Bedfordshire, Luton and Milton Keynes Health and Care Partnership

NHS

Bedfordshire, Luton and Milton Keynes Area Prescribing Committee (BLMK APC)

Iron chelation agents for the management of iron overload in transfusion dependent low to intermediate 1 risk myelodysplastic syndrome (MDS)

June 2024

Version	1.1
Date approved	July 2024
Review date	July 2027

Acknowledgements:
With thanks to Vicky Gibson, Senior Pharmacist – Clinical Quality, PrescQIPP CIC, for support with the evidence review and summary.
Thames Valley Priorities Committee Commissioning Policy Statement Policy No. TVPC79
Iron Chelation in Myelodysplastic Syndrome (MDS) December 2018

The following organisations contribute to and participate in the BLMK APC – Bedfordshire, Luton and Milton Keynes Integrated Care Board; Bedfordshire Hospitals NHS Foundation Trust; Cambridgeshire Community Services NHS Trust; Central and North West London NHS Foundation Trust; East London NHS Foundation Trust; Milton Keynes University Hospital NHS Foundation Trust

Summary of recommendations

- Iron chelation agents, deferasirox and desferrioxamine, will be commissioned for the management of iron overload due to blood transfusions on a restricted basis when the following conditions are met;

- Patient has been reviewed by a multidisciplinary team (MDT) decision and either:
  - Low risk MDS patients with a very good prognosis (greater than 2 years with an IPSS-R score of 3.0 or less), who have received at least 20 units of red blood cells or when the ferritin is 1000ug/l or more.
  - Patients who are transplant (allogeneic stem cell transplantation) eligible with high risk forms of MDS as defined by the MDT.

- Patients should have ferritin levels measured every 12 weeks.

- Iron chelation with desferrioxamine should be stopped if the ferritin falls below 1000ug/l, or 500ug/l with deferasirox.

- Deferiprone is **not recommended** for iron chelation in MDS patients.

Key points

- Myelodysplasia or the myelodysplastic syndromes (MDS) (also known as MDS or myelodysplasia) are a group of haematological medical conditions characterised by ineffective and dysplastic haematopoiesis resulting in one or more cytopenias (i.e. anaemia, leukopenia, thrombocytopenia, pancytopenia) and an increased risk of acute myeloid leukaemia.
- Low prognostic risk MDS includes patients with IPSS low/intermediate 1 (INT-1) and IPSS-R intermediate, up to 3.5 points.
- Anaemia is usually the most common feature with symptoms including pallor, weakness and fatigue.
- Treatment with an Erythropoiesis-Stimulating Agent (ESA) or erythropoietin (EPO) such as epoetin alfa is considered the first line standard of care for appropriately selected low to intermediate-1 risk MDS patients, with symptomatic anaemia and HB<100g/l. Patients should fulfil criteria predictive of a response scoring 0 or 1 on the validated Nordic model scale.
- Many patients with MDS will eventually require repeated blood transfusions, with each unit of blood delivering 200-250mg of iron, and are therefore at risk from the complications of iron overload.
- Excessive iron accumulation leads to secondary end organ failure, including cardiac disease (i.e. arrhythmias such as atrial fibrillation or ventricular tachycardia, cardiomyopathy, heart failure), liver failure, cellular necrosis leading to hepatic necrosis and then cirrhosis. Other iron overload related complications include diabetes mellitus and hypothyroidism. Most complications of iron overload can be prevented or reversed before irreversible damage and dysfunction occurs.
- The iron chelation agents; desferrioxamine (DFO) administered as a subcutaneous infusion and the oral agents deferasirox and deferiprone, are used to remove the excess iron from the body, due to repeated transfusions.
- There is no NICE guidance available regarding the management of myelodysplastic syndromes including the place in therapy of iron chelation agents.

Key points (continued)

