Targeting the Skeleton and Cancer in Bone

Samarium treatment of osteosarcoma, osteoblastic bone metastases, and neoplastic disease in the bone marrow

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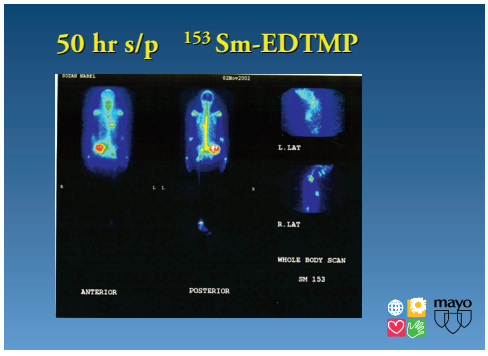
Targeted cancer therapy involves increasing the effectiveness of an intervention against cancer cells compared to normal tissue. Although chemotherapy and radiation are common and effective treatment modalities for skeletal neoplasia (1), bone-seeking radioisotopes offer a new opportunity to provide additional benefit via specific targeting of the skeleton and/or bone-forming lesions (e.g. osteoblastic metastases in the skeleton, marrow, or osteoblastic osteosarcoma). Principles of effective targeted therapy of skeletal neoplasia with a bone-seeking radiopharmaceutical, samarium will be reviewed in the context of our recent and extensive experience using high-dose samarium at Mayo Clinic.

The skeleton, osteoblastic metastases, and osteoblastic osteosarcoma lesions usually have medium, modestly avid, and very high uptake of bone-seeking phosphonates. Both ^{99m}Tc-MDP (used for routine bone scans) and ^{153}Sm-EDTMP, Quadramet (Berlex)- a therapeutic beta-emitting radioisotope that also emits a gamma photon to permit imaging and dosimetry- localize to the skeleton, osteoblastic metastases, and osteosarcomas with very high tumor (bone)/blood and tumor (bone)/muscle ratios (2-5) . The bone scan is qualitatively predictive of uptake and radiation dose that can be delivered. The high therapeutic index of radiation delivered by ^{153}Sm-EDTMP into bone-forming cancer lesions was initially demonstrated in canine osteosarcoma (6). Many of the dogs in this early series had durable clinical responses using standard doses of ^{153}Sm-EDTMP. Subsequent studies in Oslo have also shown clinical effectiveness of ^{153}Sm-EDTMP in canine osteosarcoma (7).

The therapeutic targeting of osteoblastic skeletal metastases by ^{153}Sm-EDTMP has been detailed in phase I/II clinical trials (8-15) as well as randomized clinical trials (16). The promise of targeted radiotherapy of human osteosarcoma using ^{153}Sm-EDTMP was shown for the first time by extremely impressive palliation in a 35 year man with recurrent, relapsed osteosarcoma involving the spine and associated hemiparesis (17). Pain at the L1 recurrence site in this man markedly improved; neurologic deficit (paresis) resolved for months after administration of the bone-seeking radioisotope. ^{153}Sm-EDTMP (Samarium ^{153}Sm lexidronam; Quadramet) was FDA approved for treatment of bone metastases in 1997.

Uptake, localization, and retention of ^{153}Sm-EDTMP into bone and bone-forming lesions has been studied (2, 3, 18) (19-23). Rapid blood and non-osseous tissue clearance is seen after samarium administration (3). ^{153}Sm-EDTMP remains tightly bound after



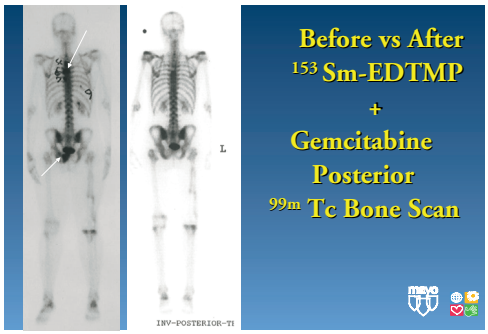
skeletal uptake with the half-life of clearance from bone (30 days) far exceeding the physical half-life of the radioisotope (47 hr)(22).

After intravenous administration of ^{153}Sm-EDTMP >90% of the injected dose is cleared from the blood within 2 hr (4). The samarium radiopharmaceutical that is not deposited in osseous sites or osteoblastic lesions is eliminated in the urine almost completely within 6 hr. Normal bone may possibly have a "ceiling value" of uptake associated with cortical surfaces (23); osteoblastic skeletal lesions have 3-7 fold higher uptake. We have not seen plateau of bone deposition using higher dose of ^{153}Sm-EDTMP.

