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EDUCATIONAL SERIES

Myelodysplastic Syndrome

About the Reviewers

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Emma-Jane is a clinical haematologist at Canterbury District Health Board. Having spent some time as a registrar in Christchurch, she is delighted to be back in New Zealand having completed advanced training in the UK. She has an interest in malignant haematology and myelodysplasia in particular. This developed whilst working in Bournemouth with Dr Sally Killick, the regional MDS and Aplastic Anaemia expert with links to Kings College Hospital, London. Emma-Jane also has an interest in medical education.

This review is intended as an educational resource for health professionals. It presents a concise background on myelodysplastic syndrome (MDS), including its prognosis and clinical management. In terms of treatment, the review highlights two newer pharmacological agents available, lenalidomide and azacitidine, approved by Medsafe for low-risk MDS and high-risk MDS, respectively. This review is sponsored by an educational grant from Celgene.

MDS is characterised by ineffective haematopoiesis, aberrant myeloid cell morphology, peripheral blood cytopenias and progression to acute myeloid leukaemia (AML) in one third of cases.[1,2] In 80–90% of patients, MDS develops without a known cause. In 10–20% of patients, MDS develops as a result of chemotherapy, radiation or, rarely, after environmental exposures. Although the reported incidence of MDS varies, worldwide annual incidence is thought to be 3–5 cases per 100,000 people.[3] While MDS is extremely rare in childhood and adolescence, it is highly prevalent in the elderly.[4] Approximately 80% of patients are aged >60 years at diagnosis and the incidence rate increases two-fold for each decade over 40 years of age.[5,6] Males typically have a higher incidence rate than females.[3] In New Zealand, MDS represents 1.3% of all cancer diagnoses with an annual incidence of 3.7 per 100,000 people.[3] MDS is most commonly classified on morphological criteria using the WHO[7] classification shown in Table 1. The WHO classification formally separates chronic myelomonocytic leukaemia (CMML) from MDS; CMML is now considered an overlap syndrome that can include features of MDS, myeloproliferative neoplasm, or both.[8]

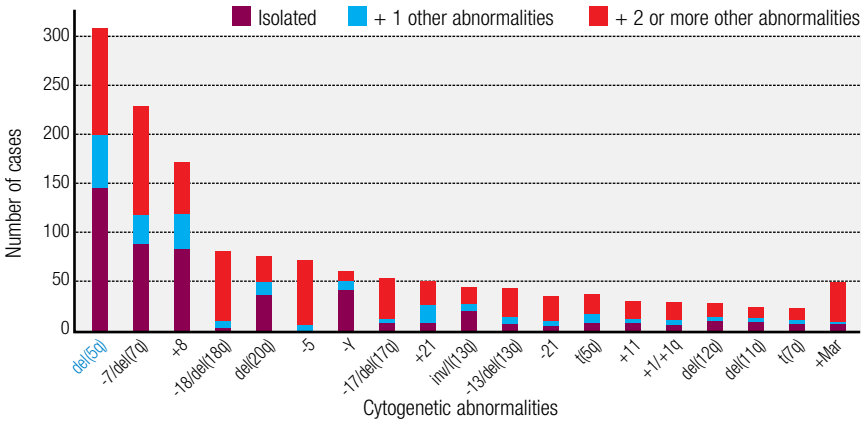
Table 1. WHO MDS classification criteria[7]

Refractory cytopenias with unilineage dysplasia (including refractory anaemia (RA), refractory neutropenia and refractory thrombocytopenia)
Refractory anaemia with ring sideroblasts (RARS)
Refractory anaemia with multilineage dysplasia (RCMD) ± RS
Refractory anaemia with excess blasts (RAEB-1 and -2)
MDS associated with isolated del(5q)
MDS unclassifiable

Diagnosis and prognosis

Patients with MDS typically present with peripheral blood cytopenias, which are recognised incidentally when a complete blood count is performed or which result in symptoms reflecting anaemia, neutropenia, or thrombocytopenia. Although anaemia is common in the elderly, a diagnosis of MDS should be considered in anaemic older adults, particularly when accompanied by other cytopaenias or unexplained macrocytosis. Because of the sometimes nonspecific symptoms and often older age of patients, it is likely there is under diagnosis and underreporting of MDS particularly in the lower risk group. Often these patients will be managed with supportive care only and do not undergo full investigation including bone marrow analysis.

