We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Introductory Chapter: Myelodysplastic Syndromes

Ota Fuchs

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/64729>

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

References

- [1] Nimer SD. Myelodysplastic syndromes. *Blood*. 2008; 111: 4841–4851. doi:10.1182/blood-2007-08-078139.
- [2] Tefferi A, Vardiman JW. Myelodysplastic syndromes. *N Engl J Med*. 2009; 361: 1872–1885. doi:10.1056/NEJMra0902908.
- [3] Adés L, Itzkson R, Fenaux P. Myelodysplastic syndromes. *Lancet*. 2014; 383: 2239–2252. doi:10.1016/S0140-6736(13)61901-7.
- [4] Bejar R, Steensma DP. Recent developments in myelodysplastic syndromes. *Blood*. 2014; 124: 2793–2803. doi:10.1182/blood-2014-04-522136.
- [5] Pellagatti A, Boulton J. The molecular pathogenesis of the myelodysplastic syndromes. *Eur J Haematol*. 2015; 95: 3–15. doi:10.1111/ejh.12515.
- [6] Zahr AA, Ramirez CB, Wozney J, Prebet T, Zeidan AM. New insights into the pathogenesis of MDS and the rational therapeutic opportunities. *Expert Rev Hematol* 2016; 9: 377–388. doi:10.1586/17474086.2016.1135047.
- [7] Rollison DE, Howlader N, Smith MT, Strom SS, Merritt WD, Ries LA, Edwards BK, List AF Epidemiology of myelodysplastic syndromes and chronic myeloproliferative disorders in the United States, 2001–2004, using data from the NAACCR and SEER-programs. *Blood*. 2008; 112: 45–52. doi:10.1182/blood-2008-01-134858.

- [8] Tamari R, Castro-Malaspina H. Transplant for MDS: challenges and emerging strategies. *Best Pract Res Clin Haematol.* 2015; 28: 43–54. doi:10.1016/j.beha.2014.11.006
- [9] Brierley CK, Steensma DP. Allogeneic stem cell transplantation in myelodysplastic syndromes: does pretransplant clonal burden matter? *Curr Opin Hematol.* 2016; 23: 167–174. doi:10.1097/MOH.0000000000000217.
- [10] Lange T, Hubmann M, Burkhardt R, Franke GN, Cross M, Scholz M, Leiblein S, Al-Ali HK, Edelmann J, Thiery J, Niederwieser D. Monitoring of WT1 expression in PB and CD34(+) donor chimerism of BM predicts early relapse in AML and MDS patients after hematopoietic cell transplantation with reduced-intensity conditioning. *Leukemia.* 2011; 25: 498–505. doi:10.1038/leu.2010.283.
- [11] Tiu RV, Visconte V, Traina F, Schwandt A, Maciejewski JP. Updates in cytogenetics and molecular markers in MDS. *Curr Hematol Malig Rep.* 2011; 6: 126–135. doi:10.1007/s11899-011-0081-2.
- [12] Otrrock ZK, Tiu RV, Maciejewski JP, Sekeres MA. The need for additional genetic markers for myelodysplastic syndrome stratification: what does the future hold for prognostication? *Expert Rev Hematol.* 2013; 6: 59–68. doi:10.1586/ehm.12.67.
- [13] Bejar R. Clinical and genetic predictors of prognosis in myelodysplastic syndromes. *Haematologica.* 2014; 99: 956–964. doi:10.3324/haematol.2013.085217.
- [14] Pellagatti A, Boultonwood J. The molecular pathogenesis of the myelodysplastic syndromes. *Eur J Haematol.* 2015; 95: 3–15. doi:10.1111/ejh.12515.
- [15] Gerstung M, Pellagatti A, Malcovati L, Giagounidis A, Porta MG, Jädersten M, Dolatshad H, Verma A, Cross NC, Vyas P, Killick S, Hellström-Lindberg E, Cazzola M, Papaemmanuil E, Campbell PJ, Boultonwood J. Combining gene mutation with gene expression data improves outcome prediction in myelodysplastic syndromes. *Nat Commun.* 2015; 6: 5901. doi:10.1038/ncomms6901.
- [16] Zahid MF, Patnaik MS, Gangat N, Hashmi SK, Rizzieri DA. Insight into the molecular pathophysiology of myelodysplastic syndromes: targets for novel therapy. *Eur J Haematol.* 2016; doi:10.1111/ejh.12771. [Epub ahead of print].
- [17] Alhan C, Westers TM, Cremers EM, Cali C, Witte BI, Ossenkoppele GJ, van de Loosdrecht AA. The myelodysplastic syndromes flow cytometric score: a three-parameter prognostic flow cytometric scoring system. *Leukemia.* 2016; 30: 658–665. doi:10.1038/leu.2015.295.
- [18] Jonas BA, Greenberg PL. MDS prognostic scoring systems – past, present, and future. *Best Pract Res Clin Haematol.* 2015; 28: 3–13. doi:10.1016/j.beha.2014.11.001.
- [19] Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, Sultan C. Proposals for the classification of the myelodysplastic syndromes. *Br J Haematol.* 1982; 51:189–199.

