NEW ASPECTS OF RADIONUCLIDE THERAPY OF BONE AND JOINT DISEASES

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Abstract. Whereas in developing countries P-32 is widely used for radionuclide therapy of painful bone metastases, in Europe three radionuclides or radiopharmaceutical agents are available for pain palliation: Sr-89, Sm-153-EDTMP, and Re-186-HEDP. Radionuclide therapy for pain palliation is indicated for bone pain due to metastatic malignancy that has involved multiple skeletal sites and has evoked an osteoblastic response on bone scintigraphy. Response rates of about 70–80% in patients with breast or prostate cancer is reported in the literature, less in metastatic lesions of other primary malignancies. Sm-153-EDTMP may also be used for curative treatment of primary bone tumours or their metastases. Radiosynovectomy as therapeutic procedure or rheumatoid arthritis, other inflammatory joint diseases, persistent synovial perfusion, and other joint diseases is widely used. Using Y-90 for the knee joint, Re-186 for middle sized joints, and Er-169 for small joints an improvement of symptoms may be observed in about 70–80%.

1. INTRODUCTION

A great German scientist and physician, Paul Ehrlich (1854–1915) first described "specific chemotherapy" as a search for a chemical substance capable to be taken up by and killing parasites without doing any harm to normal tissue or organism. To reach such an objective, Ehrlich as a student wanted to determine the microscopic and biological distribution of metals in the organism, because he thought metals to be effective therapeutic agents. He also stated that "particles must be attached to something to be effective". These are the fundamental principles of radionuclide therapy and if radionuclides were known at that time, Ehrlich could have been the father of radionuclide therapy.

In 1936, John Lawrence studied total body irradiation after intravenous administration of P-32 using an animal model of leukemic mice and various lymphomas in animals. Together with a 29-year-old student, who was diagnosed as having myelogenous leukemia Lawrence performed the first P-32 therapy. After 3 courses with a cumulative dose of 394 MBq (10.64 mCi) P-32 the student, symptomatically and clinically, was normal.

In 1940/41 a patient with prostate cancer and painful osteoblastic bone metastases was treated with 8 mCi of Sr-89 with positive effect concerning pain by C. Pecher. About ten years later Friedell reported P-32 therapy to breast cancer bone metastases.

In Europe, about 55 new patients/100 000/year with prostate cancer and 114 new patients/100 000/year with breast cancer are diagnosed. By autopsy in about 80% of patients with prostate cancer and 75% of patients with breast cancer bone metastases were observed. (Table 1). About 30% of patients with bone metastases develop severe pain syndrome which needs therapy.

TABLE I. INCIDENCE (%) OF SKELETAL METASTASES IN AUTOPSY STUDIES

Primary tumour	Mean	Range
breast	73	47–85
prostate	68	33–85
thyroid	42	28–85
kidney	35	33–40
lung	36	30–55
oesophagus	6	5–7
gastro-intestinal	5	3–11
rectum	11	8–13

2. RESULTS

2.1. Radionuclide therapy for pain palliation

For radionuclide therapy for pain palliation because of bone metastases in Europe 3 radionuclides are available: Sr-98, Sm-153, and 186-Re [1–8, see also Table II] Whereas Sr-89 exchange with calcium component of hydroxyapatite, the more recently available radiolabelled bisphosphonates (Sm-153-EDTMP and Re-186-HEDP) localize in bone by bridging the hydroxyapatite. The amount of uptake depends on metabolic activity of normal bone and tumour tissue. In Europe, P-32 no longer is used extensively for bone pain palliation because of possible myelotoxicity. Most of these patients underwent high-dose chemotherapy causing myelotoxicity prior to pain palliation therapy with radionuclides.

TABLE II. PHYSICAL CHARACTERISTICS

Radionuclide	Pharmaceutical	Half life(days)	Maximum ß energy MeV	Mean ß energy MeV	Maximum range in tissue (mm)	γ Photon keV (%)
Sr-89	chloride	50.5	1.46	0.583	6.7	--
Sm-153	EDTMP	1.95	0.8	0.224	3.4	103 (28)
Re-186	HEDP	3.8	1.07	0.349	4.7	137 (9)
P-32	orthophosphate	14.28	1.71	0.695	7.9	--
Sn-117m	DTPA	13.6	conversion	0.129	0.3	159
(in a phase III trial)			electrons	0.153		

Prior to the administration of the radiopharmaceutical agents increased osteoblastic activity in the metastases should be documented by bone scintigraphy.

Indications

Strontium-89-chloride, Sm-153 EDTMP and Re-186 HEDP (and the other unsealed beta-or conversion electron-emitting radiopharmaceuticals under development or available commercially, i.e. P-32-orthophosphate, 117m-Tn-DTPA, Re-188-bisphosphonate) are indicated for the treatment of bone pain due to a metastatic malignancy that has involved multiple skeletal sites and has evoked an osteoblastic response on bone scintigraphy.

Contraindications

Absolute

- pregnancy, continuing breast feeding.

Relative

- myelosuppression
- chronic renal failure or deterioration of renal function (urea >12mmol/l; creatinine >150mmol/l
- urinary incontinence
- acute or chronic spinal cord compression and/or metastases at the base of the skull

Where there is danger of either spinal cord compression from vertebral metastases or pathologic fracture in the extremities, radionuclide therapy for pain palliation should only be used in conjunction with other forms of management directed at these complications.

Simultaneous administration of cytotoxic agents, external wide field radiotherapy and radionuclides may cause significant myelosuppression.

