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Review Article

Role of myeloid growth factors in chemotherapy induced neutropenia

Ravinutala Srinath Bharadwaj[1], Donepudi Aruna[2]*

[1]Department of Radiation Oncology, MNJ Institute of Oncology and Regional Cancer Centre/ Osmania Medical College, Hyderabad, India
[2]Department of Clinical Pharmacology and Therapeutics Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad, India

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***Correspondence to:**
Dr. Donepudi Aruna,
Email: adonepudi@yahoo.co.in

ABSTRACT

Neutropenia is a major dose limiting toxicity of many chemo therapeutic regimens. Haemopoietic colony - stimulating factors (CSFs) have been shown to reduce the duration and severity of chemotherapy induced neutropenia (CIN) and risk of febrile neutropenia. Supportive care with myeloid growth factors improve chemotherapy delivery by minimizing chemotherapy dose reductions or treatment delays by enabling the delivery of full dose chemotherapy (dose dense) in short time intervals. The goal of this article is to give comprehensive review of current literature regarding medical practice guidelines and risk assessment models for appropriate use of myeloid growth factors and management of febrile neutropenia.

Keywords: CIN, CSFs, Dose dense chemotherapy

INTRODUCTION

Neutropenia is the most common dose limiting toxicity of cancer chemotherapy. The complications from chemotherapy - induced neutropenia (CIN) can cause significant morbidity and mortality.[1] The most significant outcome of CIN in patients with cancer is death, as a result of infection and sepsis. Neutropenia is defined as a reduction in circulating neutrophils. The absolute neutrophil count (ANC) is equal to the product of white blood cell (WBC) count and the fraction of polymorphonuclear cells (PMNs) or neutrophils and band forms noted on differential analysis.

$$\text{ANC} = \text{WBC Count cells/ µl} \times \frac{\%\text{ of (PMNs + Bands)}}{100}$$

Neutrophilic metamyelocytes and younger forms are not indicated in this calculation.[2] According to the common terminology criteria for adverse event version 4.0 neutropenia is defined as granulocyte count (ANC) ≤ 1500/µl or 1.5×10 9/L (Table 1). Neutropenic infection is assumed for any fever episodes occurring, when neutrophil count is <1000/µl. When neutrophil count is <500/µl, the risk and severity of infection is inversely related to the neutrophil count.[3] The infectious diseases society of America defined febrile neutropenia as a

single, oral temperature of ≥ 38.3^{0}C (101^{0}F) or > 38^{0}C (100.4^{0}F) sustained for more than one hour and a total neutrophil count of < 500/µl or < 1000/µl with a predicted decline to < 500/µl over the next 48 hours.[4]

Table 1: National cancer institute common toxicity criteria: neutropenia and febrile neutropenia.

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutropenia	< LLN- 1500 mm^3	< 1500-1000 mm^3	<1000-500 mm^3	< 500 mm^3	Death
Febrile neutropenia	-	-	Present	Life threatening consequences (septic shock, hypotension)	Death

LLN- lower limit of normal

Febrile neutropenia (FN) occurs with common chemotherapy regimens in 25 to 40% of treatment- naive patients, and its severity depends on the dose intensity of the chemotherapy regimen, the patient's prior history of either radiation therapy or use of cytotoxic treatment, and co morbidities.[5] Vogel et al proved the incidence of febrile neutropenia in patients treated with breast cancer, who received docetaxel 100 mg/m^2 every 3 weeks schedule for 4 cycles, is 17%.[6]

The results of the trial led to a revision in the recommendations of the national comprehensive cancer network (NCCN) practice guidelines for the use of myeloid growth factors for the primary prophylaxis of febrile neutropenia. In a prospective cohort study, first cycle febrile neutropenia occurred in 6% of adults with solid tumors, being treated with myelosuppressive chemotherapy.[7] Among patients with metastatic solid tumors, incidence of febrile neutropenia during myelosuppressive chemotherapy ranged from 13% to 21% in a large retrospective study.[8]

Table 2: Multinational association of supportive care in cancer risk score tool for febrile nutropenia.[10]

Dimension	Definition	Points scored
Burden of illness	Moribund	0
	Absence of signs and symptoms	5
	Moderate symptoms	3
Hypotension	if absent	5
COPD	if absent	4
Tumor type Fungal infection	Either solid tumor or Hematologic Malignancy without prior fungal infection	4
Dehydration	if absent	3
Patient	if an outpatient	3
Age	If younger than 60 years	2

