22.3.2 Myelodysplastic syndromes 5197 Charlotte K.

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22.3.2 Myelodysplastic syndromes 5197 for neutrophils and eosinophils, leukotrienes, prostaglandins, and platelet-activating factor. They arise in the marrow from the same myeloid precursor as eosinophils. Basophils function in immediate- type hypersensitivity. They are structurally similar to mast cells but the exact relationship between these cell types is not clear. Basophilia (> 0.2 × 106/μl) is seen in myeloproliferative disorders such as chronic myeloid leukaemia and polycythaemia vera, hypersensitivity reac- tions, and with some viral infections including varicella and influenza. Mast cell leukaemia is a rare disorder with a poor prognosis. FURTHER READING Andersohn F, Konzen C, Garbe E (2007). Systematic review: agran- ulocytosis induced by nonchemotherapy drugs. Ann Intern Med, 146, 657–65. Chiriaco M, et al. (2015). Chronic granulomatous disease: clinical, molecular and therapeutic aspects. Pediatr Allergy Immunol, 27, 242–53. Dinauer MC (2016). Primary immune deficiencies with defects in neutrophil function. Hematology Am Soc Hematol Educ Program, 2016(1), 43–50. Dinauer MC (2019). Inflammatory consequences of inherited dis- orders affecting neutrophil function. Blood, 133(20), 2130–9. Horwitz MS, et al. (2013). ELANE mutations in cyclic and severe con- genital neutropenia: genetics and pathophysiology. Hematol Oncol Clin North Am, 27, 19–41. Kiehl M, et al. (2019). Management of sepsis in neutropenic cancer patients: 2018 guidelines from the Infectious Diseases Working Party (AGIHO) and Intensive Care Working Party (iCHOP) of the German Society of Hematology and Medical Oncology (DGHO). Ann Hematol, 98(5), 1051–69. Klion A (2018). Hypereosinophilic syndrome: approach to treatment in the era of precision medicine. Hematology Am Soc Hematol Educ Program, 2018(1), 326–31. Lane A, Berliner N (2013). Nonmalignant disorders of leukocytes. ACP Medicine. http://what-when-how.com/acp-medicine/nonmalignant-

disorders-of-leukocytes-part-1/ and http://what-when-how.com/ acp-medicine/nonmalignant-disorders-of-leukocytes-part-2/. Schram AM, Berliner N (2018). Nonmalignant disorders of Leukocytes. Scientific American Medicine. Decker Intellectual Properties, Inc. DOI 10.2310/7900.1010. 22.3.2 Myelodysplastic syndromes Charlotte K. Brierley and David P. Steensma ESSENTIALS The myelodysplastic syndromes (MDS) are marrow failure syn- dromes characterized by cytopenias, blood cell dysmorphology, ac- quired clonal cytogenetic and molecular genetic mutations, and a risk of development of acute myeloid leukaemia. MDS may evolve in patients previously treated with cytotoxic chemotherapy or radio- therapy for a solid tumour, but most commonly arise de novo in pa- tients over 60 years old. Clinical features, diagnosis, and classification Most patients present with features of chronic anaemia or manifest- ations related to thrombocytopenia or infection. The diagnosis may be suggested by the presence of normocytic or macrocytic anaemia, with the peripheral blood smear showing dysplastic changes in red blood cells or neutrophils. Bone marrow aspirate and biopsy permits detailed cytogenetic study, which is critical for diagnostic classifi- cation and prognosis. Increasingly, molecular genetic assays (next- generation sequencing panels) aid in diagnosis and prognosis. The World Health Organization (WHO) classification recognizes various MDS subtypes based on the morphological appearance of the peripheral blood and bone marrow. These include MDS with ex- cess blasts, MDS with deletion of the long arm of chromosome 5, and MDS with ring sideroblasts. Treatment and prognosis Treatment is symptomatic in most cases. The only potentially curative treatment is allogeneic bone marrow transplantation, which is often precluded due to patients' advanced age or comorbidity. Higher-risk patients may experience a survival benefit from treatment with the DNA hypomethylating agent azacitidine, and decitabine delays dis- ease progression to acute myeloid leukaemia. Some patients with lower-risk disease may show a response to immunosuppression with antithymocyte globulin and ciclosporin. Patients with isolated chromosome 5q deletions and lower-risk disease may respond dra- matically to lenalidomide, an immunomodulatory drug. Prognosis varies widely (median survival <1 year to >10 years) according to particular subtype and disease features such as pro- portion of marrow blasts, karyotyping results, and the severity of cytopenias. Patients with excess blasts, a complex karyotype, and mutations of TP53 have the poorest prognosis. Most patients who do not die of unrelated conditions die as a result of either bleeding or infection, but in some, transformation to leukaemia proves fatal. Introduction The myelodysplastic syndromes (MDS) are clonal haematopoi- etic neoplasms characterized by bone marrow dysfunction with peripheral blood cytopenias, dysplastic cell morphology, acquired (somatic) cytogenetic and molecular genetic aberrations, and a vari- able risk of progression to acute myeloid leukaemia (AML). Box 22.3.1.4 Causes of eosinophilia • Allergies • Atopy • Inflammation:

— Collagen vascular diseases (rheumatoid arthritis, polyarteritis nodosa, eosinophilic fasciitis) • Infection:

— Helminths

— Parasites • Neoplasms:

