Clinical Guidelines for Leukaemia and other Myeloid Disorders – MDS

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1			Dr H Kaur
2	26/04/2017	Diagnosis updated Biologically based treatments	Dr H Kaur
3	17/05/2019	Complete overhaul	Dr H Kaur

(Please note that if there is insufficient space on this page to show all versions, it is only necessary to show the previous 2 versions)

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Index

GUIDELINES FOR THE DIAGNOSIS AND THERAPY OF ADULT MYELODYSPLASTIC SYNDROMES

Introduction

Myelodysplastic syndromes (MDS) are a group of clonal stem cell disorders characterised by qualitative and quantitative defects in haemopoiesis that predispose individuals to anaemia, neutropenia (risk of infection), thrombocytopenia (risk of bleeding), and a risk of transforming to acute myeloid leukaemia (AML). These guidelines should be read in conjunction with the British Committee for Standards in Haematology (BCSH) and European Leukaemia Net (ELN) Guidelines on MDS.

Referral Guidance

All patients with a suspected diagnosis of myelodysplastic syndrome should be referred to a haemato-oncologist for evaluation with minimum delay. Some patients with severe cytopenia(s) +/- circulating blasts or symptoms may merit an urgent 2 week wait referral pathway.

Patients with a confirmed diagnosis of myelodysplastic syndrome should be discussed at the network MDM for management review and treatment recommendation.

The following patients should be discussed at the Network MDT:

- all new patients with MDS
- all patients where a new line of therapy needs to be considered
- all patients in whom an allogeneic stem cell transplant is a consideration

Investigation and Diagnosis

Investigation of MDS is aimed at excluding secondary causes of dysplasia or cytopenias, and tests to confirm the diagnosis of MDS and exclude other clonal stem cell disorders.

Appropriate preliminary investigations should exclude the following alternative causes:

- haematinic deficiency (vitamin B12, folate, iron)
- liver dysfunction (including history taking for alcohol consumption)
- thyroid dysfunction
- haemolysis
- autoimmune disorders
- viral infections such as HIV, HBV and HCV, parvovirus
- other primary cancers
- other causes of inflammation

Initial investigations that can be requested are:

- FBC and blood film for morphologic assessment
- Haemolysis screen (DAT and Group and Save, reticulocyte count, haptoglobins, LDH, uric acid, urine haemosiderin)
- Haematinics (B12, folate, ferritin, iron studies)
- U&Es, LFTs, Thyroid function tests, CRP and ESR
- Serum electrophoresis, beta 2 microglobulin
- Viral screen: HIV, hepatitis B and hepatitis C, parvovirus (if appropriate)
- Autoimmune screen
- Serum erythropoietin levels
- Haemoglobin electrophoresis
- Plain chest x-ray

Haematology-initiated investigations:

<u>All</u> diagnostic tissue samples should be sent to the Haemato-Oncology Diagnostic Service (HODS) for formal diagnostic investigation with minimum delay.

- Peripheral blood film
    - At least 200 cells should be examined.
    - Features of dysplasia include: red cell anisocytosis +/- poikilocytosis, basophilic stippling, myeloid nuclear abnormalities (hypo- or hyper-lobation, pseudo Pelger-Huët anomaly), myeloid hypo- or degranulation, the presence of myeloblasts, platelet anisocytosis or giant platelets
- Bone marrow (aspirate and trephine)
    - Aspirate for morphology (MGG and iron stained slides)
        - Recommended minimum of 300 cell differential for each
        - Minimum requirement of ≥10% dysplasia in any lineage
        - Classification as per the 2016 revision to the World Health Organisation (WHO) classification of myeloid neoplasms and acute leukaemia (Blood 2016 127:2391-2405). (See table)
    - Trephine for morphology, assessment of reticulin fibrosis and immunohistochemistry
    - Cytogenetics (these are abnormal in up to 50% of patients with MDS) on at least 20 metaphases and reported in accordance with the International System Recommendations
    - Specific genetic tests (as clinically suspected/ indicated)
        - Molecular genetics (samples for myeloid NGS panel). Whilst not an essential test for the diagnosis of MDS and not currently incorporated into standard prognostic scoring systems, at least 52% of patients with a normal karyotype have ≥ 1 mutation, which can be helpful in confirming the diagnosis, and provide additional prognostic information to facilitate decisions regarding management.
        - TP53, RUNX1, EZH2 are known to be adverse prognostic indicators in all patients with MDS. SRSF2, ASXL1, U2AF1 and NRAS mutations are felt to confer adverse risk in patients with low blast percentage (<5%). Nazha and Bejar. *Curr Hematol Malig Rep*. 2017 Oct;**12**(5):461-7

