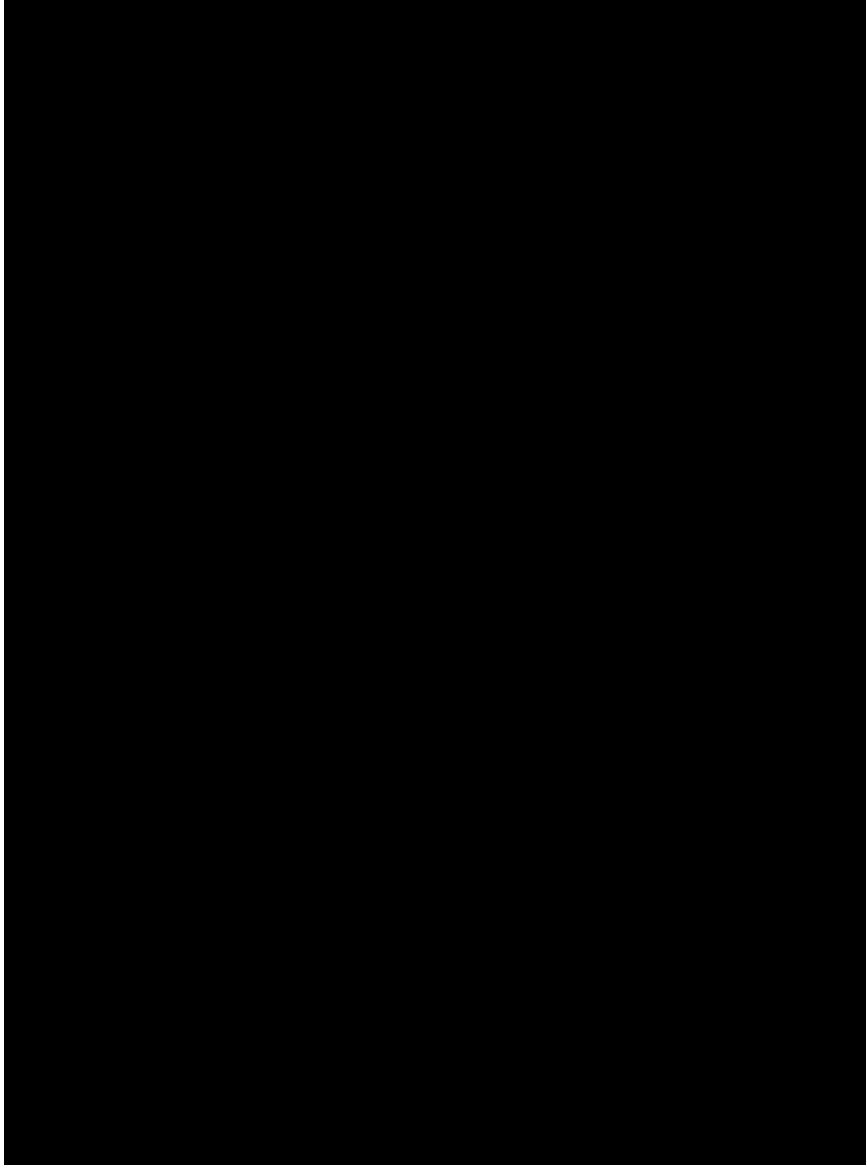


Introduction

- Nuclear medicine therapy is being used increasingly in the treatment of cancer (thyroid, leukemia/lymphoma with RIT, primary and secondary bone malignancies, and neuroblastomas).
- In all cases it is marrow toxicity that limits the amount of treatment that can be administered safely.

Introduction

- Marrow dose calculations are more difficult than for many major organs because of the intricate association of bone and soft tissue elements.
- In RIT, there appears to be no consensus on how to calculate that dose accurately, or of individual patients' ability to tolerate planned therapy.

