Greater Manchester Cancer

Haemato-Oncology Pathway Board

Greater Manchester Cancer Guidelines for the diagnosis and treatment of Myelodysplastic Syndromes

Muhammad Saif
Dan Wiseman
Clare Barnes
Eleni Tholouli
Mike Dennis

Version 3.0 **May 2019**
Revision **May 2020**

Summary of main changes from v2.0:

1. Nomenclature, classification and diagnostic criteria are updated to reflect the new WHO 2016 classification of haematopoietic malignancies.
2. Expanded discussion of the role for mutation analysis is provided.
3. Further emphasis on role for clinical trials, which are expanding in this area across Greater Manchester.
4. Discussion about the recently defined entities of clonal haematopoiesis of indeterminate potential (CHIP), idiopathic cytopenia of undetermined significance (ICUS) and clonal cytopenia of uncertain significance (CCUS).
5. Deferasirox is elevated to the first-line iron-chelating agent of choice, where available.
6. Recommendation to screen patients for mutations: in particular, for 5q- patients for TP53 mutations.
7. Amendment to NCRN AM18/19 protocols to extend inclusion to MDS patients with ≥5% blasts (vs ≥10% blasts previously).
8. Brief discussion of selected novel agents coming through clinical trials
9. Expanded section on diagnosis, prognostication and management of CMML.

An up-to-date list of all available UK MDS clinical trials 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
https://mdspatientsupport.org.uk/what-is-mds/current-trials

INTRODUCTION

The myelodysplastic syndromes (MDS) encompass a heterogeneous group of bone marrow disorders characterized by ineffective, dysplastic haematopoiesis with consequent pancytopenia. The clinical presentation ranges from mild asymptomatic anaemia, through to profound pancytopenia, complications of infection, bleeding and that of a poor prognosis with rapid transformation to acute myeloid leukaemia (AML). Numerous potential therapeutic strategies for MDS have been evaluated in clinical trials, but most have demonstrated only modest efficacy at best. Standards of care do exist and guidelines can be used for uniformity of management.

These guidelines have been written on behalf of the Greater Manchester Cancer Haemato-Oncology Pathway Board and while every attempt has been made to establish accuracy, health care professionals are advised to access source data, and consult national and international guidelines, as appropriate.

DIAGNOSIS

The diagnosis of MDS is still largely based on careful morphological examination of the blood film and bone marrow in patients with clinical evidence of cytopenias (anaemia, neutropenia and/or thrombocytopenia). Reactive causes of cytopenia and dysplasia as well as other clonal stem cell disorders should be excluded.

Patient history and examination

Should include symptoms of anaemia, infection and bleeding. Also family history, prior chemotherapy/irradiation, occupational exposure, concomitant medications, alcohol consumption and any prior transfusions should be elicited. Complete physical examination should include spleen size and any evidence of pallor and bleeding.

Recommended baseline investigations

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

Investigations to consider in selected cases

- Direct antiglobulin test (DAT); haptoglobin
- Serum erythropoietin
- Screening for Parvovirus B19 (hypoplastic MDS) and CMV
- Extensive pre-transplant virology screen if transplant candidates
- HLA typing (if transplant candidate; but also if require platelet transfusion)
- Red cell phenotype (as per *BCSH Transfusion guidelines*)
- PNH screen (all hypoplastic MDS)
- Fanconi's anaemia screen (if hypoplastic marrow; especially younger cases or those with relevant dysmorphic features/family history)

- JAK2 mutation testing (if concomitant leukocytosis or other features of myeloproliferation, e.g. significant splenomegaly)
- Myeloid mutation panel by NGS (bone marrow is optimal, peripheral blood can be used); recommended for all young patients, cases with diagnostic difficulty, and where mutations can alter management and monitoring.

Bone marrow

Evidence of morphological dysplasia on bone marrow remains the main diagnostic feature. Initial assessment may not confirm the diagnosis and reassessment may be necessary to reach a firm diagnosis or evaluate disease progression. However, there may be elderly patients or those with poor performance status where a definitive diagnosis may not be required, as it would not alter management. Here it may be reasonable to avoid this invasive test.

• Bone marrow aspirate

In line with the WHO criteria, dysplastic features should be present in at least 10% of the nucleated cells in the lineage under consideration. At least 200 marrow cells and 20 megakaryocytes should be evaluated, and the percentage of blasts enumerated on blood and marrow slides. An iron stain should always be performed at presentation 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 dependent and should be treated with caution if it is the only evident marker of dysplasia.

• Bone marrow trephine

This complements the aspirate and should be undertaken in all cases to evaluate cellularity and fibrosis (H+E, reticulin). Immunohistochemistry can be useful in identifying abnormally localised immature precursors (ALIP), excess blasts (CD34/CD117), dysplastic megakaryocytes (CD42b) and disrupted erythroid island architecture. Given that trephine is more traumatic and painful than aspirate, there may be cases of elderly, frail or high bleeding risk patients where avoiding a trephine can be justified on pragmatic grounds.

• Bone marrow immunophenotyping

Flow cytometry of CD34 (and CD117) can be utilised for determining the blast percentage, especially where enumeration of blasts on morphological grounds is difficult. Patients with high-risk MDS should have analysis comparable to that of acute leukaemia. Certain flow cytometry profiles can support the diagnosis of MDS/CMML and extended panels have been used as research tools for some time but these require validation and have yet to enter clinical use in the UK(1).

• Bone marrow cytogenetics

A gross chromosomal lesion is present in ~50% of MDS cases and provides clear evidence of a clonal disorder. MDS-defining changes irrespective of morphologic dysplasia are -5, del(5q), -7, del(7q) and i(17q), some of which have

major prognostic value. Conventional cytogenetics should be performed in all cases. FISH for prognostically relevant cytogenetic anomalies (-7, del 5q) can be performed in equivocal cases; e.g. failed karyotyping.

• Bone marrow molecular analysis

Up to 50% of patients with MDS display normal cytogenetics. With NGS somatic mutations can be found in up to 90% of cases, supporting a diagnosis in challenging cases. The most commonly mutated genes are *SF3B1, TET2, SRSF2, ASXL1, DNMT3A, RUNX1, U2AF1, TP53* and *EZH2* (2,3). Moreover, MDS phenotypes can crossover with myeloid proliferation, in which certain mutations are highly prevalent and diagnostically useful (eg JAK2 V617F in ~60% of MDS-RS with thrombocytosis; SF3B1 in >80% of RS).

Increasing evidence suggests prognostic significance for certain mutations (3). Although not currently incorporated into formal MDS prognostication systems, an international effort to develop an "IPSS-Molecular" system is underway and likely to enter the clinical arena soon. Moreover, mutation data can provide other clinically useful information, including eligibility for trials and for novel therapies (e.g. IDH2 inhibitors). Therefore, targeted sequencing should be considered in all new presenting patients' and is widely available at regional HMDS services (National Genomic Test Directory specifies a core set of tests). Circumstances in which sequencing is particularly useful include: (i) confirmation of SF3B1 mutations in suspected MDS-RS (favourable prognosis); (ii) screening for *TP53* mutations in isolated del(5q); (iii) younger patients considered for transplantation; (iv) cases of diagnostic uncertainty; (v) cases of suspected familial MDS/AML.

