Radiopharmaceuticals for pain palliation therapy in patients with skeletal metastases, and their possible integration with chemotherapy.

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Autopsy-based studies report the occurrence of skeletal metastases in up to 70% of the patients with breast or prostate cancer. Common localization of bone metastases in the axial skeleton is probably due to sluggish blood flow in the red marrow (which is particularly abundant in the axial skeleton) and to the fact that venous blood from the pelvis or breast flows through the vertebral-venous plexus (Batson circulation); both these occurrences represent predisposing conditions for tumor seeding(1).

Bone metastases are typically referred to as “lytic”, “sclerotic” or “mixed”, according to radiographic appearance of the lesions. Metastases from prostate cancer most typically originate sclerotic lesions, that can however arise from breast, lung, carcinoid and medulloblastoma tumors as well. Mixed lesions exhibit radiological or histopathological evidence of both osteolytic and osteoblastic processes(2, 3).

The major complications associated with advanced bone involvement are severe pain, spinal-cord compression and pathological fracture. Pain from bone metastasis is of variable intensity and intermittent at onset, but progresses to continuous low-level pain with episodes of breakthrough pain, which later becomes chronic pain.

The main goal of a realistic strategy for treating patients with skeletal metastases (who are often considered to be terminally ill patients) is to improve quality of their remaining life. In the more advanced stages of disease, metastatic bone pain is usually severe, arises from multiple sites and may require large amounts of pain killing medications; among these, opiates are most frequently employed, although they can, on the other hand, reduce the quality of life because of several undesired side effects such as...
sedation and constipation\(^{(4)}\). Therefore, a multidisciplinary team approach is highly desired to manage pain in these patients\(^{(5)}\). The available systemic treatment options include purely palliative therapies such as nonsteroidal anti-inflammatory drugs (usually as the initial step) and opioids, combined whenever possible with anti-tumor therapies such as hormonal treatment (in case of hormone-dependent tumors) and cytotoxic chemotherapy; local, site-directed treatments include surgical stabilization and external beam radiation therapy. Systemic therapy with bisphosphonates and with bone-seeking radiopharmaceuticals are to be placed somewhere in the middle of this spectrum due to the fact that, besides their well-established palliative effects, they can also exhibit some anti-tumor activity the potential of which is currently being explored (see further below).

In the treatment of painful bone metastases, radiometabolic therapy in general combines the advantage of being both site-selective (similarly as external beam radiation therapy) with that of possessing systemic distribution (similarly as chemotherapy or bisphosphonates). In principle, bone metastases can be treated using specific tumor-seeking radiopharmaceuticals, for instance $^{153}$Sm- and $^{186}$Re- and $^{188}$Re-, $^{177}$Lu- and $^{223}$Ra-chloride, in other cases the radionuclide is incorporated into the bone mineral component thanks to a carrier molecule (usually a phosphonate, as in the case of agents labeled with $^{153}$Sm, $^{186}$Re and $^{188}$Re, $^{177}$Lu, etc.). All such different radionuclides may variously differ in terms of efficacy, duration of pain palliation, tumoricidal effects, possibility to repeat treatments, toxicity, cost, physical properties, and dosimetry\(^{(6-22)}\).

While chemical structure of some bone-seeking radiopharmaceuticals is very simple (since in ionic form they mimic the biodistribution of calcium, as in the case of $^{89}$Sr-chloride and $^{223}$Ra-chloride), in other cases the radionuclide is incorporated into the bone mineral component thanks to a carrier molecule (usually a phosphonate, as in the case of agents labeled with $^{153}$Sm, $^{186}$Re and $^{188}$Re, $^{177}$Lu, etc.). All such different radionuclides may variously differ in terms of efficacy, duration of pain palliation, tumoricidal effects, possibility to repeat treatments, toxicity, cost, physical properties, and dosimetry\(^{(6-22)}\).

Therapy with bone-seeking radiopharmaceuticals is indicated for the treatment of refractory pain from skeletal metastases of the sclerotic or mixed type, especially from prostatic carcinoma or breast carcinoma (established indications), as well as metastases from any other tumor provided the bone scan demonstrates intense uptake at the sites of painful metastases. The most common reason for treatment failure is inappropriate patient selection. Patients must undergo bone scintigraphy using a $^{99m}$Tc-labeled bone-seeking agent for best planning of treatment; in particular, foci of increased uptake on the bone scan must be correlated with the sites of the patient's symptoms, to ensure that the pain can be attributed to osteoblastic bone metastases. Other causes/sources of pain, such as vertebral collapse, nerve root entrapment, fracture and visceral pain, will not respond to radionuclide therapy.

