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Invited review

The lower risk MDS patient at risk of rapid progression

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ABSTRACT

Most patients with myelodysplastic syndrome (MDS) are classified at diagnosis as having a low/INT-I or INT-II/high risk disease, based on the classical International Prognostic Scoring System (IPSS) criteria. The low/INT-I risk patients are usually managed mildly with supportive care, including red blood cell (RBC) transfusions, erythroid stimulating agents (ESAs), other cytokines (G-CSF, platelet stimulating agents), as well as thalidomide and lenalidomide. Some patients receive immunosuppressive therapy, and iron chelation is indicated in iron overloaded patients. Aggressive approach (hypomethylating agents, chemotherapy and stem cell transplantation) is usually not applied in such patients.

Occasionally, we observe a "low risk" patient with rapid progression of disease and poor outcome. Can we identify demographic, clinical, laboratory, cellular-biological and/or molecular parameters that can predict "poor prognostic features" (PPF) in "low risk" MDS patients?

Clinical and laboratory parameters have been reported to be associated with poor prognosis, in addition to the known "classical" IPSS criteria. These include older age, male gender, poor performance status, co-morbidities, degree of anemia, low absolute neutrophile count (ANC) and platelet counts, RBC transfusion requirements, high serum ferritin, high LDH, bone marrow (BM) fibrosis, increased number of BM CD34+ cells and multi-lineage dysplasia. Certain immunophenotypes (low CD11b, high HLA-Dr, CD34, CD13 and CD45), clonal granulocytes, multiple chromosomal abnormalities, chromosomal instability, short telomeres and high telomerase activity were also reported as PPF. Studies of apoptosis identified Bcl-2 expression and high caspase 3 as PPF, while the reports on survivin expression have been confusing.

Recent exciting data suggest that methylation of p15 INK4b and of CTNNA1 (in 5q−), high level of methylation of other genes, absence of the TET2 mutation, down regulation of the lymphoid enhancer binding factor 1 (LEF1), mutation of the polycomb-associated gene ASXL1 and a specific 6-gene signature in gene expression profiling – are all associated with poor prognosis in MDS.

Do we have data suggesting a different treatment for "low risk" MDS patients displaying PPF? Two teams, the combined Nordic-Italian and the GFM groups have reported an improved survival with ESAs. The GFM has achieved prolonged survival with iron chelation. Recently, encouraging data with survival advantage in azacitidine-treated patients have been published, including a few INT-I patients. Finally, data suggest that low/INT-I MDS patients who undergo stem cell transplantation (SCT0 do better than INT-II/high risk patients).

In summary, some patients, classified as "low risk MDS" carry PPF. An appropriate therapeutic approach is indicated. Future updated classifications and prospective trials may lead to a better outcome.

Contents

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Patients are usually diagnosed as having myelodysplastic syndrome (MDS), based on well known recognized criteria [1–7]. This is commonly followed by prognostic staging, in order to plan the therapeutic approach. The commonly used prognostic system is the International Prognostic Scoring System (IPSS) [8]. The IPSS is based on three classical criteria, i.e. blast percentage in the bone marrow (BM), originally proposed by the FAB classification [9], cytogenetics (three types: favorable, poor, and intermediate), and the number of affected cytopenias. Using these criteria, each patient is given a score, according to which he is categorized as belonging to one of the four IPSS groups, i.e. low risk (LR), intermediate-I (INT-I), intermediate-II (INT-II) and high risk (HR) MDS.

Usually, the patients classified as LR and INT-I IPSS, are referred to as "lower risk MDS" (LrMDS) and offered relatively mild and conservative treatments. These include supportive care, such as red blood cell (RBC) transfusions [1,2,4–7], erythroid stimulating agents (ESAs) [10–12] and granulocyte – macrophage colony stimulating factors (GM-CSF) [11–13]. Recently, thrombopoietic agents [14], thalidomide [15] and lenalidomide have been introduced [16–18]. Some patients, especially those with hypocellular BM receive immunosuppressive therapy [19] and iron chelation is indicated in patients with iron overload [20,21]. More aggressive therapies such as hypomethylating agents [22–24], chemotherapy and stem cell transplantation (SCT) are usually not administered to patients with LrMDS [25,26].