Differential diagnosis

The diagnosis of MDS can be difficult, especially in cases where there is no excess of blasts. Careful consideration is needed for cases of hypocellularity where there may be therapeutic options based upon cellularity (4) and consideration of other clonal disorders such as aplastic anaemia may present with apparent dysplasia. Younger patients under 40 years should have disorders such as Fanconi's anaemia, dyskeratosis congenita, Diamond-Blackfan anaemia and Scwachman-Diamond syndrome excluded. Rare cases of familial MDS are associated with germ line mutations (e.g. in *RUNX1* and *GATA2*), and should be considered where a relevant family history is identified. Variant allele frequency (VAF) can help differentiate constitutional abnormalities from acquired mutations.

WHO CLASSIFICATION

All cases of MDS should be classified according to the updated WHO 2016 classification (5)**.** This describes new entities and addresses the rapidly accumulating genetic information. MDS secondary to prior cytotoxic therapy is classified separately, under therapy-related myeloid neoplasms.

WHO 2016 classification and criteria for the myelodysplastic syndromes (5)

Subtype Name	Formerly	Blood Findings	Bone Marrow Findings
MDS with single lineage dysplasia (MDS-SLD)	RCUD	Uni/Bicytopenia No/rare blasts (<1%)	Unilineage dysplasia <5% blasts (no Auer rods) <15% ring sideroblasts †
MDS with multi-lineage dysplasia (MDS-MLD)	RCMD	Bi/Pancytopenia No/rare blasts (<1%)	Bi/Trilineage dysplasia <5% blasts (no Auer rods) <15% ring sideroblasts †
MDS with ring sideroblasts (MDS-RS)	-		
MDS-RS with single lineage dysplasia (MDS-RS-SLD)	RARS	*As for MDS-SLD*	≥15% ring sideroblasts (>5% if SF3B1 mutated) *Otherwise as for MDS-SLD*
MDS-RS with multi-lineage dysplasia (MDS-RS-MLD)	-	*As for MDS-MLD*	≥15% ring sideroblasts (>5% if SF3B1 mutated) *Otherwise as for MDS-MLD*
MDS with isolated del(5q)	MDS with isolated del(5q)	Any cytopenias (typically anaemia; normal/high platelets) No/rare blasts (<1%)	Del(5q): allowed ≤1 other abnormality [excluding monosomy 7 / del(7q)] Uni/Multilineage dysplasia <5% blasts (no Auer rods) Any ring sideroblast %
MDS with excess blasts (MDS-EB)	RAEB		
MDS-EB-1	RAEB-1	2-4% blasts Any cytopenias	5-9% blasts (no Auer rods) Uni/Multilineage dysplasia Any ring sideroblast %
MDS-EB-2	RAEB-2	5-19% blasts ± Auer rods Any cytopenias	10-19% blasts ± Auer rods Uni/Multilineage dysplasia Any ring sideroblast %
MDS, unclassifiable (MDS-U)	-		
with 1% blood blasts	-	1% blasts *(on 2 separate occasions)* Any cytopenias	Uni/Multilineage dysplasia <5% blasts (no Auer rods) Any ring sideroblast %
with single lineage dysplasia and pancytopenia	-	Pancytopenia No/rare blasts (<1%)	Unilineage dysplasia <5% blasts (no Auer rods) <15% ring sideroblasts †
based on defining cytogenetic abnormality	-	Any cytopenias	No morphologic dysplasia MDS-defining cytogenetic abnormality # <5% blasts (no Auer rods) <15% ring sideroblasts †

Cytopenias defined as: Hb <10g/dL; platelets $<100x10^9$/L; neutrophils $<1.8x10^9$/L; peripheral blood monocytes must be $<1x10^9$/L (otherwise diagnosis is CMML)

† *<5% if SF3B1 mutation present*

 # Unchanged from previous WHO 2008 classification

WHO 2016 classification of myelodysplastic/myeloproliferative neoplasms (5)

Disease	Blood findings	Bone marrow findings
Chronic myelomonocytic leukaemia (CMML)[1]		
	Peripheral blood monocytosis > $1x10^9$/L <20% blasts No BCR/ABL-1 fusion gene No rearrangement of PDGFRA/B	Dysplasia in 1+ lineage <20%blasts
Atypical chronic myeloid leukaemia, BCR-ABL1 negative (aCML)		
	Leukocytosis, neutrophilia Neutrophilic dysplasia Neutrophil precursors ≥10% of leukaemic Blasts <20% No BCR-ABL1 fusion gene No rearrangement of PDGFRA/B Minimal basophilia Monocytes <10% of leukocytes	Neutrophil dysplasia <20% blasts
Juvenile myelomonocytic leukaemia (JMML)		
	Peripheral blood monocytosis >$1x10^9$/L <20% blasts Usually WBC >$10x10^9$/L	<20% blasts Evidence of clonality (*PTPN11/KRAS/NRAS; germline NF1* or CBL)
Myelodysplastic/myeloproliferative unclassifiable (MDS/MPN)		
	Mixed MDS and MPN features No prior diagnosis of MDS or MPN No history of recent growth factor or cytotoxic therapy to explain features No BCR-ABL1 fusion gene No rearrangements of PDGFRA or PDGFRB	Mixed MDS/MPN <20% blasts
MDS/MPN with ring sideroblasts and thrombocytosis		
	Persistent thrombocytosis >$450x10^9$/L Anaemia No prior diagnosis of MDS or MPN *(except MDS-RS)* BCR-ABL1 negative No t(3;3)(q21;q26), inv(3)(q21q26) Isolated del(5q) excluded	Morphology of MDS-RS ≥15% ring sideroblasts Abnormal megakaryocytes

1 If myelodysplasia minimal or absent, CMML can still be diagnosed if the other requirements are met and there is an acquired clonal cytogenetic or molecular geneticabnormality. Bicytopenia may occasionally be observed. In absence of an acquired genetic abnormality monocytosis must have persisted for >3 months and all causes of reactive monocytosis excluded

2 If the marrow myeloblast percentage is <5% but there are 2-4% myeloblasts in the blood, the diagnostic classification is MDS-EB-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 MDS-EB-2

Clonal Haematopoiesis of Indeterminate Potential (CHIP) and other "pre-MDS" entities

An emerging concept is that mutations associated with myeloid malignancy can be found in healthy individuals with ageing, without cytopenias or other evidence of disease. This can be found in >10% of healthy individuals above 70 years of age (6) and has been termed "CHIP" (or age-related clonal haematopoiesis; "ARCH") (7,8). Genes most commonly involved are *DNMT3A*, *ASXL1* and *TET2*, typically at low VAF. These "pre-leukaemic" mutations appear to carry a low risk of transformation to myeloid malignancy (~1% per year), but seem to confer a significantly increased risk of cardiovascular events (6,9). The natural history and clinical implications of CHIP are not yet fully understood. Thus, screening for CHIP is not currently recommended; where detected, it may be reasonable to monitor blood counts infrequently (e.g. annually) for emerging progression, in a manner analogous to MGUS. Meticulous attention should be paid to other modifiable cardiovascular risk factors. Emerging factors that might increase risk of progression to frank MDS/AML include higher VAF, presence of multiple CHIP mutations, or mutations involving specific high-risk genes (e.g. *TP53, IDH2*) (10).

