BJHaem
BRITISH JOURNAL OF HAEMATOLOGY
British Society for Haematology

Guidelines for the Management of Adult Myelodysplastic Syndromes

Journal:	*British Journal of Haematology*
Manuscript ID	BJH-2021-00641.R1
Manuscript Type:	Guidelines
Date Submitted by the Author:	10-May-2021
Complete List of Authors:	Killick, Sally; University Hospitals Dorset NHS Foundation Trust, Haematology Ingram, Wendy; University Hospital of Wales, Haematology Culligan, Dominic; Aberdeen Royal Infirmary, Haematology Enright, Helen; Adelaide and Meath Hospital, Department of Haematology Kell, Jonathan; Cardiff and Vale University Health Board , Haematology Payne, Elspeth; University College London Cancer Institute, Haematology; University College London Hospitals NHS Foundation Trust, Haematology Krishnamurthy, Pramila; King's College Hospital, Dept of Haematological Medicine Kulasekararaj, Austin; Kings college Hospital, Haematology Raghavan, Manoj; Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Department of Hematology Stanworth, Simon; John Radcliffe Hospital, NHSBT/Department of Haematology Green, Simone; Hull and East Yorkshire Hospitals NHS Trust, Haematology Mufti, Ghulam; King’s College Hospital, Department of Haematological Medicine Quek, Lynn; King's College Hospital NHS Foundation Trust, Department of Haematological Medicine Cargo, Catherine; St James's University Hospital, Haematology Jones, Gail; Newcastle Upon Tyne Hospitals NHS Foundation Trust, Haematology Mills, Juliet; Worcestershire Acute Hospitals NHS Trust, Haematology Sternberg, Alex; Great Western Hospitals NHS Foundation Trust, Haematology Wiseman, Daniel; Leukaemia Biology Laboratory, Cancer Research UK Manchester Institute, The University of Manchester, Manchester, UK., Leukaemia Biology Laboratory Bowen, David; Leeds General Infirmary, Department of Haematology
Key Words:	Myelodysplastic syndromes, MDS, Guideline, Management

Guidelines for the Management of Adult Myelodysplastic Syndromes

SB Killick[1], W Ingram[2], D Culligan[3], H Enright[4], J Kell[2], E Payne[5], P Krishnamurthy[6], A Kulasekararaj[6], M Raghavan[7], S J Stanworth[8], S Green[9], G Mufti[6], L Quek[6], C Cargo[10], GL Jones[11], J Mills[12], A Sternberg[13], DH Wiseman[14], and D Bowen[10]

[1]University Hospitals Dorset NHS Foundation Trust, The Royal Bournemouth Hospital, [2]University Hospital of Wales, Cardiff, [3]Aberdeen Royal Infirmary, [4]Tallaght University Hospital, Dublin, Trinity College Medical School, [5]University College London Cancer Institute, [6]Kings College Hospital NHS Foundation Trust, London, [7]University Hospitals Birmingham NHS foundation Trust, [8]Oxford University and Oxford University Hospitals NHS Trust & NHS Blood and Transplant, [9]Hull and East Yorkshire Hospitals NHS Trust, [10]St.James's Institute of Oncology, Leeds Teaching Hospitals, [11]Newcastle Hospitals NHS Foundation Trust, [12]Worcestershire Acute Hospitals NHS Trust and Birmingham NHS Foundation Trust, [13]Great Western Hospitals NHS Foundation Trust, Swindon, [14]The Christie NHS Foundation Trust, Manchester

Correspondence PRIOR TO PUBLICATION:

Dr Sally Killick

E-mail: sally.killick@uhd.nhs.uk

Correspondence:

BSH Administrator,

British Society for Haematology,

100 White Lion Street,

London, N1 9PF, UK

E-mail: bshguidelines@b-s-h.org.uk

KEYWORDS: Myelodysplastic syndromes, MDS, guideline, management

Scope

This document represents an update of the British Society of Haematology guideline published in 2014 due to advances in understanding the biology and therapy of the myelodysplastic syndromes (MDS)[1]. The objective of these guidelines is to provide healthcare professionals with clear guidance on the management of adult patients with MDS. Individual circumstances may dictate an alternative approach. A separate BSH guideline covers the Diagnosis and Evaluation of Prognosis of Adult MDS which is published alongside this guideline. A separate good practice paper detailing the management of patients with chronic myelomonocytic leukaemia (CMML) will follow and is not considered in these guidelines.

Methodology

These guidelines were compiled according to the BSH process https://b-s-h.org.uk/media/16732/bsh-guidance-development-process-dec-5-18.pdf. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org.

Literature review details

The guideline group was selected to be representative of UK medical experts and the manuscript was reviewed by the UK MDS Patient Support Group. Recommendations are based on a review of the literature using Medline/Pubmed searches. Search terms included: Myelodysplasia, MDS, myelodysplastic, refractory an(a)emia, refractory cytopenia, deletion 5q, del(5q), management, treatment, transfusion, supportive care, iron chelation, growth factors, erythropoietin, TPO agonists, thrombopoietin agonists, romiplostim, eltrombopag, immunosuppression, lenalidomide, azacitidine, decitabine, chemotherapy, luspatercept, bone marrow transplantation, stem cell transplantation

Only English language publications from 2012 to December 2020 were included in the literature search. Additional searches using subsection heading terms were conducted by members of the writing committee at the time of final submission to the British Journal of Haematology. Titles and/or abstracts of publications obtained from the database searches described were curated and manually reviewed by members of the writing committee.

Review of the manuscript

Review of the manuscript was performed by the BSH Guidelines Committee Haemato-oncology Task Force, the BSH Guidelines Committee and the haemato-oncology sounding board of the BSH. It was also posted on the members section of the BSH website for comment. This guideline has also been reviewed by patient representatives from the MDS UK Patient Support Group (https://mdspatientsupport.org.uk). These organisations do not necessarily endorse the contents.

77

Introduction

The myelodysplastic syndromes are a group of clonal bone marrow neoplasms characterised by ineffective haematopoiesis and manifested by dysplasia of haematopoietic cells and by peripheral cytopenia(s)[2]. They have a variable predilection for the development of acute myeloid leukaemia (AML). 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)[3].

Patients with suspected MDS should be assessed by a haematologist with a specialist interest in the disease. They should be referred for a second opinion to a regional or national centre when required by the clinician, or requested by the patient. All patients with a diagnosis of MDS must be discussed at a multi-disciplinary team meeting (MDT), which should include allogeneic stem cell transplant representation. All patients diagnosed with MDS should be reported to the National Cancer Registry, via the MDT, and to MDS-specific registries if appropriate.

Management recommendations for MDS have largely evolved and been driven through the International Prognostic Scoring System (IPSS) and its revised version IPSS-R. 'Low-risk' MDS includes patients with IPSS Low/Intermediate-1 (INT-1) and IPSS-R Very Low, Low and Intermediate (up to 3.5 points[4]. 'High-risk' MDS includes those with IPSS Intermediate-2 (INT-2)/High and IPSS-R Intermediate (>3.5 points), High and Very High. Patients should be managed according to their individual clinical and biological characteristics and by patient and physician preferences. The IPSS-R should be used to evaluate prognosis in all patients.

Where available, all patients should be offered clinical trials and/or prospective Registry programmes to maximize information about the natural history and treatment of MDS in order to benefit future patients.

Supportive Care

Supportive care, including transfusions and antibiotics, is central to the management of MDS patients.

Management of Anaemia with Transfusion

Red cell transfusion dependency is associated with decreased overall and leukemia-free survival in MDS, and reduced quality of life (QoL)[5–7]. Transfusion therapy is associated with well recognised complications including risks of alloimmunisation[8,9]. Antibodies to Rh and K antigens appear the most common[10], but the exact role and cost-effectiveness of extended red cell phenotyping remains unknown and local practices vary[11]. Irradiated blood products are recommended after a stem cell transplant or treatment with antithymocyte globulin (ATG), in keeping with the current BSH Guidelines on the use of irradiated blood components[12].

Although the severity of anaemia has a major impact on QoL in MDS patients[13], the degree to which this may be ameliorated by different policies for red cell transfusion is not known. Clinicians may choose to apply a policy for red cell transfusion that is individualised and targeted to symptoms, although in practice specific haemoglobin (Hb) thresholds are often applied. A common haemoglobin threshold of around 80 g/l was identified by a UK national audit, a survey in Australia[14] and findings from the European MDS Registry (EUMDS)[13]. The only randomised trial of transfusions in MDS

patients compared two transfusion thresholds (80 g/l, to maintain Hb 85-100 g/l against 105 g/l, maintaining 110–125 g/l)[15]. In an exploratory analysis, the five main QoL domains were improved for participants in the liberal compared to restrictive arm.

Management of Neutropenia and Infection

National Institute for Health and Care Excellence (NICE) has published guidelines for the prevention and management of neutropenic sepsis in cancer patients (CG151 published September 2012)[16]. The use of prophylactic granulocyte-colony stimulating factor (G-CSF) may be considered in patients with recurrent infections who have low-risk MDS and may be used (with prophylactic antibiotics) to support the delivery of azacitidine in selected higher-risk patients.

Although a randomised, multi-centre study showed that in patients undergoing chemotherapy, posaconazole prevented invasive fungal infections more effectively than did either fluconazole or itraconazole and improved overall survival (OS)[17], there is no evidence to suggest that this should be routinely given to all patients with MDS. The American Society of Clinical Oncology and Infectious Diseases of America guidelines suggest that a mould-active triazole is recommended for patients who are at risk of profound, protracted neutropenia (defined as $<0.1\times10^9$/l ≥7 days, or other risk factors)[18].

Management of Thrombocytopenia and Bleeding

There is common but variable practice of platelet transfusion in MDS. There are no similar studies in MDS, but a retrospective study in patients with stable chronic severe aplastic anaemia desribed a ‘no-prophylaxis’ platelet

transfusion approach[19–21]. Avoiding unneccesary platelet transfusions in patients without signs of bleeding reduces the need for outpatient attendance improving QoL and may reduce the risk of platelet refractoriness. Patients with chronic thrombocytopenia presenting with bleeding of WHO grade 2 or above should receive platelet transfusions.

Alternative agents to platelet transfusions include the antifibrinolytic drug tranexamic acid and should be considered as a symptomatic measure in mucous membrane bleeding in appropriate patients with MDS, although randomised trial evidence is lacking[22].

