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Myelodysplastic syndromes and acute myeloid leukemia: Medical management and dental considerations

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ABSTRACT

The World Health Organization explained myelodysplastic syndromes as clonal hematopoietic disorders characterized by dysplasia and ineffective hematopoiesis in one or more of the hematopoietic cell lines. Myelodysplastic syndromes have a high probability of transformation into acute myeloid leukemia. Dental care professionals should have a basic understanding of myelodysplastic syndromes to help support patients and deliver safe dental treatment.

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INTRODUCTION

Myelodysplastic syndromes (MDS) described as: Myelo means bone marrow, and dysplastic means strangely or abnormally shaped. Accordingly, the word "myelodysplastic" refers to the malfunction of the bone marrow in producing the correct quality of blood cells. These mixed types of hematoncology malignancies were first recognized in the early 1900s and the current name was recognized in 1976 and revised in 1982 (1). Simply, immature blood cells in the bone marrow do not mature and therefore do not become healthy blood cells; leading to the production of low red blood cells, low platelets (thrombocytopenia) and low white blood cells (neutropenia). The dysplasia may be accompanied by an increase in myeloblasts, but the number is less than 20%, which, according to the World Health Organization (WHO) guidelines, is the requisite threshold for the diagnosis of acute myeloid leukemia (AML) (2). Accordingly, MDS is considered as a preleukaemic conditions, or is called smouldering leukemia (3). It has a high probability of transformation into AML (4). Leukaemia that develops as a result of MDS is relatively resistant to treatment. However, MDS is considered a low-malignant potential disease compared to other types of aggressive hematoncology malignancies.

Risk factors

Risk factors mostly include the same causes as other hematoncology malignancies. For example, secondary previous exposure to chemotherapy (therapy-associated MDS (t-MDS)), specifically exposure to alkylating agents is one of the most common risk factors (3; 5). This is also called late toxicity of cancer therapy in patients who received alkylating agents for hematopoietic stem cell transplant (HSCT) for other hematology malignancies (3; 5). Exposure to radiation (therapeutic or accidental) is a risk factor as well (3).

Some patients are found to be workers in an industrial area and they have been exposed to hydrocarbons, heavy metals (mercury and lead), xylene and benzene (3). Furthermore, people with Down syndrome are more susceptible to have MDS than the general population (6). A family history of MDS increases the chance of any family member having MDS (7). The definitive causes of MDS are still unknown, however, most of the mentioned risk factors lead to DNA damage (mutation in the multi-potent bone marrow stem cells) hence the development of MDS, but causality has not been proved yet. It can be difficult to prove a connection between a suspected exposure and the development of MDS, but the presence of genetic abnormalities helps to provide some supportive information. For example, a mutation called epigenetic changes leads to abnormal differentiation of bone marrow stem cells, increased strength of apoptotic cell death and increased expansion of abnormal, immature and dysfunctional cells; hence the development of MDS (8). The recognition of these types of mutation helps to uncover successful treatment, as discussed later.

Classification(s)

It is important to identify types of MDS, as some types respond very well to treatment compared to others. Also, it helps to know which patients have a high probability of transforming to AML. Below are the classification types based on the histopathology tests (lab-based) and clinical etiology.

Classifications according to histopathology tests

There are different types of MDS according to specific changes in the histopathology of the blood cells and bone marrows. In 1976, a team of pathologists from France, United States and United Kingdom developed The French-American-British classification and they classified MDS accordingly into six types (1; 9). However, the previous mentioned classification had several revisions and the WHO regularly updates this classification. The most commonly one used was modified and approved in 2016 by WHO (10).

This recent classification was based on: 1) how many cells show dysplasia (abnormality), 2) how many cells have low blood cell count (cytopenia), 3) how many of the red blood cells are ring sideroblasts (young red cells that typically have a ring of iron granules when seen under the microscope), 4) the percentage of blast cells in the bone marrow and/or blood, lastly 5) any other genetic changes (i.e., chromosome changes) – see Table 1. For example, for the chromosome changes, del(5q) is a specific type of MDS where chromosome tests show part of the chromosome five is missing. Understanding each how many types of blood cells affected will help to determine the best clinical decision in a multidisciplinary meeting with the haematoncology team. Based on these criteria, the classification (2016) includes:

- MDS with single lineage dysplasia (MDS-SLD).
- MDS with multilineage dysplasia (MDS-MLD).
- MDS with ring sideroblasts (MDS-RS).
- MDS with excess blasts (MDS-EB-1 and MDS-EB-2).
- MDS with isolated del(5q).
- MDS, unclassifiable (MDS-U).

