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THE ROLE OF GRANULOCYTE-COLONY STIMULATING FACTOR FOR THE MANAGEMENT OF CHEMOTHERAPY-INDUCED NEUTROPENIA IN ACUTE LYMPHOBLASTIC LEUKEMIA

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ABSTRACT: Chemotherapy-induced neutropenia (CIN) is a common and sometimes fatal side effect of treatment for acute lymphoblastic leukemia (ALL), the most common malignancy in individuals over 40. Antibiotics are used in addition to supportive care as a current treatment. Granulocyte-colony stimulating factor (G-CSF) has been tested in clinical studies as a supplementary treatment to reduce febrile neutropenia in children with ALL. Regarding cancer therapy, the grade and timing of CIN may have predictive and prognostic effects. The following factors are linked to CIN: advanced age, low nutritional and functional status, a history of major comorbidities, the disease's stage, particular chemotherapy regimens, and combination therapies. The management of CIN in ALL is fraught with difficulties, such as the lack of a consensus nomogram for the risk assessment of febrile neutropenia and uncertain genetic risk factors. The advantages of treating FN with granulocyte colony-stimulating factor and the best course of antibiotics in an emergency must be clarified. The purpose of the review was to explore the function of G-CSF in the management of CIN in ALL patients and to emphasize the incidence and characteristics of CIN in ALL individuals to provide the most accurate assessment and best practice recommendations.

INTRODUCTION: In India, there have been estimated to be 76,805 new cases of cancer in those under the age of 19 per year. Out of these, 20,716 suffer from leukemia, with around 15,000 cases being acute lymphoblastic leukemia (ALL) [1]. The malignant transformation and multiplication of lymphoid progenitor cells in the bone marrow, blood, and extramedullary locations are known as leukemia with ALL.

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Even though 80% of cases of ALL are in youngsters, the disease can be fatal in adults [2]. Based on the 2016 WHO categorization recommendations that incorporate the characterization of cell shape, immunophenotypes, genetics, and cytogenetics, ALL is diagnosed [3]. ALL can be treated with chemotherapy, radiation therapy, chemotherapy combined with a stem cell transplant, or targeted therapy. Clinical trials are being conducted to investigate immunotherapy therapies [4].

Chemotherapy toxicity is a prevalent source of mid- and long-term sequelae and a common cause of morbidity and mortality in the majority of pediatric cancer patients [5]. The patient's

recuperation and the healthcare system's financial standing are impacted by chemotherapy toxicity. CIN is a potentially dangerous side effect that affects most of the ALL patients and can be fatal [6]. The administration of filgrastim or a filgrastim biosimilar may be necessary in severe cases of chemotherapy-induced neutropenia, particularly when there are infectious consequences [7]. Increasing our understanding of chemotherapy-induced neutropenia, including its prevalence, features, therapies, and preventability, will help us develop appropriate treatment plans that will reduce treatment-associated hazards in these individuals as much as feasible. Our review's objectives were to discuss the impact of G-CSF on the treatment of CIN in ALL patients and to emphasize the incidence and characteristics of CIN in ALL patients.

Classification of Leukemias: Leukemias is classified as a disease where the aberrant proliferation of hematopoietic cells results in a progressive increase in bone marrow infiltration; in certain cases, however, the lymphatic tissues are specifically impacted [8]. Leukemias, or the malignant expansion of hematopoietic cells, accounts for the majority of hematopoietic neoplasms globally. Leukemias are categorized into myeloid and lymphoid subtypes and can be either acute or chronic [9]. Since each type and subtype of leukemia has a distinct prognosis and survival rate, leukemia typing is necessary for efficient therapy [10]. Acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) are the two types of acute leukemias. Chronic lymphocytic leukemia (CLL) and chronic myeloid leukemia (CML) are the two types of chronic leukemias. Compared to AML. ALL is more prevalent in children. In India, the percentage of hematological malignancies that are AML and ALL is 15% and 35%, respectively [11, 12].

