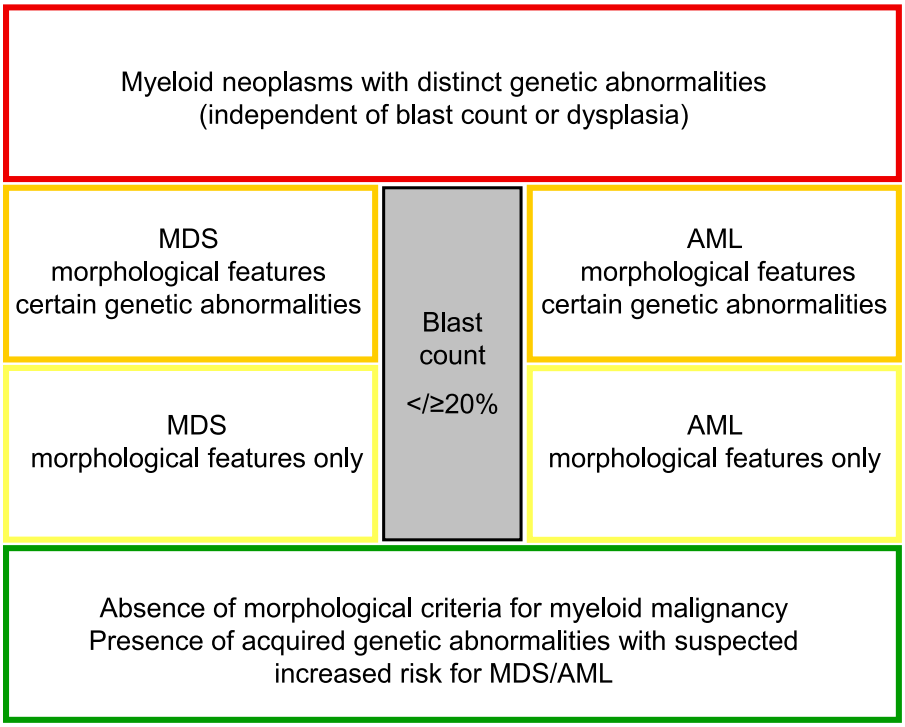


Proposal for a "work-in-progress concept" to classify myeloid malignancies until all questions are answered by genetic information.

5q deletion, or *NPM1* mutation.[8] Thus, current knowledge supports the view that any alteration can occur first and may be complemented by any other genetic abnormality. The first hits define the disease and the likelihood of certain further genetic alterations that promote the disease.

Although a major step is to define disease entities based on genetic events, an even more important aspect will be to discriminate between normal hematopoiesis and hematological disease. The tremendous increase in the knowledge of genetic imbalances and mutations has led to an increase of genetic analyses in patients with suspected diseases and even in the normal population. Frequently, the detection of a genetic abnormality is taken as proof that a clonal disease is present. However, Jacobs et al observed mosaic abnormalities, either aneuploidy or copy-neutral loss of heterozygosity, of >2 Mb in size in autosomes of cancer-free individuals. This frequency increased with age, from 0.23% at <50 years to 1.91% between 75 and 79 years.[9] In line with this, Laurie et al found that detectable clonal mosaicism in peripheral blood is low (<0.5%) from birth until 50 years of age and rises rapidly to 2% to 3% in the elderly. Many of the genetic alterations observed were characteristic of those found in hematological cancers. Although only 3% of subjects with detectable clonal aberrations had any record of hematological cancer before DNA sampling, those without a previous diagnosis had an estimated 10-fold higher risk of a subsequent hematological cancer.[10]

In summary, Gröschel et al and Lavallée et al provide important and novel insights into the biology of myeloid neoplasms with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *GATA2-EVI1* rearrangement.[1,2] Further, and possibly even more important, they initiate a discussion on novel concepts of classification and the definition of diseases against the background of current genetic knowledge.

