Kent and Medway Cancer Network

Network Guidance Document

Oncological treatment of Haematology

Myelodysplastic Syndromes (MDS)

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Contents

1.0 Introduction

1.1 Overview

This document has been written to provide guidance on the treatment of myelodysplastic syndromes in the Kent & Medway Cancer Network.

Radiotherapy schedules are as defined in the Kent Oncology Centre Quality System Clinical Protocols (Disease Management and Radiotherapy Protocols).

See network chemotherapy prescribing proformas for details of chemotherapy / anti-cancer regimens.

All patients will be considered for entry into a clinical trial (see appendix A).

All patients should be discussed within a multidisciplinary team meeting before commencing initial treatment.

Please note, some of the drugs/doses recommended within this document are outside of the U.K. licensed marketing authorisation.

2.0 Background

The myelodysplastic syndromes (MDS) are a group of clonal haematopoietic stem cell diseases characterised by cytopenia(s), dysplasia in one or more of the major myeloid cell lines, ineffective haematopoiesis, and increased risk of development of acute myeloid leukaemia (AML).
There is enhanced degree of apoptosis which contributes to the cytopenias. The threshold for cytopenias as recommended by International Prognostic Scoring System (IPSS) is: Haemoglobin <10.0 g/dl, ANC <1.8 x 10^9/l, platelets <100 x 10^9/l

2.1 Epidemiology:

- Median age 70years
- Non age corrected annual incidence 3-5/100000 but > 20/100000 above 70 years.

2.2 Clinical Features:

- Majority present with symptoms related to cytopenia (s) – anemia often leading to transfusion dependence, neutropenia with increased propensity for infections and thrombocytopenia with associated bleeding.

2.3 Diagnosis:

The diagnosis of MDS requires morphological findings of bone marrow dysplasia and evidence of impaired haematopoiesis e.g. anaemia, neutropenia and/or thrombocytopenia. It is important to distinguish MDS from reactive causes of cytopenias, dysplasia and other clonal stem cell disorders. In the absence of multilineage dysplasia, chromosomal aberrations, and proof of clonality the diagnosis may be difficult to confirm. MDS sometimes remains a diagnosis of exclusion.

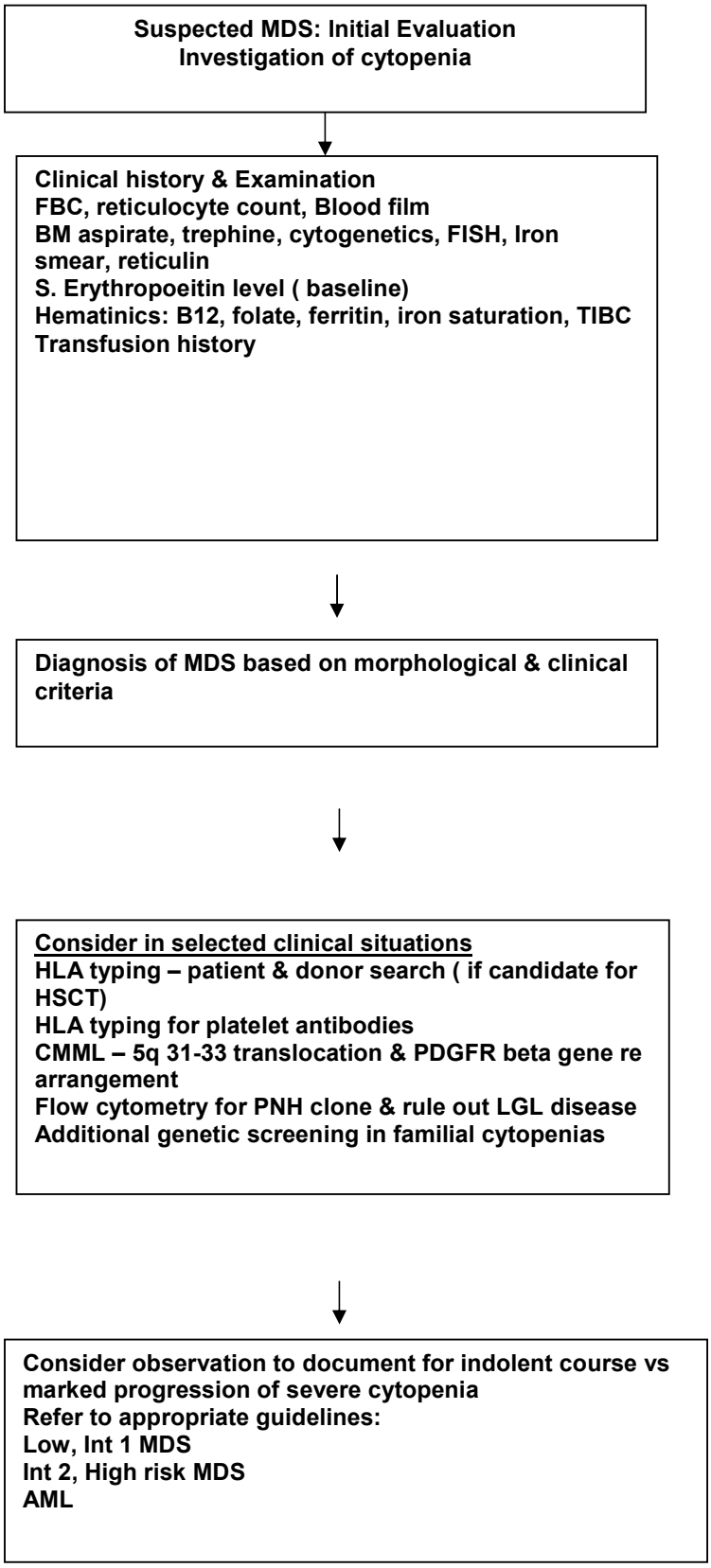
3.0 Initial investigations and haematology referral criteria

