Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

P. Fenaux1, D. Haase2, G. F. Sanz3, V. Santini4 & C. Buske5 on behalf of the ESMO Guidelines Working Group

1Service d’Hémato-onco-Logie Clinique, Groupe Francophone des Myélodysplasies (GFМ), Hôpital St Louis (Assistance Publique, Hôpitaux de Paris) and Paris 7 University, Paris, France; 2Clinics of Hematology and Medical Oncology, University Medicine, Goettingen, Germany; 3Department of Haematology, Hospital Universitario y Politécnico La Fe, Valencia, Spain; 4Functional Unit of Haematology, AOU Careggi, University of Florence, Firenze, Italy; 5Comprehensive Cancer Center Ulm, Institute of Experimental Cancer Research, University Hospital, Ulm, Germany

introduction

Myelodysplastic syndromes (MDS) are clonal haematopoietic stem cell (HSC) disorders predominating in the elderly, characterised by ineffective haematopoiesis leading to blood cytopaenias and by progression to acute myeloid leukaemia (AML) in one-third of cases [1]. Their pathophysiology is a multistep process involving cytogenetic changes and/or gene mutations [2] and widespread gene hypermethylation at advanced stages [3–5].

Diagnosis of MDS is based on the blood and marrow examination, showing blood cytopaenias, hypercellular marrow with dysplasia, with or without an excess of immature marrow cells (blasts) [6]. Prognosis is largely based on the marrow blast percentage, number and extent of cytopaenias and cytogenetic abnormalities, which are grouped in a recently Revised International Prognostic Scoring system (IPSS/IPSS-R) [7, 8]. Treatment varying from symptomatic therapy of cytopaenias, especially by transfusions, to allogeneic stem cell transplantation (alloSCT) has improved in the last few years.

incidence and aetiology

MDS are diseases of the elderly, with a median age at diagnosis of ~70 years and with >10% of the patients being younger than 50 years of age [9]. The incidence of MDS in Europe is about 4 cases/100 000 inhabitants/year (reaching 40–50/100 000 in patients aged ≥70 years) [9]. There are no known ethnic differences in the incidence of MDS, but MDS in Asian populations tend to occur at an earlier age, more often have a hypocellular marrow and present less often with isolated 5q deletion (5q-) syndrome, while trisomy 8 seems to be more frequent than in Western populations [10, 11].

The aetiology of MDS is known in only 15% of cases. Inherited predisposition to MDS is seen in one-third of paediatric MDS cases, including in Down’s syndrome, Fanconi anaemia and neurofibromatosis. It is less frequent in adults, where an inherited predisposition should also be assessed in MDS occurring in young adults or in families with other cases of MDS, AML or aplastic anaemia. Environmental factors include previous use of chemotherapy, especially alkylating agents and more recently of purine analogues [12] radiotherapy or ionising radiation [13, 14], and tobacco smoking [15]. Recognised occupational factors include benzene and its derivatives [16], while an excess of MDS is reported in agricultural and industrial workers [15, 17]. Those ‘secondary MDS’, particularly cases occurring after chemotherapy, generally have poor prognostic factors, including complex cytogenetic findings involving chromosomes 5 and/or 7 and/or 17p, constituting the so-called alkylator type, therapy-associated haematological malignancies.

diagnosis

Well-established and necessary diagnostic tools for MDS with widespread availability are peripheral and differential blood counts, cytomorphology of peripheral blood and bone marrow smears and cytogenetics of bone marrow cells. At initial diagnosis, histology of bone marrow trephine biopsies is strongly recommended, especially in the case of difficult diagnosis and because of its potential prognostic information.

The medical history of the patient can provide important information relating to differential diagnoses such as history of medication or ingestion of alcohol or other drugs, as well as an exclusion of other diseases including autoimmune disorders, renal failure, malignancies, chronic infections or inflammations, aplastic anaemia and paroxysmal nocturnal haemoglobinuria [18]. Beyond the mere diagnosis of MDS, one should classify every case according to the World Health Organisation (WHO) criteria [19] and should establish the prognosis by IPSS [7] and IPSS-R [8].

peripheral blood counts and differential blood counts

Almost all patients with MDS have peripheral blood cytopaenias, mostly anaemia with or without other cytopaenias. If blood counts only modestly deviate from normal values, repeated controls are recommended.
laboratory parameters

Important laboratory values supporting or excluding the diagnosis of MDS are lactate dehydrogenase (LDH), ferritin, transferrin and transferrin saturation, reticulocyte counts, vitamin B12 and folate concentrations, haemoglobin, endogenous erythropoietin (EPO) and creatinine levels. They can serve to exclude the differential diagnoses of iron deficiency anaemia, haemolytic anaemia, vitamin B12 or folate deficiency and renal anaemia. If MDS is diagnosed, ferritin and LDH also have a certain prognostic value, and the EPO level can support a decision for or against treatment with erythropoiesis-stimulating agents (ESAs).

cytomorphology

The hallmarks of cytology in MDS are the determination of dysplastic signs in erythropoiesis, granulopoiesis and megakaryopoiesis in the bone marrow and/or peripheral blood and the enumeration of blast cells again in the bone marrow and/or peripheral blood. In the bone marrow, histology of trephine biopsies is of great additional value.

