BIOKINETIC AND RADIOPHARMACEUTICAL STUDIES FOR INTERNAL DOSIMETRIC EVALUATIONS IN METABOLIC RADIOTHERAPY; TWO CASES AT ENEA - RADIATION PROTECTION INSTITUTE: [^{153}Sm]Sm-EDTMP AND [^{90}Y]-IBRITUMOMAB TIUXETAN

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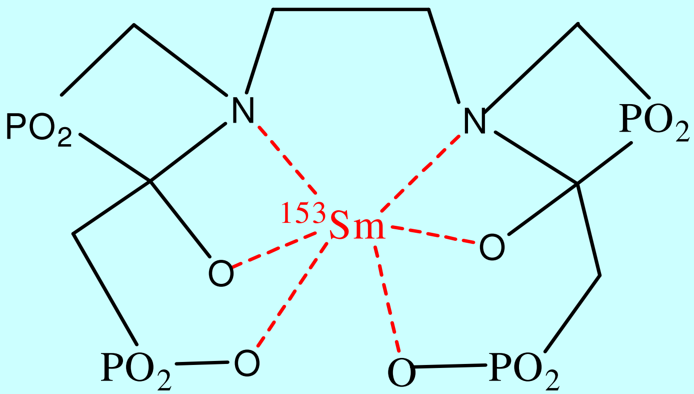
Metabolic radiotherapy with [^{153}Sm]Sm-EDTMP

Metabolic radiotherapy for bone metastases palliation with [^{153}Sm]Sm-EDTMP is due to:
• intense osteoblastic peritumoural activity which concentrates selectively ß radiation;
• high ionizing ß radiation, which irradiates the neoplastic mass and provokes an antalgic effect reducing aedema, interstitial pressure and pain transmitting substances.

Radionuclide	Carrier	$t_{1/2}$	$E_{end\text{-}point}$ (MeV)	Range (mm) average/max
^{153}Sm	***EDTMP***	***46.3 h***	***0,35/0,80***	***0,8/3,3***

Pain is reduced in 80% of cases and complete remission is obtained in 20-30% of cases. The analgetic effect begins generally 1-2 weeks after administration and continues for 3-5 months.
White blood cell and platelet counts fall to a nadir of approssimately 50% of baseline and a recovery to baseline levels generally occurs after 8 weeks → problems in patient retreatment, dosage (37 MBq/kg) increasing and administration to patients treated before with chemotherapy and external beam irradiation.

[153Sm]Sm-EDTMP: chemical and biokinetic properties



[153Sm]Sm-EDTMP

$T_{1/2}$ (ore)	***46.27***
$E_{end\text{-}point}$ (keV)	***808.2 (20.7%)*** ***705.02 (43.8%)*** ***635.35 (34.7%)***
E_{γ} (keV)	***103.18 (31.43%)*** ***97.43 (0.85%)*** ***69.67 (4.85%)***

- ^{153}Sm accumulates in bone (F_s=0,45) and liver (F_s=0,45) ⇒ not enough specific bone uptake
- ^{153}Sm labelled to a disphosphonate salt ⇒ [^{153}Sm]Sm-EDTMP for bone pathological cases (F_s=0,7)*

*=ICRP 53 average for non metastatic bone pathologies

Biokinetic data of phosphate and phosphonate salt not perfectly related to bone metastases treated with [^{153}Sm]Sm-EDTMP

What can we do?