3.1 Table of diagnostic tests and additional investigations

Diagnostic tests	Additional investigations
FBC, film and 5 part differential. Reticulocyte count BM aspirate: morphology*, cytogenetics, molecular Immunophenotyping: If suspicion of transformation or to exclude PNH clone if haemolysis Bone marrow trephine: assessment of fibrosis B12, RBC/Serum folate, Ferritin, TIBC. Serum EPO Hb and serum electropheresis.	Renal, liver & thyroid function tests Haptoglobin. Direct antiglobulin test. LDH CXR. ECG. HIV 1& 2, Hepatitis B &C. Parvovirus B19 DNA & serology Tissue banking if consent obtained Tissue typing for potential transplant candidates & identify HLA DR2+ hypoplastic MDS

*Minimum 400 marrow cells, 20 megakaryocytes and 100 erythroblasts should be evaluated. Dysplasia should be present in > 10% of the nucleated cells in the respective lineage. Subclassify according to WHO criteria

3.2 Flow chart 1 - Myelodysplastic Syndromes Diagnostic Pathway



3.3 WHO Classification (2008)

Disorder	Blood	Bone Marrow
Refractory cytopenia with unilineage dysplasia (RCUD): Refractory anaemia (RA); Refractory neutropenia (RN); Refractory thrombocytopenia (RT);	Ini or bicytopenia. No blasts (Bl)	Unilineage dysplasia > 10% in one myeloid lineage,. <15% ring sideroblasts (RS), <5% Bl
RA with ring sideroblasts (RARS)	Anaemia, No Bl	As RA but =/>15% RS Erythroid dysplasia only , < 5% Bl
Refractory cytopenia with multilineage dysplasia (RCMD)	=/>2 cytopenias. No/rare Bl (<1%). No Auer rods (AR). <1x109/l monos	As RA but 2 or more lineages show dysplasia in >10% cells, No AR
RCMD -RS-ring sideroblasts	As RCMD	As RCMD but =/> 15% RS
RA with excess blasts 1 (RAEB-1)	As RCMD. <5% Bl	As RCMD but 5-9% Bl
RAEB-2	As RCMD 5-19% Bl. AR+/-	As RAEB-1. 10-19% Bl. AR+/-
MDS unclassified	As RCMD	Unilineage dysplasia in < 10% cells with cytogenetic abn considered as presumptive evidence, <5% Bl
MDS with del 5q	Anaemia, <1% Bl. Platelets N/inc	<5% Bl, del 5q. Megakaryocytes normal or increased & hypolobated. No AR

MDS/MPD neoplasms (CMML, JMML, Atypical BCR ABL 1 negative CML, MDS/MPD neoplasm, unclassifiable) is outside the scope of this guidance. Consider appropriate clinical trial if eligible.

3.4 Risk stratification- Prognostic scoring systems

- Different scoring systems: Bournmouth, FAB, Sanz, Goesguen, Dusseldorf, Lille, Lausanne-Bournmouth, IPSS & WPSS
- IPSS & WPSS are currently in use.