Dose response of the clinical effectiveness against skeletal metastases has been seen with standard doses of ^{153}Sm-EDTMP (16, 24). Nevertheless, samarium's dose limiting toxicities are leukopenia and thrombocytopenia. These side effects occur because the bone marrow is an "innocent bystander" of radioisotope deposition throughout the skeleton- just like the "skeleton that is visible on a typical bone scan. To avoid serious hematopoietic toxicity of long duration, investigators in Germany and the United States have shown that safety is possible using high-dose samarium followed by stem cell "rescue". Hematopoietic progenitor cells, of course, must be infused after physical decay of most of the radiopharmaceutical (25-27) The MTD in our high-dose experience (30 mCi/kg) was related to hypocalcemia during infusion and practical considerations of handling and administration of 1500-3000 mCi. We now have experience at Mayo Clinic in >100 patients using high dose samarium and hematopoietic stem cell support. Skeletal cancers treated with this approach have included osteoblastic bone metastases, acute myelogenous leukemia, plasma cell dyscrasias, and osteosarcoma.

Strategies to increase effectiveness of high-dose samarium against skeletal cancer have included:

- Chemotherapy (melphalan) in hemato logic malignancies involving the marrow,



- Use with radiation in osteosarcoma and other skeletal metastases,
- Elimination of non-osseous disease with other strategies (e.g. RFA, surgery)
- PPAR gamma and RXR agonists to promote osteoblast differentiation and apoptosis
- Radiosensitization with gemcitabine

Gemcitabine was chosen because it not only has a broad spectrum of anti-neoplastic activity, but is also a potent radiosensitizer (28-34). Preliminary results of our current study using high-dose samarium follow by gemcitabine and stem cell support in osteosarcoma are yielding insights about principles and logistics of using this novel targeting strategy for skeletal neoplasia.

Acute myelogenous leukemia (AML)

Since our dosimetry studies indicate that 19-30 mCi/kg ^{153}Sm-EDTMP can provide approximately 3-4,000 cGy to the skeleton, we have used ^{153}Sm-EDTMP in a few very high risk individuals with AML and a relative contraindication to a TBI. Remission occurred after transplantation in 3/3. One patient is >2 years s/p autologous transplantation for secondary AML.

Plasma cell dyscrasias

A gratifying clinical response was seen in a man with POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome after high-dose samarium and melphalan followed by autolo-

gous peripheral blood progenitor cell infusion (35). The current study of high-dose samarium and melphalan for multiple myeloma at Mayo Clinic has nearly completed accrual (A. Dispenzieri, personal communication). This study uses a "scout dose" to define the therapy dose that will result in about 3000 cGy to the marrow. The dose required to achieve this is generally 20-24 mCi/kg.

Osteoblastic bone metastases

We have treated patients with osseous metastases of adenocarcinoma, myoepithelial carcinoma, breast cancer, chondrosarcoma, and paraganglioma. A patient with paraganglioma metastatic to bone provides an illustration of usefulness and logistics of high-dose samarium as part of an aggressive palliative "targeted cancer strategy".

Osteosarcoma

We have reported dose estimates of 3,900-22,000 cGy to osteosarcoma lesions in patients with favorable imaging (27). Results also are not durable in most patients; relapse at site of bone scan avidity and/or distant sites, particularly the lungs are common. Potential reasons for this pattern of failure include heterogeneity of uptake (i.e. new bone formation occurs only in parts of the tumor, short path length of radioactivity emitted from samarium (~1 mm), and that osteosarcoma is not considered to be a particularly radiosensitive tumor. Since osteosarcomas treated with radiation and chemotherapy had much better-than-expected results in two recent series (36, 37), it is also possible that our series is biased because it is composed of resistant, refractory patients with osteosarcoma unlikely to respond to any therapy- including radiation. Because of this we have begun using gemcitabine as a radio-sensitizer after 1 day after the samarium is essentially irreversibly bound to the osseous target sites. As in previous reports, schedule of gemcitabine administration was very important (38, 39). Low dose gemcitabine (200 mg/m2/dose qd x 5 days) was associated with grade 3 mucositis (N=1), a side effect not seen with either samarium alone or a single dose of gemcitabine (1500 mg/M2) given 1 day after samarium (N=10). The logistics of our current clinical trial is diagrammed below.

Document One or More Osteoblastic Sites (Observable on Bone Scan)
Harvest & cryopreserve PBPC (or marrow)
Goal: >5 x 10^6 CD34+/kg; Minimum: 2 x 10^6 CD34+/kg
Consider local external beam RT to large soft tissue components of identified lesions
Re-staging studies prior to treatment with samarium

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High-Dose (30 mCi/kg) ^{153}Sm-EDTMP
Gemcitabine 1500 mg/M2 x 1 dose – 1 day after ^{153}Sm-EDTMP
Dosimetry

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Infuse PBPC 2 weeks s/p samarium

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G-CSF or GM-CSF; transfuse prbc, platelets as clinically indicated

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Evaluation s/p count recovery (PET, if available, and bone scan)

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Other therapy as clinically indicated

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