Introduction

- Available dose models are designed after an idealized average, healthy individual.
- Patient-specific methods are applied in evaluation of biokinetic data, and need to be developed for treatment of the physical data (dose conversion factors) as well.
  - Age
  - Prior patient therapy
  - Disease status

Introduction

- Contributors to marrow dose:
  - Electrons
    - Activity in marrow
    - Activity in bone/on bone surfaces
  - Photons
    - Activity in marrow
    - Activity in bone/on bone surfaces
    - Activity in other organs/whole body

Dose Methods

D = N x DCF

N = the number of disintegrations in the source region (kinetic data)

DCF = dose conversion factor, the dose in the target per disintegration in the source (physical data)

Calculation of N (residence time)

No binding to marrow elements - Sgouros (1993):

$$[A_{marrow}] = [A_{P(or\,S)}] \frac{RMECFF}{1 - HCT}$$

"Working value" for RMECFF = 0.19

Calculation of N (residence time)

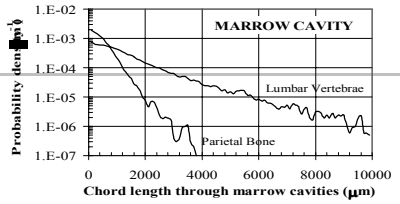
- If there is binding to marrow elements:
  - Consider both blood and marrow-fixed elements:
    - Collect data from sequential images using calibrated cameras,
    - Use conjugate imaging methods corrected for scatter and attenuation,
    - Region of interest selection defining organ boundaries.

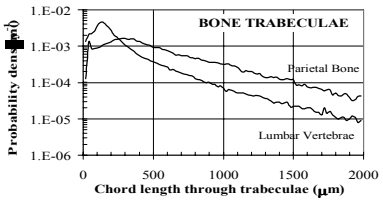
Active Marrow Distribution

- Cristy (1981), ICRP 70 (1995), Bouchet et al. (2000)
- Data from Ellis, derived from Mechanik – 13 subjects.
  - 60% of the active marrow is in the axial skeleton,
  - 25% is in the ribs, femoral head, upper humerus and sternum,
  - 10% is in the cranium and scapula.

Marrow Dose Conversion Factors

- Spiers, Beddoe and colleagues, Univ of Leeds:
  - Optically scanned prepared sections of trabecular bone.
  - Probability distributions of chord-lengths through distributions for trabeculae and marrow cavities.





Marrow Dose Conversion Factors

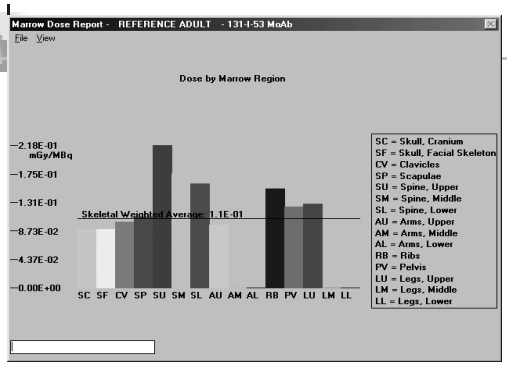
- Electrons originating in bone lost energy in that region of bone and subsequent regions of marrow or bone according to the continuous slowing down approximation (CSDA).
- Bone and marrow region dimensions chosen stochastically from frequency distributions.
- A Monte Carlo method gave averages for energy deposition in marrow from sources in bone.

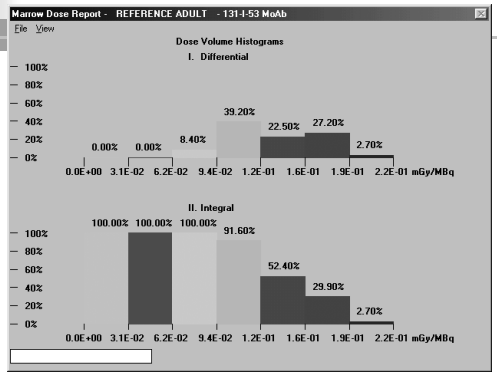
Marrow Dose Conversion Factors

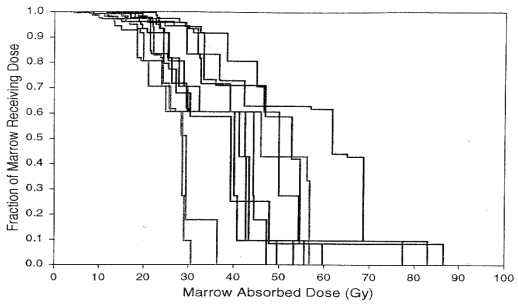
- Absorbed fractions were derived for this and other cases.
- This information, with Monte Carlo simulations for photons in the Fisher-Snyder phantom, gave the S values in MIRD Pamphlet No. 11.
- Photon AFs for bone>marrow conservative for photons<300 keV; Cristy-Eckerman improved – energy deposition of 2° electrons.

