Guidelines for the diagnosis and management of adult myelodysplastic syndromes

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Keywords: myelodysplastic syndrome, guideline, diagnosis, management.

Summary of key recommendations

Diagnosis

1. Myelodysplastic syndrome (MDS) should be suspected in patients with otherwise unexplained cytopenias(s) or macrocytosis. Grade 1A
2. The initial assessment of a patient with unexplained cytopenias(s) may not confirm a diagnosis of MDS. Further follow-up and reassessment may be necessary to reach a firm diagnosis. Grade 2B,C
3. Initial assessment of a patient with suspected MDS should include a minimum set of investigations and the differential diagnosis of marrow dysplasia should be considered. Grade 1A
4. Patients with MDS should be assessed by a haematologist and, except where clearly inappropriate, offered review by a regional or national expert given the disease rarity.
5. All cases of MDS should be classified according to the World Health Organization (WHO) Revised Classification 2008. Grade 1A
6. Bone marrow cytogenetic analysis should be performed on all patients with suspected MDS having a bone marrow examination. Grade 1A

Supportive care

1. Supportive Care should be the mainstay for all patients with MDS and symptomatic cytopenias. Grade 1A
2. Blood transfusions should be given to improve symptomatic anaemia. Grade 1A
3. A trigger haemoglobin concentration cannot be recommended for all patients, it should be individualized. Grade 1A
4. Extended red cell phenotyping should be considered for patients receiving regular red cell transfusions. Grade 2C
5. Routine platelet transfusions should not be given to stable, non-bleeding patients who are not receiving intensive chemotherapy. Grade 1A
6. Local policies should be in place for the management of neutropenic sepsis. Grade 1A
7. Emotional health needs should be continually assessed and addressed. Disease-specific information should be re-iterated regularly

Iron chelation

1. Iron chelation therapy cannot be routinely recommended for MDS patients with transfusional iron overload. Grade 1C

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Consideration may be given to chelation therapy for patients with a very good prognosis, specifically patients with WHO refractory anaemia (RA), RA with ringed sideroblasts (RARS) and isolated del(5q). Triggers may include more than 20 units of red cells transfused, serum ferritin >1000 μg/l in patients for whom continuing red cell transfusion is predicted. Grade 2C

2 Patients treated with iron chelation therapy should ideally receive this treatment within clinical trials.

4 Desferrioxamine remains the therapy of choice with the longest record of safety and efficacy of all three agents available. Deferasirox is recommended for patients intolerant of desferrioxamine. Deferiprone could be considered in patients with normal baseline neutrophil counts. Grade 2C

Growth factors

1 Patients with IPSS Low and Intermediate-1 (INT-1) MDS, symptomatic anaemia and who fulfil the criteria for a high or intermediate predictive score for response should be considered for a trial of therapy with an Erythroid-Stimulating Agents (ESA). Grade 1B

2 Patients with non-sideroblastic phenotypes should be offered a trial of therapy with an ESA. Grade 1B

3 Patients with sideroblastic phenotypes should be offered a trial of therapy with an ESA plus granulocyte colony-stimulating factor (G-CSF). Grade 1B

4 Patients should receive a maximum trial period of 16 weeks of therapy. This should comprise 8 weeks at the starting dose of ESA± G-CSF and a further 8 weeks at the higher doses, if required. Grade 2B

5 Patients achieving a complete or partial erythroid response by accepted criteria should continue on long-term therapy until the response is lost and at the minimum dose of ESAs required to maintain the response. Grade 2B

6 The haemoglobin concentration should not be allowed to rise above 120 g/l. Grade 2C

Immunosuppression

1 Immunosuppressive therapy with antithymocyte globulin (ATG) (horse ATG, currently available as ATGAM, Pfizer, New York, NY, USA) can be recommended in suitable low or INT-1 IPSS MDS patients who are typically less than 60 years of age and have a normal karyotype or trisomy 8. Grade 2C

Lenalidomide

1 Patients with IPSS Low or INT-1 MDS with del(5q), symptomatic anaemia and who fulfil the criteria for a high or intermediate predictive score for response, should be first considered for a trial of ESA therapy. Grade 1B

2 For transfusion-dependent patients unsuitable for a trial of ESA, or for non-responders/patients losing their response to ESA, who have IPSS Low or INT-1 MDS with del(5q), consider treatment with lenalidomide 10 mg daily for 21 d repeated every 28 d. Grade 1B. A careful discussion with patients about the risk and benefit is mandatory.

3 Selected MDS patients with del(5q) and IPSS Low/INT-1 may be candidates for allogeneic stem cell transplantation. These include lenalidomide-treated patients who fail to achieve transfusion independence, those losing their response, or patients with transfusion dependence not considered suitable for lenalidomide. Grade 2B

4 Lenalidomide is not currently recommended for patients with del(5q) and bone marrow blasts >5%, multiple (complex) cytogenetic abnormalities in addition to del (5q), patients with IPSS INT-2/High or with a known mutated TP53 gene. Grade 2B

Allogeneic transplant for low risk disease

1 Clinicians should discuss all patients eligible for stem cell transplantation with their local transplant unit and each case should be assessed on its own merits. Grade 2B

2 Consideration should be given to the European Group for Blood and Marrow Transplantation EBMT risk score, which has been validated for MDS, and the Haematopoietic Cell Transplantation Comorbidity Index (HCT-CI). Grade 2B

3 Consideration should also be given to additional prognostic features, such as red cell transfusion dependence, which can profoundly influence the prognosis in patients eligible for transplant. Grade 2B

4 Current data suggest that transplants from matched unrelated donors can have similar outcomes to those from matched sibling donors. Grade 2B

5 Myeloablative conditioning regimens are recommended over reduced intensity conditioning (RIC) regimens when they can be delivered safely. Grade 2C

Chronic myelomonocytic leukaemia (CMML)

1 Supportive care ± hydroxycarbamide as required is recommended for most patients. Grade 1B

2 Azacitidine is licensed for non-proliferative CMML-2 and can reasonably be recommended. Grade 2C

3 Allogeneic haematopoietic stem cell transplantation (HSCT) with or without preceding acute myeloid leukaemia (AML)-type chemotherapy should be considered for selected patients. Grade 2B

4 Patients requiring treatment should be considered for any appropriate clinical trial.
High risk patients eligible for allogeneic transplant
1 Early allogeneic stem cell transplantation with or without prior AML-type induction chemotherapy should be considered for eligible patients with high-risk MDS. Grade 2B
2 Eligibility for stem cell transplantation should be based on HCT CI and performance status rather than age. Grade 2B
3 Patients with a low comorbidity score (HCT CI < 3) should be considered for allogeneic stem cell transplantation. The role of transplantation in those patients with a high comorbidity score is unclear. Grade 2B
4 Patients with > 10% blasts should receive 1–2 courses of intensive chemotherapy to induce remission prior to transplantation. Grade 2B
5 It is recommended that serum ferritin be measured pre-transplant for additional predictive information. Grade 2B
6 Matched unrelated transplant donors are recommended where a sibling donor is unsuitable or unavailable. Grade 2B
7 Intensity of conditioning depends on the ‘risk’ of the disease and patient factors. Grade 2B
8 Patients who fail to respond to pre-transplant induction therapy should not undergo allogeneic stem cell transplantation and should be considered for experimental therapy or supportive care alone. Grade 2B
9 Autologous stem cell transplantation for MDS is not recommended outside of clinical trials. Grade 2B

High risk patients not eligible for allogeneic transplant
1 In fit older patients lacking an adverse karyotype, the options of azacitidine versus intensive chemotherapy should be carefully discussed. Standard regimens used in de novo AML should be used as intensive chemotherapy in eligible patients. Grade 2B
2 Azacitidine is recommended as first line therapy for patients ineligible for a stem cell transplant with IPSS INT-2 and High Risk MDS, CMML-2 or AML with 20–30% blasts. Grade 1A
3 The recommended dose of azacitidine is 75 mg/m² daily for seven consecutive days but a 5-2-2 schedule is acceptable where it is not practical to offer seven consecutive days. Grade 2B
4 Responding patients should continue azacitidine until their response is lost. Grade 1A
5 The decision to stop or continue azacitidine in patients who fail to achieve a response after six cycles, but who have stable disease, is dependent upon clinician and patient preference. Grade 2B

Introduction
The myelodysplastic syndromes (MDS) are a heterogeneous group of malignant haematopoietic disorders characterized by dysplastic changes in one or more cell lineages, ineffective haematopoiesis and a variable predilection to development of acute myeloid leukaemia (AML) (Swerdlow et al, 2008). The incidence of MDS is approximately 4/100 000 population/year, but it is predominantly a disease of the elderly with an incidence of >30/100 000/year over the age of 70 years.

Patients with suspected MDS should be assessed by a haematologist. As MDS is considered a rare or ‘orphan’ malignancy, patients should always be given the opportunity to be reviewed by a regional or national haematologist with a specific interest in MDS. All patients with a diagnosis of MDS must be discussed at a multi-disciplinary 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.

