



# Red marrow dosimetry and timing for autologous stem cell reinfusion in high activity treatments with $^{90}\text{Y}$ -ibritumomab tiuxetan

*The Milan Experience*

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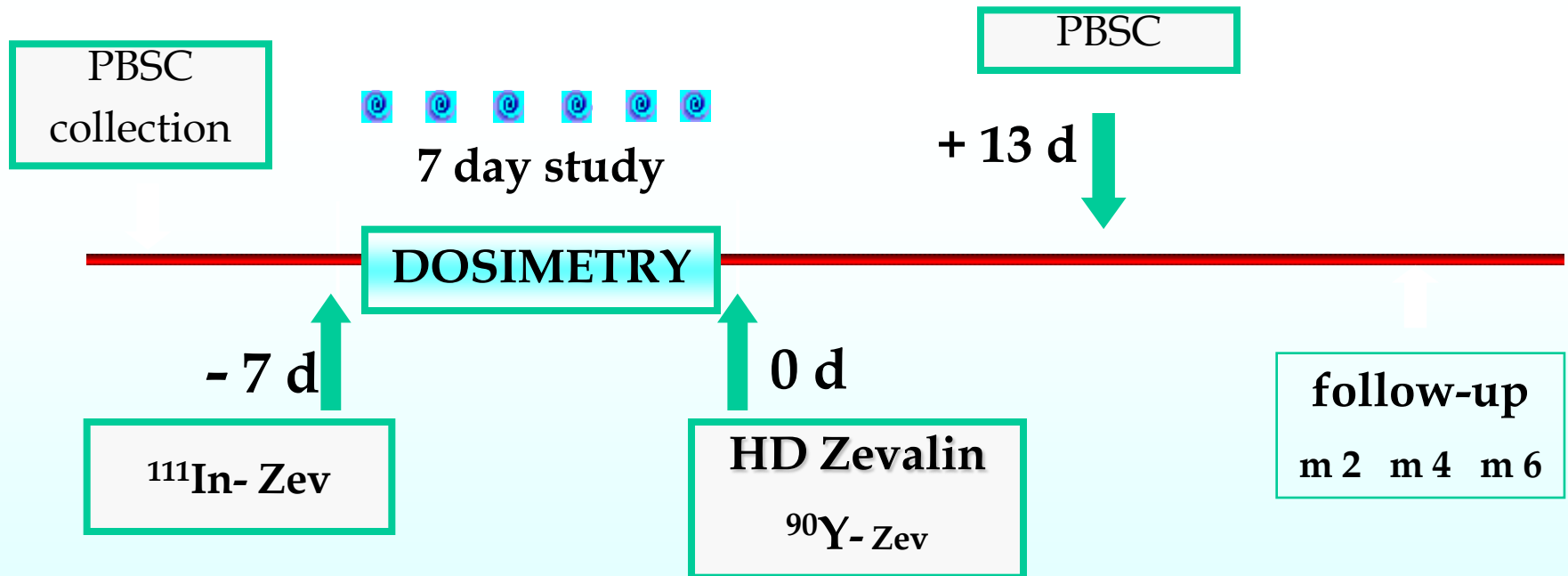
European Institute of Oncology, Milano, Italy



# Protocol

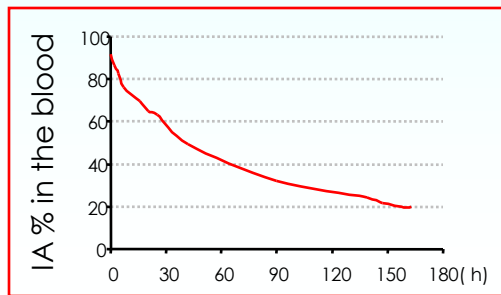
A trial based on **myeloablative activities up to 5.55 MBq/kg**, followed by autologous stem cell transplantation (**ASCT**) performed **13 days** after therapy, has been applied in our centre.

26 pts affected by NHL, with favourable dosimetry (185 MBq of  $^{111}\text{In}$ -Zevalin), have been treated to date.