The diagnosis of MDS is based on peripheral blood counts, blood film morphology, bone marrow examination, and cytogenetic analysis on the bone marrow cells.[9] At initial diagnosis, a bone marrow trephine biopsy as well as a smear is strongly recommended; it is particularly useful for assessment of cellularity and fibrosis which can be particularly helpful in cases of hypocellular MDS and overlap syndromes.[10] Immunohistochemistry can be used to assess the percentage of blast cells if the aspirate is hypocellular. Approximately 50% of MDS patients have a detectable cytogenetic abnormality.[9] A chromosome 5q deletion is the most common abnormality, being is present in up to 30% of MDS patients with cytogenetic abnormalities (see Figure 1).[11]



Adapted from Haase et al 2007.
Study Design: Retrospective study involving cytogenetic analyses of 2072 patients with a confirmed diagnosis of MDS.
684 different cytogenetic categories were identified.

Figure 1. Frequencies of most common cytogenetic abnormalities in MDS.[11]

Prognosis, with respect to AML evolution and overall survival (OS), is commonly assessed using the International Prognostic Scoring System (IPSS) which divides patients into four risk groups according to bone marrow blast percentage, marrow karyotype and number of cytopenias: low risk, intermediate-1, intermediate-2 and high risk (see Table 2).[12] The scoring system was recently updated (IPSS-R) placing increased prognostic weighting on the impact of karyotype abnormalities with five cytogenetic subgroups (very good, good, intermediate, poor and very poor), rather than three (see Table 3).[13] These prognostic scoring systems should be applied to all patients at diagnosis to predict prognosis and risk of progression to AML, and inform treatment decisions. The WHO Based Prognostic Scoring System (WPSS) is a dynamic prognostic scoring system that provides an accurate prediction of survival and risk of leukaemic evolution in MDS patients at any time during the course of their disease (see Table 4).[14]

Table 2. IPSS risk group classification of patients with MDS[adapted from Greenberg 1997][12]

Prognostic variable	Score				
	0	0.5	1.0	1.5	2.0
Bone marrow blasts (%)	<5	5–10		11–20	21–30
Karyotype	Good*	Intermediate*	Poor*		
Cytopenias	0/1	2/3			

*Good = normal, –Y, del(5q), del(20q); Intermediate = all other abnormalities;
Poor = ≥3 abnormalities or chromosome 7 abnormality

IPSS risk group	Score	Estimated median survival (years)
Low	0	5.7
Intermediate-1	0.5–1.0	3.5
Intermediate-2	1.5–2.0	1.2
High	≥2.5	0.4

Low-risk MDS = IPSS low risk and intermediate-1

High-risk MDS = IPSS intermediate-2 and high risk. These patients have a poorer survival and a high risk of progression to AML so more aggressive treatment strategies are usually sought.

Table 3. IPSS-R risk group classification of patients with MDS[adapted from Greenberg 2012][13]

Prognostic variable	Score						
	0	0.5	1	1.5	2	3	4
Bone marrow blasts (%)	≤2		>2–<5		5–10	>10	
Karyotype	Very Good*		Good*		Intermediate*	Poor*	Very Poor*
Haemoglobin	≥10		8–<10	<8			
Platelets	≥100	50–<100	<50				
ANC	≥0.8	<0.8					

*Very Good = -Y, del (11q); Good = normal, del(5q), del(12p), del(20q), double including del(5q); Intermediate = del(7q), +8, +19, i(17q), any other single or double independent clones; Poor = -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex (≥3 abnormalities); Very Poor = complex (≥3 abnormalities)

IPSS-R risk group	Score	Estimated median survival (years)
Very Low	≤1.5	8.8
Low	>1.5–3	5.3
Intermediate	>3–4.5	3.0
High	>4.5–6	1.6
Very High	>6	0.8

Table 4. WPSS risk group classification of patients with MDS[adapted from Malcovati 2007][14]

WPSS risk group	Very Low	Low	Intermediate	High	Very High
Score	0	1	2	3	5–6
WHO subtype	RA, RARS	RCMD, RCMD-RS	RAEB-1	RAEB-2	
Cytogenetics	Good*	Intermediate*	Poor*		
Transfusion requirement	No	Regular			
Estimated median survival (years)	8.5–11.8	5.5–6	3.3–4	1.8–2.2	0.75–1