International Prognostic Scoring System (IPSS)

Risk group	Score	Median survival (yrs)	Time to 25% risk AML (yrs)
Low risk	0	5.7	9.4
INT-1	0.5-1.0	3.5	3.3
INT-2	1.5-2.0	1.2	1.1
High risk	≥2.5	0.4	0.2

Variable	Score				
	0	0.5	1	1.5	2
BM blasts%	<5	5-10		11-20	21-30
Karyotype*	Good	Int	Poor		
Cytopenia**	0/1	2/3			

*Good: normal, -Y, del(5q), del(20q). Int.: other abnormalities. Poor: complex (≥ 3 abnormalities) or chromosome 7 anomalies.

* *Haemoglobin <10.0 g/dl, ANC <1.8 x 10^9/l, platelets <100 x 10^9/l.

IPSS does not include transfusion dependency as a risk criterion.

3.5 WHO Classification-Based Prognostic Scoring System for MDS (WPSS)

Variable	0	1	2	3
WHO category	RA, RARS, 5q–	RCMD, RCMD-RS	RAEB-1	RAEB-2
Karyotype*	Good	Intermediate	Poor	—
Transfusion requirement†	No	Regular	—	—

NOTE. Risk groups were as follows: very low (score = 0), low (score = 1), intermediate (score = 2), high (score = 3 to 4), and very high (score = 5 to 6).

* Karyotype was as follows: good: normal, –Y, del (5q), del (20q); poor: complex (≥ three abnormalities), chromosome 7 anomalies; and intermediate: other abnormalities.

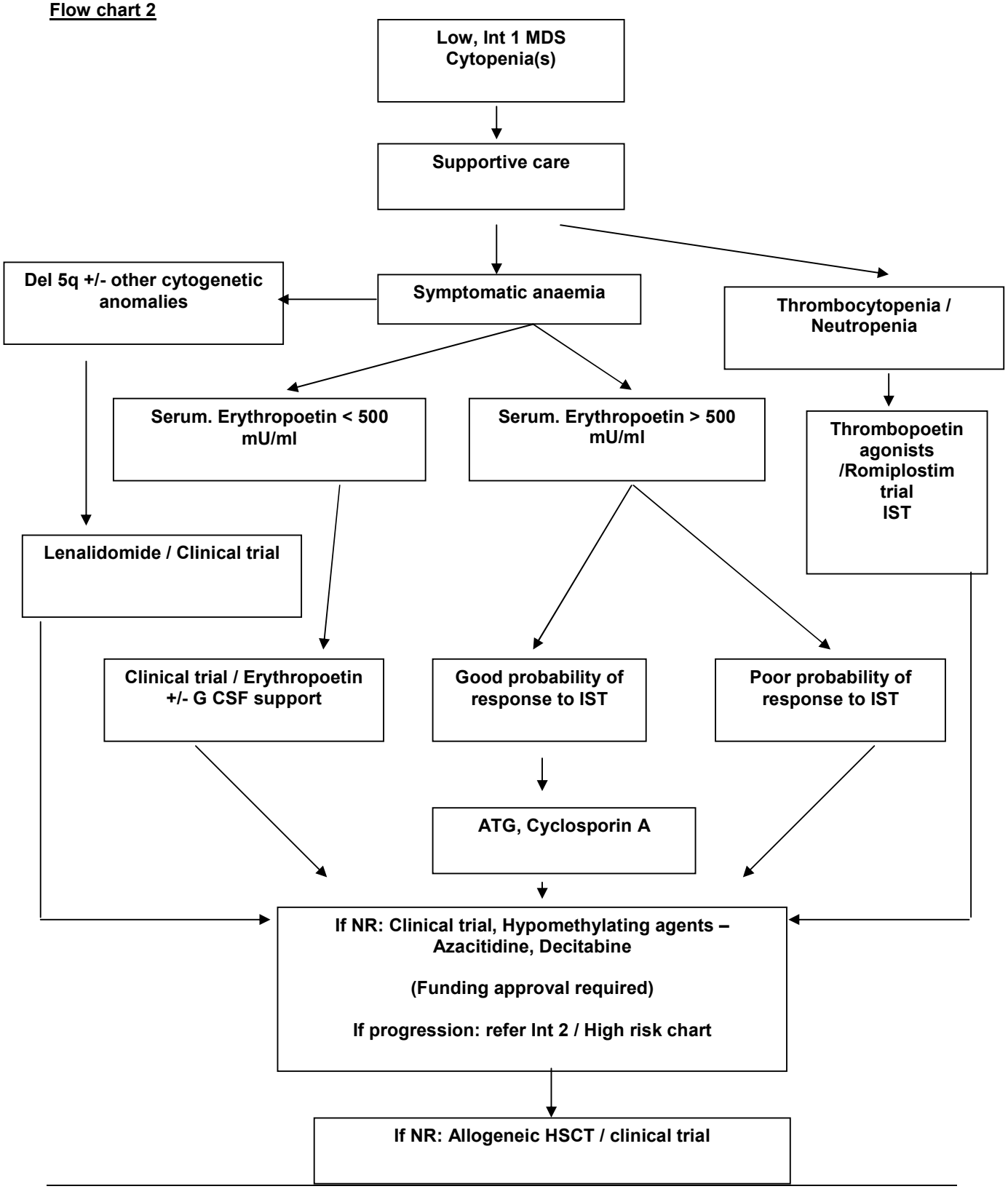
†RBC transfusion dependency was defined as having at least one RBC transfusion every 8 weeks over a period of 4 months.