# Purpose of the study

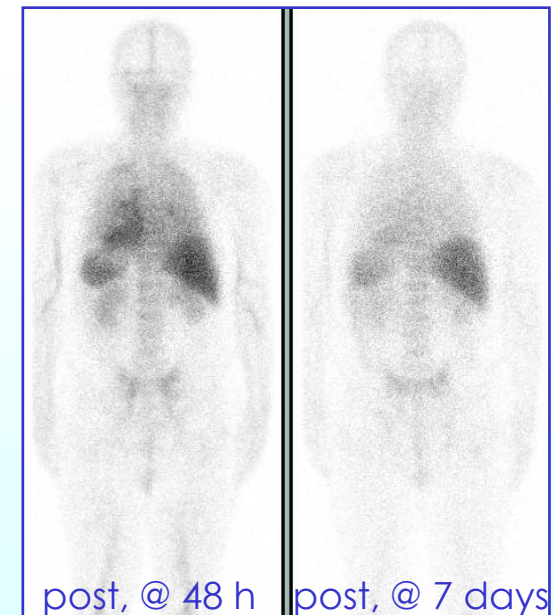
Appropriate evaluation of the dose to RM is crucial, as ASCT is considered at low risk when the **dose to reinfused stem cells (rSC)** is  $< 50$  mGy.



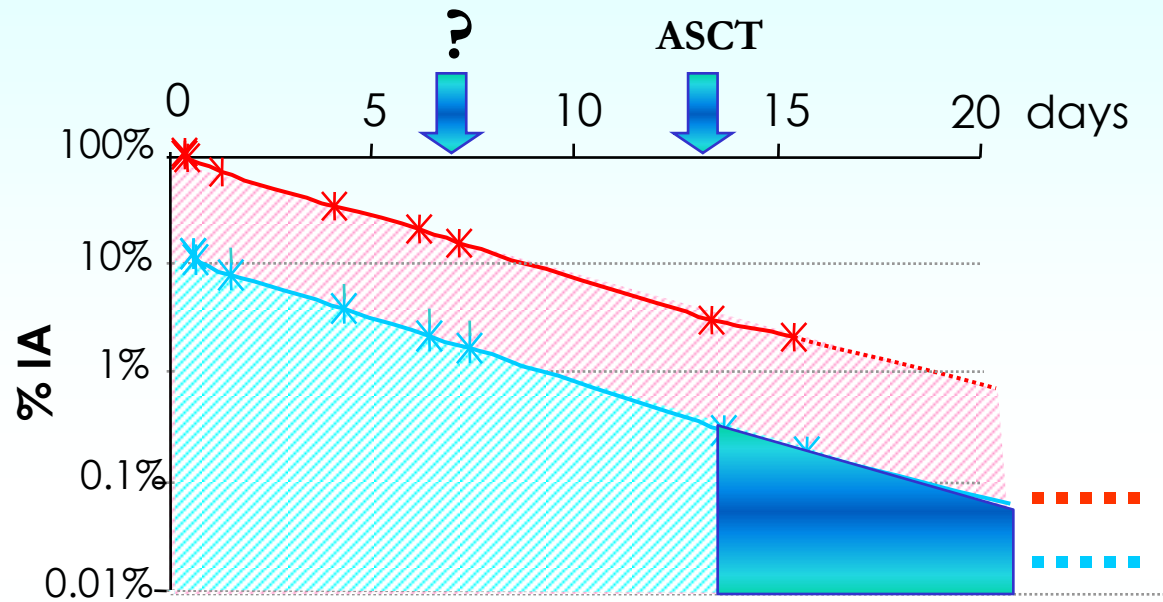
Usually, the method based on the **blood curve** is applied to evaluate RM dose for Zevalin.

Despite negative bone marrow biopsy, pts showed uptake in the reticular endothelium system of the skeleton: → the standard blood method might underestimate the dose to RM. Image analysis and marrow aspirates were introduced as alternative dosimetric approaches to:

- compare **RM doses**
- evaluate the **best timing for ASCT**



# 1) blood method (standard)



The absorbed doses to RM were evaluated using OLINDA/EXM, considering the integral activity for RM (assuming non-specific uptake) and the individual masses (body weight, RM)

