Samarium-153-EDTMP for Palliation of Ankylosing Spondylitis, Paget's Disease and Rheumatoid Arthritis

Albert S. Alberts, Stan W. Brighton, Pieter Kempff, Werner K. Louw, Alet V. Beek, Veronique Kritzinger, Henry P. Westerink and Ado J. van Rensburg

Departments of Radiotherapy, Internal Medicine, Orthopaedics and Nuclear Medicine, H.F. Verwoerd Hospital; University of Pretoria; and the Atomic Energy Corporation of South Africa, Pretoria, South Africa

Samarium-153-EDTMP is an effective agent for palliation of widespread skeletal metastases because it concentrates in bone metastases which have an osteoblastic component. Similar concentration in areas of osteoblastic activity in ankylosing spondylitis, Paget's disease and rheumatoid arthritis suggests a possible new treatment approach. Three patients with ankylosing spondylitis, one patient with Paget's disease and one patient with rheumatoid arthritis were treated with ^{153}Sm-EDTMP. Objective and subjective improvement was noted, especially in ankylosing spondylitis patients. Samarium-153-EDTMP has disease-modifying potential in ankylosing spondylitis and Paget's disease and has palliative value in resistant rheumatoid arthritis. Further trials to determine optimal dose, treatment scheduling, long-term disease-modifying potential and toxicity are needed.

Key Words: samarium-153-EDTMP; ankylosing spondylitis; Paget's disease; rheumatoid arthritis

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Samarium-153-ethylenediaminetetra-methylinephosphonic acid (^{153}Sm-EDTMP) is a currently used agent for effective palliative treatment of widespread skeletal metastases (*1–4*).

Rheumatoid arthritis, ankylosing spondylitis and Paget's disease are associated with osteoblastic activity, whether an integral part of the disease or as a reactive phenomenon. These areas will take up technetium (^{99m}Tc) and ^{153}Sm-EDTMP. Ankylosing spondylitis and rheumatoid arthritis have been treated with radium-224 (^{224}Ra), a bone-seeking agent, as previously reported (*5–7*). Efficacy and definite disease modification as well as carcinogenic potential were reported. The availability of a modern, relatively nontoxic radiopharmaceutical such as ^{153}Sm-EDTMP may provide new avenues to treat these diseases.

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For correspondence or reprints contact: Albert S. Alberts, MD, Dept. of Radiotherapy, University of Pretoria, PO Box 667, Pretoria 0001, South Africa.

CASE REPORTS

Methods

Samarium was prepared by neutron irradiation of 99% enriched $^{152}Sm_2O_3$ 1.0–2.0 mg; 48 hr; thermal neutron flux of $2{,}78 \times 10^{13}$ n cm^{-2} s^{-1} in the Safari-I Research Reactor. The targets were dissolved in 0.2 ml 1.0 *M* HCl diluted to 0.1 *M* HCl and filtered (0.22 μm). Gamma-ray spectra (Ge (Li) gamma detector) revealed the presence of ^{152}Eu ($<6.8 \times 10^{-4}$% of ^{153}Sm) ^{154}Eu ($<4.3 \times 10^{-5}$% of ^{153}Sm) and ^{155}Eu ($<2.6 \times 10^{-5}$% of ^{153}Sm) at the end of irradiation.

EDTMP was prepared by condensation of ethylenediamine, phosphorous acid and formaldehyde in the presence of HCl by a modified Mannich reaction. Recrystallization from water/methanol and water yielded white crystals, m.p. 214°C. Analysis: Found; C, 16.83%; H, 4.62%; N, 6.52%; Calculated for $C_6H_{20}N_2O_{12}P_4$; C, 16.52%; H, 4.62%; N, 6.42%.

The EDTMP reagent kits were prepared in 10-ml vials by lyophilizing 1.0-ml aliquots of 50 mg/ml EDTMP (pH 8.5). The dry products were sealed under nitrogen. Sterility, apyrogenicity and toxicity were ascertained by standard methods.

For complexing, 1.0-ml aliquots $^{153}SmCl_3$ containing the prescribed amounts of activity but not more than 70 mCi (2590 MBq/vial) were added to the kits, left for 30 min, diluted to 5 ml and counted. Samples (3.0 μl) were analyzed by chromatography on cellulose thin-layers using pyridine: ethanol: water (1:2:4) as solvent. All the preparations contained less than 1% free $^{153}SmCl_3$. After sealing, the vials containing the final products (pH 7.0–8.0) were sterilized by autoclaving and used within 20 hr after formulation.

Patients were instructed to maintain a high fluid intake to minimize contact of excreted ^{153}Sm-EDTMP in the urine. All patients gave informed consent and the protocol was reviewed by the Institutional Review Board.

