Manchester Cancer

Manchester Cancer Guideline for the diagnosis and treatment of Myelodysplastic Syndromes

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Introduction

The myelodysplastic syndromes (MDS) encompass a heterogeneous group of bone marrow disorders characterized by ineffective, dysplastic haematopoiesis with subsequent pancytopenia. Some patients live for decades with mild asymptomatic anemia, others present with profound pancytopenia, associated complications of infection, bleeding and rapid transformation to AML. Numerous potential therapeutic strategies for MDS have been evaluated in clinical trials, but the majority of these have only moderate efficacy at best. So while standards of care do exist, and guidelines can be utilized for uniformity of management, there remains a significant clinical need for the further development of well designed randomized clinical trials for MDS patients.

These guidelines have been written for Manchester Cancer haemato-oncology pathway board and while every attempt has been made to establish accuracy health care professionals are advised to confirm this accuracy with the source data.

Diagnosis

The diagnosis of MDS is largely based on careful morphological examination of the blood film and bone marrow in patients with clinical evidence of impaired hematopoiesis manifested by different combinations of anemia, neutropenia and thrombocytopenia. Reactive causes of cytopenia and dysplasia as well as other clonal stem cell disorders should be excluded.

Patient history and examination:
To include symptoms of anaemia, infection and bleeding. Also family history, prior chemotherapy and irradiation, occupational exposure,
concomitant medication, alcohol consumption and transfusions. Complete physical examination to include spleen size and evidence of pallor and bleeding.

Recommended base-line investigations:

- FBC with blood film examination
- Reticulocyte count
- Ferritin, Iron, transferrin (TIBC)
- Vitamin B12 and Folic acid
- LDH, bilirubin, serology for hepatitis B,C and HIV
- Blood group and antibody screen

Investigations in selected cases

- DAT, haptoglobin
- Serum erythropoietin
- Screening for HIV, Parvovirus B19 (hypoplastic MDS) andCMV
- HLA typing
- Red cell phenotype (as per BCSH Transfusion guidelines)

- PNH screen
- Fanconi anaemia screen
- JAK2 (MPD/MDS overlap syndromes)

Bone marrow

Initial assessment of a patient with unexplained cytopenia(s) may not confirm a diagnosis of MDS. Further follow-up and reassessment may be necessary to reach a firm diagnosis or to evaluate disease progression. However there may be elderly patients or those with a poor performance status where a definitive diagnosis may not be required as their management will not be altered.

• Bone marrow aspirate

In line with the WHO criteria for significant dysplasia, dysplastic features should be present in at least 10% of the nucleated cells in the lineage in consideration. At least 200 marrow cells and 20 megakaryocytes should be evaluated, and the percentage of blasts enumerated, with optimal staining of blood and marrow slides . An iron stain should be performed to identify the presence of ring sideroblasts. Pseudo-pelger neutrophils, ring sideroblasts, micromegakaryocytes and increased blast count show the strongest correlation with clonal markers in MDS. It should be noted that hypogranularity of neutrophils is highly stain dependant and is therefore not significant in isolation.

• Bone marrow trephine

Complements the aspirate and should be undertaken in all cases to evaluate cellularity and fibrosis (H+E and reticulin). Immunohistochemistry can be particulary useful in identifying abnormally localised immature precursors (ALIP) (CD34) and dysplastic megakaryocytes (CD42b).

• Bone marrow cytogenetics

Provides clear evidence of a clonal disorder and has major prognostic value and therefore should be undertaken in all cases with samples sent to the Christie hospital for analysis. FISH for selected cytogentic anomalies (monosomy 7, del 5q, trisomy 8) can be used in questionable cases eg. Low number of metaphases in conventional karyotyping

• Bone marrow molecular analysis

A number of dysplastic disorders have crossover to myeloid proliferation, in such cases molecular analysis can be informative eg JAK2 V617F present in up to 60% of RARS with thrombocytosis and PDGFRa/b in MPD/MDS unclassifiable.

The advent of novel genomic sequencing technologies has aided the identification of somatically acquired genetic abnormalities in up to 80% of myelodysplastic syndromes. As yet molecular analysis in not part of routine diagnosis or prognosis however it is likely to provide important information in the future.