Note: Lower risk score ≥ 21, High risk score <21

Risk assessment

The importance of risk models in determining patients, who are at high or low risk of developing neutropenic complications, was first described by Tal Cott, Finberge, Mayer and Gold man in 1988.[9] The multinational association of supportive care in cancer (MASCC) developed a predictive model for patient evaluation at the time of presentation with febrile neutropenia, in which the outcome measure was either uncomplicated recovery or development of serious complications (Table 2). Seven independent risk factors were identified using a multiple regression model. Each of the seven factors was assigned a numeric weight and each patient evaluated would score from 0-26, with a higher score (>21) predictive of an uncomplicated outcome and a lower score (<21) predictive of complicated course of febrile neutropenia. The validated model can be used to guide clinical decision making in the management of patients with cancer, receiving myelosuppressive chemotherapy.

Management of neutropenia and the concept of Relative dose intensity (RDI)

For management purposes, it is useful to identify two different conditions.

- Neutropenia that follows bone marrow ablation for treatment of some forms of acute leukemia. This type of neutropenia may last several weeks and risk of infections is > 90%. The main concern in this situation is support of the patient until marrow regeneration
- Neutropenia that develops during the treatment of solid tumors or lymphomas, with cyclic cytotoxic chemotherapy. In this situation, main concerns are infectious complications and maintenance of treatment dose intensity. In high risk patients, there may be treatment delay due to infection or dose reductions to prevent neutropenia. Neutropenia is responsible for at least 50% of cases, in which the chemotherapy dose intensity has been reduced below 85%.[3]

In this regard, the concepts of dose dense and dose-intense chemotherapy have been applied to combination

chemotherapy in recent years. They have shown improved survival outcomes in patients with breast cancer and non - Hodgkin lymphoma. Dose dense indicates the ability to deliver combination chemotherapy more frequently than in the past (e.g. every 2 weeks as opposed to every 3 weeks). Prior to use of colony stimulating factors (CSFs) chemotherapy was delivered every 21-28 days to allow recovery from bone marrow suppression. Currently with prophylactic use of CSFs recovery occurs more rapidly and allows chemotherapy to be given every 14 days, there by exposing the cancer cells to cytotoxic therapy more frequently. Dose - intense means giving the maximally tolerated doses of cytotoxic therapy to achieve the best survival benefits. An example of dose dense and dose - intense combination of chemotherapy is the accelerated R - CHOP protocol (Rituximab plus cyclophosphomide, doxorubicin, vincristine and prednisone) given every 2 weeks, with the dose of cyclophosphomide intensified to 1 gram / m^2). To achieve dose density and dose-intensity, CSFs support is necessary.[1] Relative dose intensity (RDI) is the percentage of the planned treatment dose administered during a course of treatment per unit time. Bondonna et al, first reported the importance of maintaining relative dose intensity more than 85%, in women treated with adjuvant chemotherapy for breast cancer.[11] RDI is calculated as.[3]

$$\text{RDI} = \frac{\text{D/T administered} \times 100}{\text{D/T planned}}$$

Where D is dose and T is time unit.

The effectiveness of chemotherapy is determined by RDI and it should be more than 85%. A reduction of dose intensity of doxorubicin < 85% was associated with reduced response rate and survival in patients with B cell lymphoma treated with CHOP regime. National comprehensive cancer network (NCCN 2005) developed guidelines for prophylactic use of myeloid growth factors (Table 3).[12] This depends on chemotherapy regimen and other medical conditions of the patients.

Table 3: Prophylaxis with growth factors.[12]

Treatment intention			
Risk level	Curative/ adjuvant	Prolong survival/ quality of life	Symptom management/ quality of life
High > 20%	CSF	CSF	CSF
Intermediate risk	Consider CSF	Consider CSF	Consider CSF
(10 - 20%)			
Low risk < 10%	No CSF	No CSF	No CSF

CSF - Colony stimulating factor.

