Haematology Cancer Clinical Guidelines

Haematology Expert Advisory Group (EAG)
on behalf of Northern Cancer Alliance

Title:	Haematology Cancer Clinical Guidelines
Authors:	Haematology EAG
Circulation List:	Haematology EAG Members
Contact Details:	Mrs C McNeill, Senior Administrator, Cancer Alliance
Telephone:	01138252976

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SECTION 5

GUIDELINES FOR MANAGEMENT OF MYELODYSPLASTIC SYNDROMES

Key points

- The diagnosis of Myelodysplastic syndromes (MDS) must be made according to the WHO classification (revised 2016).
- A bone marrow aspirate and trephine including an iron stain should be performed. An EDTA and unstained slides should be sent to NEHODS for flow, cytometric analysis and cytogenetic analysis. Bone marrow trephine immunohistochemistry can be considered.
- All MDS patients must have risk stratification according to the International Prognostic Scoring System (IPSS) and the revised IPSS (IPSS-R).
- All MDS patients must be discussed at the haematology multidisciplinary team meeting (MDT). Transplant eligible patients should be discussed with the bone marrow transplant team.
- It is important to note that for asymptomatic patients, a period of observation to determine the rate of progression can be helpful before formulating a management plan.
- Patients should be managed in line with the BCSH Guidelines on the management of Myelodysplastic Syndromes (2013).

Diagnosis

See NEHODS cytopenias and myelodysplasia pathways

Classification

WHO Classification of the Myelodysplastic Syndromes (2016)					
Disease	Dysplastic lineages	Cytopenias	Ring sideroblasts	Blasts	Cytogenetics
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	<15% (or <5%)	PB <1%, BM <5%, no auer rods	Any unless fulfils criteria for del(5q)
MDS with multi lineage dysplasia (MDS-MLD)	2 or 3	1 - 3	<15% (or <5%)	PB <1%, BM <5%, no auer rods	Any unless fulfils criteria for del(5q)
MDS with ring sideroblasts and single lineage dysplasia (MDS-RS-SL)	1	1 or 2	RS ≥15% (or ≥5% with SF3B1 mutation)	PB <1%, BM <5%, no auer rods	Any unless fulfils criteria for del(5q)
MDS-RS and multilineage dysplasia (MDS-RS-MLD	2 or 3	1 - 3	RS ≥15% (or ≥5% with SF3B1 mutation)	PB <1%, BM <5%, no auer rods	Any unless fulfils criteria for del(5q)
MDS with isolated del(5q)	1 - 3	1 - 2	None or any	PB <1%, BM <5%, no auer rods	del(5q) alone with 1 additional abnormality except -7 or del(7q)
MDS with excess blasts-1	0 - 3	1 - 3	None or any	PB 2 – 4%, or BM 5 –	Any

(MDS-EB-1)				9%, no auer rods	
MDS with excess blasts-2 (MDS-EB-2)	0 - 3	1 - 3	None or any	PB 5 – 19%, or BM 10 – 19% ±Auer rods <1 x 10^9/l monocytes	Any
MDS, unclassifiable (MDS-U) with 1% PB blasts	1 - 3	1 - 3	None or any	PB = 1% (on 2 occasions), BM <5%, no auer rods	Any
MDS-U with SLD and pancytopenia	1	3	None or any	PB <1%, BM < 5%, no auer rods	Any
MDS-U with defining cytogenetic abnormality	0	1 - 3	<15%	PB <1%, BM < 5%, no auer rods	MDS defining abnormality

WHO classification 2016 revision

- Note that the WHO thresholds for defining cytopenias remain the same (not lowered in keeping with IPSS-R). i.e. Hb <100 g/L, platelets <100 x 10^9/L, absolute neutrophil count <1.8 x 10^9/L.
- The thresholds for defining dysplasia remain the same (10% dysplastic cells).
- In spite of increasing knowledge of the prognostic importance of cytogenetic abnormalities in MDS, del(5q) remains the only abnormality that defines a specific subtype.
- Due to knowledge that one other cytogenetic abnormality has no adverse effects in del(5q), the entity can still be diagnosed as long as the other abnormality is not monosomy 7.
- The clinical impact of recurring genetic mutations in MDS is now recognised. Targeted sequencing can detect mutations in 80-90% MDS. These data impact risk stratification but do not yet form part of the classification criteria with the exception of mutations in the spliceosome gene SF3B1 (see above).

