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CHEMOTHERAPY INDUCED NEUTROPENIA A CASE REPORT

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ABSTRACT:

Chemotherapy is a group of drugs for variety of indications are prescribed in oncology department. they are associated with many potential adverse drug reactions. neutropenia and febrile neutropenia are typically a symptom of an underling disease [AML] in the body rather than an illness on its own. A 65 year old female patient was admitted in oncology department, with a chief complaints of buccal swelling with pain, nausea, loss of appetite, oral mucositis with pain, high grade of fever with spikes which was raised as an adverse drug reactions of AZACITIDINE and VENETOCLAX which has been used for her AML [acute myeloid leukemia]. this adverse reaction is considered as dose related type A ADR as per WHO scale. Azacytidine and venetoclax causes decrease in WBC count [neutrophils] which further causes neutropenia. Thus the hint of written report is to create awareness about chemotherapy drugs.

KEY WORDS: Neutropenia, chemotherapy, azacytidine, venetoclax, ADRs

INTRODUCTION :

Chemotherapy induced neutropenia is a major cause of hematological and dose limiting toxicities of chemotherapy it may have short or longterm impacts on treatment plans which may result in unfavourable disease control and survival. cytotoxic chemotherapy suppress the haemopoietic system impairing the host protective mechanism and limiting the dose of chemotherapy that can be tolerated. neutropenia the most serious haematologic toxicity Is associated with the risk of lifethreatening infections as well as chemotherapy dose reduction and delays that may compromise treatment outcomes.

Chemotherapy predisposes patient with cancer to infection both by supressing the production of neutrophiles and by cytotoxic effects on cells neutrophiles are the first line defence against infection as first cellular component of the inflammatory responses and key component of innate immunity

Recent surveys indicate that neutropenia and febrile neutropenia a prevalent problem associated with substantial morbidity mortality and cost and severe infection aggressive hospital management. The degree and duration of neutropenia determine the risk of infection.

A healthy person has absolute neutrophile count between 2500 to 6000. CIN characterized as decrease absolute neutrophiles count <2000 cell/ mm in peripheral blood

According to grading system classified as 4 grades

Grade 1 --- 1500 to 2000 cell/mm3

Grade 2 ---1000 to 1500 cell/ mm3

Grade 3 ---500 to 1000 cell/mm3

Grade 4 --- <500 cell/mm3

CAUSES :

Chemotherapy induced neutropenia is caused by older age, less than 5 previous chemotherapy cycles, disseminated diseases, platinum based regimens, taxanes containing regimens, combined therapy, alcoholism, chemotherapy, any disease that can damage bone marrow ,HIV ,lupus, infections that use neutrophils faster than they can be produced .

The possible causes of neutropenia are extensive. It is frequently seen in patients undergoing the chemotherapy.

The FDA has approved the combination of VENETOCLAX and AZACITIDINE for people with acute myeloid leukemia [AML] that are over the older age people who have comorbidities preclude intensive induction chemotherapy.

venetoclax may interact with BCL-2 [a protein that initiate the tumor growth, disease progression and drug resistance] and inhibits BCL-2 which can lead to cancer cell death. Azacitidine may cause cell death in rapidly dividing cells which may lead to cancer cell death. This are the standard chemotherapy treatment for patient with acute myeloid leukemia

°AZACITIDINE

BRAND NAME(Azacitidine): Vizada

°ROUTE OF ADMINISTRATION: Sub-cutaneous, intravenous, powder

°DOSES: First Treatment Cycle is 75 mg/m2 subcutaneously or intravenously, daily for 7 days. Premedicate patients for nausea and vomiting.

Subsequent Treatment Cycles Repeat every 4 weeks. The dose may be increased to 100 mg/m2 if n effect is seen after 2 cycles and if no toxicity. Then it is recommended for a minimum of 4 to 6 cycles

°USE: This medication is used to treat myelodysplastic syndrome (MDS) and acute myeloid lukemia (AML)

°CLASS: Azacitidine is in a class of medications called demethylation agents. It works by helping the bone marrow to produce normal blood cells and by killing abnormal cells in the bone marrow.

