinal core compression.
3. Hypercalcaemia risk evaluation (calcium concentration in blood serum, localization of primary focus — the highest risk of hypercalcaemia occurs in cancer of the lungs, breast, and kidney as well as myeloma).

Figure 5. Osteosclerotic lesions in the pelvis and tibia in an 82-year-old man with prostate cancer.
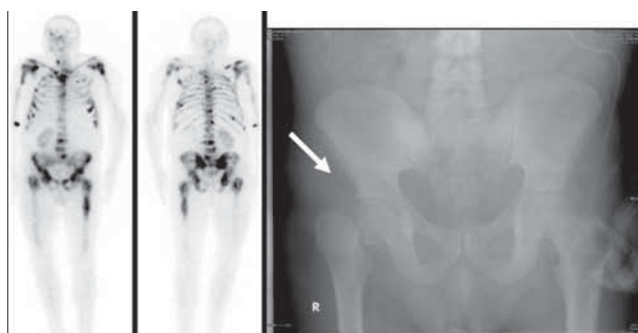

Figure 6. Pathologic fracture of the right femur revealed in X-ray during qualification for radioisotope therapy (65-year-old patient with prostate cancer).

4. Aspirative biopsy in the case of difficulties with determining primary focus.

Treatment possibilities in bone metastases

Forms of therapy used in bone metastases treatment are presented in Figure 7. Possibilities of combining isotopic therapy with other treatment methods will be discussed further in the work.

Radioisotope application in the treatment of bone metastases

The destruction of at least some neoplastic cells in bone metastatic foci due to ionizing radiation causes a considerable decrease in local release of both inflammatory and pain reaction mediators. Concurrently, metastatic mass is reduced, which leads to a decrease in mechanical stimulation of pain receptors. Treatment with radioactive isotopes is more and more frequently used in early stages of bone metastases therapy. It is supposed to prevent development of pain symptoms and other complications. In Poland, two isotopes are currently applied in bone metastases isotopic therapy: strontium-89 (Sr^{89}) and samarium-153
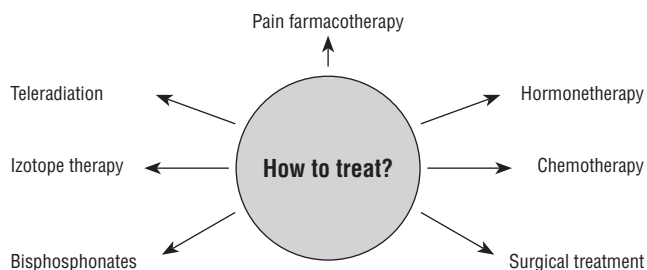

Figure 7. Forms of therapy applied in bone metastatic lesions.

(Sm^{153}) instead of previously used phosphorus 32 (P^{32}) [34–37]. Emitters of α radiation (mainly radium — 223) are still examined in clinical trials [38, 39].

Strontium-89

Strontium-89 is a pure β radiation emitter and calcium analog. It is uptaken and incorporated into collagen in all the sites of increased bone remodelling, with pathologically stimulated osteoblast, which is typical mainly of osteosclerotic foci of bone metastases. The biological half-life of Sr^{89} isotope amounts to 50.5 days. Therefore, doses might be small as the therapeutic effect will last long after incorporation into osteoblastic focus. The drug is administered intravenously (like strontium chloride), while the main means of isotope elimination are the kidneys (up to 90%).

Samarium-153

Samarium-153 is applied intravenously in the form of chelate compound with tetraphosphonate (Lexidronian), which determines the high sensitivity and specificity of drug accumulation in sites of bone remodelling (high affinity to hydroxyapatite) caused by the presence of neoplastic cells. Sm^{153} emits β therapeutic radiation and low-energy γ radiation, which allows post-therapeutic images to be obtained with the use of gamma cameras. Sm^{153} half-life period amounts to 1.9 days, which determines the necessity of applying high activities yet makes this treatment similar to classic teleradiotherapy (large dose in a short time) — it is sufficient for a therapeutic effect that the radioisotope bonds with hydroxyapatite for a short time. The main path of eliminating the isotope that is not bonded by bone tissue are the kidneys, as in the case of Sr^{89}.

Rules of qualification for metastases treatment with the use of radioisotopes

Qualification for isotope therapy includes the following factors is listed below.