Ankylosing Spondylitis

Three patients (Nos. 1–3) with unequivocal, long-standing ankylosing spondylitis who were nonresponsive to standard symptomatic therapies were treated with 0.75 mCi/kg (27.8 MBq/kg) ^{153}Sm-EDTMP (Table 1). Within 48 hr, all patients had pain relief with no acute toxicity. The visual analog pain scale (VAS) (0 = no pain, 10 = excruciating pain) decreased by four or more units in all patients.

No toxicity (hematologic and other) was observed. Pain re-

TABLE 1
Patients with Ankylosing Spondylitis Treated with Samarium-153-EDTMP

Parameter	Patient 1*	Patient 2†	Patient 3‡
Duration of symptoms	7 yr	15 yr	16 yr
Pain in back, hips buttocks, shoulders and neck	Marked	Moderate	Marked
Stiffness	Marked	Marked	Marked
Peripheral arthritis	Yes	No	None
Uveitis	Yes	No	No
Thoracic kyphosis	Yes	Marked	Yes
Radiological joint changes, sclerosis and syndesmophytes	Moderate	Marked	Moderate
^{99m}Tc bone scan	Increased activity whole spinal column, knees ankles and wrists	Patchy accumulation spinal column	Increased uptake (patchy) whole spinal column
Correlation with ^{153}Sm-EDTMP scan	Good correlation§	Good correlation	Good correlation
Response to pain (VAS scale)¶	VAS decreased from 8 to 4	VAS decreased from 5 to 0. Excellent response	VAS decreased from 8 to 2. Excellent response
Duration of response	22 wk +	12 wk and 10 wk	24 wk +

*Treated 4 yr ago by external beam radiotherapy to whole spinal column with ^{60}Co 20 gray in five fractions; temporary response.
†Retreated after 12 wk for recurrent pain; ambulation improved.
‡Patient was bedridden before treatment. Currently ambulatory.
§There was more prominent accumulation with ^{153}Sm-EDTMP than with ^{99m}Tc.
¶For VAS scale, 0 = no pain and 10 = excruciating pain.

sponse is currently maintained for 22–24 wk. Patient 3, who responded the longest, was confined to bed for 2.5 yr before treatment. He is currently ambulant and virtually pain-free.

Paget's Disease

Patient 4, a 60-yr-old man, had a lifelong history of Paget's disease with involvement of the right sacroiliac joint causing marked pain and stiffness. He was extensively treated with diphosphonates without beneficial effect. Radiographs showed the classic osteoblastic, osteolytic pattern and a ^{99m}Tc-MDP bone scan showed radionuclide concentration in the right sacro-iliac joint. The patient was treated with 0.75 mCi/kg (27.8 MBq/kg) ^{153}Sm-EDTMP and experienced marked pain relief within 48 hr. The VAS decreased from an average of 7 to 2. The post-treatment ^{153}Sm-EDTMP bone scan showed marked activity in the right sacro-iliac joint. No acute hematological or other toxicity was observed. The patient was retreated after 12 wk in an attempt to eradicate the osteoblastic activity in the sacro-iliac joint. His pain was well under control 22 wk after the second treatment. A technetium bone scan at this stage, however, still showed activity in the right sacro-iliac joint.

Rheumatoid Arthritis

Patient 5, a 47-yr-old man, had a 4-yr history of rheumatoid arthritis. The multiple small and large joints had the classic clinical features indicative of rheumatoid arthritis and laboratory findings supported the diagnosis.

A ^{99m}Tc-MDP bone scan showed intense osteoblastic activity in many large and small joints. The patient was unresponsive to symptomatic and disease-modifying treatment (including methotrexate) and had prolonged morning stiffness. He was bedridden when he was treated with 0.75 mCi/kg (27.8 MBq/kg) ^{153}Sm-EDTMP, which localized well in the areas of joint activity (Fig. 1). Within the first week, there was a marked subjective response with pain improvement from a VAS of 9 to 2. The morning stiffness decreased from 4 hr to 1 hr and the Ritchie index decreased from 123 to 77. The erythrocyte sedimentation rate fluctuated, but there was some evidence of a response at 6 wk (Table 2).

The patient could now move around without a walker. Objective assessment showed a less marked improvement with joint tenderness and swelling still present. The improvement was maintained for 12 wk after which a slow relapse occurred. The patient was then retreated with a similar but less marked response. No toxicity was observed.

