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

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Highlights:

- This ESMO Clinical Practice Guideline provides key recommendations for managing myelodysplastic syndromes
- It covers diagnosis, classification, staging and risk assessment of myelodysplastic syndromes
- Treatment recommendations for lower- and higher-risk myelodysplastic syndromes are also provided
- All recommendations were compiled by a multidisciplinary group of experts
- Recommendations are based on available scientific data and the authors' expert opinion

INCIDENCE AND EPIDEMIOLOGY

Myelodysplastic syndromes (MDS) are clonal haematopoietic stem cell (HSC) disorders predominating in the elderly, characterised by ineffective haematopoiesis leading to blood cytopaenias and progression to acute myeloid leukaemia (AML) in one-fourth to one-third of cases.[1] Their pathophysiology is characterised by a multi-step process involving cytogenetic changes and/or gene mutations,[2] abnormalities of the bone marrow microenvironment[3] and widespread gene hypermethylation at advanced stages.[4,5]

Median age at diagnosis of MDS is ~70 years and <10% are younger than 50 years.[6] The incidence of MDS is about 4 cases/100 000 inhabitants/year (reaching 40-50/100 000 in patients aged ≥70).[6] There are no known ethnic differences in the incidence of MDS, but in Asian populations, MDS tends to occur at an earlier age, more often with a hypocellular marrow and less often with isolated 5q deletion ('5q- syndrome'). Trisomy 8 also seems to occur more frequently in Asian populations compared with Western populations.[7]

The aetiology of MDS is only known in 15% of cases. An inherited predisposition to MDS is seen in one-third of paediatric MDS patients, including Down syndrome, Fanconi anaemia and neurofibromatosis. It is less frequent in adults, but an inherited predisposition should be assessed in MDS occurring in young adults or families with other cases of MDS, AML or aplastic anaemia. Point mutations of several genes including *DDX 41, GATA2, RUNX 1, ANKRD 26, ETV6* and telomerase complex genes (*TERC, TERT*) have been found in such familial cases.[8] Environmental factors include previous exposure to chemotherapy (ChT), especially alkylating agents and purine analogues,[9] radiotherapy (RT) or ionising radiation[10,11] and tobacco smoking.[12] Recognised occupational factors include benzene and its derivatives,[13] and more cases of MDS are reported among agricultural and industrial workers.[12,14] Cases of 'secondary MDS', particularly those occurring after ChT (therapy-related MDS), generally have poor prognostic factors, including complex cytogenetic findings involving chromosomes 5 and/or 7 and/or 17p.[15]

DIAGNOSIS AND PATHOLOGY/MOLECULAR BIOLOGY

Diagnosis of MDS is based on blood and bone marrow examination, showing blood cytopaenias, generally hypercellular (but sometimes hypocellular) marrow with dysplasia, with or without an excess of blasts.[16]

Well-established 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 [I, A]. At diagnosis, histology of bone marrow trephine biopsies is strongly recommended, especially to exclude other causes of cytopaenia and because of its potential prognostic information [I, A]. In difficult cases, such as cytopaenias with unspecific morphological changes and no cytogenetic changes, molecular analysis by next generation sequencing techniques to demonstrate clonality [I, A] and, in experienced hands, flow cytometry of blood and marrow cells can be useful for diagnosis [II, B].

Differential diagnoses of MDS includes a history of medication or ingestion of alcohol or other drugs and exclusion of other diseases, including autoimmune disorders, renal failure, malignancies, chronic infections, aplastic anaemia and paroxysmal nocturnal haemoglobinuria (PNH).[17]

MDS should be classified according to the World Health Organisation (WHO) criteria[16] with prognosis established by the international prognostic scoring system (IPSS)[18] or rather, its revised version (IPSS-R).[19] Prognosis is based on the marrow blast percentage, number and extent of cytopaenias and cytogenetic abnormalities, which are grouped in the IPSS-R.[18,19] Treatment varies from symptomatic therapy for cytopaenias, especially by transfusions, to allogeneic stem cell transplantation (allo-SCT).

Peripheral blood counts and differential blood counts

Almost all patients with MDS have blood cytopaenias, mostly anaemia (usually macrocytic) with or without other cytopaenias.

Laboratory parameters

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

be considered in cases with a clinical suspicion as small PNH clones can accompany MDS.

Cytomorphology

The hallmarks of cytomorphology in MDS are dysplastic features in ≥10% of marrow and/or peripheral blood cells of erythroid, granulocytic or megakaryocytic lineage. Marrow histology of trephine biopsies is of 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 marrow dysplastic features but no or very mild peripheral blood cytopaenias and normal karyotype, idiopathic dysplasia of unknown significance (IDUS)[20] can be diagnosed if no other cause of dysplasia is apparent (see **Table 1**). Patients with clonal somatic mutations and cytopaenias without dysplastic features and normal karyotype [clonal cytopaenias of uncertain significance (CCUS)] constitute a third group of patients with a higher risk of progression to MDS.[21,22]

When evaluating MDS blood films and marrow slides, certain cytological abnormalities should be considered (see **Table 2**). For an MDS diagnosis, the recommended number of cells to be reviewed per slide is 200 for the blood film and up to 500 for bone marrow.[23] The marrow blast count is crucial given its important prognostic value. ‘Blasts’ should include agranular blasts, myeloblasts and promonocytes but not promyelocytes. Staining for iron with Prussian blue (Perls stain) should always be performed in lower-risk MDS in order to evaluate the presence of ring sideroblasts.