Most LrMDS patients experience a slowly progressive disease with a long course [8,27]. However, occasionally, we encounter a patient, who is classified as having LrMDS, yet progresses rapidly, i.e. displays decreasing counts, complications, possible leukemic transformation, and a short survival.

Who are these "LrMDS" patients with rapid disease progression? Can we identify them at diagnosis upon classification or earlier? And if so, what are the additional poor prognostic features (PPF), in addition to the known classical IPSS criteria that are used to identify these patients? If and when we identify these "LrMDS" patients, who are probably not low risk, should we attempt an alternative therapeutic approach to achieve better outcome? Do we have data to support such an alternative treatment? This review will address these questions.

Table 1
Poor prognostic features (PPF) in lower risk MDS (LrMDS).

Class of markers	PPF	Refs.
Clinical/demographic	Older age	[29–32]
	Gender (male)	[32]
	Poor performance status	[29]
	Co-morbidities	[33]
	Transfusion needs	[29,34–37]
	Iron overload	[35–37]
	High serum ferritin	[37]
Lab values	Hb ↓	[28–30,37]
	PLT ↓	[29]
	ANC ↓	[30]
	High LDH	[27]
Bone marrow (BM)	BM fibrosis	[39]
	CD34+ clusters	[39–41]
	Multi-lineage dysplasia	[35,36,39–41]
	Normal/high cellularity	[42]
Immunophenotyping	↑ HLA-Dr	[43]
	Low CD11b	[43]
	↑ CD34	[44]
	↑ CD13	[44]
	↑ CD45	[44]
	Flow score	[45]
Clonality	Clonal granulocytes	[41]
Cytogenetics	Additional chromosomal abnormalities	[8,46]
	Chromosomal instability	[47]
Telomeres	Short telomeres	[48–51]
	High telomerase activity	[49,52–54]
Apoptosis	↑ BCl2	[56]
	↑ Caspase 3	[57]
	Survivin (???)	[58–60]
	Cell senescence (PIG INKa4)	[61]
Genetic/epigenetic/ molecular	P15 INK4b methylation	[62,63]
	CTNNA1	[64]
	High methylation	[65]
	Unmutated TET2	[66]
	LEF1 down regulation	[67]
	ASXL1 mutation	[68]
	6-gene poor risk signature	[69]

1. Poor prognostic features (PPF) in lower risk MDS – diagnostic tools

Studies, summarized in Table 1, have identified a list of parameters which are not used in the IPSS classification, but may have prognostic relevance. Starting with the simple clinical and demographic markers, which can be applied in every practice, one can review the original IMRAW/IPSS data. Kao et al. [28] re-examined the data on 816 MDS patients, which served for the original IPSS classification, and concluded that hemoglobin (Hb), but not neutrophile or platelet counts, was a reliable predictor for overall survival but not for time to leukemia conversion. Kantarjian at al. [29] analyzed the data on 1915 MDS patients, including 507 patients with primary MDS, treated at the MD Anderson Cancer Center. They found that older age, poor performance status, anemia, low platelet count and prior transfusion need – were all predictors of poor outcome. They also proposed a new risk model, based on these prognostic parameters. A recent Chinese prospective analysis on 435 patients, reported that age >60 year, ANC < 1000/mmc and Hb below 9 g/dl were PPF [30]. The Dusseldorf MDS registry confirmed older age, especially > 50yr, as PPF [31]. The German-Austrian MDS study group has recently summarized data on 897 patients with primary MDS and found in their retrospective analysis that older age (>66 year) and male gender were associated with poor prognosis [32]. The Austrian group has emphasized that co-morbidity, as used by the hematopoietic-stem cell transplantation-specific co-morbidity index (HCT-CI) and Charlson co-morbidity index (CCI), were additional PPF [33].

