The diagnosis and treatment of lower risk myelodysplastic syndromes in the year 2018: update of the MDS guidelines

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SUMMARY

The field of myelodysplastic syndromes has entered the molecular era. New diagnostic tools such as next-generation sequencing are rapidly entering clinical practice and will change the way we diagnose and manage patients with a myelodysplastic syndrome, especially patients considered lower risk by standard diagnostic tools. The treatment of lower risk patients has not changed much since the publication of the BHS recommendations in 2013. However, important trials in lower risk patients have recently been published and will be reviewed here. Finally, the recommendations from an international expert panel for allogeneic transplantation have been published. The key points of this paper will also be discussed as well as results of recently published trials.
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INTRODUCTION

In 2013, the BHS guidelines on the diagnosis and treatment of myelodysplastic syndromes (MDS) were published.[1] The aim of this review is to give an update on the management of patients with lower risk MDS. With the introduction of next-generation-sequencing (NGS), a giant leap forward has been made in the understanding of the pathogenesis of these highly heterogeneous disorders.[2] These techniques have made their way into the clinic and their usefulness in clinical practice is discussed. On the therapeutic side, no new drugs have made their way into the clinic. However, a new formulation of deferasirox has recently been approved and will replace the current dispersible tablets.[3] Also, and maybe 'at last', two prospective randomised clinical trials with erythropoiesis stimulating agents (ESA) have reached their primary endpoint. This will hopefully result in reimbursement of ESA for the treatment of MDS in Belgium.[4,5] Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only curative treatment option. Some lower risk patients are candidates for this treatment and the latest trials and recommendations will be discussed.

DIAGNOSTIC EVALUATION

In spite of all new technologies that have been developed throughout the years, microscopic evaluation by an experienced hematopathologist/morphologist of an optimal bone marrow sample remains a prerequisite for the diagnosis. In most patients, MDS is suspected because of cytopaenias. It is important to note that in the 2016 revision of the WHO classification the threshold to define 'cytopaenia' will change.[6] To be diagnosed with MDS, the patient needs to have a cytopaenia, defined as a haemoglobin level below 10g/dL, and/or an absolute neutrophil count below $1.800/\mu L$ and/or a platelet count lower than $100.000/\mu L$. It is estimated that about 20% of patients with a current diagnosis of MDS are not considered as having this disease by the new classification. The new WHO 2016 classification is summarised in *Table 1*.

As recommended by our BHS guidelines and the ELN guidelines published in 2013, diagnostic evaluation should include microscopy of peripheral blood and bone marrow smear.[1,7] At diagnosis, a core biopsy is also mandatory in addition to cytogenetic analysis of bone marrow aspirate.

At least twenty metaphases should be analysed whenever possible. In the case of repeated failure of standard G-banding (absent or poor-quality metaphases), fluorescence in situ hybridisation (FISH) may complement conventional cytogenetic analysis.[7] With these standard techniques it is possible to classify the patient according to the WHO 2016 classification and to give a good estimate about the prognosis of the individual patients using the IPSS and the revised IPSS.

NEXT GENERATION SEQUENCING

Whereas it has been quite silent in the discovery of new treatment modalities over the last few years, the introduction of high-throughput molecular testing has unravelled a whole new insight in the pathogenesis of this highly heterogeneous disease.[8,9] Apart from *NRAS* and *TP53* mutations, it has long been thought that gene mutations occurred only in a minority of – mainly higher risk – patients. The introduction of new platforms such as gene expression profiling, high-resolution SNP-array analysis and NGS techniques by using whole-exome-sequencing or even whole-genome-sequencing has changed the landscape of MDS. Genetic lesions (mutations, deletions, copy number alterations) can be found in over 90% of MDS patients.[9] The sensitivity of MDS to treatment with methyltransferase inhibitors, has led to the hypothesis that epigenetic silencing of genes was important in the pathogenesis of MDS. It is therefore striking that the new mutations found in MDS confer not only to epigenetic regulators, but to also to other pathways that alter gene/protein expression including the spliceosome machinery.[10] The fact that these mutations can occur in the dominant clone or even in small sub-clones adds to the complexity of the disease.[11] MDS is a disease of the stem cells. It was already shown two decades ago that cytogenetic abnormalities found in mature myeloid cells, are also found in stem cells.[12] Recent work has shown that the different mutations can also be found within the stem cell compartment.[11] These mutations render a growth advantage to these stem cells that outcompete the normal stem cells, without rendering self renewal potential to progenitor cells.

DIAGNOSTIC RELEVANCE

Since about half of patients with MDS have no apparent cytogenetic abnormalities on routine cytogenetic analysis, it is attractive to use molecular techniques and consider the presence of a mutation as an alternative 'proof' that the patient suffers from MDS. Unfortunately, these new techniques have raised more questions that they have currently been able to answer. Important is the observation that mutations can be found in healthy adults without any signs of haematological malignancy.[13] Clonal haematopoiesis is rather a phenomenon that results from aging as suggested by different authors. The finding of mutations per se is therefore no proof of MDS. The term 'clonal haematopoiesis of indeterminate potential' (CHIP) has been introduced to define individuals with signs of clonal haematopoiesis without evidence of dysplasia or cytopaenia (*Table 2*).[14] It must also be highlighted that these gene mutations are not specific for MDS and are found in other myeloid neoplasms.