Nature of metastasis

Principally, osteoblastic or mixed metastases are an indication for radioisotope therapy; osteolytic metastases require bisphosphonate treatment in the first place.

The mechanisms of radioisotope bonding in metastatic foci described above cause similar Sr^{89} and Sm^{153} effectiveness in osteoblastic bone metastases (approximately 75–80% positive response to monotherapy). In the case of Sm^{153}, a lytic osteoblastic lesion with a large amount of hydroxyapatite bonds the therapeutic complex well. In the case of Sr^{89} therapy, high osteoblast

activity allows for incorporation of a large amount of isotope into pathologically changed osteosclerotic bone matrix. The effectiveness of mixed metastases therapy decreases in inverse proportion to the increase in osteolytic component, especially in large foci (analgesic effect in monotherapy decreases to 20–40%). Based on numerous reports it can be assumed that it is the type and size of metastasis, and secondly neoplasm type, that dictate therapy effectiveness. Reports on good treatment effectiveness refer not only to prostate and breast cancer patients but also to individuals with cancer of the kidney, urinary bladder, and lungs as well as osteosarcoma [38–42].

Intensity, localization, size, and number of tracer accumulation foci in bone scintigraphy

The multi-focus nature of metastatic lesions is one of the basic indications for radioisotope treatment. Quantitative measurement of skeletal system involvement might be performed by the above-mentioned Solovay scale or BSI calculation. The more intense the radiotracer accumulation and the smaller the focus, the better the treatment effectiveness expected. The presence or high risk of pathologic fractures, particularly in the spine, indices of mechanical compression of nerve roots or vertebral cord constitute a contraindication for radioisotope therapy. The patient might be qualified for isotope treatment again following interventional orthopaedic procedure, interventional radiotherapy, or intensive intravenous bisphosphonate therapy. Patients with bone metastases and superscan scintigram might be problematic. The author's own observations suggest a good expected effect of the treatment, yet the risk of serious haematological complications amounts to approximately 50%, which indicates the need for care in calculating the dose — reduction by at least 25% is recommended [40, 41].

Patient general condition and life expectancy

It is generally acknowledged that life expectancy in a patient qualified for radioisotope therapy should not be shorter than 2–3 months. Poor general condition and considerable cachexia might also be direct causes of patient disqualification from the treatment. The first pain symptoms occur approximately after 7–14 days following dose administration and can be observed for as long as a year [43–46].

Bone marrow damage indices

Characteristics of bone marrow damage (E < 3.0 T/l, Hb < 10 g%, L < 3.000 G/l — recommended smear for determining absolute granulocyte number, which should not be lower than 1.500 G/l; PLT < 100.000–60.000 G/l) that might be directly connected with neoplastic disease or previous treatment (e.g. aggressive chemotherapy or radiotherapy) might disqualify the patient from the treatment. Administration of radioisotope dose to patients with bone marrow damage carries a risk of full-blown thrombocytopaenia, leucopoenia or anaemia [10, 34, 36, 37].

Renal failure and urine retention or urine incontinence

A lack of possibilities to eliminate a radioisotope from patient's body might lead to drug accumulation and an increase in potential side effects. Also, infection of potential catheters, urine bags, nephrofixes, etc. applied in patients with retention or incon-

tinence constitute a significant problem. Although, this issue is not an absolute contraindication for radioisotope therapy in ambulatory conditions of drug administration, it is connected with high risk of contamination persons who take direct care of the patient [47, 48].

Parameters of calcium-phosphorus metabolism

Every bone metastases patient requires regular check of calcium concentration in blood serum. Patients that take calcium preparations (for different indications) should discontinue about 10 days prior to scheduled strontium isotope treatment (potential uptake competitiveness). Failure in meeting this requirement might considerably reduce Sr^{89} uptake by bone metastases foci and thus significantly decrease treatment effectiveness. In the case of patients qualified for Sm^{153} therapy it is recommended to discontinue bisphosphonate administration for a period of 2–4 weeks (potential impediment of Sm^{153} tetraphosphonate uptake). However, in 2008 and 2009 Lam published two works connected with prostate cancer patients. The author showed that zolendronate, similarly to pamidronate, does not decrease uptake of samarium ^{153}Sm isotope. The treatment had high effectiveness and significantly low toxicity [49, 50].