*Good = normal, –Y, del(5q), del(20q);
Intermediate = all other abnormalities;
Poor = ≥3 abnormalities or chromosome 7 abnormality

Treatment of anaemia in low-risk MDS

Low-risk MDS, defined by an IPSS score of low risk and intermediate-1, is characterised by anaemia in most cases.[15] Treatment objectives include improving blood cytopaenias and quality of life (QOL). Some patients, while categorised as low-risk, have severe cytopenias and/or poor prognostic factors, or resistance to treatment, making them candidates for more intensive approaches including allogeneic stem cell transplantation (alloSCT).[15]

Red blood cell transfusion

Supportive care, primarily red blood cell (RBC) transfusion, remains an important part of treatment for low risk MDS patients, with many patients transfusion dependent. However, while RBC transfusion improves symptoms, it may be associated with iron overload,[15] reduced survival,[16-19] reduced long-term QOL,[20-22] increased risk of complications,[17-19] and significant costs.[23] Even with transfusions, patients may remain chronically anaemic.[22-25] There is also a low risk of alloimmunisation and viral infection.[15]

Transfusion dependence is associated with increased mortality in all age groups.[18] MDS patients requiring regular blood transfusions have a significantly lower probability of survival than those who are not transfusion dependent (p=0.005),[26] and are at higher risk of AML progression in the first two years following MDS diagnosis.[27] Furthermore, cardiac events are more common in MDS patients who receive transfusions.[17] A number of noncontrolled studies show inferior survival in MDS patients with iron overload following repeated transfusions.[16,28,29] The role of iron chelation therapy to combat iron overload remains controversial due to a lack of prospective studies.[30] Data is either retrospective or extrapolated from thalassaemia studies. Results of the randomised phase II trial (Telesto) in MDS patients undergoing iron chelation therapy are awaited with interest.

Erythropoiesis stimulating agents

Erythropoiesis stimulating agents (such as recombinant erythropoietin [EPO]) should be considered in transfusion dependent low-risk MDS patients without a deletion 5q cytogenetic abnormality and with an erythropoietin level <500u/L.[15] Weekly doses of erythropoiesis stimulating agents yield an erythroid response of approximately 60% with most responses occurring within 8 weeks.[15] Median duration of response to erythropoiesis stimulating agents is approximately 2 years.[15] Funding is now available for those patients with very low, low or intermediate risk MDS (WPSS scoring system). Patients with del(5q) MDS treated with EPO have responses lasting <12 months, and most have elevated endogenous EPO levels.[31]

Lenalidomide

Transfusion-dependent patients with del(5q) MDS who are either not candidates for EPO treatment or fail to respond to such therapy show particular sensitivity to lenalidomide (Revlimid®), an orally bioavailable, structural and functional analogue of thalidomide.[32] While the mechanisms of action of lenalidomide are not entirely understood, it probably acts via karyotype-dependent pathways by its effect on haplodeficient genes and karyotype-independent pathways by its effects on erythroid differentiation genes, immune function and angiogenesis.[33]

Lenalidomide is registered in New Zealand for the treatment of transfusion-dependent anaemia due to low- or intermediate-1 risk MDS associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. In a phase II trial of lenalidomide in patients with low-risk del(5q) MDS, 65.5% of patients achieved RBC transfusion-independence (TI) with a median duration of response of 2.2 years; 71.6% of patients achieved partial or complete cytogenetic response.[34,35] RBC-TI was associated with a prolonged OS (p<0.001) and a trend toward reduced relative risk of AML progression (p=0.08). The efficacy of lenalidomide was also confirmed in a phase III randomised placebo-controlled study of lenalidomide in patients with low-risk del(5q) MDS.[36] Results showed significant improvements in RBC-TI for patients randomised to lenalidomide 10mg and 5mg versus placebo (56.1% and 42.6% vs 5.9%; both p<0.001). These responses were durable, with the median duration of RBC-TI not reached after a median follow-up 1.55 years. RBC-TI was associated with a 47% reduction in the relative risk of death (p=0.021) and 42% reduction in the relative risk of AML progression or death (p=0.048). Lenalidomide was associated with significant improvements in health-related QOL at week 12 compared to placebo (p<0.005).

