RIT-NMAT: A New Hope for High-Risk Lymphoma Patients

January 19, 2015

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A number of studies have shown that patients with advanced-stage slow-growing B cell malignancies may be cured through nonmyeloablative allogeneic hematopoietic cell transplantation (NMAT). Thanks to its relatively low rate of adverse effects, NMAT can be offered also to patients who are ineligible for more aggressive therapies due to age or other health-related issues. The long-term success is, however, influenced by the disease status at the time of transplantation, and evidence points towards the importance of being in complete remission (CR), i.e. without detectable tumors, when receiving NMAT. This can be achieved through various conditioning pre-treatments, but the development of suitable regimens for patients with chemotherapy-resistant tumors has been slow. Fortunately, there are other ways of attacking the malignant cells; chemoresistant tumors may still be sensitive to ionizing radiation, which opens up a window for pre-transplant conditioning using targeted radionuclide therapy.

One such modality is radioimmunotherapy (RIT), which utilizes radiolabeled monoclonal antibodies for specific targeting of antigens on the tumor cells. Targets are subsequently exposed to the cell-killing radiation that is emitted by the decaying radionuclide. Various adaptations of this technique have been thoroughly studied over the course of several years, pioneered in part by Fred Hutch's Dr. Oliver Press and colleagues at the Clinical Research Division. Positive outcomes with RIT-augmented NMAT have been reported by several research teams for patients with indolent disease, but a formal comparison between this approach and standard conditioning was not performed until very recently.

To examine whether early CR and better long-term outcomes can be achieved through RIT conditioning, Drs. Ryan Cassaday, Ajay Gopal and colleagues in the Medical Director's Office (SCCA and Clinical Research Division) conducted a study of a group of patients with persistent indolent B cell non-Hodgkin lymphoma (iB-NHL) or chronic lymphocytic leukemia (CLL) that had received standard NMAT treatment at the Hutch between 1998 and 2009. The chosen patients then served as a control group to RIT-augmented transplants, based on eligibility criteria for a previously published RIT-NMAT phase II study targeting CD20 (Gopal et al. 2011). The results of the comparison were recently published in *Biology of Blood and Marrow Transplantation*.

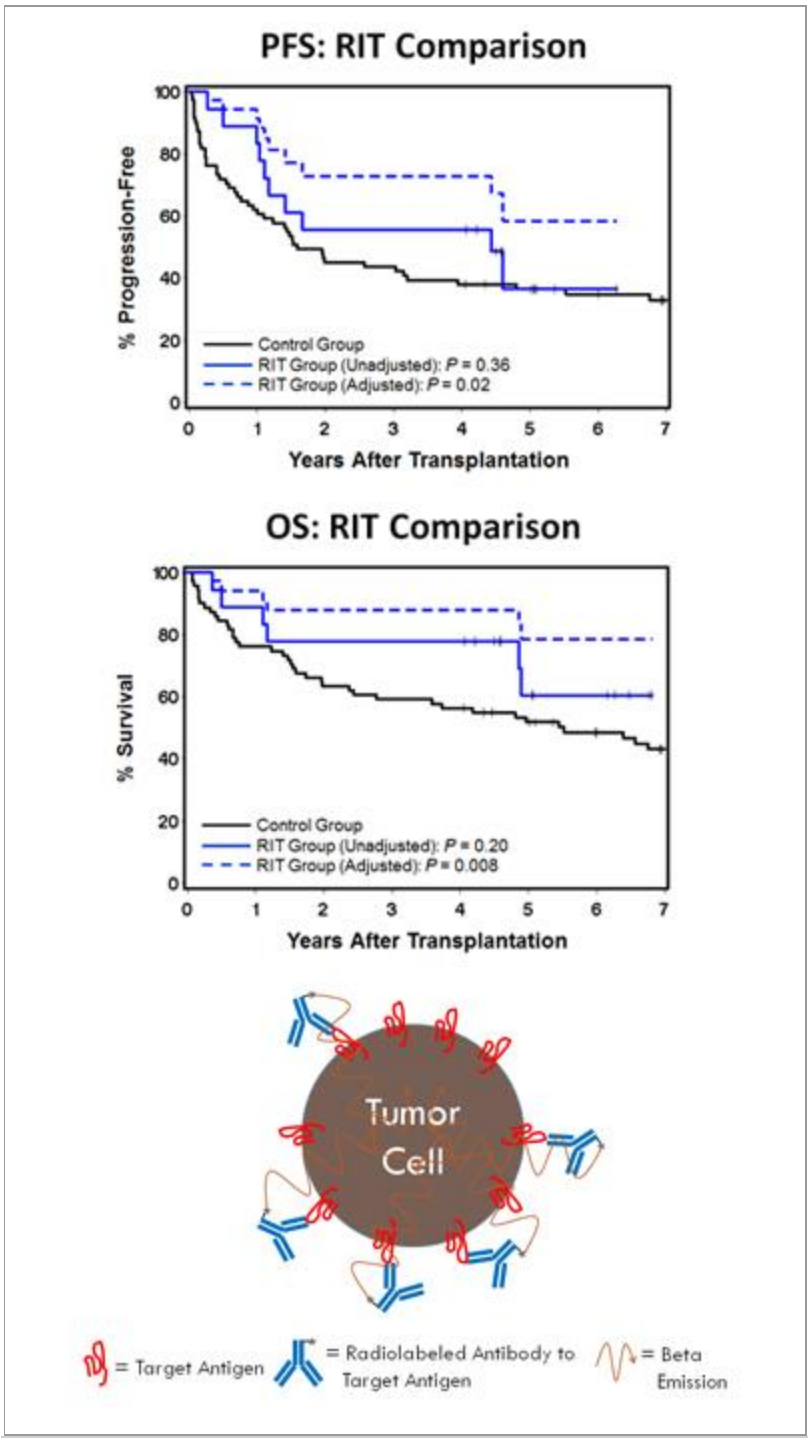
A total of 89 patients were studied, all of them at least 18 years old and with detectable disease at the time of transplant. Of them, 18 had received RIT-NMAT whereas 71 were not enrolled in the phase II trial due to reasons other than eligibility (insurance denial, patient preferences etc.). All 89 were pre-treated with fludarabine and total body irradiation; in addition, the anti-CD20-RIT group was administered rituximab and ^{90}Y-ibritumomab tiuxetan two weeks prior to transplantation.

