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Research Article

A Randomized Study Comparing the Effects of G-CSF and G-CSF/GM-CSF for the Mobilization of Peripheral Blood Stem Cells by Mitoxantrone and High-Dose Cytarabine Chemotherapy

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ABSTRACT

We investigated the efficiency of mitoxantrone (MIT) and high-dose cytarabine (Ara-C) chemotherapy followed by G-CSF and G-CSF/GM-CSF treatments for the mobilization of peripheral blood stem cells (PBSCs) in patients with leukemia and lymphoma. MIT was intravenously injected at 10 mg/(m^2·d) for 2 to 3 days, followed by Ara-C injected intravenously at 2 g/m^2 every 12 hours for 1 to 2 days. When white blood cell count recovered from the lowest value, 5 to 7.5 μg/ (kg·d) G-CSF was administered in 23 patients for 5 to 7 successive days. Another 27 patients received 3-5 μg/ (kg·d) G-CSF and 3-5μg/ (kg·d) GM-CSF. Autologous peripheral blood mononuclear cells were collected. Levels of CFU-GM and $CD34^+$ cells were determined after unfreezing. The $CD34^+$ cells and CFU-GM yields of 27 patients in G-CSF plus GM-CSF combination group [$(8.79\pm3.11)\times10^6$/kg, $(3.52\pm1.34)\times10^5$/kg, respectively] were significantly higher than those of patients receiving G-CSF alone (n=23) [$(6.14\pm2.06)\times10^6$/kg, $(2.03\pm1.06)\times10^5$/kg, respectively ($P < 0.05$)]. No obvious changes of T lymphocyte subsets in patients were observed when using G-CSF/GM-CSF, but levels of $CD34^+$ cells increased gradually ($P>0.05$). The end-point separation blood volume was all above trebling TBV. No severe complications were observed during the mobilization and collection. Autologous PBSCT obtained quick hematopoietic reconstitution. In conclusion, MA chemotherapy combined with G-CSF alone and G-CSF/GM-CSF can safely and effectively mobilize autologous PBSCs, while G-CSF plus GM-CSF is superior to G-CSF alone. Large volume leukapheresis is an important method to enhance the production rate of stem cells and decrease harvesting time.

Introduction

In the present decade, peripheral blood stem and progenitor cells have been widely used as a source of hematopoietic stem cells as they provide rapid and sustained hematologic reconstitution following autologous and allogeneic grafts. Autologous peripheral blood stem cell transplantation (PBSCT) for leukemia and lymphoma offers higher response rates and improved survival compared with conventional chemotherapy. However, successful autografting requires effective mobilization and rapid hematologic reconstitution [1, 2]. To obtain a sufficient harvest, stem cells can be mobilized into the peripheral blood using cytokines, cytotoxic chemotherapy, or a combination of both. Currently, peripheral blood stem cells (PBSCs) mobilization occurs by administering granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) alone or in combination with chemotherapy. Both cytokines differ in the number and composition of PBSCs and effector cells mobilized to the peripheral blood. Previous studies have shown a correlation between clinical outcome and graft composition [3-5]. It is generally recognized that G-CSF as a single agent mobilizes more $CD34^+$ cells than does GM-CSF

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[6]. Nevertheless, the use of these hematopoietic growth factors (HGF) was not well explored and particularly the minimal efficient dose for their concomitant administration following high-dose combination chemotherapy. We report here a randomized study comparing G-CSF to the association of G-CSF and GM-CSF.

Cytarabine has been combined with an anthracycline in the standard induction combination 7 + 3 for acute myeloid leukemia (AML) for more than three decades. High-dose cytarabine during induction or intensification improves the duration of complete remission (CR) and increases disease-free survival (DFS), especially in younger patients. Pavlovsky *et al*. report results of *in vivo* purging of autologous PBSCs using high-dose cytarabine prior to the harvest in AML in first CR, resulting in a 30-month DFS of 62% [7]. In December 2015, we started a MAG regimen for leukemia and lymphoma patients in first CR employing high-dose cytarabine combined with mitoxantrone, followed by G-CSF/GM-CSF for consolidation and mobilization before peripheral blood autograft. The purpose of this randomized study was to evaluate the safety and efficacy of high-dose chemotherapy plus G-CSF versus chemotherapy plus G+GM in patients with leukemia and lymphoma who were undergoing chemo-mobilization. We also determined the efficiency and safety of continuous processing of the patients' total blood volume.

