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# Chemotherapy Induced Neutropenia – A Narrative Review

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**ABSTRACT**

Chemotherapy Induced Neutropenia (CIN) is a common and potentially life-threatening complication of cancer treatment. This narrative review synthesizes current literature on the epidemiology , risk factors, pathophysiology, clinical manifestations, management strategies and emerging treatments. This review highlights the importance of understanding the dynamic interplay between chemotherapy agents , bone marrow suppression , and the immune system in predisposing patients to neutropenia. Additionally it, discusses the impact of neutropenic complications on treatment efficacy, quality of life, and healthcare costs. This review also explains about the use of G-CSF like filgrastim, pegfilgrastim and its biosimilars. Furthermore, the review examines evidence-based practices for prophylaxis and treatment of CIN, including the role of granulocyte.

## INTRODUCTION

The episodes of neutropenia is a potential life-threatening and common complication among the myelosuppressive chemotherapy. The life-threatening complications could be of Febrile and Afebrile neutropenia, exposure to antibiotics, hospitalization and increased rate of mortality. The patient is accounted as neutropenic if the absolute neutrophil count (ANC) is below $1.5 \times 10^9$/L (1500/$mm^3$). In Chemotherapy Induced Neutropenia (CIN), not only reduces the immunity against the micro organism by reducing the neutrophil count but also impairs the tumour clearance. [1-4] Neutropenia can be prevented by the administration of recombinant Granulocyte-Colony Stimulating Factors(G-CSFs), this G-CSFs include Filgrastim & Pegfilgrastim.[5] G-CSF is a glycoprotein responsible for the proliferation , differentiation & activation of hematopoietic cells. According to international guideline, prophylactic use of G-CSF is recommended in patients at risk of developing incidence of CIN which is greater than 20%. [18-19]

CIN is more than just an adverse event (AE) & can serve as well as a predictive marker in cancer patients.[22]

Neutropenia:

Neutropenia is defi ned as having an absolute neutrophil count (ANC) of less than 500 cells/mm3 and is a common adverse event associated with many cytotoxic chemotherapy agents. The occurrence of neutropenia other than chemotherapy induced is tend to be immune mediated reaction or idiosyncratic reaction or direct myeloid cell line damage. The episodes of non CIN is comparatively lesser than CIN. [31]

GRADES OF NEUTROPENIA

| Grade | ANC($\times 10^9$/L) |
|---|---|
| 0 | Within normal limits |
| 1 | >1.5 to<2.0 |
| 2 | >1.0 to <1.5 |
| 3 | >0.5 to <1.0 |
| 4 | <0.5 |

## RISK FACTORS

Patient related factors:

Patient related factors which contributes towards the CIN are Sex, age, race, disease progression , Lactate Dehydrogenase(LDH) & bone marrow involvement.

Studies suggest that compare to male ,female are at high risk of developing CIN, while treated with same regimen (due to different maximum tolerated dose). In case of BMI, patients who are obese are at higher risk. Individuals lacking drug metabolizing enzymes are at risk. Hyperglycemic & malnutrition patients are also at risk.As of age factor, Geriatric patients undergoing or underwent are more prone to develop CIN. People with black race have chances of developing CIN than white. Aggressive Non Hodgkin's Lymphoma (NHL) results in development of CIN which was proven in a study, this lead to the conclusion that disease progression is a major risk factor of CIN. Elevated level of LDH results in CIN.As chemotherapy is known to cause myelosuppression, which is marked as the possible risk factors of developing CIN.[4,14,15,22]

Regimen specific risk factors:

Not all chemotherapy regimens induce neutropenia ,but there are certain regimens that has chances of inducing neutropenia. For example, combined cyclophosphamide, methotrexate, and 5-fluorouracil is less toxic than AC or combined cyclophosphamide, doxorubicin, and 5-fluorouracil and, consequently, often is preferred in elderly patients with breast carcinoma.[4]

Triplet or doublet regimen of chemotherapy drugs is also a risk factor.[22]

Disease related risk factors:

Advance disease, type of cancer, bone marrow involment and infection are risk factors of the cause of chemotherapy induced neutropenia.[2]

**Difference between non chemotherapy neutropenia vs chemotherapy induced neutropenia:**

Neutropenia from nonchemotherapy drugs is much less common than neutropenia secondary to chemotherapy.

