An Unpredicted Predictor of Outcome in Pediatric AML

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Acute myeloid leukemia (AML) is a cancer of the bone marrow that has large outcome variability among affected patients. The disease is relatively rare, accounting for only 1.2 % of all cancer deaths in the United States, but is expected to increase in incidence. A number of factors have been identified to facilitate diagnostic classification and risk assessment, but when it comes to predicting individual outcomes much less is known. The few predictive markers that have been identified so far are insufficient, and there is a need in the clinic for more sophisticated characterization methods for AML.

Drs. George Laszlo and Roland Walter in the Clinical Research Division recently published results from discovery gene expression studies utilizing pediatric AML specimens. They found an association between patient outcomes and the expression level of *MMRN1*, which is a gene that encodes the protein multimerin-1, a member of the elastin microfibrillar interface protein (*EMILIN*)/multimerin family. To follow up on their findings, the Fred Hutch investigators initiated a retrospective study in which *MMRN1* expression was quantified in frozen samples of bone marrow from patients enrolled in two Children's Oncology Group AML protocols. The data were then correlated with clinical outcomes to assess the potential use of *MMRN1* as a predictive biomarker in childhood AML.

The results were recently accepted for publication in *Clinical Cancer Research*, showing large variation in *MMRN1* expression among AML patients. The researchers arbitrarily divided the patients into quartiles, making the cut point dividing the highest quartile from the lower three quartiles at a relative *MMRN1* expression of 0.5. In the first part of the study 183 specimens were compared, showing that patients with a relative expression of ≥ 0.5 (n = 45) fared worse than those with a relative expression of < 0.5 (n = 138). While there was no statistically significant difference in overall survival (OS) in this training cohort, patients with*MMRN1* ≥ 0.5 experienced shorter event-free survival (EFS; time from study entry to failed initial remission, relapse, or death), and higher relapse risk (RR).

Next, *MMRN1* expression levels were correlated with clinical outcomes and disease characteristics in 740 patients, using the established threshold. In this cohort, a significant trend indicated higher likelihood for standard- or high-risk disease characteristics among patients with a high relative *MMRN1* expression (≥ 0.5; n = 160); the same population experienced lower probability of low-risk disease. In addition, these patients were less likely to respond to initial chemotherapy, and had poorer long-term outcome in terms of OS, EFS, and RR. After adjusting for disease risk, age, bone marrow blast percentage, and treatment, it was demonstrated that *MMRN1* expression could indeed be used for prediction of aforementioned clinical endpoints in childhood AML. Subgroup analyses to assess the predictive potential in low-, standard-, and high-risk groups were limited by the relatively small sample size, but indicated that patients with high *MMRN1* expression in all three risk categories generally fared worse than those with lower relative expression.

The mechanisms behind the observed correlation have yet to be fully revealed, as *MMRN1* is previously unrecognized as a predictive biomarker for any human cancer. In fact, it "comes totally out of nowhere in terms of myeloid biology," according to Dr. Laszlo. "We stumbled upon *MMRN1* as a gene that co-segregates with a proteasomal degradation complex component, called SOCS2, which also happens to have high transcript level in poor prognosis patients, but whereas there is rationale for SOCS2 expression being aberrantly high in some bad-acting pediatric AMLs, there is very little known about *MMRN1* biology that would indicate what role it might have in leukemic cells." Besides expanding the analyses to include adult AML, the Walter Lab is thus interested in digging into the biology behind their findings to explore whether there is a biological basis for high multimerin-1 levels in myeloid cells and whether secreted multimerin-1 could serve as an AML biomarker.

Further studies are needed to assertively conclude whether *MMRN1* expression can refine the risk stratification and improve current predictive models for AML, but this unexpected finding may bring the scientists one step closer to advancing the development of individualized treatment plans - a sought-after goal.

Laszlo GS, Alonzo TA, Gudgeon CJ, Harrington KH, Gerbing RB, Wang Y-C, Ries R, Raimondi SC, Hirsch BA, Gamis AS, Meshinchi S, Walter RB. 2015. Multimerin-1 (*MMRN1*) as novel adverse marker in pediatric acute myeloid leukemia: a report from the Children's Oncology Group. *Clin Cancer Res*. [Epub ahead of print]

See also: Laszlo GS, Ries RE, Gudgeon CJ, Harrington KH, Alonzo TA, Gerbing RB, Raimondi SC, Hirsch BA, Gamis AS, Meshinchi S, Walter RB. 2014. High expression of suppressor of cytokine signaling-2 predicts poor outcome in pediatric acute myeloid leukemia: a report from the Children's Oncology Group. *Leuk Lymphoma*. 55(12):2817-21.

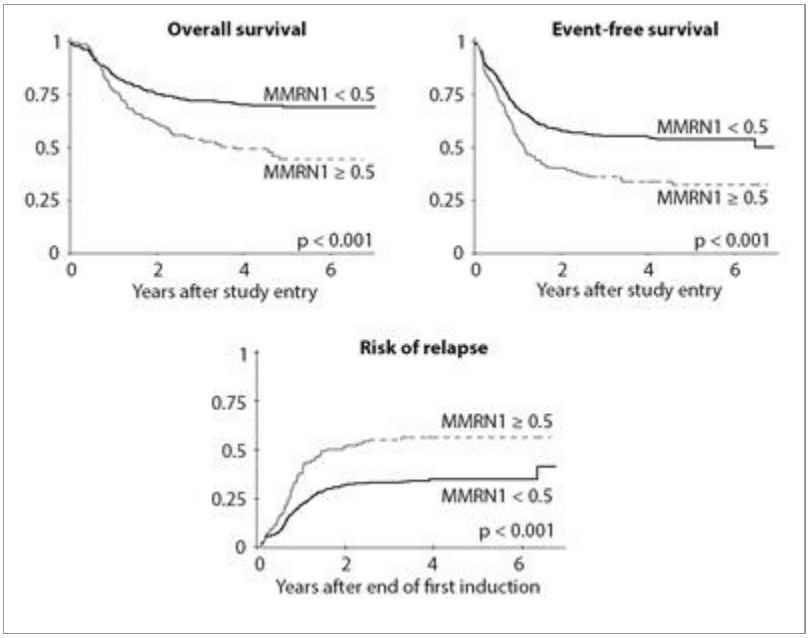

Image provided by Dr. George Laszlo

Clinical outcome in patients with high (relative mRNA expression ≥ 0.5) and low (relative mRNA expression < 0.5) MMRN1 expression in COG-AAML0531.