A Randomised Vehicle Controlled Multicenter Dose Finding Phase II Study of Glycosylated rhuG-CSF in 121 Patients after Bone Marrow Transplantation

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Recombinant DNA technology and gene cloning have made it possible to produce haemopoetic growth factors in sufficient quantities for therapeutic use over the last 5 years. Genetically engineered (recombinant) human granulocyte colony stimulating factor (rG-CSF) has been demonstrated to not only increase neutrophil counts as a consequence of induction of proliferation, but also to enhance their role as part of the defence mechanism of attacking bacteria and other micro-organisms that cause infection. Preparative regimens prior to autologous or allogeneic bone marrow transplant (BMT) cause profound and prolonged neutropenia. This period of neutropenia is frequently complicated by infection causing morbidity, and in some cases may be fatal. The management of this prolonged period of neutropenia requires expensive specialist nursing and antibiotic treatment. A reduction in the period of neutropenia would clearly be of benefit to the patient, but could also reduce the costs of BMT. It was, therefore, proposed to perform this dose-finding Phase II trial of G-CSF to evaluate the safety and efficacy of a range of rG-CSF doses in comparison with vehicle (control) on neutrophil recovery in patients who have undergone autologous or allogeneic BMT for malignant disease.

The rG-CSF used in this study is a product of Chugai Pharmaceutical Company Ltd, Tokyo, Japan. It was produced in Chinese hamster ovary cells after transformation with a vector containing G-CSF-cDNA derived from a human squamous cell carcinoma line that produces rG-CSF constitutively. The molecular weight of rG-CSF is approximately 20,000 daltons. It consists of 174 amino acids and has a carbohydrate moiety of approximately 4%. The purity of the final product is greater than 99%.

RESULTS
From August 1989 to July 1990, 121 patients (mean age 34.9:range 17-64 years) undergoing bone marrow transplantation for non-myeloid malignancies were entered from 12 participating centres from around the United Kingdom. The patients were randomised in blocks of 5 to receive once daily as a 30 minute intravenous infusion either the vehicle alone, 2, 5, 10 or 20 ug/kg/day of glycosylated rG-CSF. The randomised study medication was administered from day 1 following BMT until an absolute neutrophil count (ANC) of >1.0 x 10^9/litre for 3 consecutive days was reached, or to day 28 post-transplant which ever occurred first.

The majority of patients were male (84/121, 69%), and almost all patients were white (116/121, 96%). The primary diagnosis included Hodgkin’s disease (35/121, 29%), non-Hodgkin’s lymphoma (40/121, 33%), multiple myeloma (24/121, 20%), acute lymphoblastic leukaemia (18/121, 15%) and solid cancer (4/121, 3%). Almost all patients were able to carry on normal activity prior to BMT with a Karnofsky performance score of >80 in 93% of the patients. There were no significant differences in age, sex, race, underlying diagnosis or performance status between patient groups.
The majority of patients (102/121, 84%) underwent autologous BMT, whereas 19 (16%) patients received an allogeneic BMT, with no significant difference in the type of BMT among treatment groups. A total of 86 (71%) of patients received chemotherapy alone as the ablative regimen prior to BMT, whereas 35 (29%) of patients received a combination of chemotherapy and total body irradiation. The number of nucleated bone marrow cells at harvest ranged from $1.3 \times 10^8$ to $7.3 \times 10^8$/kg and there was no statistically significant difference in the mean number of nucleated bone marrow cells administered between the treatment groups.

In general the mean ANC showed a continuous decrease from pre-study levels during the first week following BMT; however, an increase from day 1 in mean ANC was observed on a single day (day 2) in both the 10 and 20 ug/kg groups. As can be seen in figure 1, the neutrophil counts were near 0 in all treatment groups at day 7.

![Figure 1](image)

FIG 1 - MEAN ABSOLUTE NEUTROPHIL COUNTS FROM TIME OF BMT FOR FIVE PATIENT GROUPS RECEIVING EITHER VEHICLE ALONE (CONTROL) OR 2, 5, 10 OR 20 ug/kg/DAY OF rG-CSF

The median recovery time to an ANC of $>0.5 \times 10^9$/litre in the vehicle group was day 19, compared with day 17 in the 2 ug/kg group, day 14 in the 5 and 10 ug/kg groups, and day 13 in the 20 ug/kg group (Fig 2). The recovery patterns were statistically significantly different among all 5 groups ($p < 0.001$), with a significant dose response relationship ($p = 0.014$). All 4 rG-CSF dose groups showed significantly shorter times to recovery compared with the vehicle group ($p < 0.042$). The time to recovery was also significantly shorter in the 20 ug/kg group than in the 2 ug/kg group ($p = 0.037$). No other significant differences were detected between dose groups.
FIG 2 - TIME TO ABSOLUTE NEUTROPHIL COUNT OF > 0.5 x 10^9/LITRE FROM TIME OF BMT FOR FIVE PATIENT GROUPS RECEIVING EITHER VEHICLE ALONE (CONTROL) OR 2, 5, 10 OR 20 ug/kg/DAY rG-CSF.

A similar difference was seen in the median recovery time to an ANC of > 1 x 10^9/litre for 3 consecutive days. The median time for the vehicle group was day 26, compared with day 19 in the 2 ug/kg group, day 17 in the 5 and 10 ug groups, and day 14 in the 20 ug/kg group.

Overall, a total of 100 patients (83%) experienced at least one infection during the study period, 78 of these patients presented with infection in the first week after bone marrow transplantation when the neutrophil count was falling rapidly following the ablative treatment. The rate of infection was similar in the control patients receiving vehicle only, and in those receiving rG-CSF.

The median time to discharge from hospital was day 36 for patients in the vehicle group, compared with day 23 in the 2 and 5 ug/kg groups, day 25 in the 10 ug/kg group, and day 21 in 20 ug/kg/group. The period of hospital stay was significantly longer for patients in the vehicle group, compared with all 4 groups of patients receiving rG-CSF (p < 0.001).

The rG-CSF was well tolerated and the adverse experiences were similar in the vehicle group as in those receiving rG-CSF. In the first 100 days after bone marrow transplantation there were 15 (13%) deaths which evenly spread throughout all groups, and likewise, there was no evidence of a higher relapse rate in any particular group.

CONCLUSION
In this study, the 4 dose levels of rG-CSF (2, 5, 10 and 20 ug/kg) were shown to be effective in reducing the time to neutrophil recovery compared with vehicle. This enabled patients to be discharged home earlier in the rG-CSF groups. At all dose levels, rG-CSF appeared to be safe and was generally well tolerated. The overall incidence of adverse experiences were similar for all treatment groups. A dose of 5 ug/kg of rG-CSF daily is recommended on the basis of this study on grounds of efficacy, safety, as well as cost benefit considerations for further trials of rG-CSF after bone marrow transplantation.