

# Fine-Tuning Radioimmunotherapy with an Alpha-Emitting Radionuclide

April 15, 2013

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Acute myeloid leukemia (AML) is an aggressive hematologic malignancy. Hematopoietic cell transplantation (HCT) is used to treat AML, but the chemotherapy and total body irradiation used in pre-transplant regimens are associated with high treatment related toxicity. Many patients suffer relapse of disease after HCT, suggesting the pre-transplant regimens do not adequately eliminate all cancerous cells. To selectively kill leukemic cells before transplant, radioimmunotherapy (RIT) delivers targeted doses of radiation by conjugating radionuclides to antibodies that recognize cell surface antigens on leukemic cells. The majority of RIT studies have used antibodies labeled with beta-emitting radionuclides. However, alpha-emitting radionuclides have higher decay energies and shorter path lengths, only 50-80 microns, equivalent to a few cell diameters. Using alpha-emitters for RIT has the potential to increase the radiation delivered to leukemic cells and decrease the off target killing of normal cells and tissues.

Only a few alpha-emitters are suitable for RIT, including Astatine-211 ( $^{211}\text{At}$ ), and their usage is limited by availability, *in vivo* stability, and labeling chemistry. In a recent study published in *Blood*, Drs. Johnnie Orozco, Oliver Press, John Pagel and colleagues in the Clinical Research Division studied the efficacy and toxicity of  $^{211}\text{At}$  conjugated to an anti-CD45 antibody in a mouse model of AML. CD45 is a cell surface antigen expressed on hematopoietic cells, with limited expression on other tissues, and has been used as a target for RIT for AML. In conjunction with Radiation Oncology at the University of Washington, a novel method for labeling antibodies with  $^{211}\text{At}$  was used to prevent uncoupling of the radionuclide from the antibody *in vivo*.

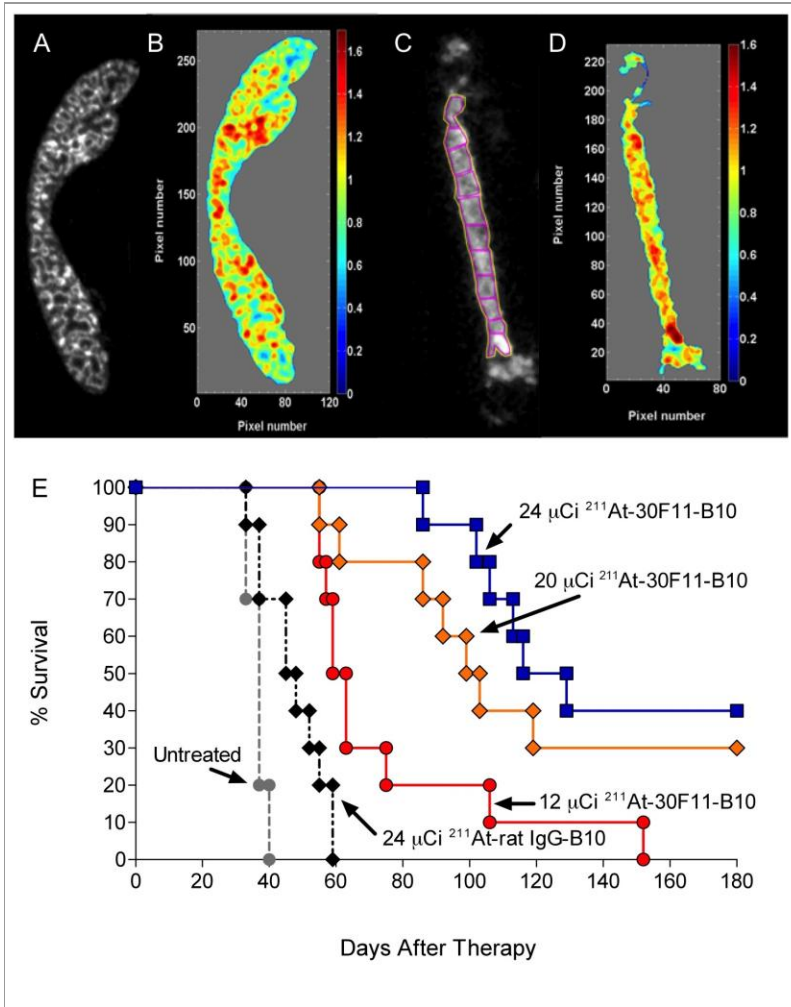
To determine if the antibody delivers radiation specifically to hematopoietic cells, the researchers first examined the biodistribution of radiation delivered throughout the body after injecting mice with  $^{211}\text{At}$ -labeled anti-CD45 antibody ( $^{211}\text{At}$ -B10-30F11).  $^{211}\text{At}$  localized to tissues rich in hematopoietic cells, the bone marrow and spleen, with less uptake in other organs, which was confirmed by alpha imaging (see figure). Then to assess the therapeutic efficacy of  $^{211}\text{At}$ -B10-30F11, the researchers used a clinically relevant disseminated murine myeloid leukemia model. The leukemic mice showed an improvement in median overall survival when treated with 12 microcurie ( $\mu\text{Ci}$ )  $^{211}\text{At}$ -B10-30F11 compare to  $^{211}\text{At}$ -labeled control antibody (69 days vs. 54 days,  $p=0.0003$ ), but both improved survival over untreated mice (36 days,  $p<0.0001$ ). Higher doses of radiation, 24  $\mu\text{Ci}$