— Hodgkin lymphoma and non-Hodgkin lymphoma

— Chronic myeloid leukaemia

— Eosinophilic leukaemia • Job’s syndrome • Idiopathic hypereosinophilic syndromes • Addison’s disease

SECTION 22 Haematological disorders 5198 MDS are clinically and genetically heterogeneous. These syn- dromes result from malignant transformation and clonal expansion of a mutated multipotent myeloid progenitor or stem cell. Disease- associated manifestations and trajectory vary significantly, from an indolent condition with a single cytopenia (most commonly an- aemia) that is stable for years, to fulminant bone marrow failure and rapid progression to AML within months. The 2016 World Health Organization (WHO) classification system delineates several MDS subtypes, based on the percentage of bone marrow blasts, the number of dysplastic lineages, and characteristic chromosomal and molecular genetic abnormalities (Table 22.3.2.1). MDS are classed as having progressed to AML once the bone marrow or peripheral blood blast count reaches a threshold of 20%. Although these syndromes were formerly known as ‘preleukaemia’, only a minority of patients (c.30%) with MDS progress to AML. The advent of next-generation sequencing technology has led to advances in our understanding of the disease, but treatment options remain limited and clinical outcomes unsatisfactory. This chapter sets out to describe our current understanding of the pathophysiology, epidemiology, clinical features, and therapeutic options for this heterogeneous group of bone marrow failure syndromes. Aetiology MDS are typically acquired disorders caused by de novo somatic mutations in a haematopoietic progenitor or stem cell. Common initiating mutations include those seen in TET2 or DMT3A, genes which encode factors involved in epigenetic regulation, and SF3B1, which encodes a component of the spliceosome. Subsequent muta- tions such as in NRAS or TP53 genes may lead to clonal evolution and diversity, and functional changes including increased cell prolif- eration and genomic instability. The primary risk factor for MDS is age, secondary to the increasing cumulative burden of somatic mu- tations in ageing stem cells. The incidence of MDS is mildly increased in petroleum and agri- cultural workers, possibly due to accelerated mutation rates sec- ondary to exposure to polycyclic aromatic hydrocarbons. Exposure to ionizing radiation from the atomic bomb explosions at Hiroshima and Nagasaki led to continued increased MDS risk among the ex- posed population for more than 50 years post event. Therapy-related MDS (t-MDS) comprises 5 to 10% of MDS, occurring in recipients of radiation or chemotherapy as treatment for other disorders such as solid tumours. Cytotoxic chemotherapies, particularly alkylating agents and topoisomerase inhibitors, and ionizing radiation predis- pose to t-MDS both by selecting for expansion of pre-existing TP53 mutant clones and by causing DNA damage and loss of chromo- somal integrity in haematopoietic stem cells. t-MDS carries an ad- verse prognosis and occurs an average of 5 to 10 years post exposure to alkylators or radiation, and sooner (1–3 years) after topoisom- erase inhibitors. Rare familial cases of MDS, accounting for less than 2% of MDS cases, have enabled identification of germline mutations in genes such as GATA2, DDX41, SRP72, RUNX1, and others. Some of these genes are also recognized as recurrent somatic mutations in de novo/t-MDS. Other inherited syndromes conferring an increased risk of MDS include Down syndrome, Fanconi anaemia, and telomeropathies such as dyskeratosis congenita. Epidemiology MDS are estimated to be one of the most common haematological malignancies with a reported age-adjusted incidence of 4.9 to 5.3 per 100 000, though this may be an underestimate. Ascertaining the exact epidemiology of MDS is difficult. Isolated cytopenias, especially mild anaemia, are often underinvestigated in the elderly. In addition, MDS diagnosis and classification are complex, and cancer registry reporting of MDS cases has been inconsistent. The median age of MDS diagnosis in the United States of America and Western Europe is approximately 70 years. Diagnosis in those younger than 50 years is rare

(unless exposed to the risk factors out- lined previously) and diagnosis in children is extremely rare, with an estimated annual incidence of one per million. However, there is a worldwide variation in age at diagnosis, with a lower average age documented in patients in Asia and Eastern Europe. The exact cause of this is unknown, but may be attributable to differing envir- onmental exposures or genetic background. For reasons that remain unclear but may be due to either occupa- tional exposure patterns or a protective effect of two copies of certain X-encoded genes, the incidence of MDS is approximately 1.5 times higher in men than women. The exception to this is the MDS disease subtype characterized by isolated loss of the long arm of chromo- some 5, known as del(5q) or 5q− syndrome, which is more common in women. Pathogenesis/pathology MDS are clonal disorders, characterized by a complex interaction between sequential acquired mutations in haematopoietic stem cells, dysfunction of immune surveillance, and permissive alter- ations in the bone marrow microenvironment. The MDS cell of origin acquires sequential genetic and epigenetic abnormalities, rendering it increasingly abnormal, initially unable to differentiate normally and sustain normal haematopoiesis, and ultimately unable to differentiate at all beyond the blast stage and frankly malignant. MDS cells undergo expansion and proliferation in the bone marrow to the detriment of healthy cells, and may ac- quire additional mutations enabling the development of subclones that may differ in behaviour from the ancestral clone. The subse- quent domination of the bone marrow by one or several mutated progenitor cells is known as clonal haematopoiesis. Clonally re- stricted haematopoiesis dominated by mutant cells leads to mor- phological cell dysplasia and cytopenias; the risk of progression to AML is a result of the genomic instability of such clones. Eight dif- ferent MDS subtypes are recognized by the WHO and these are out- lined in Table 22.3.2.1. Recent analyses have identified that haematopoietic clones bearing mutations in DNMT3A, TET2, or other MDS-associated genes occur in up to 10% of older adults, often in the absence of other features of a haematological disorder. Known as ‘clonal haematopoi- esis of indeterminate potential’ (CHIP), this disease precursor state