• Bone marrow Immunophenotyping

Flow cytometric analysis of CD34 can be utilized for determining the blast percentage, especially in cases where enumeration of blasts on morphological grounds is difficult. Patients with high risk MDS should have analysis comparable to that of acute leukaemia.

Differential diagnosis:

The diagnosis of MDS can be difficult, especially in cases where there is no excess of blasts and is often a diagnosis of exclusion. Careful consideration is needed for cases of hypocellularity where there may be therapeutic options based upon cellularity (Lim et al Leuk 2007) and consideration of clonal disorders such as aplastic anaemia may present with apparent dysplasia morphologically. Younger patients under 40, should have disorders such as Fanconi anaemia, dyskeratosis congenita, Diamond-Blackfan anaemia and Scwachman-Diamond syndrome excluded. Cytopenia present in one or more myeloid lineage for more than 6 months, which doesn't meet the criteria of an MDS and cannot be explained by any other haematologic or non-haematologic disease is termed Idiopathic Cytopenia of Uncertain (undetermined) Significance (ICUS). These patients should be carefully monitored and bone marrow repeated in the follow up to exclude or confirm MDS. Second opinions, dual reporting and HMDS evaluation should be considered.

Classification

All cases of MDS should be classified according to the WHO revised classification 2008.

WHO classification and criteria for the myelodysplastic syndromes

Disease	Blood findings	Bone marrow findings
Refractory cytopenias with unilineage Dysplasia (RCUD)		
Refractory anaemia (RA)	Uni/Bicytopenia[1]	Unilineage dysplasia
Refractory neutropenia	No or rare blasts (<1%)[2]	<5% blasts
Refractory thrombocytopenia		<15% ring sideroblasts
Refractory anaemia with ringed sideroblasts (RARS)	Anaemia No blasts	Erythroid dysplasia only ≥15% ring <5 % blasts
Refractory cytopenia with multilineage dysplasia (RCMD) (<1%)	Cytopenias (bicytopenia or pancytopenia) <5% blasts in marrow No Auer rods <1 x 10^9/l monocytes	Dysplasia in ≥ 10% of myeloid cell lines No or rare blasts No Auer rods <15% ring sideroblasts
Refractory anaemia with excess blasts – 1 (RAEB-1)	Cytopenias <5 blasts No Auer rods <1 x 10^9/L monocytes	Uni/multilineage dysplasia 5% to 9% blasts No Auer rods

Refractory anaemia with excess blasts – 2 (RAEB-2)	Cytopenias 5% to 19% blasts Auer rods ±[3] <1 x 10^9/L monocytes	Uni/multilineage dysplasia 10% to 19% blasts Auer rods ±
Myelodysplastic syndrome, unclassified (MDS-U)	Cytopenias No or rare blasts No Auer rods	Dysplasia in <10% of one or more lineage with cytogenetic abn. <5% blasts
MDS associated with isolated del (5q)	Anaemia No/rare blasts (<1%) Platelets normal or Increased	Normal to increased megakaryocytes with hypolobated nuclei <5% blasts No Auer rods Isolated del (5q)

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 RAEB-1. If the marrow myeloblast percentage is <5% and there are 1% myeloblasts in the blood, the case 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 RAEB-2

WHO classification 2008 of myelodysplastic/myeloproliferative neoplasms

Disease	Blood findings	Bone marrow findings
Chronic myelomonocytic leuk. (CMML)	Peripheral blood monocytosis > 1x109/l No BCR/ABL-1 fusion gene <20% blasts	Dysplasia in 1+ lineage[1] <20%blasts No PDGFRA/B
Atypical chronic myeloid leukaemia, BCR-ABL1 negative (aCML)	Leukocytosis, neutrophilia Neutrophilic dysplasia Neutrophil precursors =10% of leuks Blasts <20% No BCR-ABL1 fusion gene rearrangement of PDGFRA or PDGFRB Minimal basofilia Monocytes < 10% of leukocytes	Neutrophil dysplasia <20% blasts No
Juvenile myelomonocytic leukaemia (JMML)	Peripheral blood monocytosis >1x109/l <20% blasts	<20% blasts evidence of clonality

