

“Myelotoxicity Grading of Ctx for Leukemia” – A Bridge between Stethoscope & Mouth Mirror

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Abstract: The advent of dentistry relates to dentogenic infection. Egyptian colleagues already knew in 1500BC importance of treating periapical infection foci to prevent their systemic spread. Modern dentistry and the detection and use of antibiotics, on the other hand, have caused an erroneous confidence that oral infections are no longer a threat to general health.

I. Introduction

Oral healthcare needs to be meticulous in the immunocompromised host like in the patients who has undergone Chemotherapies for Hematologic Malignancies, because the increasingly effective treatment of malignant conditions leads to clinically significant side effects, such as the disruption of the mucosal barrier of the mouth and infections caused by commensals of oral microflora.^{2,3} In patients with malignancies, all potential oral infection foci must be diagnosed and appropriately treated. The treatment needs to be more radical in these patients than in healthy patients, but there are no unanimously accepted protocols in this respect.

To enable planning for the adequate dental intervention, the oral medicine team must understand the general status of patient and the intensity of the chemotherapy, which is sometimes difficult to be fully appreciated by dental staff. Therefore, a simplified grading would facilitate the sharing of information between hematologists, dentists and oral hygienists.⁴

In This article will try to throw light on myelosuppression grading of chemotherapies for hematologic malignancies and analyze the timing of occurrence of severe odontogenic infections which will be useful tool for understanding the myelosuppressive state caused by chemotherapy and facilitating communication between medical and dental staff and in treating the patients with the disease.

Surgical resection, radio and chemotherapy, either used singly or in combination, are the three most common modalities used in head and neck cancer treatment. Although these modalities are effective in eradicating the tumor, they also negatively impact the normal head and neck structures surrounding the tumor. Direct damage to the oral structures (soft and hard tissue) frequently occurs from radio-and chemotherapy, and indirect damage may also arise from systemic toxicity.⁵

Chemotherapeutic drugs are administered systemically over several weeks or months in a sequence of "treatment rounds or courses." This schedule allows some recovery of healthy tissues between each treatment of the toxic drugs. Complications arise from the direct cytotoxic effects of chemotherapeutic agents on oral tissues and/or from the indirect effects of myelosuppression. Oral manifestations are related to the drug protocol (type of drugs, dose and duration), the patient's mucosal integrity, and oral and systemic status. The reactions are often highly individualized.⁶

Myelosuppression-

Myelosuppression, is the decrease in production of cells responsible for providing immunity (leukocytes), carrying oxygen (erythrocytes), and/or those responsible for normal blood clotting (thrombocytes). The risk is especially high in cytotoxic chemotherapy for leukemia. Because the bone marrow is the manufacturing center of blood cells, the suppression of bone marrow activity causes a deficiency of blood cells.

This condition can rapidly lead to life-threatening infection, as the body cannot produce leukocytes in response to invading bacteria and viruses, as well as leading to anemia due to a lack of red blood cells and spontaneous severe bleeding due to deficiency of platelets.

Symptoms and side effects of myelosuppression:

Includes a number of side effects that result from low blood cell counts which can have significant effects on an individual's health, and they can dramatically affect the patient's short-term quality of life.

Symptoms associated with myelosuppression vary depending on the specific type. The most common side effects of myelosuppression is anemia which include fatigue, dizziness. Depending on the severity, anemic patients may also exhibit pale skin, especially at the lips and nail beds. Increased heart rate is another common symptom of anemia.

Neutropenia results in a reduction in the body's ability to fight off disease. As a result, fever and chills are the most common side effect of reduced white blood cells. Signs of infection may also be present, including

swelling, redness or an area that is warm to the touch. Other common neutropenia side effects include diarrhea and rash.

Thrombocytopenia is most commonly characterized by easy bruising and bleeding from the nose, gums or mouth. Blood may also show up in urine or bowel movements. Small red spots on the skin, called petechiae, may also manifest.⁷

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These Are Some Of The Measures Taken Prior & During & Following Chemotherapy:

Oral/Dental Evaluation Prior To Chemotherapy

Pre-chemotherapy oral/dental evaluation

To adequately assess the patient's dental status and potential problems during chemotherapy, the following must be considered in the evaluation process:

Past and current medical status, including systemic disease that may impact oral health

Integrity of hard and soft oral tissues

Radiographic evidence of pathology

Periodontal disease

Oral hygiene self-care practices

Tobacco and alcohol habits

Dietary analysis (cariogenic foods)

Medication analysis, including over-the-counter products (drugs causing xerostomia, or drugs high in sugar or acid)

Oral/Dental Management During Chemotherapy

Dental treatment

Once chemotherapy has been initiated, oral prophylaxis and restorative dental treatment can usually be scheduled within a few days of the next proposed round or course of therapy.

Generally the patient's blood counts will have recovered from the toxicity of the previous course of drugs.

Blood counts, however, should be ordered the day before dental treatment to document hematologic status.

If oral surgery is required, it should be scheduled to allow at least 7-10 days of healing prior to the anticipated date of bone marrow suppression.

It is imperative that the dentist should discuss with the oncologist prior to any invasive dental procedure, including prophylaxis.