- Guidance published by the British Society of Haematology (BSH) in 2021 recommends that all suitable lower risk patients should be considered for iron chelation around the time they have received 20 units of red cells, or when serum ferritin is more than 1000ug/l. Patients should have ferritin levels measured every 12 weeks.
- There is limited comparative evidence between different iron chelation agents, and this lack of comparative randomised controlled trial evidence remains a key limitation in differentiating survival and clinical outcomes between desferrioxamine and deferasirox.
- Deferiprone is not licensed in MDS patients, and both deferiprone and deferasirox are only licensed when desferrioxamine is ineffective or contra-indicated. Whilst desferrioxamine is considered to be the most efficient iron chelator, BSH guidance recommends deferasirox as the drug of choice, due to real world experience and expert opinion indicating better patient tolerance and compliance. Deferiprone should not be used routinely in patients with MDS.
- In TELESTO, a multicentre, randomised double blind place controlled trial, 225 lower risk MDS patients who had received 15-75 packed red blood cell units and no severe cardiac, liver or renal abnormalities and a serum ferritin greater than 2247 pmol/L randomly received either deferasirox tablets (n=149) or matching placebo (n=76). Median event free survival (EFS) was reported to be 3.9 years [95% CI, 3.2 to 4.3 years with deferasirox] vs 3.0 years [CI 2.2 to 3.7 years with placebo] respectively; (hazard ratio 0.64 [CI, 0.42 to 0.96]). Adverse events occurred in 97.3% of deferasirox patients and 90.8% of placebo patients.
- Data from several prospective observational studies and systematic reviews suggests that iron chelation is associated with improvements in overall survival and may delay progression to AML. More data is required to confirm a definitive conclusion.
- The incidence of MDS in the UK is 3.72/100,000 population/year; it is predominantly a disease of the elderly (median age at diagnosis 75.7 years), and more common in men (approximately 2:1).
- The iron chelation agents are all listed as excluded high cost drugs in the NHS Payment Scheme. Cost of 28 days treatment based on drug costs only is estimated as £1290 – £2579 for deferasirox and £392 – £1176 for desferrioxamine. Homecare and activity costs may also apply.
- In 2010, the base case cost effectiveness of deferasirox versus DFO was estimated to be £20,822 per QALY gained, based on the data included in the observational study by Rose et al. A mean survival benefit for both forms of iron chelation therapy (ICT) was estimated as 4.5 years.
- An earlier cost utility analysis published in 2008 and based on comparative data between desferrioxamine and deferasirox in beta thalassemia patients calculated the incremental cost per QALY for deferasirox as £23,000.
- Costs of treatment with iron chelation agents may be offset by a reduction in secondary care activity costs for associated iron related co-morbidities, such as treatment for cardiac, liver and kidney co-morbidities.

Background

Myelodysplasia or the myelodysplastic syndromes (MDS) are a group of haematological medical conditions characterised by in effective and dysplastic haematopoiesis resulting in one or more cytopenias (i.e. anaemia, leukopenia, thrombocytopenia, pancytopenia), and an increased risk of acute myeloid leukaemia.[1] Prognosis is largely based on the marrow blast percentage, number and extent of cytopenias and cytogenic abnormalities, which are grouped according to the International Prognostic Scoring System (IPSS) and its revised version (IPSS-R). Low prognostic risk MDS includes patients with IPSS low/intermediate 1 (INT-1) and IPSS-R intermediate, up to 3.5

points. High risk MDS includes those with IPSS Intermediate 2 (INT-2)/high and IPSS-R; intermediate, high and very high (>3.5 points).[2]
Anaemia is usually the most common feature with symptoms including pallor, weakness and fatigue. Other symptoms of MDS include fever and infections (neutropenia) and increased bruising, petechiae, epistaxis, and mucosal bleeding (thrombocytopenia). Splenomegaly and hepatomegaly are common.[1]

Figure 1 shows the 2021 BSH suggested management algorithm for low risk MDS patients.

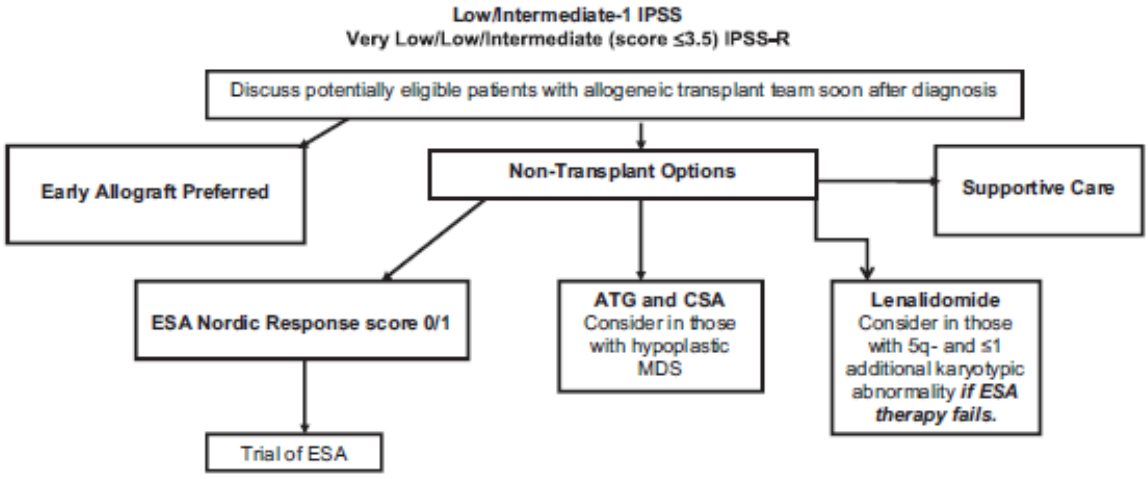

Figure 1 – Algorithm for the management of low risk MDS patients
(ATG = anti thymocyte globulin, CSA = ciclosporin A, ESA = erythropoiesis-stimulating agent, IPSS = International Prognostic Scoring System) Supportive care includes blood transfusions when needed for anaemia and antibiotics for the management of neutropenia and associated infection.[2]