Risk stratification

- The International Prognostic Scoring System (IPSS) (1997) is an important tool designed to assess the outcome of patients with untreated adult MDS.
- The revised IPPS (IPSS-R) (2012) further refined the parameters of the IPSS (cytogenetic groups, marrow blast % and cytopenias).
- The IPSS-R should be the preferred scoring system for determining prognosis but it is not a dynamic scoring system and can only be used at diagnosis.
- The IPSS-R prognostic groups low and very low risk categories map to low risk and INT-1 risk in the IPSS. Similarly, the high and very high risk patients map most closely to the INT-2 and high risk IPSS groups. The clinical significance of the newly described intermediate risk group remains to be determined in terms of treatment recommendations.

IPSS prognostic score values					
Score value	**0**	**0.5**	**1.0**	**1.5**	**2**
BM blast %	<5	5-10	-	11-20	21-30
Karyotype*	good	intermediate	Poor		
Cytopenias**	0-1	2-3			
* Good = normal, -Y, del(5q), del(20q), Poor = complex (>3 abnormalities) or Ch 7 abnormalities, Intermediate = all other					
** Hb <100, Neutrophils <1.8x10^9/L and platelets <100x10^9/L					

Risk stratification of MDS using IPSS	
IPSS score	**Risk group**
0	Low
0.5-1.0	Intermediate 1 (INT-1)
1.5-2.0	Intermediate 2 (INT-2)
≥2.5	High

IPSS-R prognostic score values							
Score value	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**
Cytogenetics	Very good		Good		Intermediate	Poor	Very poor
BM blast %	≤2		>2-<5		5-10	>10	
Hb concentration	≥100		80-<100	<80			
Platelet count	≥100	50-<100	<50				
Neutrophil count	≥0.8	<0.8					

IPSS-R Cytogenetic prognostic subgroups	
Very Good	-Y, del (11q)
Good	Normal, del(5q), del(12p), del(20q), double including del 5q
Intermediate	Del(7q), +8, +19, i(17q), any other signle or double independent clones
Poor	-7, inv(3)/t(3q), double incl -7/del(7q), complex: 3 abnormalities
Very Poor	Complex >3 abnormalities

IPSS-R prognostic risk scores and outcomes			
Risk category	Score	Survival (median – years)	25% AML evolution (median – years)
Very low	≤1.5	8.8	NR
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

Management

General points

- Supportive care is the mainstay of treatment for patients with MDS and symptomatic cytopenias.
- Red blood cell (RBC) transfusions should be considered for symptomatic anaemia.
- Platelet transfusions are not routinely indicated for stable, non-bleeding patients with MDS.

Low risk MDS

- Includes patients defined by IPSS as Low or INT-1 and by IPSS-R as Very Low and Low
- These patients have a more favourable prognosis and often present with anaemia.
- Supportive care with RBC transfusion remains important but is associated with risks of alloimmunisation and iron overload.
- Consideration should be given to treatments that reduce transfusion requirements.
- Iron chelation is not routinely recommended for patients with transfusional iron overload but should be considered in those with a very good prognosis (RA, RARS and del(5q)). Potential triggers are ferritin >1000ng/l and transfusion of >20 units of red cells.