Acronym	Full Name	Accepted Definition
CHIP/ ARCH	Clonal haematopoiesis of indeterminate potential	Identification (≥2% variant allele frequency) of somatic mutations associated with myeloid malignancy in blood or bone marrow cells in individuals without diagnostic evidence of a haematological disorder
ICUS	Idiopathic cytopenia of undetermined significance	Patients with ≥1 unexplained cytopenia but without features sufficient to diagnose MDS or another haematological disorder; typically used where CHIP/ARCH is not detected.
CCUS	Clonal cytopenia of undetermined significance	Patients with ≥1 unexplained cytopenia without features sufficient to diagnose MDS or another haematological disorder, but with associated clonal haematopoiesis.

A new nomenclature has thus emerged for conditions related to MDS but not fulfilling the formal diagnostic criteria (8): ICUS carries a ~9% risk of myeloid malignancy at 10 years (11). Evidence-based recommendations on monitoring cannot yet be made and decisions should be guided by overall clinical context. In contrast, close monitoring of CCUS is recommended, given emerging evidence that it carries a high, possibly universal, risk of progression to MDS/AML (11,12).

PROGNOSTICATION

The International Prognostic Scoring System (IPSS) for MDS (13) gives more weight to blast count than to cytogenetics, and has been superseded by the revised IPSS (IPSS-R) (14). 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 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 adults 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 (14)

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)/del(3q), double including -7/del(7q), Complex: 3 abnormalities
V Poor	Complex: >3 abnormalities

IPSS-R prognostic score values

	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 & clinical outcomes

Risk category	Risk score	Survival (median-yrs)	25% AML evolution (median-yrs)
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

However, management recommendations for MDS (e.g. from NICE) evolved through the IPSS era and as such are driven by the IPSS system. Thus, IPSS scoring retains its relevance, particularly around eligibility for azacitidine.

IPSS: derivation of patient score (13)

Prognostic variable	0	0.5	1	1.5	2
BM Blasts (%)	<5	5-10		11-20	21-30
Karyotype[1]	Good	Intermediate	Poor		
Cytopenias[2]	0/1	2/3			

1. Karyotype Good risk: Normal, -Y, del(5q), del(20q)
Poor risk: Complex (≥3 abnormalities) or chromosome 7 anomalies
Intermediate risk: All other abnormalities
2. Cytopenias defined as Hb <10g/dL, neutrophils $<1{\cdot}8\times10^9$/L, platelets $<100\times10^9$/L

IPSS risk categories/scores and clinical outcomes

Risk category	Risk score	Survival (median-yrs)	25% AML evolution (median-yrs)
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

GENERAL APPROACH TO MANAGEMENT

In clinical practice, MDS is pragmatically divided into ”low-risk”, encompassing IPSS Low and INT-1 risk, and ”high-risk”, comprising INT-2 and high-risk

disease. It is especially important that all MDS patients are categorised in this way, as therapy is vastly different for these two groups.

Core Treatment Principles

All newly diagnosed patients should be:

- Discuss at sector MDT, with therapeutic decisions based upon the IPSS and IPSS-R score
- Consider clinical trial where possible
- Refer to Christie/MFT early for assessment if suitable for transplantation
- Allocate a key worker, and give access to specialist advice in verbal and written form, with 24-hour support from their treating haematology unit
- Give information about patient support services (e.g. MDS UK Forum)

Further useful advice can be obtained from
www.ukmdsforum.org
https://bloodwise.org.uk
https://www.mds-foundation.org

Low-risk MDS (Low/Int-1 IPSS; V Low/Low/Int-1 IPSS-R)

- Supportive care, transfusion and chelation (extended red cell phenotyping should be considered for patients on regular blood transfusions)
- Erythroid stimulating agents (i.e. EPO) for patients with symptomatic anaemia who fulfil the criteria of high / intermediate predictive score for response
- For patients with MDS-RS consider a trial of EPO+GCSF
- Allogeneic stem cell transplant (AlloSCT) if suitable (age, comorbidities)
- MDS-SLD/MLD with hypoplastic marrow; consider immunosuppressive treatments (*see Aplastic Anaemia guidelines*)
- MDS del(5q) with transfusion dependency; consider lenalidomide after failure of EPO therapy
- Consider transfusion-dependent patients for clinical trials with novel potentially disease-modifying agents (e.g. Luspatercept; Roxadustat; Imetelstat)

High-risk MDS (Int-2/High IPSS/IPSS-R)

- Supportive care, transfusion and chelation (extended red cell phenotyping should be considered for patients on regular blood transfusions)
- Azacitidine is a NICE approved standard-of-care for patient with Int-2/High-risk disease not eligible for AlloSCT
- AML-type chemotherapy if MDS-EB-2 (blast ≥10%) and ineligible for azacitidine (e.g. AML trial portfolio, DA, low dose cytarabine)
- AlloSCT for suitable patients; if blast ≥10% debulk first with 1 to 2 cycles of standard AML chemotherapy (e.g. DA)

CMML

- Supportive care, transfusion and chelation (extended red cell phenotyping should be considered for patients on regular blood transfusions)

- Azacitidine is NICE approved standard-of-care for patients with CMML and bone marrow blasts >10% with WCC <13 x10^9/L
- Hydroxycarbamide for symptomatic management and cytoreduction in elderly patients with a low (<10%) marrow blast count
- AlloSCT if eligible (intensive AML induction therapy may be required first)
- Low dose cytarabine may be an option for those with proliferative disease (ineligible for azacitidine) and blast excess, but probably adds little over hydroxycarbamide in this setting

SUPPORTIVE CARE

Transfusion

For most patients with MDS transfusion is the mainstay of therapy, with the aim of improving quality of life (QoL). Published data are limited in MDS, although clinical trials are in development to establish optimal transfusion frequency and Hb threshold.

• Red cell transfusions should be offered for symptoms of anemia in accordance with local trust policies and in compliance with BCSH guidelines. Thresholds and target Hb should be set on an individual basis, taking into account co-morbidities.

• Platelet transfusions are recommended for thrombocytopenic patients with symptomatic bleeding. Allo-immunisation and platelet refractoriness are significant issues, so transfusion should not be excessive. HLA matched platelets are an option for those with antibodies. Patients with recurrent bleeding may benefit from tranexamic acid (systemically or locally e.g. mouthwash) e.g. 1g QDS PO. No strong evidence currently supports use of TPO mimetics in MDS.