 confers a risk of progression to MDS of about 0.5 to 1% per year and a higher all-cause mortality. CHIP is also a risk factor for cardiovas- cular events due to a proinflammatory interaction between clonally derived monocytes/macrophages and the vascular endothelium. In turn, some patients experience persistent cytopenias in the presence of unremarkable marrow morphology, normal cytogen- etics, and no MDS-associated genetic mutations. This condition is termed ‘idiopathic cytopenia of unknown significance’ (ICUS). Some patients with ICUS will ultimately be discovered to have an- other haematological neoplasm or a nonhaematological disorder. Patients who have idiopathic cytopenias and also have a clonal mu- tation that may be contributing to the marrow failure, but who lack other features of MDS such as extensive dysplasia or increased blast cells, are said to have ‘clonal cytopenia of unknown significance’ (CCUS). CCUS has a natural history akin to lower-risk MDS, and individuals with CCUS are at higher risk for disease progression than patients with ICUS. Clonal haematopoiesis dominates even in lower-risk MDS without excess blast cells in the marrow, and clones identified in secondary AML can be tracked back to the preceding MDS stage. Recent studies combining immunophenotyping and deep sequencing have identified a rare multipotent haematopoietic pro- genitor cell of origin in lower-risk MDS and provide evidence that MDS occur secondary to mutations sustained in a stem cell with intrinsic self-renewal capacity, as opposed to a differentiated cell that acquires self-renewal ability. Three different types of genetic anomalies have been identified in MDS: chromosomal abnormalities, aberrancies in epigenomic pattern, and single gene mutations. Chromosomal abnormalities Chromosomal abnormalities in MDS are of

prognostic relevance. Gains or losses of chromosomal material are detectable on meta- phase karyotyping in greater than 50% of de novo MDS and greater Table 22.3.2.1 World Health Organization classification of the adult myelodysplastic syndromes (2016) MDS subtype Blast proportion Dysplasia Additional notes Peripheral blood (%) Bone marrow (%) MDS with single lineage dysplasia (MDS-SLD) <1 <5 Present in >10% cells in a
single lineage • Cases with 2 cytopenias may be included here, but marrow dysplasia must be limited to 1 lineage • Ring sideroblasts represent <15% of erythroid precursors, or if SF3B1 mutation is present, ring sideroblasts represent <5% of erythroid precursors MDS with ring sideroblasts (MDS-RS) 0 <5 Dysplastic erythroid lineage (>10% of erythroid precursors) • Anaemia (normocytic/macrocytic) • Ring sideroblasts comprise ≥15% of erythroid precursors, or if SF3B1 mutation is present, ring sideroblasts represent ≥5% of erythroid precursors • If multilineage dysplasia is present, it is MDS-RS-MLD MDS with multilineage dysplasia (MDS-MLD) <1 <5 In 2+ lineages (>10% of cells in each lineage affected) • 1+ cytopenias • No Auer rods • May or may not have ≥15% ring sideroblasts; if ring sideroblasts are present, this may be denoted as MDS-RS-MLD MDS with excess blasts-1 (MDS-EB1) <5 5–9 In 1+ lineages (>10% of cells in each lineage affected) • 1+ cytopenias • No Auer rods MDS with excess blasts-2 (MDS-EB2) 5–19 10–19 In 1+ lineages (>10% of cells in each lineage affected) • 1+ cytopenias • Auer rods present in context of blast count <20%: MDS-EB2 MDS with isolated deletion of chromosome 5q (5q− syndrome) <1 <5 High numbers of megakaryocytes, many small and with hypolobated/ nonlobated nuclei Dysplasia in other lineages rare • Anaemia (often macrocytic) with or without other cytopenias/ thrombocytosis • No Auer rods • Interstitial or terminal deletion of the long arm of chromosome 5, either alone or with 1 other clonal cytogenetic alteration • Some MDS patients with del5q may better fit other categories
(e.g. if 8% marrow blasts are present, MDS-EB1 is the diagnosis) MDS, unclassifiable (MDS-U) £1 <5 Unequivocal, but dysplasia present in <10% of cells of
1+ lineages • Can progress to a specific MDS • Can include cases otherwise classified as MDS-SLD or MDS-MLD but with 1% blasts in peripheral blood • Can include cases with an MDS-associated chromosome abnormality (other than loss of the Y chromosome or trisomy 8 or deletion of chromosome 20, which are not specific enough for MDS) but without dysplasia Therapy-related MDS or AML
(t-MDS/AML) Any Any Variable • MDS resulting from prior therapy with DNA damaging chemotherapy or irradiation, usually associated with abnormalities of chromosome 5 or 7 or TP53 gene mutation in the case of alkylating agents • WHO does not distinguish t-MDS from t-AML since aetiology similar and prognosis very poor for both Note: this table does not include MDS subtypes with proliferative features (e.g. chronic myelomonocytic leukaemia), myeloid neoplasms with germ line predisposition (e.g. MDS arising as a consequence of germline mutations in GATA2, DDX41, SRP72, RUNX1, or a congenital syndrome such as a telomere disorder), or the provisional and highly heterogeneous entity of MDS-refractory cytopenias in childhood.

