Combined Therapies for Bone Metastases

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Most Common Skeletal Metastasis

- Breast (70%) ⇒ 40% osteoblastic 45-50% of all tums.
- Prostate (70%) ⇒ 80% osteoblastic
- Lung (30%) ⇒ 10% osteoblastic
- Thyroid (50%)
- Kidney-Bladder (25%)
- Stomach
- Ovary

Usually a late manifestation of cancer spread, more common in slow growing cancers.
Bone metastases

- 85% axial skeleton
  - 40% spine
  - 30% ribs and sternum
  - 10% pelvis
  - 10% scalp

- 15% long bones
The “vicious loop”

Tumor proliferation

Inflammation → pain

Disruption of normal bone remodeling

JP Vuillez, Grenoble
**Full-Blown Skeletal Metastases**

- Source of considerable morbidity: pain, hypercalcemia, compression of spinal cord, pathologic fracture, bone marrow infiltration.

- Pain initially mild to moderate, progressively increasing, becoming multifocal and refractory to various treatments.
Excruciating pain
Mobility restriction
Sleep reduction

Worsening patient’s quality of life.
Pain from Bone Metastasis

- Effective anti-tumor therapies:
  - chemotherapy
  - hormonal therapy
  - anti-tumor radiopharmaceuticals

- Bisfosfonates
- Bone-seeking radiopharmaceuticals

- Palliation therapies:
  - external beam radiation therapy
  - surgery
  - pain-killing medications
Pain from Bone Metastasis

- Multidisciplinary approach!

- Most therapies are complementary rather than competitive!
Bone-Seeking Radionuclides

- Simultaneous treatment of multiple sites.
- Ease of administration.
- Repeatability.
- Low cost.
- Integration with the other therapies.
Bone seeking radiopharmaceuticals

Bisphosphonates

Competition in bone uptake???
• Combined treatment with Zoledronic acid and $^{153}$Sm-EDTMP is feasible and safe.

• Competition was not found in lesion uptake of the bone-seeking agent.

rhTSH-stimulated $^{123}$I-WBS: multiple bone metastases from follicular thyroid cancer (serum Tg: 3810 ng/mL)
Simultaneous whole-body $^{99m}\text{Tc-HDP}$ scan for better localization of the $^{123}\text{I}$-avid lesions
Post-therapy WBS after 3.7 GBq $^{131}$I, following prior surgical debulking of the two major skull lesions.
Three-year follow-up: 0.1 ng/mL serum Tg with suppressed TSH, 0.7 ng/mL after rhTSH stimulation.
Palliation therapy with bone-seeking radionuclides can be combined with external beam radiation on selected site(s) at risk of impending fracture.
Beyond Palliation of Bone Pain
Because of their path-length in tissues, $\beta^-$ particles emitted at the osteoid layer hit all cells within the bone marrow (including metastatic tumor cells).
Biochemical Response to Therapy with Bone-Seeking Radionuclides

• Sciuto et al. J Nucl Med 2000:
  - reduced serum levels of tumor markers (PSA, Ca15.3) after $^{186}$Re-HEDP.
Response to $^{153}\text{Sm-EDTMP}$

Baseline bone scan  
Bone scan after 3 cycles

Courtesey of L. Bodei, EIO, Milan
Prolonged survival with high doses (2.5 mCi/kg) of $^{153}$Sm-EDTMP (but higher myelotoxicity).

$^{89}\text{Sr}$ slows down bone resorption up to at least 6 months after palliation (urinary pyridinium collagen cross-links).

A: Doxorubicin + $^{89}$Sr  27.7 months
B: Doxorubicinalone  16.8 months
C: Non randomised  11.1 months

$p=0.0014$


Similar results reported independently by Windsor (Clin Oncol - R Coll Radiol 2001) and by Van der Pel et al. (Urol Int 2006)
Probability of Surviving

153Sm-EDTMP alone (10 months)

153Sm-EDTMP + chemo 3-5 month apart (11 months)

153Sm-EDTMP + chemo <1 month apart (30 months)

P=0.023

P=0.008

Follow-up, months

A Phase I Study of $^{153}$Sm-EDTMP + Docetaxel in Patients with Hormone-Resistant Prostate Cancer

(Morris et al. J Clin Oncol 2009)

\[ D = \text{Docetaxel 75 mg/m}^2 \]
\[ \text{Sm} = \text{$^{153}$Sm-EDTMP 37 MBq/kg (15 to 6 hours before Docetaxel)} \]
\[ \ldots = \text{Prednisone 10 mg/day (from Day-1 of cycle 1 to Day-21 of cycle 9)} \]
PSA Response by Cohort
(Morris et al. J Clin Oncol 2009)

All pts
Taxane-naive disease

Taxane pretreated pts
Taxane-refractory disease