	Usually WBC > 10x109/l	
Myelodysplastic/myeloproliferative unclassifiable (MDS/MPN)		
	Mixed MDS and MPN features No prior diagnosis of MDS or MPN <20% blasts No history of recent growth factor or cytotoxic therapy to explain MDS or MPN features No BCR-ABL1 fusion gene of rearrangements of PDGFRA or PDGFRB	Mixed MDS/MPN
Refractory anaemia with ring sideroblasts associated with marked thrombocytosis (RARS-T) (provisional entity)2	Persistent thrombocytosis >450x109/l Anaemia BCR-ABL1 negative Cases with t(3;3)(q21;q26), inv(#)(q21q26) and isolated del(5q) are excluded	Morph of RARS > 15% ring siderobl. Abn megas

1 If myelodysplasia minimal or absent, CML can still be diagnosed if the other requirements are met and there is ann acquired clonal cytogenetic or molecular geneticabnormalityBicytopenia 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 RAEB-1. If the marrow myeloblast percentage is <5% and there are 1% myeloblasts in the blood, the case 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 RAEB-2

Prognosis

The IPSS for MDS (International Prognostic Scoring System), (Greenberg et al, Blood 1997) gives more weight to blast count than to cytogenetics and has been superseded by the Revised - IPSS (Greenberg et al, Blood 2012). All patients with MDS have a reduced life expectancy compared to age matched controls. The IPSS-R is a multivariate analysis of a largely untreated patient population of 7012 patients used to evaluate the prognosis of newly diagnosed MDS patients. The IPSS-R is the preferred scoring system for determining prognosis. It has improved prognostic ability to determine survival and AML evolution in untreated adult patients with primary MDS. Phone/tablet 'apps' can calculate this or a web-based tool can be accessed via the UK MDS forum website (www.ukmdsforum.org)

IPSS-R cytogenetic prognostic subgroups

V 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 single or double independent clones
Poor	-7, inv(3)/t(3q), double including -7/del (7q), complex:3 abnormalities
V Poor	Complex: >3abnormalities

IPSS-R prognostic score values

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	V Good		Good		Int	Poor	V Poor
Blasts (%)	<=2		>2-<5		5-10	>10	
Hb (g/l)	>=100		80<100	<80			
Plt ($x10^9$/l)	>=100	50<100	<50				
Neut ($x10^9$/l)	>=0.8	<0.8					

IPSS-R prognostic risk categories/scores and clinical outcomesRisk category	Risk score	Survival (median-years)	25% AML evolution (median-years)
Very Low	<=1.5	8.8	NR
Low	>1.5-3	5.3	10.8
Int	>3-4.5	3.0	3.2
High	>4.5-6	1.6	1.4
Very High	>6	0.8	0.73

Management recommendations for MDS evolved through the IPSS era and as such are driven by the IPSS system. No recommendations can be made to predict response to recommended therapy in relation to the IPSS-R which should be used to evaluate prognosis in all patients but not yet to guide therapy. Specifically it is unclear whether IPSS-R intermediate patients should be grouped into low-risk or high-risk categories and other biological characteristics, patient and physician preference should be considered.

International Prognostic Scoring System: derivation of patient score

Prognostic Variable	**Score Value**				
	0	**0.5**	**1.0**	**1.5**	**2.0**
BM blasts (%)	<5	5-10		11-20	21-30
Karyotype	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			

Karyotype: Good risk, normal, -Y, del(5q), del(20q)
Poor risk, complex (≥3 abnormalities) or chromosome 7 anomalies

Intermediate risk, other abnormalities.

Cytopenias defined as haemoglobin concentration <10 g/dl, neutrophils <1·8 $\times 10^9$/l and platelets <100 $\times 10^9$/l.

IPSS risk categories/scores and clinical outcomes

Risk category	Risk score	Survival (median-years)	25% AML evolution (median-years)
Low	0	5.7	9.4
Intermediate-1	0.5-1.0	3.5	3.3
Intermediate-2	1.5-2.0	1.2	1.1
High	2.5-3.0	0.4	0.2

Low risk and High risk MDS

In clinical practice, MDS is divided into so-called ”low risk” MDS encompassing IPSS low risk and INT-1, whereas ”high risk” includes IPSS INT-2 and high risk. It is especially important that all MDS patients are categorized in this way as therapy is vastly different for these two groups of patients.

