guiding tyrosine kinase inhibitor therapy in patients with chronic myeloid leukemia. Cancer n/a. doi: 10.1002/cncr.25717.
8. Jabbour E, Jones D, Kantarjian HM, O'Brien S, Tam C, Koller C, et al. Long-term outcome of patients with chronic myeloid leukemia treated with second-generation tyrosine kinase inhibitors after imatinib failure is predicted by the in vitro sensitivity of BCR-ABL kinase domain mutations. Blood. 2009;114(10):2037-43.
9. Baccarani M, Cortes J, Pane F, Niederwieser D, Saglio G, Apperley J, et al. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. J Clin Oncol. 2009;27(35):6041-51.
10. Kantarjian H, Shah NP, Hochhaus A, Cortes J, Shah S, Ayala M, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2010;362(24):2260-70.
11. Saglio G, Kim DW, Issaragrsisil S, le Coutre P, Etienne G, Lobo C, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med. 2010;362(24):2251-9.
12. Muller MC, Cortes JE, Kim DW, Druker BJ, Erben P, Pasquini R, et al. Dasatinib treatment of chronic-phase chronic myeloid leukemia: analysis of responses according to preexisting BCR-ABL mutations. Blood. 2009;114(24):4944-53.
13. Hughes T, Saglio G, Branford S, Soverini S, Kim DW, Muller MC, et al. Impact of baseline BCR-ABL mutations on response to nilotinib in patients with chronic myeloid leukemia in chronic phase. J Clin Oncol. 2009;27(25):4204-10.
14. Quintas-Cardama A, Kantarjian HM, O'Brien S, Ravandi F, Ferrajoli A, Garcia-Manero G, et al. Association of pleural effusion and bleeding in patients with chronic myelogenous leukemia receiving dasatinib. Blood. 2008;11:112 (Abstract 2112).
15. Willis SG, Lange T, Demehri S, Otto S, Crossman L, Niederwieser D, et al. High-sensitivity detection of BCR-ABL kinase domain mutations in imatinib-naïve patients: correlation with clonal cytogenetic evolution but not response to therapy. Blood. 2005;106(6):2128-37.
16. Hanfstein B, Muller MC, Kreil S, Ernst T, Schenk T, Lorentz C, et al. Dynamics of mutant BCR-ABL positive clones after cessation of tyrosine kinase inhibitor therapy. Haematologica. 2011;96(3):360-6.
17. Cortes J, Jabbour E, Kantarjian H, Yin CC, Shan J, O'Brien S, et al. Dynamics of BCR-ABL kinase domain mutations in chronic myeloid leukemia after sequential treatment with multiple tyrosine kinase inhibitors. Blood. 2007;110(12):4005-11.
18. Gambacorti-Passerini C, Kim DW, Kantarjian HM, Brummerdorf TH, Dyagil I, Griskevicius L, et al. An ongoing phase 3 study of bosutinib (SKI-606) versus imatinib in patients with newly diagnosed chronic phase chronic myeloid leukemia. Blood. 2010;21:116 (Abstract 208).
19. Cortes J, Talpaz M, Bixby D, Deininger M, Shah N, Flinn IW, et al. A phase 1 trial of oral ponatinib (AP24534) in patients with refractory chronic myelogenous leukemia (CML) and other hematologic malignancies: emerging safety and clinical response findings. Blood. 2010;21:116 (Abstract 210).

Risk assessment in myelodysplastic syndromes and myelodysplastic/myeloproliferative neoplasms

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Myelodysplastic syndromes (MDS)[1] are included in the World Health Organization (WHO) classification of the myeloid neoplasms[2] together with myeloproliferative neoplasms (MPN), myelodysplastic/myeloproliferative neoplasms (MDS/MPN) and acute myeloid leukemia (AML).

Classifications of myelodysplastic syndromes

MDS were defined and classified in 1982 by the FAB group.[3] The FAB classification included five categories: refractory anemia (RA), RA with ring sideroblasts (RARS), RA with excess of blasts (RAEB), RAEB "in transformation" (RAEB-t), and chronic myelomonocytic leukemia (CMML). This latter is now considered as a myelodysplastic/myeloproliferative neoplasm, while RAEB-t is now classified as AML.[4] Figure 1A provides a Kaplan-Meier analysis of overall survival in MDS patients classified according to the FAB classification. It is apparent that, from a prognostic point of view, this classification was essentially able to identify two risk groups based on the absence or presence of blast excess.

