Radioimmunotherapy Tuned in to Multiple Myeloma

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Multiple myeloma (MM) is the second most common blood cancer diagnosed in the United States each year. Despite significant advances in treatment over the past decade, MM remains incurable. Hematopoietic stem cell transplantation is used to treat MM. However, most patients suffer relapse of disease, suggesting the pre-transplant regimens do not eliminate all cancerous cells. Radioimmunotherapy (RIT) can be used to selectively kill cancer cells before transplant, by delivering targeted doses of radiation conjugated to antibodies that recognize cell surface proteins specific to malignant cells. A new study published in the journal *Cancer Research*, led by Drs. Damian Green and Oliver Press in the Clinical Research Division, details the first use of RIT against MM cells targeting the CD38 protein. "Our work not only demonstrates the promise of this approach, but also details how the efficacy of RIT can be enhanced through tumor pretargeting," according to lead author Dr. Damian Green.

The effectiveness of RIT in treating various blood cancers has been shown through decades of preclinical and clinical research in the laboratory of Dr. Press. In the current study, Dr. Green and colleagues extended these studies to MM and compared the biodistribution and efficacy of conventional versus pretargeted RIT. In conventional RIT, antibodies are directly labeled with radionuclides. Pretargeted RIT first targets the tumor with antibodies that are chemically linked to streptavidin. A clearing agent removes any unbound antibody, followed by infusion of a small molecule, radiolabeled-DOTA-biotin, that will bind to the streptavidin-antibody accumulated on cancer cells or will be rapidly cleared from the blood through urine (see figure). This approach further limits the amount of non-specific toxicity to normal cells and allows for higher doses of radiation to cancer cells.

Using mouse models of MM, the researchers first compared the biodistribution of the two RIT approaches using the radionuclide ^{90}Yttrium and an antibody recognizing CD38. The researchers chose CD38 as a target protein since it is expressed uniformly and at high density on myeloma cells, and is only found at low levels on normal plasma cells and other cells of hematopoietic origin.

Pretargeted RIT increased the amount of radiation that reached the tumors and decreased the amount found in normal organs: tumor to blood ratios of radiation were as high as 638:1 for pretargeted RIT versus 1:1 for conventional RIT. Green *et al*. then examined the therapeutic efficacy of pretargeted RIT. MM tumors regressed within seven days in all mice treated with CD38-pretargeted RIT with doses of 800 microCi to 1200 microCi ^{90}Yttrium, and tumors were not detectable 23 days after treatment. Furthermore, up to 100% of the treated mice achieved long-term myeloma-free survival (greater than 70 days) while no treatment-free control animal was myeloma-free ($P<0.0001$). Pretargeted RIT demonstrated superior safety with no liver or kidney toxicity compared to conventional RIT, which uniformly induced radiation toxicity before therapeutic efficacy could be determined.

Dr. Green is encouraged by the rapid and complete eradication of MM tumors by CD38-pretargeted RIT in preclinical mouse models, suggesting promise for the success of this approach in patients. In contrast, most novel FDA-approved agents that improve response rates and overall survival among MM patients only temporarily reduced myeloma growth in mouse models. The clinical response to these agents is also temporary, with eventual relapse of nearly all patients.

"Our goal is to conduct clinical trials with radioimmunotherapy targeting CD38 in multiple myeloma. Our group has a track record of successfully bringing preclinical discovery from the laboratory to patients in the clinical setting," according to Dr. Green who is actively pursuing funding to achieve these goals. In addition, the group is exploring ways to enhance their anti-myeloma RIT with agents that may radiosensitize tumor cells, including proteasome inhibitors and immunomodulatory drugs. Dr. Green has "identified agents that upregulate CD38 on myeloma cells and [we] hope to exploit this discovery to increase the absolute amount of radioactivity deposited in the tumor. This would enhance target to normal organ ratios and increase the rate of tumor regression."

Green DJ, Orgun NN, Jones JC, Hylarides MD, Pagel JM, Hamlin DK, Wilbur DS, Lin Y, Fisher DR, Kenoyer AL, Frayo SL, Gopal AK, Orozco JJ, Gooley T, Wood BL, Bensinger W, Press OW. 2013. A preclinical model of CD38-pretargeted radioimmunotherapy for plasma cell malignancies. *Cancer Research*. Epub ahead of print, doi: 10.1158/0008-5472.CAN-13-1589.

See also: Pagel JM, Orgun N, Hamlin DK, Wilbur DS, Gooley TA, Gopal AK, Park SI, Green DJ, Lin Y, Press OW. 2009. A comparative analysis of conventional and pretargeted radioimmunotherapy of B-cell lymphomas by targeting CD20, CD22, and HLA-DR singly and in combinations. *Blood* 113:4903-13.

Green DJ, Pagel JM, Nemecek ER, Lin Y, Kenoyer A, Pantelias A, Hamlin DK, Wilbur DS, Fisher DR, Rajendran JG, Gopal AK, Park SI, Press OW. 2009. Pretargeting CD45 enhances the selective delivery of radiation to hematolymphoid tissues in nonhuman primates. *Blood* 114:1226-35.

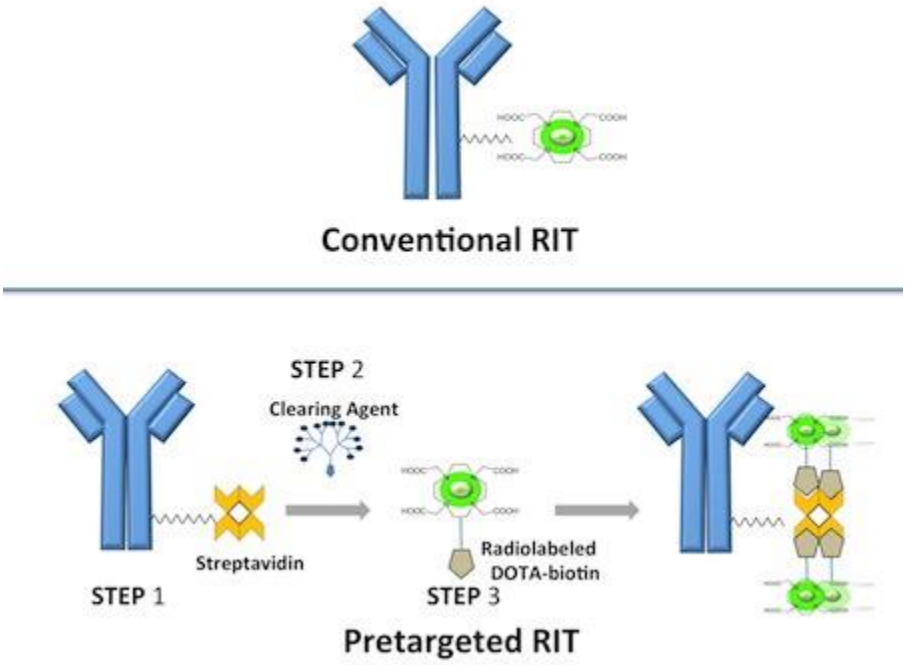

Image provided by Dr. Damian Green

Conventional radioimmunotherapy (RIT) uses antibodies directly radiolabled to specifically deliver radiation to kill cancer cells. Pretargeted RIT enhances the efficacy of radioimmunotherapy by first using streptavidin-labeled antibodies to label the tumors. A clearing agent removes unbound antibody, and then radiolabeled-DOTA-biotin binds to the antibody to kill the cancer cells or is rapidly excreted in the urine, limiting the toxicity to normal cells.