Guideline for the treatment of myelodysplastic syndromes (MDS) in South Africa


1. Introduction

Myelodysplastic syndromes (MDS) encompass a heterogeneous group of clonal haematopoietic disorders characterised by chronic and progressive cytopenias resulting from ineffective haematopoiesis. Clinically, patients present with symptomatic anaemia, recurrent infections and bleeding. The morphological hallmarks of MDS are progressive dysplastic features of haematopoietic cells at all stages of development in blood and bone marrow. In many patients, depending on a number of prognostic factors, MDS transforms over time to acute myeloid leukaemia (AML). The latter is usually highly resistant to therapy and responses, if they occur, are usually short-lived. Treatment of symptomatic anaemia with frequent blood transfusions over protracted periods of time puts patients at risk of the effects of iron overload.

In the past decade, our understanding of the pathogenesis of MDS has improved greatly. Furthermore, the classification of MDS into different clinicopathological sub-groups is undergoing constant change and novel treatments are increasing our therapeutic options. In addition to the use of allogeneic stem cell transplantation, high-dose chemotherapy and growth factor support, a number of new drugs were recently approved by the US Food and Drug Administration (FDA) and the European Medicine Authority (EMEA) in Europe for patients with MDS. These include lenalidomide (currently awaiting Medicines Control Council (MCC) approval in South Africa and available only through named-patient section 21 MCC application) and two inhibitors of DNA methyltransferase (hypomethylating agents), azacitidine and decitabine. Decitabine has not been registered in South Africa yet, but is also available on a named-patient section 21 application basis.

Although these products were originally approved on the basis of response rates, transfusion requirements and improvements in quality of life, survival data were lacking. This changed with evidence of improved overall survival and an increase in the time to progression to AML with the demethylating agent azacitidine. These benefits were apparent even in subgroups with unfavourable karyotypes. The data were recently confirmed in the large, prospective, international, multicentre, open-label, randomised phase III AZA 001 trial, and have led to changes in international guidelines, such as the US-based National Comprehensive Cancer Network (NCCN), which now include azacitidine in their therapeutic algorithms.

2. Limitations of the guidelines

The recommendations represent a consensus view on reasonable methods of management applicable to most patients, but do not exclude other reasonable management options, and success cannot...
be guaranteed in every situation. The unique circumstances of each patient should be taken into account by the responsible specialist regarding decisions on any specific therapy.

3. Objective
Our objective was to review the National Comprehensive Cancer Network (NCCN) 2009, 2010 and 2011 practice guidelines for the different subsets of MDS and adapt or modify their application to the South African clinical setting in order to provide recommendations for MDS management for South Africa.

4. Methods
A panel of South African experts from the tertiary academic and private sectors met in Franschhoek, W Cape, in April 2009 to discuss contextualisation of the NCCN MDS clinical practice guidelines in the South African setting. After an introductory discussion by author VJL, the panel specifically reviewed the treatment options for patients in the lower-, intermediate- and higher-risk groups, according to the International Prognostic Scoring System (IPSS) categories LOW, intermediate-I (INT-1) and HIGH (IPSS category HIGH, INT-2). The discussion focused, inter alia, on patients needing intensive therapy (including allogeneic stem cell transplantation), those needing less or lower-intensity therapy (defined as the use of low-intensity chemotherapy or biological response modifiers), supportive care, and the evaluation and treatment of disease-related symptomatic anaemia.

All discussions were recorded for later transcription and collated afterwards. A draft set of recommendations was presented by VJL at a follow-up meeting of an expanded panel consisting of clinical haematologists and oncologists at Kapama River Lodge in Limpopo, in July 2010. These draft recommendations took cognisance of literature published since the meeting in 2009, including the updated NCCN 2010 MDS Clinical Practice Guidelines, as well as data presented at the annual meetings of the American Society of Hematology (ASH) in December 2009 and the European Haematology Association in June 2010. Decisions were made on a consensus basis after active debate of the issues at hand. Subsequent changes based on the NCCN 2011 guidelines were included and discussed on an ad hoc basis telephonically and by e-mail among the authors.

The panel concluded that in each prognostic grouping, treatment options would be provided, which would allow tailoring of treatment in both the state and private sectors depending on the availability of treatments.