Diagnosis of MDS
The diagnosis of MDS should be considered in patients with otherwise unexplained cytopenia(s). The minimum clinical assessment and laboratory investigation of a patient with possible MDS are shown in Table I. Selected patients may require further investigations (Table II). It is important to consider alternative diagnoses and reactive causes of marrow dysplasia.

The initial assessment of a patient with unexplained cytopenia(s) may not confirm a diagnosis of MDS. In the absence of significant (>10%) marrow dysplasia or a clonal cytogenetic abnormality, a definitive diagnosis of MDS and distinction from other causes of cytopenia may be difficult. The term ‘idiopathic cytopenia of unknown origin’ may be used for patients with sustained (>6 months) cytopenia who do not fulfil the criteria for the diagnosis of MDS and where there is no other identifiable cause for the cytopenias (Valent et al, 2012). Such patients should be observed (with repeat marrow examination if necessary), as some may subsequently develop overt MDS.

Morphological features
A blood film analysis and bone marrow examination for characteristic morphological features of dysplasia are both necessary for the diagnosis, classification and prognostic evaluation of MDS. This should be performed by a haematologist or haematopathologist.

Blood film examination should include assessment of red cell, platelet and white cell morphology for features of dysplasia (Swerdlow et al, 2008; Bain et al, 2010).

Bone marrow examination should include an assessment of May–Grünewald Giemsa (or equivalent) stained smears for myeloid, megakaryocyte and erythroid maturation, with identification of dysplasia if present. 500 nucleated cells and at least 30 megakaryocytes should, where possible, be evaluated and the percentage of blasts enumerated. Dysplastic
Table I. Evaluation of suspected myelodysplastic syndrome*.

<table>
<thead>
<tr>
<th>History</th>
<th>Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior exposure to chemotherapy/radiotherapy</td>
<td>Dysmorphic features (suggesting congenital bone marrow failure)</td>
</tr>
<tr>
<td>Family history of MDS/AML or pulmonary/liver fibrosis</td>
<td>Active infection/bruising/bleeding</td>
</tr>
<tr>
<td>Recurrent infections/bleeding</td>
<td>Splenomegaly</td>
</tr>
<tr>
<td></td>
<td>Cutaneous lesions</td>
</tr>
<tr>
<td>Bloods</td>
<td></td>
</tr>
<tr>
<td>Full blood count</td>
<td></td>
</tr>
<tr>
<td>Differential white cell count (including absolute monocyte count)</td>
<td></td>
</tr>
<tr>
<td>Blood film analysis</td>
<td></td>
</tr>
<tr>
<td>Reticulocyte count</td>
<td></td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td></td>
</tr>
<tr>
<td>Ferritin</td>
<td></td>
</tr>
<tr>
<td>β₂ microglobulin</td>
<td></td>
</tr>
<tr>
<td>Blood group and antibody screen</td>
<td></td>
</tr>
<tr>
<td>Serology for hepatitis B and C and HIV</td>
<td></td>
</tr>
<tr>
<td>Bone Marrow aspirate and trephine biopsy including:</td>
<td></td>
</tr>
<tr>
<td>Morphological assessment and quantification of blast population (flow cytometric analysis can be considered)</td>
<td></td>
</tr>
<tr>
<td>Iron stain of aspirate</td>
<td></td>
</tr>
<tr>
<td>Reticulin stain of trephine biopsy section</td>
<td></td>
</tr>
<tr>
<td>Cytogenetic analysis</td>
<td></td>
</tr>
<tr>
<td>Bone marrow immunophenotyping with analysis of aberrant antigen expression and quantification of marrow blasts†</td>
<td></td>
</tr>
<tr>
<td>Marrow mutational analysis/genomic studies‡</td>
<td></td>
</tr>
</tbody>
</table>

*It is assumed that all investigations for alternative causes of macrocytic anaemia, sideroblastic change (if present) and other cytopenias have been done.
†These studies are still considered research investigations and are not yet recommended for routine evaluation of all patients with MDS (Evidence levels 2c).

features should be present in at least 10% of cells of the relevant lineage (myeloid, erythroid or megakaryocytic) (Swerdlow et al, 2008; Vardiman et al, 2009; Bain et al, 2010) (Evidence levels 2B,C). An iron stain (Prussian Blue/Perls stain) should be performed on all marrow aspirates to assess iron stores and to identify the presence and quantity of ring sideroblasts, which should be at least 15% of the total erythroblasts to be diagnostic of refractory anaemia with ring sideroblasts (RARS) or refractory anaemia with multilineage dysplasia + ring sideroblasts (RCMD-RS).

A trephine biopsy (decalcified and paraffin-embedded or plastic embedded) including reticulin staining should be performed in all patients as it contributes significantly to the assessment of patients with MDS. It can provide information regarding cellularity and fibrosis, aiding the identification of hypocellular MDS and overlap myelodysplastic/myeloproliferative syndromes (Bennett & Orazi, 2009). If the aspirate is dilute, CD34+ staining of an adequate trephine biopsy specimen may allow assessment of bone marrow blast percentage. In patients with hypocellular marrows, the diagnosis of MDS requires dysplasia in the myeloid and/or megakaryocytic series, as erythroid dysplasia is common in aplastic anaemia. (Evidence levels 2B,C).

Table II. Further investigations may be indicated in selected patients.

**Cytogenetics**

Cytogenetic analysis should be performed on all patients with suspected MDS to confirm the diagnosis, inform management options and provide prognostic information. Cytogenetic analysis should be performed on at least 25 metaphases and should be reported in accordance with the International System for Human Cytogenetic Nomenclature Recommendations (Schaffer et al, 2009). Identification of clonal chromosomal abnormalities has become essential for the application of international prognostic scoring systems [such as the International Prognostic Scoring System (IPSS) and the revised IPSS (IPSS-R)]. A new comprehensive cytogenetic scoring system has been incorporated into the IPSS-R (Schanz et al, 2012). In addition, identification of a specific cytogenetic abnormality may provide a marker for assessing response to therapy. In patients where conventional marrow cytogenetic analysis is not possible (‘dry tap’) or has failed, fluorescence in situ hybridization analysis of bone marrow or peripheral blood films for selected cytogenetic anomalies (for instance monosomy 7, deletion of 5q, trisomy 8) may help provide diagnostic and prognostic evaluation (Evidence levels 2B,C).

Classification of MDS

Despite on-going advances in molecular genetics, the classification of MDS currently remains largely based upon morphological examination with incorporation of limited genetic
information. The diagnosis and classification of MDS should be based on the World Health Organization Classification (WHO, 2008 revision) (Swerdlow et al, 2008), which has superseded the former French-American-British (FAB) Classification (Bennett et al, 1982). The specific WHO classification subtype should be identified for each patient and included in the marrow aspirate report (Table III). Due consideration should be given to the MDS/Myeloproliferative Neoplasm (MPN) category, which now includes chronic myelomonocytic leukaemia (CMML), MDS/MPN neoplasms (unclassifiable), and the provisional entity RARS with thrombocytosis (RARS-T) (Swerdlow et al, 2008). Adult patients with >20% blasts are now classified as having AML, although those with between 20 and 30% blasts were included in the IPSS. MDS secondary to prior cytotoxic therapy is classified as a separate entity by the WHO Classification (therapy-related myeloid neoplasms).

### Additional supplementary tests

**Molecular genetics.** The use of novel technologies, such as high-resolution single nucleotide polymorphism-array analysis and next-generation sequencing has led to the identification of point mutations in haematopoietic cells of many patients with MDS, some of which may have independent prognostic significance (Langemeijer et al, 2009; Bejar et al, 2011). Identification by new technologies of small clones of cells with TP53 mutations may help in identifying early clonal evolution and predict disease progression (Jadersten et al, 2011). SF3B1 mutations are especially correlated with the ring sideroblast phenotype (Papaemmanuil et al, 2011). Mutations in other genes such as ASXL1, EZH2 and RUNX1 confer adverse prognosis in univariate analysis but their prognostic significance in multivariate analysis has not yet been consistently reproduced in independent series (Bejar et al, 2011).