Ten to 15% of patients with MDS del(5q) have associated TP53 gene mutations, which is associated with a more unfavourable prognosis, and increased risk of progression to AML.[37,38] It is therefore recommended that patients with MDS del(5q) who are candidates for therapy with lenalidomide be screened for p53 muations.

MDS del(5q) has an uncertain prognosis, with the risk of AML progression possibly exceeding 20% at 5 years.[39] Prognosis worsens when additional cytogenetic abnormalities are present.[39,40] Of note, the European Medicines

Agency has raised concern over a potential risk of lenalidomide to initiate AML evolution in some low-risk MDS patients with del(5q).[15] However, in the largest cohort study examining AML progression in MDS to date (n=1248), there was no statistically significant association between lenalidomide and AML transformation in any patient subgroup, including those with low-risk MDS.[41] Emerging data suggest that AML progression rates in lenalidomide recipients are probably not drug-related but are associated with additional risk factors, including TP53 mutations.[33]

The most common grade 3 or 4 adverse events (AEs) associated with lenalidomide are neutropenia and thrombocytopenia, seen in approximately 60% of patients during the first weeks of treatment.[34,36] These events are manageable with dose reductions or interruptions. Cytopenias usually occur early during treatment and decrease thereafter. While haematological AEs are common in patients treated with lenalidomide, they may be predictive of TI.[42] Other AEs include deep vein thrombosis and pulmonary embolism. Rash is frequent but transient, whereas diarrhoea can be long lasting and limit treatment efficacy.[15]

Lenalidomide prescribing considerations

- Starting dose 10mg orally once daily on days 1–21 of repeated 28-day cycles
- A complete blood count should be performed:
  - at baseline
  - every week for the first 8 weeks
  - monthly thereafter to monitor for cytopenias
- Contraindicated in women who are pregnant
- Pregnancy test every month for women of childbearing potential

Second-line therapy

Other treatment options for low risk MDS include immunomodulatory agents (e.g. antithymocyte globulin, cyclosporin, steroids), hypomethylating agents and lenalidomide in the absence of del(5q); however, results are disappointing overall, yielding at best one-third of responses, with many patients eventually requiring long-term RBC transfusions.[15]

Treatment of neutropenia and thrombocytopenia in low-risk MDS

In low-risk MDS, neutropenia and thrombocytopenia are less frequent than anaemia and are infrequently isolated or profound. In neutropenic patients, G-CSF and granulocyte macrophage-CSF can improve symptoms but prolonged use has not demonstrated an impact on survival.[10] Broad spectrum antibiotics are recommended in the case of neutropenic fever. In patients with thrombocytopenia, high-dose androgens improve symptoms in one third of patients but the response is transient.[10] Two thrombopoietic receptor agonists, romiplostim and eltrombopag, have shown promise in preliminary clinical trials.[43,44]

Key messages – low-risk MDS

- RBC transfusion recommended for anaemia but risk of:
  - insufficient improvement of anaemia
  - iron overload
- Role of iron chelation therapy remains debated
- Erythropoiesis stimulating agents first-line treatment of transfusion-dependent anaemia in patients without del(5q) and low EPO level
- Lenalidomide recommended for treatment of transfusion-dependent anaemia in patients with del(5q) after EPO failure
  - durable RBC-TI
  - enhanced QOL
  - lower risk of AML progression (when TI is achieved vs not achieved)
  - haematological AEs are common but can be predictive of TI