°MECHANISAM OF ACTION

Azacitidine is a chemical analogue of the nucleoside cytidine, which is present in DNA and RNA. It is thought to have antineoplastic activity via two mechanisms – at low doses, by inhibiting of DNA methyltransferase, causing hypomethylation of DNA and at high doses, by its direct cytotoxicity to abnormal hematopoietic cells in the bone marrow through its incorporation into DNA and RNA, resulting in cell death.

°PHARMACOKINETICS

Azacitidine is rapidly absorbed after SC administration; the peak plasma azacitidine concentration of 750 ± 403 ng/ml occurred in 0.5 hour. The bioavailability is app 89%, distribution of IV dosing is 76 ± 26 L. SC clearance is 167 ± 49 L/hour and half-life is 41 ± 8 minutes and eliminated through urine.

°PHARMACODYNAMICS

Azacitidine is exert its antineoplastic effects by causing hypomethylation of DNA and direct cytotoxicity on abnormal hematopoietic cells in the bone marrow. Hypomethylation may restore normal function to genes that are critical for differentiation and proliferation. The cytotoxic effects of azacitidine cause the death of rapidly dividing cells. Upon uptake into cells, azacitidine is phosphorylated to 5-azacytidine monophosphate by uridine-cytidine kinase, then to diphosphate by pyrimidine monophosphate kinases and triphosphate by diphosphate kinases. 5-Azacitidine triphosphate is incorporated into RNA, leading to the disruption of nuclear and cytoplasmic RNA metabolism and inhibition of protein synthesis. The resultant metabolite is phosphorylated to 5-azadeoxycitidine triphosphate by nucleoside diphosphate kinases. 5-azadeoxycitidine triphosphate is then incorporated into DNA, leading to inhibition of DNA synthesis. Azacitidine is most toxic during the S-phase of the cell cycle.

°ADVERSE REACTIONS

Neutropenia, thrombocytopenia, elevated serum creatinine, renal failure, renal tubular acidosis, hypokalemia, hepatic coma.

Most Commonly Occurring Adverse Reactions (SC or IV Route): nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, fatigue, injection site erythema, constipation, neutropenia, ecchymosis. The most common adverse reactions by IV route also included petechiae, rigors, weakness and hypokalemia.

CONTRAINDICATIONS

VIDAZA is contraindicated in patients with a known hypersensitivity to azacitidine or mannitol. advanced malignant hepatic tumors.

VENETOCLAX

BRAND NAME: Venclexta

ROUTE OF ADMINISTRATION: orally

DOSES: 10mg,50mg,100mg Adult/For a dosing interruption >1 week during the first 5 weeks , reassess for risk of tumor lysis syndrome (TLS) to determine if reinitiation with a reduced dose is necessary

USE: Multiple myeloma, Mantle cell lymphoma, Myelodysplastic syndromes and acute myeloid lukemia

CLASS: B-Cell lymphoma inhibitor

MECHANISAM OF ACTION

Venetoclax blocks the anti-apoptotic B-cell lymphoma-2 (Bcl-2) protein, leading to programmed cell death of CLL cells. Overexpression of Bcl-2 in some lymphoid malignancies has been linked to increased resistance to chemotherapy.

PHARMACOKINETICS:

The maximum plasma concentration 5–8 hours. It is recommended that venetoclax be administered with a meal. the distribution is app 256–321 L. It is highly bound to human plasma protein. Within a concentration range of 1-30 µ M (0.87-26 µ g/. metabolized by CYP3A4/5.Those using the drug should not consume grapefruit products because they contain CYP3A inhibitors and the drugs that inhibit and excreted via the fecal route.