 than 80% of t-MDS. Smaller chromosomal amplifications/trans- locations may be detectable by fluorescence in situ hybridization (FISH) or other techniques. High-resolution techniques (e.g. com- parative genomic hybridization), have led to the detection of subtle chromosomal deletions in approximately 90% of patients. Deletion of the long arm of chromosome 5, del(5q), is the most common recurrent karyotypic abnormality, documented in ap- proximately 15% of MDS patients. As noted above, a subset of pa- tients, predominantly females, with del(5q) have the ‘5q− syndrome’ characterized by dyserythropoietic

anaemia, micromegakaryocytes, a low risk of AML transformation, and a high clinical response rate to lenalidomide therapy. The size of the 5q deletion is variable; the two commonly deleted regions are 5q31.1 and 5q32 to 5q33.3, and many patients with del(5q) MDS lose both. Loss of only the distal region is associated with a more favourable course. As most patients with del(5q) retain a normal 5q arm, haploinsufficiency is enough to cause the phenotype, and a number of genes on 5q− have been identified as relevant. Haploinsufficiency of RPS14, a ribosomal subunit gene at 5q31.2, leads to p53 activation in erythroid progenitors and dyserythropoiesis. Loss of a copy of CSNK1A1, located at 5q32 and encoding casein kinase 1, engenders lenalidomide-sensitivity. Del(5q) may also occur together with other abnormalities, in which case it bears a more adverse prognosis with poor response to lenalidomide. Del(5q) and TP53 mutations co-occur more often than should be expected by chance, suggesting pathogenic cooperation. Loss of one entire copy of chromosome 7 (monosomy 7) occurs in 5% of MDS patients. Monosomy 7 occurs most frequently after alkylating agent exposure and is a poor prognostic marker. The causative genetic loss remains unclear, although a number of recur- rently mutated genes lie on 7q. Trisomy 8, a large-scale amplification of chromosome 8, is present in about 5% of MDS patients and is nonspecific to MDS. A complex karyotype, defined as three or more chromosomal abnormalities, is common in t-MDS and associated with TP53 mu- tations in more than 50% of cases. The term ‘monosomal’ karyo- type describes loss of two or more entire chromosomes or deletion of one chromosome in association with another structural cyto- genetic abnormality. Both complex and monosomal karyotypes most commonly affect chromosomes 5 or 7 and carry an adverse prognosis. Aberrancies in epigenomic pattern Epigenetic changes are heritable alterations in chromatin struc-ture that affect gene expression, largely via DNA methylation, or by histone acetylation, methylation, or other modification. The underlying DNA sequence remains unaltered. MDS patients display aberrant methylation when compared to healthy controls—both hypermethylation in promoters of tumour suppressors and global hypomethylation elsewhere. How methylation patterns link to pathogenesis remains unclear. Hypomethylating agents (HMAs; e.g. the DNA methyltransferase inhibitors decitabine and azacitidine) have demonstrated clinical responses and survival benefits in the treatment of MDS. Reactivating tumour suppressor genes silenced by hypermethylation comprises a potential mechanism of action for HMAs, but this is yet to be proven, and no single gene or gene methylation pattern consistently correlates with response. Single gene (‘point’) mutations The most common genetic abnormalities in MDS are single gene mutations and over 50 different recurrent somatic mutations have been identified, accounting for the clinical heterogeneity of the disease. Over 90% of patients with MDS carry at least one clonal somatic mutation. No single mutation dominates, and only a few mutations occur in more than 20% of cases. Table 22.3.2.2 describes key recurrent gene mutations identified in MDS. The vast combina-torial genetic heterogeneity and apparent cooperativity of some mu- tations hints at the complexity of attributing pathogenesis to single gene alterations. Differentiating between the rarer ‘driver’ mutations of pathogenic consequence and so-called passenger mutations is a key challenge in MDS. The identification of a ‘driver’ mutation implies that the mutation is recurrent in MDS, has a plausible function contributing to pathogenesis, and, ideally, that the effect of its disruption can be recapitulated in an in vitro or in vivo model. Recent insight to the biological organization of proteins encoded by recurrently mutated genes into cellular pathways and functional pathways has increased understanding as to how the MDS clone evolves. Pathways affected include the RNA splicing machinery, DNA methylation and histone modification regulators, signal trans- duction apparatus, and haematopoietic growth factors. There is emerging evidence of the association of individual genetic mutations with prognosis and of a typical sequence of acquisition. Certain mu-

tations can inform clinical care as they are associated with specific clinical features, yet personalizing therapy to an individual’s genetic mutations is not yet a reality except in rare cases such as IDH1/2 or BRAF mutations. Clinical features The clinical features of MDS are largely a consequence of inef- fective haematopoiesis. Most patients experience symptomatic Table 22.3.2.2 Most frequent recurrent gene mutations in MDS Class of gene Gene Frequency (%) Prognosis Spliceosome components SF3B1 SRSF2 U2AF1 ZRSR2 20–30 10–15 5–12 1–4 Favourable Adverse Neutral or adverse Adverse Epigenetic modifiers TET2 DNMT3A ASXL1 EZH2 IDH1/2 20–30 8–13 10–20 5–10 <5 Neutral Unclear Adverse Adverse Unclear Transcription factors RUNX1 GATA2 10–15 Rare Adverse Adverse Genome stability TP53 PPM1D 10–12 <5 Adverse Adverse Tyrosine kinase signalling JAK2 NRAS KRAS <5 5–10 <5 Unfavourable Adverse Adverse Cohesin complex STAG2 RAD21 5–10 <5 Unclear Unclear GPCR complex GNAS Rare Unclear GPCR, G protein-coupled receptor.