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**Table III. WHO 2008 classification of myelodysplastic syndrome (MDS).**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Blood findings</th>
<th>Bone marrow findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory cytopenias with unilineage dysplasia (RCUD)</td>
<td>Unicytopenia or bcytopenia*</td>
<td>Unilineage dysplasia: 10% of the cells of the affected line are dysplastic</td>
</tr>
<tr>
<td>Refractory anaemia (RA)</td>
<td>No or rare blasts (&lt;1%)</td>
<td>&lt;5% blasts</td>
</tr>
<tr>
<td>Refractory neutropenia (RN)</td>
<td>No or rare blasts (&lt;1%)</td>
<td>&lt;15% of the erythroid precursors are ring sideroblasts</td>
</tr>
<tr>
<td>Refractory thrombocytopenia (RT)</td>
<td>Anaemia</td>
<td>Erythroid dysplasia only</td>
</tr>
<tr>
<td>Refractory anaemia with ring sideroblasts (RARS)</td>
<td>No blasts</td>
<td>≥15% of erythroid precursors are ring sideroblasts</td>
</tr>
<tr>
<td>Refractory thrombocytopenia (RT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refractory anaemia with ring sideroblasts (RARS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia (RCMD)</td>
<td>Cytopenias</td>
<td>Dysplasia in ≥10% of cells in two or more myeloid lineages (neutrophil and/or erythroid precursors and/or megakaryocytes)</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia (RCMD-RS)</td>
<td>No or rare blasts (&lt;1%)</td>
<td>≤5% blasts</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia (RCMD-RS)</td>
<td>No Auer rods &lt;1 x 10^9/l monocytes</td>
<td>No Auer rods</td>
</tr>
<tr>
<td>Refractory anaemia with excess blasts-1 (RAEB-1)</td>
<td>Cytopenias</td>
<td>Unilineage or multilineage dysplasia</td>
</tr>
<tr>
<td>Refractory anaemia with excess blasts-1 (RAEB-1)</td>
<td>No Auer rods</td>
<td>5–9% blasts²</td>
</tr>
<tr>
<td>Refractory anaemia with excess blasts-1 (RAEB-1)</td>
<td>&lt;1 x 10^9/l monocytes</td>
<td>No Auer rods</td>
</tr>
<tr>
<td>Refractory anaemia with excess blasts-2 (RAEB-2)</td>
<td>Cytopenias</td>
<td>Unilineage or multilineage dysplasia</td>
</tr>
<tr>
<td>Refractory anaemia with excess blasts-2 (RAEB-2)</td>
<td>5–19% blasts ±Auer rods§</td>
<td>10–19% blasts</td>
</tr>
<tr>
<td>Refractory anaemia with excess blasts-2 (RAEB-2)</td>
<td>≤1 x 10^9/l monocytes</td>
<td>± Auer rods¶</td>
</tr>
<tr>
<td>Myelodysplastic syndrome – unclassified (MDS-U)</td>
<td>Cytopenias</td>
<td>(a) Unequivocal dysplasia in less than 10% in one/more myeloid cell lineages but typical cytogenetic abnormality</td>
</tr>
<tr>
<td>Myelodysplastic syndrome – unclassified (MDS-U)</td>
<td></td>
<td>(b) RCUD/RCMD with 1% blasts in peripheral blood</td>
</tr>
<tr>
<td>MDS associated with isolated del(5q)</td>
<td>Anaemia</td>
<td>(c) RCUD with pancytopenia</td>
</tr>
<tr>
<td>MDS associated with isolated del(5q)</td>
<td>Usually normal or increased platelet count</td>
<td>Normal to increased megakaryocytes with hypolobated nuclei</td>
</tr>
<tr>
<td>MDS associated with isolated del(5q)</td>
<td>No or rare blasts (&lt;1%)</td>
<td>&lt;5% blasts</td>
</tr>
<tr>
<td>MDS associated with isolated del(5q)</td>
<td></td>
<td>Isolated del(5q) cytogenetic abnormality</td>
</tr>
<tr>
<td>MDS associated with isolated del(5q)</td>
<td></td>
<td>No Auer rods</td>
</tr>
</tbody>
</table>

*Note: Therapy-associated MDS and MDS/MPN should be classified in the category “Therapy-associated Myeloid Malignancies”.

†Bicytopenia may occasionally be observed. Cases with pancytopenia should be classified as MDS-U.

‡If the marrow myeloblast percentage is <5% but there are 2–4% myeloblasts in the blood, the diagnostic classification is RAEB-1. If the marrow myeloblast percentage is <5% and there are ≤1% myeloblasts in the blood, the case should be classified as MDS-U.

§Cases with Auer rods and <5% myeloblasts in the blood and <10% in the marrow should be classified as RAEB-2.

¶Reproduced, with the permission of the publisher, from Swerdlow et al (2008).
et al., 2012; Papaemmanuil et al., 2013). Molecular analysis cannot yet be incorporated into routine diagnostic or prognostic evaluation of patients with MDS but will likely provide such important information in the near future. (Evidence levels 2B,C).

Flow cytometry. Flow cytometry is not mandatory for the diagnosis of MDS. There is no specific immunophenotypic finding diagnostic of MDS. Multiple aberrant flow cytometric anomalies may support the diagnosis but should be interpreted in association with morphological and cytogenetic findings (Evidence levels 2B,C). Common findings are aberrant antigen expression on myeloblasts, maturing myeloid, monocytic and erythroid lineages, reduced numbers of B-cell progenitors (Sternberg et al., 2005), and increased CD34+ cells. Many cases also show lineage infidelity antigen expression. Recommendations for standardization of flow cytometric methodology, including consensus recommendations for cell sampling, handling and processing have been published, along with definition of minimal panels of antibodies for analysis (van de Loosdrecht et al., 2009; Della Porta et al., 2012; Westers et al., 2012a,b).

Prognosis of MDS

Since its publication in 1997, the IPSS has been an important tool for assessing the outcome of patients with untreated, primary adult MDS (Greenberg et al., 1997). Recently, additional prognostic variables have been identified, the most important of which are newer cytogenetic groupings (Table IV) that give more accurate prognostic information (Schanz et al., 2012).

Table IV. IPSS-R cytogenetic prognostic subgroups.

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>Very Good</th>
<th>Good</th>
<th>Intermediate</th>
<th>Poor</th>
<th>Very Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y, del(11q)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal, del(5q), del(12p), del(20q), double including del(5q)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>del(7q), +8, +19, i(17q), any other single or double independent clones</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−7, inv(3)(t(3q), double including -7/del(7q), complex: 3 abnormalities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex: &gt;3 abnormalities</td>
<td></td>
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</table>

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Table V. IPSS-R prognostic score values.

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>Intermediate</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics</td>
<td>Very Good</td>
<td></td>
<td>Good</td>
<td></td>
<td>1</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Bone marrow blast %</td>
<td>≤2</td>
<td>2−5</td>
<td></td>
<td>5−10</td>
<td></td>
<td></td>
<td>&gt;10</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin concentration (g/l)</td>
<td>≥100</td>
<td>80−100</td>
<td>&lt;80</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count (×10^9/l)</td>
<td>≥100</td>
<td>50−100</td>
<td>&lt;50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil count (×10^9/l)</td>
<td>≥0.8</td>
<td>&lt;0.8</td>
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</table>

The research in Table V was originally published in Blood. Greenberg et al. (2012). © the American Society of Hematology.

The Revised IPSS (IPSS-R) has recently described the relative importance of defined clinical factors with regards to prognosis by multivariate analysis of 7012 primary, adult MDS patients not treated with disease-modifying therapies. Although the IPSS-R used the same parameters as the IPSS (cytogenetic groups, marrow blast% and cytopenias), the IPSS-R has been able to refine these further by categorizing more cytogenetic subgroups, refinement of blast counts <5% and depth of cytopenias (Table V) (Greenberg et al., 2012). This new scoring system has 5 IPSS-R categories and has improved the prognostic ability to determine survival and AML evolution in untreated adult patients with primary MDS (Table VI). A web-based tool to calculate the IPSS-R can be accessed via the UK MDS Forum website (www.ukmdsforum.org). This model should be the preferred scoring system for determining prognosis.

It should be noted that the IPSS-R is not designed to be a dynamic scoring system, and therefore can only provide a prognosis at diagnosis. The WHO based-classification Prognostic Scoring System (WPSS) that encompasses the WHO diagnosis, IPSS cytogenetic criteria and transfusion need/haemoglobin concentration, and also the IPSS (Malcovati et al., 2007) allow an estimation of prognosis at any time point during the disease course.

Diagnosis and prognosis of MDS

Key recommendations
1. MDS should be suspected in patients with otherwise unexplained cytopenias(s) or macrocytosis. Grade 1A
2. The initial assessment of a patient with unexplained cytopenias(s) may not confirm a diagnosis of MDS. Further follow-up and reassessment may be necessary to reach a firm diagnosis. (Grade 2B,C)
3. Initial assessment of a patient with suspected MDS should include a minimum set of investigations and the differential diagnosis of marrow dysplasia should be considered. Grade 1A
4. Patients with MDS should be assessed by a haematologist and, except where clearly inappropriate, offered review by a regional or national expert given the disease rarity.
5. All cases of MDS should be classified according to the WHO Revised Classification 2008. Grade 1A
Management of MDS

Management recommendations for MDS have largely evolved through the IPSS era and, as such, are driven by the IPSS system. ‘Low-risk’ MDS includes patients with IPSS Low/Intermediate-1 (INT-1), and ‘high-risk’ MDS includes those with IPSS Intermediate-2 (INT-2)/High. It remains unclear whether IPSS-R Intermediate patients should be grouped into ‘low-risk’ or ‘high-risk’ categories. As such, patients should be considered for management driven by individual patients’ clinical and biological characteristics and by patient and physician preferences. No recommendations can be made to predict response to recommended therapy in relation to the IPSS-R, which should be used to evaluate prognosis in all patients, but not yet to guide therapy.