•Reduce addictional dose which increases only side effects

↑

•Do a suitable dosimetry

↑

•Elaborate a dosimetric model

↑

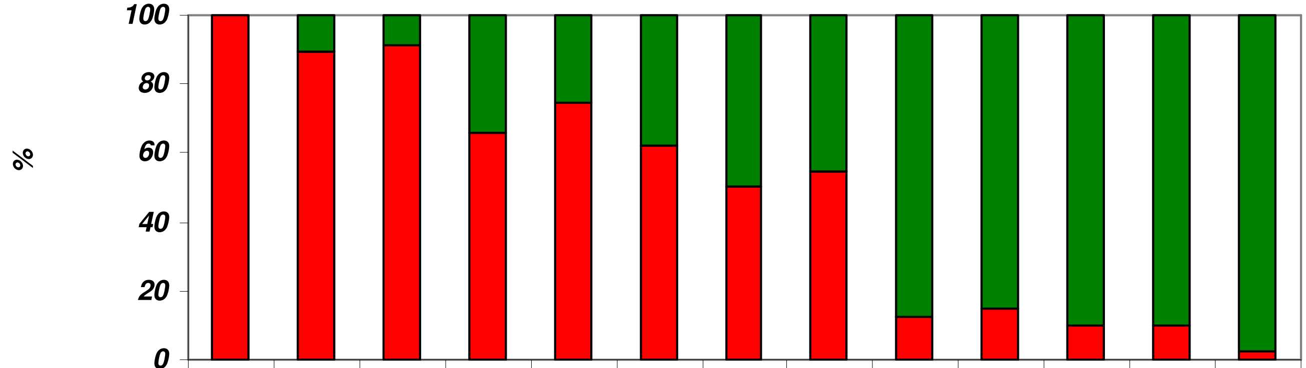
•Elaborate a suitable biokinetic model

In-vitro and in-vivo di [^{153}Sm]Sm-EDMPT stability

- Radiochemical purity (stability) has been evaluated by TLC (eluent: $H_2O:CH_3OH:NH_4OH$ 4:2:0,2, on silica gel impregnated fiber sheets) → R_f([^{153}Sm]Sm-EDTMP) = 0,80-0,95; R_f([^{153}Sm]Sm^{3+}) = 0.
- Chromatographic strip has been divided in half and the activity has been measured by β counting.
- Evaluation of the radiopharmaceutical diluted in saline solution (NaCl 0.9%) at room temperature.
- Evaluation of blood samples at prearranged times from the injection (5, 15, 45, 120, 240 min. e 24 h).
- Evaluation of urine samples collected according to spontaneous excretion of patients during the 24 h after the administration.

% ratio between labelled and unlabelled radiopharmaceutical in biological samples

Percentage of labelled and unlabelled [^{153}Sm]Sm-EDTMP in biological samples (blood and urine)



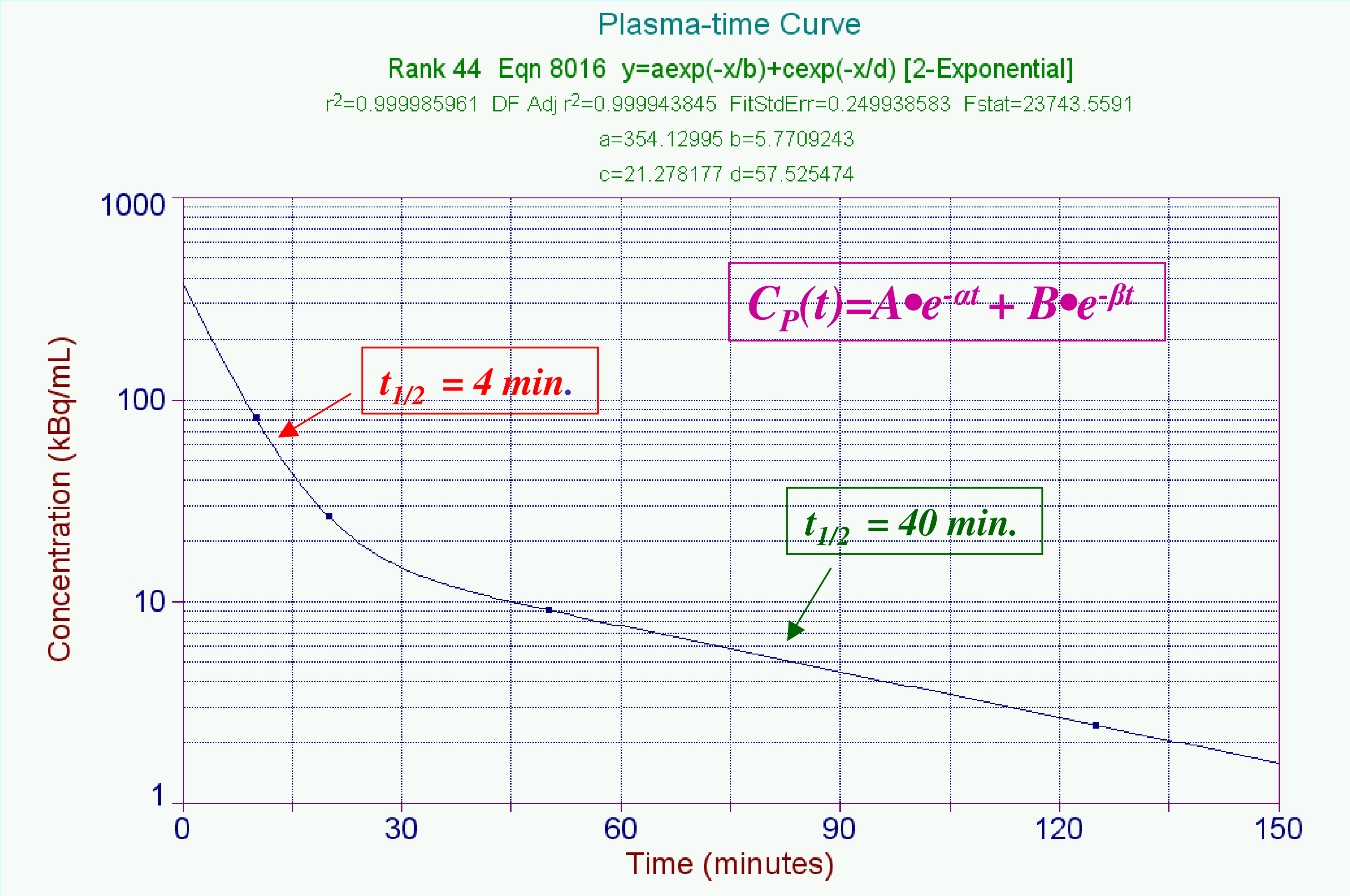
	RP	S1	S2	S3	S4	S5	U1	U2	U3	U4	U5	U6	U7
% unlabelled	0,3	11	9	34	26	38	50	45	88	85	90	90	98
% labelled	99,7	89	91	66	74	62	50	55	12	15	10	10	2