That does not mean that we should never use mutational analysis as a diagnostic tool. The spliceosome mutation *SF3B1* has been shown to be highly prevalent in low risk MDS, especially in patients with ring sideroblasts and its presence correlates with a favourable prognosis in these patients.[15] In the revised WHO 2016 classification a diagnosis of MDS-RS may be made if ring sideroblasts comprise as few as 5% of nucleated erythroid cells if an *SF3B1* mutation is identified. In the absence of *SF3B1* mutation, at least 15% ring sideroblasts are still required to make the diagnosis (*Table 1*).[6]

PROGNOSTIC RELEVANCE

Several groups already have addressed the prognostic relevance of these point mutations.[8] Especially in lower risk R-IPSS patients, the presence/absence of these mutations are of prognostic relevance. An apparent 'good' risk MDS patient can have a poor overall survival by the presence of a mutation and can be considered a transplant candidate on this reason. As said, *SF3B1* mutations tend to be a marker of favourable prognosis.[16] Bejar *et al*. looked into which somatic mutations were associated with unfavourable outcome and disease progression towards AML. They demonstrated that mutations in five genes (*TP53, EZH2, ETV6, RUNX1* and *ASXL1*) were found to be independently associated with decreased overall survival (OS) in MDS. In a study of 944 patients with MDS, Haferlach *et al*. identified fourteen genes to be associated with poor prognosis.[9]

The prognostic impact of the different mutations after stem cell transplantation have also been studied. Bejar *et al*. demonstrated a poor overall survival in patients with a *TP53, TET2* or *DNMT3A* mutation.[17] In 401 patients with MDS or secondary AML, mutations in *ASXL1, RUNX1* or *TP53* were independent risk factor for poor OS.[18]

SHOULD WE RECOMMEND NGS IN EVERY PATIENT?

Before implementing molecular diagnosis in routine clinical practice, it is important to note that different clones coexist in the marrow of MDS patients and that not all mutations occur in the same clone and different mutations can develop over time. Also the sensitivity of the technique that is used to detect mutations plays a pivotal role. All these factors

TABLE 1. The 2016 revision of the World Health Organization classification of myelodysplastic syndromes.[6]

Name	Dysplastic lineages	Cytopenias[1]	RS %[2]	BM and PB blasts	Cytogenetics
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	<15%/<5%[3]	BM< 5%, PB< 1%, no Auer rods	Any unless isolated del(5q)[4]
MDS with multi-lineage dysplasia (MDS-MLD)	2 or 3	1 – 3	<15%/<5%[3]	BM< 5%, PB< 1%, no Auer rods	Any unless isolated del(5q)[4]
MDS with ring sideroblasts (MDS-RS)					
MDS-RS with single lineage dysplasia (MDS-SLD-RS)	1	1 or 2	≥15%/ ≥5%[3]	BM< 5%, PB< 1%, no Auer rods	Any unless isolated del(5q)[4]
MDS-RS with multi-lineage dysplasia (MDS-MLD-RS)	2 or 3	1 – 3	≥15%/ ≥5%[3]	BM< 5%, PB< 1%, no Auer rods	Any unless isolated del(5q)[4]
MDS with isolated del(5q)	1 - 3	1 – 2	None or any	BM< 5%, PB< 1%, no Auer rods	Del(5q) +/-1 additional abnormality except -7, del(7q)
MDS with excess blasts (MDS-EB)					
MDS-EB-1	0 – 3	1 – 3	None or any	BM 5 – 9% or PB 2 – 4%, no Auer rods	Any
MDS-EB-2	0 – 3	1 – 3	None or any	BM 10 – 19% or PB 5 – 19% or Auer rods	Any
MDS, unclassifiable (MDS-U)					
With 1% blood blasts	1 – 3	1 – 3	None or any	BM <5%, PB =1%, no Auer rods	Any
With single lineage dysplasia and pancytopenia	1	3	None or any	BM <5%, PB<1%, no Auer rods	Any
Based on defining cytogenetic abnormality	0	1 – 3	<15%	BM <5%, PB <1%, no Auer rods	MDS-defining abnormality
Refractory cytopaenia of childhood	1 – 3	1 – 3	None	BM <5%, PB <2%	Any

[1]Cytopenias are defined as Hb < 10g/dL, platelet count < 100.000/µL and absolute neutrophil count < 1.800/µL.
[2]RS = ring sideroblasts as % of marrow erythroid elements.
[3]≥5% if *SF3B1* mutation is present.
[4]If all criteria of MDS with isolated del(5q) are met, it should be considered MDS with isolated del(5q).

should be kept in mind if one wants to predict prognosis by the presence/absence of a certain mutation. This said, accumulating numbers of gene mutations and increasing intratumoral heterogeneity characterise the clonal evolution of MDS and are associated with a worse prognosis.[8] It is also important to note that the prognostic impact of these mutations has only been investigated in patients with proven MDS. We just have no clinical data to reliably know what we should advise a patient with CHIP and a *RUNX1* mutation, for example.

