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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.

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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.

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].

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]

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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