RP=injection solution
S=blood
U=urine

Number and type of patients considered

N° patient	***Sex***	***Carcinoma***	***Injected activity MBq***
001	***M***	***PROSTATE***	2885
002	***F***	***BREAST***	2898
003*	***M***	***PROSTATE***	4395
004	***M***	***PROSTATE***	2653
005	***F***	***BREAST***	1765
006	***F***	***BREAST***	2802
007	***M***	***COLON***	3370
008*	***M***	***PROSTATE***	2710
009	***M***	***PROSTATE***	2876
010	***M***	***PENIS***	2856
011	***F***	***BREAST***	1212
012	***F***	***BREAST***	3294
013	***F***	***BREAST***	2844
014	***F***	***BREAST***	2836
015	***F***	***BREAST* + *THYROID***	2050
* the patient is the same and repeated the treatment			
TOT ***15***	7 men	***5 prostate*** 1 colon 1 penis	37 MBq/Kg
	8 women	***7 breast*** 1 breast + thyroid	37 MBq/Kg

Fit of plasma-time curve



Distribution and elimination phase

pz	α (min^{-1})	$t_{1/2}$ (min) ***(distribution)***	β (min^{-1})	$t_{1/2}$ (min) ***(elimination)***
Ca: prostate				
003	0.140 ± 0.004	5.0 ± 0.1	0.006 ± 0.004	116 ± 77
004	0.11 ± 0.01	6.3 ± 0.6	0.009 ± 0.002	77 ± 17
008	0.174 ± 0.007	4.0 ± 0.2	0.018 ± 0.001	39 ± 2
009	0.19 ± 0.01	3.6 ± 0.1	0.0084 ± 0.0004	83 ± 4
media		**4.7 ± 1.2**		**79 ± 31**
	Ca: breast			
005	0.160 ± 0.003	4.3 ± 0.1	0.0134 ± 0.0001	52 ± 1
006	0.19 ± 0.05	3.6 ± 1.0	0.012 ± 0.02	58 ± 10
011	0.09 ± 0.02	7.7 ± 1.7	0.009 ± 0.001	77 ± 9
002	0.38 ± 0.02	1.8 ± 0.1	0.0136 ± 0.0004	51 ± 1
media		**4.3 ± 2.5**		**60 ± 12**
Ca: colon				
007	0.036 ± 0.001	19.3 ± 0.5	0.003 ± 0.001	231 ± 77
Ca: penis				
010	0.23 ± 0.07	3.0 ± 0.9	0.012 ± 0.001	58 ± 5

Elimination and transfer constants of compartments

pz	**K**	**K_{12}**	**K_{21}**
	min^{-1}	*min^{-1}*	*min^{-1}*
Ca: prostate			
003	0.08 ± 0.03	0.06 ± 0.05	0.011 ± 0.004
004	0.05 ± 0.01	0.05 ± 0.01	0.019 ± 0.002
008	0.117 ± 0.007	0.05 ± 0.01	0.027 ± 0.002
009	0.032 ± 0.002	0.12 ± 0.01	0.050 ± 0.003
Ca: breast			
005	0.0225 ± 0.0004	0.056 ± 0.002	0.095 ± 0.001
006	0.034 ± 0.008	0.10 ± 0.07	0.07 ± 0.02
011	0.022 ± 0.005	0.04 ± 0.02	0.038 ± 0.009
002	0.29 ± 003	0.09 ± 0.02	0.018 ± 0.003
Ca: colon			
007	0.015 ± 0.002	0.02 ± 0.01	0.01 ± 0.001
C*a: penis*			
010	0.024 ± 0.007	0.10 ± 0.07	0.11 ± 0.04