In 2001 the World Health Organization (WHO) classification was developed.[5] This classification,[6] carries relevant prognostic information. Figure 1B provides a Kaplan-Meier analysis of overall survival in MDS patients classified according to the 2008 WHO classification. It is apparent that, among patients without an excess of marrow blasts, the presence of bone marrow multilineage dysplasia is associated with a significantly worse prognosis compared to unilineage dysplasia. Despite some concern regarding the reproducibility of the assessment of multilineage dysplasia, its prognostic value was confirmed in different independent cohorts of patients in both retrospective[7] and prospective[8] studies, clearly indicating that this parameter must be included in the prognostic evaluation of MDS patients. Survival curves of Figure 1 support the conclusion that nowadays clinical decision making in MDS cannot rely upon the FAB classification and must be based on the WHO classification.[9]

Prognostic scoring systems for myelodysplastic syndromes

To overcome the limitations of the FAB classification, Greenberg and co-workers developed the International Prognostic Scoring System (IPSS).[10] Although widely adopted, this scoring system does not consider the severity of anemia, in particular transfusion dependency,[1] which represents one of the most important negative prognostic factors in MDS. Furthermore, it underestimates the negative impact of poor cytogenetics, especially relative to blast count.

The introduction of the WHO classification, excluding patients with 20% blasts or more and those with CMML from the category of MDS, considerably modified the composition of the MDS population and demanded a refinement of prognostic factors in patients diagnosed according to the WHO criteria. We found that WHO categories, cytogenetic pattern and transfusion dependency were the most powerful prognostic indicators, and developed a prognostic model that accounted for these parameters.[11] This WHO

classification-based prognostic scoring system (WPSS) was found to be able to classify patients into five risk groups showing different survivals and probabilities of leukemic evolution. Figure 2A provides survival curves of MDS patients stratified according to their WPSS risk. The WPSS was based on a time dependent model and, therefore, is a dynamic scoring system that can be applied to predict survival and leukemia progression at any time during follow up, and can, therefore, be used to implement risk-adapted treatment strategies.[12] Figure 2B provides time-dependent Kaplan-Meier curves.

More recently, Kantarjian and co-workers[13] also highlighted the limitations of the IPSS and analyzed 1,915 patients to propose and validate a new risk model for MDS. This model (MD Anderson Prognostic Scoring System, MPSS) refines the prognostic precision of the IPSS and is applicable to all patients with primary or secondary MDS and to those with CMML. However, the MPSS ignores the WHO classification and includes a bone marrow blast range up to 29% (i.e., up to values currently considered as diagnostic of AML). In addition, it takes into account poor cytogenetic abnormalities exclusively.