Although many felt for years that MDS patients who require regular blood transfusions represent a "poor prognostic" disease, Cazzola and Malcovati [34] demonstrated that transfusion dependent MDS patients do worse than MDS patients who are transfusion free. The same Pavia team later on, comparing their data on more than 400 MDS patients with the Dusseldorf registry, reported that transfusion dependence, iron overload, and multi-lineage (as opposed to uni-lineage) dysplasia predicted poor outcome [35,36]. Based on transfusion requirements they proposed an updated version of the IPSS system – WHO classification – based prognostic scoring system (WPSS). A recent retrospective analysis of 137 patients from the Czeck Republic, confirmed that transfusion dependence, Hb < 8 g/dl, and high serum ferritin level (>2000 mg/dl) were associated with poor prognosis [37]. Germing et al. [27], reported that high serum LDH can also serve as PPF.

Regarding more complex parameters, the Pavia team retrospectively reviewed the BM samples of 301 patients and concluded that BM fibrosis, the presence of CD34+ cell clusters (a reminder of the old "Abnormal Localization of Immature Progenitors, ALIP, as suggested by Tricot et al. [38]), and multi-lineage (as opposed to uni-lineage) dysplasia were associated with poor prognosis [39].

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This was confirmed by others [40,41]. Yue et al. [42] reported that hypocellular BM correlated with a favorable outcome, compared with normal or hypercellular BM.

Immunophenotyping, both for diagnosis and for predicting prognosis of MDS patients, has attracted several groups. We found that high expression of HLA-Dr, and low CD11b expression predicted early leukemic transformation [43]. More recently, high expression of CD34, CD13, and CD45 was reported as PPF [44]. Van de Loosdrecht et al. [45] studied the immunophenotyping of CD34+ BM cells from 50 MDS patients. They found high degree of aberration of myelomonocytic antigens to which they gave a flow score, correlated with prognosis. Clonal granulocytes were also reported to predict poor outcome [41].

Cytogenetics has always been a field for investigation in these diseases, for diagnosis, staging and for predicting prognosis. In the original IPSS classification multiple chromosomal abnormalities were considered as PPF [8]. This has recently been confirmed by the MD Anderson experience with 2743 patients [46]. Chromosomal instability, as could be expected, may also predict rapid disease progression [47].

Several studies have focused on telomeres. In summary, short telomeres, resulting in genetic instability [48–51], coupled with high telomerase activity (associated with a high proliferation rate) [49,52–54], both correlate with poor prognosis.

Apoptosis was found to be increased in early MDS, and decreased in later phases of the disease [55]. Several groups have studied apoptosis-associated markers as predictors of disease course. High expression of the anti-apoptotic protein BCL-2 [56], and of caspase 3 [57], predicted poor prognosis. The current data on the apoptosis inhibitor survivin are inconclusive [58–60]. Cell senescence, determined by P16 INKa4 expression, was also found to be PPF [61].

Recent epigenetic studies have generated exciting molecular data. Methylation of p15 INK4b was found to predict poor outcome [62,63]. In MDS patients with the 5q− abnormality, methylation of the promoter of CTNNA1 correlated with poor prognosis [64].

Shen et al. [65], have recently screened 24 MDS patients for promoter CpG methylation of 24 genes and identified aberrant hypermethylation at 10 genes. They then performed quantitative methylation analysis by bisulfite pyrosequencing of the identified genes in 317 patient samples and assessed relations between methylation and clinical outcome. While methylation frequencies of individualized genes ranged from 7 to 70%, by applying an individual methylation *z* score based on all genes for each patient, they found that higher methylation correlated with a shorter median survival (12.3 vs 17.5 m) and a shorter progression free survival (6.4 vs 14.9 m).

The TET2 mutation has recently gained attention. Kosmider et al. [66], have found that not only this genetic abnormality is common in MDS (23%), but also 5-year overall survival and 3-year leukemia-free survival were significantly shorter in patients carrying non-mutated TET2 compared with patients carrying the mutated gene: 18 vs 77, and 64 vs 89%, respectively.

Pellagatti et al. [67], studied the granulopoiesis regulator lymphoid enhancer binding factor 1, LEF1, and found that its down regulation was associated with poor prognosis. This group has also reported that ASXL1 mutation could serve as a molecular marker for disease progression [68].

Finally, the Stanford team has performed detailed molecular analysis with gene expression profile in CD34+ BM cells from MDS patients [69]. Studying 40,000 CDNAs chip arrays, they detected 1175 genes that were differentially expressed. Moreover, they identified six genes (RPL23, RPS4x, RPS25, RPS19, KLK3 and TPP2), four ribosomal and two enzymes, all over expressed in patients who later on progressed and transformed to acute leukemia, thus providing a "6-gene-poor-risk-signature".

