A For Alphas: Radioimmunotherapy Scores High

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Although the advancement of radioimmunotherapy (RIT) has benefitted patients with non-Hodgkin lymphoma to a certain degree, additional improvements are needed to further reduce the relapse rates. With RIT, malignant cells are selectively killed using tumor-targeting antibodies labeled with radioactive isotopes. This technique is especially well-suited for treatment of B cell lymphomas, due to their exquisite radiation-sensitivity. While initial responses to therapy often are encouraging, for most patients with advanced stage indolent (slow-growing) non-Hodgkin lymphoma and mantle cell lymphoma the benefit is unfortunately merely temporary. The reason is spelled MRD, or "minimal residual disease", referring to microscopic clusters of treatment-resistant tumor cells that require upgraded therapy for complete eradication. For Fred Hutch's Dr. Damian Green, that upgrade comprises alpha particle emitting isotopes, or more precisely, the alpha emitter astatine-211. In a recent publication in *Blood*, Dr. Green and colleagues from the Press Lab in the Clinical Research Division demonstrated that complete eradication of disease could be achieved in 70% of mice with disseminated lymphoma after treatment with astatine-211-labeled antibodies directed against the CD20 antigen. Contrastingly, no animals survived in matching control groups.

This therapeutic success relied on the physical properties of alpha particle radiation. In contrast to the more commonly used beta emitting radionuclides, alpha emitters release particles with very high energy combined with extremely short range. In general, alpha radiation emitted from astatine-211 only travels about 50 to 70 µm in tissue, making it ideal for treating microscopic tumors while minimizing the exposure to surrounding healthy tissue. Targeted alpha therapy studies have long been hampered by production issues and a lack of efficient radiochemical labeling methods, but substantial progress has been made in recent years. "Recently, we have been able to generate sufficient quantities of short path-length alpha emitting radionuclides to support clinical applications; in addition, our collaborators at the University of Washington have discovered a way to provide critical stability to alpha particle-labeled monoclonal antibodies," Dr. Green explained. Furthermore, he added that in comparison to first-generation RIT beta emitters like yttrium-90 and iodine-131, "alpha emitters have greater than 500 times more energy per unit length, and as few as 1 to 5 alpha particle emissions can be sufficient to cause irreparable DNA damage and induce cell death."

In addition to the MRD model, the Fred Hutch research team explored targeted alpha therapy of mice with solid lymphoma tumors (approximately 100 mm^3 at the start of therapy). In this disease

setting they saw a radically different outcome; none of the animals were cured, although survival time after astatine-211-RIT was prolonged 2–3-fold in comparison with controls. Striking as this was, Dr. Green was not all that surprised. "The results confirmed our hypothesis that alpha emitting radionuclides would be most effective in micrometastatic or minimal residual disease settings." In fact, the outcome validated predictions made through mathematical models that took the features of alpha particle radiation into consideration. Depending on the distribution of radiolabeled antibodies within the tumor mass, bulky tumors may be more efficiently obliterated using beta radiation; this is due to the longer *in vivo* range of beta particles (up to about 10 mm), which may make up for a certain degree of suboptimal targeting.

"Based on our findings, the best application of targeted alpha emitter therapy is in the clinical setting of micrometastatic or minimal residual disease," concluded Dr. Green, who now hopes to translate these preclinical results into clinical trials with astatine-211 targeted to B cell lymphomas using anti-CD20 antibodies. In addition, the findings will support ongoing investigations regarding the use of alpha-RIT for treatment of multiple myeloma and other cancers of the blood and bone marrow.

Green DJ, Shadman M, Jones JC, Frayo SL, Kenoyer AL, Hylarides MD, Hamlin DK, Wilbur DS, Balkin ER, Lin Y, Miller BW, Frost SHL, Gopal AK, Orozco JJ, Gooley TA, Laird KL, Till BG, Back T, Sandmaier BM, Pagel JM, Press OW. 2015. Astatine-211 conjugated to an anti-CD20 monoclonal antibody eradicates disseminated B-cell lymphoma in a mouse model. *Blood*. pii: blood-2014-11-612770. [Epub ahead of print]

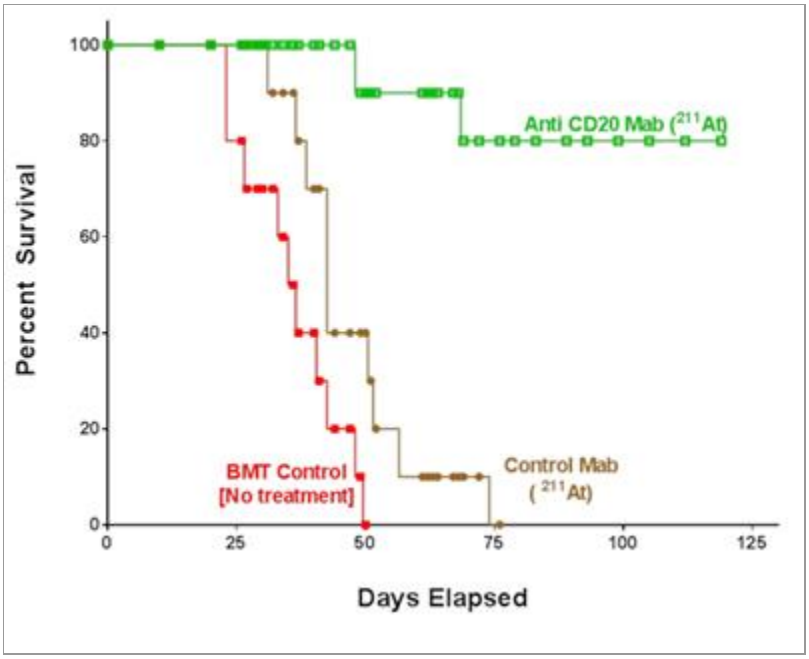

Image provided by Dr. Damian Green

Kaplan-Meier survival curves demonstrating the efficacy of astatine-211-radioimmunotherapy in a minimal residual disease model. Disease progression was monitored through bioluminescence imaging of luciferase-transduced Granta cells. Mice received 15 µCi of astatine-211 via either the anti-CD20 antibody 1F5 or a non-binding control antibody (HB8181), or no therapy (n = 10 mice per group).