*Conflict-of-interest disclosure: C.H. has part ownership in the MLL Munich Leukemia Laboratory.* ■

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● ● ● TRANSPLANTATION

Comment on Ponce et al, page 199

# ST2: the biomarker at the heart of GVHD severity

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In this issue of *Blood*, Ponce et al report that high suppression of tumorigenicity 2 (ST2) levels are significantly associated with the incidence of acute graft-versus-host disease (aGVHD) and transplant-related mortality (TRM) in recipients of double-unit cord blood transplants (CBTs).[1]

ST2 is a member of the interleukin (IL)-1 receptor family and specifically binds to IL-33. There are 2 functional ST2 isoforms that have opposite roles in innate and adoptive immunity; a transmembrane ST2 forms the complex with IL-33 and induces type 2 immune response and tissue repair. In contrast, soluble ST2 appears to work as a decoy receptor and negatively regulates IL-33 function.[2] Recently, Vander Lugt et al, using a proteomic approach, identified high ST2 levels as the biomarker most significantly associated with treatment-refractory aGVHD. This single biomarker strongly predicted for TRM when measured either at the onset of aGVHD or on day 14 after allogeneic stem cell transplantation (allo-SCT) using either peripheral blood or bone marrow grafts from related or unrelated donors.[3]

The present study by Ponce et al analyzed biomarkers in serum samples obtained from 113 patients with hematologic malignancies on day 28 following double-unit CBT. Compared with 6 other biomarkers (tumor necrosis factor receptor 1, IL-8, regenerating islet-derived protein 3α, IL-2 receptor α, elafin, and hepatocyte growth factor), ST2 emerged as the best prognostic marker in CBT. A high ST2 level (>33.9 ng/mL) at day 28 was an independent prognostic factor for both the incidence of grade III to IV aGVHD and day 180 TRM in multivariate analysis. This is the first study to demonstrate the utility of ST2 measurement for post-transplant mortality risk stratification in CBT, reinforcing the promise of ST2 as a general biomarker for aGVHD and TRM after all types of allo-SCT, irrespective of the stem cell source.

What next steps are required for ST2 to be a routine biomarker in a general transplant practice? First, the prognostic value of ST2 should be validated by a large cohort in a multicenter study including various age groups, conditioning regimens, stem cell sources, and underlying primary diseases. Second, the threshold for the cutoff value of ST2 should be standardized. The cutoff value would be set differently by condition regimen[3] and by the assay format. Third, the role of ST2 for monitoring the response to aGVHD treatment should be evaluated as recently reported for other aGVHD biomarkers.[4,5] Last, the timing of ST2 measurement should be optimized to predict the outcomes with greatest accuracy, permitting the use of the ST2 biomarker to guide preemptive treatment of aGVHD as previously proposed by Paczesny in a recent review article in *Blood*.[6]

Nevertheless, many questions related to ST2 biology remain unanswered. ST2 levels are used as a prognostic biomarker in diverse clinical scenarios: cardiovascular disease,[7] pulmonary disorders, and posttransplant engraftment syndrome.[8] Thus, a high soluble ST2 level may simply reflect the extent of tissue damage, regardless of its initiating pathology. In a mouse cardio-protection model, the therapeutic potential of recombinant IL-33 has been proposed[9]; however, the detailed roles of the IL-33/ST2 signaling pathway in GVHD remain unknown. A recent genome-wide association study of Framingham Cohort participants found that 5 single nucleotide polymorphisms (SNPs) within *IL1RL1* (the gene encoding ST2) are associated with higher soluble ST2 levels and enhanced IL-33 responsiveness.[10] This report suggests the genetic background of *IL1RL1* may also have an impact on soluble ST2 levels at baseline or under stress, although the significance of these *IL1RL1* SNPs in allo-SCT remains undetermined.

This study further confirms our perception that ST2 is an extremely powerful prognostic biomarker for aGVHD. The time has come to design prospective studies using ST2 to guide treatment approaches for aGVHD. The closer a biomarker relates to the underlying pathology, the more reliably it can serve as a predictive marker (ie, a biomarker that predicts the likely response to a specific treatment). ST2, which links both immune function and tissue damage, is the best candidate thus far for a true indicator of the severity and prognosis of aGVHD. Insight acquired into ST2 biology may, in the future, guide the development of therapeutic interventions based on the ST2/IL-33 axis.

*Conflict-of-interest disclosure: The authors declare no competing financial interests.* ■

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