Histopathology

In the European Union (EU), contrary to the United States, MDS are mainly followed-up by bone marrow aspirate rather than biopsy. Bone marrow trephine biopsy, however, is useful at diagnosis to assess cellularity and fibrosis. In case of hypocellular aspirates or dry puncture, it allows a diagnosis of hypoplastic MDS or fibrotic MDS. It may also exclude other differential diagnoses and may provide additional information on dysplastic features (mainly of megakaryocytes) and prognostic information, especially by showing fibrosis. It is therefore strongly recommended in addition to bone marrow aspiration at diagnosis.[24,25]

Cytogenetics

In MDS, clonal chromosome abnormalities are observed in 30% to >80% of patients.[26] In the remaining 20%-70% of patients with a normal karyotype, sub-microscopic alterations such as point mutations, microdeletions or amplifications, epigenetic changes or copy number neutral loss such as uniparental disomy (UPD) provide the genetic basis for the disease.[2,27] Currently, standard karyotype still has the highest prognostic value of all IPSS-R parameters.[19]

Chromosome banding analysis is performed on dividing metaphase cells. Whenever possible, 20-25 metaphases should be analysed so not to miss smaller cell clones that are frequent, especially in low-risk MDS. Complex abnormalities are defined as three or more independent abnormalities in at least two metaphases.[28] Cytogenetic analysis should follow minimal standards fixed by the 'Workpackage Cytogenetics' of the European LeukemiaNet (see **Figure 1**).[29]

In an international database of 2124 patients with MDS, 52% had one or more clonal cytogenetic abnormalities. Abnormal karyotypes were clearly associated with the severity of MDS, increasing with marrow blast count and the intensity of dysplasias.[26]

Several independent studies have proven the dismal outcome related to complex abnormalities.[26,30,31] Complex abnormalities can be further subdivided by the presence or absence of *TP53* mutations, the number of cytogenetic changes and severe anaemia.[32]

Assessing karyotype during follow-up is also useful as cytogenetic progression is associated with poorer prognosis, while cytogenetic response after a given treatment may be associated with a better outcome.[31,33,34]

Molecular genetics

Acquired molecular mutations are seen in 80%-90% of MDS patients,[35,36] affecting epigenetic regulation and chromatin-remodelling (*TET2*, *DNMT3A*, *ASXL1*, *IDH1/2*, *EZH2*), pre-mRNA splicing factors *(SF3B1, SRSF2, U2AF1)*, transcription *(TP53, RUNX1)* and signal transduction (*NRAS, CBL*), and can demonstrate clonal disease (**Table 3**). The most frequent mutations (present each in >10% of patients) affect *TET2, SF3B1, ASXL1, SRSF2, DNMT3A* and *RUNX1*, but approximately one or more of around 30 genes are

mutated in >1% of patients. Forty percent of patients have more than one mutation. Most mutations, except *SF3B1*, carry a poor prognosis, and prognosis is worse with a larger number of mutations.[35] Molecular profiling can also be a valuable diagnostic tool if MDS is uncertain in ICUS or IDUS,[37] but mutations have limited impact on the clinical management in most cases. Exceptions are *SF3B1* mutation in lower-risk MDS (associated with a favourable prognosis and likely to response to luspatercept) and *TP53* mutation in lower-risk MDS with del(5q), associated with an increased risk of leukaemic transformation, lower cytogenetic response rate and shorter response duration to lenalidomide (LEN).[38]

Clonal haematopoiesis of indeterminate potential

Somatic mutations seen in myeloid neoplasias have been observed in elderly healthy persons (10%-13% of those aged 70-80 years).[39-41] The most frequently affected gene is *DNMT3A*, followed by *TET2, ASXL1,* and less often, *JAK2*, *PPM1D*, *SF3B1*, *SRSF2* and *TP53.* Most patients have only one mutation, and generally with variant allele frequency (VAF) of ≤10%. Since individuals examined had no obvious haematological disease, the term clonal haematopoiesis of indeterminate potential (CHIP) was established.[42] CHIP is associated with a 13-fold increased risk of developing a haematological neoplasia and a 1.4-fold risk of death also related to an increased incidence of atherosclerotic cardiovascular disease.[43]

Patients with CHIP and unexplained cytopaenia but no morphological evidence for myelodysplasia have been classified as CCUS. Over 30% of patients with unexplained cytopaenias appear to have CCUS, with an increased risk of developing myeloid neoplasia depending on the type of mutation.[37,44]

Flow cytometry

Flow cytometry abnormalities of myeloid precursors may support a diagnosis of MDS, but this method should be used by experts according to published guidelines, and should not be used for the evaluation of the percentage of bone marrow blasts.[45,46]

Classification

The current WHO classification of MDS[16] divides MDS with <5% blasts into those with single lineage or multilineage dysplasia (**Table 4**). In MDS with single lineage dysplasia, patients with ring sideroblasts (MDS-RS) have a low AML progression rate and generally have a prolonged overall survival (OS) if *SF3B1* mutation is present and is isolated or at least not associated with poor prognosis mutations such as *RUNX1* mutation. The entity of del(5q) MDS is not defined by morphological criteria but by the presence of del(5q), making cytogenetic analysis mandatory. This classification has recognised entities with germline predisposition (**Table 5**).[8] Finally, chronic myelomonocytic leukaemia has been moved to myelodysplastic/myeloproliferative neoplasms.[16]

Recommendations

- Diagnosis is based on blood count, marrow aspirate and marrow karyotype [I, A].
- Bone marrow biopsy is recommended at diagnosis [I, A].
- Molecular biology is useful for diagnosis if blood and marrow tests are inconclusive [I, A].
- Flow cytometry of blood and marrow cells is useful for diagnosis in experienced hands [II, B].