Thrombopoietin receptor agonists (TPO-RA) specifically romiplostim and eltrombopag, have been evaluated in randomised placebo-controlled studies in both low-risk MDS and high-risk MDS (the latter in combination with either chemotherapy, hypomethylating agents or lenalidomide)[23-29]. There were fewer bleeding episodes and fewer platelet transfusion episodes in the romiplostim arm in the Low/INT-1 study, although this study was halted prematurely because of concerns about increasing blast cell counts in patients receiving active drug[25]. A subsequent meta-analysis of several such studies did not find a significant difference in transformation to AML between intervention with TPO-RAs and placebo[30]. A moderate reduction in bleeding events compared with placebo controls was noted, but with no improvement in mortality. Ongoing studies are evaluating the safety and efficacy of eltrombopag in Low/INT-1 MDS with severe thrombocytopenia (<30×10^9/L), and interim analysis has shown platelet responses in 47% of the eltrombopag group compared to 3% in the placebo group[31].

Although their use in high-risk MDS cannot be recommended, the results are promising for TPO-RA with platelet responses in low or intermediate-1 risk MDS (47–65%)[24,31]. TPO-RA are not currently licenced for use in MDS and although these agents should ideally be accessed within clinical trials, the overall safety data now with longer follow-up is reassuring.

Spiritual/Emotional Health Needs

The diagnosis of MDS is often overwhelming to the patient and his or her family. It can be a difficult diagnosis for the patient to understand, and there may be many treatment options (both active and supportive) to consider, including clinical trials. All patients should be offered support by a local Clinical Nurse Specialist with experience in MDS. Support groups such as the UK MDS Patient Support Group (www.mdspatientsupport.org.uk), Leukaemia Care (www.leukaemiacare.org.uk) or Blood Cancer UK (www.bloodcancer.org.uk) are valuable resources for all patients and relatives, both at diagnosis and during their treatment pathway. There is evidence that disease-specific patient information should be re-discussed regularly with patients, at least on an annual basis[5].

Recommendations:

- **Supportive care should be offered to all patients with MDS and symptomatic cytopenias (1A).**
- **Red cell transfusions should be given to improve symptomatic anaemia (1A).**

- **Policies for transfusion, including haemoglobin thresholds for red cell transfusion, should take clinical factors into consideration, including patient-related factors (1A).**
- **Matching for Rh, K or additional antigens should be offered in line with current BSH guidelines for patients expected to receive regular red cell transfusions (2C).**
- **Local policies should be in place for the management of neutropenic sepsis (1A).**
- **Patients with stable MDS not receiving intensive chemotherapy and without signs of bleeding should not be offered prophylactic platelet transfusions (1A).**
- **TPO-receptor agonists may be used to reduce bleeding events in thrombocytopenic patients with low or intermediate-1 risk MDS (1A).**
- **Emotional health needs should be continually assessed and addressed. Disease-specific information should be re-iterated regularly. Information regarding how to access MDS patient support groups should be offered.**

Management of Low-Risk MDS

The clinical sequelae encountered in low-risk MDS patients relate to the depth of cytopenias. An algorithm for the management of lower risk MDS is shown in Figure 1.

Erythropoiesis-Stimulating Agents (ESAs)

It is only recently that randomised controlled trials for ESAs have been performed in the EU[32,33] and these have led to the European license of EPO-α (Eprex®), but not darbepoetin (Aranesp®), for the treatment of symptomatic anaemia (haemoglobin ≤100 g/l) in adults with IPSS Low- or INT-1 primary MDS who have low serum EPO levels (<200 iu/l). There is a suggestion of survival advantage for responders to ESA therapy, especially if they are non-transfused prior to starting ESA[34–36], and improvements in global QoL scores for responders[32,37,38].

Who Should be Offered ESA Therapy?

ESA therapy is considered first-line standard of care for appropriately selected low-risk MDS patients who should have pre-treatment variables that predict a response. The validated Nordic score, shown in Table 1, has been widely used[37]. An alternative model is the ITACA scoring system[39]. As the Nordic model more effectively identifies likely non-responders, it remains the preferred model.

ESA therapy should be considered in patients with Low or INT-1 IPSS (or IPSS-R Very Low, Low or Intermediate with a risk score of up to 3.5), in the context of symptomatic anaemia and Hb <100 g/l. If patients are symptomatic from anaemia at a higher Hb, then starting an ESA is at the clinician's discretion. Patients should fulfil criteria predictive of response by the Nordic Score (score 0–1). There are data to suggest that starting ESA therapy within 6 months of diagnosis improves response rates and delays the onset of transfusions (80 months vs. 35 months)[34,40]. Patients with higher-risk MDS should not generally be considered for ESA therapy because of poor

responses, short survival and the likely use of hypomethylating agents and stem cell transplantation, which require red cell transfusion support.

Initial Treatment

Treatment should be initiated with EPO-α or darbepoetin alone in all patients. The recommended starting dose for EPO-α is 30,000–40,000 units subcutaneous once weekly for eight weeks (mds-europe.eu)[32,41]. If there is no response at eight weeks, the dose can be increased to a maximum dose of 60,000 units/week (divided over one or two doses) for a further 8 weeks. Doses of >60,000 units/week are not supported by scientific evidence. The starting dose for darbepoetin should be 300 µg once every 14 days or 150 µg once every 7 days (mds-europe.eu)[42,43]. This can be increased after eight weeks in non-responders to a maximum of 300 µg per week for a further eight weeks[44]. The starting dose in the randomised Phase 3 study[33] was 500 µg once every three weeks. However, 81% of patients had an increase in the dose to 500 µg every two weeks in the open-label period leading to a higher erythroid response. The starting dose of EPO-α or darbepoetin in low body weight with stable anaemia and always in the case of reduced renal function should be lower (mds-europe.eu).

Finally, it is recommended that all patients receive incremental therapy with ESA alone for 16 weeks, as above, and G-CSF is then added to the higher dose in all non-responders for a final 8-week trial[45,46]. G-CSF should be given to approximately double the starting white cell count (WBC) if $<1.5\times10^9$/l, or keep the WBC in the range $6–10\times10^9$/l. A starting dose of 300 µg per week or in 2/3 divided doses, rising to 300 µg three times per week in non-responders,

is appropriate. However, the dosing regimen should be tailored to individual patients according to need and response.

Response Monitoring, Criteria for Response and Long-Term Therapy

Response criteria for defining response[37] are as follows:

- Complete Erythroid Response: Achievement of Hb >115 g/l and transfusion independence
- Partial Erythroid Response: >20 g/l increment in Hb and transfusion independence, but Hb remains <115 g/l

Some patients may achieve potentially beneficial longer gaps between transfusions, although this is not a formally recognised response criterion. The risk of thrombosis in MDS patients responding to darbepoetin has been estimated at 2%[42] and between 0.3 and 1.1% in meta-analysis[45]. However, in the randomised trial of EPO-α there were no grade 3–4 thrombo-embolic or stroke episodes in 85 treated patients[32]. In the darbepoetin randomised controlled trial[33], 24 weeks of darbepoetin produced no new safety signals and only one thromboembolic event (PE) in the darbepoetin group. Although the risk of thrombosis is low, it seems appropriate to temporarily interrupt ESA therapy if there is a rapid rise in haematocrit, or if the Hb rises above 120 g/l. Lower doses can then be introduced with careful monitoring of response parameters.

Recommendations:

- **Patients with IPSS Low and Intermediate-1 (or IPSS-R Very Low, Low or Intermediate with a score up to 3.5) MDS with symptomatic anaemia, or asymptomatic anaemia and Hb < 100 g/l and who fulfil**

the criteria for a high or intermediate predictive Nordic score for response should be considered for a trial of therapy with an ESA (1A).

- **For maximum benefit, ESA treatment should be started as soon as appropriate after diagnosis of MDS and before established transfusion dependence (for maximum benefit) (1B).**
- **Patients should receive a maximum trial period of 24 weeks of therapy. This should comprise 8 weeks at the starting dose of ESA, a further 8 weeks at the higher doses, if required, and finally with the addition of G-CSF for a further 8 weeks, before considering the patient to have failed ESA therapy (2B).**
- **Patients achieving a complete or partial erythroid response by accepted criteria should continue on long-term therapy at the minimum dose of ESA required to maintain the response or until the response is lost (2B).**
- **The haemoglobin concentration should not be allowed to rise above 120 g/l (2C).**

Luspatercept

Luspatercept (Reblozyl) is a recombinant fusion protein that binds transforming growth factor-beta superfamily ligands to reduce SMAD signalling. It acts as an erythroid maturation agent, targeting later stages of erythropoiesis compared with conventional ESAs. Administration is by subcutaneous injection every 3 weeks. Luspatercept has been shown to reduce the severity of anaemia in patients with lower risk MDS and ring sideroblasts for whom ESA therapy has not been effective[47]. A double-blinded

placebo-controlled phase 3 trial (MEDALIST) reported transfusion independence for ≥ 8 weeks in 38% of patients in the Luspatercept arm versus 13% in the placebo arm (P<0.001)[47]. It was generally well tolerated. Luspatercept received FDA approval in April 2020 for MDS-RS patients of very low, low or intermediate-risk IPSS-R risk status who require ≥2 units of red blood cells per 8 weeks and have previously failed ESA therapy. EMA approval followed in June 2020. At the time of writing Luspatercept does not have a marketing authorisation in the UK and so cannot currently be recommended for UK use.

Iron Chelation in MDS

Patients with MDS are at risk of developing iron overload from transfusion of red cells where iron build up is inevitable (1 unit of red blood cells delivers 200–250 mg iron), and there is also increased intestinal absorption of iron driven by ineffective erythropoiesis[48], mostly relevant to MDS with ring sideroblasts (MDS-RS). Excessive iron ultimately leads to secondary end organ damage and cardiac disease remains the main non-leukaemic cause of death in MDS[49,50].

Iron Overload is Associated with Adverse Outcome in MDS

Retrospective studies have shown that OS is significantly shorter in transfusion-dependent MDS patients either through cardiac deaths, hepatic cirrhosis[51,50] or increased leukaemic progression[50]. The European LeukemiaNet MDS Registry showed that the risk of death in transfusion-dependent patients with detectable labile plasma iron levels is independent of risk of disease progression[52]. Iron overload also increases transplant related

mortality in haematopoietic stem cell transplantation (HSCT) in MDS patients[53] and total transfusion burden implied a worse prognosis in a European Society for Blood and Marrow Transplantation (EBMT) study[54].

Measuring Iron Loading

Routine estimations of iron loading can be made by serial monitoring of ferritin and tracking of red cell units transfused. However, there is little correlation between units transfused, or serum ferritin, and the degree of organ iron deposition. MR imaging for R2 (liver proton relaxation rate)[55], or cardiac & liver T2* assessments[56] can be used to help quantify hepatic and cardiac iron loading and its impact on organ function.

Iron Chelation Can Improve Natural History

Effective iron chelation may improve haemopoiesis. The EPIC study[57] and the GIMEMA group[58] showed an International Working Group (IWG) erythroid response in 15–25% of patients although median response duration was only 8 weeks in the EPIC study. Platelet and neutrophil responses were also reported.