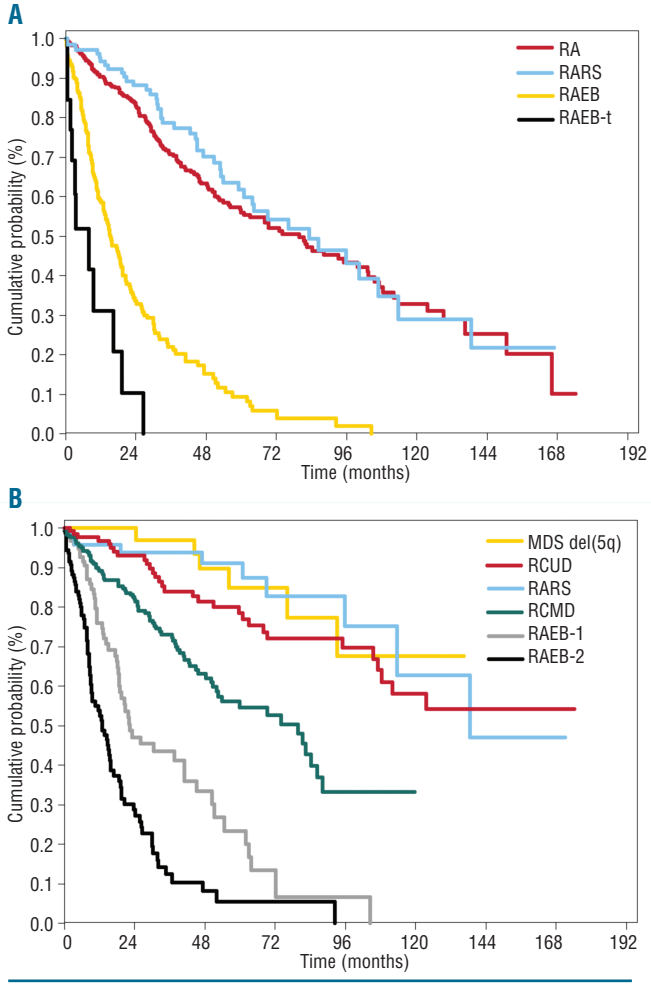

Figure 1. Kaplan-Meier survival curves of 943 patients diagnosed with MDS according to the 2008 WHO criteria at the Department of Hematology Oncology, Fondazione IRCCS Policlinico San Matteo & University of Pavia, Pavia, Italy. (A) Patients grouped according to the FAB classification (patients with 5-19% bone marrow blasts and Auer rods were classified as RAEB-t). (B) Patients grouped according to the WHO classification. Patients classified as RA or RARS according to the FAB classification (panel A) are split here (panel B) into two subgroups with different survival based on the presence of unilineage [RCUD or RARS, including also MDS with del(5q)] or multilineage dysplasia (RCMD). Moreover, patients with RAEB (panel A) are also split here into two subgroups according to their blast percentage (5-9% in RAEB-1, 10-19% in RAEB-2).

Novel MDS-related prognostic factors: the coming era of somatic mutations of genes involved in the pathogenesis of myeloid neoplasms

Clearly there are several other MDS-related prognostic factors that might be used for prognostication, including flow cytometry parameters.[14-17]

Bone marrow biopsy provides extremely useful diagnostic and prognostic information regarding cellularity, fibrosis, and CD34-positive cell topography.[18] Bone marrow fibrosis identifies a distinct subgroup of MDS with multilineage dysplasia, high transfusion requirement and poor prognosis, while the presence of $CD34^+$ cell clusters is an independent risk factor for progression to acute leukemia.[18] Bone marrow fibrosis can be included into the WPSS.[12]

However, the available evidence indicates that advances

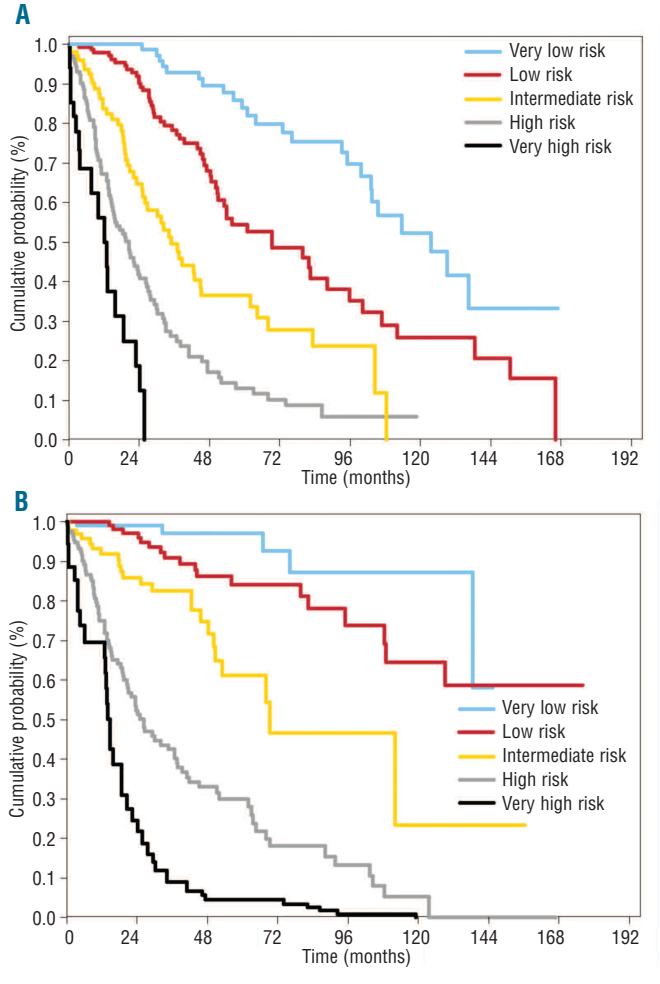

Figure 2. Survival of 644 MDS patients diagnosed according to the WHO criteria at the Department of Hematology Oncology, Fondazione IRCCS Policlinico San Matteo & University of Pavia, Pavia, Italy, and stratified according to the WPSS. (A) Kaplan-Meier curves. (B) Kaplan-Meier time-dependent curves of MDS patients grouped according to the dynamic WPSS.