TABLE 2. The spectrum of clonal haematopoiesis, ICUS and MDS.[14]

	"Non clonal" ICUS	CHIP	CCUS	Lower risk MDS	Higher risk MDS
Clonality	-	+	+	+	+
Dysplasia	-	-	-	+	+
Cytopaenias	+	-	+	+	+
BM blast %	< 5%	< 5%	< 5%	< 5%	< 19%
Overall risk	Very low	Very low	Low (?)	Low	High

ICUS: idiopathic cytopaenias of undetermined potential; CHIP: clonal haematopoiesis of indeterminate potential; CCUS: clonal cytopaenias of undetermined significance.

Should we therefore never perform NGS? As said, as clinicians we are often faced with patients with unexplained cytopaenias. Malcovati *et al.* investigated the prognostic relevance of mutations in patients with unexplained cytopenias.[19] In PB granulocytes, mutational analysis of 40 selected genes was performed. Carrying one somatic mutation with a variant allele frequency (VAF) equal to or greater than 0.10, or carrying two or more mutations had a positive predictive value for diagnosis of myeloid neoplasm equal to 0.86 and 0.88, respectively. Spliceosome gene mutations and co-mutation patterns involving *TET2, DNMT3A,* or *ASXL1* had positive predictive values for myeloid neoplasm ranging from 0.86 to 1.0. Within subjects with inconclusive diagnostic findings, carrying one or more somatic mutations was associated with a high probability of developing a myeloid neoplasm during follow-up (HR=13.9, P<.001).

I personally perform NGS in patients with an unclear diagnosis of MDS. As suggested by the previous paper, patients without mutations are unlikely to develop a myeloid neoplasm. NGS identifies patients that need a closer follow-up. I also order NGS in transplant-eligible patients to guide the decision to move directly to transplant or the wait until they evolve into a higher risk R-IPSS. And finally, in patients with more than 5% but less than 15% ring sideroblasts, as recommended by the WHO 2016 classification.

THERAPEUTIC RELEVANCE

It would be attractive to detect mutations as a predictive marker for a specific treatment to work. The presence of *TET2* mutations is associated with a higher response to azacitidine but a *TET2* mutation is not a prerequisite for response.[20,21] More recently, the presence of a *SF3B1* mutation was predictive of response to luspatercept.[22] Most relevant

to these mutations is the fact that all these newly detected pathways will open the way for new and better treatments.

TREATMENT OF SYMPTOMATIC ANEMIA
ERYTHROPOIESIS-STIMULATING AGENTS

Anaemia is a presenting symptom in approximately 70% of patients and the majority of patients with MDS will be transfusion dependent in the course of the disease. For decades, ESA's are used for the treatment of anaemia of low-risk MDS, in the absence of formal registration. Recently, the results of two prospective placebo-controlled randomised trials of ESA in anaemic patients have been presented.[4,5] The ARCADE trial was a phase III randomised, double-blind, placebo-controlled study of darbepoetin alfa in ESA-naive patients with low/int-1 risk MDS and anemia.[5] Patients with low and int-1 IPSS with Hb < 10g/dL and EPO ≤ 500 U/L and low transfusion-burden (< 4 units/8 weeks) were randomised to receive darbepoetin alfa 500 μg or matched placebo subcutaneously once every three weeks (Q3W) from week 1 to week 22 for a 24 week period. From week 25 onwards all patients in study received active treatment during a 48 week period and dose escalations were only allowed from week 31 onwards. Transfusion incidence from weeks 5–24 was significantly lower with darbepoetin alfa versus placebo (36.1% (35/97) versus 59.2% (29/49), P=0.008) and erythroid response rates increased significantly with darbepoetin alfa (14.7% (11/75 evaluable) versus 0% (0/35 evaluable), P=0.016). In the 48-week open-label period, dose frequency increased from Q3W to Q2W in 81% (102/126) of patients and this was associated with a higher hematologic improvement–erythroid (HI-E) response rate (34.7% (34/98)).

