Radiation therapy for Multiple Myeloma

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Overview

• Radiotherapy…
  – What is it?
  – How do we do it?
  – What’s it used for?
  – What are the unanswered questions?
Radiotherapy – what is it?

• Ionising radiation
  – High energy X-rays
    • Diagnostic X-rays up to ~100,000 Volts
    • Radiotherapy beams up to 18,000,000 Volts
  – Electrons for superficial (shallow) areas

• Produced by linear accelerators
  – No radioactive isotopes involved in routine external beam radiotherapy

• Focused on an anatomical target
  – Typical accuracy <3mm
How do we do it?

1. Clinical assessment
   - Haematologist → radiation oncologist

2. Simulation and planning
   - “Measure and quote”
   - CT scan in the treatment position
     • Immobilisation
     • Tattoo/reference marks
   - Accurately calibrated for treatment machine geometry
   - Radiation beams (position and shape) customised based on position, body shape, target and nearby critical structures

3. Treatment
   - One or more “fractions” (usually daily)
   - 15-20 minutes
   - Setup and checking
   - Each beam on for a few moments only
CT simulator
Planning
Linear accelerator
Where does radiotherapy fit into myeloma treatment?

• Definitive RT remains standard for localised plasma cell disease ("solitary plasmacytoma" or "extramedullary plasmacytoma")

• Continued developments in systemic therapy for multiple myeloma

• RT increasingly limited to adjunctive role in MM
  – Palliation of bone pain
  – Prevention of pathological fracture in long bones
  – (Impending) spinal cord compression/nerve root compression

• Preparation for bone marrow transplant (total body irradiation)

• ? Consolidation of residual disease after intensive drug treatment
Solitary plasmacytoma

- “Radical” radiotherapy (curative)
- 3D conformal technique or intensity-modulated radiotherapy (IMRT)
  - Multiple beams from multiple angles converging on a target
  - High dose to target
  - Minimise dose to critical structures (esp spinal cord)
- Dose 45-50.4Gy / 25-28 fractions
  - 5 – 5½ weeks of daily (Mon-Fri) treatment
- Local control 80-95%
- Progression to myeloma ~50%
- Median survival 5-10 yrs
Solitary plasmacytoma
Palliation of myeloma bone pain

• RT is effective
  – Plasma cells highly radiosensitive
  – Bone lesions
  – Soft tissue extension
  – Pain response varies
    • Within a few days up to several (4-6? weeks)
    • Occasional (~10%) “pain flare”

• Low doses to limited fields
  – 8Gy single fraction or 20-30Gy/5-10 fractions
  – Adequate for symptom relief
  – Allows re-treatment (<10% re-treatment rate)
  – Does not compromise marrow reserve
  – Safe to critical structures
Comment:

Beam Name: 1 pa t-l spine
Plan Name: t-l-s spine 2010
Trial Name: Trial_1
Plan Revision: R01.P01.D02
Pinnacle Version: 6.2b
Fri Jan 15 14:28:45 2010
Prescription: t-l spine
MU/Fraction: 492
# Fractions: 5
Beam Weight: 100.00%
Machine: TS1_600CD
Energy: 6X
Modality: Photons

SSD: 100.00
Gantry Start: 180.0
Gantry Stop: 180.0
Direction: CW
Couch: 0.0
Coll.: 0.0
Jaws:
X1: 4.00
X2: 4.00
Y1: 4.00
Y1 open: 3.50
Wedge: None
Bolus: No
Compensator: No

Iso-center: spine L-1
(Reported as table movements)
Table 0.10cm UP (looking from foot of table)
Table 1.10cm DOWN
Table 2.00cm OUT (away from the gantry)
RT for bone pain - outcomes

• Multiple retrospective series report 80-97% response rates
  – inconsistent whether complete or partial improvement, variable use of concurrent chemotherapy

• Mean duration of response 18-32 months

• No consistent dose-response relationship
  – Likelihood and duration of response similar for low vs high dose RT
  – Conclusion – low dose RT adequate for pain relief

• Does combination chemo + RT work better together?
  – Only one study suggesting melphalan together with RT improves likelihood of pain relief
  – Other chemotherapy drugs (especially anthracyclines) increase side-effect rates

but…
Hemi-body RT (HBI)

- 8Gy single fraction for lower hemi-body
- 6Gy single fraction for upper
- May be appropriate for
  - extensive disease/multiple symptomatic sites rather than multiple courses of localised RT
  - recurrent or refractory disease
    - Historically lower- followed by upper-HBI with rest period to allow marrow re-seeding
    - Effective pain relief, reduced disease burden but little impact on survival
- Benefits
  - Cover multiple sites effectively in single treatment
- Toxicities
  - Marrow suppression
  - Nausea/vomiting
  - Lung inflammation (pneumonitis)
- Current practice is to avoid HBI in the non-transplant setting
  - Low-dose TBI (2Gy)
Surgery ± RT

• **Rationale of surgery**
  – Quickly restore mechanical strength
  – Analgesic benefits

• **Post-op RT**
  – “Local control”
    • Tumour cell kill
    • Bone remineralisation
  – Little evidence to guide practice
    • Optimal RT volume?
    • Dose/fractionation?

