Role of granulocyte colony stimulating factor in haematological disorder
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Introduction
The haemopoietic growth factors are glycoprotein hormone that regulate the growth proliferation and differentiation of haemopoietic progenitor cells and the functions of mature blood cells. They may act locally at the site where they are produced or circulate in plasma. They may act locally at the site where they are produced or circulate in plasma. The biologic effects of growth features of mediate through specific receptor on target cells. An important features of growth factor action is that two or more factors may syergize in stimulating a particular cell to proliferate or differentiate. A common action of growth factors in to inhibit apoptosis of target cell. Human granulocyte colony stimulating factor (G-CSF) is a glycoprotein which regulate the production and release of functional neutrophil from the bone marrow. It is coded by gene on long arm of chromosome17. It is produced by endothelium, fibroblast, adipocytes and other bone marrow stromal cells. This is produced mainly by constitutively or after stimulation. The target cells of G-CSF are high proliferative (HPP) CFC, MixCFC and CFC.

Pharmacokinetics
Commercially prepared G CSF is Filgrastim. There is a positive Liner co-relation between dose and the serum concentration when administered intravenously or subcutaneously. Following subcutaneous administration of recommended dose, serum concentration is maintained above 10 ng/ml for to 16 hours. Clearance of filgrastim has been show to follow first order pharmacokinetic after both SC and IV administration.

Biological actions of G-CSF
In common with all haematoipoietic growth factors (HGFs). G-CSF exerts its effects by interacting with target cells membrane receptors. Studies have shown the existence of a class of G-CSF specific high-affinity receptors on cells of the neutrophil lineage from myeloblast to the mature neutrophil as well as on a subset of cells of the monocyte lineage (Nicola et al. 1987).

Neutrophil production
1. Administration of filgrastim leads to an initial transient fall in peripheral blood neutrophil counts followed within 4-5 hours by a rapid, specific, dose-dependent increase above normal values (Bronchud et at, 1987, Morstyn et al. 1988. Lindemann et al. 1989, Data on file) More modest increases in monocytes and macrophages are also observed at high concentrations.
2. The increase in neutrophils is due to both an increase in the number of lineage-specific cell divisions and decrease in the maturation time leading to accelerated release into the peripheral blood.
3. Clinical labelling studies, using tritated thymidine, showed that the increase in circulating netrophils arises via increased amplification in the maturation compartment of the marrow and earlier release of neutrophils (Lord et al. 1989). Following G-CSF administration, newly produced neutrophils were released into the circulation within one day of labelling compared with normal time of approximately 5 days.
4. The absolute neutrophil count (ANC) decreased within 24 hours of filgrastim treatment, with neutrophil counts returning to normal within 1-7 days after the end of administration (Vincent et al. 1994).
5. Neutrophils produced in response to G-CSF stimulation demonstrate normal or enhanced function, as show in assays of phagocytosis.

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and chemotaxis (Bronchud et al. 1987, Morstyn et al.)

6. They also demonstrate prolonged survival time in human peripheral blood.

7. Morphological changes, such as the appearance of secondary cytoplasmic granules and Dohle bodies, are the same as those observed during infection (Morstyn et al, 1988, Lindemann et al, 1988) and are considered indicative of functionally primed neutrophils.

**PBPC mobilization**

In addition to its effects on neutrophils, filgrastim produces large increases (up to 60 fold) in the peripheral blood content of pluripotent cells and progenitor cells of multiple cell lineages. A number of studies have confirmed that G-CSF alone can effectively mobilise haemopoietic progenitor cells from the bone marrow to the peripheral blood (Durshen et al. 1988, Hass et al.1992 Basser et al. 1995, Desikan et al. 1998, kroger et al. 1988). Mobilised peripheral blood progenitor cells (PBPC), harvested by leukapheresis, can reconstitute the bone marrow of patients receiving myeloablative chemotherapy.

**Effects on other haematopoietic cells and tumour cells**

Initially, some concerns regarding the therapeutic use of HGFs were expressed. However:

1. There is no evidence to suggest that the filgrastim-stimulated increase in neutrophils leads to depletion of pluripotent stem cells (Lord et al, 1989, Bungart et al. 1990, Countinho et al. 1990).

2. No clinically relevant adverse effects on thrombopoiesis and erythropoiesis have been found in experimental (Molineux et al. 1990, Pojda et al. 1990), or in clinical studies of up to 24 months.

3. While some HGFs, including G-CSF, GM-CSF, IL-3 and M-CSF, can stimulate clonal growth of some non-myeloid tumour cells in vitro (Berdel et al. 1990), no clinical evidence of filgrastim-induced stimulation of non-myeloid malignancies has been observed (Trillet-Lenoir et al. 1995).

4. Although in vitro studies have shown inconsistent stimulation of leukaemic cells clone proliferation by some myeloid growth factors, the use of filgrastim to support induction or consolidation chemotherapy in patients with acute myeloid leukaemia (AML) has not been associated with a detrimental effect on response or survival. (Godwin et al. 1998, Maslak et al. 1996, Heil et al. 1997). In addition, data from a study in acute lymphoblastic leukaemia (ALL) do not indicate any increased risk of relapse in patients associated with the use of filgrastim to support induction therapy (Gessier et al. 1997).