22.3.2 Myelodysplastic syndromes 5201 cytopenias, although MDS can also be diagnosed as a result of an incidental finding on a full blood count. Key features are exertional breathlessness due to anaemia, infection due to neu- tropenia and neutrophil dysfunction, and bleeding and easy bruising due to thrombocytopenia and platelet dysfunction. Fatigue is common and does not appear to correlate with the degree of anaemia, and instead may relate to cytokine release by clonal cells. Approximately 15% of MDS patients experience paraneoplastic features. These range from skin manifestations such as Sweet syndrome (characterized by neutrophilic dermatosis associated with painful plaques, fever and arthralgia) to rheumatological symptoms, such as diffuse arthralgias or inflammatory arthritis. A finding of splenomegaly or hepatomegaly should raise sus- picion of another diagnosis or of an overlap syndrome with a myeloproliferative neoplasm. MDS has a variable natural history. About 25 to 30% of patients progress to AML, which is usually fatal. More than 50% of MDS pa- tients ultimately succumb to complications of cytopenia. Infection is the most common cause of nonleukaemic death, followed by bleeding. The susceptibility to infection is not merely due to pro- longed periods of neutropenia, but also relates to functional neu- trophil defects resulting in an impaired inflammatory response. Similarly, patients with a normal platelet count may experience spontaneous bleeding due to ineffective platelet function. As pa- tients are often elderly, a significant proportion of MDS patients die of unrelated causes. Differential diagnosis Not all haematopoietic dysplasia is MDS and in the absence of clonal markers or excess blasts, MDS becomes a diagnosis of exclu- sion. A number of nonclonal disorders may exhibit similar morpho- logical changes and these need to be considered and actively ruled out in making the diagnosis. Vitamin and micronutrient deficiencies, specifically vitamin B12, folate, copper, and iron, may lead to dysplastic marrow appear- ances. Vitamin B12 and folate deficiency both cause macrocytosis and the bone marrow may demonstrate megaloblastoid changes and a preponderance of immature cells such that the appear- ance can be similar to early AML. Copper deficiency, most often observed post-gastrectomy or in the context of zinc sup- plement intake, can lead to severe anaemia and the formation of ring sideroblasts on bone marrow. Ring sideroblasts are erythroid progenitors with iron-laden mitochondria and can feature in all MDS subtypes. If at least 15% of erythroid pre- cursors are ring sideroblasts in the absence of other marrow abnormalities, or at least 5% are ring sideroblasts and a somatic mutation in SF3B1 (encoding a component of the spliceosome) is present, this is diagnostic of the WHO category ‘MDS with ring sideroblasts’ (MDS-RS). Finding an SF3B1 mutation helps exclude reactive causes of sideroblasts or late presentations of congenital sideroblastic anaemias. HIV infection may confer trilineage dysplasia, particularly in the erythroid series, and an HIV test should

be considered if chromo- some abnormalities and increased blasts are not present. Alcohol excess may also induce cytopenias accompanied by sideroblastic changes or a megaloblastic appearance. A careful history of exposure to drugs that may cause cytopenias and marrow changes mimicking MDS needs to be sought when investigating dysplasia. The list of potential culprits is long, and includes methotrexate, azathioprine, valproate, ganciclovir, and mycophenolate mofetil. MDS may also be confused with other clonal disorders. Autoimmune-induced bone marrow failure secondary to clonal T-cells (e.g. in the chronic lymphoid neoplasm, T-cell large granular lymphocyte leukaemia) may have very similar bone marrow changes. Aplastic anaemia, an oligoclonal disorder usually asso- ciated with a normal morphology and karyotype, can be difficult to differentiate from hypoplastic MDS. Finally, there are overlap syndromes of MDS/myeloproliferative neoplasm such as chronic myelomonocytic leukaemia which are categorized separately from MDS and have a unique mutational spectrum. Laboratory features MDS are primarily laboratory diagnoses (see Box 22.3.2.1 for diag- nostic criteria). Determining the MDS subtype by WHO criteria is integral to the diagnostic work-up (Table 22.3.2.1). Relevant inves- tigations include a full blood count, peripheral blood film, and bone marrow aspirate and trephine. Metaphase cytogenetic analysis is es- sential and FISH is useful if karyotyping fails. Increasingly, targeted sequence analysis contributes valuable diagnostic and prognostic information. Full blood count More than 85% of MDS patients demonstrate anaemia at presenta- tion, which is usually macrocytic but can be normocytic or in rare cases microcytic. About 50% of patients are neutropenic and ap- proximately 25% are thrombocytopenic at diagnosis; the frequency of these other cytopenias increases with time. Peripheral blood film The peripheral blood film is often suggestive of the diagnosis. Red cell abnormalities on the film vary widely. Red cells may be of unequal size (anisocytosis), unequal haemoglobinization (anisochromia), abnormally shaped (poikilocytosis), nucleated, or demonstrate Box 22.3.2.1 Diagnostic criteria for MDS Presence of a persistent and otherwise unexplained cytopenia: 1 Haemoglobin less than or equal to 110 g/litre 2 Absolute neutrophil count less than or equal to 1.5 × 109/litre 3 Platelet count less than or equal to 100 × 109/litre Plus one of the following: 1 5–19% marrow blasts 2 Dysplasia in at least 10% of cells in erythroid, myeloid, or megakaryocyte lineages 3 Evidence of a characteristic MDS-associated cytogenetic abnormality 4 Exclusion of alternative diagnosis accounting for dysplastic cell morphology