Treatment

All newly diagnosed patients will be:

1- Discussed at the sector based MDT, with therapeutic decisions based upon the IPSS and IPSS-R score.

2- Consideration given to potentially available clinical trials.

3- Patients considered suitable for allogeneic transplantation should be referred to Christie/MRI for assessment at the earliest suitable opportunity

4- All patients should have a named key worker and have access to specialist advice in verbal and written form. With 24 hour support from their treatment Haematology unit.

Further useful advice can be obtained from
www.ukmdsforum.org
http://www.llresearch.org.uk

General approach to patient management

Low-risk MDS

1. Supportive care,transfusion and chelation (extended red cell phenotyping should be considered for patients on regular blood transfusions).
2. Consider patients potential for allogeneic SCT.
3. Consider patients with RA and RCMD for immunosuppressive treatment.
4- ESA should be considered in IPSS low, INT-1, with symptomatic anaemia and fulfill the criteria for high or intermediate predictive score for response.
5. For patients with non-sideroblastic anemia, consider erythroid stimulating agent and patients with sideroblastic phenotype should be given a trial of ESA+G-CSF.
6-Patients with symptomatic transfusion dependency and del. 5q may benefit from lenalidomide therapy.

High-risk MDS

1. Consider patients potential for allogeneic SCT
2. Consider patient for AML like chemotherapy
3. Consider suitability for azacitidine in line with NICE guidance
4. Consider patient for investigational trail
5. Supportive care.

CMML

1. Consider patients potential for allogeneic SCT (intensive AML induction style therapy may be required first)
2. Hydroxycarbamide for symptomatic management in elderly patients with a low (<10%) marrow blast count.
3. Consideration of current clinical trial protocols
4. Supportive care.

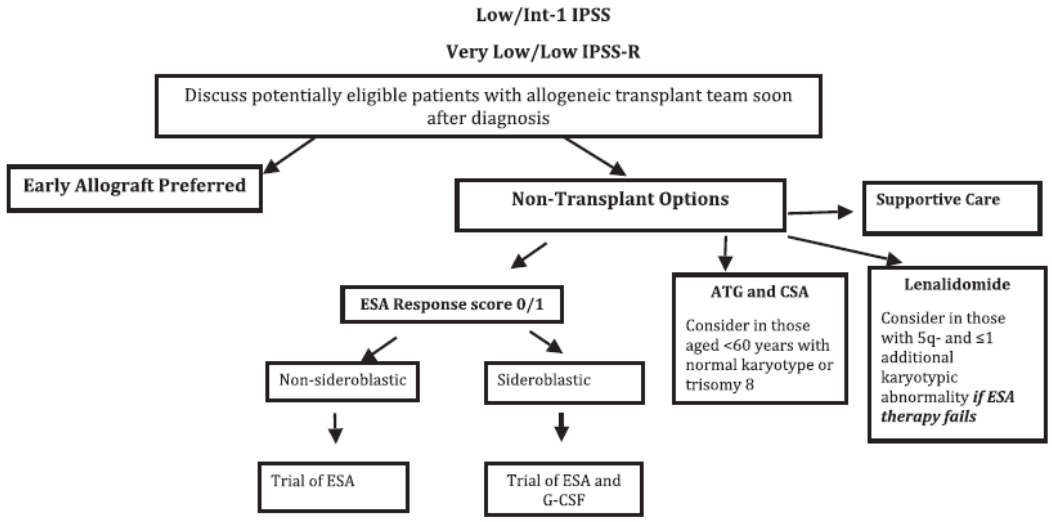

Fig 1. Algorithm for management of low risk myelodysplastic syndrome.

Supportive Care

Transfusion

For the vast majority of patients with MDS transfusion is the main stay of therapy with the aim of reducing morbidity and improving quality of life. Published data are limited in MDS, general criteria are based on clinical experience.

