Evaluation of CycloSam™ (Sm-153-DOTMP) as a Therapeutic Bone-Seeking Radiopharmaceutical

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Introduction

"Bone-seeking", beta-emitting radiopharmaceuticals are attractive for

- palliation of bone pain from skeletal metastases and
- ablation of bone marrow

Samarium-153-labeled ethylenediaminetetramethylenephosphonic acid (Sm-153-EDTMP) has been used for palliation at 1 mCi/kg with great success. At higher dosages, however, it has demonstrated a saturation effect [1] that might limit its use for bone marrow ablation. This effect has been surmised to arise from its high (≥273:1) chelant-to-metal ratio.

Sm-153-labeled 1,4,7,10-tetraazacyclododecanetetramethylenephosphonic acid (Sm-153-DOTMP) is a bone-seeking radiopharmaceutical that has a much lower chelant-to-metal ratio (ca. 1.5:1). It thus has the potential to have better skeletal uptake than Sm-153-EDTMP at high dosages.

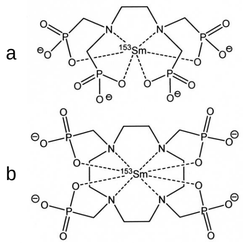


Figure 1: **Structures** a) Sm-153-EDTMP and b) Sm-153-DOTMP

Objectives

This is a preclinical study that

- assessed the skeletal saturation of Sm-153-DOTMP in a rat model
- measured the biodistribution and clearance of Sm-153-DOTMP in a rat model
- estimated the human dosimetry of Sm-153-DOTMP from the rat data, and
- assessed myeolosuppression in dogs with bone tumors at a dosage of 1 mCi/kg.

Materials

- 280 g male Sprague-Dawley rats in cohorts of seven animals.
- Sm-DOTMP prepared with 10 µCi of Sm-153 (specific activity of 358 Ci/g, $T_{1/2}$ = 46.3 hours) and sufficient unenriched Sm to simulate various activities at a chelant-to-metal ratio of 1.5:1 for the rat studies.
- Sm-153-DOTMP was prepared at a chelant-to-metal ratio of 1.5:1 and administered to five dogs with bone tumors at 1 mCi/kg.

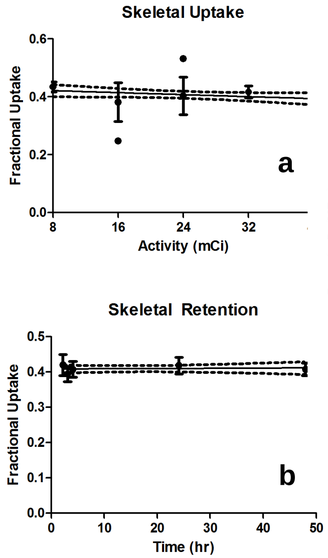
Methods

- Saturation study: simulated activities of 8, 16, 24, 32 and 40 mCi at 3 hours post-administration to rats.
- Biodistribution study: simulated activity of 40 mCi at 2, 3, 4, 24 and 48 hours post-administration to rats.
- Saturation study: skeletal uptake was plotted against simulated activity and fit by a straight line.
- Biodistribution study: organ uptakes were plotted against the time post-administration and fit by a single exponential function, a double exponential function or a collection of trapezoids as appropriate.
- Murine residence times were converted to human estimates by the ratio of the fraction of total body mass method and input into OLINDA/EXM 1.1 to estimate human target organ doses.
- Platelet and neutrophil counts were measured weekly in dogs and the counts at nadir were compared to previously treated dogs given 1 mCi/kg Sm-153-EDTMP with or without low-dose Carboplatin.

Reference

1) Bartlett ML, Webb M, Durrant S, Morton AJ, Allison R, Macfarlane DJ. Dosimetry and Toxicity of Quadramet for Bone Marrow Ablation in Multiple Myeloma and Other Haematological Malignancies. Eur J Nucl Med. 2002;29:1470-1477.