This HI-E rate is comparable to that of a phase III placebo-controlled study of epoetin-alfa in patients with low/int-1

MDS.[4] In this EPOANE 3021 trial 31.8 percent of patients treated with epoetin alfa achieved the primary endpoint of erythroid response versus 4.4 percent of placebo patients ($p<0.001$). An ad hoc analysis, accounting for the dose adjustments as per protocol, confirmed a statistically significant erythroid response for the epoetin-alfa arm, with 45.9 percent of epoetin alfa patients, versus 4.4 percent of placebo patients achieving an erythroid response ($p<0.001$). Epoetin-alfa demonstrated a statistically significant improvement of quality of life in responding patients, which was in contrast to the ARCADE trial. The EPOANE 3021 trial has resulted in the approval of epoetin-alfa in MDS by the EMA. So, for the first time, two trials have demonstrated the positive effect of ESAs on erythropoiesis in MDS patients. However, the incidence of HI-E was much lower than could be expected. This is largely due to the design of the trials. Firstly, the doses of ESA used in the trials was rather low and dose increase was only permitted after eight weeks in the EPOANE 3021 and no sooner than after 31 weeks in the ARCADE trial. An adequate dose of ESA is crucial, shown by a recent retrospective study of 543 patients treated with ESA. A higher response rate was seen in patients treated with higher doses of ESA (EPO-alpha (80.000U/week) upfront.[23] Secondly, many patients with an erythroid response (> 11.5g/dL) had to interrupt treatment due to a predefined stopping rule. For the time being, both drugs are only available in Belgium in a medical need program.

DEFERASIROX

Deferasirox is approved for the treatment of transfusion-related iron overload in transfusion-dependent lower risk (IPPS 0 – 1.5) patients and its use is recommended by the BHS and other guidelines.[1,7] A new formulation of deferasirox has been approved and the deferasirox film coated tablets (FCT) will replace the dispersible tablets (DT) at the end of 2017. Approval was based on the open label phase II 'ECLIPSE' trial that randomly assigned 171 transfusion-dependent thalassemia and MDS patients with an IPSS-R score of very low, low and intermediate risk to FCT or DT, and evaluated the safety and patient-reported outcomes over a 24 week period.[3] Patient-reported outcomes showed greater adherence and satisfaction, better palatability and fewer concerns with FCT than DT. Treatment compliance by pill count was higher with FCT (92.9%) than with DT (85.3%). Overall adverse events were consistent with the known deferasirox safety profile and were similar for each formulation (DT 89.5%; FCT 89.7%), with a lower frequency of severe events observed in patients receiving FCT (19.5% vs. 25.6% DT). This analysis suggests deferasirox FCT offers an improved formulation with enhanced patient satisfaction,

which may improve adherence, thereby reducing frequency and severity of iron overload-related complications.

LUSPATERCEPT

Not all lower risk MDS patients with anaemia will respond to ESA. This is largely due to the fact that these patients already have increased serum erythropoietin concentrations. Improving erythropoiesis can also be achieved by targeting downstream processes independent of erythropoietin regulation. Several compounds have been evaluated or are currently under investigation in ESA-refractory patients, including luspatercept and imetelstat among others.

Increased concentrations of transforming growth factor beta (TGF β) superfamily ligands, including growth differentiation factor 11 (GDF11) in the bone marrow have been linked to ineffective erythropoiesis in MDS.[24] Luspatercept (ACE-536) is a novel recombinant fusion protein containing modified activing receptor type IIB linked to the fragment crystallisable (Fc) domain of human IgG1. Luspatercept acts as a ligand trap to inhibit negative regulators of late-stage erythropoiesis, including GDF11 and activin B, thereby restoring red blood cell production in patients with lower-risk MDS.[22]

In the PACE-MDS trial, the efficacy and safety of luspatercept was evaluated in patients with lower-risk MDS who were refractory to or ineligible to receive ESAs.[22] Luspatercept was administered subcutaneously once every 21 days at dose concentrations ranging from 0.125 mg/kg to 1.75 mg/kg bodyweight. Patients were stratified according to transfusion need as having low transfusion burden (LTB), defined as requiring less than four red blood cell (RBC) units in the eight weeks before treatment (and baseline haemoglobin <10 g/dL), or high transfusion burden (HTB), defined as requiring four or more RBC units in the eight weeks before treatment. Per protocol patients were evaluated after twelve weeks of treatment. The primary efficacy endpoint in the twelve week base study was the proportion of patients achieving modified haematological improvement–erythroid (mHI-E), given the short duration of treatment. In LTB patients, mHI-E was defined as a haemoglobin increase of 1.5 g/dL or higher from baseline for fourteen days or longer (in the absence of RBC transfusions). For HTB patients, mHI-E was defined as a reduction in RBC transfusion of four units or more or a 50% or more reduction in RBC units over eight weeks versus pre-treatment transfusion burden.