Red cell transfusions:

• Transfuse for symptoms of anemia in accordance with local trust transfusion policies and compliance with the BCSH guidelines on red cell transfusion. Transfusion should be made on an individual basis by the patient and the physician, taking into account co-morbid illness as well as quality of life issues. No universal trigger or target for transfusion is recommended.

Platelet transfusion:

• Platelet transfusion is recommended in thrombocytopenic patients with symptomatic bleeding. Where transfusion is required this should be in compliance with local trust transfusion policies and BCSH guidance.

Alloimmunisation and the development of platelet refractoriness are significant issues, transfusion should not be excessive and consideration of HLA matched product transfusion can be considered for selected patients.

Tranexamic acid

• Patients with low platelet count and recurrent bleeding may benefit from tranexamic acid (systemically or locally eg mouthwash) 1g QDS PO.

Iron Chelation

The clinical importance of iron overload in MDS patients is difficult to assess. There is limited data available on iron chelation in MDS and the recommendations are primarily based on studies in thalassemia (Cappellini et al Blood 2006). In thalassemia there is strong evidence about the usefulness of iron chelation, and there is evidence that iron chelation reduces iron overload in MDS. However, there are no studies proving the effect of iron chelation on long-term outcome in MDS and overview of the evidence and guidelines has recently been published (Gattermann 2008 Int J Hem)

Patients who satisfy the following criteria could be considered for iron chelation

• Where long term transfusion therapy is likely (eg RA, RARS and 5q- patients unless very high age, or severe concomitant disease)
• In RCMD and more advanced MDS, iron chelation should only be considered for patients with a life expectancy exceeding 2 years from the time point when iron overloaded (ferritin >1500 µg/l, or after 25 units of RBC)
• Candidates for allogeneic transplantation

Desferrioxamine (DFO)
• 40 mg/kg (20-50 mg) by subcutaneous infusion over 8-12 hours 5 days per week.

Monitoring DFO:
• The target Ferritin level is <1000 µg/l.
• In case of rapidly decreasing ferritin to less than 1500µg/l, DFO dose should be reduced.
• Vitamin C 2mg/kg/d should be started 4 weeks after the onset of DFO therapy to improve iron excretion.
• Patients should have Audiometry and Opthalmology evaluation prior to starting DFO and yearly.

Oral chelators should be considered when patients are intolerant or unresponsive to DFO

Deferasirox belongs to a new class of iron chelators. Initial dose is 10-30 mg/kg, starting at lower doses may improve tolerance. Efficient mobilization of tissue iron has been demonstrated in thalassemia but there are no controlled data in MDS. Iron excretion occurs almost entirely in the faeces and is dose dependent. In studies on thalassemia patients side effects are generally mild and include transient gastrointestinal events, skin rash, mild increase in serum creatinine and increased transaminases. There are reports on patients with a rapid renal failure due to deferasirox treatment.

Deferiprone (L1) There are very few studies on the use of L1 in MDS. The reported efficacy varies. Agranulocytosis is less than initially reported and availability is frequently limited.

Treatment and prevention of infections

Unfortunately there is a lack of supporting evidence. Therefore prophylactic antibiotics are not routinely recommended. Severely neutropenic patients can be considered for GCSF during infectious episodes or for managing recurrent infections precipitated by neutropenia. MDS patients with neutropenia are at significant risk of fungal infection however there is an absence of good clinical data to support routine anti-fungal use.

Neutropenic sepsis should be managed in accordance with the local and regional policies.

Treatment with EPO / Darbepoetin alone or in combination with GCSF

Treatment with EPO may improve hemoglobin levels and as a blood sparing agent in MDS patients with anemia. Patients are most likely to respond if they have a normocellular marrow with less than 10% blasts, low or Int-1 by IPSS, low transfusion frequency and low/normal endogenous EPO production/response. The effect of Epo may be enhanced by G-CSF, which synergises with Epo to improve survival and proliferation of early erythroblasts. There is one randomised controlled phase III study on Epo alone vs placebo, and one randomised open phase III study on Epo + G-CSF vs supportive care, both showing a significant effect on hemoglobin levels. There is one randomised phase II trial showing better efficacy of the combination compared to Epo alone. In addition, a large number of phase II trials, of which some are randomised, support the use of this treatment.

