Hull University Teaching Hospitals NHS Trust

# Hull University Teaching Hospitals and North Lincolnshire NHS Trusts

# Haematology Multidisciplinary Team Guideline and Pathway

# Myelodysplastic Syndromes

## 1 BACKGROUND

The Hull and North Lincolnshire Haematology Multidisciplinary team manages patients with haematological malignancies on three sites, Diana Princess of Wales Hospital Grimsby, the Queens Centre for Haematology and Oncology at Castle Hill Hospital Hull University Teaching Hospitals NHS Trust and Scunthorpe Hospital.

Levels of service provided in these organisations is as defined in the NICE guidance "Haematological Cancers: improving outcomes NG47" 25th May 2016.

Low-to-intermediate intensity chemotherapy is delivered in Grimsby, the Queens Centre Castle Hill Hospital and Scunthorpe Hospital.

High-intensity chemotherapy and autologous stem cell transplantation is delivered at the Queens Centre, Castle Hill Hospital.

Allogeneic stem cell transplantation is delivered in the regional transplant centres in Leeds, Nottingham and Sheffield.

Azacytidine, low-dose Ara-C and hyrdroxycarbimide and lenalidomide will be delivered in sites offering low-to intermediate intensity chemotherapy.

High intensity chemotherapy including, but not limited to, DA, FLAG, FLAG-Ida, intermediate and high dose cytarabine will only be delivered in the high intensity chemotherapy unit in Queens Centre, Castle Hill Hospital.

## 2 POLICY / PROCEDURE / GUIDELINE DETAIL

The Hull and North Lincolnshire MDT has decided that patients with myelodysplastic syndromes (MDS) will be managed in line with the BCSH guidelines (Killick et al. 2014) and the European LeukemiaNet (ELN) Guidelines on the diagnosis and management of MDS (Malcovati et al. 2013).

The local management of MDS will also take account of the following NICE pathways and guidance.

NICE Myeloid Leukaemia. https://pathways.nice.org.uk/

Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia. Technology appraisal guidance (TA218) Published date: 23 March 2011.

Lenalidomide for treating myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality (TA322) Technology appraisal guidance (TA322) Published date: September 2014.

## Diagnosis

- Significant (>10%) marrow dysplasia or a clonal cytogenetic abnormality.
- Initial assessment of a patient with suspected MDS should include a minimum set of investigations as per the BCSH guidelines.
- 'Idiopathic cytopenia of unknown origin' - >6 months cytopenia who do not fulfil the criteria for the diagnosis of MDS and no other identifiable cause for the cytopenias.
- Molecular genetics:-
    - High-resolution single nucleotide polymorphism-array analysis and next-generation sequencing has led to the identification of point mutations in haemopoietic cells of many patients with MDS, some of which may have independent prognostic significance.
    - Molecular analysis for additional mutations is available from HMDS however these cannot yet be incorporated into routine diagnostic or prognostic evaluation.

## Classification

- The diagnosis and classification of MDS should be based on the World Health Organization Classification (WHO, 2008 revision).

## Prognosis

- The Revised IPSS (IPSS-) refines the parameters (cytogenetic groups, marrow blast% and cytopenias) further by categorizing more cytogenetic subgroups, refinement of blast counts <5% and depth of cytopenias. It is the preferred scoring system for determining prognosis.

## Management

- Therapeutic recommendations should be driven by the IPSS system. IPSS-R should be used to evaluate prognosis in all patients, but not yet to guide therapy.
- Supportive care, including transfusions and antibiotics, remains central to the management of MDS patients.