        - If AML is a possibility - FLT3/ NPM1 mutation testing
        - Bone marrow failure syndrome - Chromosome fragility testing, bone marrow failure NGS panel, telomere length)
    - Flow cytometry
        - This is not currently considered to be standard practice in the diagnostic pathway of MDS, however is helpful in identifying dysplasia and quantifying myeloid blasts.

Patients who are extremely fit (ECOG performance status = 0) and being considered for potentially intensive treatment options, such as allogeneic stem cell transplantation should also have a CMV IgG sent at diagnosis/ suspected progression of disease).

Patients who are deemed clinically inappropriate to have a bone marrow aspirate due to very poor performance status should have their peripheral blood film sample sent to HODS for definitive morphologic assessment +/- peripheral blood cytogenetics (especially if PB blasts are present). In patients with cytopenias and or macrocytosis in whom a diagnosis of MDS cannot be reliably confirmed it may be necessary to continue follow-up and repeat diagnostic evaluations at appropriate intervals.

Some patients may demonstrate clonality and/or cytopenias without clearly fulfilling criteria for diagnosis of MDS or other haematological disorders. Follow-up of patients with CHOP by a haematologist is advised, however management of these patients is not currently covered by this guideline and is at the discretion of individual clinicians.

2016 Revision to the World Health Organisation (WHO) Classification: MDS

Name	Dysplastic lineages	Cytopenias*	Ring sideroblasts as % of marrow erythroid elements	BM and PB blasts	Cytogenetics by conventional karyotype analysis
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	<15%/<5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1-3	<15%/<5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)					
MDS-RS with single lineage dysplasia (MDS-RS-SLD)	1	1 or 2	≥15%/≥5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS with multilineage dysplasia (MDS-RS-MLD)	2 or 3	1-3	≥15%/≥5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all 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 1 additional abnormality except −7 or del (7q)
MDS with excess blasts (MDS-EB)					
MDS-EB-1	0-3	1-3	None or any	BM 5%-9% or PB 2%-4%, no Auer rods	Any
MDS-EB-2	0-3	1-3	None or any	BM 10%-19% or PB 5%-19% or Auer rods	Any
MDS, unclassifiable (MDS-U)					
with 1% blood blasts	1-3	1-3	None or any	BM <5%, PB = 1%,‡ no Auer rods	Any
with single lineage dysplasia and pancytopenia	1	3	None or any	BM <5%, PB <1%, no Auer rods	Any
based on defining cytogenetic abnormality	0	1-3	<15%§	BM <5%, PB <1%, no Auer rods	MDS-defining abnormality
Refractory cytopenia of childhood	1-3	1-3	None	BM <5%, PB <2%	Any

*Cytopenias defined as: hemoglobin, <10 g/dL; platelet count, $<100 \times 10^9$/L; and absolute neutrophil count, $<1.8 \times 10^9$/L. Rarely, MDS may present with mild anemia or thrombocytopenia above these levels. PB monocytes must be $<1 \times 10^9$/L

†If *SF3B1* mutation is present.

‡One percent PB blasts must be recorded on at least 2 separate occasions.

§Cases with ≥15% ring sideroblasts by definition have significant erythroid dysplasia, and are classified as MDS-RS-SLD.