In early MDS with only mild morphological abnormalities, certain cases with persistent, unexplained cytopaenias are called idiopathic cytopaenias of uncertain significance (ICUS). In patients with dysplastic features in the bone marrow but no or only very mild peripheral blood cytopaenias and a normal karyotype, idiopathic dysplasia of unknown significance (IDUS) [20] can be diagnosed if no other cause of dysplasia is apparent (see Table 1). Of note, however, the terms ICUS and IDUS (although they are consensus statements from a MDS working conference) are not universally accepted and are not included in the current 2008 WHO classification.

When evaluating MDS peripheral blood films and bone marrow slides, a number of cytological abnormalities should be taken into account; a list of those items is given in Table 2 [21]. For the diagnosis of MDS, the recommended number of cells that should be reviewed per slide is 200 for the peripheral blood film and up to 500 for the bone marrow [19]. The bone marrow blast count is crucial in MDS, given its paramount prognostic value and must be evaluated morphologically in marrow aspirates (less so with other methods) according to WHO and International Working Group (IWG) criteria. ‘Blasts’ should include agranular blasts and myeloblasts, but not promyelocytes.

histopathology

In Europe, contrary to in the United States, MDS (like acute leukaemias) are mainly diagnosed by bone marrow aspirate rather than with a biopsy. Bone marrow trephine biopsy, however, is very useful in the case of hypocellular aspirates or dry puncture, where hypoplastic MDS or fibrotic MDS may be diagnosed. It may also be important for other differential diagnoses. In expert hands, histomorphology can provide additional information on dysplastic features and prognostic information, especially by showing fibrosis (see below). It is therefore strongly recommended in addition to bone marrow aspiration.

cytogenetics

In MDS, clonal chromosome abnormalities can be observed in 30% to >80% of patients depending on the MDS subtype and whether the disease is de novo or chemo- or radiotherapy-

Table 2. Signs of dysplasia in myelodysplastic syndromes

<table>
<thead>
<tr>
<th>Peripheral blood</th>
<th>Bone marrow</th>
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</thead>
<tbody>
<tr>
<td><strong>Granulocytes</strong></td>
<td>Pseudo-Pelger cells, abnormal chromatin clumping, hypo-/degranulation, left shift</td>
</tr>
<tr>
<td><strong>Platelets</strong></td>
<td>Giant platelets, anisometry of platelets</td>
</tr>
<tr>
<td><strong>Red cells</strong></td>
<td>Anisocytosis, poikilocytosis, dimorphic erythrocytes, polychromasia, hypochromasia, megalocytes, basophilic stippling, presence of nucleated erythroid precursors, teardrop cells, ovalocytes, fragmentocytes</td>
</tr>
<tr>
<td><strong>Granulocytopenia</strong></td>
<td>Left shift, increased medullary blast count, Auer rods or Auer bodies, hypo-/degranulation, Pseudo-Pelger cells, nuclear anomalies (e.g. hypersegmentation, abnormal chromatin clumping), deficiency of myeloperoxidase, increase and morphological abnormality of monocytes</td>
</tr>
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</table>

Table 1. Definition of ICUS and IDUS [11]

<table>
<thead>
<tr>
<th>Characteristics</th>
<th><strong>ICUS</strong></th>
<th><strong>IDUS</strong></th>
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<tbody>
<tr>
<td>Mild cytopaenias (haemoglobin &lt;11.0 g/dl, neutropenia &lt;1500/μl and/or thrombocytopenia &lt;100,000/μl and lack of significant dysplasia in the bone marrow but exclusion of other diseases and/or no clonal cytogenetic/molecular markers)</td>
<td></td>
<td>Mild cytopaenias for &gt;6 months (hb ≥11/dl, neutrophils ≥1500/μl, platelets ≥100,000/μl, all below lower limit of normal) or no cytopaenias but marked dysplasia in &gt;10% of cell lineages and no clonal cytogenetic/molecular markers</td>
</tr>
<tr>
<td>ICUS, idiopathic cytopaenias of uncertain significance; IDUS, idiopathic dysplasia of unknown significance.</td>
<td></td>
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induced [22]. In the remaining 20%–70% of patients with a normal karyotype, there is growing evidence that sub-microscopic alterations such as point mutations, micro-deletions, micro-amplifications, epigenetic changes or copy-number neutral loss of genetic information as by uniparental disomy provide the genetic basis for the disease [2, 23, 24]. Karyotype also has the highest prognostic weight of all parameters in the IPSS-R [8].