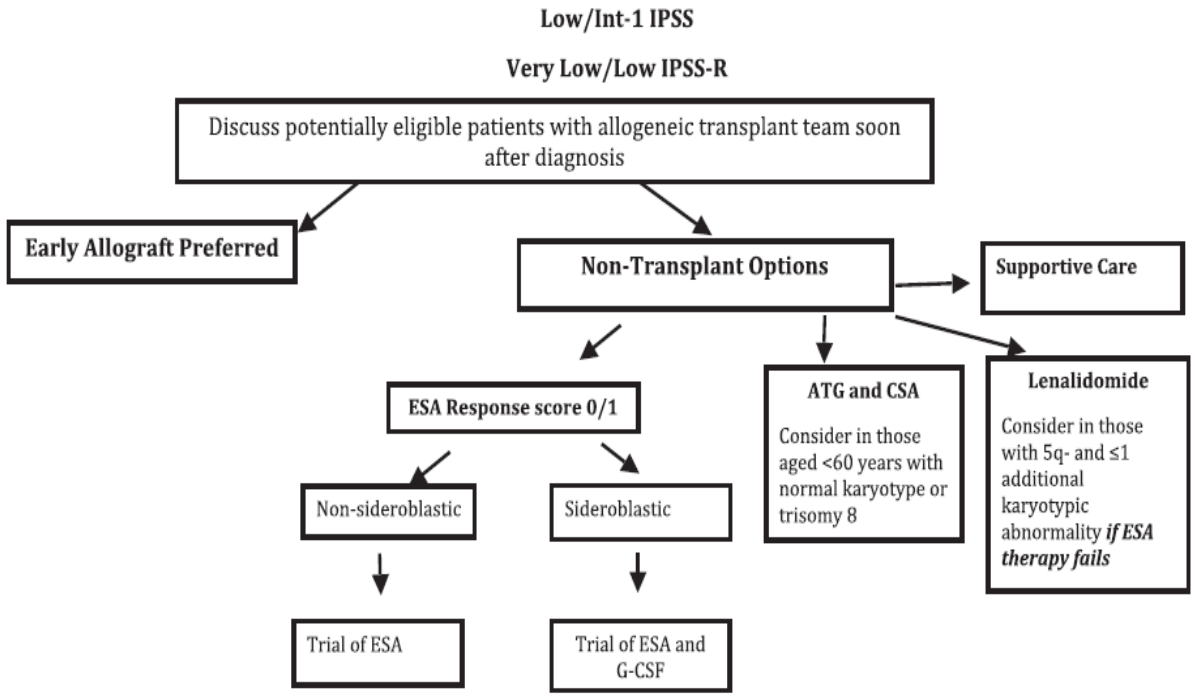
## Iron Chelation

- Transfusion dependence and elevated serum ferritin are independent adverse risk factors for survival in low-risk MDS. Raised serum ferritin is an adverse predictor of outcome in myeloablative stem cell transplantation however iron chelation cannot be

routinely recommended for MDS patients as no direct evidence to support a survival benefit for iron chelation therapy has been demonstrated in MDS.

- Chelation may be considered in patients with a very good prognosis: WHO RA, RARS and isolated del(5q).
- Triggers for chelation: >20 units of red cells transfused, serum ferritin >1000 ng/l in patients for whom continuing red cell transfusion is predicted.
- BCSH guidelines recommend that MRI (T2*) may be used to quantitate liver and cardiac iron however its relationship with transfused red cell burden/outcome has not been consistently demonstrated in MDS.
- Desferrioxamine remains the therapy of choice for iron chelation with Deferasirox being recommended for patients intolerant of desferrioxamine.

## Management of low risk MDS (IPSS: Low or INT-1, IPSS-R: Very Low and Low)




Adapted from Killick et al. British Journal of Haematology, 2014, 164, 503–525

**Erythropoiesis Simulating Agents (ESA)**

- Comparative cohort data suggests a survival advantage for responders to ESA therapy and improvements in global quality of life scores for responders.
- In the presence of anaemia ESA should be considered for patients who score 0 or 1 using the validated model for predicting response to erythropoietin.
- A maximum trial period of 16 weeks of therapy comprising 8 weeks at the starting dose of ESA +/- G-CSF and a further 8 weeks at the higher doses, if required.