STAGING AND RISK ASSESSMENT

The natural course of MDS is highly variable, with survival ranging from a few weeks to many years. Causes of deaths are mainly related to MDS in higher-risk patients, while a large proportion of patients with lower-risk MDS die from non-MDS causes, i.e. comorbidities associated with the typical age of MDS patients.[47,48] Median OS is 15-30 months and the 5-year AML progression rate is 25%-35%. Bone marrow failure (infection and haemorrhage) is the leading cause of death before AML progression.[49]

Main risk factors, allowing an individual risk-adapted treatment strategy, are cytogenetic abnormalities, marrow blasts percentage and number and severity of cytopaenias. The IPSS[18] and IPSS-R[19] (**Table 6**) are based on these variables. They have been validated in external series[50] and their use is strongly recommended for planning treatment[51] [I, A]. 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,[19] and offers better prognostic classification than the IPSS. For therapeutic purposes, the term 'lower-risk' MDS generally applies to cases with IPSS-R up to 3.5 including very low- and low-risk and part of intermediate-risk IPSS-R patients. 'Higher-risk' MDS include patients with IPSS-R ≥4.0, i.e. high- and very high-risk, and the remaining intermediate-risk IPSS-R patients. There is obviously some uncertainty for intermediate-risk IPSS-R patients where the treatment approach should take additional factors into account.

Other factors for prognosis and treatment choice, particularly for intermediate-risk patients, include patient-related characteristics such as age,[19] Eastern Cooperative Oncology Group performance status (PS)[19] and comorbidities.[52] Other disease-related factors include multilineage dysplasia, red blood cell transfusion dependence (RBC-TD), serum LDH, bone marrow fibrosis,[52] flow cytometry immunophenotyping[53] and increasingly, gene somatic mutation profiling and copy number.[2,35,54] Data on the independent prognostic impact of somatic mutations are still lacking and so their use in routine practice to guide therapeutic decisions is not recommended [II, B] except for *SF3B1* in lower-risk MDS, *TP53* mutation in lower-risk MDS with del(5q) or MDS with complex karyotype [I, A], and *IDH1* and *IDH2* mutations as these can be targeted by specific inhibitors. The diagnostic strategy may be adapted according to the availability of new targeted therapies.

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 allo-SCT and hypomethylating agents (HMAs), factors that may be prognostic in patients treated with these interventions are starting to be defined.

Recommendations

- IPSS-R is required for prognostic evaluation [I, A].
- Molecular analysis may add prognostic value [II, B], especially for *TP53* [in del(5q) MDS] and *SF3B1* mutations in patients with <5% blasts [I, A].

TREATMENT

Response criteria in MDS

Response criteria to treatment in MDS are based on recommendations of an international working group (IWG 2006)[55] that define (i) responses aimed at modifying the disease course [mainly allo-SCT, intensive ChT and HMAs, including complete remission (CR), partial remission (PR), stable disease (SD) and progression], (ii) improvement of cytopaenias ('haematological improvement' or HI) in one or several lineages (erythroid, platelet and neutrophil responses), and is particularly adapted to treatments which, like growth factors, can improve these cytopaenias with no obvious effect on the disease course. While CR and PR are generally associated with improvement in cytopaenias, the second type of response is often designed as 'stable disease with HI (on the erythroid and/or platelet and/or neutrophil) lineage'. An international group of MDS experts has recently proposed a revision to these criteria (IWG 2018).[56]

Treatment of higher-risk MDS patients

Higher-risk MDS carries a major risk of progression to AML and a short survival, and treatment should aim to modify the disease course, with options including allo-SCT, HMAs and, less frequently, ChT (mainly intensive anthracycline-cytarabine combinations).[57] In most patients with higher-risk MDS, HMAs are the first-line reference treatment (**Figure 2**).

HMAs. In patients with higher-risk MDS without major comorbidities who are not immediately eligible for allo-SCT, azacitidine is recommended [I, A]. The use of azacitidine may be preferable compared with the alternative HMA, decitabine, since findings from a randomised trial showed that azacitidine was superior to conventional care regimens [i.e. supportive care, low-dose cytarabine (LDAC) and AML-like ChT],[58,59] whereas there was no clear survival advantage with decitabine over conventional treatment in two phase III trials. Of note, while the pivotal AZA-001 phase III trial[58] suggested that azacitidine could yield a median OS of 24 months in higher-risk MDS, most large 'real life' studies have suggested a median OS of 15-18 months, a difference often observed between patients included in clinical trials versus all comers.[60]

As most patients only respond to azacitidine after several courses, at least six courses are recommended as part of the following schedule: azacitidine 75 mg/m^2/day subcutaneously for 7 consecutive days every 28 days [II, B]. However, '5-2-2' regimens

(from Monday to Friday, and Monday and Tuesday of the following week) are often easier to apply and are considered acceptable.

Besides induction of CR and PR, achievement of HI according to IWG 2006 criteria is associated with a prolongation of survival compared with supportive care or LDAC [III, B].[61]

The use of 2-6 cycles of azacitidine is quite common before haematopoietic stem cell transplantation (HSCT) to reduce blasts in bone marrow or for logistical reasons (to allow time for finding an adequate SCT donor). Its potential risks and benefits over no treatment is currently being evaluated in clinical trials [III, B].

AML-like ChT. AML-like intensive ChT has a limited indication in patients with higher-risk MDS. In particular, MDS patients with an unfavourable karyotype show few CRs and shorter CR duration than those with a normal karyotype.[62-64] It can be envisaged for fit patients (generally <70 years of age) without unfavourable cytogenetics (especially patients with a normal karyotype) and >10% marrow blasts, preferably as a bridge to allo-SCT [I, B].

Suggested regimens with equivalent efficacy are combinations of cytarabine with idarubicin, or fludarabine [IV, B].[57]

A direct comparison between AML-like ChT and azacitidine has been performed in a small number of MDS patients in one randomised phase III trial. This suggested a superiority of the HMA in terms of survival (but not CR rate) without reaching statistical significance, but the number of patients was too small to draw any definitive conclusions.[58] A retrospective comparison of AML-like ChT versus decitabine was performed in two groups of matched MDS patients, and while CR rates were equivalent, a survival advantage was seen only with the use of an HMA.[65]

Recently, CPX 351, an encapsulated form of daunorubicin and cytarabine, proved superior to conventional daunorubicin and cytarabine in AML with MDS features and AML post-MDS (AML with myelodysplasia-related changes according to WHO 2016 classification[16]), and it is approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in those AML subsets, including therapy-related AML.[66] Whether it is also superior to conventional ChT in higher-risk MDS needs to be demonstrated.