Colony Stimulating factors or myeloid growth factors or leukocyte growth factors

Endogenous leukocyte growth factor is a glycoprotein that stimulates the proliferation of one or more myeloid cell lines. Myeloid growth factor is produced naturally by a number of different cells, including fibroblasts, macrophages and T cells. The natural human glycoprotein exists in two forms, a 174 - and 177- amino-acid-long protein of molecular weight 19,600 grams per mole. They are active at extremely low concentrations and act via membrane receptors to activate JAK / STAT signal transduction pathway.[13] The G-CSF-receptor is present on precursor cells in the bone marrow, and, in response to stimulation by G-CSF, initiates proliferation and differentiation into mature granulocytes. G-CSF stimulates the survival, proliferation, differentiation, and function of neutrophil precursors and mature neutrophils. G-CSF regulates them using Janus kinase (JAK)/signal transducer and activator of transcription (STAT) and Ras/mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signal transduction pathway. G-CSF is also a potent inducer of HSCs mobilization from the bone marrow into the bloodstream, although it has been shown that it does not directly affect the hematopoietic progenitors that are mobilized.[14] G-CSF can also act on neuronal cells as a neurotrophic factor. Indeed, its receptor is expressed by neurons in the brain and spinal cord. The action of G-CSF in the central nervous system is to induce neurogenesis, to increase the neuroplasticity and to counteract apoptosis.[15,16] These properties are currently under investigations for the development of treatments of neurological diseases such as cerebral ischemia. The more-abundant and more-active 174-amino acid form has been used in the development of pharmaceutical products by recombinant DNA (r DNA) technology. In 1985 Wong et al produced recombinant form of granulocyte macrophage colony stimulating factor (GM- CSF) and Welte et al granulocyte stimulating factor (G- CSF).[17,18]

Genetics

The gene for G-CSF is located on chromosome 17, locus q11.2-q12. Nagata et al. found that the GCSF gene has 4introns, and that 2 different polypeptides are synthesized from the same gene by differential splicing of mRNA.[19] The 2 polypeptides differ by the presence or absence of 3 amino acids. Expression studies indicate that both have authentic GCSF activity. It is thought that stability of the G-CSF mRNA is regulated by an RNA element called the G-CSF factor stem-loop destabilizing element.

Preparations

The recombinant human G-CSF (rhG-CSF) synthesised in an E. coli expression system is called filgrastim. The structure of filgrastim differs slightly from the structure of the natural glycoprotein. Most published studies have used filgrastim. Filgrastim (Neupogen) and PEG-

filgrastim (Neulasta) are two commercially available forms of rhG-CSF. The PEG (polyethylene glycol) form has a much longer half-life, reducing the necessity of daily injections.

PEGylation is the process of both covalent and non-covalent attachment or amalgamation of polyethylene glycol polymer chains to molecules and macrostructures, such as a drug, therapeutic protein or vesicle. PEGylation is routinely achieved by incubation of a reactive derivative of PEG with the target molecule. The covalent attachment of PEG to a drug or therapeutic protein can "mask" the agent from the host's immune system (reduced immunogenicity and antigenicity), and increase the hydrodynamic size (size in solution) of the agent which prolongs its circulatory time by reducing renal clearance. PEGylation can also provide water solubility to hydrophobic drugs and proteins.

Another form of rhG-CSF called lenograstim is synthesised in Chinese hamster ovary cells (CHO cells). As this is a mammalian cell expression system, lenograstim is indistinguishable from the 174-amino acid natural human G-CSF. No clinical or therapeutic consequences of the differences between filgrastim and lenograstim have yet been identified, but there are no formal comparative studies.

Recombinant human G- CSF (Filgrastim)

It is a 175 amino acid glycoprotein produced in Escherichia Coli. It is identical to endogenous G- CSF except, it is not glycosylated and carries an extra N - terminal methionine.[20] The main action of Filgrastim is stimulation of CFU- G to increase neutrophil production. It also enhances the phagocytic and cytotoxic functions of the neutrophils. Recombinant forms of G - CSF include short acting (Filgrstim, lenograstim and tbo- Filgrstim) and long acting (pegfilgrstim and lipegfilgrstim) preparations. Long acting preparations cannot be eliminated from the kidneys. They are metabolized by neutrophils at the time of recovery from neutropenia. They linger in the circulation until recovery has occurred.