WPSS is a dynamic prognostic scoring system that provides a better prediction of survival and risk of leukemic evolution in MDS patients at any time during the course of their disease. This time-dependent system seems particularly useful in lower risk patients and may be used for implementing risk-adapted treatment strategies.

4.0 Treatment recommendations

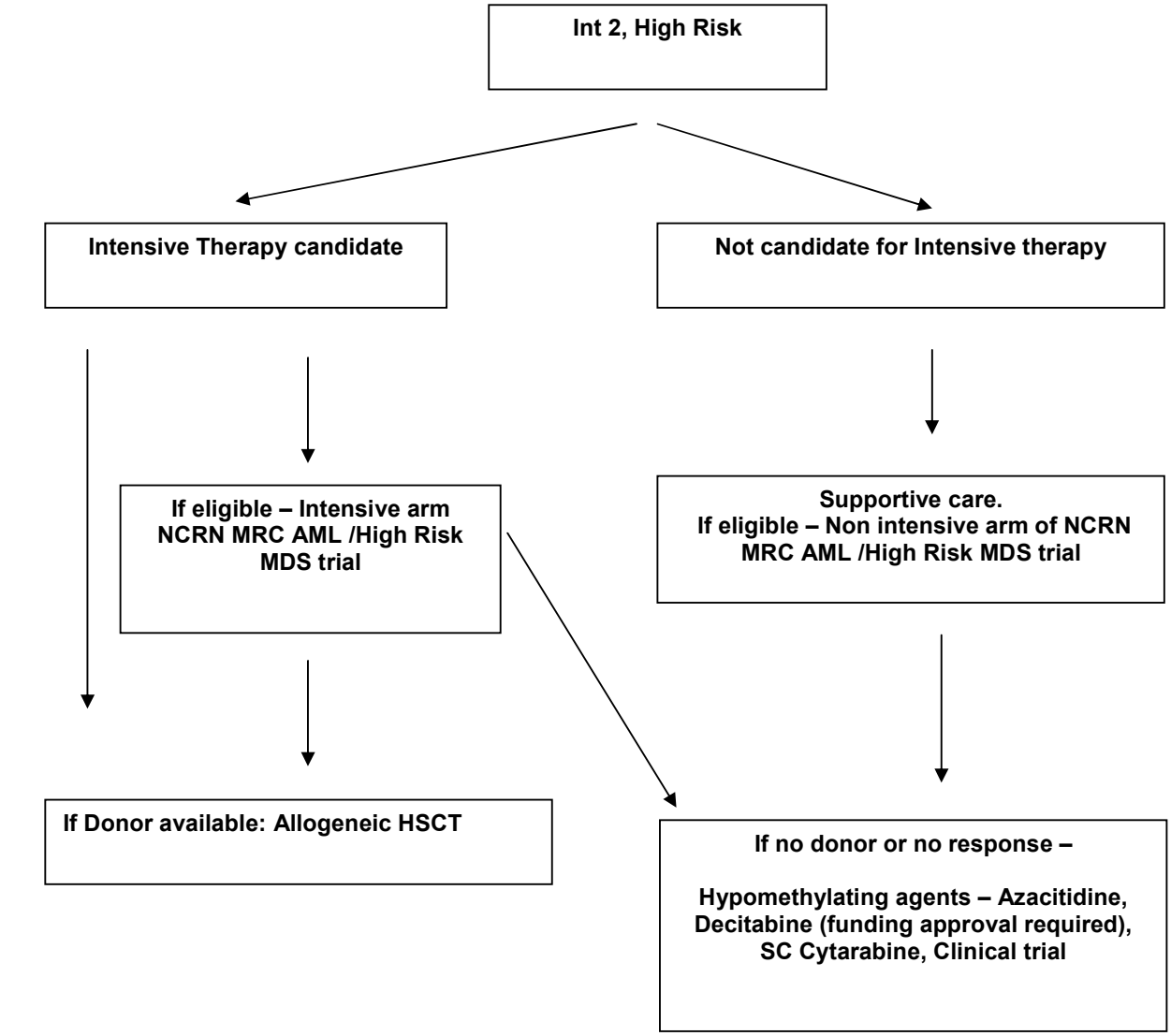
4.1 Recommendations for Treatment of Lower Risk MDS