5. Results
5.1 Risk stratification
The IPSS categories were used in planning therapeutic options because they provide risk-based patient evaluation. The panel takes cognisance of the fact that the IPSS and the World Health Organization (WHO) Prognostic Scoring System (WPSS) are being revised, but at this stage the IPSS is still the most extensively used system in South Africa. It should also be noted that novel prognostic scoring systems based on cytogenetics, co-morbidities and flow cytometry have been developed, but are not widely used in the South African setting yet.

Patients with clinically significant cytopenias are usually stratified into two major risk groups, namely:

- lower-risk patients – IPSS LOW/INT-1 categories;
- higher-risk patients – IPSS INT-2/HIGH categories.

Table I summarises the prognostic variables and risk groups with regard to scoring and median survival in years, taking different age groups (<60 years, >60 years) into account.

5.2 Aim of treatment
In lower-risk patients, therapy is aimed at haematological improvement, whereas for patients with higher-risk disease, limiting disease progression and improving survival are considered most important. Therapeutic options for consideration include supportive care, lower-intensity therapy, high-intensity therapy, biological response modifiers, immunosuppressive therapies (ISTs), stem cell transplantation and/or a clinical trial.

6. Lower-risk patients
6.1 Supportive care
All patients should receive supportive care as an adjunct to treatment, which includes observation, monitoring, transfusion of blood and blood products, psychosocial support and attending to quality of life issues. Red blood cell (RBC) transfusions (for symptomatic

| Table I. IPSS classification and its prognostic significance |

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>Points</th>
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<tbody>
<tr>
<td>Bone marrow blasts (%)</td>
<td>0 0.5 1.0 1.5 2.0</td>
</tr>
<tr>
<td>Number of cytopenias</td>
<td>0 - 1 2 - 3 - -</td>
</tr>
<tr>
<td>Cytogenetic category</td>
<td>Good Intermediate Poor</td>
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<table>
<thead>
<tr>
<th>Risk groups</th>
<th>Score</th>
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<th>&gt;60</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
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<td>0</td>
<td>11.8</td>
<td>4.8</td>
<td>5.7</td>
</tr>
<tr>
<td>Intermediate I</td>
<td>0.5 - 1.0</td>
<td>5.2</td>
<td>2.7</td>
<td>3.5</td>
</tr>
<tr>
<td>Intermediate II</td>
<td>1.5 - 2.0</td>
<td>1.8</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td>High</td>
<td>≥2.5</td>
<td>0.3</td>
<td>0.5</td>
<td>0.4</td>
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*R: Bone marrow blasts of 20 - 30% may indicate MDS (according to the French-American-British (FAB) classification) or acute myeloid leukaemia (WHO).

†Cytopenias defined as neutrophils <1.8x10⁹/l, platelets <100x10⁹/l, haemoglobin <10 g/dl.

‡Cytogenetics: Good = normal, -Y alone, del(5q) alone or del (20q) alone; Poor = complex (≥3 abnormalities) or chromosome 7 abnormalities; Intermediate = other abnormalities. Note that inv16, t(8;21) and t(15;17) indicate AML and not MDS.
anaemia), platelet transfusions (for severe thrombocytopenia or thrombocytopenic bleeding), antibiotics and antifibrinolytic agents are all frequently used as part of supportive care. In addition, iron chelation (to manage iron overload) and recombinant human erythropoietin (EPO) with or without human granulocyte colony-stimulating factor (G-CSF) may be useful in selected patients.

### 6.2 RBC and platelet transfusions

Decision-making on transfusion need is similar to other indications, but as patients are often older with co-morbid conditions, the threshold for RBC transfusion may be higher (i.e. higher haemoglobin levels) and needs to be individualised to patients’ symptoms and tolerance of chronic anaemia. As patients require recurrent transfusions, the use of pre-storage leukocyte-depleted blood is recommended to decrease the risks of platelet isosensitisation, viral infections, febrile transfusion reactions and immunosuppression. Platelets are generally only given to patients who are actively bleeding, except for those receiving active therapy (for example, allogeneic haematopoietic stem cell transplantation (HSCT), intensive chemotherapy, hypomethylating agents, IST), where prophylactic platelet transfusion may be appropriate. The use of universal irradiation of blood products is controversial, with the exception of patients considered for allogeneic HSCT.