Iron Chelation

General recommendations are primarily based on studies in thalassemia, in which there is strong evidence for iron chelation (15). There is no doubt that heavily transfused MDS patients accumulate iron to potentially harmful effect. There is evidence that iron chelation reduces iron overload in MDS, and even data suggesting reduced risk of leukaemic transformation. Iron chelation may also improve outcome after transplantation. However, there are currently no good quality controlled studies proving a survival or other long-term outcome advantage for iron chelation in MDS (16).

On balance, it is recommended that patients who satisfy the following criteria be considered for iron chelation:

• Where long-term transfusion therapy is likely (eg MDS-SLD, MDS-RS, 5q- patients; unless very high age or severe concomitant disease)

• In more advanced MDS (MDS-MLD, MDS-EB), iron chelation should be considered if life expectancy exceeds 2 years from time of iron overload (ferritin >1500 µg/l, or after 24 units of RBC).

• Candidates for allogeneic transplantation

Desferrioxamine (DFO) remains the agent with the longest experience and safety record; however, requirement for continuous infusion has a significant impact on QoL and is rarely used in MDS. Dose is 40 mg/kg (20-50mg) by subcutaneous (sc) infusion over 8-12 hours 5 days a week, aiming for a target ferritin <1000µg/L; in case of a rapidly decreasing ferritin below this threshold, DFO dose should be reduced. Vitamin C 2mg/kg/d should be started 4 weeks after the onset of DFO to improve iron excretion. Audiometry and opthalmology evaluation prior to starting DFO with yearly assessments whilst on treatment are recommended.

Deferasirox (Exjade®) is an oral agent with now many years' experience that is broadly well tolerated. Iron excretion occurs almost entirely in the faeces and is dose dependent. Caution is advised in renal and liver impairment. A film-coated preparation (FCT) is now available with better side effect profile. It is licenced but not NICE assessed (recommended by Scottish Medicines Consortium in first-line for Low/INT-1 risk MDS). Recommended starting dose is 10-30 mg/kg; starting at lower doses may improve tolerance; for FCT recommended dose is 7-21mg/kg.

Treatment and prevention of infections

There is a lack of supporting evidence for prophylactic antibiotics. Severely neutropenic patients can be considered for GCSF during infective episodes or for managing recurrent infections precipitated by neutropenia. MDS patients with neutropenia are at significant risk of fungal infection, but again there is an absence of good clinical data to support routine anti-fungal use. Neutropenic sepsis should be managed in accordance with the local policies.

ERYTHROID STIMULATING AGENTS (EPO) ± GCSF

EPO is recommended as first line for low-risk MDS to improve hemoglobin levels (17-24). EPO-α (EPREX) is also licensed for the treatment of symptomatic anaemia (Hb ≤10g/dL) in adults with Low-/INT-1-risk MDS who have low serum EPO levels (<200IU/L).

Patients are most likely to respond if they have a normocellular marrow with <10% blasts, Low/INT-1 by IPSS, low transfusion frequency and low/normal endogenous EPO production. It is generally recognized that EPO should be started for symptomatic anaemia, and recent data suggests earlier initiation may provide advantage in response, survival and QoL. An arbitrary Hb threshold of 10g/dL is commonly used; EPO response is predicted using the Nordic predictive model (25):

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%

An alternative model (ITACA) has been recently described (26); it may be more sensitive with better discriminatory power, although requires further validation.

For non-sideroblastic disease EPO should be initiated alone for the first 8 weeks; recommended starting doses are 40,000u weekly or 300µg fortnightly (or 150µg weekly). If suboptimal response, doses can be doubled for a further 8 weeks. Response is very unlikely if not seen by 16 weeks, so treatment should then be stopped. A target Hb of 12g/dL has been suggested, given concerns over thrombosis at higher Hb levels with EPO.

Some randomised trials suggest that erythroid responses are enhanced by combined treatment with GCSF. This effect is much more pronounced for MDS with ring sideroblasts, in which there is convincing evidence of synergism with an overall response rate ~50% (27,28). Therefore, addition of GCSF is recommended for MDS-RS, but is unlikely to add much in other subtypes. A reasonable starting dose is 300µg/week, adjusted to achieve doubling of WCC and maintaining in the range 6-10 $x10^9$/L.

IMMUNOSUPPRESSIVE THERAPY

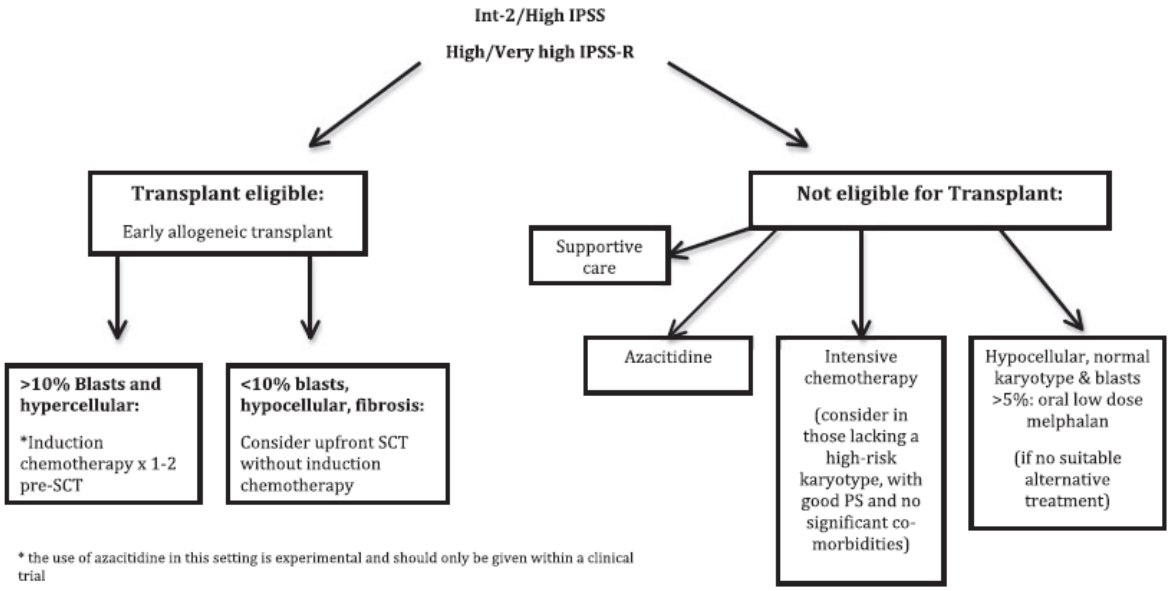
A small fraction of low risk MDS patients seem to have bone marrow failure due to autoimmune mechanisms, akin to aplastic anemia. Several international studies have demonstrated response rates of ~30% to immunosuppressive therapy with *horse* antithymocyte globulin and cyclosporin A (*see Aplastic Anaemia guidelines*). 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.