Desferrioxamine has been shown to lower cardiac iron assessed by magnetic resonance imaging measurements[59] and deferasirox has been shown to improve alanine transaminase (ALT) levels[60]. A German registry study showed that chelation therapy improved survival in almost 200 transfused lower risk MDS patients[61], supported by prospective data from the EUMDS Registry[62]. Furthermore, it is now accepted that iron chelation prior to HSCT in congenital anaemia can improve transplant-related mortality[53]. Although this is not yet proven to be the case in haematological neoplasms including MDS, a

recent EBMT joint expert panel recommend chelation in patients who have received more than 20 units of blood prior to HSCT[63].

Choice of Iron Chelator

Desferrioxamine remains the most efficient iron chelator available and is given subcutaneously in overnight infusions, which may decrease the labile iron pool. However, many patients find it uncomfortable and cumbersome, reporting quality of life issues. Deferasirox and deferiprone are given orally and are generally well tolerated, although deferiprone is associated with agranulocytosis in around 4% of patients. Deferiprone should not be used routinely in patients with MDS, and only after careful consideration with a haematologist experienced in treating MDS. It should be undertaken with very careful monitoring (weekly blood counts), and should not be used where the baseline neutrophils are $<1.5\times10^9$/L. Deferasirox is the only iron chelator currently licensed for use in MDS patients with proven reduction in labile iron and improved haemopoiesis in some patients[57,64].

Discussion of Recommendations:

Iron Chelation in Lower Risk MDS Patients

It is recommended that all suitable lower risk patients (IPSS Low and Intermediate-1; IPSSR Low and Very Low) should be considered for iron chelation therapy around the time they have received 20 units of red cells, or when the ferritin is more than 1000 µg/l. Patients should have ferritin levels measured every 12 weeks and have ophthalmological and auditory examinations before commencing therapy and annually while on treatment. Iron chelation with deferasirox should be stopped if the ferritin falls below

500 µg/land desferrioxamine should be stopped if the ferritin falls below 1000 µg/l.

Iron Chelation in Higher-risk MDS Patients

Patients who are considered suitable for HSCT should have iron levels monitored and iron chelation therapy given prior to transplant, if time allows.

Drug recommendations

Deferasirox is only licensed second line (after desferrioxamine) for the treatment of chronic iron overload due to blood transfusions in patients with anaemia, such as MDS. However, real world experience is that deferasirox is better tolerated, compliance is far superior and safety data is now mature. For these reasons, expert opinion is that deferasirox is the drug of choice for transfusion-related iron overload in patients with MDS. Desferrioxamine remains an option in those resistant to or intolerant of deferasirox. The two drugs may be combined in exceptional circumstances with heavy cardiac iron overload, but only under the supervision of a haematologist experienced in MDS treatment, although there are no data to support the combination.

There is no contra-indication to the use of iron chelation in combination with other disease modulating treatments such as lenalidomide or azacitidine.

Recommendations:

- **All suitable lower risk (IPSS Low and Intermediate-1; IPSS-R Low and Very Low) should be considered for iron chelation therapy at the time they have received 20 units of red cells, or when the ferritin is more than 1000 µg/l (1B).**

- **Iron chelation therapy should be considered in patients prior to stem cell transplant, if time allows** ~~**. Urgent transplant should not be delayed for iron chelation therapy**~~ **(2C).**
- **Expert opinion is that deferasirox (although only licensed second line in MDS) is the drug of choice based on tolerability, compliance and mature safety data (2C).**
- **Deferiprone is not routinely recommended in MDS (2C).**
- **Iron chelation therapy with deferasirox should be stopped if the ferritin falls below 500 µg/l and desferrioxamine should be stopped if the ferritin falls below 1000 µg/l (2C)**

MDS Associated with del(5q)

MDS with isolated del(5q) is a distinct diagnostic entity that features macrocytic anaemia, normal or high platelet count, characteristic non-lobulated megakaryocytes and <5% bone marrow blasts. A single additional cytogenetic abnormality other than −7 or −7q is permitted within this diagnostic category. It is associated with female preponderance and has a relatively indolent natural history, with a median survival of 6 years in those with an IPSS score of 0[65]. Independent predictors for OS include transfusion dependence, age and thrombocytopenia[66].

Responses of patients with del(5q) MDS to ESA are inferior to that seen in low-risk MDS patients lacking del(5q) (39% v 52%)[67,68]. Nonetheless, given the established safety and efficacy data for ESA, ESA should be first-line therapy for symptomatic anaemia in lower-risk MDS patients with del(5q). The MDS004 study compared lenalidomide with placebo in Low and INT-1 transfusion-dependent MDS with del(5q); 58%, 42% and 6% of patients

receiving lenalidomide 10 mg, 5 mg or placebo, respectively, achieved transfusion independence[69]. Cytogenetic responses were also seen in the lenalidomide treatment groups. Lenalidomide is licensed for transfusion-dependent Low/INT-1 MDS with isolated del(5q) (with up to one abnormality other than -7/7q) and is recommended for NHS commissioning (NICE TA322) for such patients who have failed or are unresponsive to ESAs.

Concerns about the risk of progression to AML with lenalidomide have not been confirmed in retrospective studies[70,71], post-MDS-004 study monitoring[72,73], or a recent meta-analysis[74]. Rather, improved survival and reduced risk of transformation have been shown. Nonetheless, the MDS-004 study showed that progression to AML was 40% at 5 years compared to historically reported data of 20%. Follow-up studies have demonstrated that clonal evolution from existing or acquired *TP53* mutations result in higher rates of AML transformation in del(5q) MDS patients[75–77]. However, some *TP53*-mutated cases with del(5q) have durable (2–3 year) responses to lenalidomide. Thus, *TP53* mutation is not a contraindication to lenalidomide therapy, but requires careful discussion and monitoring in this subgroup. Thromboprophylaxis should be considered on an individual basis.

Selected patients may be candidates for allogeneic stem cell transplantation. Indications include:

- intolerance to or unsuitable for lenalidomide
- lenalidomide-treated patients who fail to achieve transfusion independence
- those with *TP53* mutation
- those with clonal or overt progression

- those with bone marrow fibrosis

Recommendations:

- **Patients with IPSS Low or INT-1 or IPSS-R with a score <3.5 and MDS with del(5q) and symptomatic anaemia and who fulfil the criteria for a high or intermediate predictive score for response, should be first considered for a trial of therapy with ESAs (1B).**
- **For transfusion-dependent patients unsuitable for a trial of ESAs, and for non-responders and patients losing their response to ESAs, who have IPSS Low or INT-1 MDS with del(5q), consider treatment with lenalidomide 10 mg daily for 21 days repeated every 28 days after careful discussion with the patient about risk and benefit (1B).**
- **Selected MDS patients with del(5q) and IPSS Low/INT-1 or IPSS-R with a score <3.5 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 (2B).**
- **Lenalidomide is not currently recommended for patients with del(5q) and bone marrow blasts >5% or multiple (complex) cytogenetic abnormalities in addition to del(5q) (neither of which fall into this diagnostic category) or patients with IPSS INT-2/High (2B).**

Hypoplastic MDS

Approximately 10–20% of MDS patients have decreased marrow cellularity[78]. The WHO classification of myeloid neoplasm designates this hypoplastic MDS (h-MDS), although does not assign it a distinct category[79]. Hypocellularity in

MDS can present diagnostic difficulties with other bone marrow failure (BMF) syndromes especially aplastic anaemia. A study integrating cytohistological and genetic features in adult patients with hypocellular bone marrows has led to proposed criteria to define h-MDS[78]. This separates patients into two distinct groups, one with features highly consistent with a myeloid neoplasm and one more consistent with a non-malignant BMF. The two groups have significantly different risk of blast progression and OS. Flow cytometric immunophenotyping for paroxysmal nocturnal haemoglobinuria should be performed in patients with h-MDS.

It would seem reasonable that those patients with h-MDS and features consistent with a myeloid neoplasm should have an MDS management strategy although tolerance and efficacy need to be considered. Allogenic stem cell transplantation may be considered for eligible patients. Conversely, those with features more in keeping with BMF should be considered for treatment strategies aimed at BMF, such as immunosuppression. The BSH guidelines for the Diagnosis and Management of Adult Patients with Aplastic Anaemia should be referred to for treatment strategies of BMF[80].

Curative Options in Low-Risk MDS; the Place of Allogeneic HSCT

See section on allogenic stem cell transplantation in MDS below.

Management of High-Risk MDS

Patients with high-risk MDS (INT-2/High IPSS or High/Very High IPSS-R scores) have a significant risk of progression to AML with a median survival of 0.8–1.6 years[81]. Some IPSS-R Intermediate Risk Group patients may also have early progression of disease and poor outcomes.

Strategies for those suitable for active therapy should be aimed both at improving cytopenias and altering the natural history of disease to delay progression to AML and improve survival. Patients should be given the opportunity to take part in appropriate clinical trials.

As allogeneic HSCT is the only therapy with curative potential, clinicians should initially determine at diagnosis whether a patient is a possible transplant candidate and review this regularly. Early discussion with a transplant unit is recommended.

An algorithm for the management of high-risk MDS is seen in Figure 2.

Intensive Chemotherapy for Patients Ineligible for Allogeneic HSCT

For patients not eligible for transplantation, intensive AML-style chemotherapy can be used in an attempt to achieve disease response and improve survival. Patients should be entered into clinical trials where possible. The advantages of intensive chemotherapy are the QoL improvement if complete remission (CR) is achieved, and the small possibility of long-term disease-free survival. There have been reported cases of long-term survival (>4 years) in patients with high-risk MDS and lacking an unfavourable karyotype[82]. However, older patients frequently have comorbidities, making intensive regimens less well tolerated. Overall, remission rates are lower (40-60%) than in *de novo* AML, remission duration is often shorter (median duration 10-12 months) and therapy-related complications of marrow aplasia (infection and haemorrhage) more frequent[82–85].

Analysis of 160 patients over the age of 60 years with high-risk MDS or AML showed an early death rate of 10% and an inability to deliver consolidation chemotherapy in 40 of the 96 (42%) patients who achieved CR[84]. Compared to those with a normal karyotype who had a median survival of 18 months, those with a high-risk karyotype (involving ≥3 unrelated abnormalities or chromosome 7 abnormality) had a median survival of 4 months. The largest study of intensive chemotherapy for high-risk MDS broadly supports these data[86]. For this reason, it is recommended that cytogenetic results are available before committing to intensive chemotherapy in older patients with MDS, as there is no evidence to suggest this delay in treatment would be detrimental[87].

