ALPHA EMITTERS IN NUCLEAR MEDICINE:
from the physical dose to the biological effects in target and non-target tissues

65

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INTRODUCTION

Alpha-Targeted Therapy is emerging as a promising new modality for treatment of a variety of malignancies and a number of **α-emitters are under investigation for clinical use**. However, the delivery of the α-particle energy to the cancer cells without toxicity to healthy tissues has still been the challenge and the limiting factor.

TO NOTE : **α-emitters Radiobiology & Dosimetry are not well known at today**

Radium-223 (^{223}Ra) is the first targeted α therapy approved for clinical use for the treatment of patients (Pts) with metastatic castration resistant prostate cancer (**mCRPC**) with symptomatic bone metastases and no known visceral metastatic disease. More than **50.000 treatments** / world have been performed **until today with the standard schedule (six** ^{223}Ra injections o**f 55 kBq/kg** every **4-week)**

Schedules based on body weight may not be the most appropriate therapy for each patient considering the wide difference in clinical presentation of mCRPC and in ^{223}Ra bone uptake A personalized treatment schedule based on 3D alpha dosimetry could allow an increase in efficacy and a reduction in toxicity.

The challenge

IMPROVE KNOWLEDGE OF α-EMITTERS RADIOBIOLOGICAL EFFECTS

VALIDATE α DOSIMETRY METHODOLOGY

PERSONALIZE α-EMITTERS TREATMENT

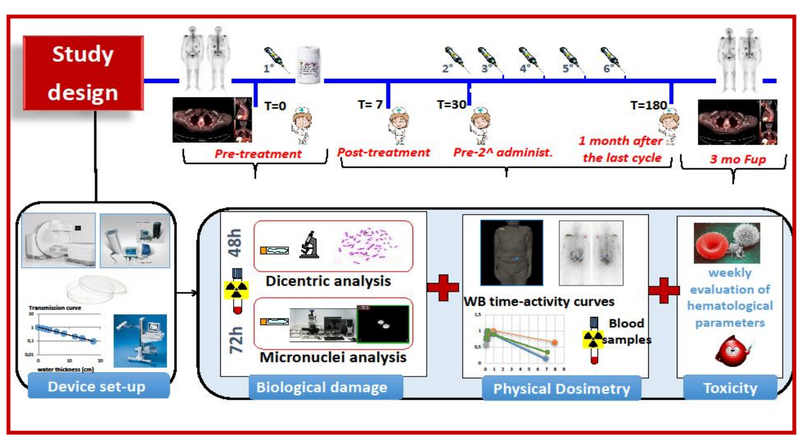
DESIGN OF THE STUDY :

Phase II feasibility study on **15 mCRPC pts.** undergoing **standard six ^{223}Ra injections** with the following **aims:**

1 assess alpha emitters **DOSIMETRY FEASIBILITY** in clinical practice

2 evaluate **BIOLOGICAL EFFECTS** of ^{223}Ra on mCRPC
- radiation-induced chromosome damage on lymphocites

3 correlate the target / non target **DOSIMETRY** with
- clinical results (efficacy and haemathological toxicity)
- biological effects (dicentric and micronuclei induction)



Next study

RCT

to compare

- PERSONALIZED TREATMENT dosimetry based *(Arm 1 : 32 pts)*

against

- STANDARD TREATMENT *(Arm 2 : 32 pts)*

METHODS

PHYSICAL DOSIMETRY is performed at each radium administration according to SPET/CT calibration protocol

1- TARGET IDENTIFICATION on pre-therapy i m a g i n g

multimodality imaging bone scan , FCH PET/CT

2- POST- THERAPY 223Ra Imaging

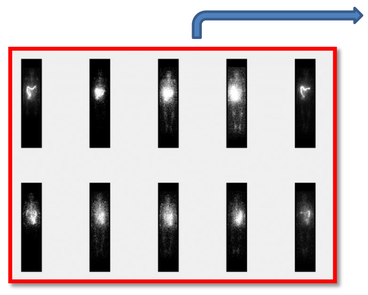
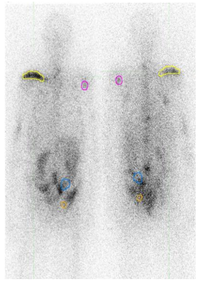
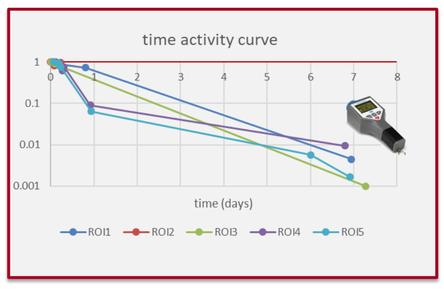


Image fusion and ROI propagation



Activity calculation for each lesion & OAR

3- POST- THERAPY Pharmacokinetic studies



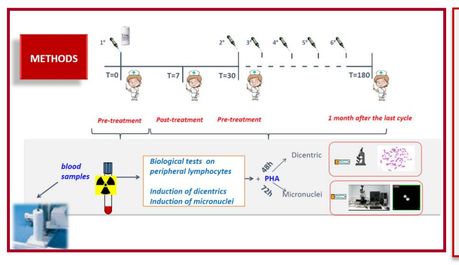
Residence time calculation & MIRD based dose calculation

