Myelodysplastic syndromes

The myelodysplastic syndromes are a group of disorders predominantly affecting elderly people, leading to ineffective haematopoiesis, and they have the potential to develop into leukaemia. Classification and prognostic systems help to divide patients with widely varying diseases into categories with a similar clinical course. Patients can then be offered treatments appropriate to their disease and comorbidities. This article describes the options available, particularly for elderly patients, including advances in supportive care, and new epigenetic and immunomodulatory therapies.

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Since the 1970s, the term myelodysplasia has been used to describe a heterogeneous group of disorders characterised by varying degrees of anaemia, leucopenia, and thrombocytopenia. In these conditions, a malignant clone of stem cells leads to ineffective haematopoiesis and the potential to evolve into leukaemia. They are predominantly diseases of elderly people, with the highest incidence in those older than 70 years,[1] although they can occur at any age (figure 1).

The incidence of myelodysplasia appears to be rising but this may be explained in part by an increase in the number of cases found incidentally on full blood counts. The diagnosis is made on testing the bone marrow, so regional differences in incidence may reflect haematologists' practice of sampling bone marrow in elderly patients.

Until recently, treatment for myelodysplasia focused on two options. The first was symptomatic support (supportive care) with transfusions of red cells or platelets, and antibiotics for infections. The second was a curative approach with intensive chemotherapy and a myeloablative stem-cell transplant. These treatments were unsatisfactory because transplantation is open only to a minority of younger, fitter patients with available donors, and supportive strategies do not influence the progression of the disease and are still associated with impaired quality of life.[2,3]

However, recently we have seen significant progress in treatment options for elderly patients with myelodysplasia. Growth factors can be helpful in supportive care, transplants are suitable for more patients and new drugs such as azacitidine and lenalidomide can be used to alter the natural history of the disease. This article aims to outline these advances as well as to provide background on the clinical features and classification of myelodysplastic syndromes.

Clinical features and diagnosis

Symptomatic patients present with one or more of the features of bone marrow failure—namely, anaemia, bleeding, or recurrent infection. Many people, however, are asymptomatic and are only diagnosed incidentally.

The full blood count may reveal a macrocytosis in addition to cytopenias. The blood film may show characteristic abnormalities such as described in table 1, but in many cases changes are quite subtle. Other causes of dysplastic morphology must be ruled out— differential diagnoses

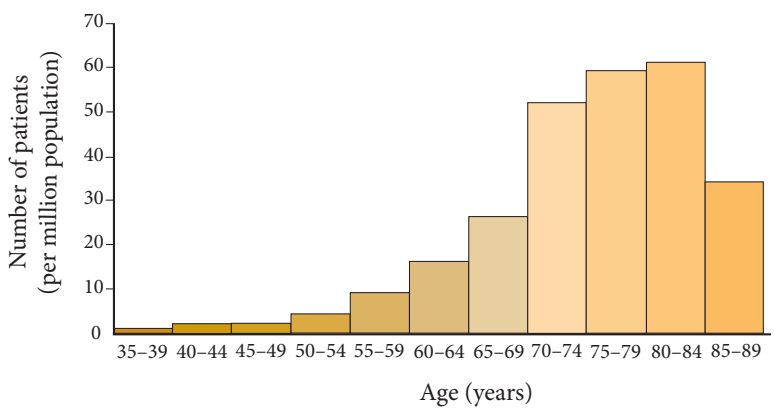

Figure 1: Incidence of myelodysplastic syndromes by age

	Blood	Marrow
Erythroid	Oval Macrocytes Basophilic stippling	Nuclear-cytoplasmic asynchrony Ring sideroblasts
Myeloid	Hypogranular neutrophils Hypolobulated neutrophil nuclei	Increased number of blasts
Megakaryocytic	Agranular platelets	Megakaryocytes with separated nuclei Monolobular megakaryocyte nuclei

Table 1: Abnormalities seen in blood cells in blood and bone marrow

include: vitamin B_{12} deficiency; folate deficiency; HIV infection; alcohol toxicity; benzene toxicity; lead toxicity; cytotoxic drugs; and dyserythropoeitic anaemias.