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

National clinical trials that are currently open and recruiting MDS patients can be found at: http://public.ukcrn.org.uk [Search Cancer, Haematological, Myelodysplastic (in title box)] OR http://www.cancerresearchuk.org/cancer-help/trials/.

Supportive care

Supportive care, including transfusions and antibiotics, is central to the management of MDS patients. Irradiated blood products are recommended after a stem cell transplant or treatment with antithymocyte globulin (ATG).

Management of anaemia with transfusion. Red cell transfusion is given primarily to correct symptomatic anaemia, thereby improving quality of life (QOL) (Nilsson-Ehle et al, 2011). The threshold haemoglobin concentration for transfusion will vary from patient to patient due to comorbidities, such as chronic pulmonary disease and heart failure, therefore no single recommendation for a transfusion trigger haemoglobin concentration can be made. Chronic red cell transfusion will lead to complications including iron overload and the development of red cell alloantibodies. Consideration should be given to extended red cell phenotyping in patients who are regularly transfused, and cytomegalovirus (CMV) testing is recommended for patients who are eligible for a stem cell transplant.

Management of neutropenia and infection. Protocols and guidelines for the management of febrile neutropenia, including the assessment and management of possible fungal infections, are well developed and clinicians are encouraged to follow local hospital guidelines. In addition, the National Institute for Health and Care Excellence (NICE) guidelines for the prevention and management of neutropenic sepsis in cancer patients are available (CG151 published September 2012) (Phillips et al, 2012). The use of granulocyte-colony stimulating factor (G-CSF) may be considered in patients with recurrent infections who have low risk disease.

Although there is meta-analysis evidence supporting the use of itraconazole as antifungal prophylaxis in patients undergoing active therapy for haematological malignancies (Glamach er et al, 2003), there is no evidence to suggest that this should be routinely given to all patients with myelodysplasia.

Management of thrombocytopenia and bleeding. The use of platelet transfusion is central to the management of bleeding episodes in myelodysplasia. Routine prophylactic platelet transfusion may be of symptomatic value in individual patients but there is no evidence to support their routine use in stable thrombocytopenia (in patients not undergoing intensive chemotherapy), even with platelet counts <10 × 10⁹/ℓ (British Committee for Standards in Haematology Blood Transfusion Task Force, 2003). The short-term use of tranexamic acid as a symptomatic measure in mucous membrane bleeding may be beneficial but caution should be shown in patients with ischaemic heart disease or haematuria. There is some evidence for the use of danazol in selected patients, in terms of short-term improvement in the platelet count (Wattel et al, 1994; Chan et al, 2002).

The thrombopoietin receptor (Tpo-R) agonist, romiplostim has been evaluated in a large randomized phase 2 study following an encouraging dose finding study (Kantarjian et al, 2010). The study was halted prematurely because of concerns about increasing blast cell counts in patients receiving active drug. It remains unclear if this translated into an increase in disease progression. There were fewer bleeding episodes and fewer platelet transfusion episodes in the romiplostim arm. Tpo-R agonists cannot currently be recommended outside clinical trials.
Spiritual/emotional health needs. The diagnosis of MDS is often overwhelming to the patient and their family. It can be a difficult diagnosis for the patient to understand, and there are many treatment options (both active and supportive) to consider. All patients should be offered support by the local Clinical Nurse Specialist with experience in MDS. The UK MDS Patient Forum (www.mdspatientsupport.org.uk) is a valuable resource for all patients, 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 (Sekeres et al, 2011).

Key recommendations

1. Supportive Care should be the mainstay for all patients with MDS and symptomatic cytopenias. Grade 1A
2. Blood transfusions should be given to improve symptomatic anaemia. Grade 1A
3. A trigger haemoglobin concentration cannot be recommended for all patients, it should be individualized. Grade 1A
4. Extended red cell phenotyping should be considered for patients receiving regular red cell transfusions. Grade 2C
5. Routine platelet transfusions should not be given to stable, non-bleeding patients who are not receiving intensive chemotherapy. Grade 1A
6. Local policies should be in place for the management of neutropenic sepsis. Grade 1A
7. Emotional health needs should be continually assessed and addressed. Disease-specific information should be re-iterated regularly

Management of low risk MDS

Patients defined by the IPSS as Low or INT-1, and by the IPSS-R as Very Low and Low have a comparatively favourable prognosis. The clinical sequelae encountered in low risk MDS patients relate to the depth of cytopenias and the treatment to support those. An algorithm for the management of low risk MDS can be seen in Fig 1.

Iron chelation in MDS. A chronic red cell transfusion programme for MDS patients results in tissue iron overload. Patients with ineffective erythropoiesis, particularly those with sideroblastic anaemia, often have a baseline excess of body iron. The key questions, yet to be resolved are:

1. Is tissue iron overload in MDS independently associated with adverse clinical outcome?
2. How best to measure iron loading to reflect the possible adverse clinical outcome?

Although serum ferritin is influenced by factors other than iron overload, most guideline recommendations for iron chelation therapy are based upon this parameter. The number of red cell units transfused may be useful but it is likely that transfusion intensity is more relevant for adverse outcome

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Low/Int-1 IPSS

Very Low/Low IPSS-R

Discuss potentially eligible patients with allogeneic transplant team soon after diagnosis

Early Allograft Preferred

Non-Transplant Options

Non-sideroblastic

Sideroblastic

Trial of ESA

Trial of ESA and G-CSF

ATG and CSA

Consider in those aged <60 years with normal karyotype or trisomy 8

Consider in those with Sq- and s1 additional karyotypic abnormality if ESA therapy fails

Supportive Care

Lenalidomide


Fig 1. Algorithm for management of low risk myelodysplastic syndrome.
than total units transfused (Malcovati et al, 2006; Durairaj et al, 2011). Magnetic resonance imaging (T2*) can be used to quantitate liver and cardiac iron but the relationship with transfused red cell burden/outcome has not been consistently demonstrated in MDS (Chacko et al, 2007; Di Tucci et al, 2008; Roy et al, 2011).

3 Can iron chelation therapy influence the natural history of chronically transfused MDS patients?

There is no direct evidence to support a survival benefit for iron chelation therapy in MDS and only randomized controlled trials will answer this definitively. A small proportion of patients have improved haematopoiesis on iron chelation. Several studies purporting to demonstrate improved survival for chelated patients are all retrospective and methodologically limited (Rose et al, 2010). Despite this, there is almost universal recommendation in national and international guidelines for iron chelation therapy in selected MDS patients (Greenberg et al, 2011).

4 Which iron chelation therapy should be used (if any)?

Deferasirox is the only licensed agent for iron chelation therapy in MDS (when deferoxamine therapy is contraindicated or inadequate). The efficacy data used for licensing are phase 2 studies comprising 47 MDS patients out of a total of 1009 (predominantly ß thalassaemia) patients (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000670/WC500033929.pdf). Larger phase 2 studies have shown a clear reduction in serum ferritin and labile plasma iron species over 1–2 years of therapy but tolerability remains unclear (List et al, 2012). Only half of all patients complete 1 year of therapy, most due to non-treatment related adverse events. The US Food and Drug Administration (FDA) has added a black box warning to the label for deferiprone for enhanced vigilance with renal impairment, hepatic impairment and gastrointestinal haemorrhage. Deferasirox remains the therapy of choice as there is the longest duration of clinical experience, it is safe and efficacious if suitably monitored, although somewhat cumbersome compared to its oral competitors. Deferiprone is efficacious but not recommended in neutropenic patients (Cermak et al, 2011).

Key recommendations

1 Iron chelation therapy cannot be routinely recommended for MDS patients with transfusional iron overload. Grade 1C

2 Consideration may be given to chelation therapy for patients with a very good prognosis, specifically patients with WHO RA, RARS and isolated del(5q). Triggers may include more than 20 units of red cells transfused, serum ferritin >1000 µg/l in patients for whom continuing red cell transfusion is predicted. Grade 2C

3 Patients treated with iron chelation therapy should ideally receive this treatment within clinical trials.

4 Desferrioxamine remains the therapy of choice with the longest record of safety and efficacy of all three agents available. Deferasirox is recommended for patients intolerant of desferrioxamine. Deferiprone could be considered in patients with normal baseline neutrophil counts. Grade 2C

Erythropoiesis stimulating agents (ESAs). Erythropoietin alfa and beta (EPO) therapy have been used to treat the anaemia of MDS for over 20 years and since the last BCSH guideline (Bowen et al, 2003), the effectiveness of other ESAs, particularly darbepoetin-alpha (DA) has been widely reported. Despite the deficiencies in the quality of trials data available, there are enough data to support the safety of ESAs in MDS compared to the concerns in solid tumours (Rizzo et al, 2010). There are also comparative cohort data to at least suggest that there may be a survival advantage for responders to ESA therapy (Jadersten et al, 2008; Park et al, 2008) and improvements in global QOL scores for responders (Hellstrom-Lindberg et al, 2003; Nilsson-Ehle et al, 2011) though not in the underpowered randomized study by Casadevall et al (2004). Unfortunately, despite numerous additional publications, the key outstanding issues relating to the use of ESAs have still not been answered by appropriately powered randomized trials. These issues include whether or not there is a significant benefit in QOL and overall survival (OS) advantage for responders to ESAs, compared to patients on regular red cell transfusion support. Two global phase 3 randomized controlled trials of ESA efficacy in MDS are now ongoing.