Clinical classifications

In addition to the previous histopathology tests classification, clinicians like to classify MDS based on the clinical cause (11). Simply, if no underlying cause is identified, it is called primary MDS (de novo). This is the most common one, affecting 80% of people with MDS (2). However, if the cause is recognized then it is called secondary MDS (i.e., associated therapy MDS or late toxicity cancer therapy MDS) (2). Secondary MDS can develop in two to 10 years following cancer therapy for another types of hematoncology malignancy (2). Determining the type of MDS is very important as secondary MDS responds less well to treatment.

The Revised International Prognostic Scoring System (IPSS-R)

The IPSS-R is used by hematoncologists to help predict a person's risk of developing AML and overall survival. It looks at factors such as the percentage of blasts found in the bone marrow, type and extent of chromosomal changes, and levels of platelets, neutrophils and hemoglobin found in red blood cells. For example, poor prognostic factors include high percentage of blasts in the bone marrow, clear type and number of chromosomal changes, and low levels of hemoglobin, platelets, and neutrophils.

The basic IPSS was developed with four MDS risk categories: low risk, intermediate-1, intermediate-2 and high-risk (12). In 2013, it was improved to the revised IPSS-R, which has been modified into five MDS risk categories: very low-risk, low-risk, intermediate, high-risk and very high-risk (13). People with MDS who have a lower IPSS-R score have the best outlook for survival and need less intensive treatment. A person diagnosed with a high-risk subtype of MDS and whose IPSS-R score is high usually needs more intensive treatment. In the near future, studies in gene mutation will provide further classification, possibly telling us which patients may respond better to specific treatments, or for whom a transplant should be attempted earlier or perhaps avoided altogether.

Signs and symptoms

Signs for MDS are non-specific and generalized for most hematoncology malignancies and related to cytopenia. Full blood counts include anemia (low level of haemoglobin and red blood cells), neutropenia (low white blood cells) and thrombocytopenia (low platelet counts). These results can be confirmed clinically by patients' symptoms. They may complain of chronic tiredness, generalized fatigue, body weakness, and breathlessness related to the low red blood cells count and low hemoglobin. Patients are prone to develop opportunistic infection. Some patients might develop sudden bleeding and/or ecchymosis related to low levels of platelets. MDS UK reported that eight in 10 patients develop anemia, whilst about two in 10 present to their physician with infections or bleeding (14). Physical examination can detect splenomegaly or rarely hepatomegaly, which could be a sign of discrepancy in blood cell production. Patients require further medical investigation (i.e., further blood tests and/or bone marrow biopsy). However, the majority of patients are asymptomatic and they are diagnosed with MDS unexpectedly with a routine blood test (14).

Diagnostic tests

Diagnosis of MDS can sometimes be difficult; however, in most cases the typical features are present in the bone marrow and the diagnosis is straightforward. Full blood count (FBC) is the

main test used for the diagnosis. Any type of blood cells might show count discrepancies (15). This then requires referral to a hematologist. In most cases, a bone marrow biopsy is usually required to confirm diagnosis. This test can be performed by taking a liquid sample and a small amount of bone from the pelvis (usually the hip bone) using a needle (16). A physical examination to rule out splenomegaly or/and hepatomegaly will also be included. Once the patient is diagnosed with MDS, another test can be used (i.e., cytogenetic or karyotype) to determine the disease behavior (i.e., aggressive or benign). This sensitive test aims to find any changes in the structure of the chromosomes in the affected cells to determine the subtypes of MDS and help to decide best treatment (15).