 inclusions of aggregated ribosomes (appearing as small blue dots at the periphery, known as basophilic stippling). Reticulocyte counts are disproportionately low. Red cell function may also be aberrant, evidenced by abnormal surface antigen expression and reduced red cell enzyme activity. One MDS subtype—α-thalassaemia MDS or acquired haemo- globin H disease—confers a red cell morphology akin to α -thalassaemia and occurs secondary to a somatic mutation in ATRX, which encodes a chromatin-remodelling protein. Red cells in this subtype are microcytic with target cells, poikilocytosis, and anisocytosis and beta chain tetramers may be evident on crystal violet or other supravital stain. In the myeloid lineage, neutrophils demonstrate visible anom- alies, such as hypogranularity, hypersegmentation, aberrant ring shapes, or a specific phenotype of condensed chromatin with bi- lobed nuclei, known as pseudo-Pelger–Huët cells (Fig. 22.3.2.1). (Pelger–Huët anomaly is a benign congenital condition of neutro- phils.) A left shift to immature myeloid cells predominates, and cir- culating early myeloid cells and blasts can occur. Platelets may also demonstrate dysplastic features such as large size or hypogranularity. Bone marrow In normal bone marrow, the ratio of myeloid to erythroid progen- itors is 2:1 to 4:1. In MDS, a profound skew to the erythroid lineage may occur, often as far as 1:2. A range of characteristic abnormal erythroid progenitors have been documented. Megaloblastoid

fea- tures with multinucleated red cell precursors and dyssynchronous nuclear/cytoplasmic maturation may be seen (Fig. 22.3.2.1). Chromatin fragments can appear in the cytoplasm as part of the destruction of the nucleus during cell death, known as nuclear karyorrhexis. Perls' stain or the Prussian Blue reaction is required to identify ring sideroblasts (Fig. 22.3.2.1). Myeloid progenitors may be hypo- or hypergranulated, hyper segmented, or feature hypolobated nuclei. Increased numbers of blasts may be evident and can serve as a marker of increased risk of AML. Micromegakaryocytes or hyper- or hypolobated megakaryocytes are seen (Fig. 22.3.2.1), and megakaryocytes may be distributed anomalously within the marrow in MDS. Management General considerations Treatment options in MDS range from conservative management with supportive care alone to high-intensity therapy including allogeneic stem cell transplantation (alloSCT), which is the only curative option. Any proposed treatment must be tailored to the patient, considering age, comorbidity, functional status, disease risk, and patient wishes. MDS is generally refractory to conventional cytotoxic chemotherapy, likely because the cell of origin is a quiescent stem cell that is resistant to cytotoxics—and also because even when the abnormal clone is cytoreduced, blood counts may recover poorly since normal haemato- poietic reserve is limited. The lack of well-defined targets in MDS means that there are no approved biologically personalized therapies. Current management is based on risk scoring algorithms. If disease risk is classed as low/intermediate-1 by the MDS risk scoring system (International Prognostic Scoring System or IPSS), or very low/low by the 2012 revised IPSS (IPSS-R), current algorithms advise close monitoring for transition of disease and transfusion or haematopoietic growth factor support, with use of lenalidomide if del(5q) is present or immunosup- pressive therapy in selected cases, and potential addition of iron chelation therapy. If disease risk is IPSS intermediate-2 or higher, or IPSS-R high or very high, then life expectancy is below 2 years and immediate disease- modifying therapy is advised, including alloSCT if the patient is young enough and fit. Treatment of IPSS-R intermediate category can be similar to either lower- or higher-risk subgroups, depending on specific disease features. Participation in clinical trials should be offered where possible. Supportive care Good supportive care is invaluable in the management of MDS. Prompt management of febrile episodes with broad-spectrum anti- biotics may be life-saving, especially in the context of neutropenia. Red cell transfusion with a transfusion trigger of 70 to 80 g/litre can minimize symptoms of anaemia. Platelet transfusions should be used ju- diciously due to the risk of alloimmunization. A randomized controlled trial (RCT) demonstrated that a prophylactic strategy with trigger of 10 × 109/litre leads to fewer significant haemorrhages than a therapeutic strategy of transfusing only in context of bleeding. Antifibrinolytics can be helpful where recurrent mucosal bleeding is a key feature. (b) (a) Fig. 22.3.2.1 (a) Peripheral blood smear in MDS showing several dysplastic neutrophils, including a pseudo-Pelger–Huët neutrophil with a bilobed nucleus. The chromatin in the neutrophils is clumped, and the red cells show a range of sizes and appearances. (b) A bone marrow aspirate with a small, monolobed megakaryocyte, typical in MDS.