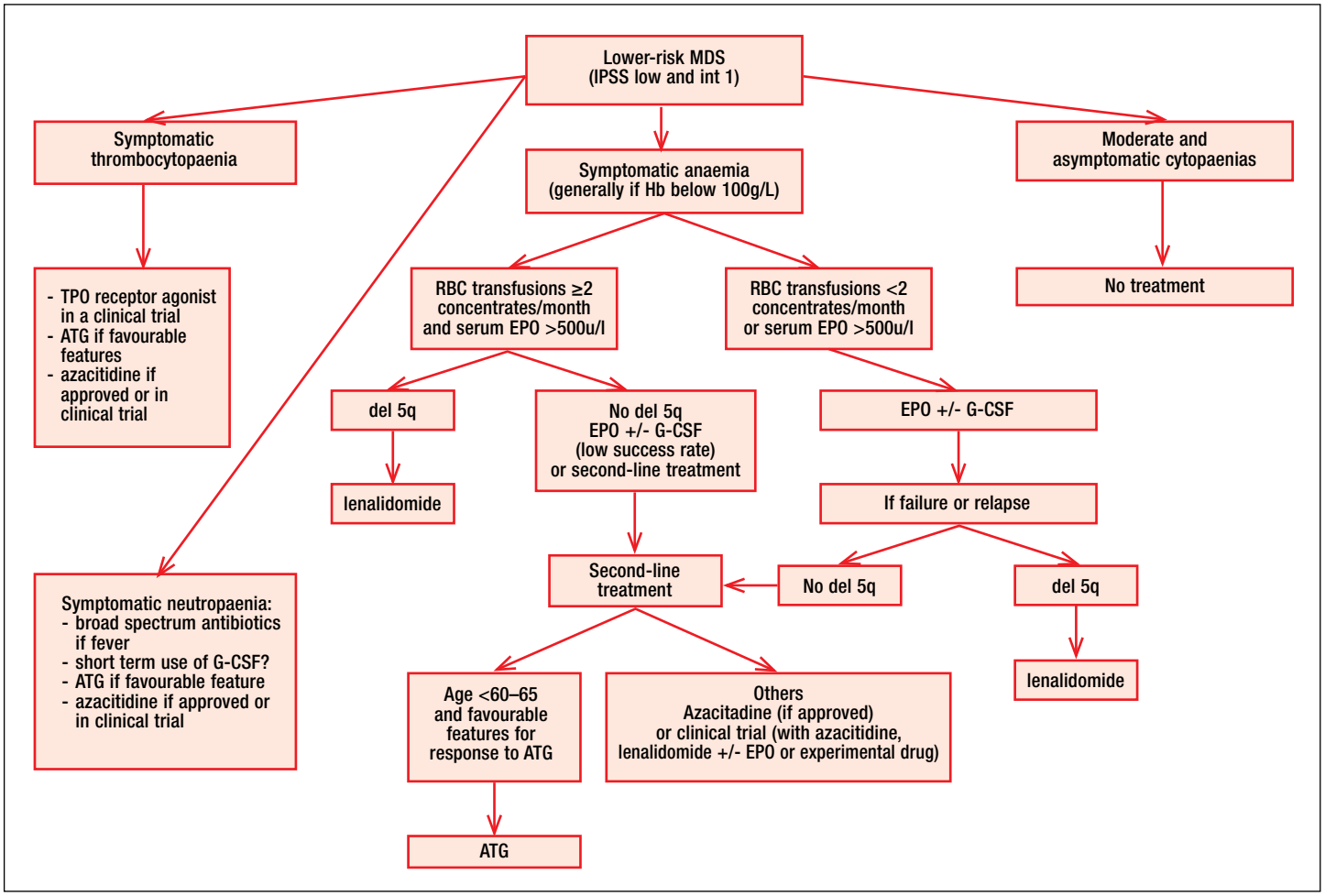


Figure 2. Treatment algorithm for low-risk MDS[10]

High-risk MDS

Patients with high-risk MDS, defined by an IPSS score of intermediate-2 or high risk, have frequent progression to AML and a short survival. Treatment should aim to modify the natural disease course and includes alloSCT, hypomethylating agents and, although now less often, chemotherapy (mainly intensive anthracycline-cytarabine combinations). In most high-risk MDS patients hypomethylating agents are the first-line treatment of choice.

Hypomethylating agents

In patients with high-risk MDS without major co-morbidities and not eligible for alloSCT, azacitidine (Vidaza®) is recommended.[10] In New Zealand, azacitidine is registered for the treatment of patients with intermediate-2 or high-risk MDS, CMML, or MDS-associated AML if the blast count is <30%.