A total of 58 patients with MDS were enrolled in the twelve week base study at nine treatment centres in Germany. Patients were treated with luspatercept once every three weeks for up to five doses. Of the 51 patients treated with higher dose concentrations of luspatercept (0·75–1·75 mg/kg),

32 (63% [95% CI 48–76]) achieved IWG HI-E across both the base and extension studies. Across both the base and extension stages of the study, HI-E response was achieved in eleven (65%) of seventeen LTB patients receiving higher dose concentrations of luspatercept. Thirteen LTB patients receiving higher dose concentrations continued treatment in the extension study and showed sustained increases from baseline in mean haemoglobin for at least fifteen months. Eleven (85%) of these thirteen patients achieved an HI-E haemoglobin response for a median duration of 8.3 months (95% CI 2.3–9.9). Mean time to response was 2.3 months (SD 3.0; 95% CI 1.3–4.2). Previous ESA use seemed not to be an important predictor of response. Response to luspatercept treatment was more frequent and more robust in patients with ring sideroblasts 15% or higher (69% achieved IWG HI-E) or *SF3B1* mutations (77%). These data indicate that luspatercept is a promising new compound for the treatment of lower-risk MDS, particularly in the 'MDS-RS' patient subgroup. Based on these data, a randomised, placebo controlled, phase III study of luspatercept in patients with lower-risk, ring sideroblast-positive myelodysplastic syndromes is currently ongoing (NCT02631070).

THROMBOCYTOPENIA

In conjunction with abnormal platelet function, thrombocytopenia contributes to an increased risk of bleeding. The thrombopoietin receptor agonists romiplostim and eltrombopag have been extensively studied in patients with MDS, in lower risk and higher risk, with or without azacitidine. Romiplostim is a peptibody approved for use in chronic immune thrombocytopenia. The results of a 58-week, placebo-controlled study of romiplostim monotherapy in thrombocytopenic patients with low/intermediate-1–risk MDS have been published.[25] Patients (n=250) were randomised to receive weekly subcutaneous romiplostim, starting at a dose of 750μg or placebo. The data monitoring committee (DMC) recommended early discontinuation of the study drug based on interim data of 211 patients of an increased peripheral blast count in patients receiving romiplostim, thereby decreasing the study's statistical power and limiting study conclusions. Only 56 patients (36 patients in the romiplostim group and 20 patients in the placebo group) completed the 58-week study. The treatment groups did not differ with respect to the primary endpoint: clinical significant bleeding event (CSBE, (grade $\geq$ 2 on the modified WHO bleeding scale). There was no demonstrated effect on survival. The overall incidences of adverse events were similar, although there were more serious adverse events with romiplostim (nonsignificant). However, platelet count increases and the incidence of platelet response were greater

in romiplostim-treated patients. Romiplostim decreased overall bleeding events (P<.026) and CSBEs in patients who had baseline platelet counts > 20.000/μL (P<.0001). The CSBE endpoint was confounded by the significantly greater rate of platelet transfusions received in the placebo group. In patients with baseline platelet counts <20.000/μL, no difference in CSBEs between treatment groups was observed. However, the percentage of patients with protocol defined platelet transfusion events (PTEs) was significantly lower in the romiplostim group overall (P<.001), particularly among patients with baseline platelet counts <20.000/μL. It is likely that PTEs in patients with baseline platelet counts <20.000/μL reduced bleeding events, which may account for the overall lack of difference in CSBEs between the placebo and romiplostim groups.

Eltrombopag was tested in patients with low-risk or IPSS intermediate-1 risk MDS with a stable platelet count of lower than 30.000/μL.[26] Ninety patients were 2:1 randomly assigned to eltrombopag (50 – 300mg) to placebo. The median follow-up time to assess platelet responses was eleven weeks (IQR 4–24). Platelet responses occurred in 28 of 59 patients (47%) in the eltrombopag group versus one of 31 (3%) patients in the placebo group (odds ratio 27·1 [95% CI 3·5–211·9], p=0·0017). During the follow-up, 21 patients had at least one severe bleeding event (WHO bleeding score $\geq$2). There were a higher number of bleeders in the placebo (13 of 31 patients [42%]) than in the eltrombopag arm (8 of 59 patients [14%]; p=0·0025). The outcome acute myeloid leukaemia evolution or disease progression occurred in 7 of 59 patients (12%) in the eltrombopag group versus 5 of 31 patients (16%) in the placebo group (χ^2=0·06, p=0·81). The increase in platelet count per se was associated with quality-of-life improvements.

In conclusion, both compounds have shown efficacy in thrombocytopenic patients with lower risk MDS.

TRANSPLANTATION

Allogeneic HSCT remains the only curative treatment for MDS. Recently the recommendations from an international expert panel for allogeneic HSCT have been published.[27] The key points of recommendations for transplantation in lower-risk patients are summarised here.

PATIENT SELECTION

In recent years new prognostic classifications have been developed that help us to estimate the prognosis of a given patient. The new cytogenetic risk score stratifies some 'lower-risk' patients in the old IPSS into higher risk IPSS-R categories. Therefore it is warranted to use the IPSS-R when evaluating a patient for transplant. The impact of this new

cytogenetic risk classification after HSCT has been studied and confirmed a better prediction of survival after HSCT for the IPSS-R compared with IPSS.[28,29] The IPSS-R changed the risk groups in about 65% of patients.[18] In particular, the very poor-risk category predicts for increased mortality and relapse following HSCT. The presence of complex karyotype abnormalities, monosomal karyotype or both predicted inferior survival after HSCT in MDS patients.[30] However, there is no consensus as to whether this patient should be proposed for HSCT immediately after diagnosis.