The dose to rSC was evaluated for

**ASCT @ 13 days**

**ASCT @ day X: rSC  $\leq$  50 mGy**

**ASCT @ 7 days**

(comparison with other protocol strategies with double ASCT)

$$\text{dose}_{\text{RM}} \div [\tilde{A}]_{\text{RM}} = \frac{0.19}{1-\text{HCT}} \times [\tilde{A}]_{\text{blood}}$$

$$\underline{\text{dose rSC}} = \text{dose RM}_{t = \text{ASCT} \rightarrow \infty}$$

## 2) imaging

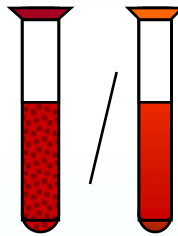
- **L2-L4 uptake** method evaluated in the whole body images, assuming

$$[\tilde{A}]_{RM} = [\tilde{A}]_{L2L4} / 6.6\%$$



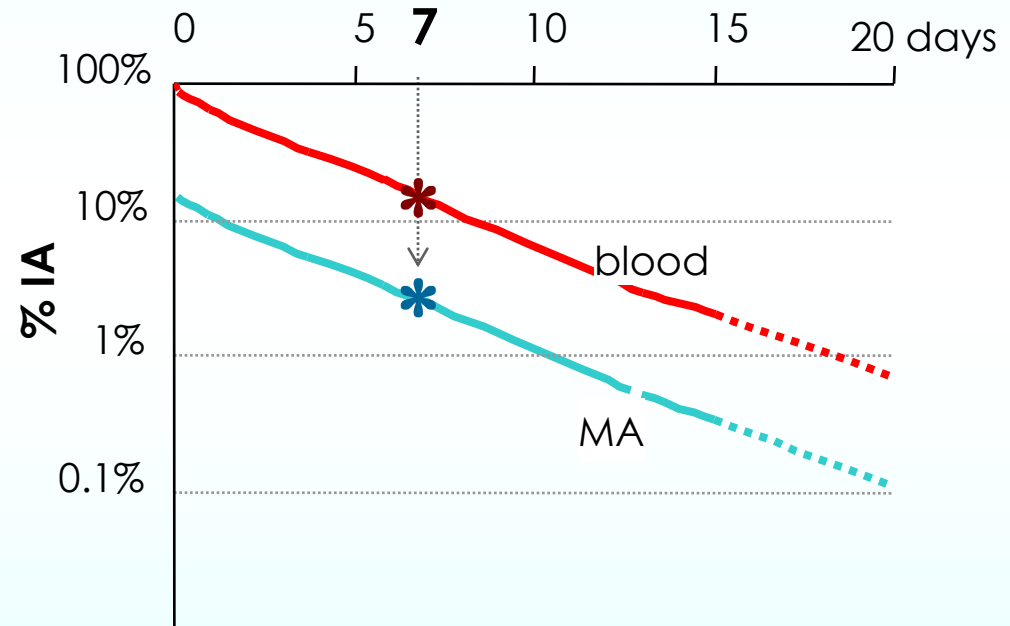
## 3) marrow aspirates

The ratio of activity concentration of *MA* (at 7 days p.i) vs. blood determines a *factor F*.



It is assumed that:

$$[\tilde{A}]_{RM} = F \times [\tilde{A}]_{blood}$$



The absorbed doses were evaluated as for the previous method (to RM; to rSC for ASCT day 13, X, 7).

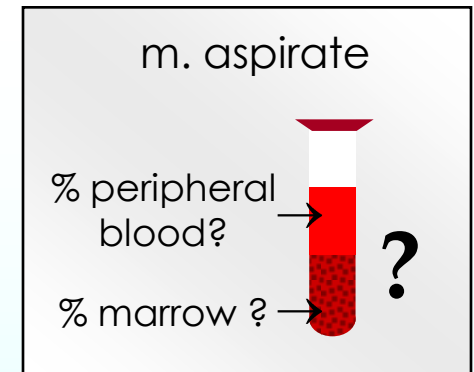
# however...