Other forms of parallel oncologic and symptomatic therapy

Most types of chemotherapy, due to potential myelotoxic effect, might block radioisotopic treatment. According to many reports, it is possible to conduct parallel local radiotherapy from external sources before and during isotopic treatment (potential strengthening effect). Radioisotopic treatment might be a continuation of radiotherapy in the case of exceeding the upper dose absorbed from external sources or risk of local complications of local radiotherapy. The pros and cons of combining radioisotopic therapy with other forms of oncologic treatment are presented in Table 5 [51–56].

No clear interactions between concurrent application of bisphosphonate and Sr^{89} have been observed (different uptake point in the bone). Moreover, bisphosphonate administration prior to Sr^{89} injections might have a beneficial impeding effect on osteoclast activity and allow for osteoblast dominance, which increases the possibility of greater radiopharmaceutical accumulation in the metastatic focus. Bisphosphonate administration directly after radioisotope injection practically eliminates the risk of hypercalcaemia development (15%) as a consequence of radiopharmaceutical administration. No reports on Sm^{153} isotope interactions with calcium preparations can be found. As mentioned above, in patients treated with Sm^{153} it is recommended to withdraw bisphosphonate prepa-

Table 5. Pros and cons of combining isotope therapy with other treatment forms

Isotope therapy	Effectiveness increase	Risk of undesirable effects
With radiotherapy	High	Moderately increased*
With bisphosphonates	High**/moderate	Low
With chemotherapy	High**/moderate	High***
With hormone therapy	High/moderate	Low

*depends on total absorbed dose; **especially in breast cancer;
***depends on chemotherapy type

rations for 2–4 weeks prior to scheduled isotope treatment. Their administration on the third day following the treatment is believed to be beneficial. Similarly to Sr[89] therapy, the risk of post-therapeutic hypercalcaemia is almost absolutely eliminated. This scheme of combining Sr[153] therapy with bisphosphonates is particularly recommended in patients with metastases that show osteolytic component and hypocalcaemic tendency [57–60].

Radioisotope choice

As mentioned above, both Sm[153] and Sr[89] have similar effectiveness in osteoblastic bone metastases treatment. In the case of mixed metastases the therapy effectiveness decreases, especially with Sr[89]. Thus, such patients should be prescribed Sm[153] isotope therapy. The reason is the disproportion of osteoblast and osteoclast activity in mixed metastases, especially with the dominance of osteolysis. The possibility of fast incorporation and longer "maintenance" of Sr[89] isotope is considerably reduced, which leads to a decrease in absorbed therapeutic dose and final therapeutic effect. Higher effectiveness of Sm[153] is probably a result of less specific mechanism of bonding therapeutic complex to hydroxyapatite — a large dose of a radiopharmaceutical will always give at least a partially therapeutic effect even when it is bonded to a lesser extent and for a short time [21, 43, 44, 57, 58, 61]. According to observations, Sr[89] isotope has slightly higher and often delayed myelotoxicity, especially in younger individuals and multiple therapies. Some observations indicate that every subsequent therapeutic dose administered might give a long lasting effect of decreasing blood platelet and leukocyte concentrations by a subsequent 10% compared to initial values. The impact on the red blood cell system is approximately 50% smaller. As regards the percentage of early clinically significant yet typically mild and spontaneously subsiding haematological complications, it is quite similar for both isotopes and amounts to approximately 25%, which is confirmed by literature reports. The risk of their occurrence not only rises proportionally with each subsequent dose administered but it is also a result of previously (or simultaneously) applied treatment, e.g. radiotherapy, chemotherapy, or hormone therapy, as well as symptomatic analgesic treatment. The analgesic effect of Sm[153] occurs slightly sooner than in the case of Sr[89]. However, some authors claim that it is also shorter and requires more frequent treatment renewal [7, 10, 34, 36, 61].