2. Poor prognostic features (PPF) in lower risk MDS – therapeutic options

Once, a patient with LrMDS but with a predicted poor survival is identified, should he be treated differently? Do we have data to suggest an alternative approach?

Although phase III controlled trials have not been published, we do have little evidence suggesting that an active approach in some LrMDS patients may attenuate the course of disease.

Erythroid stimulating agents (ESAs) have been a pivotal anti-anemic treatment for LrMDS patients. We [70–73], as well as others, have suggested that ESAs confer immunomodulatory anti-neoplastic effect(s) as well. Several trials have suggested that ESAs-treated cancer [74] and MDS [75] patients benefit from prolonged survival compared with patients who do not receive ESAs. Recently, the Nordic group has compared the outcome of their 121 MDS patients treated with recombinant erythropoietin (EPO) and G-CSF, with the outcome of 237 untreated MDS patients from the Pavia Cohort [13]. Increased overall survival was observed in EPO + G-CSF treated LrMDS patients ($p = 0.033$), but not in patients with higher risk MDS. The GFM data are similar [76].

Iron overload, aggravated by repeated blood transfusions, has been associated with organ damage, suggesting poor prognosis [20,21]. But, has iron chelation therapy (ICT) resulted in a better prognosis? No prospective comparative data are available; however, two reports summarizing retrospective cohort data have suggested a survival benefit with ICT. The GFM analysis reported a positive survival impact of ICT in regularly transfused patients with MDS: the median survival of the whole MDS group was 63 months, with 115 month survival for the ICT-treated patients, compared with only 51 months ($p < 0.0001$) for MDS patients with no ICT [77]. A Canadian cohort series observed similar results [78].

As mentioned, hypomethylating agents such as decitabine and 5-azacitidine are usually offered to higher risk MDS patients [22,23]. The recently published AZA-001 trial reported survival advantage in 179 azacitidine-treated MDS patients, compared with the control group, treated with conventional therapy (chemotherapy, low dose cytarabine, or supportive treatment). The overall survival was 24.5 months for the azacitidine group but only 15.0 months for the conventional group ($p = 0.0001$) [24]. While most patients in the AZA-001 trial were higher risk MDS patients, analyzing the data reveals that 18 patients (5%) were in fact, MDS patients classified as INT-I. Although no subset analysis has been available on that subgroup, it is tempting to hypothesize that they also might benefit from such treatment.

Finally, can stem cell transplantation (SCT) improve survival in LrMDS with PPF? Again, no prospective trial comparing SCT with less aggressive approach in this patient subpopulation has been published. But, the recently published Italian – GITMO experience with SCT outcome (1990–2006) in MDS patients, reports on 5-year overall survival of 80%, 5-year probability of relapse of only 9% and 5 year transplant-related mortality of only 14% for refractory anemia (RA) patients, and 57, 22 and 39% respectively, for refractory cytopenia (RC or RCMD) patients. These results are better than those obtained with other patients (RAEB-1, RAEB-2, and AML post-MDS) [79]. This does not mean that SCT is recommended to all LrMDS patients with or without PPF. But it suggests, that if a more aggressive than the usually applied approach is considered – it might be relatively non-toxic, and sometimes successful [25,26,79].

In summary, some MDS patients, although classified as "lower risk MDS" (LrMDS), and probably offered a mild therapeutic approach – are not really "lower risk". Such patients, despite being grouped as LrMDS experience a rapid complicated progressive course with or without leukemic transformation and a dismal prog-

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nosis. A list of poor prognostic features (PPF) described in this review, including clinical and laboratory values, others such as BM parameters, and more recently established molecular markers – can identify those LrMDS patients, and predict rapid course and poor outcome. Although, no prospective convincing data are available, emerging information suggests that a more aggressive approach might improve the outcome. Obviously, future prospective comparative trials will have to test this hypothesis, and will probably lead both to a revised updated classification and to a more individualized treatment.

Conflict of interest

All authors have no conflict of interest to declare.