Acute Lymphoblastic Leukemia (ALL): A blood-line lymphoid progenitor cell cancer, ALL is defined by a significant proliferation of indefinable lymphocytes. It is the most common type of cancer in children. It comes on by errors in the bone marrow cells' DNA, albeit in certain cases, it's not apparent where the flaws originated. Overproduction of immature bone marrow lymphocytes has impeded the generation of new red blood cells, white blood cells, and platelets[13, 14]. Anaemia, bloody nose, bone pain, dyspnea, bruising, contusions, common infections, stiff neck or paralysis of the cranial nerve (CNS involvement), paleness, skin rashes/red spots from low platelet counts, dyspnea, vomiting, weakness, and exhaustion are some of the symptoms and indications of ALL [15, 16, 17].

Type 1 neurofibromatosis, Li-Fraumeni syndrome, and Down syndrome are a few possible genetic risk factors for ALL. Among the environmental risk factors could be prior chemotherapy, radiation exposure, or present chemotherapy [13]. Some speculate that a common infection could set off an unanticipated immune response, which would then lead to its formation [18]. Others theorize that the fundamental underlying processes of fast cell division are several genetic alterations [14].

Bone marrow analysis and blood testing are typically required for diagnosis [19]. Early symptoms might be difficult to diagnose, particularly in young children. Chemotherapy is the initial treatment for ALL to induce remission. Chemotherapy is typically added to this over the years [14]. Intracerebral chemotherapy is frequently used in treatment because systemic chemotherapy may not have adequate access to the central nervous system, which is a common place where ALL regenerates [20, 21]. In cases where the disease progresses to the brain, radiation therapy may also be employed. When traditional therapy fails and the illness recurs, stem cell transplantation may be utilized [14].

A higher number of White Blood Cells at diagnosis (>30,000 for B-ALL or >100,000 for T-ALL) is associated with worse prognoses. The consequences are severe if cancer spreads to the central nervous system (brain or spinal cord). Person's first response to recovery and the lengthier period (>4 weeks) required to reach complete remission. Individuals with chromosomal abnormalities and genetic disorders like Down syndrome could react and remit differently [22].

Chemotherapy-Induced Neutropenia: One of the main causes of the hematological and dose-limiting toxicities of chemotherapy is chemotherapy-induced neutropenia (CIN). It could affect treatment strategies in the short- or long-term,

which could have a negative effect on illness control and survival. The serious repercussions of CIN may cause patients to lose out on chances for a cure. Frequent outcomes of CIN and/or febrile neutropenia (FN) include high hospital expenses, serious infections, forceful hospital administration, potential fatalities, and life-threatening morbidity [23]. Neutropenia, which is characterized by an absolute neutrophil count (ANC) of less than 500 cells/mm3, is a frequent side effect linked to several cytotoxic chemotherapy drugs [24]. FN is defined as a fever (temperature > 38°C) combined with severe neutropenia (absolute neutrophil count [ANC] < 500 cells/mm3), and profound neutropenia (ANC < 100 cells/mm3) is considered the most severe form of neutropenia [25, 26]. During each treatment cycle, neutropenia usually sets in 10–14 days after the chemotherapy is administered. After treatment, neutrophil recovery normally happens three to four weeks later. Agents that cause neutropenia to develop four to six weeks after each cycle's administration, such as carmustine, lomustine, and mitomycin, are exceptions to this rule. Neutrophil recovery will often happen six to eight weeks after therapy with these medicines. Most forms of cytotoxic chemotherapy-induced neutropenia are thought to have a fairly predictable onset and course.

The subsequent Alkylating drugs, anthracyclines, antimetabolites, camptothecins, epipodo-phyllotoxins, hydroxyurea, mitomycin C, taxanes, and vinblastine are among the chemotherapy medicines that might cause neutropenia after treatment begins [23].

