ABC of clinical haematology

The myelodysplastic syndromes

David G Oscier

The term myelodysplastic syndromes was introduced in 1975 by a group of French, American, and British haematologists (FAB group) to describe a group of disorders with characteristic abnormalities of peripheral blood and bone marrow morphology and impaired bone marrow function, which tend to evolve into acute myeloid leukaemia. Although the myelodysplastic syndromes may occur at any age, they are predominantly diseases of elderly people.

Aetiology

Primary myelodysplastic syndrome describes those cases—the majority—in which the cause is unknown. Case-control studies have shown a modest correlation between the myelodysplastic syndromes and exposure to low doses of radiation and organic chemicals.

Therapy related myelodysplastic syndrome, sometimes called secondary myelodysplastic syndrome, describes cases that have arisen as a long term complication of cytotoxic chemotherapy. The risk is highest 4-10 years after treatment with alkylating agents, such as chlorambucil and cyclophosphamide.

Diagnosis

Patients present with the features of bone marrow failure—namely, symptoms of anaemia, bacterial infections, and bleeding or bruising. Splenomegaly is present in about 10% of patients, particularly in chronic myelomonocytic leukaemia, one subtype of the myelodysplastic syndromes. Increasingly, myelodysplastic syndrome is an incidental finding in elderly patients whose routine blood count shows an unexplained anaemia, macrocytosis, neutropenia, monocytosis, or thrombocytopenia.

The myelodysplastic syndromes can be diagnosed only by a haematologist, primarily on the basis of characteristic full blood count indices, morphological abnormalities on the peripheral blood film, and characteristic bone marrow appearances. Although myelodysplastic syndrome may sometimes be diagnosed on the basis of a blood film alone, a bone marrow aspirate and trephine are necessary to make a confident diagnosis and to assess the severity of the disease. Marrow examination can safely be omitted only in elderly, infirm patients with mild cytopenias who would not need treatment regardless of the marrow findings.

Age distribution and incidence rates per 100 000 population of patients presenting with myelodysplastic syndrome in Bournemouth, 1981-90.

Blood film showing normal neutrophil (right) and dysplastic neutrophil with agranular cytoplasm and hypolobated nucleus.

Morphological abnormalities in myelodysplastic syndrome

Lineage	Blood	Marrow
Erythroid	Oval macrocytes	Abnormal nuclear shape and chromatin pattern
	Basophilic stippling	Ring sideroblasts
Myeloid	Hypogranular neutrophils	
	Hypolobated neutrophil nuclei	
Megakaryocytic	Agranular platelets	Micromegakaryocytes
		Mononuclear megakaryocytes
		Megakaryocytes with separated nuclei

Diagnosis is frequently straightforward, particularly if morphological abnormalities are found in the three major lineages—erythroid (red cells), myeloid (granulocytes, including neutrophils), and megakaryocytic series (platelets)—in the clinical context of an elderly patient with a peripheral blood cytopenia. However, morphological dysplasia is not synonymous with myelodysplastic syndrome, and similar morphological abnormalities to those found in early myelodysplastic syndromes may be seen in vitamin B₁₂ deficiency or folate deficiency, alcohol excess, after cytotoxic chemotherapy, HIV infection, and even in a minority of cells in the bone marrow of normal individuals. Problems also arise if morphological abnormalities are subtle, if they involve only one cell lineage, or if the staining of blood and marrow slides is suboptimal.

Chromosome analysis

Cytogenetic analysis of bone marrow should be performed whenever the diagnosis of myelodysplastic syndrome is suspected from the blood film. It is valuable both prognostically and when the morphological diagnosis is difficult. A clonal chromosome abnormality—that is, the same abnormality appearing in more than one cell—confirms the presence of a primary bone marrow disorder and excludes the reactive causes of dysplasia listed above. Chromosomal abnormalities are found in 30-50% of cases of primary myelodysplastic syndrome and in 80% of cases of therapy related myelodysplastic syndrome. Specific chromosomal abnormalities may be associated with particular clinical and haematological features. For example, loss of part of a long arm (“q”) of chromosome 5 occurring as the only chromosomal abnormality (5q⁻ syndrome) is associated with macrocytic anaemia in elderly women and a low risk or transformation to acute myeloid leukaemia. Loss of the short arm (“p”) of chromosome 17 is found in advanced disease and is associated with drug resistance and short survival.

Most of the chromosomal abnormalities in the myelodysplastic syndromes involve loss of genetic material, but the critical genes that are deleted are yet to be discovered. Disease progression, particularly evolution to acute leukaemia, is frequently accompanied by additional chromosomal abnormalities (“karyotypic evolution”).

