Dosimetric Impact of Ac-227 in Accelerator-Produced Ac-225

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NTRODUCTION

Actinium-225 (^{225}Ac) has a 10-day half-life and a decay scheme that yields four alpha-particle emissions. This radionuclide is produced by a generator system from the decay of thorium-229. Accelerator-produced ^{225}Ac via thorium-232 irradiation (hereafter denoted as $^{225/7}$Ac) contains 0.7% ^{227}Ac; (21.77 year half-life). This work examines the contribution of ^{227}Ac and it's daughters to tissue absorbed doses and the possible biological implications of this radionuclide when $^{225/7}$Ac -labeled antibody is administered intravenously to treat patients with hematological.

Actinium-227 decays by beta-particle emission primarily (99%) to thorium-227 (^{227}Th; 18.68d half-life) which, in turn decays to radium-223 (^{223}Ra, 11.43 d half-life) and a series of other alpha- and beta-emitting daughters to stable lead-207 (Fig. 1).

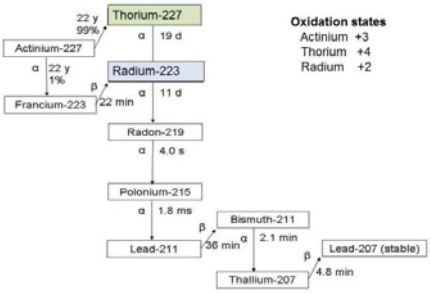

Figure 1. Actinium-227 decay scheme (1)

METHODS - Overview

Published pharmacokinetic models were used to obtain the distribution of $^{225/7}$Ac -labeled antibody and also the distribution of either free or antibody-conjugated ^{227}Th. Since ^{227}Th is obtained from the beta decay branch (99% yield) of ^{227}Ac rather than a more energetically disruptive alpha-emitter decay, it is possible that a significant fraction of the ^{227}Th generated remains antibody-conjugated. A pharmacokinetic model representing the distribution of radiolabeled antibody in patients with hematologically distributed cancer is adapted from reference (2) to obtain the pharmacokinetics for $^{225/7}$Ac and ^{227}Th-labeled antibody. A model representing the pharmacokinetics of free ^{227}Th is used to model the distribution of unconjugated ^{227}Th (3). Under both circumstances, ^{223}Ra generated by ^{227}Th decay is simulated using a pharmacokinetic model that is relevant to free ^{223}Ra (4). Calculations were performed assuming 1 kg (10^{12} antigen-positive cells) in an adult female.

METHODS -Biokinetic modeling

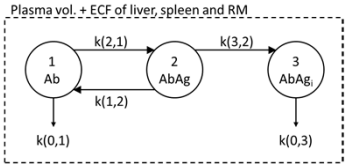

Fig. 2. PK model for radiolabeled antibody. Dotted line = distribution volume of IV-administered antibody; ECF = extracellular fluid volume. Compartments 1 and 2 represent free, (Ab) and antigen-bound antibody (AbAg), respectively. Compartment 3 represents internalized AbAg. The figure is adapted from reference (2).

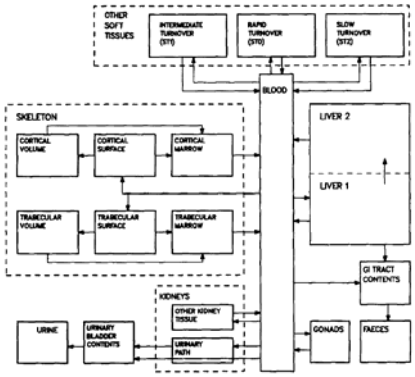

Fig. 3. ICRP biokinetic model for thorium. Details provided in reference (3).

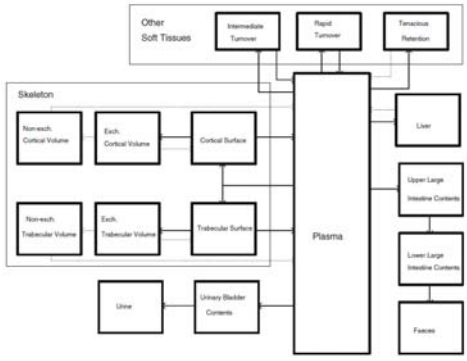

Fig. 4. Biokinetic model for radium as represented in reference (4). The solid arrows are relevant to the biokinetics of ^{223}Ra.

RESULTS

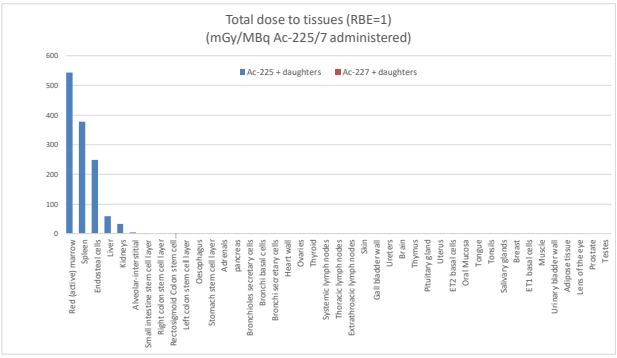

Table 5 - Percentage of total absorbed dose due to ^{227}Ac and each of its daughter of for selected critical tissues

Tissue	^{225}Ac+ daughters	^{227}Ac	^{227}Th	^{223}Ra	^{219}Rn	^{215}Po	^{211}Pb	^{211}Bi	^{207}Tl	^{211}Po	^{227}Ac+ daughters
Alveolar-interstitial	99.853%	0.003%	0.137%	0.001%	0.002%	0.002%	0.000%	0.002%	0.000%	0.000%	0.147%
Heart wall	99.824%	0.003%	0.166%	0.001%	0.002%	0.002%	0.000%	0.001%	0.000%	0.000%	0.176%
Kidneys	99.989%	0.000%	0.011%	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	0.011%
Left colon stem cell layer	99.846%	0.002%	0.144%	0.001%	0.002%	0.002%	0.000%	0.002%	0.000%	0.000%	0.154%
Liver	99.838%	0.004%	0.158%	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	0.162%
Red (active) marrow	99.820%	0.005%	0.174%	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	0.180%
Right colon stem cell layer	99.846%	0.002%	0.145%	0.001%	0.002%	0.002%	0.000%	0.002%	0.000%	0.000%	0.154%
Small intestine stem cell layer	99.838%	0.003%	0.153%	0.001%	0.002%	0.002%	0.000%	0.002%	0.000%	0.000%	0.162%
Spleen	99.663%	0.004%	0.333%	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	0.337%
Ovaries	99.808%	0.002%	0.183%	0.002%	0.002%	0.002%	0.000%	0.002%	0.000%	0.000%	0.192%
Salivary glands	99.772%	0.003%	0.214%	0.002%	0.002%	0.002%	0.002%	0.002%	0.001%	0.000%	0.228%

CONCLUSIONS

- Using a pharmacokinetic model relevant to treating patients with leukemia and models describing the PK of free thorium and radium, the dose contribution of a 0.7% ^{227}Ac in accelerator-produced ^{225}Ac is negligible in the context of therapy; less than 1.4 mGy/MBq for the top 5 highest absorbed tissues and < 0.007 mGy/MBq for all other tissues.
- The conclusions above are specific to the parameter values and assumptions used for antibody targeting of leukemia. They may not apply to lower molecular weight agents or other cancer targets.

REFERENCES

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