Erythroid Stimulating Agents (ESAs)

- Consider a trial of erythropoietin for patients with low risk MDS who score ≤1 in the predictive algorithm below

Model for predicting response to ESA (Predicted response: Score 0 = 74%, Score 1 = 23%, Score 2 = 7%)			
Transfusion requirement	Point	S-EPO	Point
<2 units RBC/month	0	<500 u/l	0
≥2 units RBC/month	1	≥500 u/l	1

- Non-sideroblastic phenotypes: Consider erythropoietin or darbopoietin alone. Erythropoietin dose is 30,000 units per week for 8 weeks. If no response double to 60,000 units once per week or 30,000 units twice per week for 8 weeks. Darbopoietin dose is either 150mcg every 7 days or 300mcg every 14 days. The dose is doubled in non-responders for a further 8 weeks at a dose of 300mcg per week.
- Sideroblastic phenotypes: The guidance with respect to erythropoietin and darbopoietin is the same but treatment should be combined with GCSF from the outset at a starting dose of 300mcg in 2/3 divided doses per week rising to 300mcg three times weekly in non-responders. The aim is to double the white cell count if it starts below $1.5x10^9$/l or to keep the count between 6-10 x 10^9/l in other patients.
- Maximum trial period should be 16 weeks.
- Patients who respond should continue on long term therapy until response is lost.
- Care should be taken if the HCT rises rapidly. The target Hb is <12g/dl in view of the 2% incidence of thrombosis associated with ESAs.

Anti thymocyte globulin (ATG) and Ciclosporin

- Consider antithymocyte globulin (ATG) and ciclosporin therapy for patients who are considered able to tolerate the treatment (typically age <60) in those with low-risk MDS (IPSS ≤ INT-1) with normal karyotype or trisomy 8.
- Ciclosporin alone may have a role for patients with a hypocellular marrow or autoimmune phenomena.

- Corticosteroids as an immunosuppressive therapy to improve cytopenias are not recommended.

Lenalidomide (Revlimid*)*
- Is licensed for use for the treatment of anaemia in IPSS ≤ INT-1 MDS with isolated del(5q).
- Can be used for the treatment of transfusion dependent anaemia in IPSS ≤ INT-1 MDS with isolated del(5q) plus one other cytogenetic abnormality.
- Lenalidomide dose is 10mg daily for 21 days, repeated every 28 days.

High risk MDS – Transplant eligible

The Role of Allograft
- In patients considered fit for transplant, HSCT can offer the only chance of long term disease free survival and early discussion with the transplant unit should be undertaken. Allogeneic SCT from a voluntary unrelated donor should be considered if there is no HLA matched sibling. Generally there is no place for SCT in those who do not achieve complete remission with induction chemotherapy.

Other indications for SCT
- Selected patients with low risk MDS should be considered for allogeneic SCT on individual grounds. Examples include young patients with platelet refractoriness, or heavy red cell transfusion requirement in the absence of an alternative cause for anaemia. Chemotherapy prior to SCT will be necessary in this group only in the rare patient with blasts 5-10% or an adverse karyotype.
- Autologous SCT should be offered only in the context of clinical trials.

Intensive chemotherapy
- Patients with >10% BM blasts and a hypercellular bone marrow should be considered for intensive AML induction chemotherapy (see Guidelines for Management of Acute Myeloid Leukaemia). NCRN AML 19 trial is available. The use of azacitidine in this setting is experimental and should only be given in the context of a clinical trial.
- Patients with <10% BM blasts are at risk of chemotherapy complications such as prolonged hypoplasia and upfront HSCT should be considered.

High risk MDS – Transplant ineligible

Intensive chemotherapy
- Patients aged >60 years with >10% blasts in marrow, considered fit to tolerate intensive chemotherapy and lacking a high risk karyotype, should be offered therapy intensive AML-style treatment in an attempt to improve survival. NCRN AML 18 trial is available.