Examination of bone marrow is critical to the diagnosis of myelodysplasia. The marrow is most often hypercellular and typical morphological abnormalities are present (table 1 and figures 2 and 3). Cytogenetic analysis of the marrow should be done in all cases, as abnormalities are found in 40–70% of patients with primary myelodysplasia.[4] Knowledge of cytogenetics is advantageous in three ways. First, the presence of a clonal chromosome abnormality may confirm a primary bone marrow disorder, and can confirm the diagnosis in cases in which the morphological abnormalities are subtle. Second, they are involved in classification systems, and provide prognostic information. Third, the cytogenetic change may determine which patients should be treated with novel disease modifying agents.

Classification and prognosis

The myelodysplastic syndromes are very heterogeneous, ranging between quite indolent conditions to those with life-threatening cytopenias and a high risk of progression to leukaemia. It has therefore been important to attempt to group patients in a way that can predict the clinical course of the condition and the prognosis. The WHO classification (table 2),[5,6] has been universally adopted for diagnosis, and the International Prognostic Scoring System (IPSS)[7] (table 3) for prognosis.

The disease may be best viewed as high or low risk based on the chance of the disease progressing to leukaemia, because the treatment approaches differ. An arbitrary blast count in the marrow of 5% is used as the cut off between these two groups, and blasts at 20% become the level at which patients are categorised as having acute myeloid leukaemia. A further group is included in WHO's classification for those who have an isolated deletion of the long arm of chromosome 5 (5q-syndrome). This has turned out to be a clinically relevant distinction because of the success of immunomodulatory drugs in these patients.

Although there are many advantages to WHO's classification, a great deal of heterogeneity remains within each group, particularly those with higher risk disease such as in refractory anaemia with excess blasts. Determining the risk status for leukaemic transformation and death can be important in deciding which treatments are most appropriate.

In 1997, the IPSS provided a tool

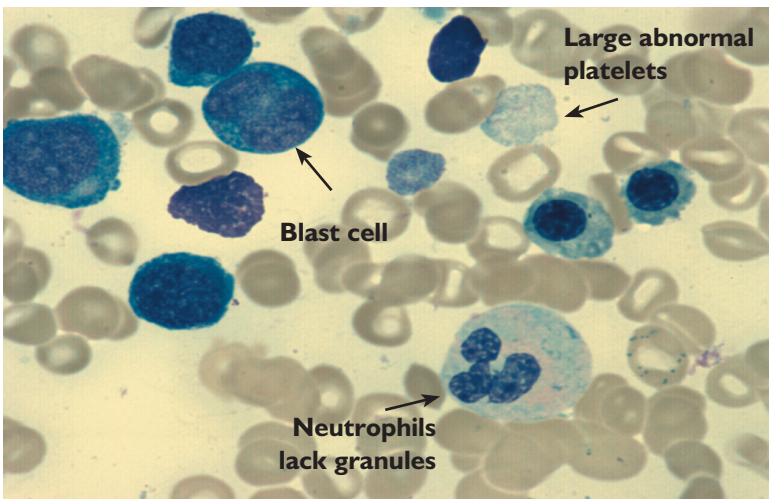

Figure 2: Myelodysplastic bone marrow

to predict the prognosis of untreated patients.[7] Scores are calculated using the karyotype, number of cytopenias, and percentage of blasts in the marrow to predict four different prognostic categories, as shown in table 3. Although this provides a more accurate way of determining risk, there is variation even within these groups. In many cases, clinical observation of the individual and serial bone marrow examinations are needed to predict the pace of disease.

Management

Treatment decisions must be made on an individual basis according to factors such as the patient's age, comorbidities, and risk category. For example, life-expectancy in patients in the WHO group with refractory anaemia aged 70 years or older is not significantly shorter than that of the general population.[8] In general, patients in low-risk groups (IPSS low risk and intermediate-1 risk) without cytopenia-related symptoms do not need any treatment but should be followed-up for signs of progression.