Chromosome banding analysis is carried out on dividing metaphase cells. Generally, whenever possible, 20–25 metaphases should be structurally analysed not to miss smaller cell clones which are quite frequent, especially in low-risk MDS. According to the International System for Human Cytogenetic Nomenclature (ISCN), an abnormal clone is defined by at least two metaphases with the same supernumerary chromosome or structural change, or at least three metaphases with loss of the same chromosome. Complex abnormalities are defined as three or more independent abnormalities in at least two metaphases. An adequate cytogenetic report should contain a correct formula describing the karyotype according to the most recent ISCN criteria [25]. Cytogenetic analysis should follow minimal standards fixed by the 'Workpackage Cytogenetics' of the European Leukaemia Net (Figure 1). These relate to cell culturing, analytical expenditure and the use of additional fluorescence in situ hybridisation analyses [26].

In an international database of 2124 MDS patients, 52% of patients had one or more clonal cytogenetic abnormality by chromosome banding. Abnormal karyotypes showed a clear association with the severity of MDS, increasing with the medul lary blast count and the intensity of cellular dysplasias [22].

Several independent studies have proven the dismal outcome related to complex abnormalities, especially in the presence of monosomies (monosom al karyotype); however, there is a growing body of evidence that it is not the monosomies per se but rather the complexity of chromosomal changes that determines the dismal outcome [22, 27–30].

**additional diagnostic tests**

When MDS is uncertain, especially in cases of ICUS or IDUS with normal karyotype, analysis of somatic mutations and flow cytometry analysis of marrow cells could be useful to ascertain diagnosis. Acquired mutations, especially in genes involved in epigenetic regulation and chromatin remodelling (TET2, DNMT3A, ASXL1, IDH1/2, EZH2), pre-mRNA splicing factors (SF3B1, SRSF2, U2AF1) transcription [TP53, RUNX1, (II) (III)] and signalling transduction (e.g. NRAS, CBL) are seen in most MDS, and can demonstrate clonal disease [31, 32] (Table 3), while some flow cytometry abnormalities of myeloid precursors

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**Figure 1.** Recommended standard algorithm for cytogenetic analysis in myelodysplastic syndromes [26]. FISH, fluorescence in situ hybridisation.
are highly suggestive of MDS, although both procedures are still used only in a minority of centres [33].

**prognosis and risk assessment**

The natural course of MDS is highly variable, with survival ranging from a few weeks to several years [35]. The median OS is 15–30 months and the risk of progression to AML is 25%–35% at 5 years [36]. Bone marrow failure (infection and haemorrhage) is the leading cause of death, with more patients dying before overt AML has occurred [36].

An individual risk-adapted treatment strategy is essential in MDS. Specific cytogenetic abnormalities, percentage of marrow blasts and number and severity of cytopenias are the main prognostic factors in MDS. The IPSS [7] and its recent revision (IPSS-R, Table 5) [8] are based on these three variables. They have been validated in external series [37], and their use is strongly recommended for predicting outcome and planning treatment [38]. The IPSS-R is used to stratify patients into five risk groups (very low, low, intermediate, high and very high risk), with clear differences in OS and risk of progression to AML [8]. Of note, currently conventional IPSS remains the most widely used system, and the system used by health agencies for drug approval in MDS. For therapeutic purposes, IPSS low and intermediate-1 patients are generally grouped in ‘lower risk’ MDS, and intermediate-2 and high-risk patients in ‘higher risk’ MDS.

Patient-related characteristics such as age [8], Eastern Cooperative Oncology Group (ECOG) performance status [8] and comorbidities [39] are also relevant for establishing prognosis and treatment choice, particularly in lower risk MDS. Other disease-related factors include multi-lineage dysplasia [40], red blood cell (RBC) transfusion dependence [40], serum LDH, ferritin and β2-microglobulin [7] and bone marrow fibrosis [39]. Finally, flow cytometry immunophenotyping [33] and gene somatic mutation profiling (especially the most frequent, i.e. TET2, SF3B1, SRSF2, ASXL1, RUNX1, DNMT3a, EZH2, TP53 and RAS, mutations) may also improve risk stratification [2, 31, 32], but data on their independent prognostic impact are still lacking to recommend use in routine practice. The prognostic impact of combined mutations as well as combinations of gene mutations with distinct karyotype abnormalities is also unclear at this time.

Finally, most prognostic factors in MDS have been established independently of treatment, particularly in cohorts receiving mostly supportive care. With the availability of treatments having an impact on disease evolution, including alloSCT and hypomethylating agents (HMAs), factors that may be prognostic of outcome in patients treated with these treatments are starting to be defined.

**response criteria in MDS**

Response criteria to treatment, in MDS, are based on recommendations of an IWG (most recently updated in 2006), that define two types of responses. The first type considers responses to treatments aimed at modifying the disease course (mainly alloSCT, intensive chemotherapy and HMAs), and includes complete remission (CR), partial remission (PR), stable disease and progression. The second type evaluates improvement of cytopenias (haematological improvement’ or HI) in one, two or three lineages (erythroid, platelet and neutrophil responses), and is particularly adapted to treatments which, like growth factors, can improve these cytopenias, but with no obvious effect on the disease course. While CR and PR are generally associated with improvement in cytopenias, the second type of response is often designed as ‘stable disease with HI’ (on the erythroid and/or platelet and/or neutrophil) lineage.’