Disease Modifying Agents in High-Risk MDS

Hypomethylating Agents

Hypomethylating agents (azacitidine, decitabine) offer an alternative to intensive treatment in high-risk MDS. They are not curative but may result in transfusion independence, improved QoL and survival benefit and are well-tolerated in the elderly and in patients with comorbidities.

Azacitidine

Azacitidine is recommended by NICE and the Scottish Medicines Consortium as a treatment option for adult patients with MDS not eligible for HSCT (IPSS INT-2 or High) and for AML with 20-30% blasts and multi-lineage dysplasia. The recommended dose is 75 mg/m^2 for 7 consecutive days, repeated at 28-day intervals.

The AZA001 study[88] showed that azacitidine significantly increased OS compared to conventional care regimens (median OS 24.5 months *versus* 15.0 months)[88]. Azacitidine also resulted in haematological responses; 45% of patients became transfusion independent compared to 11% receiving conventional care. In a subgroup analysis of patients ≥75 years, azacitidine also significantly improved 2-year OS compared to conventional care (55% vs 15%), suggesting that this is the treatment of choice in older higher-risk MDS patients with good performance status[89].

Even patients with poor prognosis cytogenetic profiles may benefit from azacitidine treatment[90]. Reliable molecular predictors of response have not been identified, although patients with poor-prognosis indicators, including *TP53* mutations may respond. However, the presence of increasing numbers of mutations may be associated with a lower likelihood of response[91].

Practical guidance for the delivery of azacitidine has been published[92]. Patients who receive less than 6 cycles or who fail to respond after 6 cycles have poor outcomes[93,94]. In the absence of progression and where azacitidine is tolerated, a minimum of 6 courses is recommended, with continued therapy for as long as response is maintained. Patients should have a marrow examination before starting treatment, after six courses (to assess response) and subsequently at clinician discretion should disease progression be suspected. In selected younger patients who achieve a CR with azacitidine and have good performance status, the option of HSCT should be re-visited. On-going studies are exploring the combination of azacitidine with other agents in high-risk MDS.

Azacitidine real world data

The benefits of azacitidine have largely (but not uniformly) been confirmed in 'real-world' studies. However, OS in four large data sets has not matched that reported in the original pivotal trial[88]. The Canadian, Spanish and French Groups reported OS for azacitidine-treated patients with higher-risk MDS of 12.4, 13.4 and 13.5 months, respectively[93–95].

Alternative dosing schedules

Alternative dosing schedules for azacitidine include 75 mg/m^2 for five days, no treatment for 2 days, and two further days of treatment (5–2–2); 50 mg/m^2 on a 5–2–5 schedule or 75 mg/m^2 for five days[96]. In the Canadian real-world study of high-risk patients there was no difference in OS for patients treated with azacitidine for 7 consecutive days compared with the 5–2–2 regimen[94],

and this is strongly preferred as the closest practical alternative if the licensed 7-day regimen is impractical.

Decitabine

Two Phase III studies comparing decitabine (15 mg/m^2 IV 8 hourly for three days every six weeks) with best supportive care in MDS have shown that some patients achieve CR, partial remission or haematological improvement. However, neither study showed significant improvement in OS[97,98]. In the ADOPT Phase II study of patients receiving decitabine 20 mg/m^2 for five days every four weeks[99], complete responses/marrow complete responses of 32% and red cell (33%) and platelet (40%) transfusion independence were observed. Median survival was 19.4 months.

No prospective randomised studies comparing azacitidine with decitabine have been reported in intermediate-2/high-risk MDS. Azacitidine is the preferred agent, and the only one approved for use in the UK.

Low Dose Chemotherapy

Although low-dose cytarabine (LDAC) has activity in high-risk MDS, the superiority of azacitidine over LDAC in the AZA 001 study renders LDAC therapy obsolete in high-risk MDS.

Low dose oral melphalan therapy could be considered for selective use in a rare group of patients, namely those with an excess of blasts (>5%) in a hypocellular marrow with a normal karyotype, for whom no alternative active therapy is available and/or appropriate. The majority of such patients will achieve complete remission with typical remission duration of 12 months[100]. Re-treatment will usually achieve a second remission but for a shorter

duration. At melphalan-refractory relapse, patients are usually chemotherapy resistant.

Recommendations:

High-Risk Patients NOT Eligible for Allogeneic Transplant

- **Patients requiring treatment should be considered for any appropriate clinical trial.**
- **In fit older patients lacking an adverse karyotype, the options of therapy with a hypomethylating agent versus intensive chemotherapy should be carefully discussed. Where intensive chemotherapy outside a clinical trial is planned, standard AML induction regimens should be used (2B).**
- **Azacitidine is the preferred hypomethylating agent and is recommended as first-line therapy for patients ineligible for stem cell transplant with IPSS Intermediate-2 and High-Risk MDS (IPSS-R Intermediate (score >3.5)/High/Very High-Risk groups) or AML with 20-30% blasts. Grade 1A (on the basis of a single randomised control trial).**
- **The recommended dose of azacitidine is 75 mg/m^2 daily for 7 consecutive days but a 5–2–2 schedule (with a 2 day weekend gap) is acceptable where it is not practical to offer 7 consecutive days and outcomes with the two schedules appear comparable (2B).**
- **Outcomes of patients treated with azacitidine in routine clinical practice show a considerably shorter overall survival than the pivotal clinical trial (12.4–18.9 months compared to 24.5 months). Patients should be made aware of this.**

- **Responding patients should continue azacitidine while their response is maintained (1A).**
- **The decision to stop or continue azacitidine in patients who fail to achieve any response after six cycles, but who have stable disease, is dependent upon clinician and patient preference (2B).**
- **Patients failing therapy with hypomethylating agents should be considered for any appropriate clinical trial.**

Allogeneic Haematopoietic Stem Cell Transplant in MDS

All transplant eligible MDS patients should be discussed with a transplant physician at an MDT, both at diagnosis and with disease progression. The decision to transplant should be made on a case-by-case basis, evaluating patient, donor and disease factors known to influence transplant outcomes[101].

Factors Influencing Timing and Decision to Transplant:

Lower-Risk MDS

The optimal time to transplant patients with lower-risk MDS remains an area of debate. Early transplant for the lowest risk patients is generally not recommended due to subsequent reduction in life expectancy[102–104].

To help guide decision-making, particularly in the IPSS INT-1 group, the ELN/EBMT guidelines[63] recommend the use of other poor prognostic factors such as transfusion dependency (≥2 units of blood per month), significant cytopenias e.g. platelet count $<30\times10^9$/l, neutrophils $<0.3\times10^9$/l, or very poor prognostic cytogenetics. Transfusion dependence, elevated ferritin and labile plasma iron levels correlate with increased transplant-related mortality (TRM) in MDS patients following transplantation[50,105–107]. Transplant should be

considered once the patient becomes transfusion dependent, before iron overload occurs. However, if there is a delay to transplant then iron chelation should strongly be considered.

Patients with progressive disease such as increasing blast cells or acquisition of adverse cytogenetic abnormalities should be considered for transplant[63]. Therapy failures, for example to ESAs or lenalidomide, convey a worse prognosis and should prompt consideration of transplantation[108,109]. Furthermore, patients with isolated del(5q) and an associated *TP53* mutation have a worse prognosis and greater chance of failing lenalidomide therapy[75,77]. Such patients should be considered for transplantation early in their disease course[110].

Patients with MDS and severe bone marrow (BM) fibrosis experience worse outcomes following HSCT compared with mild/moderate fibrosis, or those lacking fibrosis[111]. As such, the presence of BM fibrosis should prompt early transplant consideration, ideally prior to progression to severe fibrosis.

Higher-Risk MDS

Early allogeneic HSCT offers a survival advantage in higher-risk MDS and suitable patients should be referred promptly to a transplant centre[102–104,112]. Inferior survival outcomes for patients with excess BM blasts (>5%) at the time of transplant have been reported[113]. It remains unclear, however, whether cytoreduction prior to transplant improves outcomes (regardless of BM blast percentage) over upfront transplantation[114]. In the absence of prospective data, patients with >10% blasts may be considered for cytoreductive chemotherapy or HMA prior to transplant, particularly where immediate transplantation is not logistically possible[63]. Upfront transplantation

should be considered where BM blasts are 5–10% in patients with slowly progressing disease, taking into account other patient- and disease-related factors. Patients with a hypocellular BM or presence of increased BM fibrosis with BM blasts up to 10% may also be considered for upfront transplant as prolonged cytopenia may occur with chemotherapy.

Induction Chemotherapy v HMA prior to Allogeneic HSCT

Given the lack of available data from prospective, randomised trials, patients should be offered entry into a clinical trial, wherever possible. The ELN/EBMT support HSCT in suitable patients treated with HMA following attainment of complete remission (CR)[63]. However, emerging data from the VIDAZA ALLO study demonstrating early patient dropout due to treatment-related death or toxicity suggest that the number of HMA courses should be minimised[115]. For patients receiving induction chemotherapy, prolonged cytopenia may result; treatment should ideally be delivered once a donor has been identified (if a delay to commencing therapy is deemed acceptable).

Patients with a complex karyotype are more likely to exhibit *TP53* mutation, contributing to their poor prognosis and therefore we recommend that all patients with complex karyotype are screened for *TP53* mutation[110,116,117]. *TP53* mutation is associated with resistance to conventional chemotherapy and early relapse[116,117]. In contrast, comparable response rates are observed following treatment with hypomethylating agents for MDS patients with *TP53* mutation or wild type *TP53*[118–121]. Patients with complex karyotype in the absence of *TP53* mutation who require a reduction in blast count should be considered for clinical trials as there is no clear evidence to suggest whether intensive chemotherapy or HMA is better in this setting[122].

Mutation Analysis in Patients Referred for Allogeneic Transplantation

It is clear that *TP53* mutation correlates with higher relapse and poorer OS even after allogeneic HSCT, irrespective of the choice of conditioning[110,116,123–125]. The poorest outcomes are seen in patients with biallelic *TP53* mutation/loss, or in association with a complex monosomal karyotype[110], and therefore, transplant is generally not recommended for this group of patients outside of clinical trials. However, patients with a *TP53* mutation in the absence of a complex monosomal karyotype, or those with a monoallelic *TP53* mutation display relatively better outcomes and should therefore be considered for transplant[110,126]. Mutations in the *RAS* pathway, *JAK2, DNMT3A, TET2, ASXL1* and *RUNX1* genes have also been shown to correlate with poorer outcomes following transplantation[116,123–125] and might thus inform personalised transplantation decisions. Further studies are required to aid the role and timing of HSCT for such patient groups.