Absolute contraindications for radionuclide bone therapy are myelosuppression, impaired renal function, pregnancy, breastfeeding. Risk of pathologic fracture and acute spinal cord compression should be regarded as surgical or radiotherapy emergencies, and therefore should not be treated with bone-seeking radiopharmaceuticals alone. Urinary incontinence implies the risk of environmental contamination, and should be managed by bladder catheterization before radiopharmaceutical administration.
Patients should be hematologically and biochemically stable before treatment. Routinely, the recommended hematological parameters are: hemoglobin >90 g/L, white blood cell count >4x10⁹/L, and platelet count >100x10⁹/L(23). Poor renal function will delay clearance of most bone-seeking radiopharmaceuticals, leading to a higher whole-body dose and potentially increased toxicity. Recommended renal function parameters are: serum urea <12 mmol/L, and serum creatinine <200 mmol/L.

As the selection of patients as well as assessment of the parameters of response have not been standardized throughout the clinical trials, some variation in the response rates to treatment is noted. Thus, the overall response rate ranges between 45%-92%, with complete responses (disappearance of bone pain) ranging 10%-30% and partial responses (reduction of bone pain) making up the remainder. Although the onset of pain relief starts later (1-4 weeks after administration) when the longer-lived radionuclide (³²P, ⁸⁹Sr,¹¹⁷mSn) are employed, the time to response for shorter-lived radionuclides (¹⁸⁶Renate,¹⁸⁸Re,¹⁵³Sm) is 2-7 days, i.e. comparable to that of external beam radiotherapy. The duration of response also varies somewhat, but generally ranges between 2-6 months (with very long-lasting responses reported in the order of 10-12 months). Pain responses to repeat administrations are similar as those observed after the first administration both in terms of reduction in pain intensity scores and in the proportion of patients responding to treatment(6-22); instead, when the first administration is ineffective, further attempts are usually unjustified.

Treatment is in general well tolerated by patients, and long-term follow-up studies have demonstrated that radionuclide therapy carries a lower risk of leukemia and secondary cancers than chemotherapy and external beam radiotherapy(10). About 15% of the patients treated with bone-seeking radiopharmaceuticals complain of increased pain (or flare) 1–5 days post-administration; such phenomenon can last for as long as 4 days and may be associated with a good response(24). Hematologic toxicity is the most commonly observed side-effect, mostly represented by reduction of white blood cells and platelets, whereas red-cell counts change negligibly or not at all. Nadirs are usually reached at 4-6 weeks (depending on physical half-life of the radionuclide), and both platelet and leukocyte counts recover by 8-12 weeks without the need for medical interventions(25). While no differences in palliative response or toxicity have been observed among¹⁵³Sm-EDTMP,¹⁸⁶Re-HEDP,¹⁸⁸Re-HEDP and⁸⁹Sr-chloride, treatment with³²P results in more severe hematologic toxicity when compared to⁸⁹Sr-chloride(26, 27).

Treatment of bone pain with¹⁵³Sm-EDTMP may be repeated without significantly increasing toxicity, provided that adequate levels of the platelet and leukocyte counts are ascertained before each administration(28).

Recently, increasing awareness that treatment with bone-seeking radiopharmaceuticals might ensue some therapeutic effect beyond simple palliation of bone pain has prompted several groups to explore the possibility of achieving some synergistic effect by the combination of such treatment with some other anti-tumor agents, especially chemotherapy agents(29). This approach has proved to be safe and well tolerated; furthermore, in patients with metastatic prostate cancer it yields not only better PSA response and time to progression, but also longer overall survival(30,31,32,33). These findings have laid the ground to formulate the hypothesis that combined treatment would be especially effective because it permits to target both the so-called “seed” (prostate cancer cells, by the chemotherapy agent) and the “soil” (the bone matrix environment, by the bone-seeking radionuclide) of the metastatic site.

In conclusion, despite the large body of experience accumulated over several decades, our clinical knowledge regarding treatment of bone metastasis with bone-seeking radiopharmaceuticals is still at an early phase, regarding especially combined treatments. Ongoing experimental and clinical trials should address the following questions: can we treat painless osteoblastic metastases in order to delay the...
Onset of pain? Do other agents besides $^{89}$Sr delay the onset of new or recurrent bone pain? What are the best combinations of radiopharmaceuticals, hormones, and chemotherapy to treat painful bone metastases, not only to reduce pain, but also to prolong life? (34).

References