2016 Revision to the World Health Organisation (WHO) Classification: CMML

CMML diagnostic criteria
• Persistent PB monocytosis $\geq 1 \times 10^9$/L, with monocytes accounting for ≥10% of the WBC count
• Not meeting WHO criteria for *BCR-ABL1*$^+$ CML, PMF, PV, or ET*
• No evidence of *PDGFRA*, *PDGFRB*, or *FGFR1* rearrangement or *PCM1-JAK2* (should be specifically excluded in cases with eosinophilia)
• <20% blasts in the blood and BM†
• Dysplasia in 1 or more myeloid lineages. 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 genetic abnormality is present in hemopoietic cells‡
or
• The monocytosis (as previously defined) has persisted for at least 3 mo and
• All other causes of monocytosis have been excluded

*Cases of MPN can be associated with monocytosis or they can develop it during the course of the disease. These cases may simulate CMML. In these rare instances, a previous documented history of MPN excludes CMML, whereas the presence of MPN features in the BM and/or of MPN-associated mutations (*JAK2*, *CALR*, or *MPL*) tend to support MPN with monocytosis rather than CMML.

†Blasts and blast equivalents include myeloblasts, monoblasts, and promonocytes. Promonocytes are monocytic precursors with abundant light gray or slightly basophilic cytoplasm with a few scattered, fine lilac-colored granules, finely distributed, stippled nuclear chromatin, variably prominent nucleoli, and delicate nuclear folding or creasing. Abnormal monocytes, which can be present both in the PB and BM, are excluded from the blast count.

‡The presence of mutations in genes often associated with CMML (eg, *TET2*, *SRSF2*, *ASXL1*, *SETBP1*) in the proper clinical contest can be used to support a diagnosis. It should be noted however, that many of these mutations can be age-related or be present in subclones. Therefore, caution would have to be used in the interpretation of these genetic results.

2016 Revision to the World Health Organisation (WHO) Classification: Germline mutations

Myeloid neoplasms with germline predisposition without a preexisting disorder or organ dysfunction

Acute myeloid leukemia with germline CCAAT/enhancer-binding protein-A mutation

Myeloid neoplasm with germline *DDX41* mutation

Myeloid neoplasms with germline predisposition and preexisting platelet disorders

Myeloid neoplasms with germline *RUNX1* mutation

Myeloid neoplasms with germline *ANKRD26* mutation

Myeloid neoplasms with germline *ETV6* mutation

Myeloid neoplasms with germline predisposition and other organ dysfunction

Myeloid neoplasms with germline *GATA2* mutation

Myeloid neoplasms with germline predisposition with BM failure syndromes

Myeloid neoplasms with germline predisposition with telomere biology disorders

Juvenile myelomonocytic leukemia associated with neurofibromatosis, Noonan syndrome, or Noonan syndrome-like disorders

Myeloid neoplasms associated with Down syndrome

Molecular mutations currently tested in NGS/ HTS myeloid molecular panel

DNA Methylation	TET2(3-11), DNMT3A(2-23), IDH1(4), IDH2(4-5)
Chromatin Modification	ASXL1(12), EZH2(2-20)
Splicing	SF3B1(12-16), SRSF2(1), U2AF1(2,6), ZRSR2(2-11)
Transcription Factor	NPM1(12), RUNX1(4-8), BCOR(2-15), WT1(7,9), TP53(5-9), JAK2(12,14), MPL(10), CSF3R(14,17), STAT3(21a, 23b)
Signalling)	FLT3(20)‡, NRAS(2-3), KRAS(2-3), CBL(8-9), cKIT(8-17)
Cohesin complex	STAG2(3-35)
Other	SETBP1(4), CALR(9)

‡This test does not detect FLT3-ITD variants

Risk Stratification/ Prognosis

The International Prognostic Scoring System (IPSS)[3] and the Revised International Prognostic Scoring System (IPSS-R) should be used to classify patients into prognostic sub-groups at the time of presentation. The prognostic score should be used to help guide treatment decision making.