FAB classification

In 1982 the FAB group divided the myelodysplastic syndromes into five subgroups based on (a) the percentage of immature myeloid cells (blast cells) and ring sideroblasts (immature red cells with iron granules arranged in a ring around the nucleus) in the bone marrow and (b) the presence or absence of a raised peripheral blood monocyte count. This classification was rapidly adopted worldwide and is still widely used. Individual subgroups, however, should not be viewed as distinct disorders as patients may pass through several stages during the course of their disease. Although chronic myelomonocytic leukaemia shares the morphological abnormalities common to all the myelodysplastic syndromes, many patients have features such as leucocytosis and splenomegaly, which are more typical of a myeloproliferative disorder. Patients with more than 30% blasts in the bone marrow are considered to have acute leukaemia, but the distinction between myelodysplasia with more than 20% blasts and acute myeloid leukaemia in elderly people is blurred. Elderly people with acute myeloid leukaemia often have dysplastic morphology, similar chromosomal abnormalities, and a similar clinical course to patients with advanced myelodysplastic syndromes.

Large mononuclear megakaryocyte in marrow of patient with 5q⁻ syndrome.

Chromosome abnormalities in myelodysplasia		
Abnormality	Incidence (%)	
	Primary myelodysplastic syndrome	Therapy related myelodysplastic syndrome
Deletion of 5q	10-20	20
Monosomy 7	10-15	30-50
Trisomy 8	15	10
Loss of 17p	3	10

FAB classification of myelodysplastic syndrome			
Category	Peripheral blood		Bone marrow
Refractory anaemia (RA)	< 1% blasts	and	<5% blasts
Refractory anaemia with ring sideroblasts (RARS)	< 1% blasts	and	<5% blasts, > 15% ring sideroblasts
Refractory anaemia with excess blasts (RAEB)	< 5% blasts	and	5-20% blasts
Refractory anaemia with excess blasts in transformation (RAEBt)	> 5% blasts	or	21-30% blasts
Chronic myelomonocytic leukaemia (CMML)	> 1 × 10 ⁹ /l Monocytes		

Natural course and prognosis

The clinical course of the myelodysplastic syndromes is extremely variable even among patients of the same subgroup. About two thirds of patients die of marrow failure (of whom half undergo leukaemic transformation), and one third die of unrelated causes. The median survival of patients with myelodysplastic syndrome is 20 months and for all subtypes is shorter than that of age matched controls.

Although the FAB classification has prognostic significance, a more accurate prediction of survival can be achieved by using a scoring system that incorporates the presenting haemoglobin concentration, neutrophil and platelet counts, the percentage of blasts in the bone marrow, and chromosome abnormalities.

Management decisions should not be based on blood and marrow samples taken during severe bacterial infections as infections can result in acute and reversible changes in the neutrophil and platelet counts and the percentage of marrow blasts.

International prognostic scoring system for myelodysplastic syndrome

Prognostic variable	Score*				
	0	0.5	1.0	1.5	2.0
Marrow blasts (%)	<5	5-10	—	11-20	21-30
Karyotype	Good†	Intermediate‡	Poor¶		
Cytopenias	0/1	2/3			

*0 = low risk, 0.5-1.0 = intermediate risk 1, 1.5-2.0 = intermediate risk 2, ≥2.5 = high risk.
†Normal karyotype or absent Y chromosome (-Y), deletion of long arm of chromosomes 5 or 20 (del(5q), del(20q)).
‡Other abnormalities.
¶Complex karyotypic abnormalities (≥3 abnormalities), or chromosome 7 anomalies.

Management

The treatment of the myelodysplastic syndromes is generally unsatisfactory, which partially accounts for the variety of therapeutic options.

Before the most appropriate treatment can be determined, several factors must be taken into consideration. These include the patient's age and general fitness, the severity of the disease at presentation, prognostic factors, and whether the disease is stable or progressive. Consequently, whenever possible there should be a period of observation before a decision about long term treatment is made.

For most patients treatment is palliative, and the possibility of cure applies only to the minority of young patients suitable for an allogeneic bone marrow transplant. Sixty per cent of such patients without an increase in marrow blasts and 40% of patients with increased blasts will be free of disease five years after transplantation.

Low risk patients need observation only. For fit and well motivated patients under the age of 65-70 years with intermediate or poor risk disease, intensive chemotherapy currently offers the best possibility of improved quality and duration of life. Remission rates of 60% are achievable but rarely last beyond 18 months.