Medical management

Once the diagnosis of MDS is confirmed, the hematoncology team decides the best treatment for each patient differently according to the type of MDS, IPSS-R score, general health, age, fitness and the patient's wishes. Generally, a "watch and wait" strategy is fully justified and more commonly suggested among patients with MDS. However, anemia is the most frequent indication for the onset of therapy in a considerable number of patients. For example, anemia related to MDS results in fatigue, especially in elderly patients, an increased incidence of falling with the risk of bone fractures, cognitive deficiencies, lower quality of life, and a shortened overall survival (17-19). Generally, treatment of MDS has a similar approach to the treatment of other hematoncology disorders that are usually considered; supportive care and the actual treatment for the diseases itself (anti-MDS agents).

Supportive care

MDS UK explained how the supportive care works which aims to control the symptoms of MDS (20). For instance, anemia and breathlessness are usually treated by iron infusion and/or erythropoietin injection and/or blood transfusions to raise the hemoglobin level and increase the red blood cells count. Recurrent infection related to low white blood cell count is usually managed by injections of granulocyte-colony-stimulating factor (G-CSF). G-CSF is a secreted glycoprotein that stimulates hematopoietic progenitor cells to help generate more white blood cells. Some hematoncology teams usually prescribe a daily dose of antibiotics to help reduce risk of the development of recurrent infection. Moreover, platelets transfusion is considered in patients with frequent bleeding disorders.

Anti-MDS treatment regimes

For the treatment of MDS, two approaches are recognized; (i) non-intensive approach, or (ii) intensive approach, which also includes HSCT (20). Each patient has a different treatment regime, which is decided by the hematoncologist and patient.

Non-intensive approach

The non-intensive approach is the choice for unfit older adults. It aims to slow down the progression of MDS by giving the patients a range of medications (anti-MDS agents). Azacitidin and Lenalidomide are the most common anti-cancer agents used in the management of MDS and authorized by National Institute for Health and Care Excellent (21; 22). Similarly, immunosuppressive therapies (IST) have proven their effectiveness in the management of early phases of MDS (23-25). It is crucial to understand a basic knowledge of these anti-MDS agents, which outlined below.

Azacitidin (Vidaza®/Celgene®) is an anti-cancer agent (antineoplastic/cytotoxic/hypomethylating). It aims to change the behaviour of cancer cells at the DNA level, which can turn genes on and off. It is injected subcutaneously daily for seven days in upper arm, leg, buttock or stomach, followed by a rest period of 21 days. It has been recommended that patients should be treated for a minimum of six cycles (one cycle of treatment: Each day for a week, and then three weeks with no treatment). The recommended dose is 75 mg/m2 of body surface area. The most common adverse reactions are haematological reactions for 71.4% of patients, such as low level of red blood cells and haemoglobin, thrombocytopenia, neutropenia, nausea, vomiting and injection site reactions. Azacitidin has showed its clinical effectiveness in the treatment of adults who are not eligible for HSCT and have intermediate-2, high-risk MDS or AML with 20–30% blasts and multilineage dysplasia.

Lenalidomide (Revlimid®, Celgene®) is an immune-modulating therapy which aims to suppress the MDS cells by altering the immune system. It is a structural analogue of thalidomide, a strong chemotherapeutic agent. It has been most helpful to those who have acquired abnormalities of chromosome 5 (the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk MDS associated with an isolated deletion 5q cytogenetic abnormality). It has a starting dose of 10 mg orally, once daily, on days one to 21 of repeated 28-day cycles, with dose reductions (5.0 mg, 2.5 mg or 2.5 mg every other day) to manage adverse events. The most common side-effects are anemia, thrombocytopenia, neutropenia, fatigue, constipation, diarrhoea, muscle cramp and rash.

Immunosuppressive therapies (IST) such as anti-thymocyte globulin (ATG), ciclosporin or alemtuzumab, or a combination of these. The main reason to consider IST in patients with MDS was based on the premise that MDS might share with severe aplastic anaemia an autoimmune basis for bone marrow failure (25). Parikh et al (25) summarised 18 published clinical trial studies using IST for MDS and reported the effectiveness of the IST in the early phase of MDS (MDS IPSS-low-risk). They are suitable for those patients whose bone marrow cells are unusually low in number (pancytopenia).