Grading of Neutropenia: The CTCAE version 5 [25] is used to grade neutropenia and febrile neutropenia, as shown in the accompanying **Table 1.**

TABLE 1: GRADING OF NEUTROPENIA AND FN

Neutropenia	Definiation
Grade 1	ANC <LLN–1500cells/mm^3
Grade 2	ANC 1000–1500 cells/mm^3
Grade 3	ANC 500–1000 cells/mm^3
Grade 4	ANC <500 cells/mm^3
FN	ANC <1000 cells/mm^3 with a single temperature of >38.3ºC (101ºF) or a sustained temperature of ≥38ºC (100.4ºF) for>1 hour

ANC, absolute neutrophil count; CTCAE, Common Terminology Criteria for Adverse Events; FN, febrile neutropenia; LLN, lower limit of normal; mm^3, cubic millimeter.

Clinical Consequences of CIN: Clinical repercussions of CIN include FN and the prescription of oral or intravenous antibiotics as a result, unforeseen emergency room visits and hospital stays, and potentially fatal outcomes. Furthermore, to assist in reducing neutropenia, the necessity for dosage reductions that may result in low relative dose intensity (RDI) and dose delays in following chemotherapy cycles could adversely impact patient outcomes [27].

Incidence of FN: The occurrence of FN varies throughout various cancer types [28]. It is noteworthy that the probability of FN in the intermediate group, with or without risk factors, reaches 15–20% or higher across all cycles and cancer types. This suggests that the guidelines for G-CSF use in this population may need to be evaluated [29].

Risk Factors for FN: To avoid CIN-related problems, identifying patients at higher risk of developing FN is essential to cancer patient treatment. The treatment schedule is the main variable linked to FN risk. There are three categories for chemotherapy regimens: low, middle, and high FN risk. The European Organisation for Research and Treatment of Cancer (EORTC) and the National Comprehensive Cancer Network (NCCN) have published guidelines that comprise long lists of commonly used chemotherapy regimens arranged according to FN risk status and malignancy [30, 31].

There are three categories of risk factors for the development of CIN and FN: treatment-related, patient-related, and disease-related. Chemotherapy type, chemotherapy intensity, no history of preventive antibiotic use, absence of preventive G-CSF usage, prior radiation therapy or chemotherapy comes under Treatment-related. Gender, age over 65, co-morbidities, poor performance status, nutritional status, Past FN

history, recent medical procedures, open wounds, Low WBC, low hemoglobin levels, renal failure, liver dysfunction, HIV infection, and cardiovascular illness are the risk factors associated with patients. Disease-related risks include advanced disease, cancer type, bone marrow involvement, and infection [29].

Management of Neutropenia:

Prevention of Neutropenia: Primary prophylaxis with a G-CSF agent is advised by the American Society of Clinical Oncology (ASCO), EORTC, and NCCN guidelines to prevent neutropenia beginning with the first chemotherapy cycle and continuing through following cycles with regimens at higher risk of FN. In patients with one or more risk factors, main G-CSF prophylaxis is advised for intermediate-risk chemotherapy regimens.

G-CSF prophylaxis shouldn't be given to regimens with low FN risk. Every time there is a subsequent chemotherapy round, risk should be reevaluated. In following cycles, secondary G-CSF prophylaxis should be seriously considered if a patient had no G-CSF use in the previous cycle and encountered FN or a dose-limiting neutropenic episode [29].

Treatment for Neutropenia: An antipseudomonal beta-lactam antibiotic, such as cefepime, ceftazidime, piperacillin-tazobactam, meropenem, or imipenem, is typically used as an empirical treatment for neutropenic fever. When additional clinical indicators are present, such as pneumonia, skin or soft tissue infection, suspected catheter-related infection, or hemodynamic instability, treatment against methicillin-resistant Staphylococcus aureus with agents like vancomycin should be included in empirical antimicrobial regimens.