Median survival (months) of primary myelodysplastic syndrome according to FAB type

FAB type	Median survival	Range
All cases	20	7.4-28
Refractory anaemia	50	18-64
Refractory anaemia with ring sideroblasts	51	14-76
Refractory anaemia with excess blasts	13	7-21
Refractory anaemia with excess blasts in transformation	6	2.5-16
Chronic myelomonocytic leukaemia	18	4 to >60

Survival of 816 patients who had received no treatment or only supportive care on the basis of the international myelodysplastic syndrome

Treatment options in myelodysplasia

- Observation
- Supportive care
 - Red cell or platelet transfusions, or both
 - Antibiotics
 - Haemopoietic growth factors
- Intensive chemotherapy
- Low dose chemotherapy
- Differentiating agents
- Bone marrow transplantation

Low dose cytotoxic treatment with hydroxyurea or etoposide may reduce spleen size and improve the blood count in patients with intermediate and poor risk chronic myelomonocytic leukaemia, but the median survival remains poor at less than two years.

Drugs that could induce the differentiation of immature into mature myeloid cells without causing bone marrow toxicity would be highly prized in the treatment of the myelodysplastic syndromes. Low dose cytosine arabinoside and analogues of vitamin D₃ and retinoic acid have differentiating activity in vitro but so far have been disappointing in clinical use.

The cornerstone of the treatment of the myelodysplastic syndromes remains the judicious use of red cell and platelet transfusions and antibiotics for most elderly patients with symptomatic disease. Iron chelation therapy should be considered for patients who need red cell transfusion long term. Recombinant growth factors can improve the neutrophil count in over 90% of patients (granulocyte-colony stimulating factor or granulocyte-macrophage colony stimulating factor) and the haemoglobin concentration in 20-40% of patients (erythropoietin with or without either of these colony stimulating factors). Intermittent administration of either of these colony stimulating factors may be considered in patients with severe neutropenia and recurrent infections. Growth factors are expensive, however, and least effective in patients with advanced disease and severe cytopenias—those who most require treatment.

The histogram showing age distribution and incidence rates for myelodysplastic syndrome is adapted with permission from the *British Journal of Haematology* (Williamson PJ, Kruger AR, Reynolds PJ, Hamblin TJ, Oscier DG. Establishing the incidence of myelodysplastic syndrome. 1994;87:743-5). The illustration of the mononuclear megakaryocyte is reproduced with permission from *Leukaemia Diagnosis: A Guide to the FAB Classification* (Bain B, London: Mosby International, 1993).

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70 Year old woman with refractory anaemia with excess blasts in transformation showing improvement in leukaemic skin deposits after course of low dose cytosine arabinoside.

Further reading

- Mufti GJ, Galton DAG. *The myelodysplastic syndromes*. Edinburgh: Churchill Livingstone, 1992.
- Koefler HP, ed. *Seminars in hematology. The myelodysplastic syndromes. Parts I and II*. Philadelphia: Saunders, 1996.

ANY QUESTIONS

I often see shops selling, at a considerable discount, canned foods, alcohol, chocolate, etc, many months after their sell by dates. When do these become unsafe to consume?

The "sell by" date is the date beyond which the manufacturer or producer will not guarantee that the quality of the product is at the level desired. The terms "best before" or "use by" are now required by the Food Labelling (Amendment) Regulations.¹ The latter relates to food which, from a microbiological point of view, is highly perishable and likely after a short period of time to constitute an immediate danger to human health and the former to products with a longer minimum durability. The question obviously refers to those products with a "best before" date.

Products which are marked "best before" are unlikely to be unsafe to consume after the date stated. They will be of the shelf stable type (canned, dehydrated, high sugar, acidic, or alcoholic products) that are processed either to eliminate organisms—for example, by the severe heat treatment of canning—or to prevent outgrowth of organisms by reducing the water activity of the product—for example, by dehydration

or addition of sugar or salt. The products can, however, become unpalatable due to changes such as oxidation or rancidity of fats and other enzymatic changes (as with stale crisps or old chocolate).

Care should be taken with canned foods; old products often means a much handled product which may have resulted in physical damage to the cans. Dents and rusting can lead to small holes which can allow ingress of organisms which will result in either spoilage of the product or the growth of harmful organisms. Large canned hams receive only a pasteurisation treatment and should be stored at chill temperatures.

It is impossible to give a precise date at which such a variety of foods becomes unsafe; there are so many variable factors involved. The best advice is to adhere to the manufacturer's recommended minimum durability dates. Reputable producers will have undertaken challenge testing of the product to ensure safety, keeping quality, and palatability and the "best before" date will be based on such tests.

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1 The Food Labelling (Amendment) Regulations 1990 No 2488. London: HMSO, 1990.