in our ability to define the prognosis of the individual patient with MDS will likely be made possible by a better understanding of the molecular basis of these neoplasms. Somatic mutations of *TET2* represent a marker of clonal proliferation in MDS,[19] but do not appear to be associated with any WHO category or to have prognostic relevance.[20] By contrast, mutations of *EZH2*[21] or *ASXL1*[22] are found in patients with advanced disease, and point mutations of *TP53*[23] or *IDH1/IDH2*[24] appear to be associated with leukemic evolution. Recently, Ebert and co-workers[25] have studied the clinical impact of point mutations in a cohort of 438 patients with MDS. They found that mutations of *RUNX1*, *TP53*, and *ASXL1* (present in 26.3% of samples) were independent predictors of decreased survival. These observations suggest that incorporation of somatic mutations may add important information to the risk stratification systems currently used in clinical practice. It is also possible that multilineage dysplasia, a morphological parameter that is extremely important from a prognostic point of view as shown in Figure 1B, can be better defined using molecular criteria.

Prognostic relevance of comorbidities in MDS patients

Most patients with MDS are elderly and typically have co-morbid diseases.[26,27] Several scoring models are currently available for taking into account comorbidity in a clinical setting. Their *leit motiv* is that the overall survival of patient populations decreases as the burden of comorbid illness increases, but, as underlined by Geraci *et al.*,[28] most of them fail to provide information on the underlying mechanisms, e.g. on how a given comorbidity leads to reduced survival.

The aim of our study which is reported in this issue of the Journal[29] was to develop a scoring model that accounts for comorbidities commonly found in MDS patients and to establish how these comorbid conditions affect survival. The findings of this study indicate that cardiac disease is the most important comorbid condition from a prognostic point of view, and that the negative interaction between this comorbid condition and severe anemia has a profound impact on survival of MDS patients, particularly in the lower risk groups according to disease-related criteria. In higher risk groups, in fact, severe anemia more likely signifies clonally advanced and biologically more aggressive disease.[30]

In addition, the MDS-specific comorbidity index (MDS-CI) considerably improves the prognostic stratification of MDS patients classified according to the WPSS. For instance, the median survival of patients belonging to the WPSS intermediate risk group may range from about one to more than eight years based on MDS-CI. Thus, our current approach to risk stratification in MDS includes assessment of WPSS to account for disease-related prognostic factors, MDS-CI to account for extra-hematologic comorbidities specifically related to MDS, and the hematopoietic cell transplantation (HCT)-specific comorbidity index (HCT-CI)[31] for decision making concerning allogeneic transplantation.

Risk assessment in myelodysplastic/myeloproliferative neoplasms: the case of chronic myelomonocytic leukemia

Myelodysplastic/myeloproliferative neoplasms comprise chronic myelomonocytic leukemia, atypical chronic myeloid leukemia (*BCR-ABL1* negative), juvenile myelomonocytic leukemia (JMML), and myelodysplastic/myeloproliferative neoplasms, unclassifiable.[4] Attempts to define prognostic models have been made in CMML and JMML,[32] and here I will consider the former condition.

In the 2008 WHO classification, CMML is subdivided into two categories: a) CMML-1, a condition with less than 5% blasts (including promonocytes) in the peripheral blood and less than 10% in the bone marrow; b) CMML-2, a condition with 5-19% blasts in the peripheral blood or 10-19% in the bone marrow, or in any case associated with the presence of Auer rods.

Some years ago, a study at the MD Anderson showed that anemia, presence of circulating immature myeloid cells, absolute lymphocyte count, and percentage of marrow blasts were independent prognostic factors in CMML, and these parameters were used to generate a prognostic score.[33] More recently, these authors showed that the MPSS is a useful risk assessment tool not only for MDS but also for CMML.[34]

In this issue of the journal, Sanz and co-workers[35] report on a study aimed to evaluate the prognostic impact of cytogenetic abnormalities in 414 patients with CMML included in the database of the Spanish Registry of Myelodysplastic Syndromes. Three cytogenetic risk categories were identified: low risk (normal karyotype or loss of Y chromosome as a single anomaly), high risk (presence of trisomy 8 or abnormalities of chromosome 7, or complex karyotype), and intermediate risk (all other abnormalities). Additional prognostic factors for survival included anemia, leukocytosis, thrombocytopenia and blast excess, while the only factor independently associated with leukemic transformation was leukocytosis. Validating these observations in different patient populations and then translating them into a scoring system may provide clinicians with a useful prognostic model. A recent study indicates that somatic mutations of a number of genes including *TET2*, *CBL*, *KRAS*, *NRAS*, *JAK2*, and *RUNX1* are found in most patients with CMML, suggesting that they may also have prognostic relevance.[36]

Conclusions

Analysis of the available evidence clearly indicates that three parameters retain independent prognostic relevance in MDS and CMML: 1) hemoglobin level; 2) proportion of marrow blasts; and 3) cytogenetic abnormalities.