Non-intensive chemotherapy
- ***Azacitidine*** is recommended as a treatment option for adults who are not eligible for HSCT and have:
  1. INT-2 and high-risk MDS according to the IPSS
  2. Chronic myelomonocytic leukaemia (CMML) with 10–29% marrow blasts without myeloproliferative disorder
  3. Acute myeloid leukaemia with 20–30% blasts and multilineage dysplasia, according to the World Health Organization classification

  (And if the manufacturer provides azacitidine with the discount agreed as part of the patient access scheme)

  The recommended dose of Azacitidine is 75 mg/m2 daily subcutaneously for 7 days. An acceptable alternative regimen is Azacitidine daily Monday to Friday, a break over a

weekend then 2 further doses Monday and Tuesday (termed 5-2-2). Treatment is given as a 28 day cycle. It is recommended that patients be treated for a minimum of 6 cycles. Treatment should be continued as long as the patient continues to benefit or until disease progression.
- ***Oral low dose Melphalan*** should be considered for a select group of patients with >5% blasts in a hypocellular marrow with a normal karyotype.

The Role of Iron Chelation in MDS

- The benefit of iron chelation in MDS is unproven.
- Despite this, it is widely felt that iron chelation should be considered for selected low risk MDS patients and those in whom HSCT is being planned.

Patient Selection

1. Patients should fulfil criteria in point A with consideration of point B.
   A. Patients diagnosed with MDS with a very good prognosis, specifically those with RA, RARS and isolated del(5q)
   B. Iron chelation may be withheld at the discretion of the Haematologist in patients with significant organ damage (not due to iron overload) likely to reduce the above survival figures.
2. In those in whom HSCT is planned.

When to start

- Trigger for consideration of treatment is a serum ferritin consistently above 1000 ng/mL or >20 units of red cells transfused. When on chelation, serum ferritin should be checked every 3 months to allow assessment of trends.
- In practice, iron load is monitored by changes in serum ferritin concentrations, but reliance on serum ferritin alone may lead to inaccurate assessment of body iron burden in individual patients.
- Liver biopsy with samples sent for dry iron weight (liver iron content - LIC) remains the “gold standard” in patients in whom serum ferritin is unreliable. Iron chelation is recommended if there is evidence of moderate iron overload. Negotiation with local hepatologist/histopathologist will be required in advance since this test is not routinely available in most labs.

Recommendation

- An annual T2* MR scan is indicated when serum ferritin is >1000 ng/mL.
- If there is mild iron overload, T2* MR scan should be repeated at 6 months.
- Initiate chelation when there is moderate liver iron overload, i.e. LIC>5 (or equivalent T2*).
- Initiate chelation if the heart shows any evidence of iron overload.
- FerriScans are also available through Alliance Medical and provide an accurate measure of liver iron concentration.

Treatment

- ***Deferasirox***
  - Contraindicated if estimated creatinine clearance is <60 mL/min.
  - Dose: Recommended initial daily dose is 20 mg/kg. Consider 30 mg/kg for those who receive >4 units of red cells/month).
  - Monitoring:
    - Renal: use of this agent is associated with a rise in serum creatinine in about 36% of patients. It is recommended that serum creatinine should be measured twice before starting therapy then weekly for the first month or after a dose increase and monthly

thereafter. Dose should be reduced by 10mg/kg if creatinine levels rise by>33% of pre-treatment levels. Testing for proteinuria should be performed monthly.

- Hepatic: Increases in transaminases have been observed in trials. LFTs should be performed at baseline and monthly. Deferasirox is not recommended in patients with severe hepatic impairment.
- Auditory and ophthalmic testing is recommended before the start of treatment and annually thereafter.
- Interruption of deferasirox should be considered if serum ferritin levels fall consistently below 500 ng/mL.

- ***Desferrioxamine (DFO)***

  DFO may be used if there is intolerance and/or refractoriness to desferasirox.