Low-dose ChT. LDAC (generally cytarabine 20 mg/m^2/day for 10–14 days/4 weeks) was inferior to azacitidine (in terms of response and survival) in a randomised phase III study,[58] especially in patients with unfavourable cytogenetics.[67,68]

New treatments (especially in combination with an HMA). Clinical trials are testing whether the addition of another drug to azacitidine can improve outcomes but so far no combination has demonstrated a clear advantage over azacitidine alone, although some are promising in elderly patients with AML treated with an HMA-based approach.[69-71] New HMAs with a longer half-life (potentially increasing the hypomethylating effect) are currently being tested in MDS (and AML), especially oral drugs.[72,73]

IPSS higher-risk MDS patients who fail to respond to HMAs have a very poor survival (median <6 months) unless they are potentially eligible for allo-SCT.[74] The recommended approach is to enrol these patients into a clinical trial with investigational agents [IV, B].[74]

The IDH1 inhibitor, ivosidenib, and IDH2 inhibitor, enasidenib, have shown significant activity in AML with the respective mutations and are approved by the FDA in those settings.[75,76] They are also being tested in clinical trials in MDS, which carries *IDH1/2* mutations in around 15% of cases. Of note, those mutations may be absent at HMA onset and appear later in the disease course at HMA failure. The bcl2 inhibitor, venetoclax, is approved by the FDA in combination with an HMA in elderly patients with AML and is also being tested in higher-risk MDS, especially in combination with azacitidine.[71]

allo-SCT. allo-SCT remains the only potentially curative treatment for higher-risk MDS patients [I, A], but its major obstacle is age as most MDS patients are >70 years. Comorbidity, age, IPSS-R score, cytogenetics, mutations including *TP53* mutation,[77] conditioning regimen and donor selection are predictors of post-transplant outcome[78,79] and should be considered during the decision process. All patients with higher-risk MDS up to 70 years (although particularly 'fit' patients aged >70 years can sometimes be considered) should be evaluated for allo-SCT eligibility at diagnosis and whenever required during the disease course. Human leukocyte antigen (HLA)-identical (or single

antigen mismatched) siblings or matched unrelated individuals should be considered as suitable donors [I, A].[79] Haploidentical donors and, less often, cord blood are now widely used as alternative donors with comparable outcomes [II, B].

Regarding conditioning regimens, whether reduced-intensity conditioning (RIC) or myeloablative approaches should be used is often disputed. The relapse risk seems to be higher in patients receiving RIC; therefore, patients aged <55 years and without comorbidities should probably be offered myeloablative HSCT [II, B].

It is debated whether treatment aimed at reducing the blast count should be performed before allo-SCT with AML-like ChT or HMAs. This is generally considered when marrow blasts are >10%, especially for non-myeloablative allo-SCT [III, A].[80]

It is now widely accepted that systemic iron overload contributes to negative outcomes after allo-HSCT in MDS.[81] Elevated labile plasma iron levels before or during allo-HSCT predict an increased incidence of infection-related non-relapse mortality and a decreased OS in patients with AML or MDS. Therefore, eligible patients should receive appropriate iron chelation, at least until the onset of conditioning treatment [III, B].[81,82]

Treatment of lower-risk MDS

In lower-risk MDS, the risk of AML progression is lower, and around half of elderly patients die from causes other than MDS or AML. The main priority is therefore generally the treatment of cytopaenias, mainly of anaemia (usually the predominant cytopaenia), and improvement in quality of life (QoL). Still, some of these patients may be identified as having a poorer prognosis, either by their IPSS-R score[19] or by other biological characteristics like somatic mutations[83] or subsequently by their resistance to first-line treatment,[84] and may benefit from treatments generally applied to higher-risk MDS [IV, C]. This applies particularly to patients with an intermediate IPSS-R (**Figure 3**).

Anaemia due to failure of specific treatments often requires repeated RBC transfusions, leading to potential iron overload.[58]

Treatment of anaemia.

RBC transfusions or drugs? Chronic RBC transfusions can be considered as the sole treatment for anaemia in lower-risk MDS as very few drugs are approved in this

setting and none have demonstrated a survival improvement except ESA. However, repeated RBC transfusions are associated with chronic anaemia, leading to excessive morbidity, and they cannot completely correct impaired QoL.[85,86] Iron overload due to RBC transfusions may also be deleterious to various organs.[85,87] Receiving ESAs has no impact on progression to AML but is an independent, favourable prognostic factor for survival [IV, B].[88-91]

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).[88] Weekly doses of 30 000-80 000 units of EPO or 150-300 µg of DAR injection yield 40%-60% erythroid responses according to IWG 2006 response criteria[55] when the baseline EPO level is low (<200-500 U/l) and transfusion requirement is absent or limited, since low baseline serum EPO level and low or no RBC transfusion requirement are the two main prognostic factors of response to ESAs [I, A].[86,88-90,92,93]

Efficacy of ESAs can be improved by the addition of granulocyte colony-stimulating factor (G-CSF),[90,94] but there are no data showing that one ESA is superior to another. Only one ESA, i.e. EPO alpha (and its biosimilars), is formally approved by the EMA for lower-risk MDS patients with serum EPO levels below 200 U/l.[92]

Responses to ESA occur within 8-12 weeks of treatment. Median duration of response is 20-24 months.[86,88-90,92]

