
Pan-London Haemato-Oncology Clinical Guidelines

Acute Leukaemias and Myeloid Neoplasms
Part 5: Myelodysplastic Syndromes

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Disclaimer

These guidelines should be read in conjunction with the latest NICE guidance, and all applicable national/international guidance. The prescribing information in these guidelines is for health professionals only. It is not intended to replace consultation with the Haematology Consultant at the patient's specialist centre. For information on cautions, contra-indications and side effects, refer to the up-to-date prescribing information. While great care has been taken to see that the information in these guidelines is accurate, the user is advised to check the doses and regimens carefully and if there is any uncertainty about the guidance provided, you should discuss your queries with a Haematology Consultant or Senior Pharmacist. No set of guidelines can cover all variations required for specific patient circumstances. It is the responsibility of the healthcare practitioners using them to adapt them for safe use within their institutions and for the individual needs of patients.

Contact us

The writing cycle for the guidelines will be from May-July each year. If you wish to be part of the writing group, please contact us through the following link: [Pan London Blood Cancer](#) (or via uclh.panlondonbloodcancer@nhs.net).

If you wish to report errors or omissions that require urgent attention please contact us via the same email addresses.

1 Introduction

This guidance should be read in conjunction with the British Committee for Standards in Haematology (BCSH) myelodysplastic syndrome (MDS) guideline¹ and the European Leukaemia Net (ELN) guidelines on myelodysplastic syndromes.²

The myelodysplastic syndromes (MDS) are a group of clonal stem cell disorders characterised by qualitative and quantitative defects in haemopoiesis that predispose individuals to anaemia, life-threatening bleeds and infection concomitant with a risk of transforming to acute myeloid leukaemia (AML).

The incidence of MDS is 4–5 per 100,000, but it increases with age such that the incidence is 30 per 100,000 in those aged over 70; and 40 per 100,000 in those aged over 80. Some 10% of MDS are secondary, most often due to radiotherapy or chemotherapy for cancer; with increasing numbers of patients surviving chemotherapy, the incidence of therapy-related MDS may also be set to increase.

Cytogenetic abnormalities are present in 40–50% of patients and are of value both in confirming the diagnosis and indicating the risk of disease progression. More recently, molecular abnormalities that commonly occur have been identified and their prognostic value is being clarified. Thus, several prognostic indices incorporating these features have been developed in order to guide optimal management.

2 Referral Pathways

Patients with suspected MDS in primary care should be referred to a haematologist for assessment. It may be appropriate for patients with severe neutropenia, thrombocytopenia or blasts in peripheral blood to be referred via the 2 week wait pathway (often picked up on a routine blood test via the laboratory).

All new patients should be referred to the MDT for confirmation of diagnosis, prognosis and management plan taking into account their performance status, needs and co-morbidities. A joint approach with elderly care physicians and palliative care teams may be appropriate as per local guidelines.

The following patients should be brought to the MDT:

- all new patients with MDS in order to confirm the diagnosis and treatment plan
- all patients where a new line of therapy needs to be considered
- all patients with a restaging assessment of response to treatment (e.g. hypomethylating agents or immunosuppression)
- all patients in whom an allogeneic stem cell transplant is a consideration.

The MDT outcome should be documented and communicated to a primary care and secondary care referring centre (where relevant).

Patients with MDS IPSS-low and IPSS INT1 and INT2 may be managed at facilities with at least British Committee for Standards in Haematology (BCSH) Level 1 designation. MDS IPSS-high or complex patients may be referred to centres with at least BCSH Level 2 designation and with specific expertise, or which have available trials. Candidates for transplantation should be referred to a JACIE-accredited centre. For complex MDS cases, a centre with a specific interest and expertise in MDS may be asked to review the case with the requesting site.

3 Investigation and Diagnosis

Investigations are aimed at excluding secondary causes of dysplasia or cytopenias, and tests to confirm the diagnosis of MDS and exclude other clonal stem cell disorders. Investigation of MDS is usually initiated with the findings of:

- a macrocytic anaemia (or persistent macrocytosis)
- unexplained neutropenia with a blood film that suggests dysplastic features (pseudo Pelger-Huët abnormality)
- unexplained thrombocytopenia (especially when not responsive to immunosuppressive therapy/ITP treatment)
- blasts in the peripheral blood
- a persistent unexplained monocytosis $>1 \times 10^9/L$.

Appropriate investigations should exclude the following alternative causes:

- haematinic deficiency (vitamin B12, folate, selenium in appropriate patients)
- liver dysfunction
- thyroid dysfunction
- haemolysis
- autoimmune disorders
- viral infections such as HIV, HBV and HCV
- other primary cancers
- systemic inflammatory response syndrome (SIRS)/cytokine storm
- other causes of inflammation (e.g. concurrent infection).

A pertinent history should be taken including:

- smoking and alcohol intake history
- family history of thrombocytopenia, breast and other cancers, lymphoedema, pulmonary fibrosis or MDS/AML
- in younger patients, a family history of constitutional bone marrow failure such as Fanconi's anaemia, Schwachman-Diamond syndrome and dyskeratosis congenita should be sought
- prior exposure to chemotherapy particularly alkylating agents, topoisomerase inhibitors and radiotherapy (especially to the pelvis)
- occupational exposure to chemicals (e.g. benzenes)
- current medications (such as methotrexate, azathioprine, quinine)
- bleeding and infection history.

Physical examination of the patient should include the assessment of:

- abnormal skin, hair and nail changes/lesions (vasculitis, Sweet's syndrome, E. nodosum/pyoderma gangrenosum lesions, café au lait spots, premature grey, etc.)
- arthritis
- lymphoedema (Emberger syndrome)
- splenomegaly and lymphadenopathy.