Treatment with an erythropoiesis-stimulating agent (ESA) or erythropoietin (EPO) such as epoetin alfa is considered the first line standard of care for appropriately selected low to intermediate 1 risk MDS patients, with symptomatic anaemia and HB <100g/l. Patients should fulfil criteria predictive of a response scoring 0 or 1 on the validated Nordic model scale (see Table 1). There is data to suggest that starting ESA therapy within 6 months of diagnosis improves response rates and delays onset of transfusions (80 vs 35 months). Patients with higher risk MDS should not be considered for ESA therapy due to poor response rate, short survival and likely use of hypo methylating agents.[2] BSH currently recommends either epoetin alfa or darbepoetin alone in all patients. However, only epoetin alfa is currently licensed for the management of anaemia in MDS patients. [2,3,4,5]

Table 1 – Validated model for predicting response to erythropoietin.

Transfusion need	Point	S-EPO	Point
<2 units RBC/month	0	<500 u/l	0
≥2 units RBC/month	1	≥500 u/l	1

Predictive response to ESA: score 0 = 74%, score 1 point = 23%, score 2 points = 7%, RBC = red blood cells.[2]

However, many patients will eventually require repeated blood transfusions and are therefore at risk from the complications of iron overload. BSH guidance cites a treatment threshold for blood transfusions of 80g/dl haemoglobin.[2]

Each unit of red blood cells delivers 200-250mg iron with ineffective erythropoiesis also driving increased intestinal absorption of iron.[2] Excessive iron accumulation leads to secondary end organ failure, including cardiac disease (i.e. arrhythmias such as atrial fibrillation or ventricular tachycardia, cardiomyopathy, heart failure), liver failure, cellular necrosis leading to hepatic necrosis

and then cirrhosis, particularly if the liver iron concentration (LIC) exceeds 7mg/g dry weight. Other iron overload related complications include diabetes mellitus and hypothyroidism.[1,2]
Iron chelation agents are used to remove the excess iron from the body, due to repeated transfusions.[1,2] Most complications of iron overload can be prevented or reversed before irreversible damage and dysfunction occurs. Patients at risk of overload (those on regular transfusions) should be assessed for iron overload and the complications of iron overload as part of their annual review.[6]

There are currently 3 iron chelation agents available in the UK: desferrioxamine administered as a subcutaneous infusion and the oral agents; deferasirox and deferiprone.[7]

This briefing summarises the evidence for the use of iron chelators to manage iron overload and prevent the associated complications in patients with MDS who require or may have received repeated blood transfusions.

Evidence

There is no NICE guidance available regarding the management of myelodysplastic syndromes including the place in therapy of iron chelation agents.

Guidance published by the British Society of Haematology (BSH) in 2021 recommends that all suitable lower risk patients should be considered for iron chelation around the time they have received 20 units of red cells, or when serum ferritin is more than 1000ug/l. Patients should have ferritin levels every 12 weeks. Whilst the BSH guidance cites that desferrioxamine is the most efficient iron chelator and that deferasirox is only licensed for second line use after desferrioxamine, it also states that the real world and expert opinion indicates that deferasirox is better tolerated and compliance is superior, and therefore deferasirox is the drug of choice. Deferiprone should not be used routinely in patients with MDS and only after careful consideration with a haematologist experienced in treating MDS and weekly monitoring of blood counts. It is not licensed in MDS patients. Deferiprone should not be used where the baseline neutrophils are < 1.5 $x10^9$/L. [2,8,9,10]

European Society of Medical Oncology (ESMO) guidance, also published in 2021, strongly recommends iron chelation in all patients with transfusion related iron overload who are candidates for allogeneic stem cell transplantation (allo-SCT).[11]

Overall survival in transfusion dependant patients – ICT vs no ICT.
There is limited comparative evidence between different iron chelation agents, and this lack of comparative randomised controlled trial (RCT) evidence remains a key limitation in differentiating survival and clinical outcomes between desferrioxamine and deferasirox.

A Cochrane review published in 2014 aimed to review the evidence for the use of oral deferasirox for patients with MDS and identified 3 ongoing trials and one completed trial, however no data was available from any of these RCTs for inclusion in the review.[12] Only one of these, the TELESTO Study has been published in full to date. Originally planned and designed as a phase 3 trial, the TELESTO protocol was amended to phase 3 study with a reduced sample size from 630 to 210 participants due to low patient enrolment.

