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GEMCITABINE INDUCED MYELOSUPPRESSION- A CASE REPORT

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ABSTRACT

This is a case report focusing on a 60 yr old female patient who has experienced severe myelosuppression after treated with gemcitabine as a salvage regimen for the treatment of Metastatic breast cancer (MBC). In this case the patient was receiving gemcitabine as a salvage regimen after failure of CAF (cyclophosphamide, adriamycin, 5-fluorouracil) treatment, and she has developed with myelosuppression, which is a severe adverse drug reaction. Naranjo's casuality assessment algorithm was used to assess the adverse effect and it indicated gemcitabine as definite cause of myelosuppression.

Key Words:- Metastatic breast cancer, Gemcitabine, Myelosuppression.

INTRODUCTION

Breast cancer is the most common cancer in women worldwide. It is also the principle cause of death from cancer among women globally. Metastatic breast cancer is a fourth stage of breast cancer where the disease has spread to distant parts of the body (Dipiro T *et al*., 2011). Breast cancer primarily metastasizes to the bone, lungs, regional lymph nodes, liver and brain, with the most common site being the bone. The prognosis is often poor, distant metastases are the cause of about 90% of deaths due to breast cancer (Fauci *et al*., 2008).

Metastatic breast cancer is not a curable condition. However, treatment mainly with chemotherapy can prolong life, delay the progression of the cancer, relieve cancer-related symptoms, and improve quality of life. The median survival of individuals with metastatic breast cancer is 18 to 24 months, although the range in survival spans between a few months to many years (Bendre M *et al*., 2003).

Treatment Options for Metastatic Breast Cancer

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Treatment mainly includes hormonal therapy and chemotherapy and sometimes biologic therapy (Dipiro T *et al*., 2011).

Hormonal therapy

- Anti-estrogen treatment (endocrine therapy) this includes:
  - Selective estrogen receptor modulators (SERMs) — tamoxifen or toremifene
  - Aromatase inhibitors (AIs) — anastrazole, letrozole, exemestane
  - Selective estrogen receptor down regulators (SERDs) — fulvestrant
  - Progestogens — Megestrol acetate or medroxyprogesterone
  - Other sex steroid hormones — Progestins, estrogens, androgens
- Chemotherapy with biologic therapy, such as the angiogenesis inhibitor, bevacizumab.
- Individuals with HER2-positive breast cancers should receive HER2-directed therapy

(Daniel F Hayes *et al*., 2013).

Chemotherapy

For individuals who have not received prior

treatment (i.e., those who present with metastatic disease), those with ER-negative breast cancer, and those with tumors that do not respond to endocrine therapy, chemotherapy is indicated as primary treatment. There are several types of chemotherapeutic regimens (Mohan A *et al*., 2013)

- Available options include anthracyclines (eg, doxorubicin), taxanes (eg, paclitaxel or docetaxel), capecitabine, vinorelbine, gemcitabine, ixabepilone, and eribulin (Watanabe M *et al*., 2013).
- Combination options include capecitabine and docetaxel, gemcitabine and paclitaxel. For chemotherapy naïve patients, doxorubicin (alone or as part of a combination regimen) is also used (Dipiro T *et al*., 2011).
- Combination chemotherapy: For individuals with symptomatic, life-threatening disease, or disease that is involving the organs (eg, liver or lungs), combination chemotherapy with trastuzumab should be used. Most clinicians combine HER2-directed treatment with chemotherapy, such as paclitaxel, docetaxel, vinorelbine, carboplatin, and gemcitabine (Richard AH *et al*., 2006).

Myelosuppression as a Side Effect of Chemotherapy

Chemotherapy is the standard remedy for patients with cancer. Bone marrow suppression or myelotoxicity (adjective myelotoxic) or myelo suppression, is a common side effect of chemotherapy and typically is the dose limiting factor. Consequences include potentially life-threatening febrile neutropenic episodes, intravenous antibiotic treatment and prolonged hospitalization (Beveridge RA *et al*., 1998)

Myelosuppression is characterized by a decrease in blood cell production. Three different kinds of blood cells are produced in the body's bone marrow – red blood cells, white blood cells and platelets. Myelosuppression can result in the decrease in one, two or all three types of blood cells. Typically, when the drugs inducing myelosuppression are administered with bolus rather than continuous infusion, myelosuppression is more common (Carey PJ *et al*., 2003). Death occurring after chemotherapy usually results either from infection related to drug-induced leukopoenia or from bleeding related to thrombocytopenia. Chemotherapeutic agents affect the rapidly proliferating pool of blood precursors in the marrow leading to a predictable decrease in the peripheral white blood cell count at approx. 7-14 days after the drug is administered depending on the type and intensity of chemotherapy (Lena EF *et al*., 2002).