The **alternative methods** considered are affected by uncertainties:

**Imaging method:** the quantification in L2-L4 is difficult, especially in planar images, **being affected by the vascular background.**

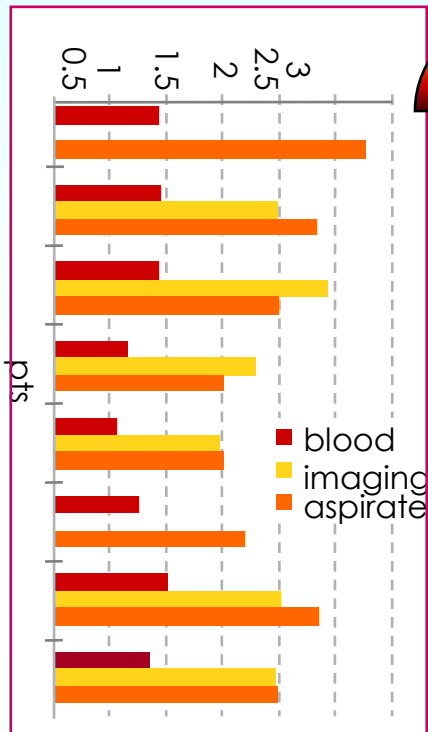
The hypothesis of uniform marrow uptake, with marrow in L2-L4 being **6.6% of total marrow is an approximation.**

**Marrow aspirates** may be **affected** by peripheral blood contamination. If so, the experimental value would not provide the real factor relating  $[A]_{\text{blood}}$  vs.  $[A]_{\text{RM}}$  but vs.  $[A]_{\text{RM+blood}}$  (i.e. the specific activity of a mixture of red marrow and some peripheral blood).



**This has to be taken into consideration when dealing with the reliability of the numerical results**

# Results



Median (range) absorbed doses to RM

method	dose to RM (mGy/MBq)	RM dose ratio vs. blood
<b>blood</b>	<b>0.8</b> (0.34 - 1.0)	<b>1</b>
<b>m. aspirate</b>	<b>2.0</b> (1.5 - 2.8)	<b>2.3</b> (2.1 - 2.9)
<b>Imaging: L2-L4</b>	<b>2.0</b> (1.2 - 2.7)	<b>2.4</b> (2.0 - 2.7)

Although imaging and MA data are affected by uncertainty, both show comparable results, suggesting that the **blood method might underestimate the RM dose by a factor > 2**

# Results

Median (range) absorbed doses to reinfused stem cells (rSC) evaluated by different methods, for ASCT at 7 and 13 days after therapy (IA: **56 MBq/kg**)

method	dose to rSC (mGy)		day X for ACST / rSC 50 mGy
	ACST @ 13 d.	ACST @ 7 d.	
<b>blood</b>	<b>11</b> (4–28)	<b>125</b> (40-280)	<b>10</b> (9-12)
<b>m. aspirate</b>	<b>25</b> (9–69)	<b>370</b> (230-500)	<b>12</b> (10-14)
<b>Imaging: L2-L4</b>	<b>27</b> (8-76)	<b>390</b> (195-590)	<b>12</b> (11-14)
<b>% of RM dose</b>	<b>0.2</b> (0.1-1.3)%	<b>3.8</b> (2.0-7.5) %	<b>1.3</b> (0.9-1.7)%

# Results

Absorbed dose values (projection) to RM for Zevalin at standard IA:  
**15 MBq/kg. Limit IA:  $\leq 1.2$  GBq for a dose to RM  $< 3$  Gy,**  
**in order to avoid high grade (hg, III-IV) hematological toxicity**

in good  
agreement

method	RM dose (Gy) 1.18 GBq	hg toxicity expected?
<b>blood</b>	<b>0.8</b> (0.5 - 1.1)	<b>...no...</b>
<b>m. aspirate</b>	<b>1.8</b> (1.6 - 2.7)	<b>possibly</b>
<b>Imaging: L2-L4</b>	<b>2.0</b> (1.4 - 3.2)	
* Ref: sacrum	<b>1.4</b> (0.8 - 2.1)	

