Radiopharmaceutical Therapy in the Setting of Bone Marrow Transplantation

Where Are We Headed Next?
Radiopharmaceutical Therapy in Bone Marrow Transplantation

Organizer: Gregory Wiseman, MD

- **Myeloablative Therapy in Multiple Myeloma**
  Gregory A. Wiseman, MD

- **Myeloablative RIT in Lymphoma and Leukemia: University of Washington Experience**
  Joseph Rajendran, MD, DMRT, FASNC

- **Patient Specific Dosimetry: Rationale and Challenges**
  Darrell R. Fisher, PhD

- **Panel Discussion**
  Ajay Gopal, MD; Darrell R. Fisher, PhD; Joseph Rajendran, MD, DMRT, FASNC; Gregory A. Wiseman, MD
Educational Objectives

1. Describe how bone marrow transplantation is used to treat hematologic tumors.
2. Describe the characteristics of the ideal radiopharmaceutical for treating hematologic tumors using marrow transplantation.
3. Review the prior clinical trials of radiopharmaceuticals in bone marrow transplant.
4. Define the role of dosimetry in tumor therapy with marrow transplant.
5. Discuss the future direction of radiopharmaceutical therapy in transplantation.
Myeloablative Therapy in Multiple Myeloma

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Multiple Myeloma

- Malignancy of antibody-secreting plasma cells
- Tumor cells reside in bone and bone marrow and secrete a monoclonal immunoglobulin
- Bone pain, hypercalcemia, pathological fractures, anemia, and recurrent infections due to profound suppression of humoral immunity
- Monoclonal immunoglobulin is a serum or urine marker for disease monitoring, renal failure, hyperviscosity and amyloid deposition
FDG PET/CT
Multiple Myeloma
Bone Marrow Transplantation in Myeloma

- High-dose chemotherapy with or without external beam radiotherapy with autologous bone marrow transplantation is the most effective treatment of myeloma.
- All patients fail either early or late after transplantation due to tumor progression.
- Radionuclide targeted radiation to the tumor cells can increase the anti-tumor therapy.
- Studies have used radiolabeled antibodies, bone seeking radiopharmaceuticals or iron radionuclides to target radiation to tumor cells.
Transplant Conditioning Regimens in Multiple Myeloma

- Until the Intergroupe Francophone du Myelome randomized controlled trial, melphalan 140 mg/m² with TBI 8.5-12 Gy was myeloma transplant conditioning regimen.
- Melphalan only arm (200 mg/m²) had faster hematologic recovery, lower transfusions, shorter hospital days, and less mucositis.
- Trend to improved overall survival without TBI.
- TBI is rarely used as part of a conditioning regimen for autologous myeloma transplants.
- Radiation therapy used in cord compression, palliation and plasmacytoma.
Radionuclides in Multiple Myeloma

- Non-transplant - $^{153}$Sm-EDTMAP in patients with refractory multiple myeloma and pain, treatment with $^{153}$Sm-EDTMAP has reduced the pain and reduced the M-component.

- Pre-clinical transplant - Turner et al. in a mouse model system for multiple myeloma found sequential treatment with $^{153}$Sm-EDTMAP, melphalan, and BMT was significantly more effective than single-agent treatment ($P < 0.01$).
Transplant Conditioning Regimens in Multiple Myeloma

- Transplant experience. The two most widely investigated modalities incorporating therapeutic radionuclides into transplant conditioning regimens include radiolabeled diphosponates and radiolabeled antibody therapy to treat CD20 positive hematologic malignancies.

- Myeloma cells are radiosensitive and even locally radiocurable.

- Higher response rates have been achieved using SCT with melphalan 140mg/m² and TBI 850 cGy than with melphalan 90-140 mg/m² alone.
The bone seeking radiopharmaceutical $^{166}\text{Holmium-DOTMP}$ has been studied by Giralt et al.

Treated 82 patients with myeloma with $^{166}\text{Holmium-DOTMP}$ in combination with melphalan 140 mg/m² and 800 cGy of TBI.

Complete remission rate was 37%, but severe adverse events were seen. Hemorrhagic cystitis (33% of patients), thrombotic microangiopathy (10%), and grade 3-4 renal toxicity (17%).
Radionuclides in Myeloma

- Transplanted a patient with POEMS syndrome - plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes that differs from classic multiple myeloma.