Severe anemia may derive from ineffective erythropoiesis (excessive apoptosis of immature red cells) in low-risk MDS, where it can interact with cardiac disease, or from impaired erythroid differentiation in high-risk MDS and CMML. Defining the molecular basis of both mechanisms of anemia might allow novel molecular prognostic markers and perhaps innovative therapeutic tools. Blast excess indicates impaired differentiation of hematopoietic progenitors and, therefore, reflects bone marrow failure. Finally, cytogenetic abnormalities reflect different genetic mechanisms responsible for clonal proliferation and leukemic transformation.

In MDS, the distinction between unilineage (in most instances erythroid) and multilineage dysplasia is of crucial importance for risk assessment, and hopefully will be soon made easier by molecular parameters.

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References

1. Cazzola M, Malcovati L. Myelodysplastic syndromes--coping with ineffective hematopoiesis. N Engl J Med. 2005;352(6):536-8.
2. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon: IARC, 2008.
3. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, et al. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol. 1982;51(2):189-99.
4. Reiter A, Invernizzi R, Cross NC, Cazzola M. Molecular basis of myelodysplastic/myeloproliferative neoplasms. Haematologica. 2009;94(12):1634-8.
5. Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. Blood. 2002;100(7):2292-302.
6. Brunning RD, Orazi A, Germing U, Le Beau MM, Porwit A, Bauman I, et al. Myelodysplastic syndromes/Neoplasms, overview. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon: IARC, 2008:88-93.
7. Malcovati L, Porta MG, Pascutto C, Invernizzi R, Boni M, Travaglino E, 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(30):7594-603.
8. Germing U, Strupp C, Kuendgen A, Isa S, Knipp S, Hildebrandt B, et al. Prospective validation of the WHO proposals for the classification of myelodysplastic syndromes. Haematologica. 2006;91:1596-604.
9. Malcovati L, Della Porta MG, Cazzola M. Predicting survival and leukemic evolution in patients with myelodysplastic syndrome. Haematologica. 2006;91(12):1588-90.
10. Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood. 1997;89(6):2079-88.
11. Malcovati L, Germing U, Kuendgen A, Della Porta MG, Pascutto C, Invernizzi R, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. J Clin Oncol. 2007;25(23):3503-10.
12. Cazzola M, Malcovati L. Prognostic classification and risk assessment in myelodysplastic syndromes. Hematol Oncol Clin North Am. 2010;24(2):459-68.
13. Kantarjian H, O'Brien S, Ravandi F, Cortes J, Shan J, Bennett JM, 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(6):1351-61.
14. Malcovati L, Della Porta MG, Lunghi M, Pascutto C, Vanelli L, Travaglino E, et al. Flow cytometry evaluation of erythroid and myeloid dysplasia in patients with myelodysplastic syndrome. Leukemia. 2005;19(5):776-83.
15. Della Porta MG, Malcovati L, Invernizzi R, Travaglino E, Pascutto C, Maffioli M, et al. Flow cytometry evaluation of erythroid dysplasia in patients with myelodysplastic syndrome. Leukemia. 2006;20(4):549-55.
16. Ogata K, Della Porta MG, Malcovati L, Picone C, Yokose N, Matsuda A, et al. Diagnostic utility of flow cytometry in low-grade myelodysplastic syndromes: a prospective validation study. Haematologica. 2009;94(8):1066-74.
17. van de Loosdrecht AA, Alhan C, Bene MC, Della Porta MG, Drager AM, Feuillard J, et al. Standardization of flow cytometry in myelodysplastic syndromes: report from the first European LeukemiaNet working conference on flow cytometry in myelodysplastic syndromes. Haematologica. 2009;94(8):1124-34.
18. Della Porta MG, Malcovati L, Boveri E, Travaglino E, Pietra D, Pascutto C, et al. Clinical relevance of bone marrow fibrosis and CD34-positive cell clusters in primary myelodysplastic syndromes. J Clin Oncol. 2009;27(5):754-62.