\* Wiseman, JNM 2004; Ca Bioth Radiat 2004

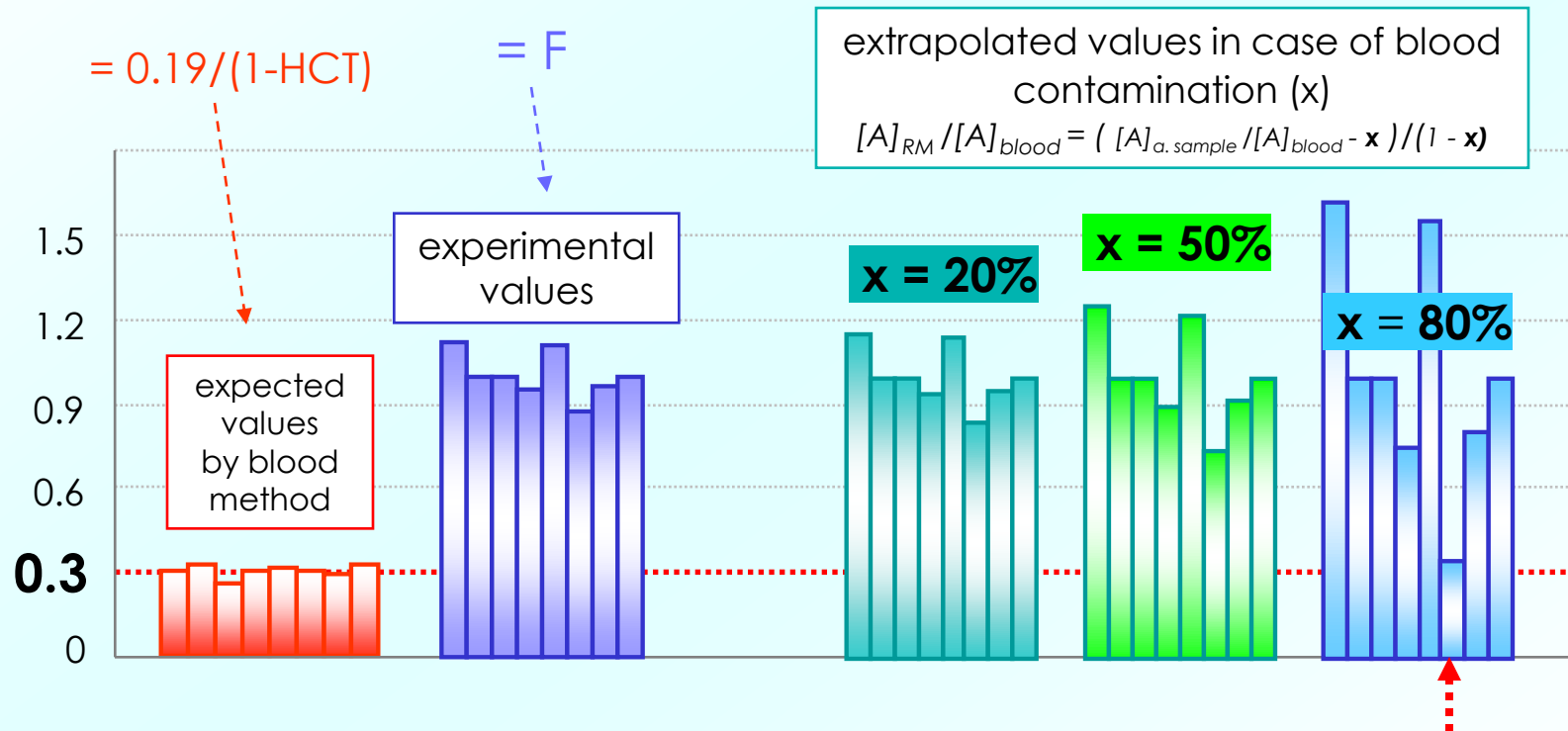
The comparison of the results addresses towards RM doses underestimated by blood method. The RM uptake can be influenced by the variable marrow reserve in this patient population (relapsed/refractory NHL).

# Conclusions

- ♣ Although imaging and marrow aspirates are affected by uncertainty, both show comparable results suggesting that the blood method may underestimate the RM dose.
- ♣ In patients receiving 55 MBq/kg of Zevalin® it is not advisable to anticipate ASCT before 13 days.
- ♣ A double ASCT – at 7 and 13 days – might be of low help.
- ♣ Further investigation on the RM dose evaluation is warranted (*bone biopsies? biological dosimetry?*)

# Can peripheral blood contamination explain the experimental values obtained ?

Individual  $[A]_{RM} / [A]_{blood}$  ("f factors") with the hypothesis of different blood contamination (x %) in the m. aspirate samples.



Even considering a blood contamination and correcting the experimental values, the derived RM to blood specific activity ratio is significantly higher than that expected by the blood method, **but in one case with blood contamination > 80%**.