### 6.3 Transfusion dependence and iron chelation

Iron overload is a frequent problem in chronically transfused patients. It has been shown that both transfusion dependency and elevated serum ferritin levels are associated with a decreased overall survival and possibly an increased risk for transformation to AML independently of cytogenetic risk groups.\(^6,11\) The effect on survival was more apparent in the lower-risk groups,\(^6\) in patients who were actively monitored for iron overload, and in patients undergoing HSCT.\(^12,13\) Iron chelation has been shown to significantly improve survival in heavily transfused patients in retrospective studies.\(^14,17\) In the prospective EPIC trial, deferasirox has been shown to be safe and effective in decreasing serum ferritin, alanine transaminase (ALT) and labile plasma iron (LPI) in 341 MDS patients with serum ferritin values >2 500 ng/ml.\(^18,19\)

A recent consensus statement was published regarding the criteria for iron chelation in patients with transfusional iron overload in MDS (see Table II).\(^20\) The panel felt that these consensus guidelines can be applied in the South African setting. In patients whose haemoglobin normalises in response to treatment of their MDS, venesection is a reasonable alternative to consider for the management of iron overload. In most patients this will not be possible, and iron chelation with the oral iron chelator deferasirox, or continuous subcutaneous or intravenous infusions of deferoxamine, should be considered. The ease of use of deferasirox makes this drug the iron chelator of choice in the setting of MDS. The aim should be to decrease serum ferritin levels to a target range of between 500 and 1 000 µg/l. Once the target range is achieved, the dosage of the iron chelator may be adjusted to maintain the patient within this range. A decrease in dose or interruption of the iron chelator is usually required once the serum ferritin level decreases below 500 µg/l.

It should be noted that, according to South African recommendations, deferasirox is contra-indicated in patients with high-risk MDS, in patients with a creatinine clearance <60 ml/min, and in patients with other haematological and non-haematological malignancies who are not expected to benefit from chelation therapy owing to rapid disease progression and limited life expectancy. Cases of acute renal failure, hepatic failure and fatal gastro-intestinal haemorrhage have been reported, with the latter occurring especially in elderly patients with advanced haematological malignancies and/or low platelet counts. Most of the patients who developed these problems had co-morbid diseases that put them at risk for these complications. Table II summarises the criteria for iron chelation therapy in MDS, and which patients with MDS are most likely to benefit from iron chelation.

### 6.4 Management and prevention of infections

Infection, especially in neutropenic patients, is a major cause of death in patients with MDS and needs to be treated aggressively and appropriately. Broad-spectrum antibiotics are usually required for patients with neutropenic fever. The use of prophylactic antibiotics is less clear and they are not routinely recommended for all patients, but individual patients receiving treatments that put them at high risk for neutropenic fever may benefit from antibacterial and antifungal prophylaxis. This decision needs to be individualised taking into account the patient's clinical condition, intensity of treatment, neutropenic fever risk and co-morbid conditions. It should also be noted that iron overload has been associated with a higher risk of bacterial and fungal infections.\(^21\)

### 7. Patients with symptomatic anaemia

Beyond the adjunctive measures of supportive care, patients are stratified according to whether they primarily present with symptomatic anaemia, thrombocytopenia or neutropenia. Symptomatic, transfusion-dependent anaemia is a common and important manifestation of MDS. It has been associated with reduced quality of life, iron overload and other complications of transfusions and the need for iron chelation therapy. Also, the cost of transfusion and iron chelation may be considerable.

#### 7.1 Deletion 5q- or other cytogenetic abnormalities

The NCCN guidelines recommend the use of lenalidomide in patients with del 5q. Lenalidomide has been shown to yield transfusion independence in 67% of lower-risk patients with del 5q and a median duration of response of more than 2 years.\(^7\) Cytogenetic responses were seen in 73% of patients (45% major and 28% minor), with

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**Table II. Iron chelation in myelodysplastic syndromes**\(^20\)

**Criteria for iron chelation therapy in MDS**

- When serum ferritin levels reach 1 000 µg/l, depending on transfusion rate
- Patient’s transfusion need is ≥2 units RCC/month and persists at this level for >1 year
- Patient is ineligible to receive or unresponsive to primary therapy, e.g. hormonal or hypomethylating therapy
- Patients with MDS most likely to benefit from iron chelation