In TELESTO, a multicentre, randomised double blind place controlled trial, 225 lower risk MDS patients who had received 15-75 packed red blood cell units and had no severe cardiac, liver or renal abnormalities and a serum ferritin greater than 2247 pmol/L randomly received either deferasirox tablets (n=149) or matching placebo (n=76). The primary end point was event free survival (EFS), defined as time from date of randomisation to first documented non-fatal event, related to cardiac or liver dysfunction and transformation to acute myeloid leukaemia (AML) or death whichever occurred first. Median time on treatment was 1.6 years (interquartile range [IQR] 0.5-3.1 years) in the deferasirox group and 1.0 (IQR, 0.6-2.0 years) in the placebo group. Median EFS was reported to be 3.9 years [95% CI, 3.2 to 4.3 years with deferasirox] vs 3.0 years [CI 2.2 to 3.7 years

with placebo]; (hazard ratio 0.64 [CI, 0.42 to 0.96]). Adverse events occurred in 97.3% of deferasirox patients and 90.8% of placebo patients.

The total number of deaths during the study, including the follow up period, was 90; 57 (38.3%) patients in the deferasirox group and 33 (43.4%) in the placebo group. Median OS was 5.2 years (3.9 to not evaluable upper bound) in the deferasirox group and 4.1 years (CI 3.0 – 4.9 years) in the placebo group. However, calculated restricted mean survival test (RMST) at 3 years was similar in both groups (difference 1.2 months [CI -1.9 to 4.4 months]). Overall estimated survival probability at 3 years was 66.0% (CI 56.8% to 73.7%) for deferasirox patients and 58.9% (CI 41.6% to 72.6%) for placebo patients.[13]

Nine observational studies (4 prospective and 5 retrospective) were identified in a systematic review and meta-analysis by Zeidan et al in 2019 which aimed to look at the association between ICT and survival and/or rates of progression to AML. ICT was defined as the use of deferasirox, deferoxamine or deferiprone. The primary outcome of interest was survival reported as either median OS or a HR (adjusted for confounders as defined by each study between the 2 groups (i.e. ICT vs non-ICT groups)). No RCTs were identified. In total 2450 patients were included in the 9 studies, of whom 942 (38.4%) received ICT. Mean age was 72 years and most of the patients had IPSS scores of low to intermediate-1. The median OS among patients with ICT and patients receiving no ICT was reported in 6 studies and was consistently longer in the ICT group. The pooled estimate of the ratio median OS was 2.10 (95% CI 1.77-2.56), indicating the median OS from patients receiving ICT is approximately twice that of patients receiving no ICT. For patients with low to intermediate-1 risk MDS, ICT was associated with an overall lower risk of mortality (aHR 0.42; 95% CI 0.28-0.62; P <0.01).[14]

A recent analysis identified 12 studies involving 3396 patients (one randomised, n=225; 11 non randomised, n=3171), with 149/225 (66.2%) and 1057/3171 (33.3%) received ICT. The weighted overall mean age was 71.5 years with most patients having IPSS scores of low to intermediate-1. The median OS for patients receiving ICT was consistently longer compared to the non ICT consistently across the 9 studies which reported it. Meta analysis of the observational studies showed that ICT was associated with an overall lower risk of mortality [aHR 0.43, 95% CI 0.32-0.57, p<0.00001 I2=56%, p=0.02]. The aHT for the included RCT was 0.83 (95% CI 0.54-1.28).[15]

A prospective observational analysis conducted by Rose et al, identified 97 patients with low to intermediate-1 risk MDS who attended one of the treatment centres of the Groupe Francophone des Myelodysplasies (GFM) between 15th May and 15th June 2005. All 97 patients had been transfused as outpatients, with 44 (45%) receiving no ICT and 53 (55%) had received ICT, either desferrioxamine or deferasirox for at least 6 months. Progression to AML occurred in 14/44 (34%) of non-chelated patients and 9/53 (17%); p=0.087 of chelated patients. 66 of the 97 patients died, including 27 (27.8%) and 38 (40.2%) of the chelated and non-chelated patients respectively. Median OS from diagnosis was 53 months and 124 months in non-chelated and chelated patients; (p<0.0003), further adjusted to 130 months in chelated patients and 70 months in non-chelated patients if certain prognostic factors (age, IPSS and transfusion requirements) were taken into consideration. Causes of death did not differ significantly between groups.[16]