Initial investigations that can be requested/performed are:

- FBC and blood film for morphologic assessment
- reticulocyte count
- DAT
- haematinics: vitamin B12 (if available, methylmalonic acid), red cell folate, ferritin
- haemoglobin electrophoresis
- thyroid function tests
- LDH and uric acid
- U&Es
- LFTs
- CRP and ESR
- serum protein electrophoresis (SPEP) with immunoglobulins (a paraprotein may occur with MDS)
- viral screen: HIV, hepatitis B and hepatitis C
- autoimmune screen
- beta 2 microglobulin
- serum erythropoietin levels
- parvovirus if appropriate
- haptoglobins.

Investigations after referral to haematology:

- bone marrow aspirate and trephine (BMAT)
- peripheral blood film morphology
- PNH screen
- specific genetic tests where there is a suspicion of an inherited or acquired bone marrow failure syndrome (e.g. telomere lengths, chromosome fragility, genetic testing).

The diagnosis of MDS is made based on the current World Health Organization (WHO) 2008 classification and morphologic assessment:

To enable better evaluation of blasts, a haemogram of >500 cells that include >100 non-erythroid cells (where erythroid cells >50% of the count) is necessary for both peripheral blood films and aspirates. In performing a haemogram, due consideration must be given in identifying blasts, promyelocytes, monoblasts and promonocytes and examining >100 erythroblasts and 30 megakaryocytes. In cases where the diagnosis is difficult, i.e. normal / non-informative cytogenetics, no excess myeloblasts or ring sideroblasts, it may be appropriate to repeat the marrow (weeks to months apart) prior to confirming a diagnosis. An observation interval of 6 months is recommended in those with unilineage dysplasia, no increase in blasts (peripheral blood or bone marrow) and where ring sideroblasts <15%.

The WHO classification requires the assessment of dysplasia in the following samples:

Peripheral blood film

It is recommended that at least 200 cells are examined. Features of dysplasia include:

- red cell anisocytosis, poikilocytosis, basophilic stippling
- myeloid nuclear hypolobation, pseudo Pelger-Huët anomaly, hypo- or degranulation
- the presence of myeloblasts
- platelet anisocytosis or giant platelets.

Bone marrow aspirate

Dysplastic features should be present in $\geq 10\%$ of the cells of the lineage in consideration to give a definition of MDS. The WHO classification stratifies patients based on the presence of dysplasia $>10\%$ of cells in any lineage. Multilineage dysplasia is defined as the presence of 10% dysplastic cells in at least two cell lineages and confers a poorer prognosis.

Features of dysplasia that are **diagnostic** of MDS are the presence of an acquired Pelger-Huët abnormality in the peripheral blood and presence of micromegakaryocytes in the bone marrow. The presence of circulating blasts of $<1\%$, 1% , $2-4\%$ or 5% alters the WHO classification, as does the presence of $5-10\%$ and $11-20\%$ blasts.

Iron stain with Prussian blue must be performed in order to identify the presence of significant numbers of ring sideroblasts (≥ 5 siderotic granules covering at least a third of the nuclear circumference in $\geq 15\%$ of erythroid cells).

Flow cytometry

This is not currently used in standard practice and is not an essential test in MDS. In this context, it may be helpful in identifying dysplasia where no clear cytogenetic or clonal marker is present, in distinguishing refractory anaemia from refractory anaemia with multilineage dysplasia (scatter properties), and in enumerating myeloblasts, although all of the above should primarily be a morphologic diagnosis. If undertaken, this test is best performed at a centre with experience with the ELNET recommendations for MDS/AML.

Cytogenetics

G-banding and/or FISH analysis is usually done on a bone marrow aspirate sample, although it may also be undertaken on peripheral blood if marrow is not available.

At least 20 metaphases should be evaluated for non-random chromosomal abnormalities and reported. Interphase FISH is useful where conventional G-banding fails or is inadequate.

Selected recurrent chromosomal abnormalities are recognised as presumptive evidence of MDS (WHO 2008), even in the absence of definitive morphological features. These include the following anomalies (incidence):

- -5 or del(5q) (10–15%)
- -7 or del(7q) (10%)
- i(17q) or t(17p) (2–3%)
- del(12p) or t(12p) (1–2%)
- del(11q) (1–2%)
- -13 or del(13q) (1–2%)
- del(9q) (1%)
- idic(X)(q13) (1%)
- inv(3)(q21q26.2) (1%)
- t(6;9)(p23;q34) (1%)
- t(3;21)(q26.2;q22.1) (<1%)
- t(1;3)(p36.3;q21.2) (<1%)
- t(1;3)(p36.3;q21.2) (<1%)
- t(11;16)(q23;p13.3) (<1%)
- t(2;11)(p21;q23) (<1%).

Molecular genetics

Single nucleotide polymorphism (SNP) based karyotyping has a higher diagnostic yield of chromosomal defects compared with that of conventional metaphase cytogenetics and may be clinically useful. The detection of acquired somatic mutations has been made possible by high throughput sequencing techniques.

Commonly mutated genes in MDS (but not exclusive to MDS) include those of the spliceosome component:

| Gene mutation | Incidence |
|---------------|-----------|
| SF3B1 | 25–30% |
| TET2 | 20–25% |
| RUNX1 | 10–20% |
| ASXL1 | 10–15% |
| SRSF2 | 10–15% |
| TP53 | 5–10% |
| U2AF1 | 5–10% |
| NRAS/KRAS | 5–10% |
| DNMT3A | 5% |
| ZRSR2 | 5% |
| EZH2 | 5% |
| IDH1&2 | 2–3% |
| ETV6 | 2% |
| CBL | 1–2% |
| NPM1 | 1–2% |
| JAK2 | 1–2% |
| SETBP1 | 1–2% |
| SF3B1 | 1–2% |
| ZRSF1 | 1–2% |
| U2AF65 | 1–2% |
| PRPF40B | 1–2% |

At least 52% of patients with a normal karyotype harbour at least one mutation and 74% have at least a copy number variation or molecular mutation, thus these tests can help confirm the diagnosis.