The prognosis of treatment-related MDS (t-MDS) is generally worse compared to *de novo* MDS. The CIBMTR analysed a series of 323 t-MDS patients treated with allogeneic HSCT.[31] Age over 35 years, poor-risk cytogenetics, advanced t-MDS, and alternative donors were negative prognostic factors for post-HSCT outcome. The major cause of failure after HSCT was non-relapse mortality (NRM). The 5-year relapse-free survival in this group of 257 patients with t-MDS/transformed AML was 29%.

The impact of mutations has also been extensively studied retrospectively. Bejar *et al.* reported prognostic significance for *EZH2* and *ETV6* mutations in a study of 87 allograft recipients.[17] *TP53* mutations and especially the combination of complex karyotype and *TP53* mutations resulted in very poor outcome. In a large retrospective series, Lindsley has shown that *RAS* pathway mutations and *JAK2* mutations were associated with a poor outcome after allogeneic HSCT, independently of *TP53* mutations in patients older than 40 years.[32] HSCT in clinical trials may be considered for patients with *ASXL1, RUNX1, RAS* pathway and *JAK2*, and especially *TP53* mutations. The relatively poor survival after HSCT for patients carrying these mutations suggests that new transplantation strategies must be developed for these patients, including post transplant strategies to prevent relapse.

Apart from IPSS-R score, the presence of severe symptomatic cytopaenias refractory to growth factors or requiring intensive RBC transfusion support may be independent indications for HSCT. These include frequent RBC transfusions (≥ 2 units per month), life-threatening cytopaenias (neutrophil counts < 300/μL, or platelet counts < 30.000/μL). If an increase of myeloblasts leads to a more advanced-risk group by IPSS-R, the expert panel also recommends proceeding to HSCT.

Currently, the MDS working group of the ELN is developing an interactive website (*https://mds-europe.eu*) supported by the MDS-Right Project (funded by the EU Horizon 2020 project no. 634789), which will support fast incorporation of new developments in the current HSCT recommendations.

TIMING OF TRANSPLANT

The optimal timing to move forward to transplantation is a balanced decision. The timing of HSCT has been studied using Markov models in several retrospective studies.[33] The recommendation to delay transplantation in low/int-1 risk MDS and offer allo HSCT to patients with int-2/ high-risk MDS has largely been adopted by most transplant centres. Recently, the same model has been applied on a large patient population that was stratified to the IPSS-R.[34] Usually, lower-risk patients at diagnosis according to IPSS-R remain in this lower risk category over time. Higher-risk patients show a decreasing risk for AML evolution over time.[35] Using IPSS-R, the estimated life expectancy was maximised when transplantation was delayed until progression from the very low or low risk to the intermediate risk, and then decreased. Allo HSCT should instead be immediately offered to eligible patients belonging to intermediate-risk category, since this strategy offers the best survival benefit. In advanced disease stages, preliminary evidence suggests that HMAs administered before transplant may have a positive impact on life expectancy.

REDUCED INTENSITY VERSUS MYELOABLATIVE CONDITIONING

The introduction of reduced intensity conditioning (RIC) regimens has led to an increased number of patients with MDS referred for allo HSCT. Several retrospective studies from the European Group of Blood and Marrow Transplantation (EBMT) as well as larger centres have reported a higher risk of relapse but a lower rate of non-relapse mortality (NRM) when comparing RIC with myeloablative conditioning regimens (MAC), which has resulted in comparable survival after both approaches.[36] Recently the results of two prospective randomised trials have been published. The RICMAC study of the EBMT was a prospective, multicentre, open-label phase III study comparing a busulfan based standard myeloablative regimen (16 mg/kg) with a busulfan-based RIC regimen (8 mg/kg) in patients aged 18 to 65 years with MDS or secondary AML with less than 20% blasts at time of transplant.[37] The cumulative incidence of relapse at two years was nearly identical independent of conditioning regimen intensity, whereas NRM tended to be higher after myeloablative conditioning, although not significantly. The only risk factor for relapse in a multivariable analysis was advanced disease status, which was defined as CMML, RAEB, or sAML. The authors therefore conclude that RIC can be offered as an alternative treatment for especially the cytogenetic low-risk group.

A second trial prospectively randomised patients age 18 to 65 years with HCT CI < 4 and less than 5% bone marrow

KEY MESSAGES FOR CLINICAL PRACTICE

1 Diagnosis of MDS still relies on careful examination of a good bone marrow sample by experienced hematopathologists.

2 Mutational analysis can be useful in patients with unexplained cytopaenias. The detection of mutations can upgrade the risk in apparent lower risk patients which make them candidates for transplantation.

3 Erythropoiesis stimulating agents have been shown in prospective randomised placebo-controlled trials to significantly alleviate anaemia in MDS patients. In real world, initial higher doses and early dose escalations can result in higher response rates than in these trials.