LENALIDOMIDE

Lenalidomide has demonstrable efficacy in patients with Low/INT-1, EPO-refractory transfusion-dependent anaemia, with 67% of patients rendered transfusion independent; 73% achieved cytogenetic remission with a median duration of 116 weeks (29). Neutropenia and thrombocytopenia are a significant issue. It is NICE approved for use for transfusion-dependent Low/Int-1 patients with del(5q) (in isolation or maximum one additional abnormality) where other therapeutic interventions including EPO are inadequate.

TP53 mutated subclones are common in 5q- MDS and will often grow through at treatment failure, rendering patients refractory to further therapy and with extremely poor prognosis from that point. Screening for *TP53* mutations is thus recommended, both at presentation and relapse. Young patients potentially eligible for allogeneic transplantation should be discussed at an early stage, since decisions on lenalidomide therapy versus early transplant are becoming increasingly complex with the emerging evidence.

ALGORITHM FOR MANAGING HIGH-RISK MDS



ALLOGENEIC STEM CELL TRANSPLANTATION

AlloSCT is the only potentially curative treatment option for patients with MDS. Decisions on timing of transplant can be difficult and early referral to a transplant centre is recommended. Conventionally transplant was reserved for patients with high-risk MDS (IPSS INT-2/High). Emerging data suggests that outcomes may be better when patients are transplanted early during their disease and favour younger age group, low-risk MDS, <12 months since diagnosis, and prior to onset of transfusion dependence. However, due to its significant morbidity and mortality, each case should be considered individually. Suitable patients should be referred early on (30).

ELN guidelines recommend that fit patients with high-risk IPSS(-R), and those with low-risk IPSS(-R) but with poor-risk genetic features, profound cytopenias and/or high transfusion burden are candidates for SCT (31). Poor risk mutations include those in ASXL1, RUNX1, RAS pathway and TP53. Patients with complex monosomal karyotype usually carry TP53 mutations and these have exceedingly poor outcome (10-15% survival) even after SCT (32).

Cytoreductive chemotherapy is recommended for patients with ≥10% marrow blasts, as a means of reducing relapse risk. This is particularly important for patients undergoing RISCT. However, there is a paucity of data to support this threshold, and some centres also advocate cytoreduction at 5-10% blasts. Several studies have investigated the optimal pre-transplant cytoreductive strategy, but with no clear advantage for either AML-style cytotoxic induction or hypomethylating agents (31). Recent data suggests that rare MDS patients

harbouring NPM1 mutations might represent a subgroup that benefit from induction chemotherapy irrespective of blast count, aiming for MRD clearance (as in AML) (33). However, this remains controversial and further studies are needed.

Currently the largest evidence supports the use of myeloablative conditioning for the younger group of patients (<40 years) and reduced intensity conditioning (RIC) for those older than 40 years. Some studies have tried to review the role of RIC regimens in those <40 years but have largely not been conclusive. Since introduction of high resolution sequencing, donor selection has improved with comparable outcomes between fully matched unrelated and sibling donors (35). Alternative donor transplants including haploidentical and cord blood transplant are also now a viable option in the absence of a fully matched donor.

Azacitidine

The hypomethylating agent Azacitidine was NICE approved in 2011 for the treatment of IPSS INT-2/High-risk MDS (and MDS/AML with 20-30% blasts) in patients not eligible for AlloSCT. Responses often require at least 4 cycles, underscoring the importance of continuing treatment until disease progression. In clinical practice full CR rates rarely exceed ~15-20%, but many more (~50-60% overall) achieve meaningful clinical benefit, including resolution of cytopenias and cytogenetic clearance. However, responses are transient and relapse inevitable. Prognosis after HMA failure is very poor and survival typically <6 months. Such patients should be directed to clinical trials where possible.

The AZA-001, a phase 3 randomised study in advanced MDS comparing azacitidine to best standard of care (BSC: low dose cytarabine, AML-style chemotherapy or supportive care only) was the basis for its NICE approval. The study demonstrated 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) (37). The FDA also approved azacitidine for patients with INT-1 disease. There may be rare INT-1 patients with significant cytopenias in whom azacitidine could be of clinical benefit (e.g. severe thrombocytopenia) but in the UK alternative funding arrangements must be sought (e.g. IFR).

The licensed dosing schedule is Azacitidine 75 mg/m^2 sc D1-7 repeated every 28 days. Alternative dosing schedules (e.g. “5-2-2”, omitting weekend doses) are frequently used in the UK, due to constraints of administration at weekends. The marrow could be assessed after 4 cycles, unless there is obvious progression. Initially treatment must be given at full dose despite cytopenias as those are likely due to the underlying disease. However, later in the treatment process, cytopenias may represent drug toxicity and dose reductions or extended treatment scheduling to e.g. 6 weekly are an option.

Decitabine is a similar hypomethylating agent in widespread use worldwide, with comparable clinical activity. It is licensed by the EMA for treatment of AML but

not NICE approved with only limited UK experience. Oral azacitidine is currently under investigation for transfusion-dependent patients with low risk MDS; it remains experimental at this stage and is not available outside clinical trials. Second generation HMAs (e.g. guadecitabine) are also being investigated.

AML-style intensive chemotherapy

Several studies have explored different combinations of AML-style induction for high-risk MDS but there is no clear evidence that AML-style chemotherapy alters the natural history of MDS. Few studies were randomised, and then often with the purpose to study the effect of growth factors with chemotherapy. Taken together these show a median CR 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 and CR durations are generally short (38,39). After azacitidine failure AML-style chemotherapy may be attempted in patients with good performance status, lacking comorbidities and with good prognostic features for achievement of CR. However, duration of remissions is likely to be short and azacitidine-failure clinical trials may be a more appropriate option.

The main indication for AML-style induction chemotherapy in MDS remains debulking of high-risk disease with excess blasts prior to AlloSCT. AML therapy may be reasonable for younger patients (with INT-2/High-risk MDS) who cannot be transplanted, and can be a reasonable palliative approach in selected cases, inducing remissions potentially lasting several months; patients should be counselled, however, that relapse is inevitable and this approach cannot be considered curative. The absence of adverse cytogenetics and a proliferative disease may support decision-making. The short duration of remission for those with adverse cytogenetics does not support using this approach (40), and such patients should be treated with investigational approaches, including transplantation, where possible.

Recent protocol amendments to the NCRN AML 18 and 19 trials has reduced the lower marrow blast threshold to include selected cases with ≥5%, extending the number of high-risk MDS patients eligible for these large studies.

Low dose chemotherapy

There are no data to indicate that low dose conventional chemotherapy is disease-modifying in MDS. High-risk patients with MDS-EB-2 can achieve blast clearance, which can be a reasonable palliative option in selected elderly/co-morbid patients unsuitable for intensive chemotherapy or azacitidine (*see Acute Myeloid Leukaemia guidelines*). However, duration of remissions is usually short, with no apparent effect on overall survival or rate of AML transformation.