Marrow Dose Conversion Factors

- ICRP 30 – very limited use of the Spiers et al. electron AFs – generally one conservatively high value applied to all energies (MIRDOSE2).
- Eckerman (1985, 2000) recalculated AFs for the 7 bone types of Spiers et al., implemented them in the 15 bone regions of the Cristy/ Eckerman phantom, using similar methods (MIRDOSE 3).
- Regional dose calculations, dose-volume histograms.







DVHs for red marrow for eleven multiple myeloma pts treated with Ho-166 DOTMP and, in some cases, whole body irradiation. All pts had concurrent systemic chemotherapy. From McCullough, 2000.

Marrow Dose Conversion Factors

- Eckerman S values slightly lower (<10%) than those of MIRD 11, but much lower (factor of 2-3) than ICRP 30.
- Bouchet et al. (1999, 2000) also did new calculations, using the Spiers et al. chord length distributions, but using a 3D model (hemispheres) and the EGS transport code.

Marrow Dose Conversion Factors

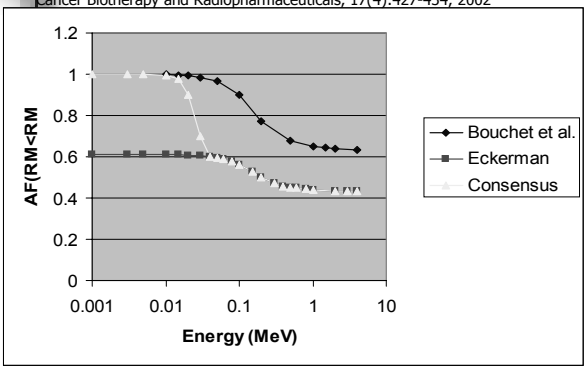
Eckerman	Bouchet et al.
▪ Electron AFs for marrow<marrow proportional to cellularity.	▪ These AFs do not depend on cellularity.
▪ "Bone surface" emitters originate from an infinitely thin layer on the surface of bone.	▪ Originate from the 120 μm layer of soft tissue.
▪ Electrons passing through 120 μm layer have uniform distributions of angles.	▪ Electrons passing through 120 μm layer have cosine distribution.

Marrow Dose Conversion Factors

- Last two differences only affect DCFs for bone surfaces. First difference affects DCFs for marrow.
- Eckerman AFs do not converge to 1.0 at low electron energies.
- Bouchet et al. AFs overestimate doses at medium-high energies (values similar to ICRP 30).

"Consensus" model:

Cancer Biotherapy and Radiopharmaceuticals, 17(4):427-434, 2002



Marrow Dose Conversion Factors

- New S values using consensus model – basis of new version of MIRDOSE code (OLINDA) and future codes.
- "Remainder of body" contribution to marrow must be correctly calculated (J. Nucl. Med. 42: 492-498, 2001).

Towards patient-specific marrow dose

Model features studied*:

1. Mass of body organs
2. S values
3. Marrow characteristics
4. Biokinetics
5. Marrow/bone involvement.
   a. Targeted uptake of free radionuclide in bone;
   b. Targeted uptake in RM/bone due to disease; and
   c. Activity retention in RM due to RES.

*Sensitivity of Model-Based Calculations of Red Marrow Dosimetry to Changes in Patient-Specific Parameters. Cancer Biotherapy and Radiopharmaceuticals. 17(5): 535-543, 2002

Mass of Body Organs

- As lean body mass changes, it is reasonable to expect proportional changes in the size of most body organs.
- The marrow self-dose term does not change with changes in lean body mass, as two terms involving organ mass cancel. The RB term does change with changes in lean body mass.

Mass of Body Organs

$D_{RM} = [\tilde{A}_{blood}] \times m_{RM} \times RMECFF/(1-HCT) \times S(RM \leftarrow RM) +$

$\tilde{A}_{RB} \times \{S(RM \leftarrow TB) \times m_{TB}/m_{RB} - S(RM \leftarrow RM) \times m_{RM}/m_{RB}\}$

First term : Mass independent
Second term: Mass dependent
Multiply by $m_{TB,model}/m_{TB,patient}$

Note: Direct mass scaling approximate but reasonable.
Expected effect on RM dose: -25% to + 150%.