In a phase III randomised trial (CALGB9221) of patients with low-* and high-risk MDS (majority high-risk), 60% of patients receiving azacitidine responded to therapy versus 5% of patients receiving supportive care (p<0.0001), with median time to leukaemic transformation or death of 21 months versus 12 months, respectively (p=0.007).[45] Azacitidine patients had delayed onset of RBC and platelet transfusions[46] and significant improvements in QOL,[47] compared with supportive care patients. In a randomised phase III study (AZA001), patients with high-risk MDS received azacitidine or a conventional care regimen (CCR) (best supportive care, low-dose cytarabine, or intensive chemotherapy).[48] At 2 years, 50.8% of patients in the azacitidine group were alive compared with 26.2% in the CCR group (p<0.0001). This survival advantage was seen irrespective of age (including patients aged ≥75 years)[49] or percentage of marrow blasts (including patients with 20–20% blasts, classified as AML using WHO criteria).[50] Progression to AML was delayed, and RBC transfusion dependency and rate of infections were significantly improved with azacitidine. Although 91% of responses occurred by 6 cycles, continued azacitidine improved response in 48% of patients.[51] Therefore, azacitidine therapy should continue for at least 6 months.

In an analysis of safety data from AZA001 and CALGB9221, cytopenias, injection-site reactions and gastrointestinal disorders were the most common AEs related to azacitidine.[52] Most AEs were transient and resolved during ongoing therapy (>83%). Haematological AEs, most frequently observed during early treatment cycles, decreased during subsequent cycles and were usually managed with dosing delays. However, a panel of experts recommends avoiding dose modifications during the first three treatment cycles where possible, as reducing the dose of azacitidine or delaying cycles may be associated with reduced efficacy.[53] Accordingly, clinicians should prepare patients for potential worsening of cytopenias during the first two cycles.

Azacitidine prescribing considerations

- Starting dose 75 mg/m² per day SC (or IV) for 7 days (or 5+2) of a 28-day cycle
- Monitor for haematological response
- Monitor for haematological and renal toxicity with dose delay/reduction as required
- Avoid dose modifications during the first three treatment cycles if possible
- Repeat cycles every 28 days for a minimum of 6 cycles
- Continue treatment for as long as patient continues to benefit or until disease progression
- Contraindicated in pregnancy
- Men should be advised not to father a child while receiving treatment

AML-like chemotherapy

AML-like intensive chemotherapy involves combinations of cytarabine with daunorubicin, idarubicin or fludarabine.[54] Such chemotherapy has limited indications in high-risk MDS patients. Patients with unfavourable karyotypes have few complete responses (CRs) and a short duration of CR.[55] It is of use in younger patients (<60–65 years) preferably as a bridge to alloSCT particularly in those patients with >10% blasts in the bone marrow.[10] There is a paucity of randomised trials comparing AML-like chemotherapy with hypomethylating agents. Sub-analysis of the AZA001 trial showed no significant difference in OS between the azacitidine and intensive chemotherapy groups, but the number of patients was too small for any conclusion.[48]

Low-dose chemotherapy

Low-dose cytarabine was significantly inferior to azacitidine in the AZA001 trial.[48] However, it may still be a treatment option in patients with normal karyotype who are not candidates for alloSCT, intensive chemotherapy or hypomethylating agents,[56] with CR and PR rates of 15–20% achievable.[57,58]

Allogeneic stem cell transplantation

Currently, alloSCT is the only potentially curative treatment for high-risk MDS.[10] However, a major impediment to alloSCT is that most high-risk MDS patients are aged ≥70 years, and as a result, alloSCT is attempted in less than 5% of patients. Patients aged <65 to 70 years (older patients may be considered if they are suitable) should be evaluated for alloSCT eligibility, taking into account co-morbidity, fitness, IPPS score, cytogenetics, conditioning regimen and donor selection.

Clinical trials

With the exception of patients eligible for alloSCT, high-risk MDS patients who are refractory or resistant to azacitidine have particularly poor survival. Retreatment with AML-like chemotherapy or low-dose cytarabine has produced disappointing results.[10] The recommended approach is to enrol such patients in a clinical trial with investigational agents and, if the patient becomes suitable for alloSCT, continue to transplant.[59]