**treatment of IPSS INT-2 and high-risk (higher risk) MDS patients**

Although the division is schematic, it is customary since publication of the classical IPSS to separate MDS into ‘higher risk’ MDS (corresponding to IPSS high or intermediate-2) and ‘lower risk’ (corresponding to IPSS low or intermediate-1). Higher risk MDS carry a major risk of progression to AML and short
survival, and treatment in those patients should aim, whenever possible, to modify the natural disease course including alloSCT, HMAs and, although now less often, chemotherapy (mainly intensive anthracycline–AraC combinations) [41]. In most higher risk MDS, HMAs are the first-line reference treatment.

In patients with MDS IPSS INT2 high risk, without major comorbidities and not eligible for alloSCT, azacitidine is recommended [I, A]. The use of azacitidine may be recommended compared with the other HMA decitabine, because in a randomised trial, azacitidine has been shown to be superior to conventional care regimens (i.e. supportive care, low-dose AraC and AML-like chemotherapy) [42, 43], whereas there was no clear survival advantage with decitabine over conventional treatment in two phase III trials.

Due to the fact that most patients respond only after several courses, at least six courses of azacitidine are recommended, with the following schedule: azacitidine 75 mg/m²/day s.c. for 7 days every 28 days [II, B] in order to properly evaluate its efficacy. Alternative schedules (such as 5-day regimens), which appear to give similar response rates as the classical 7-day regimen in lower risk MDS, have not demonstrated their efficacy in terms of survival advantage in higher risk MDS.

Besides induction of CR and PR, achievement of HI according to IWG 2006 criteria, i.e. an improvement in cytopaenias (mainly anaemia and/or thrombocytopaenia), should be considered indicative of response, because it has been shown to be associated with a prolongation of survival [III, B] [44].

The use of azacitidine before HSC transplantation (HSCT) appears promising and is currently being evaluated in clinical trials.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Blood findings</th>
<th>Bone marrow findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory cytopaenias with unilineage dysplasia (RCUD)</td>
<td>Unicytopenia or bicytopenia</td>
<td>Unilineage dysplasia: ≥10% of the cells in one myeloid lineage</td>
</tr>
<tr>
<td>Refractory anaemia (RA)</td>
<td>No or rare blasts (&lt;1%)</td>
<td>&lt;5% blasts</td>
</tr>
<tr>
<td>Refractory neutropenia (RN)</td>
<td>Anaemia</td>
<td>≥15% of erythroid precursors are ring sideroblasts</td>
</tr>
<tr>
<td>Refractory thrombocytopenia (RT)</td>
<td>No blasts</td>
<td>Erythroid dysplasia only</td>
</tr>
<tr>
<td>Refractory anaemia with ring sideroblasts (RARS)</td>
<td>Cytopaenia(s)</td>
<td>Dysplasia in ≥10% of cells in two or more myeloid lineages</td>
</tr>
<tr>
<td>Refractory cytopaenia with multilineage dysplasia (RCMD)</td>
<td>No or rare blasts (&lt;1%)</td>
<td>&lt;5% blasts in marrow</td>
</tr>
<tr>
<td>Refractory anaemia with excess blasts-1 (RAEB-1)</td>
<td>Cytopaenia(s)</td>
<td>Unilineage or multilineage dysplasia</td>
</tr>
<tr>
<td>Refractory anaemia with excess blasts-2 (RAEB-2)</td>
<td>Cytopaenia(s)</td>
<td>Unilineage or multilineage dysplasia</td>
</tr>
<tr>
<td>Myelodysplastic syndrome: unclassified (MDS-U)</td>
<td>Cytopaenias</td>
<td>Unequivocal dysplasia in &lt;10% of cells in one or more myeloid cell lines when accompanied by a cytogenetic abnormality considered as presumptive evidence for a diagnosis of MDS</td>
</tr>
<tr>
<td>MDS associated with isolated del(5q)</td>
<td>Anaemia</td>
<td>Normal to increased megakaryocytes with hypolobulated nuclei &lt;5% blasts</td>
</tr>
</tbody>
</table>

- Bicytopenia may occasionally be observed. Cases with pan cytopenia should be classified as MDS-U.
- If the marrow myeloblast percentage is <5% but there are 2%–4% myeloblasts in the blood, the diagnostic classification is RAEB-1. Cases of RCUD and RCMD with 1% myeloblasts in the blood should be classified as MDS-U.
- Cases with Auer rods and <5% myeloblasts in the blood and <10% in the marrow should be classified as RAEB-2.
- Unbalanced abnormalities: −7 or del(7q), −5 or del(5q), i(17q) or t(17p), −13 or del(13q), del(12p) or t(12p), del(9q), idic(X)(q13).
- Balanced abnormalities: t(11;16)(q23;p13.3), t(3;21)(q26.2;q22.1), t(1;3)(p36.3;q21.2), inv(3)(q21q26.2), t(2;11)(p21;q23), (6;9)(p23q34).