While these tests are not essential for the diagnosis of MDS, and do not currently form part of the classification or risk stratification in standard practice, prognostic information from such tests may assist treatment decisions in some cases. Therefore, where appropriate such tests should be used in conjunction with standard prognostic scoring systems (IPSS, IPSS-R). Incorporation of these prognostic values are likely to become part of the next revision of the IPSS.

Bone marrow trephine

This test will assess marrow cellularity, topography, presence of reticulin fibrosis and blasts, and exclude other metastatic disease or infections. The trephine biopsy should be stained with haematoxylin and eosin (H&E) or equivalent, Giemsa, myeloperoxidase, glycophorin A and C or equivalent, CD34, CD117, CD61 or CD42b for megakaryocytes, CD68 or CD68R for monocytes, CD20, CD3 and Gomori silver stain for reticulin.

Bone marrow cellularity in MDS is usually hyper- or normo-cellular but is hypocellular in 10% of patients (hypocellular MDS) and needs to be differentiated from aplastic anaemia (AA). The presence of dysplasia, reticulin fibrosis, ring sideroblasts, CD34+ cells and micro-megakaryocytes favours a diagnosis of MDS.

In 10–20% of cases, a moderate to severe bone marrow fibrosis (grade 2–3) by European consensus may be seen. Fibrotic MDS classically occurs in the absence of splenomegaly but shows concomitant dysplasia and transfusion dependence. It needs to be differentiated from primary myelofibrosis (PMF), chronic myelomonocytic leukaemia (CMML) and acute megakaryoblastic leukaemia.

Table 3.1: WHO classification of MDS (2016) – diagnostic criteria

| Disease | Blood findings | BM findings |
|---|---|---|
| MDS with single lineage dysplasia (MDS-SLD): <ul style="list-style-type: none"> • anaemia • neutropenia • thrombocytopenia | Single cytopenia or bicytopenia ¹ No or rare blasts (<1%) ^{2,4} | Single lineage dysplasia: ≥10% of the cells in one myeloid lineage <5% blasts <15% of erythroid precursors are ring sideroblasts |
| MDS with ring sideroblasts (MDS-RS) <ul style="list-style-type: none"> • With SLD • With MLD | Anaemia No blasts | ≥15% of erythroid precursors are ring sideroblasts >5% if also SB3B1 mutation Erythroid dysplasia only <5% blasts |
| MDS with multilineage dysplasia (MDS-MLD) | Cytopenia(s) No or rare blasts (<1%) ² No Auer rods <1 × 10 ⁹ /L monocytes | Dysplasia in ≥10% of the cells in ≥2 myeloid lineages (neutrophil and/or erythroid precursors and/or megakaryocytes) <5% blasts in marrow No Auer rods ±15% ring sideroblasts |
| MDS with excess blasts-1 (MDS-EB-1) | Cytopenia(s) <5% blasts ² No Auer rods <1 × 10 ⁹ /L monocytes | Single lineage or multilineage dysplasia 5%–9% blasts ³ No Auer rods |
| MDS with excess blasts-2 (MDS-EB-2) | Cytopenia(s) 5%–19% blasts Or Auer rods <1 × 10 ⁹ /L monocytes | Single lineage or multilineage dysplasia 10–19% blasts ³ Or Auer rods |
| Myelodysplastic syndrome – unclassified (MDS-U) | Cytopenias < 1% blasts ² | Unequivocal dysplasia in <10% of cells in one or more myeloid lineages when accompanied by a cytogenetic abnormality considered as presumptive evidence for a diagnosis of MDS (see Table 4.2) <5% blasts |
| MDS associated with isolated del(5q) | Anaemia Usually normal or increased platelet count No or rare blasts (<1%) | Normal to increased megakaryocytes with hypolobated nuclei <5% blasts |

| Disease | Blood findings | BM findings |
|--|---|---|
| | | Isolated del(5q) cytogenetic abnormality No Auer rods |
| MDS/MPD unclassified (MDS/MPD-U) | Uni or multilineage cytopenias with dysplastic features with the addition of proliferative or fibrotic characteristics not otherwise classified | |
| MDS/MPN with ringed sideroblasts and thrombocytosis (MDS/MPN-RS-T) | Thrombocytosis $>450 \times 10^9/L$ associated with anaemia | Dyserythropoiesis with ring sideroblasts accounting for 15% or more of erythroid precursors, and megakaryocytes with features resembling those in PMF or ET |
| Myeloid neoplasms with germ line predisposition | See below | |

¹ Bicytopenia may occasionally be observed. Cases with pancytopenia should be classified as MDS-U.

² If the marrow myeloblast percentage is $<5\%$ but there are 2–4% myeloblasts in the blood, the diagnostic classification is MDS-EB-1. Cases of MDS-SLD or MLD with 1% myeloblasts in the blood should be classified as MDS-U.

³ Cases with Auer rods and $<5\%$ myeloblasts in the blood and $<10\%$ in the marrow should be classified as MDS-EB-2. Although the finding of 5–19% blasts in the blood is, in itself, diagnostic of MDS-EB-2, cases of MDS-EB-2 may have $<5\%$ blasts in the blood if they have Auer rods or 10–19% blasts in the marrow or both. Similarly, cases of MDS-EB-2 may have $<10\%$ blasts in the marrow but may be diagnosed by the other two findings, Auer rod+ and/or 5–19% blasts in the blood.

⁴ Myeloblast percentage now considered % all cells rather than % non-erythroid cells.