Radioisotope dosage

Both Sr[89] chloride and Sm[153] tetraphosphonate are administered intravenously in a one-time injection. In the case of Sr[89] a standard dose of 150 MBq — 4 mCi is typically administered or is calculated as follows: from 1.1 to 3.0 MBq/kg of body mass. As regards Sm153, the starting therapeutic dose is calculated as follows: 37 MBq/kg of body mass. The most common indications for reduction of the calculated dose by 25–50% are limit haematological parameters and signs of moderate renal failure. Radioisotope therapy might be repeated many times, providing its effect is satisfactory and no side effects are observed. Typically, a patient is not qualified for next dose if visible side effects were seen or no improvement was observed. However, in the latter case a change of the applied isotope could be considered, especially from Sr[89] to Sm[153]. According to current Polish regulations,

Table 6. Effectiveness of isotope monotherapy and monotherapy combined with local radiotherapy

Treatment effect	Isotope monotherapy	Isotope therapy with local radiotherapy
Total pain relief	30–40 %	50–65 %
Partial pain relief	40–50 %	20–30 %
Unsatisfactory effect	20%	15–20 %

bone metastases therapy with the use of Sr[89] and Sm[153] might be conducted in ambulatory conditions in nuclear medicine departments that meet certain conditions. Due to the nature of the applied isotopes, the patient does not pose a direct threat to their surroundings, providing that certain precautions are undertaken [47, 48].

Treatment effectiveness

Treatment effectiveness depends on a few factors [51–56]:
1. Quantity, localization, and size of metastatic lesions in the bone. The more foci, the greater the lesion diameter and presence of potential cracks or fractures (especially vertebral), the greater the component of neuropathic pain, the poorer the treatment effect.
2. Scheme of treatment (monotherapy or therapy combined with radiotherapy and/or bisphosphonates) and the size of administered dose (Table 6).

Post-therapeutic patient control and potential undesirable effects

The first control after the treatment should take place after approximately 2 weeks, the second between the 4th and 6th weeks, and the third between the 8th and 12th weeks. The follow up should include evaluation of analgesic effect, neurologic condition control examination (especially in metastases to the spine), and evaluation of haematological parameters (obligatorily blood count with platelets and smear), calcaemia level, and individual evaluation of renal and hepatic parameters as well as neoplastic markers. The following potential undesirable effects should be taken into consideration:
— increased pain symptoms (in 10–20% of patients "flare syndrome" might develop), especially in the cases of presence of neuropathic pain (nerve compression etc.) — prophylactics or reduction of the said complaints is possible by short use of glycocorticosteroids (e.g. dexamethasone 4 mg/a day in a dose decreasing by 1 mg every 5–7 days). Prior to glycocorticosteroid administration a history should be taken as regards the presence of direct and indirect contraindications for this type of therapy, and the patient should be informed about possible undesirable effects of the drug;
— temporary impediment of bone marrow function. A decrease in the number of platelets and leukocytes is observed most commonly between the 2nd and 8th weeks after administration of radioisotope dose and typically does not exceed 30–50% of starting parameters. Very rarely is it necessary to hospitalize patients due to myelotoxic complications in radioisotope therapy and with proper qualification. Such a necessity is pro-

portional to the large number and massiveness of metastatic lesions diagnosed in the skeletal system. This risk increases in the case of previous treatment of high myelotoxicity probability as well as numerous clinical signs of neoplastic infiltrate within bone marrow;

— hypercalcaemia. It develops rarely. An increase in calcium concentration is connected with osteolysis in metastatic foci and is typically short and easy to control with bisphosphonates;

— pathologic fractures. Intensive post-therapeutic osteolysis of large metastatic foci that were earlier connected with high risk of fracture might lead (especially in patients who showed pain relief and sudden increase of life activity) to pathologic fractures. Such probability is more common in mixed metastases patients or those with clear domination of osteolysis localized in the spine, pelvis, or femora. In such cases standard combination of isotopic therapy with bisphosphonate treatment might be particularly beneficial [9, 57–59].

Economic aspect of radioisotope therapy

The cost of pain treatment with the use of radioisotopes is less than half the cost of conservative treatment. As regards isotope therapy patients, no clear statistical data regarding lengthening of life can be found. However, these patients report improved life quality, and a lower number of both pathologic fractures and clinical circumstances requiring hospitalization is observed [45, 61–63].

Conclusions

1. Radioisotopes are effective drugs in the treatment of osteoblastic and mixed bone metastases, in monotherapy and in combination with radiotherapy.
2. Radioisotope treatment in the case of diagnosing bone metastases might be applied even prior to development of clinical symptoms, which reduces the number of new pain sites and the risk of pathologic fractures.
3. Radioisotope treatment considerably raises quality of life and reduces both pain and necessity of administering analgesics.
4. Radioisotope therapy causes statistically significant reduction of treatment costs in bone metastases patients.

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