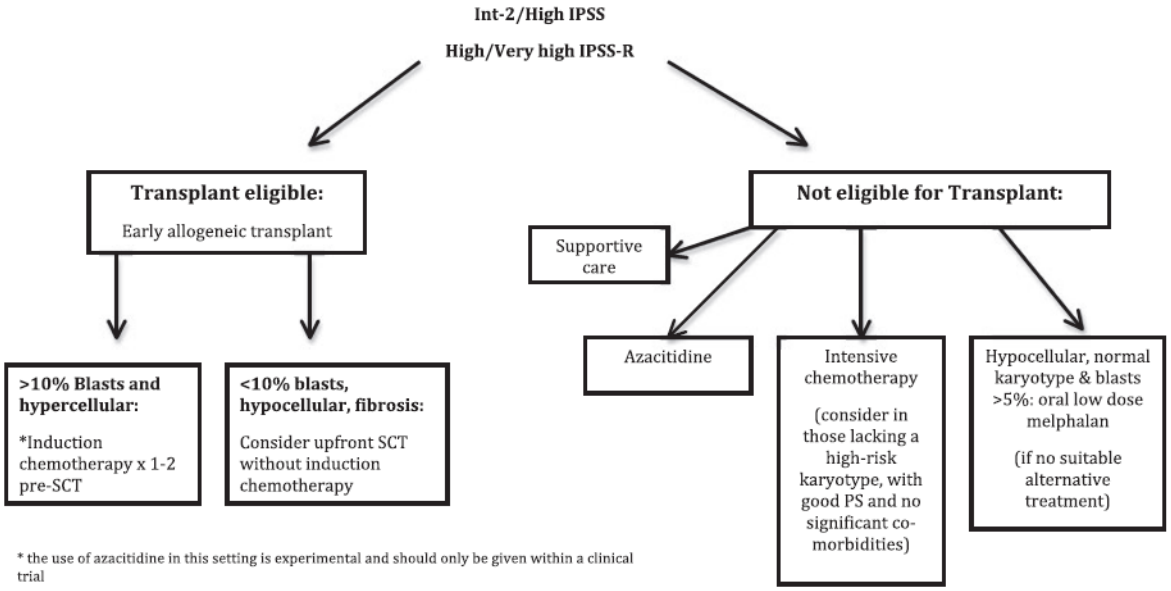
**5q- MDS**

- Lenalidomide (10 mg daily for 21 d repeated every 28 d) should be considered for transfusion dependent patients unsuitable for a trial of ESA and non-responders/patients losing their response to ESA, who have IPSS Low or INT-1 MDS with del(5q). Thrombotic risks and the need for thromboprophylaxis during therapy should be considered. Low risk patients (normal mobility, no previous venous thromboembolism (VTE)) can be considered for low dose aspirin, high risk patients (reduced mobility, previous VTE) should be considered for low molecular weight heparin at prophylactic doses.
- Selected MDS patients with del(5q) and IPSS Low/INT-1 may be candidates for allogeneic stem cell transplantation. These include Lenalidomide-treated patients who fail to achieve transfusion independence, those losing their response and patients with transfusion dependence not considered suitable for lenalidomide.

**Allogeneic stem cell transplant**

- All patients with newly diagnosed MDS should be discussed at MDT and the role of allogeneic haematopoietic stem cell transplant (HSCT) should be considered taking into account additional prognostic features, such as red cell transfusion dependence which can profoundly influence prognosis.

## Management of high risk MDS (IPSS: INT-2/High, IPSS-R: High/Very high)




Adapted from Killick et al. British Journal of Haematology, 2014, 164, 503–525

- Patients deemed fit for intensive therapy should be offered therapy within the current appropriate clinical trial.
- Eligibility for transplant should be considered in all patients taking into account comorbidities including any evidence of iron overload.

## Azacytidine

- Azacytidine be considered in patients not eligible for HSCT, MDS IPSS INT-2 or high, CMML-2 non-proliferative and AML with 20-30% blasts and multi-lineage dysplasia and treatment should be continued until response is lost.
- 45% chance of transfusion independence with a median response duration of 13 months.