Table 4. The WHO classification of myelodysplastic syndromes [34]
A ML-like chemotherapy
AML-like intensive chemotherapy has limited indication in higher risk MDS patients. In particular, MDS patients with unfavourable karyotype show few CRs and shorter CR duration [45]. This treatment can be envisaged for younger patients (generally <60–65 years of age) with favourable cytogenetics according to IPSS categories and marrow blasts >10%, preferably as a bridge to alloSCT [I, B].

Suggested regimens with equivalent efficacy deduced from retrospective analyses are combinations of cytarabine with idarubicin, fludarabine or topotecan [IV, B] [41]. No improvement of outcome was reported by the addition of granulocyte–macrophage colony-stimulating factor (GM-CSF) or granulocyte colony-stimulating factor (G-CSF) [IV, C].

A direct comparison of the efficacy of AML-like chemotherapy versus azacitidine has been carried out in a small number of MDS patients and only in one randomised phase III trial: it suggested a superiority of the HMA without reaching statistical significance, but the number of patients was too small for any conclusion. A retrospective comparison of AML-like chemotherapy versus decitabine was carried out [46] in two groups of matched MDS patients and, while CR rates were equivalent, survival advantage was obtained only with the use of an HMA.

double abnormalities including del(5q); intermediate: del(7q), +8, +19, i(17q) and any other single abnormalities, any other double abnormalities; poor: −7 and inv(3)/t(3q)/del(3q) as single abnormalities, double abnormalities including −7/del(7q), complex (3 abnormalities); very poor; >3 abnormalities.

second-line treatment
IPSS higher risk MDS patients who fail to respond to azacitidine or are primary refractory to HMAs have an extremely poor survival (median <6 months) except for patients potentially eligible for alloSCT [50]. Retreatment with AML-like chemotherapy or low-dose AraC yields dismal results. The recommended approach is to enrol such patients in a clinical trial with investigational agents and, if the patient has become eligible for alloSCT, proceed to transplant [IV, B] [50].

allogeneic stem cell transplantation
At present, alloSCT is the only potentially curative treatment of higher risk MDS patients [I, A]. The major obstacle to alloSCT is the fact that most MDS patients are above the age of 70 years. Co-morbidity, age, IPSS and IPSS-R score, cytogenetics, conditioning regimen and donor selection are predictors of post-transplant outcome [51, 52] and should be taken into account carefully during the decision process. All patients diagnosed with higher risk MDS aged <65–70 years (although particularly ‘fit’ patients aged >70 years may sometimes be considered) should be evaluated for alloSCT eligibility and human leukocyte antigen (HLA)-identical (or single antigen mismatched) siblings or matched unrelated individuals should be considered as suitable donors [I, A] [52].

Regarding conditioning regimens, there is no randomised trial comparing reduced-intensity conditioning (RIC) to myeloablative approaches. At present, relapse seems to be higher in patients receiving RIC; therefore, patients aged <55 years and without co-morbidities should probably be offered myeloablative HSCT [IV, C].

Alternative sources such as cord blood should be further evaluated in clinical trials [II, C] [52]. It is debated whether treatment aimed at reducing the blast count should be carried out before alloSCT with AML-like chemotherapy or HMAs. This is

### Table 5. Revised International Prognostic Scoring System (IPSS-R) for myelodysplastic syndromes [7]

<table>
<thead>
<tr>
<th>Prognostic characteristics</th>
<th>Points</th>
<th>Very good</th>
<th>Good</th>
<th>Intermediate</th>
<th>Poor</th>
<th>Very poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetic risk category&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≥0.5</td>
<td>0</td>
<td>0.5</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
</tr>
<tr>
<td>Blasts in bone marrow, %</td>
<td>≤2</td>
<td>0</td>
<td>0.5</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
</tr>
<tr>
<td>Haemoglobin, g/dl</td>
<td>≥10</td>
<td>0</td>
<td>0.5</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
</tr>
<tr>
<td>Platelet count, ×10⁹/l</td>
<td>≥100</td>
<td>0</td>
<td>0.5</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
</tr>
<tr>
<td>Absolute neutrophil count, ×10⁹/l</td>
<td>≥0.8</td>
<td>0</td>
<td>0.5</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
</tr>
</tbody>
</table>

<sup>a</sup>Very good: −Y and del(11q) as single abnormalities; good: normal, del(5q), del(12p) and del(20q) as single abnormalities, double abnormalities including del(5q); intermediate: del(7q), +8, +19, i(17q) and any other single abnormalities, any other double abnormalities; poor: −7 and inv(3)/t(3q)/del(3q) as single abnormalities, double abnormalities including −7/del(7q), complex (3 abnormalities); very poor; >3 abnormalities.

