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Answers for the CME: Myelodysplastic neoplasms (MDS)

Q 1 – F, T, T, F, F

Discussion (MCQ points are highlighted in bold)

Morphological diagnosis of MDS

The defining morphological feature of myelodysplastic syndromes (MDS) is dysplasia in one or more myeloid lineages. Dysplasia is identified when at least 10% of cells in any myeloid lineage show abnormal development. This dysplasia may also be associated with an increased number of myeloid blasts in the peripheral blood and/or bone marrow, though the blast percentage remains below 20%. **Notably, the specific myeloid lineages with cytopenias may differ from those exhibiting dysplasia.**

Significant dysplasia in megakaryocytes is defined as having at least 10% dysplastic megakaryocytes, assessed from smears or sections containing at least 30 megakaryocytes. The **most indicative dysplastic features in the megakaryocyte series include micromegakaryocytes and multinucleated megakaryocytes with separated nuclei.**

Certain cytogenetic abnormalities are linked to specific morphological characteristics. For instance, the well-known deletion of chromosome 5q is associated with megakaryocytes that have non-lobated or hypolobated nuclei, as well as macrocytic anemia and either a normal or elevated platelet count. An isolated deletion of 20q is linked to dysmegakaryopoiesis and thrombocytopenia, while inv(3)(q21.3q26.2) or **t(3;3)(q21.3;q26.2) is related to abnormal megakaryocytes and may result in thrombocytosis.**

In MDS, hypocellularity can complicate the differential diagnosis with aplastic anemia. Notable dysplasia (commonly micromegakaryocytes), an increased number of blasts identified through CD34 staining in bone marrow biopsy sections and **an abnormal karyotype (excluding trisomy 8, which can occur in some aplastic anaemia cases)** are valuable for making this distinction.

Dyserythropoiesis is primarily characterized by abnormalities in the nuclei of erythroid cells, such as nuclear budding, internuclear bridging, karyorrhexis and multinuclearity. **Although megaloblastoid changes are frequently seen in cases of MDS, they are not specific enough on their own to definitively confirm dyserythropoiesis.**

Q 2 – F, T, T, F, T

Discussion (MCQ points are highlighted in bold)

MDS classification on the fifth edition of WHO

A new nomenclature has emerged for conditions related to MDS but not fulfilling the formal diagnostic criteria (Table 1). These are increasingly used to describe observed states bearing isolated molecular,

cytopenic or morphological features associated with MDS, and which might predispose to haematological malignancy[2]. These include clonal cytopenia of undetermined significance (CCUS); clonal haematopoiesis of indeterminate potential (CHIP); and idiopathic cytopenia of undetermined significance (ICUS). The following table shows how these entities differ from each other.

Table 1. Characteristics of ICUS/CHIP/CCUS

Features	**CHIP**	**ICUS**	**CCUS**	**MDS**
Cytopenia	No	Yes	Yes	Yes
Dysplasia	No	No or minimal (nondiagnostic for MDS)	No or minimal (nondiagnostic for MDS)	Yes
Somatic mutations	Yes; at a variant allele frequency of ≥2%. Most commonly: DNMT3A, TET2, ASXL1	**No; ICUS defined by absence of clonality**	Yes; as in CHIP	Yes; Up to 85% of patients

The classification now uses the term myelodysplastic neoplasms, but abbreviated as MDS instead of myelodysplastic syndromes, emphasizing their neoplastic characteristics and aligning the terminology with myeloproliferative neoplasms (MPN). MDS entities are now grouped as those having defining genetic abnormalities and those that are morphologically defined (Table 2)[3].

Myelodysplastic neoplasms that exhibit specific genetic abnormalities are categorized together and include: MDS with low blasts and isolated 5q deletion (MDS-5q), **MDS with low blasts and SF3B1 mutation (MDS-*SF3B1*)**, and MDS with biallelic TP53 inactivation (MDS-*biTP53*). *T***he latter classification takes precedence over MDS-5q and MDS-*SF3B1*.**

The revised MDS classification, along with the inclusion of CCUS, eliminates the necessity for "NOS" (Not Otherwise Specified) or "unclassifiable" categories. In particular, the **previously existing "MDS, unclassifiable" category has been removed in the updated classification.**

Since the number of dysplastic lineages tends to be dynamic and often reflects the clinical and phenotypic expression of clonal evolution – rather than strictly defining a specific MDS type – **the distinction between single lineage and multilineage dysplasia is now viewed as optional.**