- Transfusion-dependent patients requiring 2 units RCC/month for >1 year
- Patients with s-ferritin >1 000 µg/l
- Patients with low-risk MDS
  - IPSS: Low or Int-1
  - WHO: RA, RARS, or 5q–
- Patients with a life expectancy ≥1 year
- Patients without co-morbidities that would limit prognosis
- Candidates for HSCT
- Patients in whom there is a need to preserve organ function

Adapted from Bennett JM. Consensus statement on iron overload in myelodysplastic syndromes. Am J Hematol 2008;83:858–861.
grade 3 or 4 myelosuppression during the first 3 months as the most prominent adverse events. Although lenalidomide has been approved by the FDA, the EMEA has been concerned about a potential increased risk of progression to AML in patients with del 5q. Preliminary results from a number of prospective clinical trials seem to be reassuring.

7.2 Erythropoiesis-stimulating agents ± G-CSF

A number of phase II clinical trials have shown response rates of 20 - 40% with single-agent erythropoiesis-stimulating agents (ESAs), with even higher response rates when treatment is instituted early. Combining ESAs with granulocyte-colony stimulating factor (G-CSF) may enhance response, owing to a synergistic effect. In a large cohort of 403 patients with MDS who received epoietin-alpha, epoietin-beta, or darbepoietin with or without G-CSF, responses were seen in 62% of patients according to the International Working Group (IWG) criteria (40% major and 22% minor). A meta-analysis of anaemic MDS patients confirmed the usefulness of epoietin-alpha and darbepoietin in the treatment of MDS.

To manage these patients as cost-effectively as possible, the subsets of patients most likely to benefit need to be recognised. The strongest association with response to treatment has been seen in patients with EPO levels ≤500 mU/ml and RBC transfusion needs. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN content are trademarks owned by the National Comprehensive Cancer Network, Inc. *Indicates a deviation from the NCCN Guidelines based on local expert opinion and availability of therapeutic agents in South Africa.

Fig. 1. Algorithm for the management of the IPSS Categories LOW and INT-1. Adapted and modified with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines”) for Myelodysplastic Syndromes V.2.2011 (National Comprehensive Cancer Network, Inc., 2011, all rights reserved). The NCCN Guidelines” and illustrations therein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN content are trademarks owned by the National Comprehensive Cancer Network, Inc. *Indicates a deviation from the NCCN Guidelines based on local expert opinion and availability of therapeutic agents in South Africa.

Fig. 2. Algorithm for the management of the IPSS Categories INT-2 and HIGH. Adapted and modified with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines”) for Myelodysplastic Syndromes V.2.2011 (National Comprehensive Cancer Network, Inc., 2011, all rights reserved). The NCCN Guidelines” and illustrations therein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN content are trademarks owned by the National Comprehensive Cancer Network, Inc. *Indicates a deviation from the NCCN Guidelines based on local expert opinion and availability of therapeutic agents in South Africa.
The likelihood of response to EPO and G-CSF in a patient with a serum EPO level ≤500 mU/ml and a transfusion need of less than 2 units of RBCs per month was 74%. In contrast, patients with an EPO level >500 mU/ml and a transfusion need of ≥2 units per month only have a 7% chance of response. It is critical to identify these patients who are unlikely to respond, as they also have an increased possibility of disease progression, especially if other more appropriate therapies, such as allogeneic HSCT and azacitidine, are delayed.

The effect of treatment on long-term outcomes has been favourable, but survival benefit was only seen in patients with a moderate pretreatment transfusion need of less than 2 units of RBCs per month. A recent study has further shown clear improvement in quality of life in responding patients that correlated with decreases in transfusion requirements. Most responses are seen within 12 weeks of treatment onset, with a median duration of response of about 2 years. The risk of progression to higher-risk MDS and AML does not seem to increase compared with patients treated with transfusion alone.

The panel concluded that the stratification of low-risk patients into symptomatic anaemia, thrombocytopenia or neutropenia and according to serum EPO levels was valid, as was stratifying patients according to serum EPO levels. The use of ESAs in combination with G-CSF was supported in selected patients, taking into account the likelihood of response in an individual patient. In patients with a low likelihood of response, alternative therapies should be considered.

