Introduction: Application of New Therapies to Myelodysplastic Syndrome

In the middle of the 20th century, Hamilton-Paterson and Block et al realized that a certain percentage of patients with acute myeloid leukemia evolved from a preleukemic state that was later dubbed myelodysplastic syndrome (MDS). It took a further 30 years for the first classification of MDS to be published by a cooperation of hematopathologists called the French-American-British (FAB) group. Although it was then possible to describe the morphological subtleties of this heterogeneous disease, the reason why many MDS patients suffered from peripheral cytopenias despite having a normo-to hypercellular bone marrow remained unclear for another 10 years. In 1993, Yoshiida correctly hypothesized that MDS hematopoietic progenitors have a defect in differentiation and undergo excess apoptosis. In later stages of the disease, apoptosis is less prominent and proliferation of immature progenitors becomes the main driver of the disease. The molecular underpinnings of these processes are complex: genetic abnormalities in the bone marrow microenvironment have been shown to cause MDS in mice, regulatory T cells are decreased and dysfunctional in a subset of MDS patients, and a wide variety of cytogenetic abnormalities have been described in hematopoietic progenitors in MDS. Furthermore, molecular aberrations in as much as 50% of MDS patients with normal karyotype have been described. Finally, loss of heterozygosity, haploinsufficiency of partially deleted chromatids, and epigenetic alterations of structurally unaltered chromosomal material add an overwhelming complexity to this already heterogeneous disease group.

The therapeutic approach to such a variable pathophysiology can follow several paths and is the basis for this issue of Seminars in Hematology. After an introduction to the field provided by Photis Beris and George Georgiou, an internationally renowned faculty presents current treatment strategies for low- and high-risk MDS: strengthening the normal hematopoiesis with growth factors can delay transfusion dependence and improve cell counts without necessarily increasing the transformation rate to acute leukemia. While erythropoietins have gained widespread use in MDS all over the world, the discontinuation of a phase III trial on thrombopoietin in low- and intermediate-1 risk disease has come as a blow to efforts to alleviate thrombocytopenia in MDS. Immunosuppressive treatment as used in the approach to aplastic anemia or with the CD52 antibody alemtuzumab will be reviewed by Parikh, Olnes, and Barrett from the US National Institutes of Health, emphasizing that patient selection is a key point to successfully applying this complex treatment strategy. The immunomodulatory thalidomide derivative lenalidomide swept the board in the treatment of International Prognostic Scoring System (IPSS) low- and intermediate-I risk del(5q) MDS. However, since a number of patients progressed to acute leukemia during treatment in clinical studies and patients treated with lenalidomide in multiple myeloma reported an increase in metachronous unrelated malignancies, questions have recently arisen whether there may be long-term safety issues with this drug. A detailed discussion about this topic will be presented in the article on lenalidomide therapy for MDS. This article also deals with the effects of lenalidomide in lower risk non-del(5q) MDS. The increasing knowledge on, and acceptance of, epigenetic abnormalities as drivers for hematopoietic insufficiency or progression to acute myeloid leukemia triggered a search for epigenetic modulators with a potential to improve cell counts in MDS. Not all have been successful. The articles by Garcia-Manero on histone deacetylase in-
hibitors, Adès and Fenaux on azacitidine, and Joeckel and Lübbert on decitabine address the potential of single and combination therapies with several epigenetically active drugs and show the light and shadow of the current epigenetic armamentarium in low- and high-risk disease. Although these treatment approaches undoubtedly harbor the potential to extend patients’ lives, the only curative treatment remains allogeneic stem cell transplantation. Improvements in donor identification, pretransplant conditioning, and supportive care have allowed patients up to the age of 70 years to undergo this hitherto very invasive treatment strategy. Uwe Platzbecker reviews the latest developments in the field and presents approaches to careful patient selection. Finally, Kulasekararaj and Mufti will allow us a glimpse of future MDS therapies. A number of promising agents are in developmental stage and might have the potential to further improve cytopenias, reduce clone size, and slow progression to acute leukemia. Importantly, many of those drugs are a direct consequence of a more detailed insight into molecular pathways that drive proliferation and apoptosis in human cell lineages. From this point of view, they truly represent the paradigm of bench-to-bedside and give us hope to tackle this puzzling disease in the (hopefully not too distant) future.

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REFERENCES
4. Yoshida Y. Hypothesis: apoptosis may be the mechanism responsible for the premature intramedullary cell death in the myelodysplastic syndrome. Leukemia. 1993;7:144–6.