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### AML-like chemotherapy

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### Low-dose chemotherapy

Low-dose cytarabine at the most prevalent schedules and dose (AraC 20 mg/m²/day, 14–21 days/every 4 weeks) was found to be significantly inferior to azacitidine (in terms of response and survival) in a randomised phase III study [42], especially in patients with unfavourable cytogenetics. However, low-dose cytarabine may still be a treatment option in higher risk MDS patients with normal karyotype [47] who are not candidates for any intensive chemotherapy or alloSCT, in particular when administration of azacitidine or decitabine is not possible (including for economic reasons) [IV, C]. In these patients, CR and PR are reached in 15%–20% of cases with significant myelosuppressive effects [48, 49].

### Second-line treatment

IPSS higher risk MDS patients who fail to respond to azacitidine or are primary refractory to HMAs have an extremely poor survival (median <6 months) except for patients potentially eligible for alloSCT [50]. Retreatment with AML-like chemotherapy or low-dose AraC yields dismal results. The recommended approach is to enrol such patients in a clinical trial with investigational agents and, if the patient has become eligible for alloSCT, proceed to transplant [IV, B] [50].

### Allogeneic stem cell transplantation

At present, alloSCT is the only potentially curative treatment of higher risk MDS patients [I, A]. The major obstacle to alloSCT is the fact that most MDS patients are above the age of 70 years. Co-morbidity, age, IPSS and IPSS-R score, cytogenetics, conditioning regimen and donor selection are predictors of post-transplant outcome [51, 52] and should be taken into account carefully during the decision process. All patients diagnosed with higher risk MDS aged <65–70 years (although particularly ‘fit’ patients aged >70 years may sometimes be considered) should be evaluated for alloSCT eligibility and human leukocyte antigen (HLA)-identical (or single antigen mismatched) siblings or matched unrelated individuals should be considered as suitable donors [I, A] [52].

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Alternative sources such as cord blood should be further evaluated in clinical trials [II, C] [52]. It is debated whether treatment aimed at reducing the blast count should be carried out before alloSCT with AML-like chemotherapy or HMAs. This is
generally considered when marrow blasts are >10%, especially for non-myeloablative alloSCT.

**treatment of lower risk MDS**

In lower risk MDS, the risk of AML progression is smaller and survival longer than in higher risk MDS, with about one-half of elderly patients dying from causes other than the consequences of MDS or AML [53]. In lower risk MDS, the main priority is generally the treatment of cytopaenias, mainly of anaemia (usually the predominant cytopaenia), and the improvement in quality of life (QoL). Still, some of these patients may be identified as carrying poorer prognosis, either rapidly by their revised IPSS score [8] or by other biological characteristics [54, 55], or subsequently by their resistance to first-line treatment [56], and may benefit from treatments generally applied to higher risk MDS.

Anaemia, because of failure of specific treatments, often eventually requires repeated RBC transfusions, leading to potential iron overload [42].

**treatment of anaemia**

**RBC transfusions or drugs?**

Chronic RBC transfusions could be considered as the sole approved treatment of anaemia of lower risk MDS, as very few drugs are approved in this situation and none has been demonstrated to improve survival. However, chronic RBC transfusions are associated with chronic anaemia, leading to excess morbidity, and they cannot completely correct impaired QoL [57, 58]. Although this remains disputed (see below), iron overload due to RBC transfusions may also be deleterious to various organs [57, 59]. Finally, researchers have found recently that, in lower risk MDS with anaemia, receiving ESAs had no impact on progression to AML but was an independent, favourable prognostic factor for survival [IV, B] [60–63].

**first-line treatment of anaemia in lower risk MDS**

*patients without del(5q)*: ESAs. ESAs, i.e. recombinant EPO or darbepoetin (DAR), remain the first choice treatment of anaemia in most lower risk MDS without del(5q) [60]. Weekly doses of 30 000–80 000 units of EPO or 150–300 μg of DAR alfa injection yield ~60% of erythroid responses, according to IWG 2006 response criteria [64], when the baseline EPO level is low and transfusion requirement is absent or limited, which is now the case in most patients where this treatment is considered [I, A] [60–62, 65, 66]. The efficacy of ESAs can be further improved by the addition of G-CSF [67, 68], and there are no data showing that one ESA is superior to another.

Responses to ESA occur within 8–12 weeks of treatment. Median duration of response to ESA is ~2 years, with longer responses in patients with major response according to IWG 2000 criteria [64], IPSS low or intermediate-1, marrow blasts <5% and no multi-lineage dysplasia [60–62].