International Prognostic Scoring System (IPSS) (Greenberg P et al , 1997)

Prognostic variable	Score value				
	0	0,5	1	1,5	2,0
Bone marrow blasts (%)	<5	5-10	....	11-20	21-30
Karyotype [1]	Good	Intermediate	Poor		
Cytopenia [2]	0/1	2/3			

IPSS Group	IPSS Total Score	Survival (median; yrs)		25% AML evolution (yrs)	
		Age at diagnosis		Age at diagnosis	
		≤70yrs	>70yrs	≤70yrs	>70yrs
Low	0	9	3,9	>9,4 (NR)	>5,8 (NR)
Intermediate-1	0,5-1,0	4,4	2,4	5,5	2,2
Intermediate-2	1,5-2	1,3	1,2	1,0	1,4
High	≥2,5	0,4	0,4	0,2	0,4

[1] **Definition of karyotype**

Good	Normal, Y-, 5q-, 20q-
Intermediate	All other
Poor	Chromosom 7 aberration and/or ≥ 3 Chromosomal aberrations.

[2] **Cytopenia**
Hemoglobin < 100 g/L (10 g/dL)
Neutrophil count < 1,8 G/L (1.800/µl)
Platelet count < 100 G/L (100.000/µl)

NR, not reached

Revised International Prognostic Scoring System (IPSS) (Greenberg P et al , Blood, 2012)

Characteristics	Score values						
	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	-	Good	-	Intermediate	Poor	Very poor
Blasts BM, %	≤2	-	>2 - <5	-	5-10	>10	-
Hb	≥10	-	8-<10	<8	-	-	-
Platelets	≥100	50-<100	<50	-	-	-	-
Neutrophils	≥0.8	<0.8	-	-	-	-	-

Risk groups	
Very low	≤1.5
Low	>1.5 – 3
Intermediate	>3 – 4.5
High	>4.5 - 6
Very high	>6

Cytogenetic risk groups

Prognostic subgroup	Cytogenetic Aberration	Median survival, yrs	Median AML-evolution 25%, yrs
Very good	-Y, del(11q)	5.4	NR
Good	Normal, del (5q), del (12p), del (20q), double including del (5q)	4.8	9.4
Intermediate	del (7q), +8, +19, i(17q, any other single or double independent clones	2.7	2.5
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities	1.5	1.7
Very poor	Complex: >3 abnormalities	0.7	0.7

Acronyms describing Clonal Haemopoiesis and Related Conditions, without fulfilling sufficient criteria for the diagnosis of MDS

Acronym	*Condition*	*Description/Definition*
ARCH	Aging related clonal hematopoiesis	Describes the presence of detectable, benign clonal hematopoiesis (defined by the presence of somatic mutations in the blood or bone marrow) whose incidence increases with age. No formal definition involving clonal abundance or types of mutations. No clinical significance is implied.
CHIP	Clonal hematopoiesis of indeterminate potential	Defined by somatic mutations of myeloid malignancy-associated genes in the blood or bone marrow present at ⩾ 2% variant allele frequency in individuals without a diagnosed hematologic disorder.
CHOP	Clonal hematopoiesis of oncogenic potential	Describes clonal hematopoiesis in a clinical context where it is associated with a significant likelihood of progressing to a frank malignancy.
IDUS	Idiopathic dysplasia of undetermined significance	Individuals with unexplained morphologic dysplasia of blood cells who are not cytopenic. Can occur with or without clonal hematopoiesis.
ICUS	Idiopathic cytopenia of undetermined significance	Patients with one or more unexplained cytopenias who do not meet diagnostic criteria for myelodysplastic syndrome or another hematologic disorder. Can occur with or without clonal hematopoiesis although often used to refer to cytopenias without evidence of clonal hematopoiesis.
CCUS	Clonal cytopenia of undetermined significance	Patients with one or more unexplained cytopenias who do not meet diagnostic criteria for myelodysplastic syndrome or another hematologic disorder, but who have somatic mutations of myeloid malignancy-associated genes in the blood or bone marrow present at ⩾ 2% variant allele frequency. Can be considered as the intersection between CHIP and ICUS.

Bejar R. Leukaemia (2017) 31, 1869-1871.

Patient Information

Patients who have been diagnosed with MDS should receive patient specific verbal and written information about the disease and treatment options, including contact numbers for the haematology department both during and out of hours. Patients should also be offered a copy of the clinic letter that is sent to the GP.

All patients should have a Clinical Nurse Specialist (CNS)/ Key Worker who should be present at diagnosis and at any further discussions, as per criteria for discussion at MDT. Where is it not possible for the CNS or deputy to be present, the CNS should be informed of the discussion that has taken place and who should then arrange to contact the patient. CNSs are well placed to liaise with other support services, including dieticians, benefits advisors and district nurses.