Table 3.2 Classification of myeloid neoplasms with germ line predisposition

| | |
|--|--|
| Myeloid neoplasms with germ line predisposition without pre-existing disorder or organ dysfunction | AML with germ line <i>CEBPA</i> mutation |
| | Myeloid disorders with germ line <i>DDX41</i> mutation |
| Myeloid neoplasms with germ line predisposition and pre-existing platelet disorder | Myeloid disorders with germ line <i>RUNX1</i> mutation |
| | Myeloid disorders with germ line <i>ETV6</i> mutation |
| | Myeloid disorders with germ line <i>ANKRD26</i> mutation |
| Myeloid neoplasms with germ line predisposition and other organ dysfunction | Myeloid disorders with germ line <i>GATA2</i> mutation |
| | Myeloid disorders with germ line bone marrow failure syndromes |
| | Myeloid disorders with germ line telomere biology syndromes |
| | JMML with Noonan syndrome, neurofibromatosis or Noonan-like syndromes. |
| | Myeloid neoplasms associated with Down's syndrome |

Chronic myelomonocytic leukaemia (CMML) – diagnostic criteria

Persistent PB monocytosis $>1 \times 10^9/L$

No Ph chromosome or BCR-ABL1 fusion gene

No rearrangement of PDGFR α or PDGFR β

$<20\%$ blasts in PB or BM

Dysplasia in ≥ 1 myeloid lines. If myelodysplasia is absent or minimal, the diagnosis of CMML may still be made if the other requirements are met, **and**:

- an acquired, clonal cytogenetic or molecular abnormality is present in haematopoietic cells, **or**
- the monocytosis has persisted for at least 3 months and all other causes of monocytosis have been excluded.

CMML-0 = blasts $<2\%$ in PB & $<5\%$ in BM

CMML-1 = blasts $<5\%$ in PB & $<10\%$ in BM

CMML-2 = blasts $5\text{--}19\%$ in PB & $10\text{--}19\%$ in BM, or the presence of Auer rods

aCML = SETBP1 or ETNK1 mutations in 1/3

3.1 Pathology

Careful attention must be paid to the labelling of forms and samples before sending to the Specialist Integrated Haematological Malignancy Diagnostic Service (SIHMDS). Samples are unlikely to be processed unless clearly and correctly labelled.

4 Risk Stratification

The risk stratification of MDS is as per the International Prognostic Scoring System (IPSS) that has recently been revised (IPSS-R) to reflect the increased recognition that cytogenetic abnormalities are independent predictors of outcome and have as much importance as the blast percentage. Both scores are validated at diagnosis and during the course of the disease. It is recommended that the IPSS and the IPSS-R are both applied at diagnosis.

The revised IPSS is a dynamic scoring system that applies to patients with primary MDS with <30% blasts in the marrow, <19% blasts in peripheral blood, WBC count <12x10⁹/L and stable disease over two months. Five cytogenetic subgroups and importance to the depth of cytopenia have been incorporated (see [Table 4.2](#)).

Table 4.1: International Prognostic Scoring System (IPSS)

Sum-up variables to arrive at risk

| Prognostic variable | Score value | | | | |
|----------------------|-------------|--------------|------|-------|-------|
| | 0 | 0.5 | 1.0 | 1.5 | 2.0 |
| BM blasts (%) | <5 | 5–10 | – | 11–19 | 20–30 |
| Karyotype* | Good | Intermediate | Poor | – | – |
| Cytopenias** | 0/1 | 2/3 | – | – | – |

* Karyotype: Good = normal, -Y, del(5q), del(20q); Poor = complex (>3 abnormalities) or chrom. 7 anomalies; Intermediate = other abnormalities.
 ** Cytopenias: Hb <10g/dL; ANC <1.8 x 10⁹/L; plts <100 x 10⁹/L.

| Risk (Score) | Median survival (years) | 25% AML progression (years) |
|------------------------|-------------------------|-----------------------------|
| LOW (0) | 5.7 | 9.4 |
| INT-1 (0.5–1.0) | 3.2 | 3.3 |
| INT-2 (1.5–2.0) | 1.2 | 1.1 |
| HIGH (> 2.5) | 0.4 years | 0.2 |

An online calculator can be found at:

www.qxmd.com/calculate-online/hematology/myelodysplastic-syndrome-prognosis-ipss

Table 4.2: MDS IPSS-Revised (IPSS-R)

IPSS-R score values

| | 0 | 0.5 | 1 | 1.5 | 2 | 3 | 4 |
|-------------------|------|-------|----------|-----|------|------|-----------|
| CGN | – | – | Good | – | Int. | Poor | Very poor |
| BM Blast % | ≤2 | – | 2.1–4.9% | – | 5–10 | >10 | – |
| Hb | ≥100 | – | 80–99 | <80 | – | – | – |
| Plts | ≥100 | 50–99 | <50 | – | – | – | – |
| ANC | ≥0.8 | <0.8 | – | – | – | – | – |

Source: Greenberg P, *et al. Blood*. 2012;**120**(12):2454–65.³

IPSS-R cytogenetic prognostic subgroups

| Very good | Good | Intermediate | Poor | Very poor |
|--------------------------|--|---|---|-----------------------------|
| Single -Y Del(11q) | Normal Single Del(5q) Del(12p) Del(20q) Double Incl. del(5q) | Single Del(7q) +8 l(17q) +19 Any other independent clone Double Any other | Single der(3q) -7 Double Incl. -7/7q- Complex 3 abnormalities | Complex >3 abnormalities |

IPSS-R prognostic risk categories/scores

| Risk category | Risk score | Survival (median years) | AML 25% evolution |
|---------------|------------|----------------------------|-------------------|
| Very low | ≤1.5 | 8.8 | – |
| Low | >1.5–3 | 5.3 | 10.8 |
| Intermediate | >3–4.5 | 3.0 | 3.2 |
| High | >4.5–6 | 1.6 | 1.4 |
| Very high | >6 | 0.8 | 0.73 |

Table 4.3: CMML-Specific Prognostic Scoring System (CPSS)

| Variable | 0 | 1 | 2 |
|---------------|-------------------|-------------------|------|
| WHO subtype | CMML-1 | CMML-2 | – |
| FAB subtype | CMML-MD (WBC <13) | CMML-MP (WBC >13) | – |
| CGN* | Low | Intermediate | High |
| RBC dependent | No | Yes | – |

*Low = normal, -Y; Intermediate = other abnormalities; High = +8, complex (≥3 anomalies), chrom. 7 anomalies.