Lower-risk MDS with del(5q): LEN. Anaemia of lower-risk MDS with del(5q) is associated with lower response rates and significantly shorter responses to ESA compared with other lower-risk MDS.[95] However, it responds to LEN in 60%-65% of patients, with a median duration of RBC transfusion independence (RBC-TI) of 2-2.5 years [I, A].[96,97] The recommended initial dose is 10 mg/day for 3 weeks every 4 weeks.[98] Cytogenetic response (CyR) is achieved in 50%-75% of patients (including 30%-45% complete CyR). *TP53* gene mutations, found in ~20% of lower-risk MDS with del(5q), confer resistance to LEN and a higher risk of AML progression.[38] Thus, patients with del(5q) lower-risk MDS harbouring or developing a *TP53* mutation (during LEN treatment) require intensified disease surveillance, including regular bone marrow assessment of

clonal evolution [III, A]. Patients with a chromosomal abnormality in addition to del(5q) appear to have similar outcomes as those with isolated del(5q), except for some additional abnormalities like +8,[97] -7 or del(7q), or when there are two or more additional abnormalities, but those patients are not classified as lower-risk MDS.[96,97]

Grade 3 or 4 neutropaenia and thrombocytopaenia, seen in ~60% of patients during the first weeks of treatment, constitute the most common adverse events of LEN.[96,97] Close monitoring of blood counts is therefore required during this period, with dose reduction and/or addition of G-CSF if required.

In the EU, LEN is approved for the treatment of lower-risk MDS with del(5q) and RBC-TD only after failure or ineligibility to ESA.

Second-line treatments for anaemia in lower-risk MDS.

Patients without del(5q). Treatment after ESA failure (primary or secondary resistance) in patients who remain with IPSS low or intermediate-1 MDS is disappointing, with most patients eventually requiring long-term RBC transfusions. Second-line treatments currently used, but not approved in most countries, include anti-thymocyte globulin (ATG), HMAs and LEN.

ATG, ± cyclosporine, can yield an erythroid response (associated with response of other cytopaenias, especially thrombocytopaenia) in 25%-40% of patients [II, B].[99-101] ATG results are better in relatively young (<65 years), lower-risk MDS patients with a recent RBC transfusion history, normal karyotype (or possibly trisomy 8), no excess blasts and HLA DR15 genotype, and in patients with thrombocytopaenia, a small paroxysmal nocturnal haemoglobinuria clone or with marrow hypocellularity [III, B].[102] Therefore, this treatment is generally proposed to a minority of patients. As in aplastic anaemia, horse ATG appears to achieve better results than rabbit ATG.[101]

HMAs yield RBC-TI in 20%-40% of patients,[103,104] and may also improve other cytopaenias in lower-risk MDS [III, B].[105] They are approved in this setting in several countries, including the United States, but not in Europe.

LEN yields an RBC-TI in 25%-30% of lower-risk MDS patients without del(5q) resistant to ESA,[106,107] and the combination of LEN and ESA may yield higher RBC-TI rates than LEN alone in this setting [I, B].[108] However, LEN is not approved in non-del(5q) patients.

Luspatercept (ACE-536) has recently shown promising results in RBC transfusion-dependent, lower-risk MDS, with erythroid response and RBC-TI of 63% and 38%, respectively, with limited toxicity in a phase II study, and even better results in patients with MDS-RS or *SF3B1* mutation. Results were confirmed in a phase III placebo-controlled randomised study of luspatercept in RBC transfusion-dependent IPSS-R very low-, low- or intermediate-risk MDS-RS or with *SF3B1* mutation refractory to ESA,[109] and this drug has recently been approved in this setting by the FDA and EMA [I, A].[110]

Patients with del(5q). Resistance to LEN in lower-risk MDS with del(5q) is associated with a poor prognosis, even if no immediate progression to high-risk MDS is observed. Patients with *TP53* gene mutation may have a particularly poor outcome[38] and are considered candidates for approaches that have demonstrated a survival benefit in higher-risk MDS, including HMAs, and whenever possible, allo-SCT [IV, B].[108]

Treatment of neutropaenia and thrombocytopaenia. In lower-risk MDS, neutropaenia and thrombocytopaenia are less frequent than anaemia, and are rarely isolated or profound.

Neutrophils are <1500/mm^3 in only 7% of lower-risk MDS, and neutropaenia is rarely associated with life-threatening infections if no drugs worsening neutropaenia are used. G-CSF can improve neutropaenia in 60%-75% of these cases and can be added to anti-infective drugs [III, C], but its prolonged use has not demonstrated any impact on survival.

Platelets below 50 000/mm^3 are seen in ~30% of low-risk MDS. High-dose androgens can improve thrombocytopaenia in one-third of thrombocytopaenic lower-risk MDS, but response is generally transient [III, C].[111,112] The thrombopoietin (TPO) receptor agonist (TPO-RA), romiplostim, at high doses (500-1000 µg/week) yielded a 55% platelet response in a phase II trial in patients with lower-risk MDS and thrombocytopaenia. However, in ~15% of patients, a transient rise in marrow blasts and/or the appearance of peripheral blasts was seen which was reversible after drug discontinuation.[113] In a randomised phase II study versus placebo in patients with lower-risk MDS and thrombocytopaenia, romiplostim significantly reduced the incidence of severe bleeding and platelet transfusions.[114] While there was a suspected increase in AML risk upon first

analysis, this was not confirmed by later follow-up.[114] Results of a randomised trial in lower-risk MDS patients treated with eltrombopag, an oral TPO-RA, showed a 47% platelet response and a reduction in bleeding events with no obvious safety concerns and no observed rise in marrow blasts.[115] TPO-RAs are not approved for MDS in Europe and currently cannot be recommended outside of clinical trials or registries at this time. They should also be restricted to patients without excess of marrow blasts [II, C].

ATG ± cyclosporine (in selected cases, as described above) and HMAs achieve platelet response in 35%-40% of cases of lower-risk MDS in addition to erythroid responses [III, C][99-101] (see **Figures 2** and **3**).