**Indications of G-CSF**

1. Prophylactic use of filgrastim in patient under going myelosuppressive chemotherapy. This interns reduces the duration of hospitalization and need for antibiotic and is of obvious benefit to patient, who spend fewer days in hospital.

2. G-CSF Priming combined with chemotherapy (Idarubicin, Ara-C, VP-16) yield higher remission rates in patients with advanced myelodysplastic syndromes and high risk AML. Filgrastim is given both prior to and during chemotherapy, with the aim of increasing the sensitivity of leukaemic blast cells to cytotoxic agents as well as reducing the duration of neutropenia following chemotherapy.

3. Use of G-CSF for induction of maturation in patient with AML. In certain situation leukaemic cells can be provoked to terminal differentiation.

4. Filgrastim in PBPC mobilization and allogenic BMT. Increased population of monocyte in peripheral blood harvested from donors mobilized with filgrastim leads to suppression of T cell activation. This will reduced severity of acute graft versus host disease (GVHD) following transfusion of peripheral blood progenitor cells. G-CSF may also be used to stimulate bone marrow prior to harvest for allogenic bone marrow transplantation. Filgrastim primed bone marrow transplanted from HLA matched donor is capable of rapid, stable engraftment with an acceptable incidence of chronic GVHD.

5. Mobilization of peripheral blood progenitor
cells. High dose cyclophosphamide usually with combination with G-CSF is generally used for mobilization of peripheral blood progenitor cells to autologous transplant to patient with multiple myeloma. G-CSF alone for mobilizing PBPC avoid the toxic effect of high dose cyclophosphamide. This approach existing renal may particularly benefit older patient and those with existing renal or cardiac problem.

6. Harvest of PBPC from healthy donors. This is generally done for allogenic transplant from relatives.


**Clinical problems with neutropenia**

The risk of developing febrile neutropenia varies depending on the type and doses of chemotherapy administered. As expected, higher doses of chemotherapy are usually associated with a greater incidence of febrile neutropenia.

**Hospitalization**

The standard approach to the management of febrile neutropenia in cancer patients remains prompt hospitalization and the empiric use of broad-spectrum anti-infective therapy (Freifeld and Pizzo 1996). There may be a subset of 'low risk' febrile neutropenic cancer patients who have a better prognosis in terms of morbidity and mortality. These patients, who are thought to represent around 25% of patients with febrile neutropenia, may be able to be treated in an outpatient setting. A scheme which may reduce the demands on the healthcare system (Kiastersky et al. 1998). However, it has been cautioned that even low risk' febrile neutropenic patients are prone to rapid and serious alterations in their medical condition and thus require close observation.

Neutropenia and febrile neutropenia lead to dose reduction dose delay

The treatment of chemotherapy-sensitive solid tumours and haematological malignancies usually involves cycles of intensively dosed chemotherapy. Following chemotherapy-induced toxicity, it is common practice in clinical oncology to reduce the dose of chemotherapy or to delay of the next cycle. Thus, in practice, many patients continue to receive chemotherapy at doses lower than found to be effective in clinical trials.

**Dose modification compromises treatment outcome**

Evidence that dose intensity is an important of ensuring optimal clinical outcome is growing. In retrospective analyses conducted in the 1980s, Hryniuk and colleagues showed clear relationship between dose intensity and clinical outcome in breast cancer patients (Hryniuk and Levine 1986). Recently published results, using a single scale to compare the dose intensity of chemotherapy regimens in breast cancer, have confirmed the early findings (Hryniuk et al. 1998).

**Dose and amininistration**

**Established cytotoxic chemotherapy**

05 MU (5 micro gram) / kg/day

Myeloablative therapy followed by BMT
Starting dose 1.0 MU (10 micro gram)/kg/day given as a 30 minutes or 24 hours IV or SC infusion. Once nadir has passed, the daily dose of filgrastim should be titrated against the neutrophil response as follows. Neutrophil count > 1.0 x 10^9/L for further 3 days, then discontinue the drug.

**PPBC mobilization**

When used alone the dose is 1.0 MU/kg/day for 6 consecutive days. When used with myelosuppressive chemotherapy the dose is 0.5 (5 micro gram)/kg/day until the expected neutrophil nadir has passed.

**Contraindications of use of filgrastim**

1. Should not be used to patient known to be hypersensitive to the product or its constituents.
2. It should not be used to patient with established congenital neutropenia (kost Mann's syndrome).

**Hazards of filgrastim**

1. Administration of filgrastim at the recommended dose. dosage is frequently associated with musculoskeletal pain.
2. Less frequently adverse events include mild or moderate dysuria.
3. Transient decrease in blood pressure, not requiring clinical treatment have been reported occasionally.
4. White cell count of 100 x 10^9/L or greater have been observed in less than 5% of patient receiving filgrastim at above 0.3 MU (3 MG) /kg/day. No adverse events directly attributed to this degree of leucocytosis been reported.

Bibliography