Patients with symptomatic anaemia (Hb <10g/dl) should be evaluated according to the predictive model for a response to Epo + G-CSF. With a target Hb of 12g/dl.

Predictive model for treatment of the anemia of MDS with Epo + G-CSF.
(Hellström-Lindberg E 2003) ,(Jädersten Blood. 2005)

Transfusion need	point	Serum EPO	Point
<2 units RBC / month	0	<500 U/l	0
≥2 units RBC / month	1	≥500 U/l	1

Predicted response. 0 point 74%, 1 point 23%, 2 points 7%

Treatment should be considered for patients with a score of 0/1. EPO should be initiated alone for the first 8 weeks. Then in combination with GCSF for a further 8 weeks. If no response after 16 weeks it should be terminated.

Darbepoetin dosing
• In general, start with 300 µg / 14 days. Maximum dose in case of no response 300 µg / week.
• The starting dose in low weight patients with stable anemia, and always in case of reduced renal function should be lower, 150 µg / 14 days.

G-CSF dosing

• Start with 300 µg / week, sc, in three divided doses.

• Treatment should aim at a clear rise in neutrophil count, in previous studies 6-10 x 109/l. If no response, increase the dose to a maximum of 300 µg x 3 / week.

• In case of high neutrophil counts, reduce to 2 – 1 injections / week, then reduce dose / injection.

Immunosuppressive treatment

A small fraction of low risk MDS patients seem to have bone marrow failure due to autoimmune mechanisms, as seen in aplastic anemia. Several international studies have demonstrated response rates in the order of 30% to immunosuppressive therapy antithymocyte globulin in some investigations combined with cyclosporin A (Broliden et al Haem 2006, Killick et al BJHaem 2003). HLA-DR15 positivity, young age, short duration of red cell transfusion dependence, PNH positivity and normal cytogenetics seem to predict for a response to immunosuppressive therapy in MDS patients

Deletion 5q/Lenalidomide

Lenalidomide has demonstrable efficacy in patients with INT-1, EPO refractory transfusion dependant anaemia- with 67% of patients rendered transfusion independent, 73% achieved cytogenetic remission with a median duration of 116 weeks (List et al NEJM 2006). Neutropenia and thrombocytopenia are a significant issue. It is now EMEA approved for transfusion dependent low/int-1 patients with del 5 q (in isolation) where other therapeutic interventions are inadequate. Since September 2014 this indication has NICE approval (TA322).

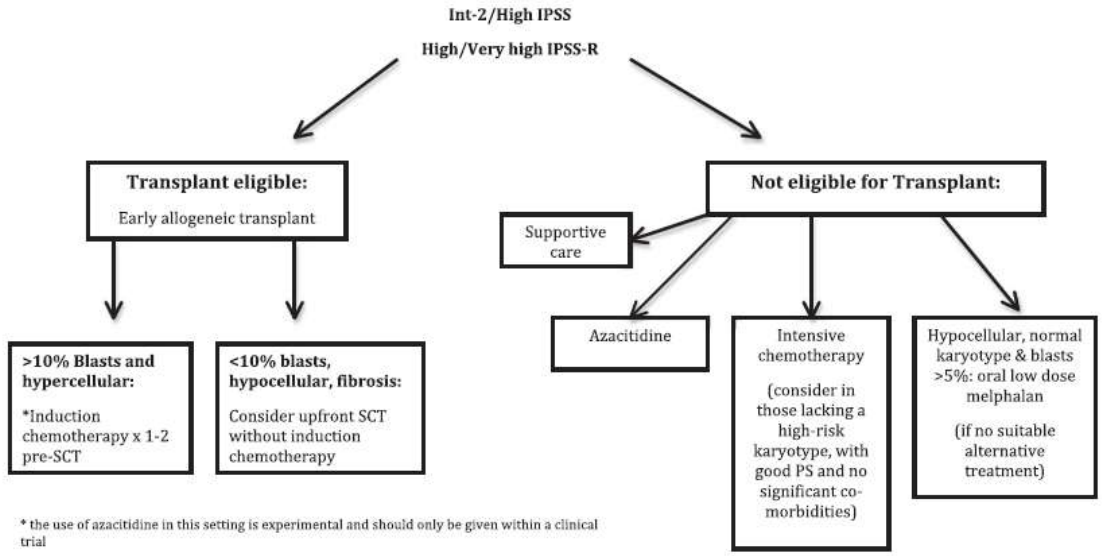

Fig 2. Algorithm for management of high risk myelodysplastic syndrome.