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References

[1] De Angelo DJ, Stone RM. Myelodysplastic syndromes: biology and treatment. In: Hoffman R, et al., editors. Hematology – basic principles and practice. 4th ed. Philadelphia: Elsevier; 2005. p. 1195–208.
[2] Mittelman M. The myelodysplastic syndromes – 1990. Isr J Med Sci 1990;26:468–78.
[3] Bowen D, Culligan D, Jowitt S, et al. Guidelines for the diagnosis and therapy of adult myelodysplastic syndromes. Br J Haematol 2003;120:187–2000.
[4] List AF, Pedersen-Bjergaard J, Garcia-Manero G. Myelodysplastic synsdromes. Hematology 2007 – Am Soc Hem Education Program Book, p. 392–411.
[5] Nimer SD, Hellstrom-Lindberg E, Cazzola M, Kroger N. Myelodysplastic syndromes. Hematology 2008 – Am Soc Hem Education Program Book, p. 43–67.
[6] Steensma DP, Sekeres MA, Leitch HA, Vickars LM. Myelodysplastic syndromes. Hematology 2009 – Am Soc Hem Education Program Book, p. 645–674.
[7] Tefferi A, Vardiman JW. Myelodysplastic syndromes. N Engl J Med 2009;361:1872–85.
[8] Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89:2079–98.
[9] Bennett JM, Catovski D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol 1982;51:189–99.
[10] Mittelman M, Floru S, Djaldetti M. Subcutaneous erythropoietin for treatment of refractory anemia in hematologic disorders. Blood 1992;80:841–2.
[11] Hellstrom-Lindberg E, Gulbrandsen N, Lindberg G, et al. A validated decision model for treating the anaemia of myelodysplastic syndromes with erythropoietin + granulocyte colony-stimulating factor: significant effects of on quality of life. Br J Haematol 2003;120:1037–46.
[12] Hellstrom-Lindberg E, Negrin R, Stein R, et al. Erythroid response to treatment with G-CSF plus erythropoietin for the anemia of patients with myelodysplastic syndrome: proposal for a preditive model. Br J Haematol 1997;99:344–51.
[13] Jadersten M, Malcovati L, Dybedal I, et al. Erythropoietin and granulocyte-colony stimulating factor treatment associated with improved survival in myelodysplastic syndrome. J Clin Oncol 2008;26:3607–13.
[14] Kantarjian H, Feneaux P, Sekeres MA, et al. Safety and efficacy of romiplostim in patients with low-risk myelodysplastic syndrome and thrombocytopenia. J Clin Oncol 2010;28:437–44.
[15] Raza A, Meyer P, Dutt D, et al. Thalidomide produces transfusion independence in log-standing refractory anemias of patients with myelodysplastic syndromes. Blood 2001;98:958–65.
[16] List A, Dewald G, Bennett J, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. N Engl J Med 2006;355:1456–65.
[17] Raza A, Reeves JA, Feldman EJ, et al. Phase 2 study of lenalidomide in transfusion-dependent, low-risk and intermediate-1-risk myelodysplastic syndromes with karyotypes other than deletion 5q. Blood 2008;111:86–93.
[18] Fenaux P, Giagounidis A, Selleslag D, et al. RBC transfusion independence and safety profile of lenalidomide 5 or 10 mg in pts with low- or Int-1-risk MDS with del 5q−: results from a randomized phase III trial (MDS-004). Blood 2009;114 [Abs # 944].
[19] Molldrem J, Leifer E, Bahceci E, et al. Anti thymocyte globulin to treatment of the bone marrow failure associated with myelodysplastic syndromes. Ann Intern Med 2002;137:156–63.
[20] Bennett JM. Consensus statement on iron overload in myelodysplastic syndromes. Am J Hematol 2008;83:859–61.
[21] Mittelman M, Lugassy G, Merkel D, et al. Iron chelation therapy in patients with myelodysplastic syndromes – consensus conference guidelines (For the MDS Israel Group and The Israel Society of Hematology). Isr Med Assoc J 2008;10:374–6.
[22] Gore SD, Baylin S, Sugar E, et al. Combined DNA methyl transferase and histone deacetylase inhibition in the treatment of myeloid neoplasms. Cancer Res 2006;66:6361–9.
[23] Silverman LR, McKenzie DR, Peterson BL, et al. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8241, 8921, and 9221 by the Cancer and Leukemia Group B. J Clin Oncol 2006;24:3895–903.
[24] Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomized, open-label, phase III study. Lancet Oncol 2009;10:223–32.
[25] de Witte T, Suciu S, Verhoef G, et al. Intensive chemotherapy followed by allogeneic or autologous stem cell transplantation for patients with myelodysplastic syndromes (MDSs) and acute myeloid leukemia following MDS. Blood 2001;98:2326–31.
[26] Deeg HJ, Storer B, Slattery JT, et al. Conditioning with targeted busulfan and cyclophosphamide for hemopoietic stem cell transplantation from related and unrelated donors in patients with myelodysplastic syndrome. Blood 2002;100:1201–7.