Patient Characteristics and Donor Selection

Patient age *per se* is not a limiting factor for transplant[113]. Careful selection of older patients (>70 years) with good performance status and low haematopoietic cell transplantation-specific comorbidity index (HCT-CI) improves outcomes[127]. Patients with high-risk MDS and high comorbidity scores (HCTCI ≥3) have the worst outcomes[128] and alternative treatments should be considered. Well-matched unrelated donor transplants increasingly show comparable survival to sibling transplants[129] whilst haploidentical/umbilical cord transplants may be options for fitter patients with high-risk disease lacking a suitably-matched unrelated donor[63].

Choice of Conditioning Regimen

The RICMAC trial showed no statistically significant difference in OS, RFS or cumulative incidence of relapse at 2 years with RIC (reduced intensity conditioning) or MAC (myeloablative conditioning)[130]. A similar prospective trial demonstrated higher relapse rates for RIC vs MAC (48.3% v 13.5% P<0.001) leading to early trial closure[131]. In keeping with ELN/EBMT guidance, high-risk patients with good performance status, lacking in comorbidity, may be candidates for MAC, reserving RIC for older, less fit patients[63].

Management of Relapse Post-Transplant

Currently there are no standardised recommendations directing choice of therapy for relapse post-HSCT and is therefore not discussed further in this guideline. Such patients may be best managed through accessing clinical trials where available.

Recommendations:

Allogeneic Transplant in MDS

- **All transplant-eligible MDS patients should be discussed with a transplant physician at a Multi-Disciplinary Team Meeting (MDT) both at diagnosis and at disease progression (2B).**
- **Additional prognostic factors such as transfusion burden, depth of cytopenias, cytogenetics and bone marrow fibrosis should be assessed when considering the optimal timing of transplant for lower-risk MDS patients (2B).**

- **Higher-risk MDS patients with >10% blasts should be considered for cytoreductive therapy or hypomethylating agents prior to transplant (2B).**
- **Upfront transplant may be considered in patients with 5–10% blasts with slowly progressive disease or in those with a hypocellular or fibrotic BM (2B).**
- **Transplant is not routinely recommended for patients with *TP53* mutation in association with a complex monosomal karyotype due to poor outcomes (2B).**
- **Eligibility for transplant should be guided by HCT-CI and EBMT risk score (2B).**
- **Performance status and age should be used to inform choice of myeloablative or reduced intensity conditioning (2B).**

Acknowledgments

All the authors contributed to the writing of these guidelines.

The writing committee would like to thank: the team of MDS experts at the MDS UK Patient Support Group for their critical review of the manuscript on behalf of the UK MDS Patient Group, Jacky Wilson for her help in undertaking the initial literature review, also the BSH Haemato-oncology task force, the BSH sounding board and the BSH guidelines committee for their support in preparing this guideline.

Declaration of Interests

All authors and the UK MDS Patient Support Group have made a declaration of interests to the BSH and Task Force Chairs which may be viewed on request.

Review Process

Members of the writing group will inform the writing chair if any new pertinent evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BSH guidelines website (https://b-s-h.org.uk/guidelines/).

Disclaimer

While the advice and information in this guidance is believed to be true and accurate at the time of going to press, neither the authors, the BSH nor the

802 publishers accept any legal responsibility for the content of this guidance.

Table 1: Validated model for predicting response to erythropoietin[37]

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

Abbreviations: ESA, erythropoietin-stimulating agent; RBC, red blood cells
Predictive response to ESA: Score 0=74%, Score 1 point=23%, Score 2 points=7%

REFERENCES

1. 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;164:503–525.
2. 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;127:2391–2405.
3. Roman E, Smith A, Appleton S, Crouch S, Kelly R, Kinsey S, et al. Myeloid malignancies in the real-world: Occurrence, progression and survival in the UK's population-based Haematological Malignancy Research Network 2004–15. Cancer Epidemiol. 2016;42:186–198.
4. Pfeilstocker M, Tuechler H, Sanz G, Schanz J, Garcia-Manero G, Sole F, et al. Time-dependent changes in mortality and transformation risk in MDS. Blood. 2016;128:902–910.
5. Sekeres MA, Maciejewski JP, List AF, Steensma DP, Artz A, Swern AS, et al. Perceptions of disease state, treatment outcomes, and prognosis among patients with myelodysplastic syndromes: results from an internet-based survey. Oncologist. 2011;16:904–911.
6. Malcovati L, Della Porta MG, Strupp C, Ambaglio I, Kuendgen A, Nachtkamp K, et al. Impact of the degree of anemia on the outcome of patients with myelodysplastic syndrome and its integration into the WHO classification-based Prognostic Scoring System (WPSS). Haematologica. 2011;96:1433–1440.
7. Wood EM & Mc Quilten ZK. Outpatient transfusions for myelodyplastic syndromes. Hematology Am Soc Hematol Educ Program. 2020;167–174.
8. Evers D, Middelburg RA, de Haas M, Zalpuri S, de Vooght KM, van de Kerkhof D, et al. Red-blood-cell alloimmunisation in relation to antigens' exposure and their immunogenicity: a cohort study. Lancet Haematol. 2016;3:e284–292.
9. Singhal D, Kutyna MM, Chhetri R, Wee LYA, Hague S, Nath L, et al. Red cell alloimmunization is associated with development of autoantibodies and increased red cell transfusion requirements in myelodysplastic syndrome. Haematologica. 2017;102:2021–2029.
10. Lin Y, Saskin A, Wells RA, Lenis M, Mamedov A, Callum J, Buckstein R. Prophylactic RhCE and Kell antigen matching: impact on alloimmunization in transfusion-dependent patients with myelodysplastic syndromes. Vox Sang. 2017;112: 79–86.
11. British Committee for Standards in Haematology, Milkins H, Berryman C, Cantwell J, Elliott C, Haggas C, Jones R, Rowley J, Williams M, Win N. Guidelines for pre-transfusion compatibility procedures in blood transfusion laboratories. British Committee for Standards in Haematology. Transfus Med. 2013;23(1): 3–35.
12. Foukaneli T, Kerr P, Bolton-Maggs PHB, Cardigan R, Coles A, Gennery A, Jane D, Kumararatne D, Manson A, New HV, Torpey N, BCSH Committee. Guidelines on the use of irradiated blood components. Br J Haematol. 2020;191(5): 701–724.
13. Stauder R, Yu G, Koinig KA, Bagguley T, Fenaux P, Symeonidis A, et al. Health-related quality of life in lower-risk MDS patients compared with

age- and sex-matched reference populations: a European LeukemiaNet study. Leukemia. 2018;32:1380–1392.
14. Mo, A., McQuilten, Z.K., Wood, E.M. & Weinkove, R. (2017) Red cell transfusion thresholds in myelodysplastic syndromes: a clinician survey to inform future clinical trials. Intern Med J, 47, 695–698.
15. Stanworth SJ, Killick S, McQuilten ZK, Karakantza M, Weinkove R, Smethurst H, et al. Red cell transfusion in outpatients with myelodysplastic syndromes: a feasibility and exploratory randomised trial. Br J Haematol. 2020;189(2):279–290.
16. Phillips R, Hancock B, Graham J, Bromham N, Jin H & Berendse S. Prevention and management of neutropenic sepsis in patients with cancer: summary of NICE guidance. BMJ. 2012;345:e5368.
17. Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med. 2007;356:348–359.
18. Taplitz RA, Kennedy EB, Bow EJ, Crews J, Gleason C, Hawley DK, et al. Antimicrobial Prophylaxis for Adult Patients With Cancer-Related Immunosuppression: ASCO and IDSA Clinical Practice Guideline Update. J Clin Oncol. 2018;36:3043–3054.
19. Estcourt LJ, Birchall J, Allard S, Bassey SJ, Hersey P, Kerr JP, et al. Guidelines for the use of platelet transfusions. Br J Haematol. 2017;176:365–394.
20. Kaufman RM, Djulbegovic,B, Gernsheimer T, Kleinman S, Tinmouth AT, Capocelli KE, et al. Platelet transfusion: a clinical practice guideline from the AABB. Ann Intern Med. 2015;162:205–213.
21. Sagmeister M, Oec L & Gmur J. A restrictive platelet transfusion policy allowing long-term support of outpatients with severe aplastic anemia. Blood. 1999;93:3124–3126.
22. Desborough M, Estcourt LJ, Chaimani A, Doree C, Hopewell S, Trivella M, et al. Alternative agents versus prophylactic platelet transfusion for preventing bleeding in patients with thrombocytopenia due to chronic bone marrow failure: a network meta-analysis and systematic review. Cochrane Database Syst Rev. 2016. DOI:10.1002/14651858.cd012055
23. Dickinson M, Cherif H, Fenaux P, Mittelman M, Verma A, Portella MSO, et al. Azacitidine with or without eltrombopag for first-line treatment of intermediate- or high-risk MDS with thrombocytopenia. Blood. 2018;132:2629–2638.
24. Fenaux P, Muus P, Kantarjian H, Lyons RM, Larson RA, Sekeres MA, et al. Romiplostim monotherapy in thrombocytopenic patients with myelodysplastic syndromes: long-term safety and efficacy. Br J Haematol. 2017;178:906–913.
25. Giagounidis A, Mufti GJ, Fenaux P, Sekeres MA, Szer J, Platzbecker U, et al. Results of a randomized, double-blind study of romiplostim versus placebo in patients with low/intermediate-1-risk myelodysplastic syndrome and thrombocytopenia. Cancer. 2014;120:1838–1846.
26. Greenberg PL, Garcia-Manero G, Moore M, Damon L, Roboz G, Hu K, et al. A randomized controlled trial of romiplostim in patients with low- or intermediate-risk myelodysplastic syndrome receiving decitabine. Leuk Lymphoma.2013;54:321–328.