Source: Such E, et al. *Blood*. 2013;121:3005–15.⁴

| Risk group | Overall score |
|----------------|---------------|
| Low | 0 |
| Intermediate-1 | 1 |
| Intermediate-2 | 2–3 |
| High | 4–5 |

Additional genetic risk factors associated with single (or multiple) gene mutations

Mounting evidence for the role of mutations in the prognosis of different subtypes of MDS is accumulating. Current evidence is summarised below. This is not currently incorporated into the IPSS-R or other scoring systems but is likely to become so. At present where such information is available it should be interpreted with caution.

Table 4.4: Summary of current literature on prognostic impact of gene mutations in MDS

| Mutated Gene | Blasts <5% | Blasts 5-30% | Notes |
|---------------------|----------------------|---------------------|---|
| TP53 | Adverse | Adverse | Associated with secondary disease and complex karyotype |
| RUNX1 | Adverse | Adverse | Associated with MDS-EB, MDS-MLD and thrombocytopenia |
| EZH2 | Adverse | Adverse | More common in CMML |
| CBL | Neutral | Adverse | More common in CMML |
| SRSF2 | Adverse | Neutral | More common in CMML, in association with TET2 |
| ASXL1 | Adverse | Neutral | More common in CMML |
| U2AF1 | Adverse | Neutral | MDS-EB, MDS-MLD |
| NRAS | Adverse | Neutral | More common in CMML with thrombocytopenia |
| SF3B1 | Favourable | Neutral | Associated with ringed sideroblasts |
| TET2 | Neutral | Neutral | Often normal karyotype |
| DNMT3A | Neutral | Neutral | MDS-EB, MDS-MLD |
| IDH1/IDH2 | Neutral | Neutral | MDS-EB, MDS-MLD |
| JAK2 | Neutral | Neutral | Higher frequency in MDS/MPD |

Source: Nazha and Bejar. *Curr Hematol Malig Rep.* 2017 Oct;**12**(5):461-7.⁵

5 Patient Information/Support

If the diagnosis of MDS is certain, patients should be informed that MDS is a clonal disorder and that it is considered malignant/neoplastic. Their prognosis based on the IPSS/ IPSS-R should be discussed, along with possible treatment options.

All patients must have access to a key worker. This is usually (but not always) the clinical nurse specialist.

The clinical nurse specialist/key worker should be present at diagnosis and at any significant discussion where treatment changes and outcomes are discussed. Where it is not possible for the clinical nurse specialist or a deputy to be present, patients should be given the clinical nurse specialist's contact numbers. The clinician leading the consultation should advise the clinical nurse specialist who should then arrange to make contact with the patient.

The clinical nurse specialist should ensure that all patients are offered a Holistic Needs Assessment (HNA) at key pathway points, including: within 31 days of diagnosis; at the end of each treatment regimen; and whenever a person requests one. Following each HNA, every patient should be offered a written care plan. This plan should be developed with the patient and communicated to all appropriate healthcare and allied healthcare professionals.

Written and verbal information are essential and the key worker/clinical nurse specialist plays a key role in ensuring that patients have access to appropriate and relevant written information about their condition.

The Macmillan Cancer Support, MDS Foundation and MDS UK Patient Support Group websites and information booklets are good sources of patient information at diagnosis and are available for download on the following websites:

www.macmillan.org.uk/Cancerinformation/Cancerinformation.aspx

<https://www.mds-foundation.org/patient-caregiver-resources/#Programs>

<http://mdspatientsupport.org.uk/what-is-mds/information-material>

6 Treatment

The management of MDS may vary from monitoring blood counts for evidence of disease progression in early MDS and supportive care, to intensive chemotherapy followed by stem cell transplantation in those with advanced disease. Patients with ICUS should be followed up in the same way as for low risk MDS until the diagnosis is clear. Responses to treatment should be recorded using the Cheson 2006 criteria.

The goals of treating MDS are to prolong survival, improve quality of life and improve the blood counts. In order to achieve these goals, treatment options vary from best supportive care, replacement therapy, low intensity therapy and high intensity therapy. In early MDS, the predominant goal is haematological improvement with best supportive care. The imminent threat to life in high risk MDS makes disease-modification the primary goal.

As patients with MDS are usually older and likely to have co-morbidities, the use of the Cumulative Illness Rating Scale (CIRS) to assess the impact that co-morbidities may have on treatment is recommended when planning treatment for MDS.

Formal written consent should be obtained for all patients before commencing any cytoreductive or epigenetic therapy including HU.

6.1 Low or intermediate-risk MDS

Also see [section 7: Management of Disease and Treatment-related Complications](#).

Patients with IPSS-low or IPSS-INT1 may be eligible for a clinical trial.

6.1.1 Growth factor support (EPO +/- G-CSF)

For those patients with low risk disease and primarily anaemia and an EPO predictive score that is low (serum erythropoietin <500IU and less than 2U blood transfusion), treatment with recombinant human erythropoietin (EPO) 30,000 to 60,000 IU SC weekly for at least 8 weeks, followed by a higher dose for 8 weeks, is recommended. The addition of G-CSF 300µg once a week (to maintain neutrophils between 5–10 x 10⁹/L) should be considered in all patients with refractory anaemia with ring sideroblasts (RARS) and other patients where the response to EPO alone is suboptimal. The target Hb is 10-12g/dl but dose adjustments need to be made prior to this to prevent overshooting. The ferritin should be maintained >100µg/ml for those on erythropoietin replacement with IV iron infusions. Regular blood pressure monitoring and appropriate therapy should accompany EPO treatment.

6.1.2 Anti-thymocyte globulin (ATG)/ciclosporin

Hypocellular/normocellular patients who have a normal karyotype or trisomy 8 may respond to immunosuppressive therapy with ATG/ciclosporin. The HLA-DR15 haplotype is a good predictor of response to immunosuppressive therapy, especially ATG. Patients not suitable for ATG may receive Campath-1H currently available under compassionate program.