A more recent prospective non randomised analysis of the Canadian MDS registry published in 2017, identified 239 patients with IPSS low or intermediate risk 1 MDS at the time of first documented red blood cell transfusion dependence; 83 received iron chelation therapy (ICT) and 156 did not. Of the patients receiving ICT, 63 (75.9%) received deferasirox, 7 patients (8.43%) received desferrioxamine and 13 (15.7%) received desferrioxamine followed by deferasirox. Overall survival (OS) was defined as the time to death or last follow up measured from the date of first transfusion dependence. Leukaemia free survival (LFS) was defined as the time to AML progression, death or last follow up from transfusion dependence. Transfusion dependence was defined as receiving at least one RBC transfusion every 8 weeks over a 4 month period. Patients receiving ICT were then matched to non ICT patients in respect of age, IPSS scores, number of RBC units transfused per month and time from MDS diagnosis to transfusion dependence. No patients received deferiprone. Chelation patients were younger; 71 vs 76 years p=0.002, more likely

to have ring sideroblasts, and fall within a lower risk category (61% vs 43%; P=0.009). Chelated patients became transfusion dependent at a longer interval from MDS diagnosis than non ICT patients (median 18 months vs 6 months; P=0.003) and a higher serum ferritin at the time of transfusion dependence (median 1373 vs 697ug/l; P<0.0001). Characteristics which did not differ between groups included gender, ethnicity, IPSS score, WHO category, RBC units transfused per month and importantly there were no significant differences in frailty, comorbidity or disability scores between groups. Patients received ICT for a median of 12.4 months (range 1.2-123.5). Twelve patients (5%) underwent allogeneic SCT [5 ICT and 7 non ICT patients, P=NS]
From the time of RBC transfusion dependence, the OS was 2.9 [95% CI 2.2-3.6] years for all patients, but was longer for ICT versus non ICT patients (5.2 vs 2.1 years, P<0.0001). Despite restricting ICT to IPSS low and intermediate-1 risk MDS only, on further analysis 38 patients were found to have progressed to high and very high risk MDS prior to TD, however when these patients were excluded from the survival analysis (n=201), the results were maintained with OS for ICT vs non ICT patients reported as 5.5 vs 2.2 years; P=0.003).[17]

A separate analysis by Hoeks et al, published in 2020, identified 1161 low to intermediate 1 risk patients who received at least one red blood cell transfusion, of which 199 patients received iron chelation therapy, with either desferrioxamine, deferasirox or deferiprone. Mean age of chelated patients was 70 years versus the non-chelated patients (n=490); mean age 76 years. The hazard ratio for OS was 0.57 (95% CI 0.45 - 0.73). Out of the 199 chelated patients, 150 received deferasirox as the initial chelator, 36 desferrioxamine and 13 deferiprone. 22 patients switched from one chelator to another or were treated with all 3 chelators consecutively, but usually the treatment period of the second chelator was shorter than the treatment period of the first. The median time of chelation for all 199 patients was 13 months (range 3 - 41 months) and patients initially treated with desferrioxamine had inferior OS compared to deferasirox treated patients (adjusted HR: 2.46, 95% CI 1.12 - 5.41). The OS of the desferrioxamine treated patients was similar to non-chelated patients (adjusted HR: 0.98, 95% CI 0.52 - 1.86).[18]

Safety

Deferiprone is associated with agranulocytosis in 4% of patients.[2,10]

The main adverse events experienced with deferasirox are gastrointestinal (GI) disturbance, mainly diarrhoea and nausea, and decrease in creatinine clearance. High dropout rates of approximately 50% of patients within one year were observed in the majority of clinical studies with deferasirox, with gastrointestinal adverse events cited as the main reason. In the phase 3 trial by Gattermann et al, 66% of the 327 MDS patients experienced adverse events that were considered to be drug related, with diarrhoea, nausea, vomiting and abdominal pain reported in 33%, 12%, 8% and 8% of patients respectively. 25 patients discontinued due to GI adverse events. In the one year GIMEMA trial, only 43% of patients completed the trial, with 33% of patients citing adverse event as the reason for discontinuation and 45% of treatment related adverse events reported as GI in nature.[19]

In a German prospective, multicentre non interventional observational study, 429 patients with transfusion related iron overload were included in the safety analysis, of which 276 (68% had MDS) were receiving deferasirox; mean prescribing dosage 13.6mg/kg (range 10-<30mg/kg). Median duration of exposure to DF was 322 days (range 2-1078 days). Of 406 patients, 290 (72%) discontinued the treatment prematurely after a median time of 235 days (range 1-808 days), with 205 (70%) discontinuing treatment within the first 12 months. Discontinuation was reported to be due to the death of the patient in 83 (29%), adverse events in 67 (23%), lost to follow up in 28 (9.6%), progression of primary disease or progression to AML in 24 (8.2%), and deterioration of the general condition of the patient in 21 (7.2%) of cases. 377 patients (88%) experienced an AE. Gastrointestinal disturbance and a decrease in creatinine clearance were reported in 131 (31%) and 96 (22%) patients respectively. Diarrhoea (n=67; 16%) and nausea (n=45, 10%) were the most prevalent gastrointestinal disturbances.[20]