## Management of Chronic Myelomonocytic Leukaemia (CMML)

- There is a paucity of evidence to guide management. Non-transplant treatment modalities include:-

  Supportive care only.

  Hydroxycarbamide for proliferative symptoms and control of leucocytosis.

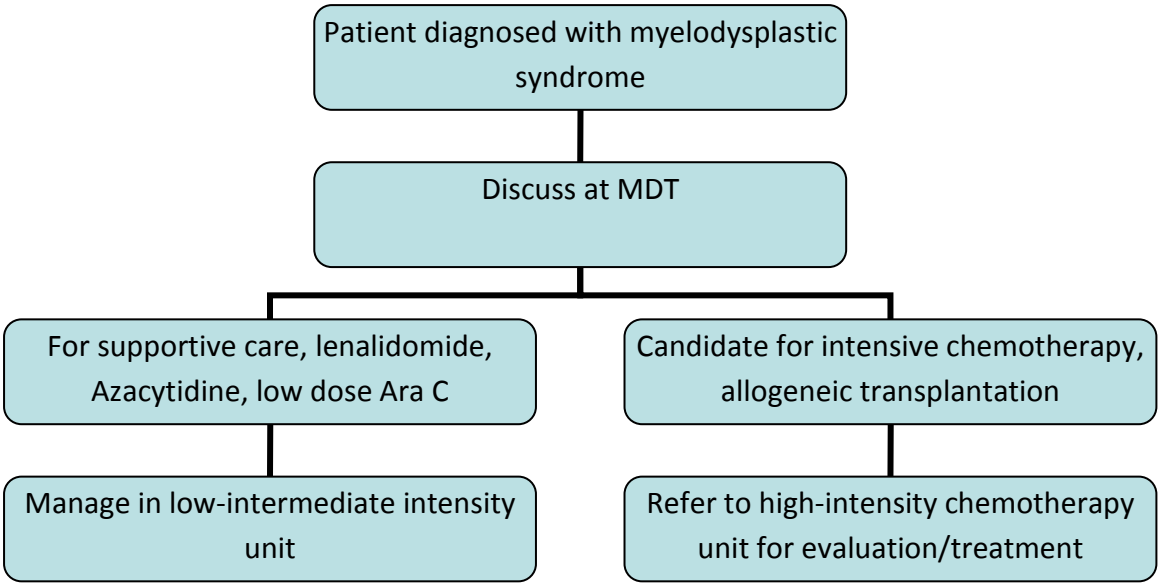
  Hypomethylating agents.

  Clinical trials.

  Azacitidine is licensed for non-proliferative (WBC < 13 x $10^9$/l) CMML-2.

Allogeneic HSCT with or without preceding AML-type chemotherapy should be considered for selected patients.

**Patient Pathway**



## 3 PROCESS FOR MONITORING COMPLIANCE

Compliance will be audited within the MDT audit programme.

## 4 REFERENCES


- Hull and North Lincolnshire Haematology MDT operational policy September 2017.
- Haematological cancers: improving outcomes. NICE guideline [NG47] Published date: May 2016
- Malcovati L, Hellström-Lindberg E, Bowen D, Adès L, Cermak J, Del Cañizo C, Della Porta MG, Fenaux P, Gattermann N, Germing U, Jansen JH, Mittelman M, Mufti G, Platzbecker U, Sanz GF, Selleslag D, Skov-Holm M, Stauder R, Symeonidis A, van de Loosdrecht AA, de Witte T, Cazzola M; European Leukemia Net. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. Blood. 2013 Oct 24;122(17):2943-64.
- Killick SB, Carter C, Culligan D, Dalley C, Das-Gupta E, Drummond M, Enright H, Jones GL, Kell J, Mills J, Mufti G, Parker J, Raj K, Sternberg A, Vyas P, Bowen D; British Committee for Standards in Haematology. Guidelines for the diagnosis and management of adult myelodysplastic syndromes. Br J Haematol. 2014 Feb;164(4):503-25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