 Iron chelation The use of iron chelators such oral deferasirox and parenteral desferrioxamine in MDS remains highly controversial. Patients with MDS are often heavily transfused and retrospective studies indicate that transfusion dependency and high serum ferritin are markers of poor outcome. Whether this reflects a more advanced disease state or complications of iron overload cannot be demonstrated retro- spectively. Retrospective case cohort studies and meta-analyses demonstrating benefit of iron chelators suffer from selection bias. No definite prognostic benefit has yet been demonstrated prospectively, although a composite endpoint of potentially iron related events was reduced with chelation therapy in a

randomized trial of deferasirox versus placebo. Competing risks such as clonal progression and com- plications of cytopenias dominate the clinical picture in most cases. However, some patients who undergo chelation will experience improvement in organ function or haematopoiesis. Current pub- lished consensus guidelines state that iron chelators can be con- sidered for patients with lower-risk disease and multiple transfusions in whom end-organ damage is anticipated. Haematopoietic growth factors Erythropoiesis-stimulating agents Erythropoiesis-stimulating agents (ESAs) have been extensively in- vestigated as therapy to reduce transfusion needs in MDS. Results from over 20 studies demonstrate that 40 to 50% of MDS patients re- spond to ESAs with modest benefit that lasts a median of 1 to 2 years. ESAs are most effective in low-risk disease that is not heavily transfu- sion dependent and in patients with normal blast counts, low inflam- matory markers, and low baseline serum erythropoietin levels (<500 U/litre). In current clinical practice, ESA therapy is initiated when the haemoglobin falls below 100 g/litre and continued to a target of 110 to 120 g/litre with response assessed at 2 to 3 months. For pa- tients with MDS-associated anaemia in whom ESAs are no longer effective, luspatercept, an activin receptor ligand trap molecule that binds to erythropoiesis-inhibitor cytokines of the transforming growth factor beta superfamily, reduced transfusion needs and in- creased haemoglobin compared to placebo in a randomized trial. Granulocyte colony-stimulating factor and granulocyte– monocyte colony-stimulating factor While granulocyte colony-stimulating factor (G-CSF) and granulocyte–monocyte colony-stimulating factor (GM-CSF) can improve the absolute neutrophil count, these myeloid growth fac- tors do not compensate for neutrophil dysfunction and there is no evidence that G-CSF or GM-CSF improves survival in MDS. In high-risk disease it is feared that GM-CSF may accelerate leukaemic expansion, though this appears to be rare. Thrombopoiesis-stimulating agents Bleeding is the second most common cause of nonleukaemic death in MDS, and low platelet count limits the tolerability of disease- modifying therapies. Two thrombopoietin receptor activators, romiplostim and eltrombopag, have demonstrated efficacy in re- ducing platelet transfusions and bleeding in low-risk MDS. RCTs for each agent demonstrated a modest increased risk of disease pro- gression; the trial with romiplostim was stopped early by the data monitoring committee, though with 5-year follow-up there was no difference between romiplostim and placebo with respect to AML progression. Individual patients with platelet alloimmunization and severe thrombocytopenia in whom the bleeding risk outweighs leukaemia progression risk can be considered for thrombopoiesis- stimulating agent use on a case-by-case basis. Disease modification Lenalidomide RCT evidence supports the use of lenalidomide, a derivative of thalido- mide, in reversal of anaemia in lower-risk MDS associated with isolated del(5q). Patients with del(5q) MDS achieve high response rates with lenalidomide, with 70% achieving transfusion independence and more than 30% cytogenetic normalization, lasting a median of 2 years. This is currently the only example in MDS of a genetic abnormality dictating treatment choice. Responses are more likely with a higher dose (10 mg daily vs 5 mg daily) and AML progression risk is not affected. A novel mechanism of action of lenalidomide has recently been elucidated. Lenalidomide binds cereblon, a component of an E3 ubi- quitin ligase complex, which modifies its affinity for ubiquitination of casein kinase 1α, accelerating proteasomal degradation of the latter. The gene encoding casein kinase 1α, CSNK1A1, lies on 5q and haploinsufficiency renders the 5q− cells sensitive to lenalidomide with a therapeutic window. In the absence of 5q−, response rates to lenalidomide lie at 25% and last a median of 8 to 9 months. Side effects of lenalidomide in- clude diarrhoea, rash, and cytopenias. Hypomethylating agents HMAs are the mainstay of treatment for higher-risk MDS and can be considered for those with lower-risk disease who are refractory to other treatments. The use of HMAs resulted from the recognition that MDS genomes display highly aberrant methylation

patterns. Two agents, azacitidine (AZA) and decitabine, are azanucleoside ana- logues that bind to and inhibit DNA methyltransferase irreversibly, thereby reducing methylation status and changing gene expression. HMAs are also able to exert direct cytotoxicity via incorporation into DNA as a false nucleotide similarly to cytarabine, and it remains un- clear which is the more relevant mechanism of response. HMA efficacy is underpinned by RCT evidence. AZA is the only drug with a demonstrated survival benefit in MDS; in one multicentre RCT, AZA prolonged life by 9 months compared with a supportive care or conventional chemotherapy control arm. Approximately 40 to 50% of MDS patients achieve a response with AZA, while 15% have complete pathological response. Most respond within 6- monthly cycles of therapy, and patients experience better quality of life and delayed disease progression with AZA when compared to conventional care. Side effects are mild, most commonly cytopenias and gastrointestinal upset. TET2 mutation status predicts a slightly higher likelihood of response to AZA and ASXL1 mutation predicts a lower likelihood of response, but is not currently part of treatment choice algorithms since many patients who are TET2 wildtype or ASXL1 mutant will also respond to AZA. Decitabine is a structurally similar compound to AZA but is directly incorporated into DNA whereas most AZA is incorpor- ated into RNA. At low doses, decitabine acts as a hypomethylating agent, whereas at higher doses it induces DNA crosslinking and cell cycle arrest. RCTs have not demonstrated a survival benefit with decitabine compared to observation, possibly due to suboptimal