Who should be offered ESA therapy?—The characteristics of patients who are predicted to have a high chance of responding to EPO are well documented and have not changed significantly since the last guideline (Hellstrom-Lindberg et al, 1998, 2003; Remacha et al, 1999; Bowen et al, 2003). The validated model for predicting response to EPO should be used (Hellstrom-Lindberg et al, 2003; Jadersten et al, 2005). The model was designed and validated for use with EPO, but is extrapolated for use with DA. The model is used as shown in Table VII:

ESA therapy should be considered for anaemic MDS patients with an IPSS score of Low or INT-1 who fulfil the above criteria for predicting response (Score 0 and 1).

Table VII. Validated model for predicting response to erythropoietin

<table>
<thead>
<tr>
<th>Transfusion need</th>
<th>Point</th>
<th>S-EPO</th>
<th>Score 1 point</th>
<th>Score 2 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 units RBC/month</td>
<td>0</td>
<td>&lt;500 u/l</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>≥2 units RBC/month</td>
<td>1</td>
<td>≥500 u/l</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Guideline

Patients with higher risk MDS are, in general, not to be considered for therapy with ESA because of poor responses, short survival times and the increasing use of hypomethylating agents and stem cell transplantation, which require red cell transfusion support.

Initial treatment—For non-sideroblastic phenotypes, treatment should start with EPO or DA alone. The recommended starting dose for EPO is 30 000 units per week for 8 weeks (Garypidou et al, 2003). If there is no response at 8 weeks the dose can be doubled to 60,000 units once per week or 30,000 units twice per week for a further 8 weeks.

The starting dose for DA should be 300 µg once every 14 d or 150 µg once every 7 d (Giraldo et al, 2006; Gabri-love et al, 2008). The dose can be increased after 8 weeks in non-responders to a maximum of 300 µg per week for a further trial period of 8 weeks (Mannone et al, 2006). There are small randomized trials suggesting that erythroid responses to the addition of granulocyte G-CSF to EPO are better than EPO alone (Hellstrom-Lindberg et al, 1998; Baleari et al, 2006; Greenberg et al, 2009). However, the addition of G-CSF to non-sideroblastic cases is not generally as successful as when used in sideroblastic cases.

Treatment of sideroblastic phenotypes (RARS and RCMD-RS) is similar, but there is convincing evidence of synergism with G-CSF, leading to an overall response rate of 50% in RARS (Hellstrom-Lindberg et al, 1998; Greenberg et al, 2009). It is recommended, therefore, that the above ESA schedules should be combined with G-CSF from the outset in sideroblastic cases. G-CSF should be given so as to approximately double the starting white cell count if <1.5 × 10^9/l or keep the white cell count in the range of 6–10 × 10^9/l. Most clinical experience suggests that a starting dose of 300 µg per week in 2/3 divided doses, rising to 300 µg three times per week in non-responders, is appropriate. Paediatric dosing of 105 µg 2/3 times per week is a popular and cost effective way of starting the treatment.

One study has suggested that starting ESA therapy within 6 months of diagnosis improved response rates and delayed the onset of transfusions, 80 months vs. 35 months, compared to later initiation of ESA (Park et al, 2010).

Response monitoring, criteria for response and long term therapy—As outlined above, a maximum trial period of 16 weeks therapy should be considered. Some studies have suggested that prolonging the trial of therapy period to 26 or 36 weeks increases the proportion of responders (Mantovani et al, 2000; Terpos et al, 2002). However, the response criteria used were less stringent than in other studies. Stringent criteria for defining response used in the predictor of response model (Hellstrom-Lindberg et al, 2003) 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.

Patients who achieve a complete erythroid response have been shown to have a longer duration of response than those who only achieve a partial erythroid response (29 months vs. 5-5 months) (Hellstrom-Lindberg et al, 2003). For patients who have achieved a durable complete erythroid response the dose of ESA should be slowly reduced, to the lowest dose that maintains the response. If the response is lost at maximum doses then functional iron deficiency should be considered, but this seems much less common in MDS patients treated with ESA than in patients with renal anaemia.

The risk of thrombosis in MDS patients responding to ESA has been estimated at 2% in one study using DA (Gabrilove et al, 2008) and the authors of this guideline have seen occasional thrombotic episodes in their practice when haemoglobin concentrations have risen significantly above 120 g/l, especially in patients with increased vascular risk factors, such as previous stroke, diabetes mellitus or hypertension. It, therefore, seems appropriate to temporarily interrupt ESA therapy if the haemoglobin climbs above 120 g/l or if there is a rapid rise in the haematocrit. Lower doses can then be introduced with careful monitoring of the parameters of response.

Key recommendations

1 Patients with IPSS Low and INT-1 MDS, symptomatic anaemia and who fulfil the criteria for a high or intermediate predictive score for response should be considered for a trial of therapy with an ESA. Grade 1B
2 Patients with non-sideroblastic phenotypes should be offered a trial of therapy with an ESA. Grade 1B
3 Patients with sideroblastic phenotypes should be offered a trial of therapy with an ESA plus G-CSF. Grade 1B
4 Patients should receive a maximum trial period of 16 weeks of therapy. This should comprise 8 weeks at the starting dose of ESA ± G-CSF and a further 8 weeks at the higher doses, if required. Grade 2B
5 Patients achieving a complete or partial erythroid response by accepted criteria should continue on long term therapy until the response is lost and at the minimum dose of ESA required to maintain the response. Grade 2B
6 The haemoglobin concentration should not be allowed to rise above 120 g/l. Grade 2C

Immunosuppressive therapy. There seems to be a component of immunological dysregulation in at least some patients with low-risk MDS. These include a greater than expected incidence of autoimmune abnormalities (Hamblin, 1996), augmented cytotoxic T-cell activity (Kochenderfer et al, 2002) and dysregulation of regulatory T cells (Kordasti et al, 2007). There is also an overlap between low-risk MDS and aplastic anaemia. These provide the rationale for immunosuppressive agents, which are now an established and effective treatment for a small subgroup of patients.
Immunosuppressive therapy should be considered in patients alongside stem cell transplantation.

**Antilymphocyte/antithymocyte globulin (ALG/ATG)**—The response rate to ATG in unselected low risk MDS patients is approximately 30–40% (Moldrem et al, 2002; Lim et al, 2007). In contrast to aplastic anaemia, modelling data suggest a lower response rate to ATG with increasing age in MDS patients (Sloand et al, 2008), although patient numbers are small.

The initial assumption that this therapy would be effective only in patients with hypocellular bone marrow is incorrect and responses in patients with normocellular and even hypercellular marrows have been reported. Data suggests that patients have a higher response rate if treated early after transfusion dependence (Saunthararajah et al, 2003), however HLA DR15 status and presence of a paroxysmal nocturnal haemoglobinuria (PNH) clone has not been a consistent discriminator for response (Lim et al, 2007; Sloand et al, 2008).

Treatment with ATG is associated with a considerably higher morbidity/mortality in older patients with aplastic anaemia (Tichelli et al, 1999) and its use in MDS should be restricted to fit, relatively younger patients (typically <60 years). ATG must be administered as an in-patient in units experienced with such therapy. The preferred source of ATG is horse-derived (currently only available as ATGAM, Pfizer). In aplastic anaemia there is emerging evidence for a lower efficacy and higher morbidity/mortality in patients treated with rabbit ATG compared with horse ATG (Scheinberg et al, 2011; Marsh et al, 2012), however evidence for this differential efficacy and toxicity in MDS is lacking.

Ciclosporin should be introduced following ATG (Sloand et al, 2008) and continued for at least 6 months, aiming to keep the trough level 100–200 μg/L. Blood pressure, renal and liver function must be carefully monitored. Following withdrawal of ciclosporin at 6 months, median duration of response is 2 years. In the absence of toxicity, it is reasonable to continue ciclosporin therapy until maximal response is achieved. A slow tapering of dose should then be tried but may result in a loss of response, in which case the ciclosporin dose should be titrated back up in an attempt to achieve a further haematological response. Responders may have a tri-lineage response although red cell transfusion independence is usually the most clinically significant.

**Ciclosporin**—Ciclosporin may have a niche role for older patients with associated evidence of autoimmune phenomena or a hypocellular bone marrow. Response is lower than for ATG and earlier studies indicating a high response rate (Okamoto et al, 2000) have not been easily reproduced.