*lower risk MDS with del 5q: lenalidomide.* Anaemia of lower risk MDS with del 5q, compared with that of other lower risk MDS, shows lower response rates and significantly shorter responses to ESA [69]. However after ESA failure, it responds to lenalidomide (LEN) in 60%–65% of the subjects, with a median duration of RBC transfusion independence (RBC-TI) of 2–2.5 years [I, A] [70, 71]. The recommended initial dose is 10 mg/day, 3 weeks out of every 4 weeks [71]. Cytogenetic response (CyR) is achieved in 50%–75% of subjects (including 30%–45% complete CyR). TP53 gene mutations, found in ~20% of lower risk MDS with del 5q, seem to confer resistance to LEN and a higher risk of AML progression [72], and their presence may require more aggressive treatment. Grade 3 or 4 neutropaenia and thrombocytopaenia, seen in ~60% of patients during the first weeks of treatment, constitute the most common adverse events associated with LEN [70, 71]. Close monitoring of blood counts is therefore required during this period, with dose reduction and/or addition of G-CSF if required.

**second-line treatments for anaemia of lower risk MDS**

*patients without del 5q.* Treatment after ESA failure (primary resistance or relapse after a response) in patients who remain with IPSS low or intermediate-1 MDS is still disappointing overall, with most patients eventually requiring long-term RBC transfusions. Second-line treatments currently used include anti-thymocyte globulin (ATG), HMAs and LEN.

Immunosuppressive drugs, including anti-lymphocyte or ATG, with or without ciclosporin, can yield an erythroid response (associated with response of other cytopaenias, especially thrombocytopaenia), in 25%–40% of the patients treated [73–77]. ATG results are better in relatively young (<65 years) low-risk MDS patients with a RBC transfusion history of <2 years, with normal karyotype (or possibly trisomy 8), with no excess blasts, HLA DR15 genotype, and possibly in patients with thrombocytopaenia in addition to anaemia, a small paroxysmal nocturnal haemoglobinuria clone or with marrow hypopcellularity [III, B] [73]. Therefore, this treatment is generally proposed to a relatively small minority of patients. HMAs have been reported to yield RBC-TI in 30%–40% of the patients [78, 79], and may also be effective on other cytopaenias in lower risk MDS [III, B]. They are approved in this situation in several countries, including the United States.

LEN yields RBC-TI in 25%–30% of lower risk MDS without del 5q resistant to ESA [80, 81], and the combination of LEN and ESA may yield higher RBC-TI rates than LEN alone in patients resistant to an ESA alone [I, B] [82].

*patients with del 5q.* Resistance to LEN in lower risk MDS with del 5q is associated with poor prognosis, even if no immediate progression to high-risk MDS is observed. Patients with TP53 gene mutation may have a particularly poor outcome [72]. Although no prospective data exist, these patients are likely to be suitable candidates for approaches having demonstrated a survival benefit in MDS, including HMAs and, whenever possible, alloSCT [IV, B] [82].

**treatment of neutropaenia and thrombocytopaenia**

In lower risk MDS, neutropaenia and thrombocytopaenia are less frequent than anaemia, and are infrequently isolated or profound.

White blood cells are <1.500 mm⁻³ in only 7% of lower risk MDS [83], and neutropaenia is rarely associated with life
threatening infection if no drugs worsening neutropaenia are used. G-CSF and GM-CSF can improve neutropaenia in 60%–75% of these cases, and can be considered in the treatment of neutropaenic fever in addition to anti-infective drugs, but their prolonged use has not had a demonstrated impact on survival.

Platelets <50 000/mm³ are seen in ∼30% of low-risk MDS [83]. High-dose androgens can improve thrombocytopaenia in about one-third of thrombocytopaenic lower risk MDS, but response is generally transient [III, C] [84–86]. The thrombopoietic (TPO) receptor-agonist romiplostim at high dose (500–1 500 μg/week) yielded 55% platelet responses in a phase II trial in lower risk MDS with thrombocytopaenia. However, in ∼15% of the patients, a transient rise in marrow blasts was seen, which was reversible after drug discontinuation. In a randomised phase II study versus placebo in lower risk MDS with thrombocytopaenia, romiplostim significantly reduced the incidence of severe bleeding and platelet transfusions [87]. While there was a suspected increase in the AML risk upon first analysis, this was not confirmed by later follow-up [87]. Eltrombopag, the other available TPO receptor agonist, is also currently being tested in both lower risk and higher risk MDS. Lower risk MDS patients seem to be particularly responsive to treatment with eltrombopag [88].

ATG and HMAs appear to give platelet response in 35%–40% of the cases of lower risk MDS, in addition to erythroid responses [III, C] [74, 77, 89]. See Figures 2 and 3.

**Supportive care and chelation therapy in MDS**

Supportive care is required in all patients with MDS at some point of the disease, and may be the only treatment of some patients in the long term, especially those with transfusion-dependent anaemia not responding to any of the agents described above [90]. In patients requiring repeated RBC transfusions, it is recommended to administer transfusions at sufficiently high haemoglobin threshold, i.e. at least 8 g/dl, and 9 g/dl or even 10 g/dl in case of co-morbidities worsened by anaemia or in case of poor functional tolerance and/or poor QoL or in elderly persons who are still very active. A sufficient number of RBC concentrates should be transfused each time, if necessary over 2 or 3 days, to increase the haemoglobin level >10 g/dl, and thereby limit the effects of chronic anaemia, especially on QoL [IV, A].