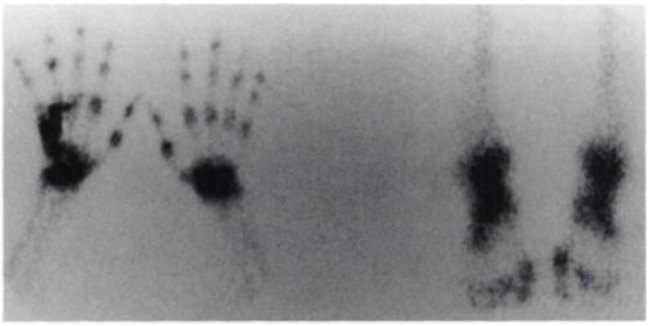

FIGURE 1. Samarium-153-EDTMP accumulation in the hand and foot joints of a patient with rheumatoid arthritis.

TABLE 2A
Response to Treatment of Rheumatoid Arthritis with Samarium-EDTMP (Patient 5)

Treatment (Rx) status	Pre-Rx	3 days post Rx	1 wk post Rx	2 wk post Rx
Ritchie index	123	77	85	65
VAS (0–10)*	9	2	4	5
Morning stiffness (hr)	4	1	1	1
Sedimentation rate (mm Westergren)	64	—	175	20

*0 = no pain and 10 = excruciating pain.

DISCUSSION

Samarium-153-EDTMP has efficacy in three benign diseases of different etiology.

In ankylosing spondylitis, the basic pathologic process includes an inflammatory process of the synovium of the joint and at the insertion of ligaments, tendons and capsules (*8*). Samarium-153-EDTMP can theoretically decrease the inflammation due to the nonspecific anti-inflammatory effect of radiation and can potentially stop the ossification process due to inhibition of osteoblastic activity. It may also prevent the final crippling sequela and mortality of this untreatable disease. Bertrand et al. reported a beneficial short-term effect of ^{224}Ra in 65% of patients (*6*). Hedde and Winkler reviewed extensive German studies with ^{224}Ra and suggested that there is definite slowing of the disease course if treatment is instituted early enough (*5*).

Paget's disease may also include a basic inflammatory process (*9*). Excessive resorption and formation of new pagetic bone may lead to a turnover rate of more than 20 times the normal rate. The incorporation of ^{153}Sm-EDTMP into the area of new bone formation can theoretically prevent excessive bone formation and may also influence excessive osteoclastic activity, thus modifying the pathophysiologic mechanism of the disease. Such efficacy is an indication for more study of ^{153}Sm-EDTMP in Paget's disease.

In rheumatoid arthritis, the inflammatory reaction and pannus formation leads to destruction of the articular cartilage and underlying bone with reactive osteoblastic activity (*10*). Samarium-153-EDTMP is concentrated in this area and locally irradiates the inflammatory reaction. The pathophysiology of the disease process cannot be modified, but a high local radiotherapy dose may give substantial palliation because the pannus is close to the osteoblastic activity.

Local external radiotherapy has been applied for these indications with moderate but usually short-lived success (*11,12*). Its use is controversial; concern focuses on long-term, soft-tissue complications. High local doses could be achieved with ^{153}Sm-EDTMP on the order of five times more without damage to surrounding tissues and normal bone marrow (*2*). Samarium-153-EDTMP treatment can also be repeated with acceptable toxicity (*1*). Repeat treatment cannot be done with external radiotherapy.

Recurrent bone tumors and leukemia are of great concern. An association of leukemia induced by extensive radiotherapy in ankylosing spondylitis has been reported (*13*). A long-term follow-up study of the late effects in 1531 ^{224}Ra-treated ankylosing spondylitis patients reported a moderate increase in malignant bone tumors (*7*). This should be seen in relation to the significant excess risk of a fatal outcome of the disease itself (*14*). The oncogenic potential of ^{153}Sm-EDTMP is unknown, but its favorable biologic distribution (away from the bone marrow) decreases the chances of leukemia as a complication. The intense alpha particle irradiation from ^{224}Ra is potentially more oncogenic than ^{153}Sm-EDTMP.

CONCLUSION

Samarium-153-EDTMP has efficacy in controlling not only the acute symptoms but also in modifying the disease process in ankylosing spondylitis and Paget's disease. It may also provide significant palliation in severe rheuma-

TABLE 2B
Response to Treatment of Rheumatoid Arthritis with Samarium-EDTMP (Patient 5)

Treatment (Rx) status	Pre Rx	3 wk post Rx	4 wk post Rx	6 wk post Rx	8 wk post Rx	10 wk post Rx	12 wk post Rx
Ritchie index	123	46	88	46	52	60	80
VAS (0–10)*	9	5	6	7	2	2	2
Morning stiffness (hr)	4	0.5	0.5	1.5	1	1	2
Sedimentation rate (mm Westergren)	64	51	77	45	34	40	70

*0 = no pain and 10 = excruciating pain.

toid arthritis. The acute toxicity is within acceptable limits, and the potential for long-term side effects is unknown. Phase I and II trials are needed to determine the optimal dose and disease modification potential (especially when administered earlier in the disease course) as well as long-term toxicity.

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