Contribution ID: **100** Type: **not specified**

Radiolabeling of DOTA-conjugated Lintuzumab with 225Ac: Comparison of Th-229-produced and High-Energy Proton Accelerator-produced 225Ac

Lintuzumab is a humanized monoclonal antibody (mAb) against CD33, an antigen widely expressed on myeloid stem cells and leukemic blast cells in patients with Acute Myeloid Leukemia (AML). Actinium Pharmaceuticals is advancing several targeted radio-immunotherapy programs utilizing Lintuzumab conjugated with the potent alpha emitting radionuclide Actinium-225 (225Ac) to treat cancer patients. Currently, the supply of 225Ac for clinical manufacturing is produced by a generator system from the decay of Thorium-229 (229Th); however, the capacity of 229Th generators to supply Ac-225 is limited (< 2 Ci/year). A highly promising source of Ac-225 supply is via high-energy linear proton accelerator (Linac) where 225Ac is produced via irradiation of Thorium-232. Linac-produced 225Ac, however, contains minor quantities (0.1-0.7% activity) of low energy 227Ac which has a half-life of 21.8 years. 225Ac has a half-life of 10 days. Because of the large differences in decay rates of these two isotopes, even at very low activity levels, the 227Ac molecule is present in high quantities in the mixture. For example, at 0.3% activity, the molar ratio of 227Ac to 225Ac is approximately 2.3. At this level, the 227Ac in linac preparations of 225Ac may have a negative impact on labeling efficiency, stability and potency.

In order to assess the potential impact of the 227Ac impurity on antibody labeling efficiency and other parameters, we conducted experimental studies where lintuzumab-DOTA conjugates were comparatively labeled with 225Ac produced by both 229Th generator and linac. In these studies, we compared radiolabeling efficiency and critical quality attributes of the radiolabeled finished drug product. Previously, in vivo mouse studies of linac-produced 225Ac, free or DOTA-chelated, demonstrated similar biodistribution/dosimetry/toxicity profiles to 229Th generated 225Ac [1]. In our experimental scheme, a preparation of lintuzumab-DOTA conjugate was first prepared using a qualified manufacturing process. The lintuzumab-DOTA conjugate was then divided into two parts, and one part was radiolabeled with 229Th generated 225Ac and the second part with Linac-generated 225Ac. Both 225Ac radioisotope lots were supplied by the Department of Energy (DOE). Post-labeling, the radiolabeled lintuzumab-DOTA-Ac-225 preparations were passed through separate size exclusion chromatography columns to remove unlabeled 225Ac from the preparation. The eluents were analyzed for radiochemical purity and immunoreactivity. Further, radiolabeling efficiency was determined for both 225Ac radionuclide preparations. For verification of results, the study was repeated a second time with new lots of 225Ac from each source. Our results demonstrated that, radiolabeling of lintuzumab-DOTA with 225Ac generated by high energy proton accelerator exhibited similar characteristics in terms of radiolabeling efficiency, immunoreactivity and radiochemical purity to 229Th generated 225Ac, suggesting that the elevated molar concentration of low energy 227Ac in linac preparations does not have a significant negative impact on the labeling of monoclonal antibodies for the generation of radioimmunoconjugates.

Email Address

dludwig@actiniumpharma.com

Presentation Type

Poster

Primary author: Dr LUDWIG, Dale (Actinium Pharmaceuticals)

Co-authors: Dr RAY, Nitya (Actinium Pharmaceuticals); Dr PATEL, Vimal (Actinium Pharmaceuticals)

Presenter: Dr LUDWIG, Dale (Actinium Pharmaceuticals)