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Impact of Target Cell Number on Target cell and Tissue Dose for Antibody-Mediated delivery of Alpha-Emitters

225Ac-Lintuzumab- is an alpha-particle emitter labeled anti-CD33 antibody that is in clinical trial evaluation for the treatment of patients with leukemia and myelodysplastic syndrome (MDS). It is also being developed as a targeted conditioning regimen to irradiate and ablate the bone marrow as part of a marrow transplant treatment regimen. We examine the influence of target cell number on the absorbed dose to organs considered critical from the perspective of acute toxicity or late stage or stochastic effects
A previously published pharmacokinetic (PK) model [1] is used to obtain the distribution of 225Ac -labeled antibody for 109 up to 1012 antigen-positive cells corresponding approximately to a range of 1 to 1000 g cells. The PK output was integrated to provide time integrated activity (TIA) input for dosimetry. Absorbed dose calculations were performed using the MIRD Committee S-value based method as described in pamphlet 21 [2]. The International Commission on Radiological Protection (ICRP) recently released absorbed fractions for a new series of phantoms that include far more tissues than were previously available [3]. These were used to perform the dosimetry calculations provided in this report. Decay schemes and half-lives for 225Ac were obtained from ICRP publication 107 [4]. A detailed comparison of the results obtained using OLINDA and the new set of ICRP data has been published [5].
The results for different numbers of antigen positive cells are shown below.
Absorbed dose (mGy/MBq)
Ag+ cells marrow kidneys liver lungs
109 402 2939 468 416
1010 1150 2385 431 337
1011 2444 869 333 123
1012 2708 157 289 22

The results obtained are derived from model-based simulations of anti-CD33 antibody pharmacokinetics in patients with leukemia. The model makes it possible to project the impact of different antigen-positive numbers of cells (e.g., tumor burdens) on pharmacokinetics and dosimetry. The low red marrow and high kidney dose under the condition of 109 antigen-positive cells reflects the low retention of 225Ac-Ab in the marrow when there are very few targets in the marrow. The high kidney dose occurs because low target cell number reduces the capture of free 213Bi by internalization. The model assumes that 50% of free 213Bi in circulation will decay in the kidneys.
The model suggests that organ absorbed doses will vary based on the number of antigen positive cells.

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