they occur in less than 20–30% of the clonal cells as well as the inability to adequately distinguish individual subclones within a sample. In addition, the use of paired normal (germinal) DNA from the same patient is critical to determine whether CNVs/CNAs or CN-LOH detected using arrays are somatic or inherited. In fact, interpretation of earlier studies in MDS patients was hampered by the use of pooled DNA from nonaffected individuals to serve as controls, instead of using paired diseased marrow and normal DNA from each patient, owing to overestimation of copy number and CN-LOH aberrations. When a matched germinal sample is not available, strategies for minimizing, although not completely eliminate, the false discovery rate include the use of public database repositories to differentiate acquired CNAs from inherited CNVs or size- or physical-location-based exclusion criteria for CN-LOH.

Despite array-based platforms improve our ability to detect CNAs, the clinical utility of this approach has not been validated or incorporated in common prognostic scores, so clinical use of array-based studies for MDS has not yet become routine. Nevertheless, aCGH/SNPa, as a mature technology with fully developed analysis tools, may continue to play a role in clinical laboratories, particularly for challenging cases. Next-generation sequencing (NGS) approaches will be increasingly applied and may become the standard approach in the near future.

3
EPIGENETIC DEREGULATION

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Myelodysplastic syndromes (MDS) are a clinically and cytogenetically heterogeneous group of clonal diseases characterized by ineffective hematopoiesis, peripheral blood cytopenias and an increased risk of progression to AML. Mutations in epigenetic modifiers occur frequently in this disease and have been shown to be sufficient to induce recapitulation of the disease in murine models. Moreover, the distinct sensitivity of this disease to DNA methyltransferase inhibitors as well as the presence of markedly abnormal epigenetic profiles hint to the importance that epigenetic deregulation plays in contributing to the disease phenotype. Using genome-wide approaches we have explored the epigenetic profiles of aged human hematopoietic stem cells as well as those of a cohort of MDS patients with distinct clinical outcomes. In the meeting, we'll discuss how epigenetic profiles change as we age and how they contribute to disease phenotype in MDS.

4
PREDICTING TRANSPLANTATION OUTCOMES

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Despite improved understanding of the molecular pathogenesis of myelodysplastic syndromes (MDS) currently available therapies lead to prolongation of life and no cure. Therefore, allogeneic hematopoietic stem cell transplantation (HSCT) is increasingly used as a curative treatment option [1,2]. This increase in HSCT activity can be attributed largely to the introduction of reduced-intensity regimens that have extended the indication for HSCT to older patients with comorbidities or reduced fitness. Despite its curative potential, because of the inherent complications of the transplantation leading to treatment-related mortality and the risk of relapse, a careful calculation of the benefit for each patient is mandatory, taking into account disease status, comorbidities and effective nontransplant therapies [2]. The definition of disease-related risk in MDS is based on the use of International Prognostic Scoring System (IPSS). A number of studies have shown that advanced disease risk at transplantation is associated with inferior survival, and cytogenetic abnormalities (i.e., complex/monosomal karyotype) have been found to be predictive of high risk of disease relapse [1,3]. Recently a revised version of IPSS (IPSS-R) was proposed, including five cytogenetic risk groups together with refined categories for marrow blasts and cytopenias [4]. In patients receiving HSCT, IPSS-R score significantly improves the prediction of patient prognosis with respect to IPSS [5]. The implementation of IPSS-R is expected to result in a more effective selection of candidates to HSCT among patients with early disease stage. Mutations in several genes have been reported to influence survival and risk of disease progression in MDS. MDS associated with SF3B1 mutations form a distinct entity with a favourable prognosis, while SRSF2, RUNX1, U2AF1, ASXL1 and TP53 mutations are associated with increased risk of leukemic evolution [6]. The integration of somatic mutations into prognostic scoring systems may provide more accurate risk stratification of individual patients and further refine clinical decision-making in MDS. A recent study in 401 patients who received HSCT for MDS or MDS/AML showed that somatic mutations in ASXL1, RUNX1, or TP53 were associated with unfavorable outcomes and shorter survival [7]. A larger CIBMTR trial reported relevant new findings. RAS pathway mutations and JAK2 mutations were associated with a poor outcome after HSCT, independently of TP53 mutations in patients >40 years [8]. Possible interventions in patients with high risk of disease relapse according to genotype may include the anticipation of the transplant procedure in early disease phase, the use of innovative conditioning regimens to increase the probability to eradicate MDS clone, and prophylaxis of disease recurrence after transplantation. The results of these studies serve as a proof of concept that the integration of somatic mutations significantly increase the capability to capture prognostic information in MDS patients receiving HSCT, and may provide a basis for improving transplantation decision-making.

References

1. Alessandrino EP, Della Porta MG, Bacigalupo A, Van Lint MT, Falda M, Onida F, et al WHO classification and WPSS predict posttransplantation outcome in patients with myelodysplastic syndrome: a study from the Gruppo Italiano Trapianto di Midollo Osseo (GITMO). Blood 2008;112:895–902.
2. de Witte T, Bowen D, Robin M, Malcovati L, Niederwieser D, Yakoub-Agha I, et al Use of hematopoietic cell transplantation for patients with myelodysplastic syndrome and chronic myelomonocytic leukemia. Blood. 2017 Jan 17. [Epub ahead of print].
3. Lim Z, Brand R, Martino R, van Biezen A, Finke J, Bacigalupo A, et al Allogeneic hematopoietic stem cell transplantation for patients 50 years or older with myelodysplastic syndromes or secondary acute myeloid leukemia. J Clin Oncol. 2010;28: 405–11.
4. Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Solé F, et al Revised International Prognostic Scoring System (IPSS-R) for myelodysplastic syndromes. Blood. 2012;120: 2454–65.
5. Della Porta MG, Alessandrino EP, Bacigalupo A, van Lint MT, Malcovati L, Pascutto C, et al Predictive factors for the outcome of allogeneic transplantation in patients with MDS stratified according to the revised IPSS-R. Blood. 2014;123:2333–42.
6. Papaemmanuil E, Gerstung M, Malcovati L, Tauro S, Gundem G, Van Loo P, et al Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood. 2013; 122:3616–27.