- [20] Greenberg P, Cox C, LeBeau MM, Fenau P, Morel P, Sanz G, Sanz M, Vallespi T, Hamblin T, Oscier D, Ohyashiki K, Toyama K, Aul C, Mufti G, Bennett J. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood*. 1997; 89: 2079–2088.
- [21] Malcovati L, Porta MG, Pascutto C, Invernizzi R, Boni M, Travaglino E, Passamonti F, Arcaini L, Maffioli M, Bernasconi P, Lazzarino M, Cazzola M. Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. *J Clin Oncol*. 2005; 23: 7594–7603. doi:10.1200/JCO.2005.01.7038.
- [22] Malcovati L, Germing U, Kuendgen A, Della Porta MG, Pascutto C, Invernizzi R, Giagounidis A, Hildebrandt B, Bernasconi P, Knipp S, Strupp C, Lazzarino M, Aul C, Cazzola M. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. *J Clin Oncol*. 2007; 25: 3503–3510. doi:10.1200/JCO.2006.08.5696.
- [23] Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Solé F, Bennett JM, Bowen D, Fenau P, Dreyfus F, Kantarjian H, Kuendgen A, Levis A, Malcovati L, Cazzola M, Cermak J, Fonatsch C, Le Beau MM, Slovak ML, Krieger O, Luebbert M, Maciejewski J, Magalhaes SM, Miyazaki Y, Pfeilstöcker M, Sekeres M, Sperr WR, Stauder R, Tauro S, Valent P, Vallespi T, van de Loosdrecht AA, Germing U, Haase D. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood*. 2012; 120: 2454–2465. doi:10.1182/blood-2012-03-420489.
- [24] Della Porta MG, Tuechler H, Malcovati L, Schanz J, Sanz G, Garcia-Manero G, Solé F, Bennett JM, Bowen D, Fenau P, Dreyfus F, Kantarjian H, Kuendgen A, Levis A, Cermak J, Fonatsch C, Le Beau MM, Slovak ML, Krieger O, Luebbert M, Maciejewski J, Magalhaes SM, Miyazaki Y, Pfeilstöcker M, Sekeres MA, Sperr WR, Stauder R, Tauro S, Valent P, Vallespi T, van de Loosdrecht AA, Germing U, Haase D, Greenberg PL, Cazzola M. Validation of WHO classification-based Prognostic Scoring System (WPSS) for myelodysplastic syndromes and comparison with the revised International Prognostic Scoring System (IPSS-R). A study of the International Working Group for Prognosis in Myelodysplasia (IWG-PM). *Leukemia*. 2015; 29: 1502–1513. doi:10.1038/leu.2015.55.
- [25] Zeidan AM, Sekeres MA, Wang XF, Al Ali N, Garcia-Manero G, Steensma DP, Roboz G, Barnard J, Padron E, DeZern A, Maciejewski JP, List AF, Komrokji RS. MDS Clinical research consortium. Comparing the prognostic value of risk stratifying models for patients with lower-risk myelodysplastic syndromes: Is one model better? *Am J Hematol*. 2015; 90: 1036–1040. doi:10.1002/ajh.24173.
- [26] Greenberg PL, Sun Z, Miller KB, Bennett JM, Tallman MS, Dewald G, Paietta E, van der Jagt R, Houston J, Thomas ML, Cella D, Rowe JM. Treatment of myelodysplastic syndrome patients with erythropoietin with or without granulocyte colony-stimulating factor: results of a prospective randomized phase 3 trial by the Eastern Cooperative