Dental Management Following Chemo Therapy

At completion of all planned courses of chemotherapy, closely monitor the patient until all side effects of therapy have resolved, including immunosuppression. The patient may then be placed on a normal dental recall schedule. Since these patients may need to undergo additional myelosuppressive therapy if they relapse in the future, it is very important to maintain optimal oral health.⁶

There was an attempt made by Masaya Akashi, Yasuyuki Shibuya et al, to make a grading system for the myelosuppression which was done on the intensity of the scheduled chemotherapy.⁴

They graded chemotherapeutic agents on the Severity of Myelosuppression which was classified on the basis of the World Health Organization Scheme as follows

Table-1

Toxicity	Hemoglobin (g/dL)	Leukocytes (×1000)	Neutrophils (×1000)	Platelets (×1000)
1 (mild)	9.5-10.9	3-4.5	1.5-1.9	75-100
2 (moderate)	8-9.4	2-2.9	1-1.4	50-74
3 (severe)	6-7.9	1-1.9	0.5-0.9	25-49
4 (severe & persistent immunodeficiency)	4-5.9	0.5-0.9	0.1-0.4	<25
5	Death	Death	Death	Death

The myelosuppressive intensity of grade A chemotherapies includes the following oral agents and infusions: tyrosine kinase inhibitors for chronic myeloid leukemia; all-trans retinoic acid (ATRA) for acute promyelocytic leukemia; fludarabine phosphate intravenous use or intravenous drip, rituximab monotherapy, and

etoposide internal use for chronic lymphoid leukemia or malignant lymphoma; melphalan plus prednisone (MP) for multiple myeloma, etc. These chemotherapies were mostly performed for outpatients and the myelosuppressive intensity was mild. Which was determined by the plasma FLT3-L levels which will predict bone marrow recovery from myelosuppressive therapy.

The myelosuppressive intensity of grade B chemotherapies that included many different regimens (e.g. consolidation regimens for leukemia; CHOP, ABVD and ESHAP for malignant lymphoma) was moderate.

The myelosuppressive intensity of grade C chemotherapies that included remission induction therapy for acute leukemia was severe.

The chemotherapies that caused the most severe myelosuppression and persistent immunodeficiency (known as myeloablative conditioning regimens) were classified as grade D.

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Table 2

Myelosuppression grading	
Grade A	mild myelosuppression
Grade B	moderate myelosuppression (2–3 weeks for bone marrow recovery)
Grade C	severe myelosuppression (4 weeks for bone marrow recovery)
Grade D	severe myelosuppression and persistent immunodeficiency
Regimens	
Grade B	Consolidation therapy for leukemia:
	DA (DNR, Ara-C); MA (MIT, Ara-C); high-dose Ara-C
	Chemotherapy for Malignant lymphoma:
	ABVD (ADR, BLM, VLB, DTIC); CHOP (CPA, ADR, VCR, PSL); ESHAP (ETP, Ara-C, CDDP, mPSL); Hyper-CVAD/MA (course 1: CPA, VCR, ADR, DEX, course 2: MTX, Ara-C, mPSL)
Grade C	Remission induction therapy for acute leukemia
	ATRA, IDR, Ara-C; DCM (DNR, Ara-C, 6-MP); DNR, VCR, CPA, L-Asp, PSL; HAM (high dose Ara-C, MIT); IDR, Ara-C
	High-dose chemotherapy with peripheral blood stem cell harvest:
	high dose VP-16
	Salvage chemotherapy for T-cell lymphoma:
	SMILE (MTX, ETP, IFM, L-Asp, DEX)
Grade D	Conditioning regimen for transplant:
	MCVC (MCNU, CBDCA, ETP, CPA); HD-ICE (IFM, CBDCA, VP-16); Flu/BU; Flu/Mel/TBI; TBI/CY

(ADR adriamycin, Ara-C cytarabine, BLM bleomycin, BU Busulfan, CBDCA carboplatin, CDDP cisplatin, CPA/CY cyclophosphamide, DEX dexamethasone, DNR daunorubicin, DTIC dacarbazine, ETP/VP-16 etoposide, Flu fludarabine, IDR idarubicin, IFM ifosfamide, L-Asp L-asparaginase, MCNU ranimustine, Mel melphalan, MIT mitoxantrone, mPSL methylprednisolone, MTX methotrexate, PSL prednisolone, TBI total body irradiation, VCR vincristine, VLB vinblastine, 6-MP 6-mercaptopurine.)

The simplified grading introduced is considered a useful tool for understanding the myelosuppressive state caused by chemotherapy and facilitating communication between medical and dental staff.

Based on this grading, myelosuppression grade B-to-C chemotherapies may place the patient at the risky phase of experiencing severe odontogenic infections, perhaps because these types of chemotherapies are commonly given to patients with *de novo* hematologic malignancies. Thus, caution should be exercised by the oral

medicine team when considering grade B to C chemotherapies especially for *de novo* hematologic malignancy patients, irrespective of whether invasive treatment is to be performed.

The period around primary chemotherapy for hematologic malignancy patients is considered to be a risky phase with regard to the development of severe odontogenic infections owing to instability in the immune system caused by the myelosuppressive chemotherapy and the untreated hematologic tumor.

The oral medicine team should be mindful of rectifying poor oral hygiene to reduce this risk with conservative therapies, but dentists should avoid radical treatment during this period. When the status of hematologic malignancy patients is improved by grade B or C chemotherapy, invasive procedures should be performed rapidly during the intervals between chemotherapy cycles, and completed before the initiation of grade D chemotherapy.⁴

More studies are needed on the relative contributions of odontogenic infections to local and systemic complications during the myelosuppressive chemotherapy. The use of myelosuppression grading to aid in structuring prophylactic dental treatment has great potential in reducing oral complications in patients with hematologic malignancies, but requires further validations.

II. Conclusion

The myelosuppression grading system can be used as a tool ,for providing and planning better dental treatment for myelosuppressive patient ,and it will also help to facilitate the better quality of life

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