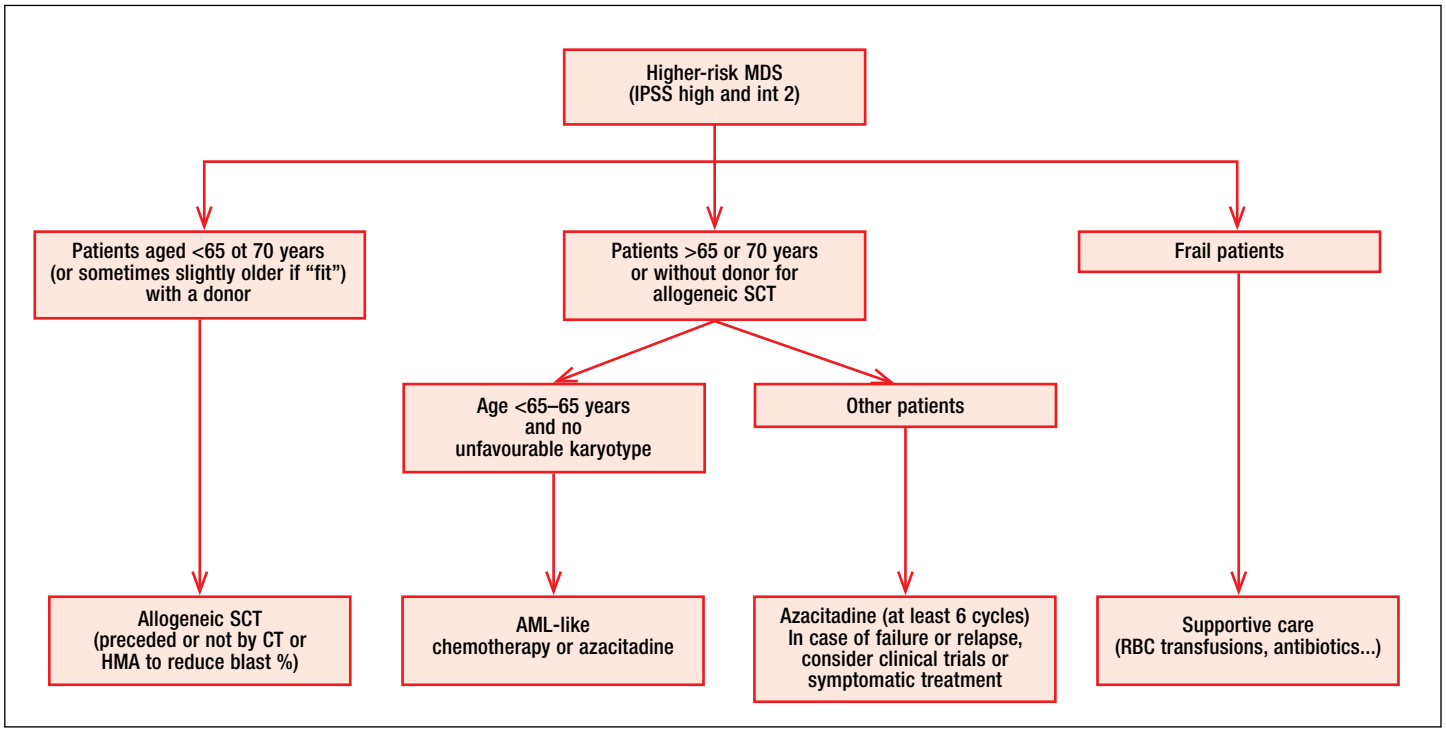


Figure 3. Treatment algorithm for high-risk MDS[10]

*Azacitidine is not indicated for lower risk MDS

Key messages – high-risk MDS

- AlloSCT only potential cure but attempted in <5% of patients
- Azacitidine first agent in MDS to improve OS
  - doubles 2 year OS vs CCR (26% to 51%)
  - triples 2 year OS in elderly (≥75 years) vs CCR (15% to 55%)
  - triples 2 year OS in AML vs CCR (16% to 50%)
  - provides improved QOL and lowers rates of TI, infection and hospitalisation vs CCR
  - important to persist with therapy – aim for at least 6 cycles before assessing response
  - most AEs with azacitidine occur early in treatment
  - treat to progression and manage AEs to ensure continuation of therapy as there may be late responses
  - prepare patients for potential worsening of cytopenias during the first 2 cycles
  - azacitidine is registered in New Zealand for high-risk MDS

EXPERT COMMENTARY
Peter Browett

The myelodysplastic syndromes represent a very heterogeneous group of disorders, with patient variable outcomes, including rapid transformation to AML in high risk patients. Significant advances have been made over the past decade in further understanding the biology and natural history of these conditions, and we are now moving towards a risk adapted and personalised strategy for therapy in our patients.