$K_{12}/K_{21}(prostate)_{av.} = 2.78 \pm 0.25$

$K_{12}/K_{21}(breast)_{av.} = 0.65 \pm 0.02$

Dose to bone and red marrow

$\tilde{A}_{SK}=A_i-CL-U$
$\tilde{A}_{SK}$: bone cumulated activity
A_i: injected activity
CL: clearance
U: excreted activity

$$D_{(SK\rightarrow SK)}=S_{(SK\rightarrow SK)}\bullet \tau_{SKC}\bullet A_i$$

$$D_{(SK\rightarrow RM)}=S_{(SK\rightarrow RM)}\bullet \tau_{SKT}\bullet A_i$$

Ca.	***$D_{(SK\rightarrow SK)}$ (kin.) (Gy)***	***$D_{(SK\rightarrow SK)}$ (im.) (Gy)***	***$D_{(SK\rightarrow SK)}$ (bibl.) (Gy)***	***$D_{(SK\rightarrow RM)}$ (kin.) (Gy)***	***$D_{(SK\rightarrow RM)}$ (im.) (Gy)***	***$D_{(SK\rightarrow RM)}$ (bibl.) (Gy)***
Prostate (pz. 008)	***16.4***	***16.3***	***18.32***	***3.5***	***3.5***	***4.17***

Kin.: biokintic approach

Im.: imaging approach (Brenner)

Bibl.: bibliographic data (Schering)

Radioimmunotherapy with [^{90}Y]Ibritumomab tiuxetan

Refractory CD20+ follicular B-cell non-Hodgkin lymphoma is a very serious neoplasia and radioimmunotherapy with ***[^{90}Y]-Ibritumomab tiuxetano*** ***(Zevalin™)*** is a valid therapeutic approach , because β-emittiter ***^{90}Y***, bound by monoclonal antibodies to tumour-associated antigens, irradiates selectively cancer cells. Administration occurs generally acccording to patient weight and platelet count. Biodistribution is generally evaluated labelling the same antibody with the γ-emitter ***^{111}In***, using a corrective factor to pass from ***^{111}In*** to ***^{90}Y*** activity.

^{90}Y and ^{111}In are similar?

- position in periodic table — different
  - → chemical reactivity — ?
- emitted radiation and energy — different
  - → radiolysis problems — ?

What is possible to do?

•Evaluate radiochemical purity and *in-vivo* stability by β counting of biological samples, blood and excreta → direct measurement.

•[^{90}Y]-ibritumomab tiuxetan administered by intravenous push injection, taking approsimatively 10 min duration time → serial blood samples collected at 15 min., 1, 3, 5, 16, 24, 48, 90 and 130 h and at 7 days after injection.

•In order to evaluate the excretion of the radiopharmaceutical →collection of urine and faecal samples.

•According to collected data from biological sample calculate pharmacokinetic parameters.

•In order to evaluate any additional dose to target and critical organs → check the presence of radioactive impurities in the radiopharmaceutical solution.

•Blood and urine samples withdrawn immediately before and at defined time-points after the administration (after 1 month, 6 months and 1 year) may be useful to estimate the risk of early and late health effects from the therapy → radiation-induced genetic damage with direct effects on the individual (secondary cancers) and hereditary effects which can impact successive generations.

Project work packages

1. **Determination of radionuclidic purity and evaluation of *in-vivo* stability and metabolism of [^{90}Y]-Ibritumomab tiuxetan.**
2. ***Elaboration of an optimised biokinetic based on metabolic data, obtained by experimental tests and sowtwere.***
3. ***Evaluation of inflammatory status, plasmatic clastogentic factors and DNA damage.***
4. ***Elaboration of a dosimetric model with the support of kinetic and biological data.***
5. ***Considerations on benefit to risk ratio of radioimmunotherapy with* Zevalin™.**
6. **Dissemination of results (publications on scientific journals, partecipations to congresses, etc.).**

Conclusions

- We have assessed a radiochromatographic technique useful to discriminate labelled and unlabelled [^{153}Sm]Sm-EDTMP to study the biokinetics of the chemical species.
- Pharmacokinetic parameters of [^{153}Sm]Sm-EDTMP have showed the importance to elaborate an individual administration for the radiopharmaceutical, not only based on the patient weight → the type of primary tumour may be a first criterion for the dosage.
- We intend to apply an analogous experimental approach to [^{90}Y]-Ibritumomab tiuxetan treatment.
- Elaborating a simplified dosimetric model optimizes the dose to patients and promote the personalization of the therapy, minimising the dose to critic organs and evaluating the risk to benefit ratio.

Thank you for your attention

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