19. Langemeijer SM, Kuiper RP, Berends M, Knops R, Aslanyan MG, Massop M, et al. Acquired mutations in TET2 are common in myelodysplastic syndromes. Nat Genet. 2009;41(7):838-42.
20. Smith AE, Mohamedali AM, Kulasekararaj A, Lim Z, Gaken J, Lea NC, et al. Next-generation sequencing of the TET2 gene in 355 MDS and CMML patients reveals low-abundance mutant clones with early origins, but indicates no definite prognostic value. Blood. 2010;116(19):3923-32.
21. Nikoloski G, Langemeijer SM, Kuiper RP, Knops R, Massop M, Tonnissen ER, et al. Somatic mutations of the histone methyltransferase gene EZH2 in myelodysplastic syndromes. Nat Genet. 2010;42(8):665-7.
22. Boultwood J, Perry J, Pellagatti A, Fernandez-Mercado M, Fernandez-Santamaria C, Calasanz MJ, et al. Frequent mutation of the polycomb-associated gene ASXL1 in the myelodysplastic syndromes and in acute myeloid leukemia. Leukemia. 2010;24(5):1062-5.
23. Jadersten M, Saft L, Pellagatti A, Gohring G, Wainscoat JS, Boultwood J, et al. Clonal heterogeneity in the 5q- syndrome: p53 expressing progenitors prevail during lenalidomide treatment and expand at disease progression. Haematologica. 2009;94(12):1762-6.
24. Cazzola M. IDH1 and IDH2 mutations in myeloid neoplasms--novel paradigms and clinical implications. Haematologica. 2010;95(10):1623-7.
25. Bejar R, Stevenson K, Abdel-Wahab O, Marie M, Lin K, McAuley JR, et al. Point mutations in myelodysplastic syndromes are associated with clinical features and are independent predictors of overall survival [abstract]. Blood. 2010;116(21):136.
26. Zipperer E, Pelz D, Nachtkamp K, Kuendgen A, Strupp C, Gattermann N, et al. The hematopoietic stem cell transplantation comorbidity index is of prognostic relevance for patients with myelodysplastic syndrome. Haematologica. 2009;94(5):729-32.
27. Della Porta MG, Malcovati L. Clinical relevance of extra-hematologic comorbidity in the management of patients with myelodysplastic syndrome. Haematologica. 2009;94(5):602-6.
28. Geraci JM, Escalante CP, Freeman JL, Goodwin JS. Comorbid disease and cancer: the need for more relevant conceptual models in health services research. J Clin Oncol. 2005;23(30):7399-404.
29. Della Porta MG, Malcovati L, Strupp C, Ambaglio I, Kuendgen A, Zipperer E, et al. Risk stratification based on both disease status and extra-hematologic comorbidities in patients with myelodysplastic syndrome. Haematologica. 2011;96(3):441-9.
30. Pardanani A, Tefferi A. Prognostic relevance of anemia and transfusion dependency in myelodysplastic syndromes and primary myelofibrosis. Haematologica. 2011;96(1):8-10.
31. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2005;106(8):2912-9.
32. Bresolin S, Zecca M, Flotho C, Trentin L, Zangrando A, Sainati L, et al. Gene expression-based classification as an independent predictor of clinical outcome in juvenile myelomonocytic leukemia. J Clin Oncol. 2010;28(11):1919-27.
33. Onida F, Kantarjian HM, Smith TL, Ball G, Keating MJ, Estey EH, et al. Prognostic factors and scoring systems in chronic myelomonocytic leukemia: a retrospective analysis of 213 patients. Blood. 2002;99(3):840-9.
34. Beran M, Wen S, Shen Y, Onida F, Jelinek J, Cortes J, et al. Prognostic factors and risk assessment in chronic myelomonocytic leukemia: validation study of the M.D. Anderson Prognostic Scoring System. Leuk Lymphoma. 2007;48(6):1150-60.
35. Such E, Cervera J, Costa D, Sole F, Vallespi T, Luno E, et al. Cytogenetic risk stratification in chronic myelomonocytic leukemia. Haematologica. 2011;96(3):375-83.
36. Kohlmann A, Grossmann V, Klein HU, Schindela S, Weiss T, Kazak B, et al. Next-generation sequencing technology reveals a characteristic pattern of molecular mutations in 72.8% of chronic myelomonocytic leukemia by detecting frequent alterations in TET2, CBL, RAS, and RUNX1. J Clin Oncol. 2010;28(24):3858-65.