As outlined in this article, it is critical that patients with suspected MDS undergo a comprehensive workup, including bone marrow examination, cytogenetic studies, and in selected cases flow cytometry and additional molecular studies. The results of these investigations are used to stratify patients into different prognostic groups, particularly the IPSS and the updated IPSS-R which places an increased emphasis on karyotypic abnormalities. These prognostic scoring systems enable clinicians to adequately educate their patients about the risks for leukaemic transformation and complications of bone marrow failure. It also informs treatment decisions. For example, in low risk patients who are transfusion dependent and have a low serum EPO level, EPO has been shown to improve the haemoglobin level and reduce the transfusion requirements. In the subgroup of low risk patients with deletion of chromosome 5q, there is predictable response to the immunomodulatory drug lenalidomide. Recent data however suggest that up to 15–20% of these patients may harbour a p53 gene mutation. This subgroup of patients has a poor response to lenalidomide, and is at high risk of transforming to AML. They may benefit from increased surveillance, and if of an appropriate fitness and age, may be considered for alloSCT.

In patients with high-risk MDS, karyotypic abnormalities provide us with critical prognostic information and inform treatment recommendations. Patients may be considered for alloSCT, and as summarised in this review, the hypomethylating agents have been shown to not only improve peripheral blood counts and reduce transfusion requirements, but also to improve OS.

The advances in the field of MDS are ongoing, and we are now moving into an area of molecular typing. Not only will this give greater insight into the pathobiology of MDS, but also the potential to further enhance our prognostic stratification and ability to offer patients risk adapted therapies.

EXPERT COMMENTARY
Emma-Jane McDonald

The availability of azacitidine in New Zealand has changed our approach to managing patients with higher risk MDS. Younger, fitter high risk patients are treated with AML induction-style chemotherapy prior to transplantation however as the incidence of MDS increases with age there is a significant proportion of patients who are not eligible for this intensive treatment. Azacitidine has been shown to improve median OS and TI in higher risk patients when compared to conventional treatment and can be offered to a wider patient population.[48]

Initial studies used a dosing regimen of 75 mg/m^2 daily for 7 days however weekend dosing is not practical in the majority of hospital settings. Alternative dosing regimens have been compared (although mainly in lower risk MDS) and shown to have similar haematological improvements.[60] Dosing regimens which include a break over the weekend provide a more practical approach for patients.

Azacitidine is generally well tolerated as a subcutaneous injection however skin reactions can be problematic. Strategies for managing these reactions include correct injection technique, rotating the injection site, topical treatment with evening primrose oil or steroid cream and analgesics. It is rare for patients to discontinue treatment as a direct result of these skin reactions.

A response to treatment may not occur until several courses have been given and in fact cytopenias may worsen before they improve with an associated increase in transfusion requirements and hospital admissions due to infection during the first few cycles. Patients should be advised of these risks before commencing treatment and understand the importance of prompt medical review if they become unwell. It is important to continue treatment until at least six cycles have been received before assessing the response. Patients who achieve a response should be considered for ongoing treatment with azacitidine until there is evidence of disease progression although the optimal length of treatment has not been formally investigated.

Take-home messages

- MDS are clonal marrow stem-cell disorders characterised by ineffective haematopoiesis leading to blood cytopenias and progression to AML in a third of patients
- MDS is underdiagnosed and underreported
- Treatment of patients with low-risk MDS, especially for anaemia, includes growth factors, iron chelation, lenalidomide and transfusions
- Treatment of high-risk patients includes hypomethylating agents and, whenever possible, alloSCT
- Lenalidomide:
  - registered in New Zealand for low-risk del(5q) MDS
  - produces durable TI and improved QOL
- Azacitidine:
  - registered in New Zealand for high-risk MDS
  - first agent in MDS to improve OS
  - can be used effectively in elderly and low blast count AML
  - provides improved QOL and decreases rates of transfusion dependence, infection and hospitalisation vs CCR
  - Important to persist with therapy – aim for at least 6 months

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