[27] Germing U, Hildebrandt B, Pfeilstocker M, et al. Refinement of the International Prognostic Scoring system (IPSS) by including LDH as an additional prognostic variable to improve risk assessment in patients with primary myelodysplastic syndromes (MDS). Leukemia 2005;19:2223–31.
[28] Kao JM, McMillan A, Greenberg PL. International MDS risk analysis workshop (IMRAW)/IPSS reanalyzed: impact of cytopenias on clinical outcomes in myelodysplastic syndromes. Am J Hematol 2008;83:765–70.
[29] Kantajian H, O'Brien S, Ravandi F, et al. Proposal for a new risk model in myelodysplastic syndrome that accounts for events not considered in the original International Prognostic Scoring System. Cancer 2008;113: 1351–61.
[30] Wang XO, Ryder J, Gross SA, et al. Prospective analysis of clinical and cytogenetic features of 435 cases of MDS diagnosed using the WHO (2001) classification: a prognostic scoring system for predicting survival in RCMD. Int J Hematol 2009;90:361–9.
[31] Kuendgen A, Strupp C, Aivado M, et al. Myelodysplastic syndromes in patients younger than age 50. J Clin Oncol 2006;24:5358–65.
[32] Nosslinger T, Tuchler H, Germing U, et al. Prognostic impact of age and gender in 897 untreated patients with primary myelodysplastic syndromes. Ann Oncol 2010;21:120–5.
[33] Sperr WR, Wimazal F, Kundi M, et al. Comorbidity as prognostic variable in MDS: comparative evaluation of the HCT-Ci and CCI in a core dataset of 149 patients of the Austrian MDS Study Group. Ann Oncol 2010;21:114–9.
[34] Cazzola M, Malcovati L. Myelodysplastic syndromes – coping with ineffective hematopoiesis. N Engl J Med 2005;352:536–8.
[35] Malcovati L, Della Porta M, Pascutto C, et al. Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision-making. J Clin Oncol 2005;23:7594–603.
[36] Malcovati L, Germing U, Kuendgen A, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. J Clin Oncol 2007;25:3503–10.
[37] Cermak J, Kacirkova P, Mikulenkova D, Michalova K. Impact of transfusion dependency on survival in patients with early myelodysplastic syndrome without excess blasts. Leuk Res 2009;33:1469–74.
[38] Tricot G, De Wolf-Peeters C, Vietinck R, Verwilghen RL. Bone marrow histology in myelodysplastic syndromes. II. Prognostic value of abnormal localization of immature precursors in MDS. Br J Haematol 1984;58:217–25.
[39] Della Porta MG, Malcovati L, Boveri E, et al. Clinical relevance of bone marrow fibrosis and CD34-positive cell clusters in primary myelodysplastic syndromes. J Clin Oncol 2009;27:754–62.
[40] Orazi A. Histopathology in the diagnosis and classification of acute myeloid leukemia, myelodysplastic syndromes, and myelodysplastic/myeloproliferative diseases. Pathobiology 2007;74:97–114.
[41] Cermak J, Belickova M, Krejcova H, et al. The presence of clonal cell subpopulations in peripheral blood and bone marrow of patients with refractory cytopenia with multilineage dysplasia but not in patients with refractory anemia may reflect a multistep pathogenesis of myelodysplasia. Leuk Res 2005;29:371–9.
[42] Yue G, Hao S, Fadare O, et al. Hypocellularity in myelodysplastic syndrome is an independent factor which predicts a favorable outcome. Leuk Res 2008;32:553–8.
[43] Mittelman M, Karcher DS, Kammerman LA, Lessin LS. High Ia (HLA-DR) and low CD11b (Mo1) expression may predict early conversion to leukemia in myelodysplastic syndromes. Am J Hematol 1993;43:165–71.
[44] Lorand-Metz I, Califani SM, Ribeiro E, et al. The prognostic value of maturation-associated phenotypic abnormalities in myelodysplastic syndromes. Leuk Res 2008;32:205–7.
[45] van de Loosdrecht AA, Westers TM, Westra AH, et al. Identification of distinct prognostic subgroups in low- and intermediate-1-risk myelodysplastic syndromes by flowcytometry. Blood 2008;111:1067–77.
[46] Kantarjian H, O'Brien S, Ravandi F, et al. The heterogenous prognosis of patients with myelodysplastic syndrome and chromosome 5 abnormalities: how does it relate to the original lenalidomide experience in MDS? Cancer 2009;115:5202–9.
[47] Helig CE, Loffler H, Mahlknecht U, et al. Chromosomal instability correlates with poor outcome in patients with myelodysplastic syndromes irrespectively of the cytogenetic risk group. J Cell Mol Med 2009;(September) [on line].
[48] Ohyashiki JH, Ohyashiki K, Fujimura T, et al. Telomere shortening associated with disease evolution patterns in myelodysplastic syndromes. Cancer Res 1994;54:3557–60.