Treatment outcome was evaluated in terms of progression-free survival (lack of relapse, progression or death from any cause), overall survival and nonrelapse mortality, with a median follow-up of 6.8 years for the entire cohort. In general, the RIT-treated patients showed more high-risk features compared with the control group, such as chemoresistance, bulky disease, unfavorable HCT-comorbidity index scores and low platelet counts prior to transplant. The investigators accounted for this imbalance through multivariate statistical analysis and demonstrated significantly improved progression-free survival and overall survival in the RIT-treated group. Notably, addition of RIT was the only factor that was significantly associated with the observed improvements. Neither nonrelapse mortality nor incidence of acute or chronic graft-versus-host disease differed significantly between the two treatment groups.

Although the sample size was modest, the results were no less encouraging: 46% of the treated patients were still alive and progression-free three years after NMAT, despite persistent disease. This indicates that patients who traditionally have been excluded from transplant regimens also may benefit from the treatment. "Our data demonstrate that transplantation can be effective in patients unable to achieve complete remission, an important finding to reassure patients and their physicians that this remains a viable approach", said Dr. Cassaday, emphasizing the incentive to move forward with RIT conditioning protocols. "The observation that the addition of standard radioimmunotherapy further improved outcomes provides compelling evidence to support the study or potential clinical use of this approach."

Cassaday RD, Storer BE, Sorror ML, Sandmaier BM, Guthrie KA, Maloney DG, Rajendran JG, Pagel JM, Flowers ME, Green DJ, Rezvani AR, Storb RF, Press OW, Gopal AK. 2014. Long-term outcomes of patients with persistent indolent B-cell malignancies undergoing nonmyeloablative allogeneic transplantation. *Biol Blood Marrow Transplant*. [Epub ahead of print]

See also: Gopal AK, Guthrie KA, Rajendran J, Pagel JM, Oliveira G, Maloney DG, Matesan MC, Storb RF, Press OW. 2011. ^{90}Y-Ibritumomab tiuxetan, fludarabine, and TBI-based nonmyeloablative allogeneic transplantation conditioning for patients with persistent high-risk B-cell lymphoma. *Blood*. 118(4):1132–1139.



Images provided by Dr. Ryan Cassaday

Kaplan-Meier curves of progression-free survival (PFS) and overall survival (OS) in the control and radioimmunotherapy (RIT) groups. The solid lines represent the observed outcomes and the dashed lines represent estimates adjusted with regard to the imbalance in high-risk features within the two patient populations. At the bottom is a schematic visualizing the RIT concept.