Patients and Methods

I Patient Eligibility

Of 50 patients with leukemia and lymphoma in CR who received consolidation and mobilization treatment at our institution from November 2015 to December 2020, 47 received autologous PBSCT. All patients with a histologically confirmed history of hematological malignancies and requiring a high dose myeloablative chemotherapy with PBPCs rescue were eligible. Patients with the central nervous system or bone marrow involvement at the time of the relapse were excluded. They were diagnosed according to the FAB classification criterion and new WHO proposals. Complete remission and complete response were defined according to the FAB criteria [8, 9]. Thirty-two males and 18 females, averaged 31 years ranging from 7 to 56 years and weighted (54±17) kg, were recruited to the study. Among them, 21 patients had AML, 10 with M2, M1 and M5 each 4 cases, 3 with M4. 29 patients had non-Hodgkin lymphoma (NHL) (18 cases at stage II-III, 2 cases were respectively in the periods of IIIB and IVB, 4 case of small intestine lymphoma and 5 cases of ileocecal lymphoma). All of the patients that were recruited were in complete remission after conventional chemotherapy. No tumor cell infiltration was observed in bone marrow cytological examination. The functions of the main organs such as heart, lung, liver and kidney were normal. These patients also underwent an average of 6-course chemotherapy (4~8 courses) before the mobilization.

II MAG Mobilization Regimen

Mitoxantrone was intravenously injected at 10 mg/(m^2·d) for 2 to 3 days, followed by cytarabine intravenously injected at 2 g/m^2 every 12 hours for 1 to 2 days. When the white blood cell (WBC) count recovered from the lowest value, 5 to 7.5 μg/ (kg·d) G-CSF (produced by Kirin Company) was applied in 23 patients for 5 to 7 successive days. GM-CSF (2.5 μg/ kg·d), G-CSF (5 μg/ kg·d) were administered to an additional 27 patients in the morning or evening until the end of PBSCs harvesting. Fifty patients were chosen by random number table for G-CSF or G+GM-CSF treatment. All the patients were injected with dexamethasone (5mg, body mass < 40 kg) or 10mg, body mass > 40 kg) 3 hours prior to harvesting.

III Harvesting and Cryopreservation PBSCs [10-12]

PBSCs harvesting started when WBC>$2.5\times10^9 L^{-1}$, especially when $CD34^+$ cells≥1%, WBC were doubled. Standard apheresis procedures 1 or modified procedure 3 were chosen to undergo peripheral blood mononuclear cells (MNCs) separation by CS3000 plus blood cell separator. The end-point separation blood volume was determined by the total blood volume (TBV) and expectable MNCs out-put. The separated MNCs were counted, smeared, classified and dyed with trypan blue. Cold preservation 80 (CP-80) with 6.25% dimethylsulfoxide and 7.5% dextran and 6.25% human blood albumin were used as cryoprotective agents (provided by Shanghai Central Blood Station). The collection was cryopreserved at –80°C without programme-controlled freezing. The numbers of MNCs and $CD34^+$ cells were determined before cryopreservation.

IV Culture of Hematopoietic Progenitor Cells

MNCs were cultured for 14 days in a CO_2 incubator by the conventional method. CFU-GM assays were performed in a methyl-cellulose-based clonogenic assay. The colonies were counted under an inverted microscope (CFU-GM≥40 cells as one colony unit).

V Determination of $CD34^+$Cells and T Lymphocyte Subsets

MNCs were separated in PBSCs fluid and mixed with FITC-labeled $CD34^+$, CD3 and CD8 monoclonal antibodies as well as CD4PE-labeled CD4 monoclonal antibody (BD Company, USA) at 4°C for 30 minutes. 5×10^5 cells were determined and $CD34^+$, CD3, CD4 and CD8 were determined by XL flow cytometer (Coulter Company, USA). The $CD34^+$ level and T lymphocyte subsets were calculated.

VI Supportive Therapy

Patients were maintained in a laminar air flow or positive pressure room from the first day of hospitalization until discharge. They received oral norfloxacin and antifungal prophylaxis in the form of oral fluconazol. For fever ≥37.8°C all patients had cultures from blood and other sites as clinically indicated. Transfusions were given to maintain the haemoglobin above 100 g/L and the platelet count above $2.0\times10^{10} L^{-1}$. Antibiotics were given as prophylaxis when WBC<$1.0\times10^9 L^{-1}$. Ten percent calcium gluconate was injected intravenously once to patients' that displayed hypocalcemia symptoms, including numbness of the mouths and lips.

VII Pretransplant Regimens

Modified busulfan (Bu)/ cyclophosphamide (Cy) regimen was applied in 13 cases of AML and 14 cases of ALL as described previously [13-