Once symptomatic, most patients are treated with supportive care with the aim of improving their quality of life. The exceptions are those in the WHO isolated-5q category and those suitable for immunosuppression. In groups at higher risk, the choice is between curative approaches (stem-cell transplantation), other treatments aimed at altering the progression of the myelodysplasia, or simply supportive care.

Supportive therapies

Red-cell transfusion

Transfusion is often the sole therapy, because myelodysplastic syndromes are most common in elderly patients, many of whom have clicically significant comorbidities. Treatment is initiated once anaemia-related symptoms become apparent. Target haemoglobin levels should be individualised to the patient according to their symptoms and comorbidities. Transfusion-dependent patients have an increased risk of non-leukaemic death compared with those who are independent.[8] This may be partly due to a higher rate of heart-failure related mortality, and may be explained by lower median haemoglobin levels and an impact of cardiac iron overload in some patients.

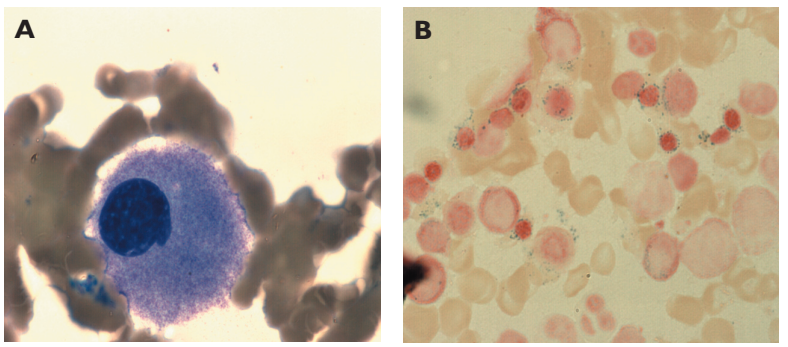

Figure 3: Features of myelodysplastic bone marrow
A: An abnormal megakaryocte with only one lobe of the nucleus
B: Iron is seen in dark rings around the red cells (sideroblastic anaemia)

Iron chelation therapy

A concern with long-term transfusion therapy is iron overload, with resultant cardiac, hepatic, or endocrine sequelae. Data for myelodysplasia is limited, but current guidelines suggest giving chelation therapy once approximately 25 units of blood have been transfused, and only in those expected to survive long enough for the effects of iron overload to become clinically important.[9] Desferrioxamine is administered subcutaneously through a pump over 12 hours for 5 days a week. This method is obviously unpopular with patients. A new oral drug, deferasirox, has been licensed for cases in which desferrioxamine is contraindicated or inadequate. The UK haematological community feels that further work is needed to clarify the benefit of iron chelation therapy on overall survival in elderly patients and further research is ongoing.

Haematopoietic growth factors

Haematopoietic growth factors work by stimulating the marrow to improve cytopenias. They are appropriate only for patients with low-risk disease and are expensive. A validated predictive scoring system can be used to justify their cost with response rates between 7% and 74%,[2] and this is the topic of an ongoing UK prospective randomised clinical trial.

Supportive therapy in neutropenia and thrombocytopenia

Severe neutropenia usually occurs in the context of pancytopenia. Unless there is a prospect of recovery of counts through disease modifying therapy or covering episodes of sepsis, prophylactic granulocyte colony stimulating factor (GCSF) is not usually used, nor are long-term prophylactic antibiotics, which may lead to resistant strains

	Main criteria	Median survival
Refractory anaemia	Erythroid dysplasia only <5% marrow blasts	69 months
Refractory anaemia with ring sideroblasts	Erythroid dysplasia only <5% blasts >15% ring sideroblasts	69 months
Refractory cytopenia with multilineage dysplasia	Dysplasia in 2 or more lineages <5% blasts	33 months
Refractory cytopenia with multilineage dysplasia and ring sideroblasts	Dysplasia in 2 or more lineages <5% blasts >15% ring sideroblasts	32 months
Myelodysplasia associated with isolated del(5q) chromosome abnormality	Typical megakaryocytes <5% blasts	116 months
Refractory anaemia with excess blasts	Type-1: 5–9% blasts Type-2: 10–19% blasts	18 months 10 months

Table 2: WHO classification and expected survival for myelodysplastic syndromes[5,6]

of bacteria. Similarly in severe thrombocytopenia, prophylactic platelet transfusions are given only to patients with active bleeding.