4 Luspatercept is a promising drug to reduce transfusion-need in lower risk MDS patients and has marked activity in patients with MDS-RS.

blasts pre-HSCT to receive MAC (n=135) or RIC (n=137) from matched related or unrelated donors.[38] The primary end point was OS 18 months post–random assignment based on an intent-to-treat analysis. Secondary end points included relapse-free survival (RFS) and TRM. As expected, TRM was significantly lower among patients in the RIC arm (4.4% v 15.8%), but this difference was less than expected and offset by substantial differences in relapse. Eighteen patients randomly assigned to MAC experienced relapse compared with 66 patients randomly assigned to RIC, for a cumulative incidence at eighteen months of 13.5% (95% CI, 8.3% to 19.8%) and 48.3% (95% CI, 39.6% to 56.4%), respectively (p< 0.001). Among patients with MDS, cumulative incidence was 3.7% (95% CI, 0.3% to 16.3%) with MAC and 37% (95% CI, 19.2% to 55%) with RIC. The DSMB halted accrual because of a presumed benefit for MAC. OS was inferior in patients receiving RIC, even though the difference did not reach statistical significance. The sample size was reduced as a result of DSMB safety concerns, resulting in decreased power to detect a difference.

The choice between conditioning regimen in lower risk patients therefore is still an open question and the decision should be individualised. The unavailability of azacitidine to treat relapse in Belgium might influence this choice. Patients with presumed 'higher risk' (e.g. *TP53* mutation) which is not captured in the IPSS-R, could be offered a MAC conditioning to prevent relapse, whereas a patient with severe cytopaenias without high risk cytogenetic/molecular findings could be offered RIC conditioning.

CONCLUSIONS

In recent years, much progress has been made in the understanding of the disease. The advent of high throughput molecular analysis, will allow us as haematologists to be more confident about the diagnosis and will allow to discern patients with a dismal outcome that look lower risk with current standard techniques. In future years, the newly discovered pathways will lead to new treatments, especially in the lower risk patients.

REFERENCES

1. Meers S, Breems D, Bries G, et al. Management of myelodysplastic syndromes in adults: guidelines from the Belgian Haematological Society. Acta Clin Belg. 2013;68:253-62.

2. Meers S. The myelodysplastic syndromes: the era of understanding. Eur J Haematol. 2015;94:379-90.

3. Taher AT, Origa R, Perrotta S, et al. New film-coated tablet formulation of deferasirox is well tolerated in patients with thalassemia or lower-risk MDS: Results of the randomised, phase II ECLIPSE study. Am J Hematol. 2017;92:420-8.

4. Fenaux P, Santini V, Spiriti MA, et al. Randomised, double-blind, placebo-controlled, multicenter study evaluating epoetin alfa versus placebo in anaemic patients with IPSS Low-Int1 risk MDS. Haematologica. 2016;101(Suppl.1): abstract P248.

5. Platzbecker U, Symeonidis A, Oliva EN, et al. A phase 3 randomised placebo-controlled trial of darbepoetin alfa in patients with anaemia and lower-risk myelodysplastic syndromes. Leukemia. 2017;31:1944-50.

6. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukaemia. Blood. 2016;127:2391-405.

7. Malcovati L, Hellstrom-Lindberg E, Bowen D, et al. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. Blood. 2013;122:2943-64.

8. Bejar R, Stevenson K, Abdel-Wahab O, et al. Clinical effect of point mutations in myelodysplastic syndromes. N Engl J Med. 2011;364:2496-506.

9. Haferlach T, Nagata Y, Grossmann V, et al. Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. Leukemia. 2014;28:241-7.

10. Yoshida K, Sanada M, Shiraishi Y, et al. Frequent pathway mutations of splicing machinery in myelodysplasia. Nature. 2011;478:64-9.

11. Woll PS, Kjallquist U, Chowdhury O, et al. Myelodysplastic syndromes are propagated by rare and distinct human cancer stem cells in vivo. Cancer Cell. 2014;25:794-808.

12. Nilsson L, Astrand-Grundstrom I, Arvidsson I, et al. Isolation and characterization of hematopoietic progenitor/stem cells in 5q-deleted myelodysplastic syndromes: evidence for involvement at the hematopoietic stem cell level. Blood. 2000;96:2012-21.

13. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal haematopoiesis associated with adverse outcomes. N Engl J Med. 2014;371:2488-98.

14. Steensma DP, Bejar R, Jaiswal S, et al. Clonal haematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. Blood. 2015;126:9-16.

15. Malcovati L, Karimi M, Papaemmanuil E, et al. SF3B1 mutation identifies a distinct subset of myelodysplastic syndrome with ring sideroblasts. Blood. 2015;126:233-41.

16. Papaemmanuil E, Cazzola M, Boultwood J, et al. Somatic SF3B1 mutation in myelodysplasia with ring sideroblasts. N Engl J Med. 2011;365:1384-95.

