

Timing of MDS Relapse: A Multifaceted Case to Crack

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Myelodysplastic syndrome (MDS) comprises a group of hematological disorders in which hematopoietic stem/precursor cells in the bone marrow do not develop properly into healthy blood cells. Allogeneic hematopoietic cell transplantation (HCT) represents a possible cure, but 10 to 50 % of patients relapse, which is suggestive of a poor outcome. Most relapses occur within 12 to 18 months after HCT. However, there is no defined time point beyond which the patient is considered "safe" - some relapses are diagnosed several years after transplantation.

The question thus arises: what factors determine who will relapse and when? This occupied the Clinical Research Division's Drs. Cecilia Yeung and Joachim Deeg, whose results from analysis of relapse patterns among 1,007 transplanted MDS patients were recently presented in *Biology of Blood and Marrow Transplantation*. "This is the first large study to examine risk factors for and features of late relapse after HCT for MDS," Dr. Yeung said, further explaining that this kind of in-depth look at late-relapse clonal characteristics could help identify patients who might benefit from targeted interventions after HCT to prevent disease progression.

Disease progression and relapse after HCT are mainly determined by changes in the structure or function of cells and chromosomes, referred to as clonal cytogenetic abnormalities, likely supported by somatic (i.e. non-inherited) mutations. Although there is limited knowledge about the prognostic effect of molecular abnormalities, recent findings indicate that MDS clones present at the time of post-HCT relapse often differ from those identified pre-HCT, although the "relapse clones" have yet to be properly characterized.

In the patient cohort analyzed by Dr. Yeung and colleagues, relapses before 18 months were categorized as "early" and those after 18 months as "late", and differences in risk factors between the two data sets were assessed through logistic regression analysis. From the initial cohort, 973 MDS patients were included; of those, 25 % eventually relapsed; 213 before 18 months (median 100 days), and 41 after 18 months (median 2.6 years). As expected, the hazard of relapse in the entire cohort declined steadily, though without any distinct time point at which the trend changed significantly. The difference in median survival after relapse was not statistically significant between early- and late-relapsing patients (91 and 220 days, respectively; $p = 0.07$). Multivariable regression

analysis of patients who were relapse-free and alive at 18 months (n = 408) identified a number of risk factors, including the finding that MDS that had developed into acute myeloid leukemia implied higher risk of late relapse than untransformed MDS. Another conclusion was that late relapse was less likely among patients with chronic graft-versus-host disease (GVHD) compared to those without chronic GVHD - a finding that concurred with the documented graft-versus-leukemia/tumor effect. "The alloreactivity of donor cells is a major contributor to the eradication of the patient's disease," explained Dr. Yeung.

In general, few significant differences were noted in characteristics of early- and late-relapsing patients. Poor-risk cytogenetics were associated with higher probability of early relapse, as was pre-HCT conditioning with reduced-intensity regimens. Genetic analysis performed on sequential bone marrow samples from 36 late-relapsing patients revealed additional clonal abnormalities at relapse besides those detected in pre-HCT samples in 41 %; 30 % had their pre-HCT abnormalities replaced by new clones; 17 % exhibited the same clone pre-HCT and at relapse; and in 10 % no abnormalities were revealed for either time point.

Three patients in the "late" group were further analyzed by chromosomal genomic array testing of pre-HCT and post-relapse DNA, to examine potentially prognostic alterations that may be undetectable by standard methods. Interestingly, post-relapse-unique abnormalities were discovered for all three patients. Still, higher-sensitivity techniques may be needed to confidently exclude the possibility of the deviations being present at very low levels already before HCT.

Dr. Yeung concluded that further refined mutational analyses should be undertaken. "We hypothesized that late relapses may be due to an 'escape' from surveillance (by donor alloreactivity) due to the evolution of new clones/subclones. However, results do not show clear differences in clonal architecture between early and late relapse." The team, in collaboration with Dr. Jerry Radich's laboratory, will now continue the studies of MDS progression dynamics and molecular profiles through single cell techniques and massive deep sequencing, in addition to exploring emerging questions regarding late relapse versus "new disease", which might have to be handled differently.

[Yeung C, Gerds AT, Fang M, Scott BL, Flowers ME, Gooley T, Deeg HJ](#). 2015. Relapse after allogeneic hematopoietic cell transplantation for myelodysplastic syndromes - analysis of late relapse using comparative karyotype and chromosome genome array testing. *Biol Blood Marrow Transplant* [Epub ahead of print].

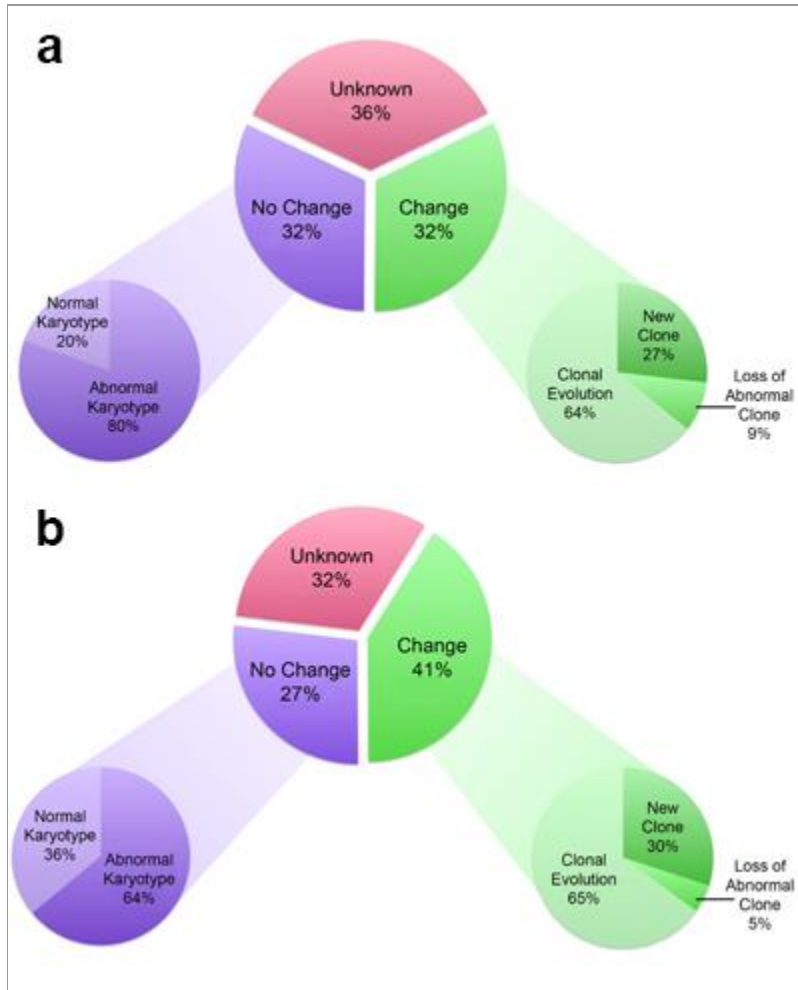


Image provided by Dr. Cecilia Yeung

(a) Bone marrow karyotypes before HCT (broken pie chart) and at the time of relapse (intact pie charts) in 213 patients with early relapse. (b) Bone marrow karyotypes before HCT (broken pie chart) and at the time of relapse (intact pie charts) in 41 patients with late relapse.