Results



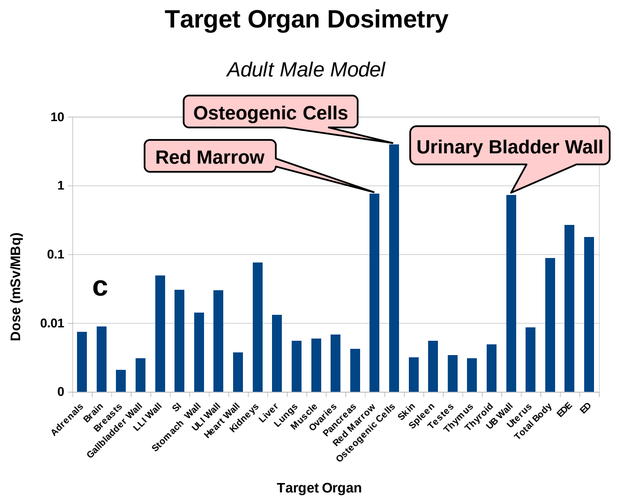


Figure 2: Rat Studies. a) Skeletal uptake at 3 hours as a function of simulated administered activity. The circles show two excluded outliers. b) Skeletal retention of the 40 mCi simulated administered activity. The dashed lines indicate the 95% confidence interval of the fits. c) Human dosimetry estimated by scaling murine residence times to human. The vertical scale is logarithmic.

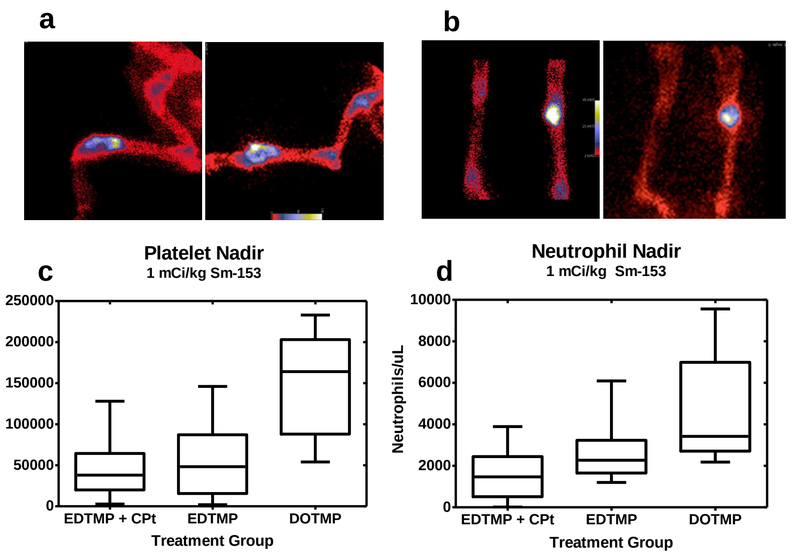


Figure 3: **Dog Studies.** a and b) Distal radius osteosarcoma, l) Tc-99m-MDP, r) Sm-153-DOTMP. c) Platelet counts at nadir. d) Neutrophil counts at nadir. DOTMP = Sm-153-DOTMP, EDTMP = Sm-153-EDTMP, CPt = low-dose Carboplatin

Results

- Saturation: Linear fit to skeletal uptake vs. administered activity has a slope that is not significantly different from zero (P=0.26).
- Biodistribution: Skeletal uptake is 40.8% (39.6%-41.9%) with a measured effective half-life of 47.3 (42.3-53.7) hours. (Range = 95% confidence interval)
- Myelosuppression: Absolute neutrophil and platelet nadirs were significantly higher with Sm-153-DOTMP than with Sm-153-EDTMP (P = 0.045 and P = 0.003 respectively).

Discussion

- The saturation study activities correspond to human activities of 2,4,6,8 and 10 Ci.
- No saturation point of Sm-153-DOTMP is evident below 10 Ci, whereas it is reported to be at only 0.68 Ci for Sm-153-EDTMP[1].
- Using the estimated human residence times from this rat study, an administered activity of 1.43 Ci would deliver a 40 Gy dose to the red marrow.
- The dose to the urinary bladder wall is based upon the dynamic voiding model with a four-hour voiding interval. This dose could be reduced by catheterization and irrigation of the bladder or by more frequent voiding.
- An unexpected finding is that Sm-153-DOTMP is less myelosuppressive than is Sm-153-EDTMP at 1 mCi/kg.

Conclusion

Sm-153-DOTMP has strong potential to be an effective bone-seeking radiopharmaceutical for therapeutic applications.

Acknowledgments

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