The CNS should ensure that all patients are offered Holistic Assessment at diagnosis, change of treatment and end of treatment.

Additional local and national patient information and support may be gained from the following websites:

UK MDS Forum: www.mdspatientsupport.org.uk

Leukaemia Care: https://www.leukaemiacare.org.uk/support-and-information/help-and-resources/information-booklets/

MacMillan Cancer Support: https://www.macmillan.org.uk/

Cavendish Centre (Sheffield): https://cavcare.org.uk/

Cancer Support Centre (Sheffield): http://www.cancersupportcentre.co.uk/

Management

The management of MDS depends varies widely depending on:

1) Patient fitness and comorbidities
2) Degree of cytopenias
3) Percentage of blasts
4) Patient choice

The goals of treatment for MDS are to improve Quality of Life and prolong survival. In order to achieve these goals, treatment options range from active monitoring ("watchful waiting"), best supportive care +/- replacement therapy, low intensity treatment and high intensity treatment. The only potentially curative treatment option is allogeneic stem cell transplantation. The majority of patients with this diagnosis will be >70 years and likely to have comorbidities, the impact of which on treatment should be formally assessed with tools such as CIRS, CGA, timed "up and go" test.

Supportive Care and Replacement Therapy

Management of Anaemia

1. Red cell transfusion:

Red cell transfusion should be considered in any patient with symptomatic anaemia irrespective of haemoglobin level.

2. Erythropoietin:

Erythropoietin as single agent or in combination with G-CSF may improve the anaemia in selected patients with myelodysplastic syndrome. Serum erythropoietin levels (serum erythropoietin less than 200 U/L) are informative for response, and should be checked before initiating therapy.

Iron overload

Patients with low risk or intermediate-1 myelodysplasia (predicted survival of at least 4 years) should be considered for iron chelation therapy and should be commenced once patients have received more than 25 units of red cells. It is recommended that all patients being considered for chelation have formal assessment of iron overload with MRI scan (specifically requested as "test for iron overload"), baseline audiology and ophthalmology review. Patients being considered for Exjade should have normal renal function at baseline.

The choice of iron chelator in the UK lies between desferrioxamine and desferasirox. 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. Further, compliance is improved using oral therapy. Clinical judgement relating to suitability, patient compliance and co-morbidities should define the choice of chelating agent.

Management of Thrombocytopenia

Platelet transfusion support should be offered to those patients with symptomatic thrombocytopenia, or to cover planned interventional procedures.

Management of neutropenia and infection

Neutropenic sepsis should be treated with broad spectrum antibiotics according to the local neutropenic antibiotic guideline policy. There is no evidence to support the routine use of prophylactic antibiotic therapy, but prophylactic G-CSF may have a role in patients with recurrent infections due to neutropenia.

Low-intensity therapy

Where possible, patients who are eligible should be offered treatments as part of a clinical trial. For all other patients, therapeutic options include:

1. Anti-Thymocyte Globulin/Ciclosporin

   Patients with low-risk or intermediate-1 disease should be considered for immunosuppressive therapy if they have hypoplastic myelodysplasia or Refractory anaemia with HLA DR15 or presence of a large PNH clone.

2. Lenolidomide

   Patients with 5q syndrome should be considered for therapy with Lenolidomide, preferably in the context of a clinical trial

3. Azacytidine

Patients with intermediate-2, or high-risk myelodysplasia who are not fit enough for intensive chemotherapy should be considered for treatment with Azacytidine.

4. Low dose oral Melphalan

A subset of older patients may benefit from low dose melphalan (2mg daily po).

Intensive chemotherapy and allogeneic transplantation

Allogeneic transplantation is potentially curative therapy for patients with high-risk disease. Patients with high-risk myelodysplasia in whom curative therapy is deemed appropriate should referred to the Sheffield Haematopoietic Stem Cell Transplant for appropriate counselling, and should be treated with intensive chemotherapy and allogeneic transplant, preferably in the context of a clinical trial.