Supportive care and chelation therapy in MDS

Supportive care is required in all MDS patients at some point in the disease and may be the only long-term treatment for unfit patients and those not responding to the agents described above. In patients requiring repeated RBC transfusions, administration at a sufficiently high haemoglobin threshold is recommended (i.e. at least 8 g/dl, and 9 g/dl or even 10g/dl in cases of comorbidities or poor functional tolerance). A sufficient number of RBC concentrates should be transfused each time, over 2 or 3 days if needed, to increase the haemoglobin level above 10 g/dl and limit the effects of chronic anaemia, especially on QoL [IV, A].

Aside from patients receiving myelosuppressive drugs, prophylactic platelet transfusions are not commonly used. Prophylactic antibiotics and/or G-CSF are not recommended in case of neutropaenia, but rapid onset of broad-spectrum antibiotics is mandatory in case of fever or symptoms of infection [II, A]. Short-term use of G-CSF during severe infections could be useful in neutropaenic patients.

Psychosocial support and contact with patient support groups should be offered.

A debate exists about the deleterious effect of iron overload in MDS patients and the role of iron chelation in those patients. While heart iron overload is a well-documented cause of heart failure in children with thalassaemia,[116,117] its clinical consequences are less certain in transfused MDS patients, particularly as many have other causes of cardiac morbidity.[118,119] However, cardiovascular magnetic resonance (CMR) imaging studies show that heart iron overload [reflected by a decrease in T2-star (T2*) CMR imaging] is frequent in patients who have received at least 70-80 RBC concentrates, a frequent

situation in low-risk MDS, and that heart T2* <20 milliseconds is associated with decreased left ventricular ejection fraction and a risk of heart failure.[120] Retrospective studies suggest that adequate chelation in highly-transfused patients may improve their survival [IV, C].[98,121] The TELESTO trial prospectively examined iron chelation in lower-risk MDS, suggesting a significant improvement in event-free survival in chelated patients.[122] However, this was a composite endpoint, including survival, cardiac and liver function.

Published recommendations for iron chelation therapy [I, V][123] generally advocate starting chelation in patients with a relatively favourable prognosis (i.e. low- or intermediate-1-risk MDS) who have received 20-60 RBC concentrates, or if serum ferritin rises above 1000-2500 U/l. Potential candidates for allo-SCT should, however, be chelated early. Indeed, although the underlying mechanisms are unclear, it appears that even a relatively moderate iron overload before allo-SCT is associated with increased transplant-related mortality [III, B].[81,82,124] Chelation may also be strongly recommended in patients with lower-risk MDS who are not candidates for allo-SCT but have signs of major iron overload, including significantly reduced cardiac T2* by MRI imaging [III, B].

Iron chelation is made easier by the availability of oral iron chelators (especially deferasirox) in addition to the classical parenteral deferoxamine. Deferasirox cannot be used in patients with renal failure.[125] Deferiprone, another oral iron chelator, is currently not approved for use in MDS in most countries because it can also cause neutropaenia in a small number of patients, which is problematic in MDS.[126]

Recommendations

- Azacitidine is recommended in patients with higher-risk MDS without major comorbidities not immediately eligible for allo-SCT [I, A].
- AML-like ChT is recommended for fit patients (generally <70 years of age) with favourable cytogenetics according to IPSS and marrow blasts ≥10%, preferably as a bridge to allo-SCT [I, B].
- allo-SCT should be proposed to all higher-risk MDS patients <70 years old without major comorbidities and with a donor [I, A].

- Reducing the marrow blast count before allo-SCT with AML-like ChT or HMAs is generally considered when marrow blasts are ≥10%, especially for non-myeloablative allo-SCT [III, A].
- ESAs (especially EPO alpha) are recommended for the first-line treatment of anaemia in lower-risk MDS in patients without del(5q) [I, A].
- For transfusion-dependent anaemia of lower-risk MDS with del(5q), LEN is the most effective drug [I, A].
- After ESA failure, ATG (± cyclosporine) has efficacy in specific younger patient cohorts of lower-risk MDS [II, B].
- After ESA failure in RBC transfusion-dependent MDS-RS, luspatercept is recommended [I, A].
- Other second-line treatments for anaemia after ESA failure include LEN ± ESA [II, B] and HMAs [II, B], but they are not approved in Europe for this indication.
- TPO-RAs (romiplostim, eltrombopag) have some efficacy in cases of severe thrombocytopaenia but they are not approved in MDS and should only be used in patients with marrow blasts <5% [II, C].
- In patients with transfusion iron overload, iron chelation is strongly recommended in candidates for allo-SCT [III, B].
- In non-transplant candidates with lower-risk MDS, iron chelation is strongly recommended in patients with major iron overload (e.g. significantly reduced cardiac T2*) [III, B], but its use is more controversial in patients without major iron overload [I, V].

PERSONALISED MEDICINE

Most prognostic factors in MDS have been defined irrespective of treatment and it is often unclear if they are predictive of efficacy of a given treatment.

The IPSS and IPSS-R offer a valuable means of patient stratification and have therefore served as a basis for **Figures 2** and **3** to summarise treatment recommendations. For example, anaemia of lower-risk MDS often responds to ESAs, except in case of del(5q) where LEN is very effective. On the other hand, in higher-risk

patients, while azacitidine has shown it could improve survival, there are currently limited alternative options (except allo-SCT for a minority of patients).

Consideration of the patient's age, PS, comorbidities, frailty and desire (after adequate information provided by the medical team) is also crucial before making any treatment decision.

FOLLOW-UP

Except for specific treatments, follow-up of MDS is largely based on regular blood counts to detect worsening cytopaenias [anaemia or severe thrombocytopaenia requiring transfusions, or severe neutropaenia mandating preventive measures against infection (e.g. during invasive procedures)] and rapid onset of broad-spectrum antibiotics in case of symptoms of infection.

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

METHODOLOGY

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. Levels of evidence and grades of recommendation have been applied using the system shown in **supplementary Table S1,** available at *Annals of Oncology* online.[127] Statements without grading were considered justified standard clinical practice by the authors.