Non chemotherapy drugs that causes neutropenia in patients are Clozapine, Dapsone, Hydroxychloroquine, Infliximab, Lamotrigine, Methimazole, Oxacillin, Penicillin G, Procainamide, Propylthiouracil, Quinidine/Quinine, Rituximab, Sulfasalazine, Trimethoprim, sulfamethoxazole, Vancomycin

Chemotherapy drugs which induce neutropenia in patients are Alkylating agents, Anthracyclines, Antimetabolites, Camptothecins , Epipodophyllotoxins , Hydroxyurea, Mitomycin C ,Taxanes, Vinblastine

Non chemotherapy drug induced neutropenia is likely to be less virulent than the CIN.[31]

**GCSF:**

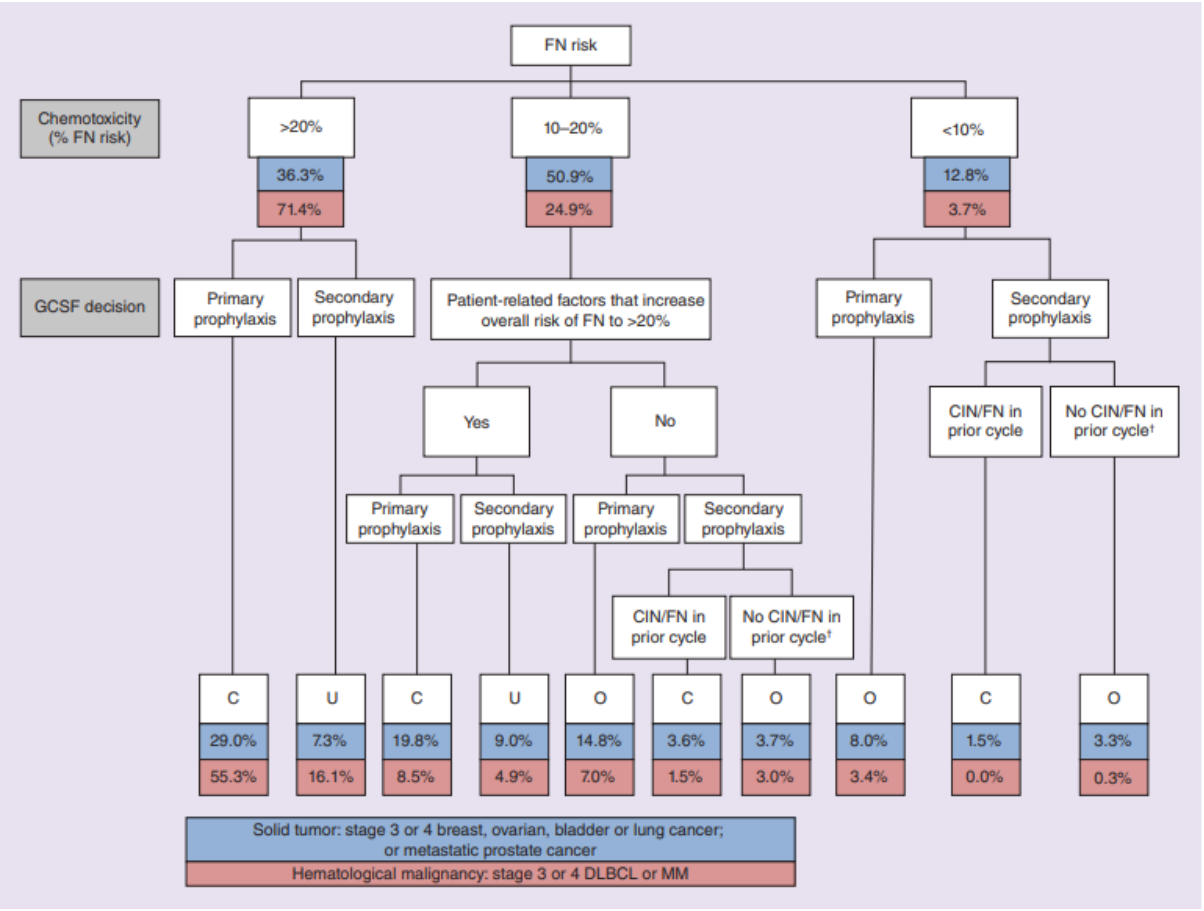
GCSF is a glycoprotein which helps for the proliferation, differentiation and activation of haematopoietic cells. Primary prophylaxis with GCSF is recommended by international guidelines to reduce frequency ,severity and duration and risk of CIN. When the risk associated with FN is greater than or equal to 20%. In patient with 10-20% of greater than or equal to 65 years , hepatic or renal dysfunction GCSF is indicated as prophylaxis.[19]