Allogeneic stem cell transplantation (SCT) in MDS

Allogeneic stem cell transplantation is potentially the only curative treatment option in patients with MDS. Emerging data suggests that outcomes are better when patients are transplanted early on during their disease and favour younger age group, low-risk MDS, < 12 months since diagnosis and prior to the onset of transfusion dependence. However, due to significant morbidity and mortality associated with this procedure each case should be considered individually.
Therefore suitable patients should be discussed with a transplant center at time of diagnosis and a treatment plan devised (Killick et al, BCSH Guidelines, BJH 2013).

The best evidence available is on full intensity/myeloablative transplants where registry data shows disease free survival rates around 40%, transplant related mortality (TRM) around 40% and relapse rates 20% (Castro-Malaspina et al Blood 2002). Risk factors for TRM are high age, advanced disease stage, therapy related MDS, in addition to the presence of comorbidities, including iron overload. Risk factors for relapse are high age, advanced disease stage and poor risk cytogenetics.

Reduced intensity stem cell transplants (RISCT) are feasible and potentially curative even in patients up to 70 years. However the published series of RISCT are still limited though increasing. Overall survival average 40%, ranging from 27 to 60%. Relapse rates range from 25 to 47% with TRM from 15 to 41% (Laport et al BBMT 2008, Ho et al Blood 2004, Lim et al JCO 2010).

Therefore where possible a myeloablative conditioning regimen should be used over a reduced intensity regimen. There is also increasing evidence that outcomes using fully matched unrelated donors are equal to transplants using sibling donors.

Potential comorbidities should be assessed using the HCT-CI (Sorror, Blood 2005) to enable an informed discussion on transplant outcomes. The transplant conditioning, immunosupression and supportive management will be determined by the transplant unit at Christie/MRI as appropriate.

Although there is a paucity of data to support the approach it is generally accepted that cytoreductive chemotherapy is required for patients with >10% blasts, as a means of reducing the relapse risk. This is particularly important for patients undergoing RISCT.

Treatment of high-risk MDS in patients not suitable for allogeneic stem cell transplantation

In general age is the major factor in determining eligibility for transplant, however patients may be ineligible due to significant comorbidity, lack of donor availability (sibling or unrelated donor), psychosocial issues or may after reasonable consideration feel the risks are unacceptably high.

Azacitidine

The hypomethylating agent Azacitidine was approved by the EMEA in 2008 for treatment of IPSS INT-2 and high risk MDS and MDS/AML with 20-30% blasts in patients not eligible for haematopoietic stem cell transplantation. The was approved by NICE in 2011. The AZA-001 randomised phase III study of patients with advanced MDS compared azacitidine to best standard of care (BSC) (Fenaux et al Lan Onc 2009), where the treating physician could choose between best supportive care only, best supportive care with low dose cytarabine or best supportive care with AML-like chemotherapy. The study demonstrated a significant improvement in overall survival with azacitidine (24 vs 15 months, p=0.0001) and time to AML transformation (24 vs 12 months, p=0.004). Responses require at least 4 courses, underscoring the importance of continuing treatment. Based on these findings, azacitidine is generally recommended as first choice for Int-2 and high risk-MDS unless the patient is young with good prognostic features for response to AML-like chemotherapy.

The FDA have also approved azacitidine additionally for patients with INT-1 disease, there may be rare INT-1 patients with significant cytopenias where azacitidine may be of clinical benefit.

The licensed dosing schedule is Azacitidine 75 mg/m2 sc d 1-7 repeated every 28 days. (alternative dosing schedules have been used due to constraints of reconstitution and administration at weekends. In general the marrow should be assessed after 4 cycles of therapy unless there is obvious progression. Data from the AZA-001 study suggests the therapy is required to be ongoing and no definitive recommendations can currently be made on dose reductions or interval spacing for responding patients.