The 5q-syndrome and immunomodulatory drugs

The WHO classification of 5q- syndrome refers to a specific type of low-risk myelodysplasia. Lenalidomide, an immunomodulatory drug, has been shown to produce striking responses in this group.[10,11] At least two-thirds of patients become transfusion independent, and half of those remain so for more than 2 years. Frequent complete responses are seen, including loss of the cytogenetic clone. This treatment is suitable for elderly patients. The mechanism of action is complex but appears to include direct targeting of the 5q-clone.[12]

Immunosuppression

Accumulating evidence suggests an immunological process involved in the pathogenesis of myelodysplastic syndromes. For this reason, as with aplastic anaemia, several groups have had success treating low-risk disease with antithymocyte globulin. Approximately one-third of patients will have a response to treatment, evident by an improvement in blood counts and a reduction or cessation of blood products.[13] There seems to be a trend towards better response rates in patients with hypocellular myelodysplasia. The treatment is not curative but durable responses have been noted. Ciclosporin, probably acting by a similar mechanism, may be considered for those not suitable for antithymocyte globulin.[14]

Epigenetic therapy

5–azacitidine and decitabine

Azacitidine has been shown to be the first non-intensive therapy to significantly improve survival in myelodysplastic disease. This class of drugs reduce DNA methylation and induce re-expression of key silenced genes.[15] They have mainly been used for the treatment of IPSS intermediate-2 and high-risk patients. A prospective randomised trial of azacitidine versus conventional care showed a superior overall survival for azacitidine.[16] At 2 years there was a twofold advantage, with 51% of patients in the azacitidine group alive compared with 26% in the conventional-care arm. Another advantage of these drugs is that they are quite well tolerated, and are often suitable for patients who are not appropriate for intensive chemotherapy regimens. Epigenetic therapy will probably change the way that high-risk myelodysplasia is treated, especially in elderly patients.

High-intensity chemotherapy

Inpatient-based high intensity chemotherapy is a treatment option for younger patients with high-risk disease. It is usually given to induce remission before a stem-cell transplant, but it can be considered as sole therapy. However, when such treatment is compared with that for de novo acute myeloid leukaemia, remission rates are lower and the time to relapse is often short (5–15 months). Used alone, it is not curative, but for those achieving a response, it can offer excellent quality of life. Morbidity and mortality from this treatment should not be underestimated.

Stem-cell transplantation

Allogeneic transplantation remains the only curative option for myelodysplastic syndromes, but it carries significant risk. The success of the transplant is due to the conditioning chemotherapy (radiotherapy may

be included) and the graft itself, which has an immunological effect similar to graft-versus-host disease (graft versus leukaemia). The patient must be fit enough to endure the therapy and have no contraindicating comorbidities. More recently, mini-transplants with reduced-intensity conditioning have been developed that extend the age limit because the transplant-related mortality is lower. The risk of relapse is higher than that of standard transplants, and so the overall survival is similar (3-year survival 41–45%).[17]

Conclusion

Myelodysplasia remains a diverse and challenging group of disorders. Supportive care is still the cornerstone for the majority of elderly patients. However, innovative treatments are becoming available to a range of patients who previously had few options. Continued research will hopefully lead to more treatments targeted to defined subgroups.

Dr Sally Killick has been part of national advisory boards on behalf of Novartis, Genzyme, and Celgene.

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	Proportion of bone marrow blasts	Karyotype	Cytopenias	Risk category	Overall median survival for all age groups
0	<5%	Good risk	0 or 1 lineages	Low	5·7 years
0·5	5–10%	Intermediate	2 or 3 lineages	..	..
1·0	..	Poor risk	..	Intermediate-1	3·5 years
1·5	11–20%	..	..	Intermediate-2	1·2 years
2·0	>20%	..	..	..	..
≥2·5	..	..	..	High	0·4 years

Table 3: International prognostic scoring system (IPSS)[10] and resulting risk categories and expected survival