The following recommendations have been suggested to minimise or prevent GI disturbance with deferasirox:

- Consider pre-prandial evening dosing
- Take at least 30 minutes before food.
- Do not recommend take with food
- Initiate with low dose (500mg)
- Dose escalate to target in a timely fashion
- Calculate target dose based on serum ferritin and transfusion frequency
- BD dosing is not recommended due to negative impact on adherence, lack of PK data and expert opinion.[12]

Use of prophylactic proton pump inhibitors (PPIs) has not been shown to be beneficial – treat symptomatically if needed. Patients with lactose intolerance are infrequent – there is not enough evidence to recommend excluding lactose intolerance prior to treatment or to recommend the prophylactic use of Lactobacillus preparations. Potential effects of any new formulations need to be evaluated.[19]

Ocular and auditory effects are listed as uncommon adverse effects with both desferrioxamine and deferasirox. The BSH recommends that auditory and ocular assessments are conducted at baseline and repeated annually.[2,8,9,10]

Commissioning & Financial considerations

Desferrioxamine is licensed for the treatment of chronic iron overload, e.g. transfusional haemosiderosis in patients receiving regular transfusions. It is given by subcutaneous injection usually by an overnight infusion and many patients find it uncomfortable. Deferasirox and deferiprone are given orally. Deferasirox is also indicated for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in adult and paediatric patients with anaemias other than beta thalassemia, aged 2 years and older. Deferiprone is only licensed for the treatment of iron overload in patients with thalassaemia major. Both oral agents are only licensed in patients where desferrioxamine is contraindicated or inadequate.[2,8,9,10]

NHS England (NHSE) currently commission iron chelation therapy for the treatment of iron overload for transfused and non-transfused patients (all ages) with chronic inherited anaemias such as thalassaemia and sickle cell disease according to their published commissioning policies. Patients with transfusional iron loading due to other conditions such as myelodysplasia, aplastic anaemia and haematological malignancies, and patients with iron overload for other reasons, are excluded from these clinical commissioning policies and are not eligible for routine NHSE commissioning for treatment with iron chelation therapy.[22,23,24] Integrated Care Boards (ICBs) are responsible for commissioning all other local haematology services and conditions.[21]

With the delegation of commissioning of specialised services from NHSE to ICBs from April 2024, the commissioning responsibility of certain specialised services within haematology for adults and children has been delegated to ICBs whilst some highly specialised services remain with NHSE at the current time. The overall delegation of specialised services commissioning is an ongoing programme and is expected to be further updated in April 2025. At the time of this review, the commissioning responsibility for specialist haematology children services has been delegated to ICBs as from April 2024, whilst the specialist adult haematology service involving Castleman disease is considered to be suitable and ready for delegation to ICBs from April 2025, and the specialist adult haematology service involving thrombotic thrombocytopenic purpura (TTP) currently remains nationally commissioned. Regardless of the delegation status, NHSE has budgetary responsibility for high cost drugs (HCDs) within specialised services (until further notice).

Iron chelating drugs are currently already in use at Milton Keynes University Hospital (MKUH) in the management of MDS, as they have been following the Thames Valley Priorities Committee

Commissioning Policy for management of this condition from before they were transferred to the East of England regional network.[25] With a view to aligning the use of iron chelators in MDS across BLMK and to optimise choice of the available iron chelating drugs, BLMK APC has agreed to recommend commissioning based on the criteria outlined below.

Cost – drug costs only based on DM&D list prices and based on 70kg adult weight [26,27].

Deferasirox, deferiprone and desferrioxamine 500mg vials are listed in the primary care Drug Tariff and are also excluded high cost drugs listed in Annex A of the NHS Payment Scheme.[27,28] NHS payment scheme activity costs and homecare charges will also apply.[28] The ESAs, epoetin alfa, beta and zeta and darbepoetin are only excluded from the NHS payment scheme, where these are being used in patients also receiving renal dialysis; these agents are also listed in the primary care Drug Tariff.[27,28]

Table 2 – Drug costs – indicative only

Drug	Route	Daily dose	Daily dose for 70kg adult	Cost per mg (£)	Cost per day (£)	Cost per 28 days (£)
Deferasirox	Oral	14 - 28mg/kg/day	980 – 1960mg	0.047	£46.06 – 92.12	£1290 – 2579
Deferiprone	Oral	75mg/kg/day	5250mg	0.0026	£13.65	£382
Desferrioxamine	Slow S/C infusion	20 - 60mg/kg/day 5 - 7 times per week	1400 – 4200mg	0.01	£14 – 42	£392 – £1176

Cost effectiveness and impact

The incidence of MDS in the UK is 3.72/100,000 population/year; it is predominantly a disease of the elderly (median age at diagnosis 75.7 years), and more common in men (approximately 2:1).[2] In 2010, the base case cost effectiveness of deferasirox versus desferrioxamine (DFO) was estimated to be £20,822 per QALY gained, based on the data included in the observational study by Rose et al. A mean survival benefit for both forms of ICT was estimated as 4.5 years.[29]

An earlier cost utility analysis published in 2008 and based on comparative data between desferrioxamine and deferasirox in beta thalassemia patients calculated the incremental cost per QALY for deferasirox as £23,000.[30]

Costs of treatment with iron chelation agents may be offset by a reduction in secondary care activity costs for associated iron related co-morbidities, such as treatment for cardiac, liver and kidney co-morbidities.