Intensive approach followed by HSCT

This approach includes three phases of chemotherapy. The induction phase involves high doses of chemotherapy (three to six cycles). It aims to slow down the progression of MDS, kill the abnormal cells, and generate normal cells that can work effectively; hence achieving the remission phase. This is then followed by either controlling or stabilizing the remission phase (by regular follow-up for the blood samples with or without chemotherapy), and this is considered as the maintenance phase. Candidate patients who are eligible for HSCT have a last phase of high doses of chemotherapy before HSCT for young, fit and well patients. One third of MDS patients who had received treatment with HSCT became free of disease (20). However, it is not easy to initiate HSCT unless matching analysis tests show positive results, and the exact donor (allogeneic stem cell transplant) participant is available. To some extent, this approach is like the treatment of AML. Unfortunately, HSCT has many side effects, and it is important that the decision to have an allogeneic stem cell transplant is carefully assessed for

suitability.

Dental management

Evidence-based clinical guidance reported that dental management of patients with MDS and AML is not straightforward (4). This is because MDS and AML increase the risk of pancytopenia, putting the patients at risk of infection and oral bleeding. Accordingly, patients require oral and dental assessment before starting treatment for MDS. This includes maintaining good oral hygiene as the patients have a high risk of developing gingival inflammation and periodontitis.

Before starting treatment for MDS, oral lesions could be easily undiagnosed, and dentists should be vigilant for both symptomatic and asymptomatic oral diseases. Additionally, patients should be advised of gentle tooth brushing to avoid gingival bleeding. If oral bleeding is already initiated due to the low level of platelets, wet cotton soaked in high-fluoride toothpaste can be used instead to clean the teeth. Dentists can also consider patients' diet analyses to advise avoiding cariogenic food and fizzy drinks. Lastly, before starting treatment for MDS, patients should be advised about the importance of regular follow up with dentists every 3-6 months.

G-CSFs with or without platelets transfusion can be used during dental extraction before starting treatment for MDS to reduce the risk of dental infection and oral bleeding. Indeed, details about the dosage of G-CSF and platelets transfusion and the timing of dental extraction should be discussed with the patient's physician.

It is suggested to avoid invasive dental procedures during the active period of MDS therapy, however, dental treatment of acute dental pain (i.e., spontaneous gingival bleeding, recurrent dental infection, and oral ulcers) during the active period of MDS therapy should be discussed with the patient's physician to avoid developing complications related to MDS therapy such as severe oral bleeding or dental infection which might develop septicemia. As MDS can develop into AML, dentists should spot any changes in oral and dental health such as prolonged sudden oral bleeding, gingival swelling, and oral ulceration that do not heal for more than two weeks or do not respond to prescribed medications. Furthermore, dentists housed also know other general manifestations that indicate the development of MDS to AML such as fever, lymphadenopathy, or laryngeal pain – See Table 2 which includes dental considerations for patients with MDS and AML.

CONCLUSIONS

MDS refers to the malfunction of the bone marrow in producing the correct quality of blood cells, producing low red blood cells, low platelets (thrombocytopenia), and low white blood cells (neutropenia). It has a high probability of transformation into AML. Leukemia that develops because of MDS is relatively resistant to treatment. Future research aims to determine definitive causes of the development of MDS by understanding the pathophysiology of DNA damage in patients with MDS.

Dental management of patients with MDS and AML is required liaison with the patient's physician to reduce the risk of oral bleeding and dental infection. Dentists might help to spot any dysplastic changes in the patient's oral cavity that indicate any transformation from MDS to AML such as frequent oral bleeding, recurrent dental infection, lymphadenopathy, and gingival swelling. Lastly, the timing of dental treatment with the patient's physician is important to decide the proper time of delivering dental treatment as the patient is in a fluctuant stage of pancytopenia.

Ethical Approval

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The authors would like to declare no conflict of interest in the present review.

Authorship contributions

HA planned the investigation, wrote the original draft, and modified/revised based on the input of all other authors. HSS, AD, DA, and MB revised the tables and the review. HA, MB, AA, AD, HSS and KA were responsible for the article processing charges alongside revising the final proof of the review.