Except in patients receiving myelosuppressive drugs, prophylactic platelet transfusions are less used than RBC transfusions in MDS, especially in the long term. Likewise, prophylactic antibiotics and/or G-CSF are not recommended in case of neutropaenia, as they have not shown any impact on survival, but rapid onset of broad spectrum antibiotics is mandatory in these patients in case of fever or symptoms of infection. Short-term use of G-CSF during severe infections could be useful in neutropaenic patients, but this indication has not been validated.

Psychosocial support and contacts with patient support groups (when they exist) should be systematically offered.

A large debate exists about the deleterious effect of iron overload in MDS patients and whether iron chelation may be useful in patients with iron overload. In particular, while heart iron overload is a well-documented cause of heart failure in children with thalassaemia [91, 92], its incidence and clinical consequences are less certain in MDS patients receiving transfusions, particularly as many already have other causes of cardiac morbidity [40, 93]. However, heart MRI studies show that heart iron overload (reflected by a decrease in MRI heart T2*) is frequent in patients having received at least 70–80 RBC concentrates or more,
a frequent situation in low-risk MDS, and that a heart T2* value <20 ms is associated with decreased left ventricular ejection fraction and a risk of heart failure [94]. It has been suggested in retrospective studies that adequate chelation in highly transfused patients may improve their survival [IV, C] [95–97]. Prospective randomised studies are underway to confirm those results.

In the absence of prospective studies, published recommendations for iron chelation therapy so far only result from expert opinions [V] [98], which generally advocate starting chelation in patients with relatively favourable prognosis (i.e. low or intermediate-1-risk MDS), who have received 20–60 RBC concentrates, or if serum ferritin raises above 1000–2500 U/l, or if cardiac T2* is significantly reduced. Future candidates to alloSCT should be chelated early. Indeed, although the underlying mechanisms are unclear, it appears that even relatively moderate iron overload before alloSCT is associated with increased transplant-related mortality [II, B] [99–101].

Iron chelation is now made easier by the availability of oral iron chelators (especially deferasirox), in addition to the classical parenteral deferoxamine. Deferasirox is however frequently associated with gastrointestinal side-effects, and cannot be used in patients with renal failure [102]. Deferiprone, another oral iron chelator, is currently not approved for MDS in most countries, and can cause neutropenia in a small percentage of patients, a side-effect that is problematic in MDS [103].

**personalised medicine**

While many prognostic factors have been established in MDS, as seen above, most of them have been defined irrespective of treatment, in patient cohorts that mainly received supportive care, and it is often unclear if they are predictive of the efficacy of a given treatment. Furthermore, in spite of recent improvements, there are still too few effective treatment options in MDS, and there is limited choice for most patients.

The classical IPSS offers a valuable patient stratification, and this is why it served as a basis in Figures 2 and 3 summarising treatment indications: e.g. anaemia of IPSS low and intermediate-1 MDS often responds to ESAs, except in case of del 5q, where LEN is very efficacious. On the other hand, in IPSS intermediate-2 and high-risk patients, while azacitidine has shown it could improve survival, there are currently limited other options (except alloSCT, possible in a minority of patients).

Given the usual age of MDS patients, considering the patient’s age, general condition and co-morbidities is also crucial before making any treatment decisions.

**patient follow-up**

Except for follow-up of specific treatments, follow-up of MDS is largely based on regular blood counts, to detect anaemia that
will require RBC transfusions, while severe thrombocytopenia may require platelet transfusions and severe neutropenia mandates preventive measures against infection (e.g. during invasive procedures), or, more importantly, rapid onset of broad spectrum antibiotics in case of fever or symptoms of infection.

Bone marrow examination, with or without karyotype, is generally triggered by worsening of cytopaenias or appearance of circulating blasts rather than systematically carried out at regular intervals.

**note**

Levels of evidence and grades of recommendation have been applied using the system shown in Table 6. Statements without grading were considered justiﬁed standard clinical practice by the experts and the ESMO faculty.

**conflict of interest**

VS has reported honoraria received for lecturing from: Janssen-Cilag, GlaxoSmithKline, Novartis and Celgene. GS has reported Amgen (honoraria, advisory board, research funding); Boehringer-Ingelheim (advisory board); Celgene (honoraria, advisory board, research funding); Janssen-Cilag (honoraria, advisory board); Merck Sharp & Dohme (advisory board); Mirati Therapeutics, (advisory board); and Novartis (honoraria, advisory board, research funding). CB has reported consultancy/honoraria from Celgene, Pfizer and Roche. The other authors have reported no potential conflicts of interest.

**references**