- Oncology Group (E1996). *Blood*. 2009; 114: 2393–2400. doi:10.1182/blood-2009-03-211797.
- [27] Ornstein MC, Mukherjee S, Sekeres MA. More is better: combination therapies for myelodysplastic syndromes. *Best Pract Res Clin Haematol*. 2015; 28: 22–31. doi:10.1016/j.beha.2014.11.002.
- [28] Bejar R, Steensma DP. Recent developments in myelodysplastic syndromes. *Blood*. 2014; 124: 2793–2803. doi:10.1182/blood-2014-04-522136.
- [29] Loiseau C, Ali A, Itzykson R. New therapeutic approaches in myelodysplastic syndromes: hypomethylating agents and lenalidomide. *Exp Hematol*. 2015; 43: 661–672. doi:10.1016/j.exphem.2015.05.014.
- [30] List A. New therapeutics for myelodysplastic syndromes. *Leuk Res*. 2012; 36: 1470–1474. doi: 10.1016/j.leukres.2012.08.010.
- [31] Carrancio S, Markovics J, Wong P, Leisten J, Castiglioni P, Groza MC, Raymon HK, Heise C, Daniel T, Chopra R, Sung V. An activin receptor IIA ligand trap promotes erythropoiesis resulting in a rapid induction of red blood cells and haemoglobin. *Br J Haematol*. 2014; 165: 870–882. doi:10.1111/bjh.12838.
- [32] Thepot S, Boehrer S, Seegers V, Prebet T, Beyne-Rauzy O, Wattel E, Delaunay J, Raffoux E, Hunault M, Jourdan E, Chermat F, Sebert M, Kroemer G, Fenaux P, Adès L; Groupe Francophone des Myelodysplasies (GFM). A phase I/II trial of Erlotinib in higher risk myelodysplastic syndromes and acute myeloid leukemia after azacitidine failure. *Leuk Res*. 2014; 38: 1430–1434. doi:10.1016/j.leukres. 2014.09.014.
- [33] Platzbecker U, Wong RS, Verma A, Abboud C, Araujo S, Chiou TJ, Feigert J, Yeh SP, Götze K, Gorin NC, Greenberg P, Kambhampati S, Kim YJ, Lee JH, Lyons R, Ruggeri M, Santini V, Cheng G, Jang JH, Chen CY, Johnson B, Bennett J, Mannino F, Kamel YM, Stone N, Dougherty S, Chan G, Giagounidis A. Safety and tolerability of eltrombopag versus placebo for treatment of thrombocytopenia in patients with advanced myelodysplastic syndromes or acute myeloid leukaemia: a multicentre, randomised, placebo-controlled, double-blind, phase 1/2 trial. *Lancet Haematol*. 2015; 2: e417–e426. doi: 10.1016/S2352-3026(15)00149-0.
- [34] Santini V. Life after hypomethylating agents in myelodysplastic syndrome: new strategies. *Curr Opin Hematol*. 2015; 22: 155–162. doi:10.1097/MOH.0000000000000117.
- [35] Santini V, Fenaux P. Treatment of myelodysplastic syndrome with thrombomimetic drugs. *Semin Hematol*. 2015; 52: 38–45. doi:10.1053/j.seminhematol. 2014.10. 005.
- [36] Borthakur G, Popplewell L, Boyiadzis M, Foran J, Platzbecker U, Vey N, Walter RB, Olin R, Raza A, Giagounidis A, Al-Kali A, Jabbour E, Kadia T, Garcia-Manero G, Bauman JW, Wu Y, Liu Y, Schramek D, Cox DS, Wissel P, Kantarjian H. Activity of the oral mitogen-activated protein kinase kinase inhibitor trametinib in RAS-mutant

- relapsed or refractory myeloid malignancies. *Cancer*. 2016; 122: 1871–1879. doi:10.1002/cncr.29986.
- [37] Garcia-Manero G, Fenaux P, Al-Kali A, Baer MR, Sekeres MA, Roboz GJ, Gaidano G, Scott BL, Greenberg P, Platzbecker U, Steensma DP, Kambhampati S, Kreuzer KA, Godley LA, Atallah E, Collins R Jr, Kantarjian H, Jabbour E, Wilhelm FE, Azarnia N, Silverman LR. ONTIME study investigators. Rigosertib versus best supportive care for patients with high-risk myelodysplastic syndromes after failure of hypomethylating drugs (ONTIME): a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2016; 17: 496–508. doi:10.1016/S1470-2045(16)00009-7.
- [38] Komrokji RS. Searching for a light at the end of the tunnel? Beyond hypomethylating agents in myelodysplastic syndromes. *Am Soc Clin Oncol Educ Book*. 2016; 35: e345–e352. doi:10.14694/EDBK_161221.
- [39] Mies A, Bulychева E, Rogulj IM, Hofbauer LC, Platzbecker U. Alterations within the Osteo-Hematopoietic Niche in MDS and their Therapeutic Implications. *Curr Pharm Des*. 2016; 22: 2323–2332.
- [40] Issa JP, Garcia-Manero G, Huang X, Cortes J, Ravandi F, Jabbour E, Borthakur G, Brandt M, Pierce S, Kantarjian HM. Results of phase 2 randomized study of low-dose decitabine with or without valproic acid in patients with myelodysplastic syndrome and acute myelogenous leukemia. *Cancer*. 2015; 121: 556–561. doi:10.1002/cncr.29085.
- [41] DiNardo CD, Daver N, Jabbour E, Kadia T, Borthakur G, Konopleva M, Pemmaraju N, Yang H, Pierce S, Wierda W, Bueso-Ramos C, Patel KP, Cortes JE, Ravandi F, Kantarjian HM, Garcia-Manero G. Sequential azacitidine and lenalidomide in patients with high-risk myelodysplastic syndromes and acute myeloid leukemia: a single arm, phase 1/2 study. *Lancet Haematol*. 2015; 2: e12–e20. doi:10.1016/S2352-3026(14)00026-X.