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Highly Effective Treatment of CD38 Positive Experimental Lymphoma with 225Actinium-Daratumumab.

Daratumumab is a human cytolytic antibody specific for CD38 that is used clinically for treatment of patients with multiple myeloma (MM). Current therapeutic regimens require multiple injections over months of treatment, therefor increasing the potency of daratumumab to shorten the length of treatment would be very advantageous. 225Ac is an α-particle emitting radionuclide that has potent cytotoxic activities over relatively short distances, allowing for precise targeting of a lethal dose of radiation. Previously we have established that labeling daratumumab with 225Ac increased more than 10-fold its ability to kill MM cell lines in vitro. In this study we evaluated the therapeutic potential of 225Ac-daratumumab by treating mice with established CD38-positive tumors. Mice deficient in T- and B-cells were injected subcutaneously with human tumor (Daudi) cells and once tumors reached an average volume of ~200 mm3, mice were treated with 225Ac-daratumumab. To determine the localization of daratumumab within the tumor-bearing mice it was labeled with 111In, which can be easily imaged and is used as a surrogate to estimate the localization of 225Ac-daratumumab. The distribution of the 111In-daratumumab was then followed for 10 days using a microSPECT/CT scanner. To evaluate the antitumor ability of the 225Ac-daratumumab, tumor-bearing mice were injected with 225Ac- daratumumab at a dose of 400 nCi/0.3 μg of antibody, and 200 nCi/0.3 μg of antibody. As a control, mice were injected with either saline or an equivalent amount of unlabeled daratumumab. In addition, a group of mice was also treated with 30 times greater dose of unlabeled daratumumab (10 μg) - a dose which was previously shown to be effective against established tumors. 111In-daratumumab begun to accumulate in the tumor 24 hours after intraperitoneal injection and by 7 days was exclusively present in the tumor. The growth of the tumors in mice treated with 400 nCi/0.3 μg was significantly retarded compared to mice treated with equal concentration of unlabeled daratumumab or saline. Tumor growth was similar between mice treated with 400 nCi/0.3 μg of 225Ac-daratumumab and mice treated with 10 μg of unlabeled daratumumab. In conclusion, this study shows that labeling daratumumab with 225Ac increases its antitumor activity at least 30-fold. This study suggests that 225Ac labeling daratumumab increases its potency and could greatly reduce the amount of daratumumab needed for treatment in the clinic. This study also highlights the potential of targeting α-emitters to tumors as a viable therapeutic approach.

Email Address

w.dawicki@usask.ca

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Primary authors: Dr DADACHOVA, Ekaterina (University of Saskatchewan); Dr DAWICKI, Wojciech (University of Saskatchewan)

Co-authors: Dr LUDWIG, Dale (Actinium Pharmaceuticals Inc.); Dr THOMAS, Keisha (Actinium Pharmaceuticals Inc.); Dr ALLEN, Kevin (University Of Saskatchewan); Mrs MALO, Mackenzie (University of Saskatchewan); Dr BURGER, Mark (Actinium Pharmaceuticals Inc.); Dr JIAO, Rubin (University of Saskatchewan)

Presenter: Dr DAWICKI, Wojciech (University of Saskatchewan)