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 ~30% in the LDAC arm, but no benefit in terms of overall survival and transformation to AML

(44). Fatal hematological toxicity at a frequency of up to 19% was reported for LDAC. However, in selected cases of MDS-EB-2 ineligible or refractory to azacitidine, LDAC can be a reasonable palliative approach and would be the favoured low dose cytotoxic in this setting.

Melphalan:
Three small phase 2 studies in high-risk MDS report a response rate of up to 30% in selected patients (hypo/normocellular marrow and normal karyotype), i.e improved blood counts and reduced/abolished transfusion need. Toxicity was mild at 2mg/day until response (~8 weeks) or progression (41-43). However, this approach is not supported by randomised evidence and rarely used in MDS.

Novel Agents
With advances in understanding MDS biology a host of novel agents have entered clinical trials. Some may be available through compassionate access schemes for selected patients.

Luspatercept is an FDA approved novel drug that in the phase 2 PACE-MDS study of 58 low/int-1 risk MDS patients showed it to be well tolerated, demonstrating haematological improvement in 63% and transfusion-independence in 38% of patients. Responses were highest in those with ring sideroblasts, low transfusion burden and lower serum EPO, but were irrespective of prior EPO treatment (45). Phase 3 trials are underway to clarify its potential role as a disease-modifying agent in MDS. Inhibitors of mutant IDH1 (ivosidenib) (46) and IDH2 (enasidenib) (47) have been approved by the FDA for AML, and may have a future role for selected MDS patients. The BCL2 inhibitor venetoclax is also FDA approved for AML in combination with HMA (48) or LDAC (49), and may become an option for elderly higher-risk MDS in the near future.

CHRONIC MYELOMONOCYTIC LEUKAEMIA (CMML)
CMML is the most common MDS/MPN overlap syndrome and has its own distinct clinicopathological entity. Cytogenetic abnormalities are less common than in MDS (~30%) and are rarely prognostic; by contrast, >95% have mutations in a short list of recurrent genes, including *TET2* (~60%), *SRSF2* (~50%), *ASXL1* (~40%) and *N/KRAS* (~30%). CMML is clinically heterogeneous, ranging from an indolent dysplastic disease requiring watchful waiting, to an aggressive proliferative leukaemia with very short survival (50).

Diagnosis
Diagnosis requires presence of myeloid dysplasia and persistent monocytosis >1 $x10^9$/L (≥10% of WBCs). The WHO classification has re-classified CMML on the basis of blasts into CMML-0 (<2% blood; <5% marrow), CMML-1 (2-4% blood; 5-9% marrow) and CMML-2 (5-19% blood; 10-19% marrow), reflecting differences in prognosis. It has also re-introduced the distinction between proliferative (WCC ≥$13x10^9$/L) and dysplastic (WCC <$13x10^9$/L) forms, with the former enriched for Ras pathway mutations and a significantly poorer prognosis (5).

Diagnostically challenging cases can be supported by the finding of a CMML-specific molecular abnormality, which now supersedes the absolute requirement for morphologic dysplasia or for monocytosis to persist >3 months before securing the diagnosis.

Prognostication

The CMML specific prognostic scoring system (CPSS) (51) has been updated into the CPSS-Molecular score, to incorporate mutational information (52). Mutations in *ASXL1, SETBP1, RUNX1* and *KRAS* contribute (alongside karyotype) to a Genetic Score, which is combined with BM blast %, WBC count and transfusion dependency to assign an overall risk category. The CPSS-Mol is clinically informative and now widely used (see below). Risk prognostication could influence management decisions particularly in patients who are candidates for intensive therapy and AlloSCT. Hence mutation profiling and early referral to a transplant centre is recommended in all suitable patients.

CPSS-Molecular Score (52)

A	**CPSS cytogenetic risk group**	***ASXL1***	***NRAS***	***RUNX1***	***SETBP1***
Variable score					
0	Low	Unmutated	Unmutated	Unmutated	Unmutated
1	Intermediate	Mutated	Mutated	—	Mutated
2	High	—	—	Mutated	—
Genetic risk group	**Score**	Cytogenetic risk groups are defined as: low, normal, and isolated –Y; intermediate, other abnormalities; and high, trisomy 8, complex karyotype (≥3 abnormalities), and abnormalities of chromosome 7			
Low	0				
Intermediate-1	1				
Intermediate-2	2				
High	≥3				

B		**BM blasts**	**WBC count**	**RBC transfusion dependency**
Variable score				
0	Low	<5%	<13 × 10^9/L	No
1	Intermediate-1	≥5%	≥13 × 10^9/L	Yes
2	Intermediate-2	—	—	—
3	High			
CPSS-Mol risk group	**Score**	**Overall Survival (Median; months)**		**Rate of AML transformation (at 2y)**
Low	**0**	Not reached		0%
Intermediate-1	**1**	68		8%
Intermediate-2	**2-3**	30		24%
High	**≥4**	17		52%

Management

Many CMML patients are elderly with monocytosis, modest cytopenias and no symptoms, and so can reasonably be followed without treatment. In general treatment is indicated for symptomatic, proliferative or progressive disease. Constitutional symptoms (fever, weight loss, night sweats) and splenomegaly are relatively common and can improve with treatment.

Allogeneic stem cell transplantation:
At diagnosis, consideration should be given to whether the patient is a candidate for allogeneic SCT, as this remains the only curative approach (31). All potential patients should be discussed with a transplant centre at an early stage. In general, induction chemotherapy is recommended for those with blast excess (as for MDS), but not for cytoreduction of proliferative disease. The age range of CMML patients dictates that RIC conditioning is invariably employed.

Hydroxycarbamide:
One randomised trial of Hydroxycarbamide vs Etoposide showed superiority in response (60% vs 36%) and survival (20 months vs 9 months) (53). This remains the only randomised trial to demonstrate survival advantage in CMML, and Hydroxycarbamide is recommended as first-line treatment for older patients with a low (<10%) marrow blast count and for whom the main aim is to reduce symptoms. Target WCC threshold should be individualised based on the balance of symptoms, transfusion burden and side effects; aiming for WCC ≤30 $x10^9$/L is a reasonable guide.

Azacitidine:
Azacitidine is NICE approved for CMML with 10-29% marrow blasts without myeloproliferative disorder (defined as WCC ≥13 $x10^9$/L), in line with the AZA001 trial inclusion criteria (37). Subsequently the UK single-arm CMML-201 phase 2 study of 32 CMML patients showed a disappointing CR rate of 7%, with overall short-lived response rates of only 43% (54). Other small studies have reported better results and undoubtedly some patients with non-proliferative disease derive meaningful benefit, including transfusion-independence.

Low dose cytarabine:
Can be an effective cytoreductive agent in CMML, but is typically associated with higher side effects and has no proven advantage over hydroxycarbamide alone. LDAC for proliferative CMML with blast excess (CMML-2) can be an appropriate palliative option, and complete blast clearance (albeit generally brief) can be observed in a minority of cases.