S Values

$S(RM \leftarrow RM) = \Delta_i \times AF(MS \leftarrow MS) \times CF/m_{RM}$

- Values of AF(MS←MS) do not vary substantially with subject size.
- Choice of model gender: main source of difference is TB and RM mass, which are accounted for by mass considerations.
- CF should be accounted for.

Marrow Characteristics

$D_{RM} = [\tilde{A}_{blood}] \times m_{RM} \times RMECFF/(1\text{-}HCT) \times S(RM \leftarrow RM)$

Because S(RM←RM) contains cellularity factor, CF, even though mass cancels in first term of RM dose equation:

RMECFF x (1-RMECFF)

Assuming CF ≅ 1-RMECFF, this residual term generally treated as a constant. As people age CF generally decreases; prior therapy may also affect CF.

Biokinetics

Ratio of TB-to-blood cumulated activity influences RM-to-RM dose component:

	^{131}I, T_e = 64 h			
	MIRDOSE 3 S Values		MIRD 11 S Values	
TB/blood	D_{RM}	% RM cont.	D_{RM}	% RM cont.
1	2.04	77	2.21	83
2	1.27	62	1.31	70
3	1.02	52	1.01	60
4	0.89	44	0.86	53
6	0.76	34	0.71	43
8	0.70	28	0.64	36
10	0.66	24	0.59	31

Changes in Body Mass

^{131}I agent, T_e = 64 h
RM component changes as *f*(patient mass); % component to total dose constant

	M=73700 g			M=45000 g			M=100000 g		
TB/blood	D_{RM}	D_{RM_r-RM}	D_{RM_r-RB}	D_{RM}	D_{RM_r-RM}	D_{RM_r-RB}	D_{RM}	D_{RM_r-RM}	D_{RM_r-RB}
1	2.04	1.58	0.46	3.35	2.59	0.76	1.51	1.16	0.34
2	1.27	0.79	0.49	2.09	1.29	0.79	0.94	0.58	0.36
3	1.02	0.53	0.49	1.67	0.86	0.81	0.75	0.39	0.36
4	0.89	0.39	0.50	1.46	0.65	0.81	0.66	0.29	0.37
6	0.76	0.26	0.50	1.25	0.43	0.82	0.56	0.19	0.37
8	0.7	0.2	0.50	1.15	0.32	0.82	0.52	0.15	0.37
10	0.66	0.16	0.50	1.08	0.26	0.82	0.49	0.12	0.37

Marrow/Bone Involvement

Targeted uptake of free radionuclide in bone:

	D_{RM}	D_{RM}		D_{RM}	
	No free ^{90}Y	5% free ^{90}Y		10% free ^{90}Y	
TB/blood	D	D	ratio	D	ratio
1	8.04	8.77	1.09	9.50	1.18
2	4.92	5.65	1.15	6.38	1.30
3	3.88	4.61	1.19	5.35	1.38
4	3.36	4.10	1.22	4.83	1.43
6	2.84	3.58	1.26	4.31	1.51
8	2.59	3.32	1.28	4.05	1.57
10	2.43	3.16	1.30	3.89	1.60

Marrow/Bone Involvement

Targeted uptake in red marrow due to disease involvement:

	5% marrow involvement		10% marrow involvement	
TB/blood ratio	^{131}I ratio with/without marrow involvement	^{90}Y ratio with/without marrow involvement	^{131}I ratio with/without marrow involvement	^{90}Y ratio with/without marrow involvement
1	1.44	1.45	1.87	1.90
2	1.7	1.73	2.39	2.47
3	1.87	1.93	2.74	2.86
4	2.00	2.07	3.00	3.15
6	2.16	2.27	3.33	3.54
8	2.27	2.40	3.54	3.79
10	2.35	2.49	3.69	3.97

Marrow/Bone Involvement

Targeted uptake in bone due to disease involvement:

	5% bone uptake		10% bone uptake	
TB/blood ratio	^{131}I ratio with/without bone uptake	^{90}Y ratio with/without bone uptake	^{131}I ratio with/without bone uptake	^{90}Y ratio with/without bone uptake
1	1.14	1.18	1.28	1.36
2	1.22	1.30	1.45	1.59
3	1.28	1.38	1.56	1.75
4	1.32	1.43	1.64	1.87
6	1.37	1.51	1.75	2.03
8	1.41	1.57	1.82	2.13
10	1.43	1.60	1.86	2.20

Conclusions

1. Adjustments for patient mass should be made in RM dose calculations when patients are truly more than 10% different from the assumed model geometries.
2. Biokinetics should be measured.
3. Cellularity factors should be evaluated.
4. Ensure no marrow/bone uptake. If present, must be accounted for:

- Bone or marrow uptake of free radiometal or catabolized products may have a significant impact.
- Marrow or bone involvement with disease may change RM dose by between 20% and a factor of 4.
- With all factors combined, changes of up to a factor of 10, over simple model-based values, are possible.

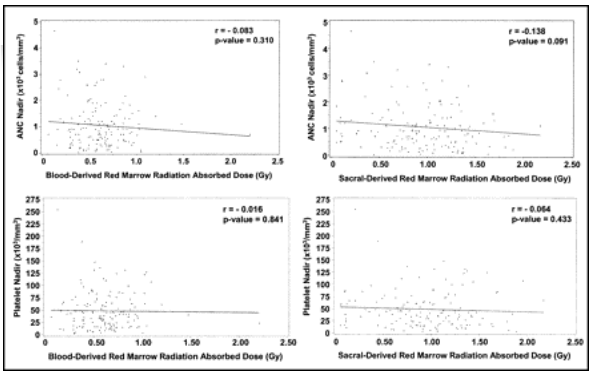
Conclusions

5. Radionuclide therapy patients, particularly RIT patients, are a heterogeneous group in terms of their bone marrow radiosensitivity.

Radiation dose-toxicity correlations may still be poor if BM radiosensitivity not accounted for.

Correlating Dose and Effect: Take Home Messages

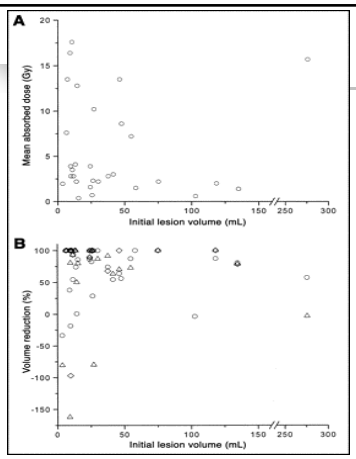
- Wiseman et al. Cancer 2002 Feb 15;94(4 Suppl): 1349-57: “Hematologic toxicity was manageable and did not correlate with estimates of red marrow or total-body absorbed radiation dose.”
- Wiseman et al. JNM 44(3):465-474: “Hematologic toxicity did not correlate with estimates of red marrow radiation absorbed dose, total-body radiation absorbed dose, blood effective half-life, or blood AUC.”
- IDEC product information: “Clinical studies demonstrated no correlation between hematologic toxicity in patients and dosimetric parameters.”



Wiseman et al. JNM 44(3):465-474

Take Home Messages

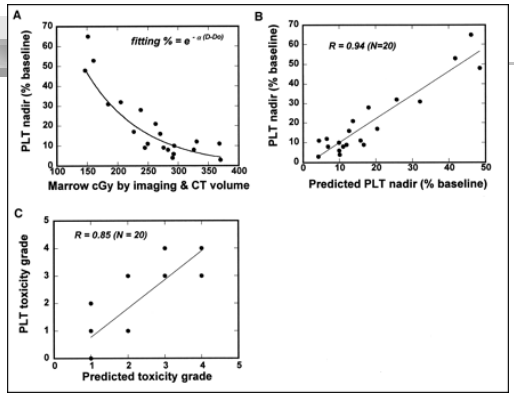
- Sgouros et al. JNM Vol. 44(2):260-268: “None of the absorbed dose parameters (mean, minimum, maximum, uniformity) were found to have a significant correlation with tumor response.”



