Chapter 1

Introductory Chapter: Myelodysplastic Syndromes

Ota Fuchs

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Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis, peripheral cytopenias, frequent karyotypic abnormalities, and risk of transformation to acute myeloid leukemia (AML) [1–5]. MDS are rare in young people, and median age of patients with MDS is approximately 70 years [6, 7]. Current management in MDS includes supportive care, drug therapy, and allogeneic stem cell transplantation. MDS patients older than age 70 years are not good candidates for allogeneic stem cell transplantation [8, 9]. The major complication of MDS patients after allogeneic stem cell transplantation with reduced intensity conditioning is relapse of malignant disease. Relapse can be predicted by monitoring of Wilms' tumor 1 (WT1) gene expression by real-time PCR and $CD34^+$ donor chimerism analysis [10].

Single-nucleotide polymorphism array (SNP-A) analysis, standard metaphase cytogenetics, and rapid progress in flow cytometric analysis, genes mutation analysis, and gene expression profiling have identified key deregulated genes and signaling pathways important for accurate prognostication and risk stratification for individual patients with MDS [11–18]. The initial French–British–American (FAB) classification system of MDS was published in 1982 [19] and was later refined to the International Prognostic Scoring System (IPSS) [20] and to World Health Organization (WHO) Prognostic Scoring System (WPSS) [21, 22]. The new revised IPSS (IPSS-R) integrated marrow cytogenetic subset, marrow blast percentage, and depth of cytopenias (hemoglobin, platelet, and absolute neutrophil count) and was published in 2012 [23]. Validation of WPSS for MDS and comparison with IPSS-R has been recently described [24]. Two other prognostic systems for MDS subgroups (M.D. Anderson lower risk MDS prognostic scoring system; chronic myelomonocytic leukemia /CMML/ prognostic scoring system) exist [18, 25].

In lower risk MDS, treatment focuses on amelioration of consequences of cytopenias and transfusions and improving of quality of life. The first line of therapy of lower risk MDS with normal chromosome 5 is treatment with erythropoiesis-stimulating agents (erythropoietin)

with or without of granulocyte colony-stimulating factor [26]. Transfusion-dependent lower risk MDS patients with del(5q) are treated with immunomodulatory or cereblon-binding drug lenalidomide [27]. Thrombocytopenia occurring sometimes in combination with anemia or without anemia can be treated with romiplostin (thrombopoietin agonist) [27]. Neutropenia is treated with growth factors (G-CSF and GM-CSF) [27]. Higher-risk MDS if untreated have median survival only about 12 months. Two hypomethylating agents (azacitidine and decitabine) inhibit DNA methyltransferases 3A and 3B and reverse the aberrant methylation involved in MDS progression to AML. The development of novel therapeutic strategies in MDS is dependent on recent advances in the molecular pathogenesis of MDS [6, 16, 28–39]. Various combination therapies in MDS are also intensively studied [27, 40, 41].

Author details

Ota Fuchs*

Address all correspondence to: Ota.Fuchs@uhkt.cz

Institute of Hematology and Blood Transfusion, Prague, Czech Republic

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