Indications

Filgrastim is effective in the treatment of severe neutropenia

- Induced by high dose cancer chemotherapy. Filgrastim shortens the period of severe neutropenia and reduce morbidity, secondary to bacterial and fungal infections. It can decrease the frequency of hospitalization for febrile neutropenia and interruptions in the chemotherapy protocol, when used as a part of an intensive chemotherapy regimen in cancers like lymphomas and solid tumors. A positive impact on patient survival has not been demonstrated
- After autologous hemopoietic stem cell transplantation. Filgrastim is routinely used in patients undergoing peripheral blood stem cell (PBSC) collection for stem cell transplantation. It promotes the release of CD 34+ progenitor cells from the marrow, reducing the number of collections necessary for transplant. Moreover, filgrastim - mobilized PBSCs are more capable of rapid engraftment. PBSC - transplanted patients require fewer days of platelet and red blood cell transfusions and shorter duration of hospitalization than the patients receiving autologous bone marrow transplants
- Severe congenital neutropenia
- Patients with myelodisplasia (aplastic anaemia) or marrow damage due to tumor infiltration
- Nutropenia in AIDS patients receiving zidovudine. One indication for G-CSF presently under investigation is leukocyte donors. Like platelet infusions for bleeding due to thrombocytopenia, neutrophil transfusion could diminish the infectious complications of neutropenia.[13] G-CSF when given early after exposure to radiation may improve white blood cell counts, and is stockpiled for use in radiation incidents due to its neuroprotective properties. G-CSF is currently under investigation for cerebral ischemia in a clinical phase IIb and several clinical pilot studies are published for other neurological disease such as amyotrophic lateral sclerosis.[21-23]

Time of administration

Prophylactic use of CSFs is warranted, when risk of febrile neutropenia is approximately 20% or higher. Primary prophylaxis is recommended in patients who are at risk, on the basis of age, medical history, disease characteristics, patients exposed to lethal doses of total body irradiation and myelotoxicity of the chemotherapeutic regimen. American Society of Clinical Oncology revised the recommendations for the use of WBC growth factors in 2015.[18] Filgrastim or pegfilgrastim should be administered 1-3 days after administration of chemotherapy (Table 4) to decrease the risk of neutropenic infections, which begin with the first cycle of chemotherapy treatment. Many randomized, controlled studies demonstrated that primary prophylaxis decreased the risk of neutropenic infections, not only during the first course of treatment but throughout the treatment. In secondary prophylaxis CSFs are reserved for those patients who had already experienced an episode of neutropenic fever. AIDs patients on Zidovudine therapy or patients with cyclic neutropenia, need long term treatment with G- CSF.[3]

Dose and dosage regimen

For prophylactic use, filgrastim is administered once daily for a minimum of 7-10 days. It is given as subcutaneous injection (SC) or intravenous (IV) infusion

at least over 30 minutes at a dose of 1-20 µg/kg/day. The usual starting dose in a patient receiving myelosuppressive chemotherapy is 5 µg/day. For therapeutic use, once daily administration of filgrastim for 14 - 21 days may be required.[13] Doses of different CSFs are given in (Table 4).

Table 4: Dosing and administration of CSFs.[24]

Agent	Dosing and administration
Filgrastim	Filgrastim should be started 1-3 days after administration of myelotoxic chemotherapy. In settings of high dose therapy and autologous stem cell rescue filgrastim can be started 1 to 5 days after administration of high dose therapy. Filgrastim should be given until ANC reaching ≥ 2 to 3 × 10^9/ L. For PBPC mobilization filgrastim should be started ≥ 4 days before first leukopheresis procedure and continued until last leukopheresis. In adults, recommended filgrastim dose is 5 µg/kg/day for all clinical settings other than PBPC mobilization. In setting of PBPC mobilization, dose of 10µg/kg/day may be preferable. Preferred route of filgrastim administration is subcutaneous.
Filgrastim- sndz	Same as filgastrim
Tbo- Filgrastim	TboFilgrastim should be started 1-3 days after administration of myelotoxic chemotherapy. In adults, recommended tbo-filgrastim dose is 5 µg/kg/day, Preferred route of tbo - filgrastim administration is subcutaneous.
Pegfilgrastim	Pegfilgrastim 6 mg should be started 1- 3 days after chemotherapy. Pegfilgrastim is also available in a timed automated - injectable device that delivers 6 mg of pegfilgrastim subcutaneously, 27 hours after the device is placed on the skin and activated. Pegfilgrastim is not currently indicated for stem cell mobilization. Six mg formulation should not be used in infants, children or adults weighing < 45 kg.
Sargramostim	GM- CSFs have been licensed specifically for use in mobilization, after transplantation of autologous PBPCs, after autologous or allogeneic bone transplantation and AML. GM- CSFs should be initiated on day of bone marrow infusion and not < 24 hours after last chemotherapy and 12 hours after most recent radiotherapy. GM- CSFs should be continued until ANC > 1.5 ×10^9/ L for 3 consecutive days, is achieved. Drug should be discontinued early or dose is reduced by 50% if ANC increases to > 20×10^9/ L. Recommended dose for adults is 250 µg / m^2/ day.