**Key recommendations**

1. Immunosuppressive therapy with horse ATG (currently available as ATGAM, Pfizer) can be recommended in suitable low or INT-1 IPSS MDS patients who are typically less than 60 years of age and have a normal karyotype or trisomy 8. Grade 2C.

**MDS associated with del 5q.** The 5q- syndrome is characterized by a refractory anaemia, usually seen in older women with macrocytosis, thrombocytosis, characteristic nonlobulated megakaryocytes and erythroid hypoplasia. It has a relatively indolent natural history, with a median survival of at least 6 years, but patients are often transfusion-dependent and the AML transformation rate at 5 years is approximately 20%. Other patients with MDS can also have del(5q) without the typical features above, or with atypical features, such as trilineage dysplasia, increased medullary blasts and additional cytogenetic abnormalities. Independent predictors for OS in MDS with del(5q) include transfusion dependence, age, thrombocytopenia and >1 additional cytogenetic aberration. Factors predictive of AML transformation are bone marrow blast count and transfusion dependence (Germing et al, 2012).

Response of del(5q) MDS to ESA in the pre-lenalidomide era appears inferior to that in patients without this lesion [39% v 52%, International Working Group (IWG) 2006 criteria (Cheson et al, 2006)] (Kelaidi et al, 2008).

List et al (2005) described the response of MDS with del (5q) to the immunomodulatory drug lenalidomide, a 4-amino-glutarimide analogue of thalidomide in a phase 1–2 study in 43 patients with MDS resistant to ESA (List et al, 2005). Patients with the characteristic 5q31-1 deletion had an 83% response rate compared to 57% in patients with normal cytogenetics and only 12% among patients with other cytogenetic abnormalities. This gave rise to a larger phase 2 study (List et al, 2006). One hundred and forty-eight patients with 5q deletion were treated with 10 mg daily, given for either 21 or 28 d in a 28-d cycle. At 24 weeks of treatment, 66% of patients were transfusion independent with a median time to response of 4–5 weeks although some patients took up to 48 weeks to demonstrate a response. The main toxicities were neutropenia and thrombocytopenia. At 2 years, 55 of 112 responders (49%) remained transfusion independent.

Fenaux et al (2011) reported the results of the phase 3 randomized MD5004 study in low and INT-1 risk transfusion dependent MDS with del(5q), which compared two doses of lenalidomide (10 mg daily for 21 d in a 4-week cycle, or 5 mg daily for 28 d) with placebo. The 10 mg dose resulted in transfusion independence in 58% of patients with del(5q), compared with 42% in the 5 mg group and 6% in the placebo. Transfusion independence was associated with a lower risk of transformation to AML. Cytogenetic responses were seen in 50% and 25% of the two lenalidomide treatment groups. In this study, a normal baseline platelet count appears to predict response (80%) compared to patients presenting with thrombocytopenia (19%).

Based on these data, lenalidomide was licensed in the United States for the treatment of del(5q) with IPSS Low or
INT-1, but it initially failed to gain regulatory approval in Europe based on a perceived increased risk of progression to AML. This risk was reviewed in a study by the French MDS Group, who examined 95 patients treated with 10 mg lenalidomide daily for 21 d in a 28-d cycle (Ades et al, 2012). Six patients (6.3%) progressed to AML during the duration of the study. The authors compared these data to a group of 99 patients with del(5q) who had never received lenalidomide, controlling for confounding factors using propensity scoring. At 4 years, the risk of progression was 9% with lenalidomide and 15.8% without lenalidomide; this difference did not reach statistical significance. These data are similar in a larger study also providing some reassurance about the risk of AML transformation in patients treated with lenalidomide (Kuendgen et al, 2013). Other groups have reported an increased risk of secondary malignancies with lenalidomide in myeloma (Attal et al, 2012). This increased risk (3-1 cases per 100 patient-years compared to 1-2 cases per 100 patient-years, \( P = 0.002 \)) appears limited to myeloma and chronic lymphocytic leukaemia and, apart from the perceived risk of AML in MDS patients, is not reported in del(5q) patients.

The European Medicines Agency’s (EMEA): Committee for Medicinal Products for Human Use (CHMP) has now adopted a positive opinion for lenalidomide for the treatment of patients with transfusion-dependent anaemia due to low or INT-1-risk MDS associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate. This recommendation is narrower than the US FDA market approval, which includes all patients with del(5q) and IPSS Low/INT-1 irrespective of the number of additional cytogenetic abnormalities.

Patients with small \( TP53 \)-mutated clones and/or \( \geq 2\% \) strongly positive \( TP53 \)-staining bone marrow cells by immunohistochemistry have a poorer prognosis and largely fail to respond to lenalidomide. This may be an emerging factor to consider in the decision to use lenalidomide (Jadersten et al, 2011).

Thrombo-prophylaxis can be considered where benefit outweighs risk on an individual basis.

Selected patients with del(5q) and IPSS Low/INT-1 may be candidates for allogeneic stem cell transplantation. These include lenalidomide-treated patients who fail to achieve transfusion independence, those losing their response, or patients with transfusion dependence not considered suitable for lenalidomide (Gohring et al, 2010).

Key recommendations

1 Patients with IPSS Low or INT-1 MDS with del(5q), 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. Grade 1B.

2 For transfusion dependent patients unsuitable for a trial of ESA, or for non-responders/patients losing their response to ESA, who have IPSS Low or INT-1 MDS with del(5q), consider treatment with lenalidomide 10 mg daily for 21 d repeated every 28 d. Grade 1B. A careful discussion with patients about the risk and benefit is mandatory.

3 Selected MDS patients with del(5q) and IPSS Low/INT-1 may be candidates for allogeneic stem cell transplantation. These include lenalidomide-treated patients who fail to achieve transfusion independence, those losing their response, or patients with transfusion dependence not considered suitable for lenalidomide. Grade 2B.

4 Lenalidomide is not currently recommended for patients with del(5q) and bone marrow blasts >5%, multiple (complex) cytogenetic abnormalities in addition to del (5q), patients with IPSS INT-2/High or with a known mutated \( TP53 \) gene. Grade 2B.

Curative options in low risk MDS; the place of allogeneic haematopoietic stem cell transplantation (HSCT). Allogeneic HSCT is the only treatment modality with proven curative potential for MDS. Therefore all patients with newly diagnosed MDS should be discussed at a MDT and the role of allogeneic HSCT should be considered. Appropriate patient selection for transplantation is an important determinant of outcome and the decision to transplant patients with low risk disease involves balancing the risk of disease progression, the chances of a transplant strategy succeeding and the risk of transplant-related mortality (TRM). As such, regular review of the appropriateness of transplantation should continue through the patient’s disease course.

In favour of an early transplant are the data that patients transplanted with low risk MDS have a lower relapse risk than those transplanted with high-risk disease (Runde et al, 1998; de Witte et al, 2000; Lim et al, 2010). Allogeneic HSCT for low risk disease is most likely to be successful if patients are transplanted at a younger age, with disease duration of <12 months and prior to the onset of transfusion dependence (Anderson et al, 1996; Al-Ali et al, 2007; de Witte et al, 2009). Against this, are the data from Cutler et al (2004), which suggest that delaying transplantation until the time of disease progression for patients with IPSS Low and INT-1 maximizes OS. However this analysis did not include patients treated with reduced intensity conditioning (RIC) regimens or patients with matched unrelated donors, and did not take into account comorbidity scores. In addition several prognostic factors, such as red cell transfusion dependence, bone marrow fibrosis and molecular abnormalities (RUNX1, ASXL1 mutation), which have emerged since then, were not included in the IPSS and could confer a more adverse prognosis than previously realized for a given IPSS score. Data are currently lacking for the outcome of such poorer risk patients following allogeneic HSCT. However these factors are not considered in the Cutler model or in the IPSS per se.

There is some evidence that WPSS (including red cell transfusion dependence) can predict transplant outcome (Alessandrino et al, 2010).
Patient age per se does not have a major impact on transplant outcome but the comorbidities that are associated with increasing age should be taken into account when assessing MDS patients for transplantation. The HCT-CI (Sorror et al., 2005) and the European Group for Blood and Marrow Transplantation (EBMT) risk score (Gratwohl et al., 1998) have both been validated for MDS and shown to predict OS and TRM (Sorror et al., 2007; Gratwohl et al., 2009; Sperr et al., 2010). Iron overload is not part of most comorbidity scores and, when assessed by serum ferritin, has been associated with a higher non-relapse mortality (NRM) and increased risk of infection after allogeneic HSCT and MA conditioning (Armand et al., 2007; Pullarkat et al., 2008). More recently the possibility that the adverse prognostic impact of pre-HSCT hyperferritinaemia may be related to factors independent of iron overload has been raised (Armand et al., 2012) and it remains unclear how to treat iron overload in patients who undergo allogeneic HSCT.