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[49] Ohyashiki K, Iwama H, Yahata N, et al. Telomere dynamics in myelodysplastic syndromes and acute leukemic transformation. Leuk Lymphoma 2001;42:291–9.
[50] Sieglova Z, Zilovcova S, Cermak J, et al. Dynamics of telomere erosion and its association with genome instability in myelodysplastic syndromes (MDS) and acute myelogenous leukemia arising from MDS: a marker of disease prognosis? Leuk Res 2004;28:1013–21.
[51] Fern L, Pallis M, Ian Carter G, et al. Clonal haemopoiesis may occur after conventional chemotherapy and is associated with accelerated telomere shortening and defects in the NQO1 pathway; possible mechanisms leading to an increased risk of t-AML/MDS. Br J Haematol 2004;126:63–71.
[52] Li B, Yang J, Andrews C, et al. Telomerase activity in preleukemia and acute myelogenous leukemia. Leuk Lymphoma 2000;36:579–87.
[53] Gurkan E, Tanriverdi K, Baslamisli F. Telomerase activity in myelodysplastic syndromes. Leuk Res 2005;29:1131–9.
[54] Fu C, Chen Z. Telomerase activity in myelodysplastic syndrome. Chin Med J 2002;115:1475–8.
[55] Raza A, Gezer S, Mundle S, et al. Apoptosis in bone marrow biopsy sample involving stromal and hematopoietic cells in 50 patients with myelodysplastic syndromes. Blood 1995;86:268.
[56] Davis RE, Greenberg PL. Bcl-2 expression by myeloid precursors in myelodysplastic syndromes: relation to disease progression. Leuk Res 1998;22:767–77.
[57] Ohshima K, Karube K, Shimazaki K, et al. Imbalance between apoptosis and telomerase activity in myelodysplastic syndromes: possible role in ineffective hemopoiesis. Leuk Lymphoma 2003;44:1339–46.
[58] Invernizi R, Travaglino E, Klersy C, et al. Survivin expression in acute leukemias and myelodysplastic syndromes. Leuk Lymphoma 2004;45:2229–37.
[59] Yamamoto K, Abe S, Nakagawa Y, et al. Expression of IAP family proteinsin myelodysplastic syndromes transforming to overt leukemia. Leuk Res 2004;28:1203–11.
[60] Gianelli U, Fracchiolla NS, Cortelezzi A, et al. Survivin expression in "low-risk" and "high-risk" myelodysplastic syndromes. Ann Hematol 2007;86:185–9.
[61] Wang YY, Cen JN, He J, et al. Accelerated cellular senescence in myelodysplastic syndrome. Exp Hematol 2009;37:1310–7.
[62] Quesnel B, Guillerm G, Vereeccque R, et al. Methylation of p15 (INK4b) gene in myelodysplastic syndromes is frequent and acquired during disease progression. Blood 1998;91:2985–90.
[63] Kim M, Oh B, Kim SY, et al. p15INK4b methylation correlates with thrombocytopenia, blast percentage, and survival in myelodysplastic syndromes in a dose dependent manner: quantitation using pyrosequencing study. Leuk Res 2009;(September) [on line].
[64] Ye Y, McDevitt MA, Guo M, et al. Progressive chromatin repression and promoter methylation of CTNNA1 associated with advanced myeloid malignancies. Cancer Res 2009;69:8482–90.
[65] Shen L, Kantarjian H, Guo Y, et al. DNA methylation predicts survival and response to therapy in patients with myelodysplastic syndromes. J Clin Oncol 2010;28:605–13.