Pharmacokinetics

Half- life is 3.5 hours. The distribution and clearance are similar for both routes of administration. It is pregnancy category C drug.

Adverse effects

Bone pain, generally occurs during the first 5 days of treatment and may lead to discontinuation of treatment. Side effects are mostly reversible, after the withdrawal of the drug. Local skin reactions following subcutaneous injections, rarely necrotizing cutaneous vasculitis. Mild to moderate splenomegaly has been observed in patients on long term therapy. These drugs are very expensive. Cost also should be considered as complication. Pegfilgrastim may be more effective and certainly appears more cost-effective than short acting preparations.

Recombinant human GM - CSF (Sargramostim)

It is 127 amino acid glycoprotein produced in yeast (saccharomyces cerevisiae). It is identical to endogenous human GM - CSF except for the substitution of leucine in position 23 and variable levels of glycosylation. Its primary therapeutic effect is to stimulate myelopoiesis.[13]

Three different recombinant human GM - CSFs are available and they are sargramostim, molgramostim and regramostim. Molgramostim is not glycosylated and is derived from Escherichia Coli. Regramostim is fully glycosylated and is derived from Chinese hamster ovary cells. Sargramostim is the only one approved for use in USA. The different formulations appear to have similar pharmacologic activity.[3]

Therapeutic uses

A number of studies demonstrated that GM - CSF decreases the duration of neutropenia and risk of neutropenia infections in lymphoma and solid tumors and is a reasonable choice for this purpose. It can also be used in allogenic bone transplantation and as an adjuvant for immunotherapy, based on its stimulation of dendritic cell growth and development. At present, the studies comparing filgrastim and sargramostim provided inconclusive and somehow conflicting evidence of the superiority of one drug over the other.

FDA approved indications

Sargramostim is indicated for use following induction chemotherapy in older adult patients with acute

myelogenous leukemia (AML) to shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections and infections resulting in death. It is also indicated for the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis and indicated for acceleration of myeloid recovery in patients with non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) and Hodgkin's disease undergoing autologous bone marrow transplantation (BMT). In addition, sargramostim is indicated for acceleration of myeloid recovery in patients undergoing allogeneic bone marrow transplantation (BMT) from HLA-matched related donors and indicated in patients who have undergone allogeneic or autologous bone marrow transplantation in whom engraftment is delayed or has failed.[24]

Dose and dosage regimen

Sargramostim is administered by subcutaneous injection or slow IV infusion at doses of 125 - 500 µg/m^2/day. When given intravenously, infusion should be maintained 3-6 hours. Half - life is 2-3 hours. There is transient decrease in leukocyte count, secondary to margination and sequestration in the lungs, at the initiation of therapy. This is followed by a dose - dependent biphasic increase in leucocyte count over next 7 - 10 days. Once the drug is discontinued, leucocyte count returns to baseline within 2-10 days. When GM - CSF is given in low doses, the response is primarily neutrophilic, whereas monocytosis and eosinophilia are observed at higher doses. It is given daily during the period of maximum neutropenia until, a sustained raise in granulocyte count is observed. Frequent blood counts are essential to avoid an excessive raise in granulocyte count.[13] Dose may be increased if the patient fails to respond after 7-14 days of therapy. Higher doses are associated with more pronounced side effects.

Adverse effects

Malaise, Flu - like symptoms, bone pain, fever, diarrhoea, dyspnea and rash. In sensitive patients an acute reaction to the first dose, characterized by flushing, hypotension, nausea, vomiting, dyspnea and with a fall in arterial oxygen saturation due to granulocyte sequestration in pulmonary circulation. In a few patients with prolonged administration a capillary leak syndrome may occur, with peripheral edema, plural and pericardial effusions. Other serious side effects are transient supra ventricular arrhythmias, dyspnoea and elevation of serum creatinine, bilirubin and hepatic enzymes.

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