$^{211}\text{At}$ -B10-30F11, resulted in non-leukemic death for 70% of mice due to killing of normal hematopoietic cells in the bone marrow and subsequent infection. The mice still had normal kidney and liver function.

The researchers then evaluated whether  $^{211}\text{At}$ -B10-30F11 treatment followed by bone marrow transplant would improve outcomes in the mouse model. A dose-dependent improvement in median overall survival was observed for mice treated with 12, 20, or 24  $\mu\text{Ci}$   $^{211}\text{At}$ -B10-30F11 (OS of 61, 101, and 123 days ( $p < 0.001$ )) compared to untreated (37 days) or  $^{211}\text{At}$ -labeled control antibody treated mice (46.5 days,  $p = 0.0023$ ) followed by bone marrow transplant. Importantly, bone marrow transplant reconstituted the immune systems of the mice improving survival over 24  $\mu\text{Ci}$   $^{211}\text{At}$ -B10-30F11 treatment alone (see figure). Furthermore, toxicity studies only showed transient myelosuppression after treatment that fully recovered within four weeks, with no impact on kidney or liver function.

"Historically, increasing radiation or chemotherapy dose may decrease relapse rates, but the added toxicity negates any potential survival benefit," according to Dr. Orozco in regards to pre-transplant conditioning regimens for AML. "Our new studies show that with CD45 targeting, we can dramatically escalate radiation doses to CD45+ hematopoietic target tissues by virtue of the significantly higher decay energies of alpha-emitters over other radionuclides previously studied, largely beta- and gamma-emitters that have lower decay energies by one or two orders of magnitude." Future clinical trials are warranted to study if this RIT strategy can improve outcomes in human AML patients post transplant.

[Orozco JJ, Bäck T, Kenoyer A, Balkin ER, Hamlin DK, Wilbur DS, Fisher DR, Frayo SL, Hylarides MD, Green DJ, Gopal AK, Press OW, Pagel JM](#). 2013. Anti-CD45 radioimmunotherapy using  $^{211}\text{At}$  with bone marrow transplantation prolongs survival in a disseminated murine leukemia model. *Blood* Epub ahead of print, doi: 10.1182/blood-2012-11-467035.



*Image modified from manuscript with authors' permission.*

Anti-CD45 radioimmunotherapy targets alpha-emitting radiation to hematopoietic organs and prolongs survival in a murine myeloid leukemia model. Alpha camera imaging confirms targeting of radiation to mouse spleen (A) and femur (C) three hours after intravenous injection of  $^{211}\text{At}$ -labeled anti-CD45 antibody (B10-30F11), with quantitative histograms displayed to the right of the respective organs (B, D). Improved survival curves with increasing doses of  $^{211}\text{At}$ -B10-30F11 compared to control antibodies prior to hematopoietic stem cell transplant in a murine myeloid leukemia model (E).