27. Kantarjian H, Fenaux P, Sekeres MA, Becker PS, Boruchov A, Bowen D, et al. Safety and efficacy of romiplostim in patients with lower-risk myelodysplastic syndrome and thrombocytopenia. J Clin Oncol2010;28:437–444.
28. Mittelman M, Platzbecker U, Afanasyev B, Grosicki S, Wong RSM, Anagnostopoulos A, et al. Eltrombopag for advanced myelodysplastic syndromes or acute myeloid leukaemia and severe thrombocytopenia (ASPIRE): a randomised, placebo-controlled, phase 2 trial. Lancet Haematol. 2018;5:e34–e43.
29. Wang ES, Lyons RM, Larson RA, Gandhi S, Liu D, Matei C, et al. A randomized, double-blind, placebo-controlled phase 2 study evaluating the efficacy and safety of romiplostim treatment of patients with low or intermediate-1 risk myelodysplastic syndrome receiving lenalidomide. J Hematol Oncol. 2012;5:71.
30. Dodillet H, Kreuzer KA, Monsef I & Skoetz N. Thrombopoietin mimetics for patients with myelodysplastic syndromes. Cochrane Database Syst Rev. 2017;9:CD009883.
31. Oliva EN, Alati C, Santini V, Poloni A, Molteni A, Niscola P, et al. Eltrombopag versus placebo for low-risk myelodysplastic syndromes with thrombocytopenia (EQoL-MDS): phase 1 results of a single-blind, randomised, controlled, phase 2 superiority trial. Lancet Haematol. 2017;4:e127–e136.
32. 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-alpha in anemic patients with low-risk MDS. Leukemia. 2018;32:2648–2658.
33. 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. 2017;31:1944–1950.
34. Garelius HK, 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;281:284–299.
35. Jadersten M, Malcovati L, Dybedal I, Della Porta MG, Invernizzi R, Montgomery SM, et al. Erythropoietin and granulocyte-colony stimulating factor treatment associated with improved survival in myelodysplastic syndrome. J Clin Oncol. 2008;26:3607–3613.
36. 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;111:574–582.
37. Hellstrom-Lindberg E, Gulbrandsen N, Lindberg G, Ahlgren T, Dahl IM, 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;120:1037–1046.
38. Nilsson-Ehle H, Birgegard 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;87:244–252.
39. 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. 2017;92:1037–1046.
40. Park S, Kelaidi C, Sapena R, Vassilieff D, Beyne-Rauzy O, Coiteux V, et al. Early introduction of ESA in low risk MDS patients may delay the need for RBC transfusion: a retrospective analysis on 112 patients. Leuk Res. 2010;34:1430–1436.
41. Garypidou V, Verrou E, Vakalopoulou S, Perifanis V, Tziomalos K & Venizelos I. Efficacy of a single, weekly dose of recombinant erythropoietin in myelodysplastic syndromes. Br J Haematol. 2003;123:958.
42. Gabrilove J, Paquette R, Lyons RM, Mushtaq C, Sekeres MA, Tomita D & Dreiling, L. Phase 2, single-arm trial to evaluate the effectiveness of darbepoetin alfa for correcting anaemia in patients with myelodysplastic syndromes. Br J Haematol. 2008;142:379–393.
43. Giraldo P, Nomdedeu B, Loscertales J, Requena C, de Paz R, Tormo M, et al. Darbepoetin alpha for the treatment of anemia in patients with myelodysplastic syndromes. Cancer. 2006;107:2807–2816.
44. Mannone L, Gardin C, Quarre MC, Bernard JF, Vassilieff D, Ades L, et al. High-dose darbepoetin alpha in the treatment of anaemia of lower risk myelodysplastic syndrome results of a phase II study. Br J Haematol. 2006;133:513–519.
45. 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;174:730–747.
46. Park S, Greenberg P, Yucel A, Farmer C, O'Neill F, De Oliveira Brandao C & Fenaux P. Clinical effectiveness and safety of erythropoietin-stimulating agents for the treatment of low- and intermediate-1-risk myelodysplastic syndrome: a systematic literature review. Br J Haematol. 2019;184:134–160.
47. Fenaux P, Platzbecker U, Mufti GJ, Garcia-Manero G, Buckstein R, Santini V, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. NEJM. 2020;382(2):140–151.
48. Weintraub LR, Conrad ME & Crosby WH. Regulation of the Intestinal Absorption of Iron by the Rate of Erythropoiesis. Br J Haematol. 1965;11:432–438.
49. Della Porta MG & Malcovati L. Clinical relevance of extra-hematologic comorbidity in the management of patients with myelodysplastic syndrome. Haematologica. 2009;94:602–606.
50. Malcovati L, Porta MG, Pascutto C, Invernizzi R, Boni M, Travaglino E, et al. Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. J Clin Oncol. 2005;23:7594–7603.
51. Goldberg SL, Chen E, Corral M, Guo A, Mody-Patel N, Pecora AL & Laouri M. Incidence and clinical complications of myelodysplastic

syndromes among United States Medicare beneficiaries. J Clin Oncol. 2010;28:2847–2852.
52. de Swart L, Reiniers C, Bagguley T, van Marrewijk C, Bowen D, Hellstrom-Lindberg E, et al. Labile plasma iron levels predict survival in patients with lower-risk myelodysplastic syndromes. Haematologica. 2018;103:69–79.
53. Grossekatthofer M, Guclu ED, Lawitschka A, Matthes-Martin S, Mann G, Minkov M, et al. Ferritin concentrations correlate to outcome of hematopoietic stem cell transplantation but do not serve as biomarker of graft-versus-host disease. Ann Hematol. 2013;2:1121–1128.
54. Cremers EM, van Biezen A, de Wreede LC, Scholten M, Vitek A, Finke J, et al. Prognostic pre-transplant factors in myelodysplastic syndromes primarily treated by high dose allogeneic hematopoietic stem cell transplantation: a retrospective study of the MDS subcommittee of the CMWP of the EBMT. Ann Hematol. 2016;95:1971–1978.
55. St Pierre TG, Clark PR, Chua-anusorn W, Fleming AJ, Jeffrey GP, Olynyk JK, et al. Noninvasive measurement and imaging of liver iron concentrations using proton magnetic resonance. Blood. 2005;105:855–861.
56. Anderson LJ, Holden S, Davis B, Prescott E, Charrier CC, Bunce NH, et al Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. Eur Heart J. 2001;22:2171–2179.
57. Gattermann N, Finelli C, Della Porta M, Fenaux P, Stadler M, Guerci-Bresler A, et al. Hematologic responses to deferasirox therapy in transfusion-dependent patients with myelodysplastic syndromes. Haematologica. 2012;97:1364–1371.
58. Angelucci E, Santini V, Di Tucci AA, Quaresmini G, Finelli C, Volpe A, et al. Deferasirox for transfusion-dependent patients with myelodysplastic syndromes: safety, efficacy, and beyond (GIMEMA MDS0306 Trial). Eur J Haematol. 2014;92:527–536.
59. Jensen PD, Jensen FT, Christensen T, Eiskjaer H, Baandrup U & Nielsen JL. Evaluation of myocardial iron by magnetic resonance imaging during iron chelation therapy with deferrioxamine: indication of close relation between myocardial iron content and chelatable iron pool. Blood. 2003;101:4632–4639.
60. Gattermann N, Finelli C, Porta MD, Fenaux P, Ganser A, Guerci-Bresler A, et al. Deferasirox in iron-overloaded patients with transfusion-dependent myelodysplastic syndromes: Results from the large 1-year EPIC study. Leuk Res. 2010;4:1143–1150.
61. Neukirchen J, Fox F, Kundgen A, Nachtkamp K, Strupp C, Haas R, Germing U & Gattermann N. Improved survival in MDS patients receiving iron chelation therapy - a matched pair analysis of 188 patients from the Dusseldorf MDS registry. Leuk Res. 2012;36:1067–1070.
62. Hoeks M, Yu G, Langemeijer S, Crouch S, de Swart L, Fenaux P, et al. Impact of treatment with iron chelation therapy in patients with lower-risk myelodysplastic syndromes participating in the European MDS registry. Haematologica. 2019; 105(3):640–651.
63. 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;129:1753–1762.
64. List AF, Baer MR, Steensma DP, Raza A, Esposito J, Martinez-Lopez N, et al. Deferasirox reduces serum ferritin and labile plasma iron in RBC transfusion-dependent patients with myelodysplastic syndrome. J Clin Oncol. 2012;30:2134–2139.
65. Giagounidis AA, Germing U, Haase S, Hildebrandt B, Schlegelberger B, Schoch C, et al. Clinical, morphological, cytogenetic, and prognostic features of patients with myelodysplastic syndromes and del(5q) including band q31. Leukemia. 2004;18:113–119.
66. Germing U, Lauseker M, Hildebrandt B, Symeonidis A, Cermak J, Fenaux P, et al. Survival, prognostic factors and rates of leukemic transformation in 381 untreated patients with MDS and del(5q): A multicenter study. Leukemia. 2012;26:1286–1292.
67. Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood. 2006;108:419-425.
68. Kelaidi C, Park S, Brechignac S, Mannone L, Vey N, Dombret H, et al. Treatment of myelodysplastic syndromes with 5q deletion before the lenalidomide era; the GFM experience with EPO and thalidomide. Leuk Res. 2008;32:1049–1053.
69. Fenaux P, Giagounidis A, Selleslag D, Beyne-Rauzy O, Mufti G, Mittelman M, et al. A randomized phase 3 study of lenalidomide versus placebo in RBC transfusion-dependent patients with Low-/Intermediate-1-risk myelodysplastic syndromes with del5q. Blood. 2011;118:3765–3776.
70. Ades L, Le Bras F, Sebert M, Kelaidi C, Lamy T, Dreyfus F, et al. Treatment with lenalidomide does not appear to increase the risk of progression in lower risk myelodysplastic syndromes with 5q deletion. A comparative analysis by the Groupe Francophone des Myelodysplasies. Haematologica. 2012;97:213–218.
71. Kuendgen A, Lauseker M, List AF, Fenaux P, Giagounidis AA, Brandenburg NA, et al. Lenalidomide does not increase AML progression risk in RBC transfusion-dependent patients with Low- or Intermediate-1-risk MDS with del(5q): a comparative analysis. Leukemia. 2013;27:1072–1079.
72. List AF, Bennett JM, Sekeres MA, Skikne B, Fu T, Shammo JM, et al. Extended survival and reduced risk of AML progression in erythroid-responsive lenalidomide-treated patients with lower-risk del(5q) MDS.[Erratum appears in Leukemia. 2015 Dec;29(12):2452; PMID: 26648407]. Leukemia. 2014;28:1033–1040.
73. Sanchez-Garcia J, Del Canizo C, Lorenzo I, Nomdedeu B, Luno E, de Paz R, et al. Multivariate time-dependent comparison of the impact of lenalidomide in lower-risk myelodysplastic syndromes with chromosome 5q deletion. British Journal of Haematology. 2014;166:189–201.
74. Lian XY, Zhang ZH, Deng ZQ, He PF, Yao DM, Xu ZJ, et al. Efficacy and Safety of Lenalidomide for Treatment of Low-/Intermediate-1-Risk Myelodysplastic Syndromes with or without 5q Deletion: A Systematic Review and Meta-Analysis. PLoS One. 2016;11:e0165948.