References

1. Bento LC, Correia RP, Pitangueiras Mangueira CL, De Souza Barroso R, Rocha FA, Bacal NS, et al. The Use of Flow Cytometry in Myelodysplastic Syndromes: A Review. Front Oncol. 2017;7:270.

2. Bejar R, Stevenson K, Abdel-Wahab O, Galili N, Nilsson B, Garcia-Manero G, et al. Clinical effect of point mutations in myelodysplastic syndromes. N Engl J Med. 2011 Jun 30;364(26):2496–506.

3. Papaemmanuil E, Gerstung M, Malcovati L, Tauro S, Gundem G, Van Loo P, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood. 2013 Nov 21;122(22):3616–27–quiz3699.

4. Lim ZY, Killick S, Germing U, Cavenagh J, Culligan D, Bacigalupo A, et al. Low IPSS score and bone marrow hypocellularity in MDS patients predict hematological responses to antithymocyte globulin. Leukemia. 2007 Jul;21(7):1436–41.

5. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016 May 19;127(20):2391–405.

6. Jaiswal S, Fontanillas P, Flannick J, Manning A, Grauman PV, Mar BG, et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med. 2014 Dec 25;371(26):2488–98.

7. Steensma DP, Bejar R, Jaiswal S, Lindsley RC, Sekeres MA, Hasserjian RP, et al. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. Blood. 2015 Jul 2;126(1):9–16.

8. Bejar R. CHIP, ICUS, CCUS and other four-letter words. Leukemia. Nature Publishing Group; 2017 Sep;31(9):1869–71.

9. Jaiswal S, Natarajan P, Silver AJ, Gibson CJ, Bick AG, Shvartz E, et al. Clonal Hematopoiesis and Risk of Atherosclerotic Cardiovascular Disease. N Engl J Med. 2017 Jul 13;377(2):111–21.

10. Cargo CA, Rowbotham N, Evans PA, Barrans SL, Bowen DT, Crouch S, et al. Targeted sequencing identifies patients with preclinical MDS at high risk of disease progression. Blood. 2015 Nov 19;126(21):2362–5.

11. Malcovati L, Gallì A, Travaglino E, Ambaglio I, Rizzo E, Molteni E, et al. Clinical significance of somatic mutation in unexplained blood cytopenia. Blood. 2017 Apr 19;:blood–2017–01–763425–9.

12. Kern W, Meggendorfer M, Haferlach C, Haferlach T. Integrated Diagnostic Approach for Suspected Myelodysplastic Syndrome As a Basis for Advancement of Diagnostic Criteria. Blood. 2016 Feb 24;(128):299.

13. Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood. 1997 Mar 15;89(6):2079–88.

14. Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Solé F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012 Sep 20;120(12):2454–65.

15. Cappellini MD, Cohen A, Piga A, Bejaoui M, Perrotta S, Agaoglu L, et al. A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with beta-thalassemia. Blood. American Society of Hematology; 2006 May 1;107(9):3455–62.

16. Killick SB. Iron chelation therapy in low risk myelodysplastic syndrome. Br J Haematol. 2017 May;177(3):375–87.

17. Fenaux P, Santini V, Spiriti MAA, Giagounidis A, Schlag R, Radinoff A, et al. A phase 3 randomized, placebo-controlled study assessing the efficacy and safety of epoetin-α in anemic patients with low-risk MDS. Leukemia. Nature Publishing Group; 2018 Dec;32(12):2648–58.

18. Platzbecker U, Symeonidis A, Oliva EN, Goede JS, Delforge M, Mayer J, et al. A phase 3 randomized placebo-controlled trial of darbepoetin alfa in patients with anemia and lower-risk myelodysplastic syndromes. Leukemia. Nature Publishing Group; 2017 Sep;31(9):1944–50.

19. Park S, Fenaux P, Greenberg P, Mehta B, Callaghan F, Kim C, et al. Efficacy and safety of darbepoetin alpha in patients with myelodysplastic syndromes: a systematic review and meta-analysis. Br J Haematol. 2016 Sep;174(5):730–47.

20. Garelius HKG, Johnston WT, Smith AG, Park S, de Swart L, Fenaux P, et al. Erythropoiesis-stimulating agents significantly delay the onset of a regular transfusion need in nontransfused patients with lower-risk myelodysplastic syndrome. J Intern Med. 2017 Mar;281(3):284–99.

21. Jädersten M, Malcovati L, Dybedal I, Giovanni Della Porta M, Invernizzi R, Montgomery SM, et al. Erythropoietin and Granulocyte-Colony Stimulating Factor Treatment Associated With Improved Survival in Myelodysplastic Syndrome. J Clin Oncol. 2008 Jul 20;26(21):3607–13.

22. Park S, Grabar S, Kelaidi C, Beyne-Rauzy O, Picard F, Bardet V, et al. Predictive factors of response and survival in myelodysplastic syndrome treated with erythropoietin and G-CSF: the GFM experience. Blood. 2008

Jan 15;111(2):574–82.

23. Hellstrom-Lindberg E, Gulbrandsen N, Lindberg G, Ahlgren T, Dahl IMS, Dybedal I, et al. A validated decision model for treating the anaemia of myelodysplastic syndromes with erythropoietin + granulocyte colony-stimulating factor: significant effects on quality of life. Br J Haematol. 2003 Mar;120(6):1037–46.

24. Nilsson-Ehle H, Birgegård G, Samuelsson J, Antunovic P, Astermark J, Garelius H, et al. Quality of life, physical function and MRI T2* in elderly low-risk MDS patients treated to a haemoglobin level of ≥120 g/L with darbepoetin alfa ± filgrastim or erythrocyte transfusions. Eur J Haematol. 2011 Sep;87(3):244–52.

25. Hellström-Lindberg E, Negrin R, Stein R, Krantz S, Lindberg G, Vardiman J, et al. Erythroid response to treatment with G-CSF plus erythropoietin for the anaemia of patients with myelodysplastic syndromes: proposal for a predictive model. Br J Haematol. 1997 Nov;99(2):344–51.

26. Buckstein R, Balleari E, Wells R, Santini V, Sanna A, Salvetti C, et al. ITACA: A new validated international erythropoietic stimulating agent-response score that further refines the predictive power of previous scoring systems. Am J Hematol. John Wiley & Sons, Ltd; 2017 Oct;92(10):1037–46.

27. Hellström-Lindberg E, Ahlgren T, Beguin Y, Carlsson M, Carneskog J, Dahl IM, et al. Treatment of anemia in myelodysplastic syndromes with granulocyte colony-stimulating factor plus erythropoietin: results from a randomized phase II study and long-term follow-up of 71 patients. Blood. 1998 Jul 1;92(1):68–75.

