[Intervention Protocol]

Pegylated granulocyte colony stimulating factor versus non-pegylated granulocyte colony stimulating factor for patients after hematopoietic stem cell transplantation

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To compare the efficacy and safety of pegylated G-CSF versus non-pegylated G-CSF for patients after HSCT.

BACKGROUND

Description of the condition

Since the first bone marrow transplant in 1958 by Georges Mathé, a French oncologist, and the use of bone-marrow-derived stem cells pioneered by a team led by E. Donnall Thomas at the Fred Hutchinson Cancer Research Center (Seattle, WA, US) from the 1950s through the 1970s, there have been many advances in this field. One of the major breakthroughs was the discovery of granulocyte colony stimulating factor (G-CSF).

G-CSF is a glycosylated hormone produced by the human body for the function of granulocyte production stimulation. The production of this hormone is controlled by the gene located on chromosome 17q21-22. The first successful purification of this hormone was in 1985 (Nomura 1986; Welte 1985) following the successful purification of the G-CSF from rat in 1983 (Nicola 1983). G-CSF was initially used to treat and shorten chemotherapy-induced neutropenia. However, it was later found to be effective in increasing the number of circulating hematopoietic stem cells and enabling the adequate number of stem cells to be collected from the peripheral blood using an apheresis machine. Hence peripheral blood stem cells have emerged as another source of hematopoietic stem cells with less pain and less postdonation restriction compared with conventional bone marrow transplantation (Siddiq 2009). The term "bone marrow transplantation" was then changed to 'hematopoietic stem cell transplantation' (HSCT).

Shortly after HSCT, morbidity and mortality is mainly dependent on how soon the engraftment occurs. The sooner the engraftment takes place, the lower the risks of morbidity and mortality due to neutropenic sepsis. This situation is similar to postchemotherapy neutropenia. G-CSF was found to have shortened the engraftment time and thus reduced hospitalization period, morbidity and mortality post HSCT (Dekker 2006; Schmitz 1995; Sung 2007). Hence, G-CSF is indicated in patients following HSCT to promote engraftment, which is another important use for G-CSF in addition to peripheral blood stem cell mobilization. However, the initial form of recombinant human G-CSF has a very short half-life and needs to be administered daily or even twice daily in order to achieve a sustained effective blood concentration. Therefore, a new form of recombinant human G-CSF, pegylated G-CSF, with a longer half-life and higher potency, has been developed to overcome this problem.

Description of the intervention

Currently there are only a few non-pegylated recombinant human G-CSF available commercially (i.e. filgrastim, lenograstim and nartograstim). All of the G-CSFs are administered subcutaneously and have a short half-life (with the exception of nartograstim).

Filgrastim (Neupogen®, Amgen Inc.) is a non-glycosylated G-CSF with one additional amino acid, methionine, at its *N*-terminal compared with human G-CSF. It is derived from *Escherichia coli* (*E. coli*) and was the first recombinant human G-CSF approved for clinical use in the US (Molineux 2004). The half-life of filgrastim is about three and a half hours. It is eliminated via a static phase that correlates with renal excretion, which is the predominant route, and a phase that varies with the white cell count because of neutrophil receptor-mediated endocytosis and degradation.

Lenograstim (Granocyte®, Chugai Pharmaceutical Co. Ltd.) is an authentic glycosylated recombinant human G-CSF that is derived from Chinese hamster ovary cells. Its half-life at steady state is about three to four hours if given subcutaneously but only one to two hours if given intravenously. As glycosylated G-CSF is more stable than non-glycosylated G-CSF in terms of temperature, pH and degradation by proteases in vitro, lenograstim can be transported and stored at room temperature. Glycosylated G-CSF is also more potent than non-glycosylated G-CSF on a weight for weight basis. Despite the physical chemistry and bioactivity advantages, there are no prospective randomized control trials to show the superiority of lenograstim over filgrastim after HSCT. However, there are two retrospective studies comparing lenograstim versus filgrastim after HSCT (Huttmann 2005; Kim 2003). One of the studies showed no difference in terms of effectiveness between these two G-CSFs (Huttmann 2005) but the other favored filgrastim in reducing the duration of neutropenia, thrombocytopenia and days of G-CSF administration, leading to earlier hospital discharge (Kim 2003). The differences observed in this study could be attributed to gender differences as lenograstim has been reported to be more effective in mobilizing stem cells in males than in females (Fischer 2005; Ings 2006).

Nartograstim (Neu-Up®, Kyowa Hakko Kirin Co. Ltd.) is a non-glycosylated mutated recombinant human G-CSF derived from *E. coli*. It has two to four times higher specific activity, and more physicochemical, biologic, and pharmacokinetic stability, than filgrastim (Okabe 1990). Its half-life is about nine hours and one hour via subcutaneously and intravenously injection, respectively. Currently pegfilgrastim and pegnartograstim are the only two pegylated forms of recombinant human G-CSF.

Pegfilgrastim (Neulasta®, Amgen Inc. and Peglasta®, Kyowa Hakko Kirin Co. Ltd.) is the pegylated form of filgrastim. It is a product of covalent conjugation between filgrastim and a monomethoxypolyethylene glycol (PEG) molecule at the *N*-terminal of the methionyl residual. Pegfilgrastim has limited renal clearance owing to the increased molecular weight of the PEG group. Hence, neutrophil-regulated kinetics become the primary route of clearance (> 99%) for pegfilgrastim. The half-life of pegfilgrastim ranges from 15 to 80 hours after subcutaneous injection for a patient with a normal neutrophil count. For a patient who is neutropenic following chemotherapy, the drug concentration remains in the therapeutic range initially and starts to fall as the neutrophil count recovers (Fenk 2006; Mey 2007; Zamboni 2003).

Pegnartograstim (synonym: Ro-25-8315, Kyowa Hakko Kirin Co.