75. Jadersten M, Saft L, Smith A, Kulasekararaj A, Pomplun S, Gohring G, et al. TP53 mutations in low-risk myelodysplastic syndromes with del(5q) predict disease progression. J Clin Oncol. 2011;29:1971–1979.
76. Lode L, Menard A, Flet L, Richebourg S, Loirat M, Eveillard M, et al. Emergence and evolution of TP53 mutations are key features of disease progression in myelodysplastic patients with lower-risk del(5q) treated with lenalidomide. Haematologica. 2018;103:e143–e146.
77. Scharenberg C, Giai V, Pellagatti A, Saft L, Dimitriou M, Jansson M, et al. Progression in patients with low- and intermediate-1-risk del(5q) myelodysplastic syndromes is predicted by a limited subset of mutations. Haematologica. 2017;102:498–508.
78. Bono E, McLornan D, Travaglino E, Gandhi S, Galli A, Khan AA, et al. Clinical, histopathological and molecular characterization of hypoplastic myelodysplastic syndrome. Leukemia, doi: 10.1038/s41375–41019–40457–41371 [Epub ahead of print]. 2019.
79. Hasserjian RPO, A Brunning R, Germing U, Le Beau MM, Porwit A. Myelodysplastic Syndromes; Overview. In: WHO Classfication of Haematopoietic and Lymphoid Tissues. 2017;pp.98–106. IARC, Lyon, France.
80. Killick SB, Bown N, Cavenagh J, Dokal I, Foukaneli T, Hill A, et al. Guidelines for the diagnosis and management of adult aplastic anaemia. Br J Haematol. 2016;172:187–207.
81. Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Sole F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012;120:2454–2465.
82. Wattel E, De Botton S, Luc Lai J, Preudhomme C, Lepelley P, Bauters F & Fenaux P. Long-term follow-up of de novo myelodysplastic syndromes treated with intensive chemotherapy: incidence of long-term survivors and outcome of partial responders. Br J Haematol. 1997;98:983–991.
83. Kantarjian H, O'Brien S, Cortes J, Giles F, Faderl S, Jabbour E, et al. Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. Cancer. 2006c;106:1090–1098.
84. Knipp S, Hildebrand B, Kundgen 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. 2007;110:345–352.
85. Morita Y, Kanamaru A, Miyazaki Y, Imanishi D, Yagasaki F, Tanimoto M, et al. Comparative analysis of remission induction therapy for high-risk MDS and AML progressed from MDS in the MDS200 study of Japan Adult Leukemia Study Group. Int J Hematol. 2010;91:97–103.
86. 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. 2006a;106:1099–1109.
87. Sekeres MA, Elson P, Kalaycio ME, Advani AS, Copelan EA, Faderl S, et al. Time from diagnosis to treatment initiation predicts survival in younger, but not older, acute myeloid leukemia patients. Blood. 2009;113:28–36.

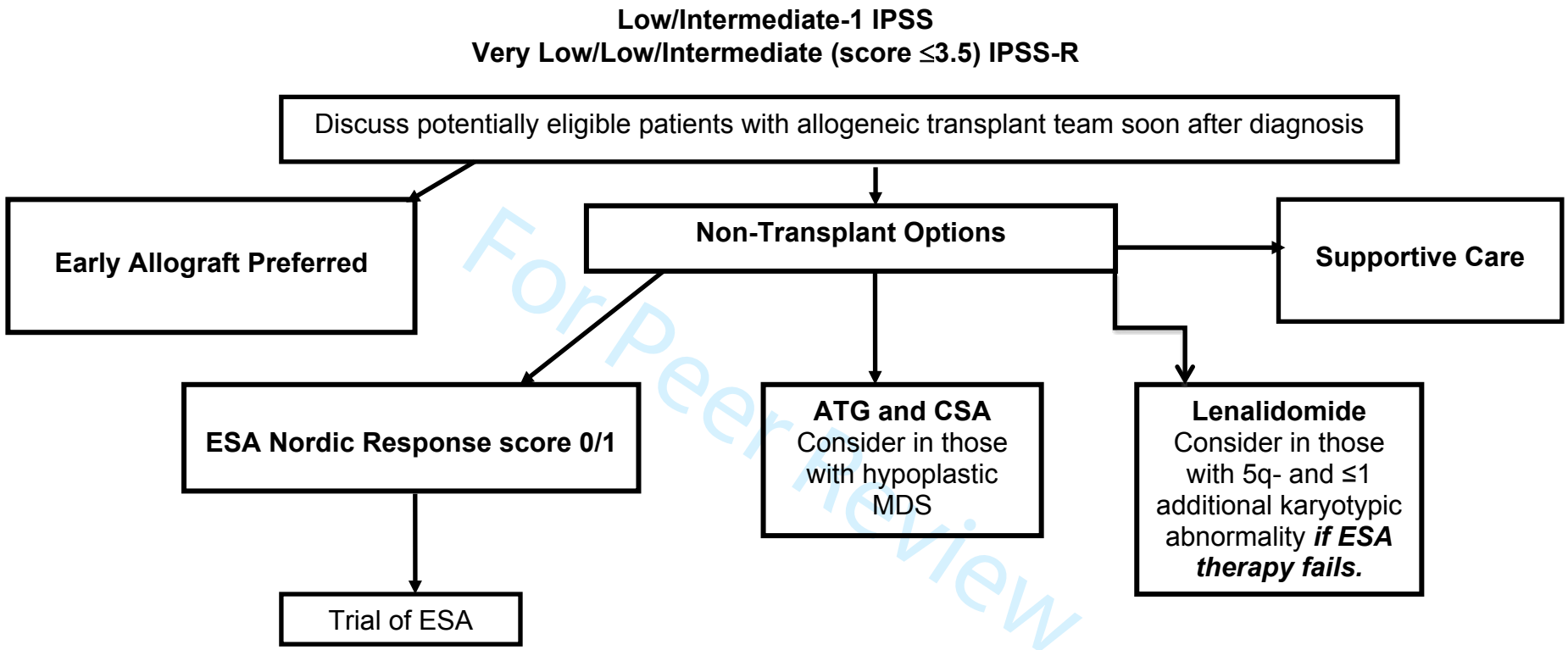
88. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol. 2009;10:223–232.
89. Seymour JF, Fenaux P, Silverman LR, Mufti GJ, Hellstrom-Lindberg E, Santini V, et al. Effects of azacitidine compared with conventional care regimens in elderly (>/= 75 years) patients with higher-risk myelodysplastic syndromes. Crit Rev Oncol Hematol. 2010;76:218–227.
90. Ravandi F, Issa JP, Garcia-Manero G, O'Brien S, Pierce S, Shan J, et al. Superior outcome with hypomethylating therapy in patients with acute myeloid leukemia and high-risk myelodysplastic syndrome and chromosome 5 and 7 abnormalities. Cancer. 2009;115:5746–5751.
91. Montalban-Bravo G, Takahashi K, Patel K, Wang F, Xingzhi S, Nogueras GM, et al. Impact of the number of mutations in survival and response outcomes to hypomethylating agents in patients with myelodysplastic syndromes or myelodysplastic/myeloproliferative neoplasms. Oncotarget. 2018;9:9714–9727.
92. Fenaux P, Bowen D, Gattermann N, Hellstrom-Lindberg E, Hofmann WK, Pfeilstocker M, et al. Practical use of azacitidine in higher-risk myelodysplastic syndromes: an expert panel opinion. Leuk Res. 2010;34:1410–1416.
93. Bernal T, Martinez-Camblor P, Sanchez-Garcia J, de Paz R, Luno E, Nomdedeu B, et al. Effectiveness of azacitidine in unselected high-risk myelodysplastic syndromes: results from the Spanish registry. Leukemia. 2015;29:1875–1881.
94. Mozessohn L, Cheung MC, Fallahpour S, Gill T, Maloul A, Zhang L, et al. Azacitidine in the 'real-world': an evaluation of 1101 higher-risk myelodysplastic syndrome/low blast count acute myeloid leukaemia patients in Ontario, Canada. Br J Haematol. 2018;181:803–815.
95. Itzykson R, Thepot S, Quesnel B, Dreyfus F, Beyne-Rauzy O, Turlure P, et al. Prognostic factors for response and overall survival in 282 patients with higher-risk myelodysplastic syndromes treated with azacitidine. Blood. 2011;117:403–411.
96. Lyons RM, Cosgriff TM, Modi SS, Gersh RH, Hainsworth JD, Cohn AL, et al. Hematologic response to three alternative dosing schedules of azacitidine in patients with myelodysplastic syndromes. J Clin Oncol. 2009;27:1850–1856.
97. Kantarjian H, Issa JP, Rosenfeld CS, Bennett JM, Albitar M, DiPersio J, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. Cancer. 2006b;106:1794–1803.
98. Lubbert M, Suciu S, Baila L, Ruter BH, Platzbecker U, Giagounidis A, et al. Low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: final results of the randomized phase III study of the European Organisation for Research and Treatment of Cancer Leukemia Group and the German MDS Study Group. J Clin Oncol. 2011;29:1987–1996.

99. Steensma DP, Baer MR, Slack JL, Buckstein R, Godley LA, Garcia-Manero G, et al. Multicenter study of decitabine administered daily for 5 days every 4 weeks to adults with myelodysplastic syndromes: the alternative dosing for outpatient treatment (ADOPT) trial. J Clin Oncol. 2009;27:3842–3848.
100. 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;10:609–614.
101. Shaffer BC, Ahn KW, Hu ZH, Nishihori T, Malone AK, Valcarcel D, et al. Scoring System Prognostic of Outcome in Patients Undergoing Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndrome. J Clin Oncol. 2016;34:1864–1871.
102. Cutler CS, Lee SJ, Greenberg P, Deeg HJ, Perez WS, Anasetti C, et al. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: delayed transplantation for low-risk myelodysplasia is associated with improved outcome. Blood. 2004;104:579–585.
103. Della Porta MG, Jackson CH, Alessandrino EP, Rossi M, Bacigalupo A, van Lint MT, et al. Decision analysis of allogeneic hematopoietic stem cell transplantation for patients with myelodysplastic syndrome stratified according to the revised International Prognostic Scoring System. Leukemia. 2017;31:2449–2457.
104. Koreth J, Pidala J, Perez WS, Deeg HJ, Garcia-Manero G, Malcovati L, et al. Role of reduced-intensity conditioning allogeneic hematopoietic stem-cell transplantation in older patients with de novo myelodysplastic syndromes: an international collaborative decision analysis. J Clin Oncol. 2013;31:2662–2670.
105. Alessandrino EP, Porta MG, Malcovati L, Jackson CH, Pascutto C, Bacigalupo A, et al. Optimal timing of allogeneic hematopoietic stem cell transplantation in patients with myelodysplastic syndrome. Am J Hematol. 2013;88:581–588.
106. Armand P, Kim HT, Cutler CS, Ho VT, Koreth J, Alyea EP, et al. Prognostic impact of elevated pretransplantation serum ferritin in patients undergoing myeloablative stem cell transplantation. Blood. 2007;109:4586–4588.
107. Wermke M, Eckoldt J, Gotze KS, Klein SA, Bug G, de Wreede LC, et al. Enhanced labile plasma iron and outcome in acute myeloid leukaemia and myelodysplastic syndrome after allogeneic haemopoietic cell transplantation (ALLIVE): a prospective, multicentre, observational trial. Lancet Haematol. 2018;5:e201–e210.
108. Park S, Hamel JF, Toma A, Kelaidi C, Thepot S, Campelo MD, et al. Outcome of Lower-Risk Patients With Myelodysplastic Syndromes Without 5q Deletion After Failure of Erythropoiesis-Stimulating Agents. J Clin Oncol. 2017;35:1591–1597.
109. Jabbour EJ, Garcia-Manero G, Strati P, Mishra A, Al Ali NH, Padron E, et al. Outcome of patients with low-risk and intermediate-1-risk myelodysplastic syndrome after hypomethylating agent failure: a report on behalf of the MDS Clinical Research Consortium. Cancer. 2015;121:876–882.