17. Bejar R, Stevenson KE, Caughey B, et al. Somatic mutations predict poor outcome in patients with myelodysplastic syndrome after hematopoietic stem-cell transplantation. J Clin Oncol. 2014;32:2691-8.

18. Della Porta MG, Alessandrino EP, Bacigalupo A, et al. Predictive factors for the outcome of allogeneic transplantation in patients with MDS stratified according to the revised IPSS-R. Blood. 2014;123:2333-42.

19. Malcovati L, Galli A, Travaglino E, et al. Clinical significance of somatic mutation in unexplained blood cytopaenia. Blood. 2017;129:3371-8.

20. Itzykson R, Kosmider O, Cluzeau T, et al. Impact of TET2 mutations on response rate to azacitidine in myelodysplastic syndromes and low blast count acute myeloid leukemias. Leukemia. 2011;25:1147-52.

21. Bejar R, Lord A, Stevenson K, et al. TET2 mutations predict response to hypomethylating agents in myelodysplastic syndrome patients. Blood. 2014;124:2705-12.

22. Platzbecker U, Germing U, Gotze KS, et al. Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study. Lancet Oncol. 2017;18:1338-47.

23. Buccisano F, Piccioni AL, Nobile C, et al. Real-life use of erythropoiesis-stimulating agents in myelodysplastic syndromes: a "Gruppo Romano Mielodisplasie (GROM)" multicenter study. Ann Hematol. 2016;95:1059-65.

24. Zhou L, Nguyen AN, Sohal D, et al. Inhibition of the TGF-beta receptor I kinase promotes haematopoiesis in MDS. Blood. 2008;112:3434-43.

25. Giagounidis A, Mufti GJ, Fenaux P, et al. Results of a randomised, double-blind study of romiplostim versus placebo in patients with low/intermediate-1-risk myelodysplastic syndrome and thrombocytopenia. Cancer. 2014;120:1838-46.

26. Oliva EN, Alati C, Santini V, et al. Eltrombopag versus placebo for low-risk myelodysplastic syndromes with thrombocytopenia (EQoL-MDS): phase 1 results of a single-blind, randomised, controlled, phase 2 superiority trial. Lancet Haematol. 2017;4:e127-e136.

27. de Witte T, Bowen D, Robin M, et al. Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel. Blood. 2017;129:1753-62.

28. Schanz J, Tuchler H, Sole F, et al. New comprehensive cytogenetic scoring system for primary myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukaemia after MDS derived from an international database merge. J Clin Oncol. 2012;30:820-9.

29. Gauthier J, Damaj G, Langlois C, et al. Contribution of Revised International Prognostic Scoring System Cytogenetics to Predict Outcome After Allogeneic Stem Cell Transplantation for Myelodysplastic Syndromes: A Study From the French Society of Bone Marrow Transplantation and Cellular Therapy. Transplantation. 2015;99:1672-80.

30. van Gelder M, de Wreede LC, Schetelig J, et al. Monosomal karyotype predicts poor survival after allogeneic stem cell transplantation in chromosome 7 abnormal myelodysplastic syndrome and secondary acute myeloid leukaemia. Leukemia. 2013;27:879-88.

31. Litzow MR, Tarima S, Perez WS, et al. Allogeneic transplantation for therapy-related myelodysplastic syndrome and acute myeloid leukaemia. Blood. 2010; 115:1850-7.

32. Lindsley RC, Saber W, Mar BG, et al. Prognostic Mutations in Myelodysplastic Syndrome after Stem-Cell Transplantation. N Engl J Med. 2017;376:536-47.

33. Cutler CS, Lee SJ, Greenberg P, et al. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: delayed transplantation for low-risk myelodysplasia is associated with improved outcome. Blood. 2004;104:579-85.

34. Della Porta MG, Jackson CH, Alessandrino EP, et al. Decision analysis of allogeneic hematopoietic stem cell transplantation for patients with myelodysplastic syndrome stratified according to the revised International Prognostic Scoring System. Leukemia. 2017;31:2449-57.

35. Pfeilstocker M, Tuechler H, Sanz G, et al. Time-dependent changes in mortality and transformation risk in MDS. Blood. 2016;128:902-10.

36. Martino R, Iacobelli S, Brand R, et al. Retrospective comparison of reduced-intensity conditioning and conventional high-dose conditioning for allogeneic hematopoietic stem cell transplantation using HLA-identical sibling donors in myelodysplastic syndromes. Blood. 2006;108:836-46.

37. Kroger N, Iacobelli S, Franke GN, et al. Dose-Reduced Versus Standard Conditioning Followed by Allogeneic Stem-Cell Transplantation for Patients With Myelodysplastic Syndrome: A Prospective Randomised Phase III Study of the EBMT (RICMAC Trial). J Clin Oncol. 2017;35:2157-64.

38. Scott BL, Pasquini MC, Logan BR, et al. Myeloablative Versus Reduced-Intensity Hematopoietic Cell Transplantation for Acute Myeloid Leukemia and Myelodysplastic Syndromes. J Clin Oncol. 2017;35:1154-61.