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Table 1: The World Health Organization Classification Criteria of myelodysplastic syndromes (2016).

Type	Dysplastic lineages	Cytopenias	Ring sideroblasts (RS) in erythroid elements of bone marrow (BM)	Blasts	Cytogenetics
MDS-SLD	1	1 or 2	RS<15% (or <5%)	PB <1% BM <5%	Any, unless fulfills criteria for isolated del(5q)
MDS-MLD	2 or 3	1-3	RS<15% (or<5%)	PB <1% BM <5%	
MDS-RS-SLD	1	1 or 2	RS≧ 15% (or ≧5%)	PB <1% BM <5%	
MDS-RS-MLD	2 or 3	1-3	RS≧ 15% (or ≧5%)	PB <1% BM <5%	
MDS-EB-1	0-3	1-3	None or any	PB 2 ~ 4% or BM 5 ~ 9%	
MDS-EB-2	0-3	1-3	None or any	PB 5 ~ 19% or BM 10% ~ 19% or Auer	
MDS with isolated del(5q)	1-3	1-2	None or any	PB <1% BM <5%	del(5q) alone or with one additional abnormality except -7 or del(7q)
MDS-U with 1% PB blast	1-3	1-3	None or any	PB = 1%, BM < 5%,	Any, unless fulfills criteria for isolated del(5q)
MDS-U with SLD and pancytopenia	1	3	None or any	PB <1% BM <5%	

Note: PB: Peripheral blood, Cytopenias MDS-defining: Haemoglobin < 10g/dL, platelets < 100 × 109/L, ANC < 1.8 × 109/L; absolute monocytes count < 1.0 × 109/L.

Table 2: Dental considerations for patients with MDS and AML.

1. General recommendations to avoid complications

- Medical consultation to know the degree of disease and status of the patient including medications and other comorbidities.
- Pre-dental treatment laboratory tests should be obtained such as CBC counts with differential, PT, aPTT, bleeding time, and platelet count.
- Precautions to avoid excessive infection: WBC count depressed; Neutrophil count $< 1 \times 10^9$ /L, consider Antibiotic prophylaxis and/or G-CSFs.
- Precautions to avoid excessive bleeding: Platelet count $< 50 \times 10^9$/L, consider blood/platelet transfusion.
- Precautions to avoid anemia complications: Consider blood transfusion and erythropoietin injections.

2. Dental assessment before starting treatment for MDS

- Thorough dental evaluation: Any susceptible infection, gingivitis, periodontitis, bleeding, (petechia or ecchymosis) gingival swelling, or oral ulceration that does not heal for more than two weeks.
- maintaining good oral hygiene: Gentle tooth brushing, wet cotton soaked in high-fluoride toothpaste, flossing, topical fluorides, antiseptic mouthwash.
- Diet modification: Avoid cariogenic food and fizzy drinks.
- Smoking and alcohol cessation.
- Regular follow-up with dentists every 3-6 months.

3. Active period of MDS therapy

- Thorough dental evaluation to diagnose AML: Fever, lymphadenopathy, or laryngeal pain. mucosal pallor, prolonged sudden oral bleeding (petechia or ecchymosis), mucositis, sequestration, herpes simplex infections, candidiasis, and large oral ulceration that do not heal for more than two weeks.
- Avoid invasive dental procedures to avoid severe oral bleeding or dental infection to prevent septicaemia.
- Symptomatic teeth are treated atraumatically with the least invasive method (i.e., pulpectomy, antibiotic, and analgesic).
- Only emergency dental care should be provided, as confirmed by medical consultation, and it should be as non-invasive as possible – See **Table 3**.
- Elective dental treatment as time and necessity permit.

Table 3: Differences between “invasive” and “non-invasive” dental procedures.

Non-invasive dental treatment	**Invasive dental treatment**
Plaque control, calculus removal	Surgical dental extraction
Dental restoration	Periodontal surgery
Non-surgical root canal treatment	Subgingival scaling, and root planning
Denture	Surgical endodontic treatment