In general, patients should not have received long-acting myelosuppressive chemotherapy for 6-8 weeks prior to administration of Sr-89 and for 6–12 weeks after Sr-89 administration because of the potential for severe leukopenia or thrombocytopenia. Caution should be used if Sr-89 is used in conjunction with myelosuppressive chemotherapy. In patients to be treated with Sm-153 or Re-186 the intervals could be shorter, depending on blood cell counts.

The patient should not have received external beam hemibody radiation within 2–3 months prior to administration of Sr-89, Sm-153 or Re-186 to reduce the probability of combined myelotoxicity from the external and internal radiation sources during this period.

Complete blood cell counts should usually be obtained within 7 days prior to administration of Sr-89, Sm-153 or 186-Re. The patient's platelet count should probably exceed 60,000 and preferably 100,000/mL; the leukocyte count should probably exceed 2,400 – 3,000 and preferably 5,000/mL; and the absolute granulocyte count should exceed 2,000/mL to receive Sr-89, Sm-153 or Re-186. Results below these blood cell levels are not absolute contraindications to treatment but raise the chance of infection or bleeding. Haematological toxicity should be monitored at 3–6 weekly intervals for up to 3 months post Sr-89 therapy and at 1–2 weekly intervals up to 6–8 weeks post Sm-153 or Re-186 therapy.

Other contraindications are renal failure, changing pharmacokinetics of the tracers, and active disseminated intravascular coagulation.

The usual administered activity of Sr-89 ranges from 1.5–2.2 MBq/kg (150 MBq in a single dose vial) (40–60 μCi/kg), of Sm-153-EDTMP 37 MBq/kg body weight and of Re-186-HEDP 1295 MBq. Radionuclides should be administered by slow intravenous injection via a peripheral vein using a butterfly cannula or an intravenous catheter. The cannula or catheter should be flushed thoroughly with normal saline (0.9% NaCl) post injection.

The mean absorbed dose by bone metastases is about 23cGy/MBq (range 6–61cGy) after Sr-89 administration, 1000–14000 cGy for a therapeutic dose of 1295 MBq Re-186-HEDP and 86,5Gy for a therapeutic dose of 2590 MBqSm-153-EDTMP.

The therapeutic procedure may be repeated 12 or more weeks, using Sr-89, 4–6 weeks using Sm-153 or Re-186 after the first injection if blood cell counts are at the suggested levels. The response rate after the first treatment is about 70–80%, after the second treatment about 50%. Only few patients may become really pain-free, but most patients treated with radionuclide therapy may reduce medication especially opioids.

Independent from the radionuclide used for pain palliation the onset of pain relief is more rapidly after Sm-153 or Re-186 administration than after Sr-89, but the mean duration of response after Sr-89 is longer (6 months vs. 3 months). That is why some centres prefer a "cocktail" treatment to optimize the effect of pain palliation without increasing the risk of primary adverse effects.

In animal experiments Sm-153 was used for curative treatment of primary bone tumours. Clinical dose escalation trials are running in some centres in the US and Europe treating metastases of primary bone tumours. Preliminary results are quite promising.

2.2. Radiosynovectomy

Radiosynovectomy is a well accepted therapeutic procedure in inflammatory joint diseases [9,10]. There are several radionuclides available for this treatment (see Tables III and IV).

TABLE III. PHYSICAL CHARACTERISTICS:

Nuclide	Y-90	Re-186	Er-169
phys. half-life	64 h	90,6 h	9,4 d
mean range (soft tissue)	3.6 mm	1.2 mm	0.3 mm
max. range	11.0 mm	3.6 mm	0.7 mm

Indications

- Rheumatoid arthritis
- other inflammatory joint diseases (except bacterial, tuberculous)
- persistent synovial effusion (knee prosthesis)
- pigmented villonodular synovitis
- haemophilic joint disease
- chronic pyrophosphate arthropathy

Relative indications

- persistent effusion after knee prosthesis
- Baker's cyst
- activated arthropathy
- polyarthrosis of finger and toe joints

Contraindications

Absolute

- pregnancy and continuing breast feeding

Relative

- in children and young patients (< 45 years) the radionuclide should be administered only if it has been estimated that the benefits to be gained outweigh the potential hazards.

Before radionuclide administration for radiosynovectomy a three-(two-)phase scintigraphy and/or scintigraphy with ^{99m}Tc-HIG is recommended to study the degree of inflammation in the joint to be treated. By ultrasound or MRI the joint space, structure of the synovia and amount of effusion should be evaluated to ensure that homogeneous distribution of the tracer is possible.

The puncture of the joint has to follow precautions for asepsis. The needle should be flushed with 0.9% NaCl before being withdrawn. Simultaneous administration of corticosteroids may improve the results of radiosynovectomy of large or middle size joints. For the puncture of middle and smaller joints X-ray control is mandatory.

A particle size of the colloids used for radiosynovectomy of 2–10 nm is essential to avoid leakage from the joint.

TABLE IV. ACTIVITY, RECOMMENDED FOR THE JOINTS TO BE TREATED

	Nuclide (MBq)		
Joint	Y-90	Re-186	Er-169
Knee	185–222		
Hip		150	
Shoulder		110	
Elbow, ankle, wrist		75	
Metacarpo-phalangeal			20–40
Metatarso-phalangeal			30–40
prox. Interphalangeal			10–20

The volume administered to middle size joints should not exceed 1–3 mL, to small joints 1 mL, depending on the joint space.

After nuclide administration the treated joint has to be immobilized for at least 48 hours.

The results of treatment depend on the stage of the disease and bone destruction. The overall results in joints without severe destruction show an improvement in about 70–80%. Nearly same results were published for surgical synovectomy. First preliminary results of treatment with systemically administered Sm-153-EDTMP in patients suffering from rheumatoid arthritis are promising.

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