Decitabine is a similar hypomethylating agent in widespread use worldwide, with potentially comparable clinical activity. It is licensed by the EMEA for treatment of AML. There is limited UK experience, azacitidine is therefore the agent of choice.

AML chemotherapy

A number of studies have been published where patients with HR-MDS have been treated with different combinations of induction chemotherapy. Only few studies were randomized, and then often with the purpose to study the effect of growth factors in combination with chemotherapy. All studies taken together showed a median complete remission rate of 43% (range: 18-74%), and overall survival varying between 6-21 months. Between 10-25% of the patients died within the first month of treatment. CR durations are generally short and there is no evidence, that AML like chemotherapy alters the natural history of MDS. There is no data, beyond anecdote to support intensive chemotherapy with autologous stem cell support compared AML like chemotherapy.

AML therapy may be reasonable for younger patients (with INT-2/High) who cannot be transplanted, the absence of adverse cytogenetics and a proliferative disease may support decision making. The durability of remissions for those with adverse cytogenetics does not support this approach (Knipp et al Cancer 2007) and these patients should be treated with investigational approaches including transplantation.

Where azacitidine has failed, AML like chemotherapy can be attempted in patients in good performance status, without comorbidities and with good prognostic features for achievement of CR.

Low dose chemotherapy

No data to indicate this presents disease modification with no apparent effect on overall survival or rate of AML transformation.

Melphalan
Three small phase 2 studies in high-risk MDS patients report a response rate of up to 30 % in selected patients (hypo/normocellular marrow and normal karyotype), i.e improved blood cell counts and reduced/abolished transfusion need. The toxicity was mild. The dose was 2 mg/day until response (usually 8 weeks) or progression (Denzlinger et al BJHaem 2000, Omoto et al Leuk 1996, Robak et al Neoplasma 2003).

Low-dose cytosine arabinoside (LDAC)
One large randomised study comparing LDAC and supportive care in predominantly high-risk MDS patients showed a response rate of approximately 30% in the LDAC arm, but no benefit in terms of overall survival and transformation to AML (Miller et al annals Haem 1992). Fatal hematological toxicity at a frequency of up to 19% was reported for LDAC.

Chronic myelomonocytic leukaemia

Many CMML patients are elderly with only monocytosis and no symptoms and can therefore reasonably be followed without treatment. In general treatment is indicated for symptomatic disease- fever, weight loss, splenomegaly, progressive disease and cytopenias. A recent CMML specific prognostic scoring system (CPSS) has been described, validated and is clinically informative (Such etal Blood 2013).

Allogeneic stem cell transplantation
At diagnosis, consideration should be given as to whether the patient is a candidate for allogeneic stem cell transplantation as this remains the only potentially curative approach.

Hydroxycarbamide

One randomized trial with Hydroxycarbamide vs. VP 16 showed superiority in response (60% vs.36%) and survival was 20 months vs. 9 months respectively (Wattel et al Blood 1996). Hydroxycarbamide is recommended as first-line treatment for elderly patients with a low (<10%) marrow blast count and for whom the main aim is to reduce symptoms.

Azacytidine
Azacitidine is NICE approved for CMML with 10-29% marrow blasts without a myeloproliferative disorder in line with the AZA001 trial inclusion criteria. There are no published studies specifically designed for CMML, but there are reviews that have analyzed the very small CMML cohort within larger studies.

MDS trials within Manchester Cancer currently open to recruitment at a number of sites.

AML 18- NCRN study for older newly untreated patients with MDS/AML, intensive/non-intensive chemotherapy and transplantation.

AML19- NCRN study for untreated patients with MDS/AML, intensive chemotherapy and transplantation.

Li1- NCRN non intensive chemotherapy for untreated patients and some azacitidine failures.

RAVVA- azacitidine +/- vorinostat in untreated and relapsed MDS/AML patients.

MDS Bio- biobanking and registry study

An up-to-date list of available studies can be found at:-

http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/clinical-trials-search?f[0]=field_trial_status%253A4222&populate=Myelodysplastic%20syndrome%20%28MDS%29

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