110. Bejar R, Stevenson KE, Caughey B, Lindsley RC, Mar BG, Stojanov P, et al. Somatic mutations predict poor outcome in patients with myelodysplastic syndrome after hematopoietic stem-cell transplantation. J Clin Oncol. 2014;32:2691–2698.
111. Kroger N, Zabelina T, van Biezen A, Brand R, Niederwieser D, Martino R, et al. Allogeneic stem cell transplantation for myelodysplastic syndromes with bone marrow fibrosis. Haematologica. 2011;96:291–297.
112. Kuendgen A, Strupp C, Aivado M, Hildebrandt B, Haas R, Gattermann N & Germing U. Myelodysplastic syndromes in patients younger than age 50. J Clin Oncol. 2006;24:5358–5365.
113. Lim Z, Brand R, Martino R, van Biezen A, Finke J, Bacigalupo A, et al. Allogeneic hematopoietic stem-cell transplantation for patients 50 years or older with myelodysplastic syndromes or secondary acute myeloid leukemia. J Clin Oncol. 2010;28:405–411.
114. Schroeder T, Wegener N, Lauseker M, Rautenberg C, Nachtkamp K, Schuler E, et al. Comparison between upfront transplantation and different pretransplant cytoreductive treatment approaches in patients with high-risk myelodysplastic syndrome and secondary acute myelogenous leukemia. Biol Blood Marrow Transplant. 2019;25(8):1550–9.
115. Kroeger N, Sockel K, Wolschke C, Bethge W, Schlenk RF, Wolf D, et al. Prospective multicenter phase 3 study comparing 5-azacytidine (5-Aza) induction followed by allogeneic stem cell transplantation versus continuous 5-Aza according to donor availability in elderly MDS patients (55–70 years) (VidazaAllo study). Blood. 2018;132 (Suppl.1): 208.
116. Rucker FG, Schlenk RF, Bullinger L, Kayser S, Teleanu V, Kett H, et al. TP53 alterations in acute myeloid leukemia with complex karyotype correlate with specific copy number alterations, monosomal karyotype, and dismal outcome. Blood. 2012;119:2114–2121.
117. Sallman DA, Komrokji R, Vaupel C, Cluzeau T, Geyer SM, McGraw KL, et al. Impact of TP53 mutation variant allele frequency on phenotype and outcomes in myelodysplastic syndromes. Leukemia. 2016;30:666–673.
118. Bally C, Ades L, Renneville A, Sebert M, Eclache V, Preudhomme C, et al. Prognostic value of TP53 gene mutations in myelodysplastic syndromes and acute myeloid leukemia treated with azacitidine. Leuk Res. 2014;38:751–755.
119. Kulasekararaj AG, Smith AE, Mian SA, Mohamedali AM, Krishnamurthy P, Lea NC, et al. TP53 mutations in myelodysplastic syndrome are strongly correlated with aberrations of chromosome 5, and correlate with adverse prognosis. Br J Haematol. 2013;160:660–672.
120. Muller-Thomas C, Rudelius M, Rondak IC, Haferlach T, Schanz J, Huberle C, et al. Response to azacitidine is independent of p53 expression in higher-risk myelodysplastic syndromes and secondary acute myeloid leukemia. Haematologica. 2014;99:e179–181.
121. Welch JS, Petti AA, Miller CA, Fronick CC, O'Laughlin M, Fulton RS, et al. TP53 and Decitabine in Acute Myeloid Leukemia and Myelodysplastic Syndromes. N Engl J Med. 2016;375:2023–2036.
122. Damaj G, Duhamel A, Robin M, Beguin Y, Michallet M, Mohty M, et al. Impact of azacitidine before allogeneic stem-cell transplantation for

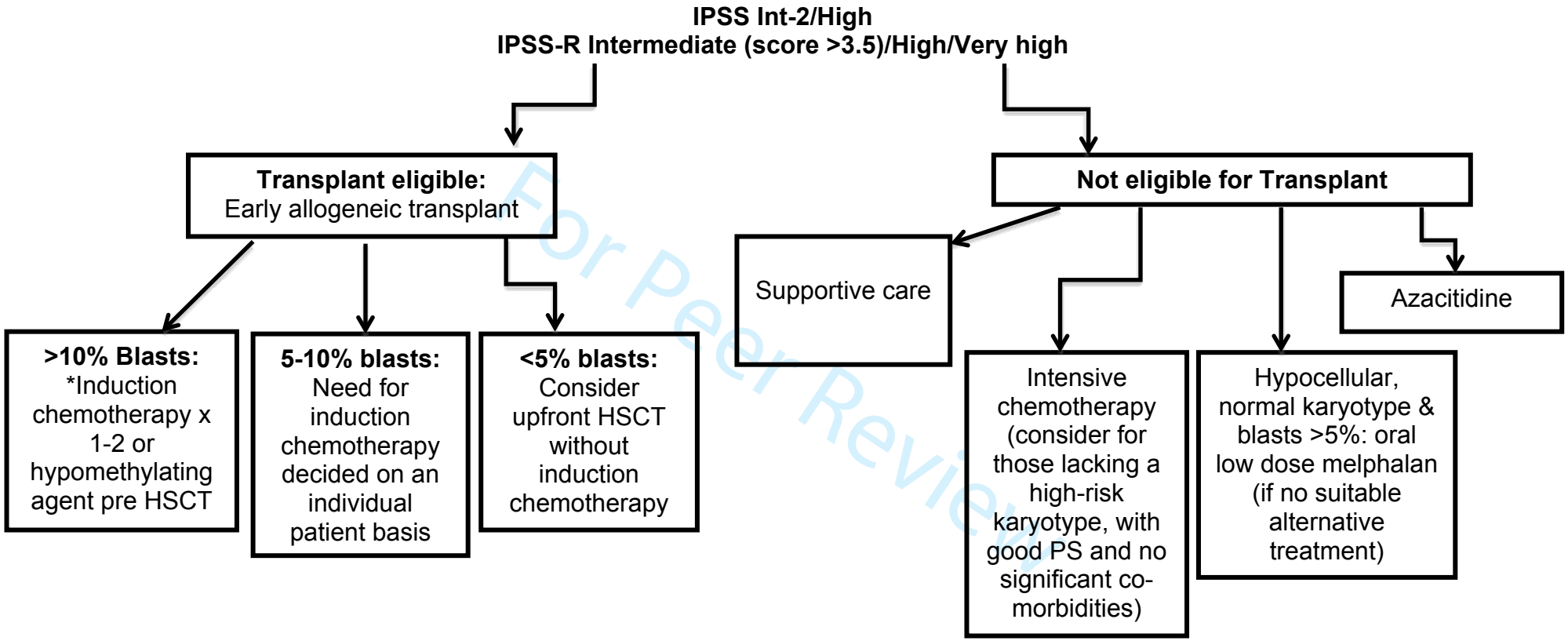
myelodysplastic syndromes: a study by the Societe Francaise de Greffe de Moelle et de Therapie-Cellulaire and the Groupe-Francophone des Myelodysplasies. J Clin Oncol. 2012;30:4533–4540.
123. Della Porta MG, Galli A, Bacigalupo A, Zibellini S, Bernardi M, Rizzo E, et al. Clinical Effects of Driver Somatic Mutations on the Outcomes of Patients With Myelodysplastic Syndromes Treated With Allogeneic Hematopoietic Stem-Cell Transplantation. J Clin Oncol. 2016;34:3627–3637.
124. 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;376:536–547.
125. Yoshizato T, Nannya Y, Atsuta Y, Shiozawa Y, Iijima-Yamashita Y, Yoshida K, et al. Genetic abnormalities in myelodysplasia and secondary acute myeloid leukemia: impact on outcome of stem cell transplantation. Blood. 2017;129:2347–2358.
126. Bernard E, Nannya Y, Hasserjian RP, Devlin SM, Tuechler H, Medina-Martinez JS, et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. Nat Med. 2020;26(10):1549–56.
127. Heidenreich S, Ziagkos D, de Wreede LC, van Biezen A, Finke J, Platzbecker U, et al. Allogeneic Stem Cell Transplantation for Patients Age >/= 70 Years with Myelodysplastic Syndrome: A Retrospective Study of the MDS Subcommittee of the Chronic Malignancies Working Party of the EBMT. Biol Blood Marrow Transplant. 2017;23:44–52.
128. Sorror ML, Sandmaier BM, Storer BE, Maris MB, Baron F, Maloney DG, et al. Comorbidity and disease status based risk stratification of outcomes among patients with acute myeloid leukemia or myelodysplasia receiving allogeneic hematopoietic cell transplantation. J Clin Oncol. 2007;25:4246–4254.
129. Ayuk F, Beelen DW, Bornhauser M, Stelljes M, Zabelina T, Finke J, et al. Relative Impact of HLA Matching and Non-HLA Donor Characteristics on Outcomes of Allogeneic Stem Cell Transplantation for Acute Myeloid Leukemia and Myelodysplastic Syndrome. Biol Blood Marrow Transplant. 2018;24:2558–2567.
130. Kroger N, Iacobelli S, Franke GN, Platzbecker U, Uddin R, Hubel 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;35:2157–2164.
131. Scott BL, Pasquini MC, Logan BR, Wu J, Devine SM, Porter DL, et al. Myeloablative Versus Reduced-Intensity Hematopoietic Cell Transplantation for Acute Myeloid Leukemia and Myelodysplastic Syndromes. J Clin Oncol. 2017;35:1154–1161.

Figure 1: Algorithm for the Management of Low-Risk MDS



Abbreviations: ATG, antithymocyte globulin; CSA, ciclosporin-A; ESA, Erythropoiesis-Stimulating Agent; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome

Figure 2: Algorithm for the Management of High-Risk MDS



Abbreviations; IPSS, international prognostic scoring system; IPSS-R, IPSS-revised; HSCT, haematopoietic stem cell transplant; PS, performance status
* Where possible, patients should be offered entry into a clinical trial