Criteria for commissioning

Iron chelation agents, deferasirox and desferrioxamine, will be commissioned following a multidisciplinary team (MDT) decision to recommend treatment for:

- Low risk MDS patients with a very good prognosis (greater than 2 years with an IPSS-R score of 3.0 or less), who have received at least 20 units of red blood cells or when the ferritin is 1000ug/l or more.
- Patients who are transplant (allogeneic stem cell transplantation) eligible with high risk forms of MDS as defined by the MDT.

Review and Stopping criteria

Patients should have ferritin levels measured every 12 weeks. Ophthalmological and auditory examinations are required at baseline and then annually.[2]
Iron chelation with desferrioxamine should be stopped if the ferritin falls below 1000ug/l, or 500ug/l with deferasirox.[2]

Audit requirements

Baseline and outcome data must be submitted to the commissioner for the purposes of auditing this policy. Blueteq funding forms will be used to monitor outcomes and usage.

References

1. Myelodysplastic syndrome. BMJ Best Practice. Last updated 22nd September 2022. https://bestpractice.bmj.com/topics/en-gb/377?q=Myelodysplastic%20syndrome&c=recentlyviewed
2. Killick, S.B., Ingram, W., Culligan, D et al., British Society for Haematology guidelines for the management of adult myelodysplastic syndromes. British Journal of Haematology 2021; 194: 267 - 281. https://doi.org/10.1111/bjh.17612
3. Bohlius J, Bohlke K, Castelli R, et al. Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH Clinical Practice Guideline Update. Journal of Clinical Oncology 2019; 37:1336-1351. DOI: 10.1200/JCO.18.02142
4. Summary of Product Characteristics. Eprex 10,000 IU/ml solution for injection in pre-filled syringe. Janssen-Cilag Ltd. Last updated 7th July 2021. https://www.medicines.org.uk/emc/product/3443/smpc
5. Summary of Product characteristics. Aranesp solution for injection in pre-filled syringe. Amgen Ltd. Last updated: 06 Apr 2022. https://www.medicines.org.uk/emc/product/7993/smpc
6. Shah T, Porter JB, Sadasivam N et al. Guidelines for the monitoring and management of iron overload in patients with haemoglobinopathies and rare anaemias. British Journal of Haematology 2022; 196: 336-350. https://doi.org/10.1111/bjh.17839
7. Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press. https://bnf.nice.org.uk/ Accessed 5th May 2023.
8. Summary of Product Characteristics. Desferal Vials, 500mg. Novartis Pharmaceuticals UK Ltd. Last update 6th August 2020. https://www.medicines.org.uk/emc/product/3813
9. Summary of Product Characteristics Exjade 360 mg film-coated tablets. Novartis Pharmaceuticals UK Ltd. Last updated 30th November 2022. https://www.medicines.org.uk/emc/product/4329/smpc
10. Summary of Product Characteristics. Ferriprox 500 mg film-coated tablets. Last updated 24th February 2023. https://www.medicines.org.uk/emc/product/10908/smpc
11. Fenaux P, Haase D, Santini, V et al. Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up. Annals of Oncology 2021; 32: 142 - 156. https://doi.org/10.1016/j.annonc.2020.11.002
12. Meerpohl JJ, Schell LK, Rücker G et al.. Deferasirox for managing iron overload in people with myelodysplastic syndrome. Cochrane Database of Systematic Reviews 2014, Issue 10. Art. No.: CD007461. DOI: 10.1002/14651858.CD007461.pub3. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD007461.pub3/full
13. Angelucci E, Greenberg P, Izquierdo M et al. Iron Chelation in Transfusion-Dependent Patients With Low- to Intermediate-1-Risk Myelodysplastic Syndromes. Annals of Internal Medicine 2020; 173 (7): 595-596. https://doi.org/10.7326/L20-1056
14. Zeidan AM, Giri S, DeVeaux M et al. Systematic review and meta-analysis of the effect of iron chelation therapy on overall survival and disease progression in patients with lower-risk myelodysplastic syndromes. Annals of Haematology 2019; 98 (2) :339-350. https://doi.org/10.1007/s00277-018-3539-7
15. Yang S, Zhang MC, Leong R, et al. Iron chelation therapy in patients with low- to intermediate-risk myelodysplastic syndrome: A systematic review and meta-analysis. British of Journal of Haematology 2022; 197 (1): e9-e11. https://doi.org/10.1111/bjh.17998