7.3 Failure to respond to ESA
In patients not responding to ESA and G-CSF, the available options in South Africa include hypomethylating agents, IST, a clinical trial or allogeneic HSCT in selected patients.

7.4 Anaemic patients with serum EPO level >500 mU/ml
These patients should be evaluated to determine whether they have a good probability of responding to IST, or whether they would be candidates for the use of a hypomethylating agent.

7.5 Immunosuppressive therapy
Patients most likely to respond to IST include IPSS LOW or INT-1 patients with one or more of the following features: ≤60 years old, HLA-DR15+, the presence of a paroxysmal nocturnal haemoglobinuria (PNH)-positive clone, or hypocellular bone marrow. Also, patients with a recent onset of RBC transfusion requirement, very few or no blasts and normal cytogenetics seem to respond better to IST. In these selected patients, antithymocyte globulin (ATG) in combination with cyclosporin should be considered, as responses can be expected in 30 - 40% of lower-risk patients resistant to EPOs. The panel concurred with the treatment pathway defined by the NCCN, i.e. that if patients are non-responders to IST, they would be considered for treatment with hypomethylating agents or a clinical trial.

Patients with a low probability of responding to IST should be considered for treatment with hypomethylating agents or a clinical trial. Once available, lenalidomide may become an appropriate option in selected patients. Patients not responding to any of these could be considered for allogeneic HSCT.

It is worth noting that very promising results have been seen in small studies with novel immunosuppressive regimens. In one study, alentuzumab 10 mg/day was given for 10 days, with responses seen in 17 (77%) out of 22 patients with evaluable INT-1 disease, and in 4 (57%) out of 7 with evaluable INT-2 disease. Median time to response in this study was 3 months.

7.6 Patients with predominant thrombocytopenia and/or neutropenia
In clinical practice, patients with true isolated neutropenia have shown very good responses to the addition of growth factors. As such, patients should be given a trial of growth factors or azacitidine, or be considered for a clinical trial. In the event of no or limited response, IST or allogeneic HSCT should be considered. The role and safety of romiplostim in MDS has not been fully delineated.

8. Higher-risk patients (IPSS INT-2/HIGH)
Therapeutic options for higher-risk patients include allogeneic HSCT, high-intensity therapy, low-dose chemotherapy (for example, low-dose cytarabine), hypomethylating agents, and an array of novel experimental agents or supportive care.

Patients in the INT-2 and HIGH risk categories according to the IPSS have a median survival of only 1.2 and 0.4 years, respectively. Time to AML progression is generally less than 1 year. Taking into account the very poor outcomes in this patient group, patients should be carefully evaluated and offered treatment that will positively change outcome and survival. Treatment for higher-risk patients is therefore dependent on whether they are felt to be candidates for intensive therapy, such as allogeneic HSCT or intensive chemotherapy.

Factors that influence this decision include patient age, performance status, absence of major co-morbid conditions, psychosocial status, and the availability of an HLA-matched donor. MDS is generally a disease of older patients who should be carefully evaluated for co-morbid disease that may influence their ability to tolerate intensive chemotherapy and/or HSCT. The HSCT co-morbidity index has been shown to be an accurate predictor of non-relapse mortality after HSCT. The panel agreed that the timing and selection of MDS patients for HSCT was critical. IPSS INT-2 and HIGH risk patients ≤60 years old should ideally proceed to allogeneic HSCT as early as possible. In LOW or INT-1 risk patients, HSCT is usually delayed until evidence of disease progression is observed. Non-myeloablative HSCT is usually preferred in order to reduce treatment-related mortality, except in younger patients, where full myeloablation is still often used. It has been suggested that potential transplant candidates may benefit from azacitidine pre-transplant during the period in which the donor search is ongoing, especially in patients with an unfavourable karyotype. Patients with unfavourable karyotypes are usually refractory to conventional chemotherapy. This concurs with the NCCN guidelines, that qualify the option of HSCT with the fact that azacitidine may be used as a bridge to transplant while awaiting improved patient status or donor availability. In patients with a more favourable karyotype, intensive chemotherapy may be useful to decrease blast percentages pre-transplant and thus limit post-transplant relapse rates.