• Benefit of RT less clear if further chemo treatment is planned
Spinal cord/nerve root compression

- Cord compression in up to 10-20% of MM cases
  - severe back pain, weakness, altered sensation of limbs, or bladder/bowel dysfunction or incontinence

- Benefit of surgery unclear (in myeloma)
  - Tissue for diagnosis if first presentation
  - Conflicting evidence on *functional* benefit of surgery versus RT alone for myeloma
  - Decompression indicated if no response to RT or if compression due to retropulsed bone fragment
Spinal cord/nerve root compression

• Optimal dose/fractionation of RT uncertain
  – Randomised trial pending (20Gy/5# vs 8Gy/1#)
  – Retrospective series suggesting improved local control and functional (motor) outcome with long-course RT (8-20Gy/1-5# vs 30-40Gy/10-20#)

• *Time from developing symptoms to starting RT the single most important predictor of outcome*

• Balance against clinical factors including expected course of disease

• Commonly 20-30Gy/5-10 fractions
Spinal cord/nerve root compression
Total body irradiation (TBI)

- **Goals of TBI**
  - Increase “marrow space” by eliminating residual marrow
  - Immunosuppression - allow grafting of donor bone marrow without rejection
  - Eradication of malignant cells

- **Benefits over chemo:**
  - No "sanctuary" sites (e.g. testes, brain)
  - Delivered dose is independent of blood supply
  - Delivered dose is independent of kidney and liver function
  - No cross-resistance with other agents
  - Dose can be homogeneous, and tailored to "boost" areas at risk and "spare" more sensitive organs

- **Drawbacks**
  - Toxicities – esp. lung, kidney

- **Doses**
  - 12Gy in 6 fractions over 3 days (myeloablative)
  - 2Gy single fraction
    - For non-myeloablative transplants – do not destroy host marrow, but cause immunosuppression to promote engraftment of transplant
Total-body irradiation technique
Questions and controversies
RT after kypho/vertebroplasty?

- Effectiveness supported in prospective, uncontrolled trials
  - Pain relief in 80-85%
  - Sustained for ≥12mo
  - ~40% VB height restored
  - Improved physical function

- Physical properties of PMMA not affected by RT

- Lack of evidence on role of RT post-plasty
  - No clear benefit, especially if systemic treatment planned
Targeted radiation therapy – the future?

- Exploits radiosensitivity of myeloma cells

- Radio-isotope therapy
  - $^{153}$Sm-EDTMP
    - Bone-seeking radiopharmaceutical
    - Selective uptake in bone lesions $\rightarrow$ localised irradiation

- Gene/molecular targeted radiation therapy
  - Radio-isotope (eg. $^{131}$I) attached to targeted molecule that accumulates in malignant cells
  - Delivers radiation focally into clusters of malignant cells
“Consolidation” RT?

- 61 y/o man with MM
- Bone disease + supraclav, subcarinal and mediastinal masses
- RT to L hip/femur
- 4xPAD → Auto transplant 11/09
- Residual mediastinal mass 3.5cm (prev 11.5cm)
- ? Role for consolidation RT
  - Propensity for relapse at “bulky” disease sites not well established for MM
  - Optimal dose/fractionation unclear
- 36Gy/12 fractions in this case
Evidence-based optimal RT utilisation

- Proportion of Australian myeloma patients who would benefit from RT is estimated at 38%

- Actual utilisation 24-55%
  - 34% in SA (as of 2003)

Featherstone et al, Cancer 2005
Summary

• Radical RT remains standard treatment for solitary plasmacytoma

• RT offers effective palliation for bone pain
  – Optimal dose/fraction not determined, typically use 1-10 fractions
  – Low-dose/local fields effective

• Surgery for long bones
  – ± post-op RT

• Early RT for spinal cord compression

• Ongoing developments offer more options
  – Vertebro/kyphoplasty
  – Targeted radio-isotopes

• Role for consolidation RT for bulky disease sites?

• Utilisation of RT for myeloma in SA has historically been appropriate