6.1.3 Lenalidomide

Patients with transfusion dependent anaemia and del(5q) with low risk or Int-1 (IPSS) who are unresponsive to or unsuitable for ESAs are eligible for treatment with lenalidomide. Where blast percentage is >5%, response rates may be lower and advice from a haematologist with sub-specialist expertise is advisable. Responses occur rapidly at a median of 4 weeks from starting therapy, and therapy should be continued until loss of response or disease progression. Starting dose for patients with creatinine clearance ≥ 60 ml/min is 10mg daily for 21 out of 28 days. Dose modifications as follows for renal impairment are shown below:

| | |
|--|---|
| CrCl 30 to 60 mL/min | 5 mg once daily |
| CrCl <30 mL/min (not requiring dialysis) | 2.5 mg once daily |
| CrCl <30 mL/min (requiring dialysis) | 2.5 mg once daily. On dialysis days, administer the dose following dialysis |

Cytopenias are the most common toxicity with lenalidomide. Recommendations for dose reductions for cytopenias can be found here:

<https://www.revlimid.com/mds-hcp/dosing/how-to-dose-modify/>

6.2 High risk MDS

Patients should be assessed for eligibility to undergo an allogeneic stem cell transplant: assess fitness and co-morbidities using the HC-TCI, and carry out tissue typing for potential donors, including siblings where familial MDS is not suspected.

6.2.1 Allogeneic stem cell transplant

If patients are transplant-eligible, a donor should be identified at the earliest possible opportunity. Patients may be treated either directly with a myeloablative transplant (if fit, young and blasts <10%) or following induction chemotherapy with daunorubicin/cytarabine (DA 3+10) or a similar regimen to remission (blasts <5% and no MRD by normal karyotype). For older patients, or for those with co-morbidities, a RIC transplant is preferred, although the risk of relapse is higher. Results from an allele-matched 10/10 VUD donor approximate those of a matched sibling transplant and is a viable option.

For those who have tolerated chemotherapy and regenerated within 4–5 weeks, one cycle of treatment to consolidate the remission is preferably to be administered prior to an allogeneic stem cell transplant. It is recognised that a proportion of patients with MDS may develop chemotherapy-induced aplasia and experience a prolonged time to recover counts, in which case a rescue allograft may be necessary.

For patients with a complex karyotype or monosomal karyotype, there is some evidence to suggest that treatment with hypomethylating agents such as 5'-azacitidine may be a good option.

In cases that are refractory to chemotherapy, the use of sequential chemotherapy and transplantation is experimental; if it is being considered, it should be undertaken early in the course of treatment.

6.2.2 Hypomethylating agents: 5'-azacitidine (5'-aza)

Where a patient declines, or is not a suitable candidate for, allogeneic stem cell transplantation, the standard of care is treatment with 5'-aza based on a Phase III open label randomised controlled trial that demonstrated disease-modifying activity in IPSS-INT2 high risk patients, non-proliferative CMML and in AML with less than 30% blasts. The licensed regimen consists of 5'-aza 75mg/m² SC daily for 7 days every 28 days, for at least 4–6 cycles to assess response, and continued until loss of response or disease progression. The trial demonstrated improved overall survival at 2 years of approximately 50%, compared with 24% for low dose cytarabine, but there was no difference compared with chemotherapy. Treatment with 5'-aza may result in a complete remission in 16% of cases. Given that the median time of response to 5'-aza is 18–24 months, in suitable cases an allogeneic stem cell transplant in CR may be considered.

6.2.3 Hypomethylating agents: decitabine

Decitabine 20mg/m² IV for five days every 28 days and, more recently, an extended 10-day schedule may be useful in high risk MDS as an alternative to 5'-aza. However, the drug is not licensed for MDS in Europe, and so IFR funding or treatment on a clinical trial should be sought.

6.2.4 Patients refractory to induction chemotherapy or hypomethylating agents

- Best supportive care
- Treatment on a clinical trial
- Referral to palliative care teams may be considered.

6.3 Chronic myelomonocytic leukaemia (CMML)

CMML was part of the original FAB classification. However, in WHO (2008) it has been included in the MDS/MPN overlap category. Patients with CMML may have varying prognosis and the Dusseldorf scoring system or the CMML-specific prognostic score is recommended in order to determine prognosis.

6.3.1 Active monitoring

For some patients (CMML-1 and some stable CMML-2 patients), active monitoring may be sufficient.

6.3.2 Supportive care

Treatment with supportive care and hydroxycarbamide to control counts is recommended in the absence of excess blasts.

6.3.3 5'-azacitidine

The National Institute for Health and Care Excellence (NICE) has approved the use of 5'-aza for patients requiring treatment for CMML-2 only. For proliferative (WBC <13,00) CMML, 5'-aza at conventional dosing may be used, but a funding application may be required.

6.3.4 Intensive chemotherapy

For patients with disease progression to CMML-2, AML induction chemotherapy followed by an allogeneic stem cell transplant may be considered, based on patient characteristics and donor availability.

6.4 Fertility

For young patients with MDS due to undergo AML induction-type chemotherapy and or a stem cell transplant, the options for fertility preservation should be discussed and the patient referred to an onco-fertility specialist for preservation of sperm, ovarian tissue or fertilised embryos.

Consideration of fertility preservation should be made for those of reproductive age (men below the age of 55 and women below the age of 40).

7 Management of Disease and Treatment-related Complications

7.1 Anaemia

The onset of symptomatic anaemia is an independent prognostic factor in MDS. It is important to record the number of transfusions a patient has had, with transfusion-dependence defined as the need for >2 units per month for 4 months.

Assessment of anaemia should include haematinics, screening for haemolysis and infection. Identification of 5q- syndrome, a PNH clone or hypocellularity may alter therapies. Serum erythropoietin levels may be low in elderly patients and should be measured in all patients with MDS.

