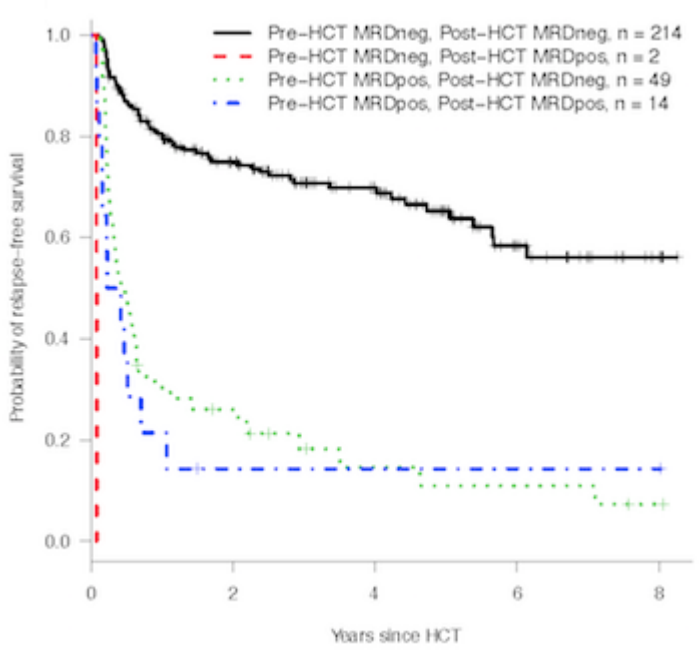
Ask not if, but when for MRD

May 16, 2016

J Herman



Association between MRD dynamics and outcomes for AML patients following myeloablative HCT, stratified by positive/negative MRD status. Kaplan-Meier estimate of relapse free survival following myeloablative allogeneic HCT for adults with AML.

Figure provided by Dr. Roland Walter.

Since the inception of hematopoietic cell transplantation (HCT) many studies have found this therapy to significantly improve patient outcomes and survival. However, as with all clinical studies, success is determined for a population of patients, and individual responses can range widely. In acute myeloid leukemia (AML), patient relapse after HCT has been correlated with 'depth of remission'. The unique nature of AML as a hematopoietic cancer makes assessing remission very difficult. Morphological remission is determined by microscopic review of marrow and peripheral blood cell smears. However, advances in diagnostic tools have revealed that some patients in morphological remission still harbor cancer cells in their body. This sub-microscopic cancer cell population is termed MRD and its presence correlates with high relapse rates and worse outcomes for patients. MRD is thought to result from rare leukemia cells that were resistant to the therapy that led to morphological remission, and is prognostic for high risk of relapse. In transplant patients MRD has largely been evaluated using highly sensitive methods like flow cytometry at a single point, either before or after HCT. In a recent study published in Leukemia, Dr. Roland Walter and colleagues in the Clinical Research Division instead evaluated MRD both prior to and after HCT in order to understand how disease burden dynamics correlate with patient outcomes.

One of the main challenges to understanding MRD is reliably detecting it. In this study MRD was detected with multi-parameter flow cytometry. This technique uses three antibody combinations to detect 17 unique cellular markers and the presence of residual leukemia cells is determined by visual inspection for variation among these markers. The present study consisted of 311 AML patients who were in either first or second morphological remission prior to HCT. Patients' MRD status before HCT was routinely determined as standard care leading up to transplant, while post transplant MRD status was determined 21 to 35 days after the procedure. To understand how MRD affected patient outcomes (survival, relapse, and non-relapse mortality) patient follow up continued up to 8 years after transplant.

MRD likely consists of therapy resistant leukemia cells and thus may correlate to patient outcomes differently if a patient has experienced relapse. Patients were grouped by first or second morphological remission and these two groups were further sub-divided by MRD status prior to HCT (positive or negative). As the authors have shown in a previous publication, relapse-free survival correlated with negative MRD status, independent of remission number. This suggests a key to patient survival is achieving MRD negative status regardless of a patient's therapeutic history. Next, researchers compared the prognostic value of MRD status before and after HCT. The most common patient group was pre-HCT MRD negative patients that remained MRD negative. Conversion to MRD positive status after HCT was rarely observed. Oppositely, pre-HCT MRD positive patients most commonly were MRD negative post-HCT, though some were unchanged. When patients were grouped by both their pre- and post-HCT MRD status it became strikingly clear that pre-HCT MRD negative patients who remained MRD negative had the highest survival outcomes, while patients that were MRD positive either pre or post-HCT were at increased risk for relapse.

In general, AML patients undergoing HCT are not only at risk of relapse, but also graft versus host disease (GVHD) where donor immune cells elicit a response against host tissue. Possible GVHD necessitates immunosuppression in transplant patients, which also carries health risks due to infection. When patient groups were analyzed for these non-relapse mortalities the risk did not seem to correlate with MRD status. Said Dr. Walter, "I think the fact that the outcome difference between MRDpos and MRDneg patients is primarily due to differences in relapse risk just speaks for the fact that MRD is a marker of inherent insensitivity of the leukemia to (prior) therapy and, thus, a marker for disease recurrence, rather than a marker to tolerability of transplant. This association makes the case that a major focus should be in finding treatment strategies that reduce relapse risk in MRDpos patients."

While pre-HCT and post-HCT MRD status were quite predictive of patient survival, it is still unclear if the presence of MRD actually drives relapse, or is merely a predictor. Dr. Walter explained the next step for these studies, "I think the fundamental study that needs to be done is a study that documents the value of MRD directed therapy. That is, there is no doubt that MRD identifies patients at high risk of relapse and short survival. What is not established with solid data is the idea that treating MRD will improve outcomes." This work begs for follow up studies that may dramatically change the approach to patient care for AML.

Funding for this research was provided by the National Institutes of Health and the Leukemia and Lymphoma Society.

Zhou Y, Othus M, Araki D, Wood BL, Radich JP, Halpern AB, Mielcarek M, Estey EH, Appelbaum FR, Walter RB. 2016. Pre- and post-transplant quantification of measurable ('minimal') residual disease via multiparameter flow cytometry in adult acute myeloid leukemia. *Leukemia*. doi: 10.1038/leu.2016.46. [Epub ahead of print]