[66] Kosmider O, Gelsi-Boyer V, Cheok M, et al. TET2 mutation is an independent favorable prognostic factor in myelodysplastic syndromes (MDSs). Blood 2009;114:3285–91.
[67] Pellagatti A, Marafioti T, Paterson JC, et al. Marked down regulation of the granulopoiesis regulator LEF1 is associated with disease progression in the myelodysplastic syndromes. Br J Haematol 2009;146:86–90.
[68] Boultwood J, Perry J, Pellagatti A, et al. Frequent mutations of the polycomb-associated gene ASXL1 in myelodysplastic syndromes and acute myeloid leukemia. Blood 2009;114(Suppl.) [Am Soc Hem (ASH)].
[69] Sridhar K, Ross DT, Tibshirani R, et al. Relationship of differential gene expression profiles in CD34+ myelodysplastic syndrome marrow cells to disease subtype and progression. Blood 2009;114:4847–58.
[70] Mittelman M, Zeidman A, Kanter P, Katz O, Oster H, Rund D, et al. Erythropoietin has an anti-myeloma effect – a clinical observation supported by animal studies. Eur J Haematol 2004;72:155–65.
[71] Mittelman M, Neumann D, Peled A, Kanter P, Haran-Ghera N. Erythropoietin induces tumor regression and anti-tumor immune responses in murine myeloma models. Proc Natl Acad Sci USA 2001;98:5181–6.
[72] Prutchi-Sagiv S, Golishevsky N, Oster HS, Katz O, Cohen A, Naparstek E, et al. Erythropoietin treatment in advanced multiple myeloma is associated with improved immunological functions: could it be beneficial in early disease? Br J Haematol 2006;135:660–72.
[73] Prutchi-Sagiv S, Golishevski N, Katz O, Oster HS, Naparstek E, Hoffman M, et al. T-cell abnormalities in patients with myelodysplastic syndromes: improved immunological functions in patients treated with recombinant erythropoietin. Blood 2006;108(756a) [Abs # 2675].
[74] Littlewood TJ, Bajetta E, Nortier JW, et al. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. J Clin Oncol 2001;19:2865–74.
[75] Wallvik J, Stenke L, Bernell P, et al. Serum erythropoietin (EPO) levels correlate with survival and independently predict response to EPO treatment in patients with myelodysplastic syndromes. Eur J Haematol 2002;68:180–5.
[76] Park S, Grabar S, Kelaidi C, et al. Predictive factors of response and survival in myelodysplastic syndrome treated with erythropoietin and G-CSF: the GFM experience. Blood 2008;111:574–82.
[77] Rose C, Brechignac S, Vassilief D, et al. Positive impact of iron chelation therapy (CT) on survival in regularly transfused MDS patients. A prospective analysis by the GFM. Leuk Res in press [Blood 2007;110(Suppl.):80–81 (abstract)].
[78] Leitch HA, Leger CS, Goodman TA, et al. Improved survival in patients with myelodysplastic syndrome receiving iron chelation therapy. Clin Leuk 2008;2:205–11.
[79] Alessandrino EP, Della Porta MG, Bacigalupo A, et al. WHO classification and WPSS predict post transplantation outcome in patients with myelodysplastic syndrome: a study from the Gruppo Italiano Trapianto di Midollo Osseo (GITMO). Blood 2008;112:895–902.

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