Table 2. Classification of MDS-WHO 5th edition

	Blasts – peripheral blood	Blasts – Bone marrow	Cytogenetics	Mutations
MDS with defining genetic abnormalities				
MDS with low blasts and isolated 5q deletion (MDS-5q)	<2%	<5%	5q deletion alone or with 1 other abnormality other than monosomy 7 or 7q deletion	
MDS with low blasts and SF3B1 Mutation (MDS-SF3B1)[a]	<2%	<5%	Absence of 5q deletion, monosomy 7, or complex karyotype	SF3B1
MDS with biallelic SF3B1TP53 inactivation (MDS-biTP53)	<20%	<20%	Usually complex	Two or more TP53 mutations, or 1 mutation with evidence of TP53 copy number loss or cnLOH
MDS, morphologically defined				
MDS with low blasts (MDS-LB)	<2%	<5%		
MDS, hypoplastic (MDS-h)[b]	<2%	<5%		
MDS with increased blasts (MDS-IB)				
MDS-IB1 MDS-IB2	2-4% 5-19% or Auer rods	5-9% 10-19%		
MDS with fibrosis (MDS-f)	2-19%	5-19%		

[a] Detection of ≥15% ring sideroblasts may substitute for SF3B1 mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts.

[b] By definition, ≤25% bone marrow cellularity, age adjusted.

cnLOH copy neutral loss of heterozygosity.

Q 3 – T, T, T, F, T

Discussion (MCQ points are highlighted in bold)

Management of MDS

Management guidelines for MDS have significantly advanced, largely shaped by the International Prognostic Scoring System (IPSS) and its updated version, IPSS-R. Treatment should be tailored to each patient**'**s specific clinical and biological features, taking into account both the patient's and physician's preferences[4].

Thrombopoietin receptor agonists (TPO-RA), specifically romiplostim and eltrombopag **may be used to reduce bleeding events in thrombocytopenic patients with low or intermediate-1 risk MDS** although they are not given as a recommendation. TPO-RA use in high risk MDS is not recommended.

Luspatercept is a recombinant fusion protein that **binds to ligands of the transforming growth factor-beta superfamily, thereby reducing SMAD signalling. It functions as an erythroid maturation agent, focusing on the later phases of erythropoiesis,** unlike traditional ESAs. Luspatercept has demonstrated effectiveness in alleviating anaemia in patients with lower-risk MDS and ring sideroblasts who have not responded to ESA therapy.

It is recommended that all eligible lower-risk patients (those with IPSS low and intermediate -1, or IPSS-R low and very low) should be considered for iron chelation therapy when they have received around 20 units of red cell concentrates or when their ferritin is more than 1,000 µg/L. In real-world practice, deferasirox has shown better tolerability, significantly improved compliance, and well-established safety data compared to desferrioxamine. Consequently, **expert consensus considers deferasirox is the preferred treatment for transfusion-related iron overload in MDS patients.** Desferrioxamine remains a viable alternative for those who are resistant to or cannot tolerate deferasirox.

All transplant eligible MDS patients should be evaluated by a transplant physician at a multidisciplinary team (MDT) meeting, both at the time of diagnosis and disease progression. When determining the best timing for the haemopoietic stem cell transplant in lower-risk MDS patients, additional factors such as transfusion dependency, severity of cytopenias, poor prognostic cytogenetics and bone marrow fibrosis should be considered. For higher-risk MDS patients with more than 10% blasts, cytoreductive therapy or hypomethylating agents may be recommended before transplant. In cases with 5-10% blasts, a transplant may be considered early for patients with slowly progressing disease or those with hypocellular or fibrotic bone marrow. **However, transplant is generally not recommended for patients with TP53 mutations combined with a complex monosomal karyotype due to poor outcomes.**

Imetelstat is a telomerase inhibitor that acts on cells with hyperactive telomerase and short telomere lengths and is a critical pathway to maintain normal haematopoiesis. The drug binds to the template region of the RNA component of telomerase and results in inhibition of telomerase enzymatic activity. **In June, 2024, the Food and Drug Administration approved imetelstat, for adults with low to intermediate-1 risk myelodysplastic syndromes (MDS) with transfusion-dependent anaemia** requiring four or more units of red cell concentrates over 8 weeks and who have not responded to or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESAs)[5].

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