16. Rose C, Brechignac S, Vassilief D et al. Does iron chelation therapy improve survival in regularly transfused lower risk MDS patients? A multicenter study by the GFM (Groupe Francophone des Myélodysplasies). Leukemia Research 2010; 34(7):864-70. https://doi.org/10.1016/j.leukres.2009.12.004
17. Leitch HA, Parmar A, Wells RA et al. Overall survival in lower IPSS risk MDS by receipt of iron chelation therapy, adjusting for patient related factors and measuring from time of first red blood cell transfusion dependence : an MDS-CAN analysis. British Journal of Haematology 2017; 179: 83-97. https://doi.org/10.1111/bjh.14825
18. Hoeks M, Yu G, Langemeijer S et al. Impact of treatment of iron chelation therapy in patients with lower risk therapy myelodysplastic syndromes participating in the European MDS registry. Haematologica 2020; 105(3): 640 - 651. https://doi.org/10.3324/haematol.2018.212332
19. Nolte F, Angelucci E, Breccia M, Gattermann N, Santini V, Vey N, Hofmann WK. Updated recommendations on the management of gastrointestinal disturbances during iron chelation therapy with Deferasirox in transfusion dependent patients with myelodysplastic syndrome - Emphasis on optimized dosing schedules and new formulations. Leukemia Research. 2015 Oct;39(10):1028-33. https://doi.org/10.1016/j.leukres.2015.06.008
20. Nolte F, Nückel H, Schmidt B, Geer T, Rubanov O, Hebart H, Jarisch A, Albrecht S, Johr C, Schumann C, Hofmann WK. Tolerability and efficacy of deferasirox in patients with transfusional iron overload: results from a German 2-year non-interventional study. Journal of Cancer Research & Clinical Oncology 2018; 144(8): 1531-1538. https://doi.org/10.1007/s00432-018-2665-x
21. NHS England. Prescribed specialised services manual. 22nd March 2023. https://www.england.nhs.uk/publication/manual-for-prescribed-specialised-services/
22. NHS England High Cost Drugs Commissioning list. Version 19, 2024-2025. Last updated 10th April 2024. Accessed 3rd June 2024. https://www.england.nhs.uk/publication/nhs-england-drugs-list/
23. NHS England. Clinical Commissioning policy: Treatment of iron overload for transfused and non-transfused patients with chronic inherited anaemia [16070/P]. 26th August 2016. https://www.england.nhs.uk/wp-content/uploads/2018/07/Treatment-of-iron-overload-for-transfused-and-non-transfused-patients-with-chronic-inherited-anaemias.pdf
24. NHS England. Clinical commissioning policy. Treatment of iron overload for transfused and no transfused patients with chronic inherited anaemias (all ages). (URN 2109) [221004P]. October 2022 version number: v1.0. https://www.england.nhs.uk/wp-content/uploads/2022/10/2109-Clinical-commissioning-policy-treatment-of-iron-overload-for-transfused-and-non-transfused-patients-with-.pdf
25. Thames Valley Priorities Committee Commissioning Policy Statement, Policy No 291 (TVPC79): Iron Chelation in Myelodysplastic Syndrome (MDS). Date of issue December 2018. tvpc291-iron-chelation-in-myelodysplastic-syndrome-mds.pdf (icb.nhs.uk)
26. NHS Prescription Services. dm&d browser, accessed 3rd June 2024. https://services.nhsbsa.nhs.uk/dmd-browser/
27. NHS Business Services Authority. Drug Tariff. June 2024. https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff
28. NHS England. 2023-2025 NHS Payment Scheme (amended) – Annex A, 2024-25 prices workbook. First published 30th March 2023, updated/reissued 27th March 2024. Accessed 3rd June 2024. https://www.england.nhs.uk/wp-content/uploads/2023/03/23-25NHSPS_Annex-A_2024-25.xlsx
29. Tolley K, Oliver N, Miranda E, Migliaccio-Walle K, Bozkaya D, Li Q. Cost effectiveness of deferasirox compared to desferrioxamine in the treatment of iron overload in lower-risk, transfusion-dependent myelodysplastic syndrome patients. Journal of Medical Economics 2010; 13(3): 559-70. https://doi.org/10.3111/13696998.2010.51
30. Karnon J, Tolley K, Oyee J, Jewitt K et al.. Cost-utility analysis of deferasirox compared to standard therapy with desferrioxamine for patients requiring iron chelation therapy in the United Kingdom. Current Medical Research & Opinion 2008; 24(6): 1609-21. https://doi.org/10.1185/03007990802077442