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Figure 1. Recommended standard algorithm for cytogenetic analysis in MDS[29]

FISH, fluorescence *in situ* hybridisation; ISCN, International System for Human Cytogenetic Nomenclature; MDS, myelodysplastic syndrome.

Figure 2. Treatment algorithm for higher-risk MDS

allo-SCT, allogenic stem cell transplant; AML, acute myeloid leukaemia; ChT, chemotherapy; HMA, hypomethylating agent; IPSS-R, revised international prognostic scoring system; MDS, myelodysplastic syndrome; RBC, red blood cell.

[a] For IPSS-R intermediate-risk MDS patients, whether they should initially receive treatment for lower-risk MDS or higher-risk MDS is also based on other factors including age, comorbidities, importance of cytopaenias, somatic mutations, effect of first-line treatment, etc.

Figure 3. Treatment algorithm for lower-risk MDS

ATG, antithymocyte globulin; EPO, erythropoietin; G-CSF, granulocyte colony-stimulating factor; GoR, grade of recommendation; Hb, haemoglobin; IPSS-R, revised international prognostic scoring system; LoE, level of evidence; MDS, myelodysplastic syndrome; MDS-RS, myelodysplastic syndrome with ring sideroblasts; RBC, red blood cell; TPO-RA, thrombopoietin receptor agonist.

[a] For IPSS-R intermediate-risk MDS patients, whether they should initially receive treatment for lower-risk MDS or higher-risk MDS is also based on other factors including age, comorbidities, importance of cytopaenias, somatic mutations, effect of first-line treatment, etc.

Table 1. Definition of ICUS, IDUS, CHIP and CCUS[21,22]

	Characteristics
ICUS	• Mild cytopaenia for at least 4 months (haemoglobin <11.0 g/dl, neutropaenia <1500/µl and/or thrombocytopaenia <100 000/µl • No or only mild (<10%) marrow dysplasia • Marrow blasts <5% • No clonal cytogenetic or molecular markers • Exclusion of other diseases
IDUS	• No significant cytopaenia (i.e. haemoglobin ≥11g/dl, neutrophils ≥1500/µl and platelets ≥100 000/µl) • Marked dysplasia in >10% of neutrophilic and/or erythroid and/or megakaryocytes lineages • Marrow blasts <5% • No clonal cytogenetic or molecular markers
CHIP	• No significant cytopaenia • No or only mild (<10%) dysplasia • Marrow blasts <5% • Presence of one or more MDS-related mutation • Clonality defined by mutation of myeloid disorder associated genes (including particularly *DNMT3A*, *ASXL1*, *TET2*, *JAK2* and *TP53* genes), with a VAF of between 2% and 30%
CCUS	• Cytopaenia for at least 4 months (haemoglobin <11.0 g/dL and/or neutropaenia <1500/µL and/or thrombocytopaenia <100 000/µL • No or only mild (<10%) marrow dysplasia

	• Marrow blasts <5% • Presence of one or more MDS-related mutation • Clonality defined by mutation of myeloid disorder associated genes (including particularly *DNMT3A*, *ASXL1*, *TET2*, *JAK2* and *TP53* genes), with a VAF of between 2% and 30%

CCUS, clonal cytopaenias of uncertain significance; CHIP, clonal haematopoiesis of indeterminate potential; ICUS, idiopathic cytopaenias of uncertain significance; IDUS, idiopathic dysplasia of unknown significance; MDS, myelodysplastic syndromes; VAF, variant allele frequency.

Table 2. Signs of dysplasia in myelodysplastic syndromes

Peripheral blood	
• Granulocytes	Pseudo-Pelger-cells, abnormal chromatin clumping, hypo-/degranulation, left shift
• Platelets	Giant platelets, anisometry of platelets
• Red cells	Anisocytosis, poikilocytosis, dimorphic erythrocytes, polychromasia, hypochromasia, megalocytes, basophilic stippling, presence of nucleated erythroid precursors, tear drop cells, ovalocytes, fragmentocytes
Bone marrow	
• Cellularity of the marrow	Typically hypercellularity, rarely hypocellularity
• Erythropoiesis	Megaloblastoid changes, multinuclearity, nuclear budding, non-round nuclei, karyorrhexis, nuclear bridges, atypical mitoses, sideroblastosis, ring sideroblasts, Periodic Acid Schiff-positive red cell precursors
• Megakaryopoiesis	Micromegakaryocytes, mononuclear megakaryocytes, dumbbell-shaped nuclei, hypersegmentation, multinuclearity with multiple isolated nuclei
• Granulocytopoiesis	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

Table 3. Most frequent somatic mutations observed in MDS[a35,36]

Gene function	Gene	Mutation frequency (%)
Epigenetic regulators and chromatin-remodelling factors	*TET 2*	15-25
	ASXL1	10-20
	DNMT3a	10
	IDH1/2	5-10
Pre-mRNA splicing factors	*SF3B1*	15-30
	SRSF2	10-15
	U2AF1	5-10
Transcription factors	*RUNX 1*	10-15
	TP 53	5-10
Signalling molecules	*N RAS/K RAS*	10
Cohesin complex	*STAG2*	5-7

MDS, myelodysplastic syndromes.

[a] Other mutations are seen in <5% of cases.