G-CSF is administered to patients with neutropenic fever who also have other risk factors for serious side effects, such as pneumonia, hypotension, multi-organ failure, or invasive fungal infections, as well as an ANC of less than 100 cells/mm^3. G-CSF encourages and facilitates neutrophil development and activation. It facilitates the mature neutrophils that are imprisoned in the bone marrow's exodus. G-CSF is effective in reducing the frequency, severity, and length of neutropenia after chemotherapy employing these processes [32].

G-CSF: In 1991, filgrastim became the first myeloid growth factor based on G-CSF to be approved as a FN-prophylactic agent [33]. Following this, filgrastim biosimilars such as tbo-filgrastim, filgrastim-sndz, and filgrastim-aafi were created and authorised for clinical application [29]. With a circulation half-life of roughly 4-6 hours, filgrastim and its biosimilars are quickly removed from the body by renal filtration; as a result, a daily dosage is necessary until neutrophil recovery. For best results, G-CSF should be administered for at least five days and maybe up to eleven days, or until post-nadir recovery [34].

Pharmacologic methods were used to increase the retention of G-CSF in circulation to avoid the inconvenience of daily administration. These methods included fusing G-CSF with human albumin, conjugating it to the FC fraction of monoclonal antibodies or transferrin, adding an inert polyethylene glycol tail to G-CSF (PEGylation), and circularising it. The most successful, PEGylation has increased the size of the molecule and prevented renal excretion. G-CSF's serum half-life can be extended by up to 42 hours with pegylation, allowing for a single dose every cycle in the dosage schedule. Pegfilgrastim, which was authorized for use in 2002, was the first PEGylated G-CSF agent. Following this, several long-acting biosimilar molecules-pegfilgrastim-jmdb, pegfilgrastim-cbqv, pegfilgrastim-bmez, and pegfilgrastim-apgf—have become accessible [29].

The Prophylactic Use of G-CSF: An integrated examination of follow-up information from five multicenter prospective, randomized studies conducted in Australia, Austria, Poland, France, and Sweden. Out of 347 adult ALL patients, 185 were given prophylactic G-CSF, while 162 received treatment without G-CSF support. G-CSF was given either sequentially or concurrently with treatment. Patients receiving G-CSF had remissions that lasted noticeably longer than those of controls, with a median follow-up of 3.2 years. For patients assigned to the G-CSF arm, the 5-year chance of leukemia-free survival was 38%, while for the remaining participants, it was 23%. Additionally, there was a propensity for the overall survival rate to rise in favor of G-CSF-treated patients.

The prophylactic use of G-CSF was linked to a lower risk of relapse and treatment failure in a multivariate study that was adjusted for age, starting WBC, and the presence of the Ph chromosome. It has been determined that prophylactic G-CSF administration during induction and consolidation of adult ALL patients is linked to a lower risk of relapse and a better life [35]. Children with ALL treated with G-CSF benefit from shorter hospital stays and fewer infections, according to a randomized, cross-over research. On the other hand, neither a reduction in treatment delays nor a shorter duration of neutropenia was seen [36]. Physician concerns about reimbursement, noncompliance, patient financial concerns, and a lack of knowledge about guideline recommendations can all contribute to the underutilization of G-CSF prophylaxis [37].

Time of Administration: The timing of G-CSF delivery after chemotherapy is essential to its effectiveness. According to NCCN guidelines, G-CSF agents must be given once throughout each treatment cycle, starting on the first day following chemotherapy and ending on the fourth. Filgrastim dosing on the same day is not ideal, and it is ineffective when done on day 8 [29].