 dosing/scheduling in trials. High response rates have been reported with decitabine treatment of patients with higher-risk MDS or AML with TP53 mutation; these responses are not durable. HMAs are not curative, and once they fail the patient life expect- ancy is sub 6 months with no useful treatment options beyond sup- portive care. Numerous agents are being combined with HMA in the clinical trial setting with early promise, including venetoclax, immune checkpoint inhibitors, and targeted agents. Cytotoxic chemotherapy Intensive induction chemotherapy with regimens similar to those used for AML is sometimes used in young patients with high-risk MDS, but is generally not effective because of clonal resistance and impaired blood count recovery. Low-dose cytarabine, low-dose melphalan, and other cytotoxics are also used but are of limited value. Remission rates are less than 20% and there is a theoretical risk of selecting for a quiescent, malignant clone. Immunosuppression Some cases of MDS feature an autoimmune pathophysiology akin to aplastic anaemia. In such cases, autoreactive T-cells inhibit haemato- poiesis, and are susceptible to immune suppression with antithymocyte globulin (ATG) or calcineurin inhibitors such as tacrolimus or ciclosporin. In retrospective analyses, these immunosuppressive therapy agents have demonstrated improved overall survival and reduced risk of AML trans- formation in responding patients, but selection of appropriate MDS pa- tients for immunosuppressive therapy has proven challenging. In various series, hypoplastic marrow, trisomy 8 or normal karyotype, younger age and female sex, HLA DR15, and presence of a paroxysmal nocturnal haemoglobinuria clone predicted a higher likelihood of response to immunosuppressive therapy. In the largest study of immunosuppres- sive therapy to date—367 patients from 13 centres—only hypocellular marrow predicted response, and the response rate to equine ATG plus ciclosporin was higher than to rabbit ATG or ATG without ciclosporin. Allogeneic haematopoietic stem cell transplantation AlloSCT is an option only for those who are young and fit enough to undergo high-intensity treatment. Despite recent advances in trans- plant medicine including reduced intensity conditioning regimens, improved supportive care, and availability of new stem cell sources, alloSCT remains a high-risk procedure conferring a transplant- related mortality of 15 to 20%. However, at least one-third of patients achieve long-term disease-free survival. The decision to transplant is difficult, as alloSCT imposes an immediate risk of mortality for the

possibility of long-term survival and there is a lack of randomized, quality data to guide clinicians. Many practical questions remain, including defining the optimal conditioning regimen, the timing of alloSCT, and the role for bridging therapy or reducing disease burden prior to alloSCT. Mathematical models indicate that alloSCT should be considered in all fit patients with higher-risk disease under the age of 75. Patients with TP53 mutations or Ras pathway mutations have a higher relapse rate than other genotypes. Prognosis The heterogeneous nature of MDS renders prognostication difficult. In response, a number of scoring systems have been developed to aid clinical decision-making and differentiate low-risk patients with stable disease from high-risk patients at risk of fulminant cytopenia and rapid progression to AML. The most widely used scoring system for prognostication is the IPSS, originally published in 1997 and revised in 2012 as the IPSS-R. The IPSS-R is now the standard method to predict risk of death in MDS with supportive care only. It stratifies patients into five risk categories by marrow cytogenetics, blast percentage, and number and degree of cytopenias. Other adverse markers of prognosis not included in the IPSS-R include the presence of comorbidities, high ferritin or lactate de- hydrogenase levels, aberrant myeloid cell surface marker expres- sion, and the presence of certain high-risk molecular abnormalities, such as mutations in TP53 or EZH2. No scoring system to date in- cludes all identified prognostic variables to predict individual dis- ease trajectory. Areas of uncertainty, controversy, and future developments Clinical outcomes for MDS remain disappointing. Recent major ad- vances in our understanding of MDS disease biology will advance clinical management in coming years. Clinically defined subtypes are genetically highly heterogeneous, which to date has posed a major barrier to development of reliable therapeutic targets. As our understanding of pathogenic driver mutations in MDS grows, the chances of identifying treatable molecular targets are increasing. Yet many more basic questions remain. Genetic profiling is cur- rently formally integrated into disease classification only with re- spect to SF3B1 and MDS-RS. The frequency of complications secondary to iron overload and the consequent role for chelation therapy in MDS remains unclear. Few agents in clinical trials today offer hope of major advances in current treatment, as most focus on refinement of drug dosing or combine established treatments. Going forward, prospective recruitment for MDS registry studies and trials will be critical in engendering a step change in clinical outcomes. FURTHER READING Bejar R, Steensma DP (2014). Recent developments in myelodysplastic syndromes. Blood, 124, 2793–803. Bejar R, et al. (2011). Clinical effect of point mutations in myelodysplastic syndromes. N Engl J Med, 364, 2496–506. Fenaux P, et al. (2009). Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol, 10, 223–32. Fenaux P, et al. (2011). A randomized phase 3 study of lenalidomide versus placebo in RBC transfusion-dependent patients with low-/ intermediate-1-risk myelodysplastic syndromes with del5q. Blood, 118, 3765–76. Gattermann N (2008). Overview of guidelines on iron chelation therapy in patients with myelodysplastic syndromes and transfusional iron overload. Int J Hematol, 88, 24–9. Genovese G, et al. (2014). Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. N Engl J Med, 371, 2477–87.

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