**COMPLICATIONS OF GCSF**

Even though GCSF helps the chemotherapy patients by preventing the CIN, it has its own ADR. Both filgrastim and pegfilgrastim has similar occurrence for developing their ADR like bone pain is likely due to bone marrow expansion, activation of pro-inflammatory circuits, and sensitization of peripheral nerve fibers to pain stimuli headache (15–70%), nausea and/ or vomiting (3–18%), fever/chills/sweats (0–27%), fatigue (9–59%), skin reaction (1–3%), and myalgias (13–68%), compared with each other but:

Pegfilgrastim: Pyrexia and back pain is more when compared to filgrastim.

Filgrastim: Neutropenia and febrile neutropenia occurrence is more when compared to pegfilgrastim. [2,19]




**PROPHYLACTIC USE OF GCSF:**

For regimens with incidence of grade III or IV neutropenia is high,use of prophylactic gcsf support is effective in overcoming this as a dose limiting toxicity. But the routine use of GCSF is discouraged as per American society of oncology and they should be used based on the risk group criteria. GCSF provided after the first cycle of chemotherapy is known as primary prophylaxis, whereas GCSF provide after the second and the following chemotherapy cycle is known as secondary prophylaxis.

Pegfilgrastim is administered with a dose of 6mg/0.6ml per cycle after 24 hrs of chemotherapy as a prophylaxis. Filgrastim is administered as a dose of 5mcg/kg/day for a period of 3-5 days after receiving chemotherapy as prophylactic.[22,13,6]

## OTHER COMPLICATIONS OF CHEMOTHERAPY:

Chemotherapy induced complications is more than just an adverse event and can serve as well as predictive marker in cancer patients. One among the common complications that serves as a marker is CIN. The other surrogate markers are chemotherapy induced thrombocytopenia and chemotherapy induced anemia.

## COST EFFECTIVNESS OF G-CSF:

Some studies suggest that pegfilgrastim is more cost effective than filgrastim as primary and secondary prophylaxis in CIN with a cost effective threshold of US$ 50,000 per QALY gained. [10]

## FUTURE DIRECTIONS THAT HELPS:

Regimen employing dose to neutrophil, Surrogate markers & Risk predictive modelling will be helpful in treating the patients regarding their quality of life.[22]

## CONCLUSION:

CIN can significantly impact cancer treatment. It can lead to delays in chemotherapy cycles, compromising treatment efficacy and potentially affecting disease outcomes. By understanding the risk factors , clinical presentation and management strategies for CIN, healthcare professionals can optimize patient care and minimize the impact of neutropenia on cancer treatment. Ongoing research holds promise for developing more effective strategies like prophylactic use of G-CSF to prevent and manage CIN, ultimately improving the outcomes for patients with cancer.

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