Symptoms associated with myelosuppression vary depending on the specific type of cells decreased e.g., anaemia, leukopoenia, thrombocytopenia (Hollis G *et al*., 2004)

Management of myelosuppression

The use of dose intensive chemotherapeutic regimens makes the management of myelosuppression increasingly important. The use of colony stimulating factor (CSF) in patients with established neutropenia after chemotherapy is mostly routine (Morstyn G *et al*., 1988). Blood cell numbers typically begin to drop seven to 10 days after chemotherapy begins. Once chemotherapy is completed, blood counts should return to normal after a few weeks. In mild cases, no treatment may be necessary. However, in rare cases chemotherapy can cause irrepairable damage. If early signs of such damage are identified, or blood counts dip dangerously low, then chemotherapy may be stalled, reduced or stopped altogether to allow the bone marrow to recover (Rostad Me *et al*., 1990).

Transfusions can be effective in replenishing red blood cells and platelets. However, relief is typically short-term and requires repeated treatments. An alternative to transfusions is growth factor injections. These growth factors are natural chemicals that boost bone marrow performance. Different kinds of growth factors can be used to target the reproduction of red blood cells, white blood cells (e.g., Filgrastim (recombinant human granulocyte colony stimulating factor, rG-CSF) is a hematopoietic growth factor which regulates the production and function of neutrophils. Filgrastim controls proliferation of committed progenitor cells and influences their maturation into mature neutrophils. Filgrastim also stimulates the release of neutrophils from bone marrow storage pools and reduces their maturation time. Filgrastim acts to increase the phagocytic activity of mature neutrophils. In patients receiving cytotoxic chemotherapy, filgrastim can accelerate neutrophil recovery, leading to a reduction in duration of the neutropenic phase (Duhrsen U *et al*., 1988).

Gemcitabine

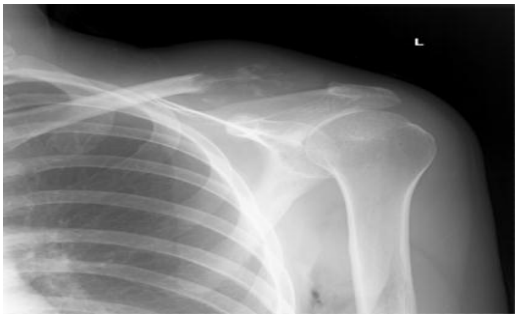
Gemcitabine is a member of a general group of chemotherapy drugs known as anti-metabolites. It acts by preventing the cells from making DNA and RNA, which stops cell growth and causes the cells to die (Aapro MS *et al*., 1998). Gemcitabine is a new anticancer nucleoside that is an analogue of deoxycytidine. It is used in various carcinomas: non-small cell lung cancer, pancreatic cancer, bladder cancer and breast cancer. It is being investigated for use in esophageal cancer, and is used experimentally in lymphomas and various other tumor types (Green MR *et al.*, 1996). Neutropenia was the most commonly reported adverse effect (90% of patients). Other serious adverse effects were mostly hematologic. Less common side effects associated with gemcitabine are

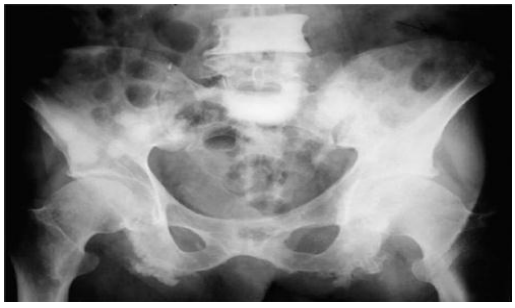
sore mouth, diarrhoea, constipation, alopecia, rhinitis, bullous rash, bruising and bleeding, fatigue (Montreal QC *et al*., 2013).

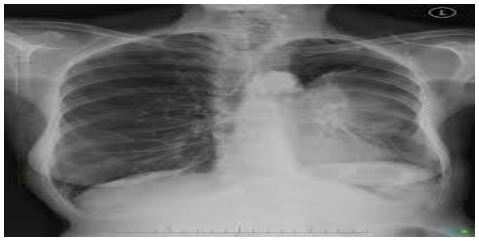
It is beneficial in Breast cancer that has metastasized (spread to other parts of the body) as salvage regimen. This medication is given by injection into a vein by a healthcare professional, usually over 30 minutes once a week or as directed by the medical oncologist. The dosage is based on the medical condition and response to therapy (Montreal QC *et al*., 2013). Here in the present discussion, gemcitabine is given as a Salvage therapy, also known as rescue therapy, is a form of treatment given after an ailment does not respond to standard treatment. Salvage therapy drugs or drug combinations have, in general, much more severe side effects than the standard line of therapy may be due to already compromised bone marrow function (Dipiro T *et al*., 2011).

