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A randomized double blind control trial comparing filgrastim and pegfilgrastim in cyclophosphamide peripheral blood hematopoietic stem cell mobilization

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ABSTRACT

There are few randomized trials comparing filgrastim and pegfilgrastim in peripheral blood stem cell mobilization (PBSCM). None of the trials studied the effects of the timing of pegfilgrastim administration on the outcomes of mobilization. We conducted a randomized triple blind control trial comparing the outcomes of filgrastim 5 μg/kg daily from day 3 onwards, 'early' pegfilgrastim 6 mg on day 3 and 'delayed' pegfilgrastim 6 mg on day 7 in cyclophosphamide PBSCM in patients with no previous history of mobilization. Peripheral blood (PB) CD34+ cell count was checked on day 8 and day 11 onward. Apheresis was started when PB CD34+ ≥ 10/μl from day 11 onward. The primary outcome was the successful mobilization rate, defined as cumulative collection of $\geq 2 \times 10^6$/kg CD34+ cells in three or less apheresis. The secondary outcomes were the day of neutrophil and platelet engraftment post transplantation. There were 156 patients randomized and 134 patients' data analyzed. Pegfilgrastim 6 mg day 7 produced highest percentage of successful mobilization, 34 out of 48 (70.8%) analyzed patients, followed by daily filgrastim, 28 out of 44 (63.6%) and day 3 pegfilgrastim, 20 out of 42 (47.6%) ($p = 0.075$). Pegfilgrastim day 7 and daily filgrastim reported 1.48 ($p = 0.014$) and 1.49 ($p = 0.013$) times higher successful mobilization rate respectively as compared to pegfilgrastim day 3 after adjusting for disease, gender and exposure to myelotoxic agent. Multiple myeloma patients were three times more likely to achieve successful mobilization as compared to acute leukemia or lymphoma patients. Pegfilgrastim avoided the overshoot of white cells compared to filgrastim. There was no difference in the duration of both white cells and platelet recovery post transplantation between the three interventional arms.

This trial was registered with National Medical Research Registry as NMRR-10–755-6906.

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1. Introduction

Granulocyte colony stimulating factor (GCSF) is an endogenous glycosylated hormone with a molecular weight of about 19 kDa. The first recombinant GCSF approved for clinical usage is filgrastim. It is a non-glycosylated GCSF derived from *Escherichia coli* with one additional amino acid, the methionine, at its N-terminal. It has a short half-life of about 3 1/2 hours. Pegfilgrastim is a pegylated form of filgrastim, with covalent conjugation between the N-terminal methionyl residual of filgrastim and a 20 kDa mono-methoxypolyethylene glycol molecule. In contrast to filgrastim which is eliminated mainly via renal excretion, pegfilgrastim is eliminated via neutrophil receptor-mediated endocytosis and degradation. Hence, its half-life is much longer – 15–80 hours after a subcutaneous injection in a healthy subject – in comparison to filgrastim. Pegfilgrastim remains in the therapeutic range and only drop during neutrophil recovery in patient with post-chemotherapy neutropenia [1].

Besides the main usage in neutropenia, GCSF is also used in peripheral blood hematopoietic stem cell (PBSC) mobilization because it can increase the number of circulating hematopoietic stem cells by 58 times higher than the amount during steady state [2]. However, there were very few randomized trials comparing the effectiveness of filgrastim and pegfilgrastim in PBSC mobilization [3–9]. There was no clinical trial comparing the timing of pegfilgrastim against successful PBSC mobilization despite the concern that early administration of pegfilgrastim after chemotherapy (CT) will reduce the optimal drug level (as the chemotherapy-induced neutropenia has not set in) which could affect the mobilization. The higher cost of pegfilgrastim as compared to filgrastim has caused dilemma in deciding the choice of drug as there was no concrete evidence on the superiority of one drug against another. Hence, we conducted a clinical trial to compare the effectiveness of filgrastim and pegfilgrastim in PBSC mobilization.

2. Materials and methods

2.1. Study design and patient eligibility

This was a randomized controlled, triple blinded (investigator, subjects, and statistician), single center trial, carried out in Ampang Hospital, Selangor, Malaysia – the national referral center for hematological malignancies – from September 2010 to December 2012. The objective of this trial is to compare the effectiveness of filgrastim against pegfilgrastim in patients undergoing cyclophosphamide PBSC mobilization with respect to (1) successful mobilization and (2) neutrophil and platelet engraftment post-transplantation.

All patients admitted to Ampang Hospital for cyclophosphamide-GSCF PBSCM during the trial period were eligible to be enrolled as study patients. The exclusion criteria include (1) history of CT-GCSF or GCSF PBSC mobilization, and (2) inability or refusal to give written informed consent from self or legal representative. The study patients were randomly assigned to receive either one of the three intervention arms, i.e. (1) daily filgrastim dose of 5 μg/kg per day starting from day 3 of CT onward, (2) single pegfilgrastim dose of 6 mg on day 3, and (3) single pegfilgrastim dose of 6 mg on day 7. The patients were followed up until the primary and secondary end-point data were collected.

This study was approved by Medical Research and Ethics Committee, Ministry of Health Malaysia and registered under Malaysia National Medical Research Register (trial registry number: NMRR-10-755-6906). The Malaysian National Medical Research Register NMRR is a not-for-profit registry which complies with all the requirements specified by the International Clinical Trials Registry Platform (ICTRP) of the World Health Organization and the International Committee of Medical Journal Editors (ICMJE). The study was conducted according to Malaysian Good Clinical Practice Guideline which conforms to the ethical principles as specified in the Declaration of Helsinki. All participants were counseled and written informed consent was obtained for each participant prior to the enrollment. The access to primary clinical trial data was limited to the authors.

2.2. Randomization, blinding and interventions

A sequence for random allocation into three interventional arms was generated using Stata Intercooled software version 11.1. The information on the allocated intervention was concealed in a sealed opaque sequentially numbered envelope. The allocation concealment was prepared by the chief investigator without the knowledge of other investigators and the envelope was kept by the pharmacist in charge of drug preparation. Each study patient was given a unique patient number by the pharmacist according to the chronological order of enrollment into the study. The pharmacist opened the envelope with the sequential number matching the unique patient number and allocated the appropriate intervention according to the information stated in the envelope. The pharmacist prepared the interventional drug based on the random allocation sequence without acknowledging the treating doctor. A placebo was prepared using normal saline. All interventional drugs and placebo were prepared in identical 10 ml opaque syringes to mask the amount of the medication from the administrator. The patients were blinded from the type of treatment using placebo. The treating doctor was blinded from the treatment allocation by allocation concealment procedure and the use of placebo. Data entry and data cleaning was done by an independent research assistant not involved in any part of the patient care. Data analysis was performed by a biostatistician, blinded from the type of treatment arm by concealing the name of the treatment arm from the database.

On day 1 of CT, all study patients received cyclophosphamide 2 g/m^2, diluted in 250 ml normal saline and infused over 1 hour. Mesna 500 mg/m^2 diluted in 500 ml normal saline was given over 6 hours every six hourly on day 1 and day 2. The first dose of mesna was given 4 hours before the cyclophosphamide infusion. From day 3 onward, all study patients were given one of the interventional drugs via subcutaneous injection prepared in a 10 ml syringe administered at 6 pm every day until day 10. The content of the syringe was masked using opaque sticker. The first interventional arm was daily filgrastim of 5 μg/kg from day 3 to day 10 of CT, whereas the second and third interventional arms were single dose of pegfilgrastim 6 mg on day 3 and day 7 of CT

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