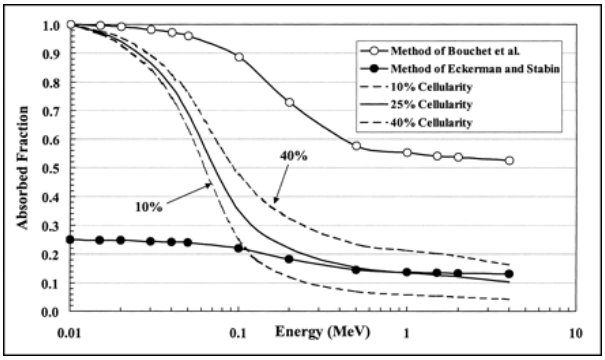
Sgouros et al. JNM Vol. 44(2):260-268

Take Heart Messages

- Shen et al. JNM 43 No. 9 1245-1253: "Marrow dose estimated from the blood radioactivity method was not a good predictor of myelotoxicity for non-marrow-targeting ^{90}Y-antibody therapy…The best prediction was obtained (r = 0.85 for n = 20) using patient-specific L2–L4 marrow mass estimated from CT."



Shen et al. JNM 43 No. 9 1245-1253



Electron absorbed fractions for self-irradiation of TAM within femoral head of 51-y-old man, with modifications for % cellularity. Bolch et al. Journal of Nuclear Medicine Vol. 43 No. 1 97-108

Take Heart Messages

- Siegel et al. JNM 44(1): 67-76: "FLT3-L–adjusted red marrow radiation doses provide improved correlation with hematologic toxicity…The highest correlation observed was between red marrow dose or total body dose and 1/PN (r = 0.86)."
- Dose parameters correlated with:
  - (PTG) Platelet Toxicity Grade
  - (PPD) Percent Platelet Decrease
  - (PN) Platelet nadir
  - (1/PN) 1/Platelet nadir

Results

Comparison of Correlation Coefficients (r) between Hematologic Toxicity and Administered Activity Unadjusted and FLT3-L Adjusted		
Platelet Toxicity	**Administered Activity**	**FLT3-L Adjusted Administered Act.**
PTG	**0.05**	**0.61**
PPD	**0.15**	**0.51**
PN	**0.03**	**0.60**
1/PN	**0.21**	**0.53**

Results

Comparison of Correlation Coefficients (r) between Hematologic Toxicity and Administered Activity per unit Body Weight Unadjusted and FLT3-L Adjusted		
Platelet Toxicity	**Administered Activity/Body Wt.**	**FLT3-L Adjusted Activity/Body Wt.**
PTG	**0.28**	**0.72**
PPD	**0.33**	**0.59**
PN	**0.18**	**0.75**
1/PN	**0.04**	**0.79**

Results

Comparison of Correlation Coefficients (r) between Hematologic Toxicity and Total Body Dose Unadjusted and FLT3-L Adjusted		
Platelet Toxicity	**Total Body Dose**	**FLT3-L Adjusted Total Body Dose**
PTG	**0.23**	**0.68**
PPD	**0.06**	**0.46**
PN	**0.16**	**0.75**
1/PN	**0.17**	**0.86**

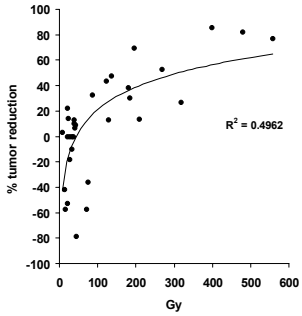
Results

Correlation Coefficient (r) between Hematologic Toxicity and Red Marrow Dose Unadjusted and FLT3-L Adjusted		
Platelet Toxicity	**Red Marrow Dose**	**FLT3-L Adjusted Red Marrow Dose**
PTG	**0.28**	**0.70**
PPD	**0.15**	**0.48**
PN	**0.22**	**0.76**
1/PN	**0.20**	**0.86**

Toxicity Prediction Results

Comparison of Adjusted and Unadjusted RMD as a Predictor of Grade 3 or > Plt Toxicity		
	FLT3-L Adjusted Red Marrow Dose (200cGy Threshold)	Unadjusted Red Marrow Dose (100cGy Threshold)
Sensitivity	100%	100%
Specificity	91%	41%
Accuracy	93%	57%
PPV	80%	38%
NPV	100%	100%

Correlation of tumor response vs dose (Gy) at end of treatment,n = 32



Dr. S. Pauwels, 15th IRIST Meeting, Rotterdam, May-2002