For those with an EPO predictive score that is low (serum erythropoietin <500IU and less than 2U blood transfusion), treatment with recombinant human erythropoietin (EPO) 30,000 to 60,000IU SC weekly for at least 8 weeks, followed by a higher dose for 8 weeks, is recommended. The addition of G-CSF 300µg once a week (to maintain neutrophils between 5–10 x 10⁹/L) should be considered in all patients with RARS) and in other patients where the response to EPO alone is suboptimal. The target Hb is 10–12g/dl, but dose adjustments need to be made prior to this to prevent overshooting.

The ferritin should be maintained at >100µg/ml for those on erythropoietin replacement with IV iron infusions.

Blood transfusions may be the mainstay for those predicted to have a low response to EPO (serum erythropoietin >500IU and >2U blood transfused).

It is important to identify patients who may need iron chelation.

7.2 Severe neutropenia

There is no evidence to support routine use of G-CSF in neutropenic patients.

There is also no evidence to support routine prophylaxis with antimicrobials or antifungal drugs.

In patients with hypoplastic MDS, the use of immunosuppression with anti-thymocyte globulin (ATG) and ciclosporin (CYA) or single agent ciclosporin may be helpful with responses, depending on the patient's age and the severity of neutropenia. HLA-DR15 haplotype may be a good predictor of response.

It is important to examine a peripheral film to exclude T-LGL, as treatment with ciclosporin and methotrexate may be beneficial.

7.3 Neutropenic sepsis

Patients with neutropenic pyrexia or sepsis should be treated according to local protocols for neutropenic sepsis (and following National Institute for Health and Care Excellence/NICE guidance).

7.4 Severe thrombocytopenia

Platelet anisocytosis/clumping may give artefactually low platelet counts. An element of immune destruction may also cause thrombocytopenia in MDS.

Platelet transfusion may be used in MDS if there is bruising or bleeding. Steroids, IV immunoglobulin in doses used to treat ITP may be tried if an immune component is suspected. For non-bleeding patients and those not at high risk of spontaneous bleeding (i.e. not hypertensive), transfuse platelets only when clinically indicated. Consider tranexamic acid in order to maintain haemostasis. When a platelet transfusion programme is initiated, use single-donor apheresis platelet products only, in order to avoid platelet refractoriness, unless in an emergency.

In refractory cases, patients should be assessed for the presence of HLA antibodies and splenomegaly. Eltrombopag may be useful in such situations (unlicensed and unfunded indication) or in a clinical trial as trilineage responses to these drugs have been reported.

Clinical trials may be available for such patients.

7.5 Haemostasis and thrombosis

Although counts may be adequate, platelets (and neutrophils) may be dysfunctional in MDS. Such patients may need platelet transfusions regardless of count for surgical procedures and/or tranexamic acid in order to maintain haemostasis.

Platelet transfusion may be used in MDS if there is severe bruising or bleeding. For non-bleeding patients and those not at high risk of spontaneous bleeding (i.e. not hypertensive), transfuse platelets only when clinically indicated. Consider tranexamic acid in order to maintain haemostasis when platelets $<20 \times 10^9/L$ or in the bleeding/high risk patient.

Ensure that patients have good control of blood pressure (if they are known to be hypertensive) and do not suffer from constipation – if not appropriately managed, both conditions can increase the risk of severe life-threatening haemorrhage.

7.6 Transfusional iron overload

Blood transfusions contribute to iron overload and transfusion in excess of 100 units may result in evidence of end-organ damage (abnormal liver function, glucose intolerance or reduced left ventricular ejection fraction). Iron chelation therapy is recommended for patients with a serum ferritin $>1000\text{ng/ml}$ or who have received in excess of 20 blood transfusions or evidence of transfusional iron overload by ferriscan or cardiac MRI, and are expected to have a life expectancy in excess of 3 years. If a patient has a life expectancy of <3 years when the transfusion regimen commences, they are unlikely to become symptomatically iron-overloaded and chelation therapy should not normally be started. An exception to this may be patients with underlying cardiac problems (e.g. AF or CHD) who may also be more susceptible to the effects of iron overload and patients in whom a transplant may be considered since iron overload is a negative prognostic factor in transplant outcomes. It is recommended that all patients receiving chelation have a baseline surrogate measure of labile plasma iron using ferriscan along with baseline audiology.

The serum ferritin is the most convenient way to monitor iron accumulation. However, it is an acute phase reactant and may be elevated in liver disease as well. It is not clear in MDS at what levels of ferritin end-organ iron-overloading occurs. However, iron-overload may contribute to dyserythropoiesis. It is also an independent predictor of poor outcomes following stem cell transplantation.

It is recommended that a cumulative record of number of units transfused be kept in the notes and serum ferritin be checked after 20 units of blood have been transfused. Thereafter, ferritin levels

should be measured after every further 10 units transfused until a decision is made to chelate. Consider a clinical trial for this patient group, if available.

The choice of iron chelator in the UK lies between desferrioxamine and deferasirox. Currently, funding for deferasirox is recommended for inherited transfusion dependent anaemias by NHS England. However, cost analysis by NHS England for this purpose indicated similar costs for desferrioxamine when infusers and needles were incorporated compared to deferasirox. Furthermore, compliance is improved using oral therapy. Clinical judgement relating to suitability, patient compliance and co-morbidities should define the choice of chelator.

8 Supportive Care

8.1 Anaemia

See [section 7: Management of Disease and Treatment-related Complications](#).

Transfusion triggers should be chosen in advance for patients, depending on their co-morbidities. For patients with no co-morbidities or bleeding risk, and in those who do not lead active lifestyles, it would be reasonable to aim for a target Hb<80g/L.

8.2 Transfusions

See [section 7: Management of Disease and Treatment-related Complications](#).