  Administration: DFO may be administered in a variety of ways:

  - Via a SC "Graseby" infusion pump over 8-12 hours (preferably overnight).
  - Via a Balloon infuser (Baxter or similar) SC over 12-24 hours. Balloon infusers delivering DFO over several days are also available.
  - IV ambulatory DFO administered via balloon infusers through implantable venous access ports or Hickman lines are associated with rapid reduction of iron burden and improvement in cardiac function in severe iron overload.
  - There is no role for infusing DFO concomitantly with a blood transfusion.
  - Iron excretion induced by DFO is enhanced by vitamin C given at a maximal dose of 200mg daily and should be started 4 weeks after initiation of DFO. It should be given separately from food and is contraindicated in patients with cardiac failure.

  Dose: Start at the lowest effective dose, usually between 20-50mg/kg daily SC infusion. Usual starting dose is 2g/day 3-5 days/week.

  Monitoring:

  - Baseline and annual ophthalmic examination, early retinal and optic nerve disturbances are reversible. Diabetic patients are at greater risk and may require monitoring and more frequent intervals.
  - Baseline and annual audiometry to detect high frequency sensorineural deafness.
  - Ophthalmic and audiometric assessments should be more frequent in patients on intensive continuous chelation or in patients where a rapid fall in iron load is achieved.
  - Cautious use on renal impairment.
  - Greater risk of Yersinia infections. DFO should be stopped in febrile patients until Yersinia infection is ruled out.
  - 24 hour urine collection for iron excretion is not generally required.
  - The majority of patients on regular transfusion will require regular chelation though dosage or frequency may need to be reduced according to the DFO toxicity index. DFO toxicity increases in well-chelated patients. The DFO therapeutic index should be kept <0.025.
  - Therapeutic index = mean daily dose (mg/kg) / serum ferritin (ng/mL) 42

Myelodysplastic/myeloproliferative neoplasm

WHO classification of Myelodysplastic/myeloproliferative neoplasms (2008 versus 2016 revision)

2008	2016
Chronic myelomonocytic leukaemia	Chronic myelomonocytic leukaemia • CMML-0 • CMML-1 • CMML-2
Atypical chronic myeloid leukaemia, BCR-ABL negative	Atypical chronic myeloid leukaemia
Juvenile myelomonocytic leukaemia	Juvenile myelomonocytic leukaemia
Refractory anaemia with ring sideroblasts and thrombocytosis (RARS-T) *(provisional entity)*	MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
MDS/MPN, unclassifiable	MDS/MPN, unclassifiable

WHO diagnostic criteria

- PB monocytosis >1 x 10^9 and monocytes accounting for >10% of the WBC differential count.
- Not meeting criteria for BCR ABL+ CML, PMF, PV or ET
- No evidence of PDGFRA, PDGFRB or FGFR1 rearrangement or PCM1-JAK2 (specifically exclude in patients with eosinophilia)
- <20% blasts in blood and BM
- Dysplasia in 1 or more lineages
- If dysplasia is absent or minimal, diagnosis may still be made if other requirements are met and there is an acquired cytogenetic or molecular abnormality present
- OR there is a persistent monocytosis for >3 months and all other causes of monocytosis have been excluded

- ***CMML-0:*** < 2% blasts in the peripheral blood and <5% blasts in BM
- ***CMML-1:*** 2-4% blasts in PB and 5-9% in BM
- ***CMML-2:*** 5-19% blasts in PB or 10%-19% in the BM and/or Auer rods are present

Prognosis of CMML

Both prognostic scoring systems below have value:

- **Düsseldorf score** which takes into account BM blast %, LDH, Hb concentration and platelet count.
- **CPSS** which takes into account WHO subtype, FAB subtype, CMML specific cytogenetic risk classification and RBC transfusion dependency.

Treatment of CMML

- Transplant eligible patients should be considered for an allogeneic SCT.
- Supportive care +/- hydroxycarbamide remains the mainstay of care for the majority of patients with CMML.
- There are clinical and molecular differences between proliferative (WCC >13) and non proliferative (WCC <13) CMML.
- Azacitidine is approved for use in non-proliferative CMML-2 with 10-29% marrow blast