8.1 High-intensity therapy
Intensive therapy is usually limited to patients less than 65 years of age with more favourable karyotypes and no allogeneic stem cell donor. In patients with unfavourable karyotypes, hypomethylating agents are preferred. In older patients, azacitidine is the treatment of choice, although careful attention to co-morbid disease is required. Anthracyclines and cytarabine combinations remain the preferred choice for intensive chemotherapy, and complete remission (CR) rates of between 40% and 60% are usually attained. Unfortunately, CR is not often sustained, with a median duration of CR of less than 12 months, with less than 10% of patients achieving a prolonged CR. Toxicity is often higher than that seen in patients treated for AML with similar regimens, and is often characterised by prolonged cytopenias due
to bone marrow hypoplasia.41-45 Patients who generally benefit most from intensive chemotherapy are younger patients with favourable cytogenetics. Complete remission rates are low and CR duration is generally short in patients with an unfavourable karyotype. In higher-risk patients, a clinical trial with an azacitidine-based combination may be considered before intensive treatment, especially in older patients. This is supported by data from the AZA 001 trial,7 a large, international, multicentre, open-label, randomised phase III trial. Findings demonstrated improved overall survival rates at 2 years (50.8% v. 26.2%) using azacitidine when compared with conventional care (best supportive care, intensive chemotherapy and low-dose cytarabine).7 This benefit in overall survival was independent of age, karyotype, the number of bone marrow blasts and the FAB or WHO type.7 Of note was the survival advantage seen in patients with poor-risk cytogenetics (-7/-7q-) in all patient groups receiving azacitidine.74 It is important to emphasise that responses often occurred only after 4 - 6 cycles, with the median number of cycles being 9 and 14 given to non-responders and responders, respectively.7 In another analysis of the AZA 001 trial, azacitidine was shown to improve overall survival when compared with low-dose cytarabine, with fewer grade 3 - 4 cytopenias in the azacitidine group.74 A useful prognostic scoring system has been developed to predict responses to azacitidine.72 A second demethylating agent, decitabine, has not been found to confer a survival advantage in controlled trials, but this may at least in part have been due to the nature of the trials, in which therapy was limited to 4 cycles and a mixed population of MDS patients were treated.73,74 A more recent prospective, randomised phase III study75 showed that decitabine may lead to responses in older MDS patients, but without a significant improvement in overall and AML-free survival. Transformation to AML was significantly decreased in this study. In this multidisciplinary analysis showed that patients with a shorter duration of MDS had a worse outcome when given decitabine.75 Treatment options for patients who are not candidates for intensive therapy are similar to those in low-risk patients, being azacitidine-based regimens, supportive care, low-dose cytarabine or other experimental agents where available and appropriate. Older patients with poor-risk cytogenetics, who are not eligible for intensive chemotherapy, are usually offered an azacitidine-based therapy or best supportive care.

8.2 Non-intensive therapy
As a relatively low-cost intervention, low-dose cytarabine, given at a dose of 20 mg/m²/d for 14 - 21 days out of every month, may yield partial and complete remission rates of 20% and 15%, respectively. Compared with azacitidine, response rates were fewer and shorter, overall survival lower and toxicity higher.48 Low-dose cytarabine could be considered as an adjunct to supportive care if azacitidine treatment has failed or is not available.

9. Experimental agents
It is generally felt that patients should be included in clinical trials as far as possible. Many new agents and drug combinations are being investigated. In patients with higher-risk MDS who are eligible for a transplant and have an available donor, allogeneic HSCT with or without a preceding hypomethylating agent is the treatment of choice. In all other patients, a hypomethylating agent would be the treatment of choice. In case of failure or loss of response after a hypomethylating agent, intensive chemotherapy or low-dose cytarabine are therapeutic options that may be considered. Supportive care should be offered to all patients while taking individual risk-benefit factors into account when making decisions on the use of more expensive treatment modalities, such as growth factors, EPOs and iron chelation.

10. Conclusion
The management of MDS is a complex process requiring expertise and skills in managing the complications of the disease as well as complications of treatment used. Continuous progress in the understanding of the molecular pathogenesis of MDS has led to the development of a number of therapeutic agents with acceptable side-effect profiles and improvements in survival and quality of life of MDS patients. The results from ongoing, prospective, randomised trials on novel agents and therapeutic combinations are eagerly awaited.

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