Transfusion triggers should be chosen in advance for patients, depending on co-morbidities. For patients with no co-morbidities or bleeding risk, and in those who do not lead active lifestyles, it would be reasonable to aim for a target of Hb>80g/L providing this does not lead to significant symptoms.

Administer CMV-negative blood products until the patient's CMV status is known. All platelet products should be single donor collections in order to limit the risk of allo-sensitisation. HLA-typing should be done prior to starting treatment in order to address donor status if transplantation is appropriate for the patient, and in case HLA-matched platelets become necessary during treatment (as often occurs in women who have had children). Irradiated blood products should be requested for patients on protocols containing fludarabine, cladribine and clofarabine and for at least one month prior to a planned SCT.

8.3 Haemostasis and thrombosis

See [section 7: Management of Disease and Treatment-related Complications](#).

8.4 Infection prophylaxis

There is no evidence to support routine use of G-CSF in neutropenic patients. There is also limited evidence to support routine prophylaxis with antimicrobials or antifungal drugs (see [section 7: Management of Disease and Treatment-related Complications](#)).

Patients with high risk MDS should be managed as AML.

In neutropenic patients with recurrent infections, prophylactic antimicrobial and antifungal therapy should be administered according to local flora and sensitivities, and as per local protocols on neutropenic sepsis.

In non-neutropenic patients, neutrophils may be dysfunctional and in this case patients may have recurrent infections. Such patients may benefit from prophylactic antimicrobial and antifungal therapy directed towards local flora and sensitivities according to local protocols. Such patients may also benefit from intermittent G-CSF. Local guidance from microbiology should be sought in such cases.

Mouthwashes should be used as per local protocols in susceptible patients.

9 Treatment Summary and Care Plan

The MDT outcome and clinic letters will serve to communicate new lines of treatment with the patient's GP.

Most therapies are administered until loss of response or disease progression. It is important to ensure that a treatment summary is completed when there are any significant changes in treatment or follow-up plans.

Holistic Needs Assessments (HNAs) should be offered through follow-up, with a care plan completed to document the plans to address the issues raised by the patient.

9.1 Treatment summary and care plan

There are two related but distinct documents which patients should be given when there are changes in treatment.

- A **treatment summary** provides a summary of the cancer treatments received by the end of the first treatment, planned follow-ups (including mechanisms for these), and signs and symptoms of which to be aware. Their aim is to provide information not only to the patient but also to the GP about possible consequences of cancer and its treatment, signs of recurrence and other important information.
- A **care plan** is generated as a result of an HNA and is the agreed plan between the patient and healthcare professional about how the identified areas of concern will be addressed. This may cover provision of information (e.g. through an information prescription), onward referral for specialist assessment and intervention (e.g. breathlessness management), or things which the patient themselves can do (e.g. contact their HR department about graduated return to work options).

Recommendation:

An end of treatment consultation should be offered to every patient when there are any significant changes in treatment and follow-up arrangements. This should include an HNA and associated written care plan and should also include the discussion and provision of a comprehensive treatment summary.

10 Follow-up Arrangements

Patients with low risk MDS not on treatment or supportive care may be followed up every 6–12 months.

Patients on treatment will need more frequent monitoring, depending on the therapy and the degree of supportive care required. Patients with intermediate-2 or high risk disease on therapy may need weekly (or more) blood count monitoring and supportive therapies.

Patients may have shared care between a specialist site and the local treating hospital. These arrangements must be clearly outlined so that the patient is clear where to attend in an emergency and understands the lines of communication between the sites.

11 End-of-life Care

For older patients and in those with high risk diseases, discussions regarding prognosis and treatment options should also include discussions of end-of-life care. These discussions are to facilitate transitions between active disease-modifying therapy and clinical trials to supportive care only, at the time of disease progression/non-response. Care may be required from specialist palliative care teams.

To support consideration of referral to specialist palliative care, please refer to the local referral criteria for specialist palliative care.

The named clinical nurse specialist (CNS)/key worker, patient, family members and palliative care teams, as well as members of the inpatient ward team, may be involved. Clear documentation of the discussion with guidance to the treating teams is helpful in communicating these discussions and outputs to the wider team that may care for the individual.

12 Data Requirements

Accurate data collection is essential to monitor outcomes, and the collection of this information, particularly clinical data, remains the responsibility of the members of the multidisciplinary team with support from a data manager. Haematology services are required to submit data to nationally mandated datasets for all patients diagnosed with haematological cancer; further details on these datasets are available in [Annex 1](#).

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Annex 1: Data Requirements

Haematology oncology services within London are required to submit data to the following nationally mandated datasets for all patients diagnosed with haematological cancers.

The Cancer Outcomes and Services Dataset (COSD)

The core dataset for all tumour types including haematological cancers is mandated from January 2013, and the site-specific dataset is mandated from July 2013. Details of the dataset can be found on the National Cancer Intelligence Network website:

www.ncin.org.uk/collecting_and_using_data/data_collection/cosd.aspx

The local cancer registry will be collating this dataset using Trust data feeds which should include all these items. The feeds are:

- Trust PAS
- Trust pathology
- Trust radiology
- Trust multidisciplinary team (MDT) feed.

In line with the requirements set out in Provider Trust contracts, this data should be submitted within 25 working days of the end of the month in which the activity took place.

Three groups of haematological cancers are considered stageable by the Registry:

- Lymphomas, using Ann Arbor (or Murphy St Jude for children)
- Myelomas, using ISS
- CLLs, using Rai and Binet

For the purposes of COSD, any other haematological cancers are not counted as stageable.

For CLL both Rai (0-IV) and Binet (A-C) stages need to be recorded and submitted to COSD to be considered “fully staged”.

MGUS does not need to be recorded and submitted as it is not defined as an invasive tumour.

Systemic Anti-Cancer Therapy dataset (SACT)

Provider Trusts that provide chemotherapy to patients are required to submit data to the SACT dataset. Details of the audit and the dataset requirements are available on the dataset homepage:

www.chemodataset.nhs.uk/home.aspx

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