Table 4. The WHO 2016 classification of myelodysplastic syndromes[16]

Name	Dysplastic lineages	Cytopaenias[a]	Ring sideroblasts as % of marrow erythroid elements	BM and PB blasts	Cytogenetics by conventional karyotype analysis
MDS-SLD	1	1 or 2	<15% / <5%[b]	BM <5%, PB <1%, no Auer rods	Any, unless fulfils criteria for MDS with isolated del(5q)
MDS-MLD	2 or 3	1-3	<15% / <5%[b]	BM <5%, PB <1%, no Auer rods	Any, unless fulfils criteria for MDS with isolated del(5q)
MDS-RS-SLD	1	1 or 2	≥15% / ≥5%[b]	BM <5%, PB <1%, no Auer rods	Any, unless fulfils criteria for MDS with isolated del(5q)
MDS-RS-MLD	2 or 3	1-3	≥15% / ≥5%[b]	BM <5%, PB <1%, no Auer rods	Any, unless fulfils criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	1-3	1-2	None or any	BM <5%, PB <1%, no Auer rods	Del(5q) alone or with one additional abnormality except -7 or del(7q)
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-U with 1% blasts	1-3	1-3	None or any	BM <5%, PB =1%[c], no Auer rods	Any
MDS-U with single lineage dysplasia and pancytopaenia	1	3	None or any	BM <5%, PB <1%, no Auer rods	Any
MDS-U based on defining cytogenic abnormality	0	1-3	<15%[d]	BM <5%, PB <1%, no Auer rods	MDS-defining abnormality
Refractory cytopaenia of childhood	1-3	1-3	None	BM <5%, PB <2%	Any

BM, bone marrow; MDS, myelodysplastic syndromes; MDS-EB, myelodysplastic syndrome with excess blasts; MDS-MLD, myelodysplastic syndrome with multilineage dysplasia; MDS-RS-MLD, myelodysplastic syndrome with ring sideroblasts with multilineage dysplasia; MDS-RS-SLD, myelodysplastic syndrome with ring sideroblasts with single lineage dysplasia; MDS-SLD, myelodysplastic syndrome with single lineage dysplasia; MDS-U, myelodysplastic syndrome unclassifiable; PB, peripheral blood; WHO, World Health Organisation.

[a] Cytopaenias defined as haemoglobin <10 g/dl, platelet count <100 x 10^9/l and absolute neutrophil count <1.8 x 10^9/l; rarely, MDS may present with mild anaemia or thrombocytopaenia above these levels. PB monocytes must be <1 x 10^9/l.

[b] If *SF3B1* mutation is present.

[c] 1% PB blasts must be recorded on at least two separate occasions.

[d] Cases with ≥15% ring sideroblasts have significant erythroid dysplasia and are classified as MDS-RS-SLD.

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Table 5. Myeloid neoplasms with inherited germline predisposition[16]

Myeloid neoplasms with germline predisposition without a pre-existing disorder or organ dysfunction	• AML with germline *CEBPA* mutation • Myeloid neoplasms with germline *DDX41* mutation[a]
Myeloid neoplasms with germline predisposition and pre-existing platelet disorders	• Myeloid neoplasms with germline *RUNX1* mutation[a] • Myeloid neoplasms with germline *ANKRD26* mutation[a] • Myeloid neoplasms with germline *ETV6* mutation[a]
Myeloid neoplasms with germline predisposition and other organ dysfunction	• Myeloid neoplasms with germline *GATA2* mutation • Myeloid neoplasms associated with BM failure syndromes • Myeloid neoplasms associated with telomere biology disorders • Juvenile myelomonocytic leukaemia associated with neurofibromatosis, Noonan syndrome or Noonan syndrome-like disorders • Myeloid neoplasms associated with Down syndrome[a]

AML, acute myeloid leukaemia; BM, bone marrow.

[a] Lymphoid neoplasms also reported.

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Table 6. IPSS-R for myelodysplastic syndromes[19]

Prognostic characteristic	Points						
	0	0.5	1	1.5	2	3	4
Cytogenetic risk category[a]	Very good		Good		Intermediate	Poor	Very poor
Blasts in bone marrow (%)	≤2		>2-5		5-10	>10	
Haemoglobin (g/dl)	≥10		8-<10	<8			
Platelet count (x 10^9/l)	≥100	50-<100	<50				
Absolute neutrophil count (x 10^9/l)	≥0.8	<0.8					

IPSS-R risk group	Score	Median OS (years)	Median time to 25% AML evolution (years)
Very low	≤1.5	8.8	NR
Low	>1.5-3	5.3	9.4
Intermediate	>3-4.5	3.0	2.5
High	>4.5-6	1.6	1.7
Very High	>6	0.8	0.7

AML, acute myeloid leukaemia; IPSS-R, revised international prognostic scoring system; NR, not reached; OS, overall survival.

[a] 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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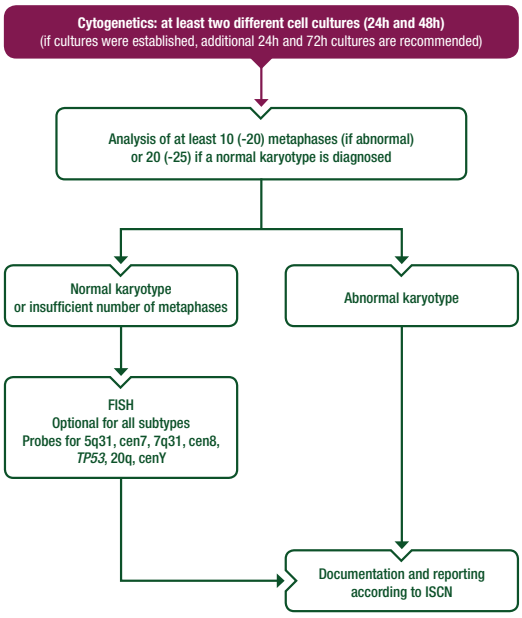
Cytogenetics: at least two different cell cultures (24h and 48h)
(if cultures were established, additional 24h and 72h cultures are recommended)
Analysis of at least 10 (-20) metaphases (if abnormal)
or 20 (-25) if a normal karyotype is diagnosed
Normal karyotype
or insufficient number of metaphases
Abnormal karyotype
FISH
Optional for all subtypes
Probes for 5q31, cen7, 7q31, cen8,
TP53, 20q, cenY
Documentation and reporting
according to ISCN