- Samarium-153 EDTMP 111 MBq/kg and melphalan 200 mg/m^2

- Neurologic improvement both clinically and electrophysiologically. The patient progressed from being wheelchair-bound to independent ambulation and was doing well in remission at 23 months when last seen.
# Beta-Emitting Therapeutic Radioisotopes

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<th>Half-life (days)</th>
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$^{153}$Samarium EDTMP
$^{153}$Sm-EDTMP

- High selective binding to new bone, normal bone and osteoid in bone tumors
- Rapid clearance from non-osseous tissues
- Beta emitter ~ 1.0 mm pathlength
- Gamma emitter allows scanning for dosimetry
- FDA approved for bone metastases pain treatment at 1 mCi (37 MBq) per kilogram
Whole Body Scans - $^{99m}$Tc-MDP and Sm-153-EDTMP
Myeloma Treatment Schedule

PBSCT Infusion
Stem Cells
Day 0

Melphalan
200 mg/m²
Day –1

153 Sm-EDTMP
Day -12

Total body
153 Sm <3.6 mCi

2008 Annual Meeting

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$^{153}$Sm EDTMP and Melphalan Autologous Transplant in Myeloma

**Phase I**
- 4 dose levels: 6, 12, 19.8, 30 $^{153}$Sm EDTMP mCi/kg
- 3 patients per level
- Standard SCT support
- GM-CSF beginning on day 6

**Phase II**
- $^{153}$Sm EDTMP dose = 4000 cGy to red marrow
- 36 patients total
- Standard SCT support
- GM-CSF beginning on day 6

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Myeloma Autologous Transplant with Sm-153 EDTMP and Melphalan 200 mg/m²

Phase I: 18 patients treated
- 3 at each of 4 dose levels (6, 12, 19.8, 30 mCi/kg)
- 6 with patient specific red marrow target dose of 4000 cGy

Phase II: 36 patients treated
- Red marrow target dose of 4000 cGy (median = 17.1 mCi/kg with range 14.3 to 27 mCi/kg)
Myeloma Autologous Transplant with Sm-153 EDTMP and Melphalan 200 mg/m2

- For the combined Phase I/II cohorts, the rates of continued or new complete response (CR), very good partial response (VGPR), and partial response rates among the 58 patients were as follows: 29% (17/58), 14% (9/58), and 52% (30/58), respectively. In the Phase II cohort the CR/VGPR rate was 52%.

- Results show safely delivery of 40 Gy to the red marrow using $^{153}\text{Sm}$-EDTMP with response rates comparable to (or higher than) current conditioning regimens.
Myeloma Autologous Transplant with Sm-153 EDTMP and Melphalan 200 mg/m²

- Phase I/II trial using $^{153}\text{Sm}}$-EDTMP followed by melphalan 200 mg/m² and peripheral stem cells

- No dose limiting toxicity or cases of thrombotic thrombocytopenic purpura, radiation nephritis or bladder toxicity was observed during follow-up.

- Times to engraftment were comparable to other myeloma patients being treated at Mayo contemporaneously with melphalan 200 mg/m² alone.

- There was one death from infection with cytopenia during transplant nadir in 58 patients.

- With a median follow-up of 37 months (range 28 to 44) for the Phase I and 14.2 months (range 1.5 to 36.3 months) for Phase II cohort, we have not observed any delayed toxicity.
Conclusions

- Targeted radionuclide therapy can boost the treatment of myeloma tumor cells without significantly increasing toxicity.
- Treatments to increase tumor cell and tumor stem cell killing with targeted radionuclides could potentially result in longer remissions and longer survival.
- Current studies have shown promising results but the added benefit of adding radionuclides to transplant will require randomized trials.
- Radionuclides in transplant requires short-life isotopes so stem cells can be re-infused prior to infection and bleeding complications.
- Dosimetry in high dose trials is necessary in transplantation studies.
Transplant Conditioning Regimens in Multiple Myeloma

- Many reports in the literature using Sm-153 EDTMP as part of myeloablative and non-myeloablative conditioning regimens.
- The drug has been used both in the context of autologous and allogeneic stem cell transplantation for an assortment of hematologic malignancies. No unusual toxicities have been observed thus far.
- Another bone seeking radiopharmaceutical (\(^{166}\) Holmium-DOTMP) has been studied by Giralt et al. They treated 82 patients with myeloma with \(^{166}\) Holmium-DOTMP in combination with...