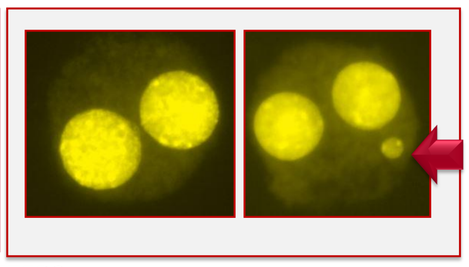
RBE factor of about 5 (MIRD 22)

METHODS

BIOLOGICAL EFFECTS & **RADIATION-induced CHROMOSOME DAMAGE** are evaluated as number of **dicentric cells** and **micronuclei** induced on peripheral lymphocites by $^{223}RaCl_2$.

Blood samples are collected before the $^{223}RaCl_2$ treatment (T0), after 7 days (T7), 30 days (T30) and at month 6 (T180) at the end of the therapy.





HAEMATOLOGICAL TOXICITY PARAMETERS are weekly monitored during therapy until to one month after the end of 6^ cycle and analysed along with doses to blood and non-target tissues.

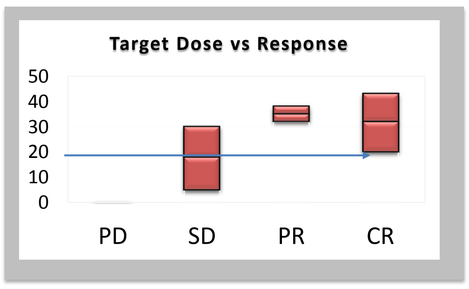
PRELIMINARY RESULTS –Dosimetry

TARGET DOSIMETRY & RESPONSE

1. **Target doses** ranged from

0.001 Gy to 43.7 Gy *(median 30.1 Gy)*

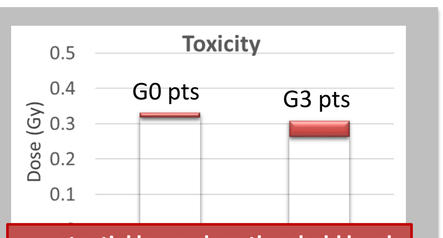
2. A **dose response relationship** for target lesions has been observed with a threshold of ***20 Gy***



NON TARGET DOSIMETRY & TOXICITY

Red marrow dose was < 2 Gy limit in all cases

- patients without any haematological toxicity received higher red marrow dose
- patients with G3 haematological toxicity (anemia), previously treated with CHT, received lower dose



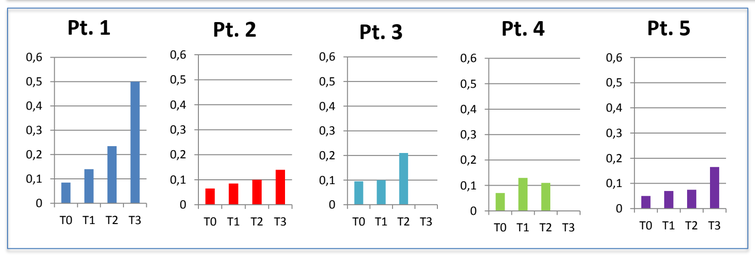
a potential lower dose threshold level for heavily treated patients

PRELIMINARY RESULTS – Biological Effects

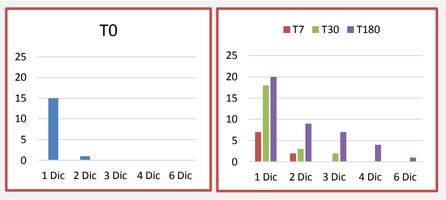
1 **Baseline dicentric/cell is higher than general population with a wide inter-individual variability @T= 0**

2 **A statistical significant increased frequency of chromosomal aberrations is registered after administration @ T = 7** - expression of ^{223}Ra induced damage

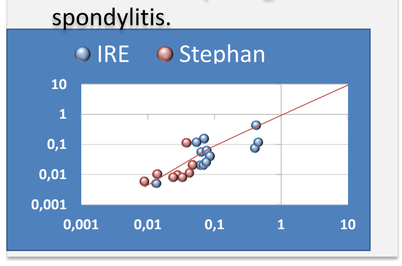
3 **Further increase in DC frequency @ T = 30 (before the 2nd cycle) without further administration and @ T180 (end therapy).** The increase of chromosome damage (almost double) observed between T7 and T30 is not due to an $^{223}RaCl_2$ addition dose, suggesting that circulating lymphocytes were exposed to an extra dose by the emission from target organs.



4 The **type of damage is very different between photon (EBRT) and alpha radiation in the same patient**



5 A linear correlation has been found between dosage and number of dicentric in agreement with Sthephen results obtained with 224 Radium in ankylosing spondylitis.



Impact of the study

PREDICTIVE ROLE OF DOSIMETRY, for both clinical outcome and biological effect, is expected to allow a personalized treatment that is still missing worldwide for α-emitters

BIOLOGICAL EFFECTS need to be clearly elucidated before an exstensive α-emitters clinical use

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