A study examined the effects of giving filgrastim to ALL patients after treatment with a hyper-CVAD (cyclophosphamide, doxorubicin, vincristine, and dexamethasone) after delaying its delivery from Day 5 to Day 10. In this investigation, the examination was extended to 199 patients who, following a single course of induction chemotherapy, had achieved total disease remission. Based on when filgrastim was administered, two sequential treatment groups were evaluated: 151 patients started receiving filgrastim on Day 5 of induction chemotherapy, and 48 patients started receiving filgrastim on Day 10. There is no discernible increase in the risk of infection, but there may be a modest increase in the time it takes for neutrophil counts to recover and an increased risk of mucositis as a result of the filgrastim dosing delay [38].

Pegfilgrastim versus the Conventional G-CSF: A retrospective analysis compared the traditional G-CSF during the hyper-CVAD chemotherapy regimen for ALL to examine the safety and kinetics of neutrophil recovery with pegfilgrastim. This study effectively matched 124 G-CSF-supported cycles from 38 patients treated between January 1999 and July 2005 with 124 pegfilgrastim-supported cycles from 43 patients. There were no statistically significant variations seen in baseline or treatment-related characteristics between the pegfilgrastim and G-CSF groups. In both groups, the median length of time for grade IV neutropenia was four days. Both groups saw identical outcomes in terms of time to neutrophil recovery, incidence of febrile neutropenia, positive blood cultures, and post-chemotherapy delay. Pegfilgrastim dosed once every cycle seems to be as safe and efficient as G-CSF given daily in supporting the hyper-CVAD chemotherapy treatment [39].

Financial Concerns: Financial concerns could arise for the patient as well as their treating physician because G-CSF injection results in unexpected excessive medical expenses above and beyond planned care. Biologics (filgrastim, pegfilgrastim) are generally expensive, which may prevent many patients from accessing them. However, by using G-CSF biosimilar medications, which have been demonstrated to offer considerable savings in cost-efficiency assessments in both the US and the European G5 countries, these financial pressures may be lessened [40].

Clinical Problems Associated with G-CSF Use: Bone pain is the most common adverse event linked to all approved G-CSF medicines, occurring in 25–83% of patients [29]. The enlargement of bone marrow, the activation of pro-inflammatory circuits, and the sensitization of peripheral nerve fibers to pain stimuli are likely the mechanisms behind G-CSF-induced bone pain. There isn't much proof to support the use of acetaminophen, nonsteroidal anti-inflammatory drugs, and prophylactic antihistamines in the treatment of G-CSF-induced bone pain [41].

Additional side effects linked to G-CSF agents include headache, nausea, vomiting, fever, chills, sweats, exhaustion, skin response, and myalgias; however, these side effects may be a result of the chemotherapy that the G-CSF agents are used in conjunction with [29]. Following G-CSF therapy, there has also been evidence of an increased

incidence of secondary malignancies, most often acute myeloid leukemia and myelodysplastic syndrome [42].

CONCLUSION: Clinical ramifications from the development of CIN may have a negative effect on patient outcomes. Although the clinical consequences of FN have decreased due to the approval and widespread use of prophylactic G-CSF agents, these agents come with several drawbacks, such as side effects, delayed onset of action, inconvenience from daily dosing of short-acting agents, difficulties getting insurance approval and reimbursement, and insufficient tools for risk stratification. By enhancing access and preserving the efficacy and safety profile of the original molecules, the introduction of biosimilar G-CSF medications has assisted in easing the financial pressures on certain patients. Further research could clarify the relevance of these novel drugs as the new norm for chemotherapeutic regimens in conjunction with CIN and FN prevention in ALL cases.

Implications for Research: Limited research has been done on applying G-CSF to treating FN in patients with ALL. To ascertain G-CSF's true role in preventing febrile neutropenia in ALL patients receiving myelosuppressive chemotherapy, future studies should concentrate on determining the ideal G-CSF dosage, usage of G-CSF during all cycles of the most intense phases of treatment, and long-term follow-up. High-quality trials that properly evaluate and report the primary outcomes, including mortality, must be conducted. It is important to analyze the cost-effectiveness of routinely using G-CSF in ALL therapy while considering various economic circumstances.

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