PHARMACODYNAMICS:

Venetoclax induces rapid and potent onset apoptosis of CLL cells, powerful enough to act within 24h and to lead to tumor lysis syndrome. Selective targeting of BCL2 with venetoclax has manageable safety and has response in patients with relapsed CLL (chronic lymphocytic leukemia) or SLL (small lymphocytic leukemia). Venetoclax has efficacy in various types of lymphoid malignancy

ADVERSE DRUG REACTIONS

Common side effects of venetoclax include neutropenia (low white blood cell count), nausea, Anemia , diarrhea ,upper respiratory tract infection, fatigue, and thrombocytopenia (low platelet count). Major side effects include tumor lysis syndrome and severe neutropenia. Additionally, this drug may cause fertility problems in males.

CONTRAINDICATIONS: Electrolyte imbalance, renal failure, tumor lysis syndrome (TLS) ,Anemia, infection, neutropenia, thrombocytopenia ,Renal disease, renal impairment, Hepatic disease, Multiple myeloma.

CASE REPORT:

A 65year old female patient was admitted in the oncology ward of KIMS-hyderabad (Krishna institute of medical sciences) with her chief complaints of B/L buccal swelling with pain , Nausea , loss of appetite, oral mucositis with pain , high grade fever with spikes.

Has a past history of illness AML [acute myeloid lukemia] positive ,post cycle-1 chemotherapy with Azacytadine(8days) with Tab.venetoclax(low dose), and now patient is on G-CSF, oral antibiotics (T- Augmentinduo) for acute myeloid leukemia. And now patient admitted for supportive care in case of chemo-induced febrile neutropenia.

H/O HTN - since 4years

H/O DM - since 4years

H/O heart disease - Acyanotic VSD,infective endocarditis.

H/O thyroid - hypothyroidism.

H/O lung disease - pulmonary T.B

H/O surgery - Total thyroidectomy left sided neck D

Other specify - papillar thyroid carcinoma (1998) replace carcinoma of thyroid (2015)

H/O - cerebrovascular accidents in (2014)

On general examination she was conscious and coherent. On physical examination her vitals were found to be Blood pressure- 100/60 mmHg, Temperature- 100.5F°, spo2- 98%, Heart rate - 86 b/min RR- 20 b/min.

On systemic examination reveals that, S1,S2 –(+),BAE -clear, BS-(+) , P/A - soft , ps-2 oral mucositis(+) buccal swelling (+)-B/L , CVS/RS - NAD.

For further confirmation she was subjected to laboratory investigations such as CBP, LFT, RFT, blood c/s, urine c/s, CRP which are as follows and cardiology and dental consultation and infectious diseases

WBC - 330cells/cumm, Hb- 8.1mg/dl ,PCV-24.2 ,RBC- 2.39,platelets-1.23,and creatinine- 1.12mg/dl, total bilirubin-7.05.So she was treated with,

INJ. Magnex Forte -3gm IV BID, INJ. Pan-40mg IV BD, INJ. Neukine - 300mg s/c BD, IV Fluids - Ns/RL - 75ml, INJ.MVI -1ampin any 10ns, Syp. Mucobenz - oral gargling – QID, Syp. Sacral-o -10ml TID, chlorohexidine 4% body wash bath- BD, sitz bath-TID with betadine, tab. Metrogyl-400mg, tab.Telma-OD, tab.metxl-80mg-OD, tab.eptus-50mg-OD, tab.chymoral forte-BD, tab.dalacin, tab.lyser forte, tab.raeo-B, hexigel gum, 0.1% kenaort ointment. then the patient showed steady improvement with given therapy, and was discharged.

DISCUSSION :

Thus the above mentioned drugs which are used in treating AML [acute myeloid lukemia] has synergistic effect leading to neutropenia and febrile neutropenia. this adverse drug reaction is dose related and can be labelled as type A class of adverse effects. it can be considered as probable ADR as per WHO scale. neutropenia is not a illness on its own .it is a side effect of chemotherapy drugs.

CONCLUSION:

Thus, the main motive of this written report is to create awareness in hospital sectors about the adverse drug reactions and necessity to provide patient counselling of long term usage of chemotherapy.

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