Flow chart 2



4.2 Recommendations for Treatment of Advanced MDS

Flow chart 3



5.0 Guidelines for iron chelation in Myelodysplastic Syndromes

There is some evidence, albeit retrospective, that transfusional iron overload can lead to an increase in morbidity and mortality in MDS patients.
Primary organ systems affected are – cardiac, liver & endocrine. See references.

5.1 Recommendations for Patient selection for Iron Chelation Therapy

Consider iron chelation in transfusion dependent patients with Low,Int 1 risk MDS and:

- Serum Ferritin > 1000 ug/l
- Consider entry in clinical trial (TELESTO)

Consider iron chelation in transfusion dependent patients with Int 2,High risk MDS and:

- Serum Ferritin > 1000 ug/l **and**
- Who are candidates for Allo HSCT or
- A life expectancy > 1year

5.1.1 Treatment options :

Clinical trial if eligible/available

There are 3 iron-chelating agents that are available worldwide. These are desferrioxamine, which is the old standard, deferiprone and deferasirox, which is a new oral agent.
Much more experience is available for the use of desferrioxamine. However, because desferrioxamine is administered by prolonged subcutaneous or intravenous infusion, it can be quite burdensome for patients and many may choose the alternative oral agent.

6.0 Appendix: Licensed indications for iron chelating agents

1. Desferrioxamine is indicated for:
Iron overload - acute iron poisoning; primary and secondary haemochromatosis including thalassaemia and transfusional haemosiderosis; in patients in whom concomitant disorders (e.g. severe anaemia, hypoproteinaemia, renal or cardiac failure) preclude phlebotomy; and for the diagnosis of iron storage disease and sideroblastic anaemia, auto-immune haemolytic anaemia and other chronic anaemias.
Aluminium overload - in patients on maintenance dialysis for end stage renal failure where preventative measures (e.g. reverse osmosis) have failed and with proven aluminium-related bone disease and/or anaemia, dialysis encephalopathy; and for diagnosis of aluminium overload.
Desferrioxamine mesilate has limited efficacy in children under three years of age

2.Deferiprone is indicated for the treatment of iron overload in patients with thalassaemia major when deferoxamine therapy is contraindicated or inadequate.

3.Deferasirox is indicated for the treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older.
Deferasirox is also indicated for the treatment of chronic iron overload due to blood transfusions when desferrioxamine therapy is contraindicated or inadequate in the following patient groups:
- in patients with other anaemias,
- in patients aged 2 to 5 years,
- in patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells).

7.0 References

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2.SELCN MDS guidelines
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9. Takatoku M et al. *Eur J H Haematol.* 2007;78:487-494.
10. Malcovati L et al. *J Clin Oncol.* 2005;23:7594-7603.
11. Wells RA et al. *Leuk Res.* 2008;32:1338-1353

APPENDIX A: Clinical Trials

Refer to the local research team who will provide on request an orientation handbook, list of current trials and associated trial protocols and summaries.

Contact numbers

MTW – Clinical Trials Office	01622 225 033
Darent Valley Hospital – Clinical Trials Office	01322 428 100 ext 4810
Medway Hospital – Clinical Trials Office	01634 825 094

East Kent Hospitals – Clinical Trials Office:

Solid Tumours (excluding Gynae)	01227 866 393
Gynae Clinical Trials	01843 234 343
Haematology Clinical Trials	01227864 129

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Document Location

The document is located in the Kent and Medway Cancer Network office, in hardcopy and electronic format. It is also located on the Kent & Medway Cancer Network Intranet: (http://www.kentmedwaycancernetwork.nhs.uk/).

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DATE OF NEXT REVIEW

This item is next to be reviewed in November 2012 by the HOG

Revision History

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