Key recommendations

1 Clinicians should discuss all patients eligible for stem cell transplantation with their local transplant unit and each case should be assessed on its own merits. Grade 2B
2 Consideration should be given to the EBMT risk score, which has been validated for MDS, and the HCT-CI. Grade 2B
3 Consideration should also be given to additional prognostic features, such as red cell transfusion dependence, which can profoundly influence prognosis in patients eligible for transplant. Grade 2B
4 Current data suggest that transplants from matched unrelated donors can have similar outcomes to those from matched sibling donors. Grade 2B
5 MA conditioning regimens are recommended over RIC regimens when they can be delivered safely. Grade 2C.

Management of CMML

This is a challenging disorder largely due to the advanced median patient age (76 years) and the paucity of evidence to guide management. The median survival is short; 20 months overall, range 7–60 months (Germing et al., 2004) and therefore treatment planning is recommended at diagnosis, as younger patients and/or patients with poor risk disease may be considered for an allogeneic stem cell transplant at the outset. As CMML was not incorporated in the WPSS (nor was proliferative CMML incorporated in the IPSS), alternative prognostic scores may be utilized, such as the Dusseldorf score (Aul et al., 1992), and cytogenetic abnormalities should also be taken into account (Such et al., 2011). A recent CMML-specific prognostic score (CPSS) has been developed, which incorporates a cytogenetic classification, CMML-Myelodysplastic [MD, white blood cell (WBC) count <13 × 10^9/l] vs. Myeloproliferative (MP, for cases with a WBC count ≥13 × 10^9/l), CMML-1 vs CMML-2 and trans- fusion dependency. This score has been validated on independent cohorts of CMML patients, and appears discriminatory enough to be useful in clinical practice (low risk patients exhibit a median OS of 72 months versus 5 months for high risk) (Such et al., 2013).

Non-transplant treatment approaches include supportive care only, hydroxyurea for proliferative symptoms and control of leukocytosis, hypomethylating agents or clinical trials. There are no supportive care data specific to CMML. Hydroxyurea was superior to etoposide in the only randomized trial performed specifically in CMML (Wattel et al., 1996). There is little evidence to support alternative chemotherapy regimens (e.g. low dose cytarabine) as specific studies in CMML are lacking. Azacitidine is now licensed by the EMEA for non-proliferative (WBC < 13 × 10^9/l) CMML-2 on the basis of 1 patients included in the registration AZA001 trial (Fenaux et al., 2009). Previous small case series have described efficacy in this disorder (Costa et al., 2011; Breccia et al., 2012; Thorpe et al., 2012). However a recent multicentre Phase 2 trial by the UK NCRI (National Institute for Health Research [NIHR] Cancer Research Network) MDS Trial Subgroup demonstrated limited activity but with a small number of clinically meaningful responses (Drummond et al., 2012). Decitabine also has reported efficacy in CMML but remains unlicensed by the EMEA (Aribe et al., 2007; Kantarjian et al., 2007; Oki et al., 2008; Wijermans et al., 2008; Braun et al., 2011). A recent French study demonstrated a 38% response rate in a high-risk CMML population, including 10% complete response and 21% bone marrow response (Braun et al., 2011). 75% patients on hydroxyurea were able to stop this treatment, a similar proportion to that in the UK trial of azacitidine (Drummond et al., 2012). The role of hypomethylating agents has not been definitively established in all CMML patients and azacitidine can only be recommended for use within the licensed indication or in clinical trials. Intensive AML-type chemotherapy may be considered for selected patients (Wattel et al., 1997) requiring cytreduction pre-allograft. Intensive chemotherapy alone rarely, if ever produces durable complete remission (Wijermans et al., 2008). Allogeneic transplant can result in long term survival for carefully selected patients (Cheng et al., 2012) although reported long term survival rates vary significantly and randomized studies are lacking.

Key recommendations

1 Supportive care ± hydroxyurea as required is recommended for most patients. Grade 1B
2 Azacitidine is licensed for non-proliferative CMML-2 and can reasonably be recommended. Grade 2C
3 Allogeneic HSCT with or without preceding AML-type chemotherapy should be considered for selected patients. Grade 2B
Patients requiring treatment should be considered for any appropriate clinical trial.

Management of high risk MDS

Patients with high risk MDS (INT-2/High IPSS or High/Very high IPSS-R scores) have a 33% to 45% chance, respectively, of progression to AML and a median survival of around 12 months without intervention (Greenberg et al., 1997). Given the poor prognosis, treatment strategies for patients appropriate for active therapy should be aimed at altering the natural history of the disease to improve survival. Patients should be given the opportunity to take part in appropriate clinical trials given that allogeneic HSCT is the therapy with greatest curative potential, clinicians should initially determine whether a patient is a possible transplant candidate at diagnosis and review this regularly throughout the disease course. Early discussion with the transplant unit is recommended to ensure early tissue typing and donor identification. An algorithm for the management of high risk MDS can be seen in Fig 2.

Stem cell transplantation for high risk MDS. For patients with IPSS INT-2/High risk disease, median survival independent of age is short. Early intensive treatment and consolidation with an allogeneic transplant probably offers a survival advantage (OS 26 months for allograft vs 8 months without treatment) (Kuendgen et al., 2006). In patients <60 years with INT-2/High Risk MDS, early MA sibling donor transplantation has been found to be most beneficial for OS (Cutler et al., 2004). Markov modelling of older patients with INT-2/High Risk MDS may also support early RIC transplantation, due to improved survival over treatment with demethylating agents, which persists when adjusted for the presence of graft-versus-host disease (GVHD) post-transplant (Koreth et al., 2011).

The IPSS score and the WPSS (Malcovati et al., 2007) predict post-transplant outcomes. The WPSS score also predicts 5-year post-transplant relapse rates, which increase from 9% in low risk to 70% in very high-risk WPSS groups (Alessandrino et al., 2008). In multivariate analyses, age does not influence OS, disease free survival, NRM, or relapse (Lim et al., 2010; McClune et al., 2010). Other patient factors that need consideration include performance status and the comorbidities of transplant recipients (Sorror et al., 2007). For patients with high-risk disease and HCT-CI ≥ 3, the benefit of a RIC transplant needs to be weighed against the possible benefit from non-transplant options. Pre-transplant serum ferritin concentration >2500 µg/l correlates with significantly increased TRM whereas this risk is lower when ferritin is <2000 µg/l (Armand et al., 2011).

Several retrospective comparisons of RIC with MA conditioning suggest that RIC yields satisfactory survival for this older, high risk group of patients with a lower incidence of acute GVHD and TRM at the expense of increased relapse rates of 30–40%, which remains the biggest reason for treatment failure (Massenkel et al., 2005; Alyea et al., 2006; Scott et al., 2006; Valcarcel et al., 2008; Lim et al., 2010; Luger et al., 2012).

Retrospective studies also suggest that the results from fully matched volunteer unrelated donors are similar to those with sibling donors (Lim et al., 2006). Therefore, transplantation from unrelated donors when a sibling is not available, may be considered.

Fig 2. Algorithm for management of high risk myelodysplastic syndrome.
The role of induction chemotherapy prior to HSCT—Given that disease status at the time of transplant significantly affects relapse risk (Warlick et al, 2009; Lim et al, 2010), it seems reasonable to attempt to reduce tumour burden prior to transplantation. For patients with <10% bone marrow blasts or slowly progressing disease, or where the risk of significant chemotherapy complications, such as prolonged chemotherapy-induced hypoplasia, are high (e.g., hypocellular marrow or excessive reticulin fibrosis), a decision to proceed directly to transplant should be considered. Conversely, patients with >10% blasts and hypercellular marrows may benefit from initial therapy to reduce tumour bulk. This can best be achieved by using intensive chemotherapy. The aim is to induce a complete cytogenetic response and/or reduce the blast percentage to <5%. The role of pre-transplant treatment in those patients without an excess of blasts, but a karyotypic abnormality is unclear. As the risk of delayed marrow recovery and post-chemotherapy aplasia is higher in MDS than de novo AML, it is sensible to identify a donor prior to commencing chemotherapy if time allows.

An additional benefit of pre-transplant therapy is to identify those patients with chemotherapy-resistant disease, in whom the outcome following allograft is extremely poor. Such patients should be considered for experimental therapy or supportive care alone. Novel therapies, such as sequential chemotherapy-transplant protocols [e.g. FLAMSA (fludarabine, cytarabine, amsacrine)-RIC] appear promising (Schmid et al, 2005).

Recent retrospective, non-randomized studies in MDS comparing azacitidine and intensive chemotherapy pre-transplant, showed that azacitidine was associated both with less toxicity and equivalent post-transplant outcomes (Damaj et al, 2012; Gerds et al, 2012). Such studies are of potential interest but methodologically limited. As such, azacitidine cannot be routinely recommended as a bridge to transplant in high-risk MDS outside of clinical trials.