28. Greenberg PL, Sun Z, Miller KB, Bennett JM, Tallman MS, Dewald G, et al. Treatment of myelodysplastic syndrome patients with erythropoietin with or without granulocyte colony-stimulating factor: results of a prospective randomized phase 3 trial by the Eastern Cooperative Oncology Group (E1996). Blood. American Society of Hematology; 2009 Sep 17;114(12):2393–400.

29. List A, Dewald G, Bennett J, Giagounidis A, Raza A, Feldman E, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. N Engl J Med. 2006 Oct 5;355(14):1456–65.

30. Killick SB, Carter C, Culligan D, Dalley C, Das-Gupta E, Drummond M, et al. Guidelines for the diagnosis and management of adult myelodysplastic syndromes. Br J Haematol. 2014 Feb;164(4):503–25.

31. de Witte T, Bowen D, Robin M, Malcovati L, Niederwieser D, Yakoub-Agha I, et al. Allogeneic hematopoietic stem cell transplantation for MDS and

CMML: recommendations from an international expert panel. Blood. 2017 Mar 30;129(13):1753–62.

32. Lindsley RC, Saber W, Mar BG, Redd R, Wang T, Haagenson MD, et al. Prognostic Mutations in Myelodysplastic Syndrome after Stem-Cell Transplantation. N Engl J Med. 2017 Feb 9;376(6):536–47.

33. Montalban-Bravo G, Kanagal-Shamanna R, Sasaki K, Patel K, Ganan Gomez I, Jabbour E, et al. NPM1 mutations define a specific subgroup of MDS and MDS/MPN patients with favorable outcomes with intensive chemotherapy. Blood Adv. American Society of Hematology; 2019 Mar 26;3(6):922–33.

34. Kröger N, Iacobelli S, Franke G-N, Platzbecker U, Uddin R, Hübel K, et al. Dose-Reduced Versus Standard Conditioning Followed by Allogeneic Stem-Cell Transplantation for Patients With Myelodysplastic Syndrome: A Prospective Randomized Phase III Study of the EBMT (RICMAC Trial). J Clin Oncol. 2017 Jul 1;35(19):2157–64.

35. Saber W, Cutler CS, Nakamura R, Zhang M-J, Atallah E, Rizzo JD, et al. Impact of donor source on hematopoietic cell transplantation outcomes for patients with myelodysplastic syndromes (MDS). Blood. 2013 Sep 12;122 (11):1974–82.

36. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2005 Oct 15;106(8): 2912–9.

37. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol. 2009 Mar;10(3): 223–32.

38. Beran M, Shen Y, Kantarjian H, O'Brien S, Koller CA, Giles FJ, et al. High-dose chemotherapy in high-risk myelodysplastic syndrome: covariate-adjusted comparison of five regimens. Cancer. 2001 Oct 15;92(8):1999–2015.

39. Kantarjian H, Beran M, Cortes J, O'Brien S, Giles F, Pierce S, et al. Long-term follow-up results of the combination of topotecan and cytarabine and other intensive chemotherapy regimens in myelodysplastic syndrome. Cancer. 2006 Mar 1;106(5):1099–109.

40. Knipp S, Hildebrand B, Kündgen A, Giagounidis A, Kobbe G, Haas R, et al. Intensive chemotherapy is not recommended for patients aged >60 years who have myelodysplastic syndromes or acute myeloid leukemia with high-

risk karyotypes. Cancer. John Wiley & Sons, Ltd; 2007 Jul 15;110(2):345–52.

41. Omoto E, Deguchi S, Takaba S, Kojima K, Yano T, Katayama Y, et al. Low-dose melphalan for treatment of high-risk myelodysplastic syndromes. Leukemia. 1996 Apr;10(4):609–14.

42. Denzlinger C, Bowen D, Benz D, Gelly K, Brugger W, Kanz L. Low-dose melphalan induces favourable responses in elderly patients with high-risk myelodysplastic syndromes or secondary acute myeloid leukaemia. Br J Haematol. 2000 Jan;108(1):93–5.

43. Robak T, Szmigielska-Kapłon A, Urbańska-Ryś H, Chojnowski K, Wrzesień-Kuś A. Efficacy and toxicity of low-dose melphalan in myelodysplastic syndromes and acute myeloid leukemia with multilineage dysplasia. Neoplasma. 2003;50(3):172–5.

44. Miller KB, Kim K, Morrison FS, Winter JN, Bennett JM, Neiman RS, et al. The evaluation of low-dose cytarabine in the treatment of myelodysplastic syndromes: a phase-III intergroup study. Ann Hematol. 1992 Oct;65(4): 162–8.

45. Platzbecker U, Germing U, Götze KS, Kiewe P, Mayer K, Chromik J, et al. Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study. Lancet Oncol. 2017 Oct;18(10):1338–47.

46. Dinardo CD, Stein EM, de Botton S, Roboz GJ, Altman JK, Mims AS, et al. Durable Remissions with Ivosidenib in IDH1-Mutated Relapsed or Refractory AML. N Engl J Med. 2018 Jun 21;378(25):2386–98.

47. Stein EM, Dinardo CD, Pollyea DA, Fathi AT, Roboz GJ, Altman JK, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. Blood. American Society of Hematology; 2017 Aug 10;130(6):722–31.

48. Dinardo CD, Pratz K, Pullarkat V, Jonas BA, Arellano M, Becker PS, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood. American Society of Hematology; 2019 Jan 3;133(1):7–17.

49. Wei AH, Strickland SA, Hou J-Z, Fiedler W, Lin TL, Walter RB, et al. Venetoclax Combined With Low-Dose Cytarabine for Previously Untreated Patients With Acute Myeloid Leukemia: Results From a Phase Ib/II Study. J Clin Oncol. 2019 Mar 20;:JCO1801600.

50. Ball M, List AF, Padron E. When clinical heterogeneity exceeds genetic heterogeneity: thinking outside the genomic box in chronic myelomonocytic

leukemia. Blood. 2016 Oct 5.

51. Such E, Germing U, Malcovati L, Cervera J, Kuendgen A, Porta Della MG, et al. Development and validation of a prognostic scoring system for patients with chronic myelomonocytic leukemia. Blood. 2013 Apr 11;121 (15):3005–15.

52. Elena C, Gallì A, Such E, Meggendorfer M, Germing U, Rizzo E, et al. Integrating clinical features and genetic lesions in the risk assessment of patients with chronic myelomonocytic leukemia. Blood. 2016 Sep 8;128 (10):1408–17.

53. Wattel E, Guerci A, Hecquet B, Economopoulos T, Copplestone A, Mahe B, et al. A randomized trial of hydroxyurea versus VP16 in adult chronic myelomonocytic leukemia. Groupe Français des Myélodysplasies and European CMML Group. Blood. 1996 Oct 1;88(7):2480–7.

54. Drummond MW, Pocock C, Boissinot M, Mills J, Brown J, Cauchy P, et al. A multi-centre phase 2 study of azacitidine in chronic myelomonocytic leukaemia. Leukemia. 2014 Jul;28(7):1570–2.