Case report

A 60 yrs old female patient with metastatic breast cancer was admitted in a tertiary care hospital. She is already underwent the surgery for the cancer of left breast 2 yrs back (2010) and not received adjuvant therapy (chemotherapy or radiation) and lost the follow-up. In the month of January(2013), she was admitted in the hospital with the complaints of severe, progressive pain of the affected bones and chest pain ,chronic cough, dyspnoea when investigated found to be having the pulmonary and bone secondaries.







Initially, the patient was prescribed with 6 cycles of CAF chemotherapy regimen (Cyclophosphamide, Adriamycin, 5-fluorouracil) which was given without any indication and after that the disease is only partially regressive and later it is progressive. In order to improve the patient condition physician included Gemcitabine (1250 mg/m² IV infusion over 30 minutes) to her therapy. Complete Blood count was performed before the administration of gemcitabine as salvage regimen and the counts were found to be normal. After administration of gemcitabine the patient complains of fever, severe throat pain, and fatigue. Here the patient experience severe myelosuppression which were revealed by the clinical laboratory data (haematological tests) a decrease in W.B.C (2000 cell/mm^3), Hb (9 gm/dl) and platelets count (50,000cells/mm^3) were observed, gradually the blood cell count decreased after starting gemcitabine. The diagnosis was made as drug (gemcitabine) induced myelosuppression on the basis of these clinical laboratory values and the reversible condition is observed in the patient after the drug was discontinued, which minimized the secondary outcomes and improved patient condition. **(Table 1)**

Measures initiated by the physician for the Management

- Patient was isolated to a single room and was advised to use the nasal mask in order to avoid the cross infection.
- Prophylactic treatment with broad spectrum antibiotics was given to the patient which include cefotaxime, metronidazole, amikacin and also an antifungal drug i.e., fluconazole.
- Supportive treatment in the form of I.V fluids and high protein diet was also recommended to the patient.
- Then, a 300 mcg of filgrastim was administered subcutaneously once daily to treat the drug induced myelosuppression.

The filgrastim was administered repeatedly based on the results of the haematological tests in order to prevent the severe complications as well as death. Gemcitabine induced myelosuppression was managed with filgrastim 300 mcg, the patient was stable and the blood cells count was observed to be improved after the filgrastim administration.

Table 1. Haematological observations after gemcitabine therapy

Date	Total White blood cell count (Cell/mm3)	Neutrophil % in differential leucocyte count
Before starting gemcitabine		
	11,000	62%
After gemcitabine administration		
Day 1	9000	51%
Day 2	7000	38%
Day 3	4000	29%
Day 4	2000	18%
After filgrastim administration		
Day 1	2200	20 %
Day 2	2500	30%
Day 3	2900	35%
Day 4	3200	40%
Day 5	4600	50%

DISCUSSION

In this case, Gemcitabine -induced myelo suppression was diagnosed and treated on the basis of clinical laboratory investigation which is a main key for diagnosing the decreased blood cell counts. Furthermore the patient was treated with filgrastim with the identification of the drug that is causing the myelosuppression. Filgrastim is considered to be a drug of choice in this case. Here, it was shown that myelosuppression was the most common side effect of chemotherapeutic agents .Taking all these informations in to consideration, a causality assessment was done by using naranjo's causality assessment scale (Naranjo CA *et al*., 1981) and the naranjo score was found to be 10(Definite ≥9).And the WHO causality assessment scale gives the ADR as a certain one.

This case report accentuates the importance of collecting complete data of patient's history such as; past medical history, past medication history, current clinical laboratory tests etc before initiating any treatment .Also monitoring, reporting and management of ADR's are necessary in order to avoid such types of severe events. Commercially available granulocyte colony stimulating factors (G-csf) preparations have been administered which can significantly improve the quality of life (Qol) of the patients with myelosuppression (filgrastim is routinely indicated).

CONCLUSION

Our case report, reflects the importance of Clinical pharmacist intervention when comes to the Pharmaceutical care. By the knowledge of clinical pharmacist can reduce the incidence of adverse drug reactions, ADR induced hospitalization and cost of the treatment. Hence, it is his duty as health care professional to implement RUD (Rational use of drugs), which improves Patient's Quality Life.

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