Intensive chemotherapy for high risk MDS who are not eligible for HSCT. For those patients not eligible for transplantation, intensive AML-style chemotherapy can be used in an attempt to achieve disease response and improve survival. These patients should be entered into clinical trials where possible. The advantages of intensive chemotherapy are the QOL improvement if complete remission 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 (Wattel et al, 1997). 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 (de Witte et al, 1995; Wattel et al, 1997; Kantarjian et al, 2006a; Knipp et al, 2007; Morita et al, 2010).

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 that achieved complete remission (Knipp et al, 2007). 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) had a median survival of 4 months. The largest study of intensive chemotherapy for high risk MDS broadly supports these data (Kantarjian et al, 2006b). 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 (Sekeres et al, 2009). Grade of evidence 2B.

Disease modifying agents in high risk MDS. Hypomethylating agents—Hypomethylating agents, such as azacitidine and decitabine, offer an alternative to intensive treatment approaches in high risk MDS. They do not offer a cure but, by modifying the disease, may offer a survival benefit and are well tolerated in the elderly and those with comorbidities. The advantages of azacitidine are the fact that it is an outpatient based treatment with a reasonable chance of transfusion independence (45%), albeit with a median response duration of 13 months, and a survival advantage compared with supportive care. Azacitidine is recommended above decitabine due to the positive results of the AZA001 phase 3 trial (Fenaux et al, 2009). The use of decitabine should be restricted to that within clinical trials.

Azacitidine—Azacitidine has been recommended by NICE (TA218) (Miller et al, 2011) and the Scottish Medicines Consortium as a treatment option for adult patients not eligible for HSCT, with MDS (IPSS INT-2 or High), CMML-2 (non-proliferative) and AML (WHO with 20–30% blasts and multi-lineage dysplasia). Patients should be treated for a minimum of six courses. The recommended dose is 75 mg/m², which is injected for seven consecutive days, followed by a rest period of 21 d. The main evidence for the efficacy of azacitidine in these patient groups comes from the AZA 001 study (Fenaux et al, 2009). This study showed that treatment with azacitidine significantly increased OS compared to conventional care regimens (specifically, best supportive care,
low-dose cytarabine or intensive AML-type chemotherapy) (median OS 24-5 months vs. 15-0 months \( P = 0.0001 \)) (Fenaux et al, 2009). Azacitidine also resulted in clinically meaningful haematological responses, with 45% of patients becoming transfusion independent compared to 11% on the conventional care arm \( (P < 0.0001) \). In a subgroup analysis of the 87 elderly \( (\geq 75 \text{ years}) \) patients within the trial, azacitidine also significantly improved OS compared to conventional care (2-year OS: 55% vs. 15% \( (P < 0.001) \)), suggesting that this is the treatment of choice in patients aged \( \geq 75 \) years with good performance status and higher-risk MDS (Seymour et al, 2010).

Whilst azacitidine has been shown to be effective in all cytogenetic subgroups, comparison with conventional care regimens highlights that patients with isolated -7/del7q have a median OS of 13-1 months with azacitidine versus 4-6 months for conventional care (Fenaux et al, 2009). Similarly, patients with monosomy 5 or 7, either alone or as part of a complex karyotype, treated with hypomethylating agents appear to have a survival advantage over those treated with conventional AML-type chemotherapy (Ravandi et al, 2009).

The optimal duration of treatment is unknown but continued therapy for as long as a response is maintained is recommended. Responding patients enjoy a significant enhancement in QOL, with those having at least four cycles of azacitidine experiencing the greatest improvement (Kornblith et al, 2002). Continuation of therapy for stable disease should be at the patient and physician’s discretion.

It is recommended that patients undergo a bone marrow assessment (for morphology and cytogenetics) just prior to starting treatment, after six courses (to ensure the disease has not progressed) and then at the discretion of the clinician should there be suspicion there is evidence of disease progression/relapse.

Alternative dosing schedules for azacitidine include 75 mg/m² given for 5 d, no treatment for 2 d, two further days of treatment (5-2-2); 50 mg/m² dose given on a 5-2-5 schedule or a 75 mg/m² dose given for 5 d (Lyons et al, 2009). These dosage regimens have been studied predominantly in low risk MDS, but yielded similar haematological improvements. The 5-2-2 schedule is a practical alternative regimen to the seven continuous day dosing regimen and is strongly preferred as the closest practical alternative to the licensed seven consecutive day regimen.

Practical guidance for the delivery of azacitidine can be found in the article by Fenaux et al (2010).

In selected younger patients who achieve a complete remission with azacitidine, have a good performance status and an improvement in comorbidities, the option of a HSCT should be re-visited.

Decitabine—Two Phase III studies of decitabine versus best supportive care in MDS have been conducted (Kantarjian et al, 2006c; Lubbert et al, 2011). Both studies used intravenous decitabine 15 mg/m² given 8 hourly for 3 d every 6 weeks. Modest numbers of patients achieved complete remission, partial remission and haematological improvement but neither study was able to show significant improvements in OS. Responding patients had longer progression-free survival, indicating that decitabine has activity in MDS. These studies may have been confounded by the fact that a significant number of patients received 2 or less cycles of decitabine.

The ADOPT Phase II study treated patients with decitabine 20 mg/m² for 5 d every 4 weeks as outpatients for a median of 5 cycles (Steensma et al, 2009). Complete responses (complete response + marrow complete response according to IWG 2006 criteria [Cheson et al, 2006]) of 32%, red cell (33%) and platelet (40%) transfusion independence similar to the response rate in the AZA-001 study were observed. However, 63% of patients were hospitalized during the course of the study, usually within the first two cycles.

Low dose chemotherapy—Although low-dose cytarabine (LDAC) has activity in both low-risk and 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 a selective and 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 (Omoto et al, 1996). Retreatment will usually achieve a second remission but for a shorter duration. At melphalan-refractory relapse, patients are usually chemoresistant.

Key recommendations

Transplant-eligible patients:
1 Early allogeneic stem cell transplantation with or without prior AML-type induction chemotherapy should be considered for eligible patients with high-risk MDS. Grade 2B
2 Eligibility for stem cell transplantation should be based on HCT-CI and performance status rather than age. Grade 2B
3 Patients with a low comorbidity score (HCT-CI <3) should be considered for allogeneic stem cell transplantation. The role of transplantation in those patients with a high comorbidity score is unclear. Grade 2B
4 Patients with >10% blasts should receive 1–2 courses of intensive chemotherapy to induce remission prior to transplantation. Grade 2B
5 It is recommended that serum ferritin be measured pre-transplant for additional predictive information. Grade 2B
6 Matched unrelated donor transplants are recommended where a sibling donor is unsuitable or unavailable. Grade 2B

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7 Intensity of conditioning depends on the ‘risk’ of the disease and patient factors. Grade 2B
8 Patients who fail to respond to pre-transplant induction therapy should not undergo allogeneic stem cell transplantation and should be considered for experimental therapy or supportive care alone. Grade 2B
9 Autologous stem cell transplantation for MDS is not recommended outside of clinical trials. Grade 2B

Patients not eligible for transplantation:
1 In fit older patients lacking an adverse karyotype, the options of azacitidine versus intensive chemotherapy should be carefully discussed. Standard regimens used in de novo AML should be used as intensive chemotherapy in eligible patients. Grade 2B
2 Azacitidine is recommended as first line therapy for patients ineligible for a stem cell transplant with IPSS INT-2 and High Risk MDS, CMML-2 or AML with 20–30% blasts. Grade 1A
3 The recommended dose of azacitidine is 75 mg/m² daily for seven consecutive days but a 5-2-2 schedule is acceptable where it is not practical to offer seven consecutive days. Grade 2B
4 Responding patients should continue azacitidine until their response is lost. Grade 1A
5 The decision to stop or continue azacitidine in patients who fail to achieve a response after six cycles, but who have stable disease is dependent upon clinician and patient preference. Grade 2B

Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines. The British Committee for Standards in Haematology (BCSH) will review this guideline on an annual basis to ensure it remains up-to-date guidance. Please see the website at www.bcshtags.org to find out if the guideline has been updated or amendments added. The website will also show the date the guideline was last reviewed.

Development of the guidelines

The guideline group was selected to be representative of UK-based myelodysplastic syndrome (MDS) medical experts. Recommendations are based on review of the literature using MEDLINE and PUBMED up to December 2012 under the heading: ‘myelodysplastic syndrome’. The writing group produced the draft guideline, which was subsequently revised with consensus by members of the Haematology Task Force of the British Committee for Standards in Haematology (BCSH). The guideline was then reviewed by a sounding board of approximately 50 UK haematologists, the BCSH and the British Society for Haematology Committee. Comments were incorporated where appropriate. Levels of evidence and grades of recommendation have been assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) nomenclature for assessing the quality of evidence and providing strength of recommendations (http://www.gradeworkinggroup.org/index.htm). The objective of this guideline is to provide healthcare professionals with clear guidance on the management of patients with MDS. The guidance may not be appropriate to every patient and in all cases individual patient circumstances may dictate an alternative approach.

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References

Guideline


Guideline