15]. Bu was taken orally at 1mg/kg, and once every 6 hours on days -6, -5. Cy was injected intravenously at 1.8g/(m^2·d) on days -4, -3. Ara-C was injected intravenously at 2g/(m^2·d) on days -7. Hydroxycarbamide was taken at 2g/m^2, once every 12 hours, on days -9, -8. Me-CCNU was taken orally at 250 mg/m^2 on days -2. MAC regimen was carried out in 4 cases of AML. Melphalan was taken orally at 180mg/m^2 on days -2. Ara-C was taken at 1g/(m^2·d) on days -2, -1. Cy was taken at 1.8g/(m^2·d) on days -2, -1. BEAC/CBV regimen was carried out in 15 cases of NHL, 4 cases of HL, and 2 cases of ALL. The BEAC regimen that includes BCNU was injected intravenously at 300mg /m^2 on days -6. VP-16 was intravenously injected at 100mg /m^2 once every 12 hours on days -5, -4, -3 and -2. Ara-C was injected intravenously at 100mg /m^2 once every 12 hours on days -5, -4, -3 and -2. Cy was injected intravenously at 1.5g/(m^2·d) on days -5, -4, -3 and -2. The CBV regimen consists of Cy taken at 1.5g/(m^2·d) on days -6, -5, -4 and -3, BCNU at 300mg/m^2 on days -6, and VP-16 at 150mg/m^2 once every 12 hours on days -6, -5, -4.

VIII PBSCs Unfreezing and Back Perfusion

Autologous PBSCs were reinfused 36 to 48 hours after pre-disposal treatment. The frozen package was quickly placed into a 40°C water bath to unfreeze and autologous PBSCs were intravenously back infused without filtration. MNCs count and trypan blue drying were performed to determine levels of CFU-GM and $CD34^+$ cells after unfreezing.

IX Statistical Analysis

Quantity parameters were made using Mean±SD. Groups′ comparisons of continuous data were analysed according to Student’s t-test. P≤0.05 was considered statistically significant.

Results

I Changes of $CD34^+$ Cell and T Lymphocyte Subset Before and After Mobilization

Without hematopoietic growth factors (HGF), the percentage of $CD34^+$ cells in the peripheral blood of the patients was 0.054±0.032%. The levels of $CD34^+$ cells increased to 1.77±0.79% after G-CSF/GM-CSF treatment compared to with or without using HGF (P<0.001). The $CD34^+$ cells and CFU-GM yields in C-CSF plus GM-CSF combination group was 8.79±3.11×10^6/kg, and 3.52±1.34×10^5/kg, respectively (n=27). These were significantly higher than those in the G-CSF only-treated group (n=23) [(6.14±2.06)×10^6/kg, (2.03±1.06)×10^5/kg, respectively (P<0.05)]. The levels of CD4/CD8 peripheral blood cells in patients with leukemia and lymphoma were abnormal (<1) irrespective of hematopoietic factors used. Although $CD34^+$ cells increased gradually (P>0.05), there were no obvious changes in T lymphocyte counts in patients that were administered G-CSF/GM-CSF.

II PBSCs Mobilization and Harvesting

Fifty patients received 13.41±3.48 days of chemotherapy on average. The WBC decreased to its lowest level at 0.60±0.43×10^9L^{-1}. G-CSF and GM-CSF were also administered on 13.83±4.35 and 6.15±1.63 successive days, respectively. The WBC increased to 9.77±4.54×10^9L^{-1} on day 17.88±4.07 after chemotherapy. PBSCs harvesting started when the percentage of peripheral blood $CD34^+$ cells was 1.77±0.79%. Circulation blood volume was 10 to 16L (end-point separation blood volume was all above 3 TBV). Thirty-eight to fifty cases reached a $CD34^+$ cell threshold dosage required by hematopoietic reconstruction in one harvesting. Each case was harvested twice. Data of autologous PBSCs in these two harvestings are shown in (Table 1).

Table 1: Autologous PBSCs harvesting of 50 patients ($\bar{x}$±s).

	Circulating Blood Volume (ml/kg)	Blood Flow Velocity (ml/min)	Time (min)	End-point Separation Blood Volume (TBV)	MNC (×10^8/kg)	$CD34^+$ cells (×10^6/kg)	CFU-GM (×10^5/kg)
The First Time	219.70±33.85	57.0±10.6	218.67±30.33	3.39±0.37	3.61±2.53	4.37±2.15	2.09±1.59
The Second Time	186.86±31.50	60.2±12.3	210.38±40.79	3.57±0.41	2.53±1.66	3.97±2.48	1.43±1.37
Total					5.84±2.44	7.48±3.40	2.89±2.56

PBSCs: Peripheral Blood Stem Cells; MNCs: Mononuclear Cells; CFU-GM: Colony-Forming Units of Granulocytes/Macrophage.

III PBSCs Mobilization-Relative Adverse Effects

II~III degree hair loss was seen in all the patients. Blood platelets decreased by 56.43±25.48×10^9L^{-1}. Infective fevers (37.8℃~41.0℃) occurred in 34 patients and were treated with antibiotics. Patients initially received broad-spectrum intravenous antibiotics, later individually modified according to microbial culture and sensitivity data. The side effects of G-CSF and GM-CSF were mild and reversible that were easily controlled with paracetamol or steroids. Bone pain (mainly in the lumbosacral region) occurred in 19 patients when WBC rapidly increased.

IV PBSCs Back-Perfusion Volume

PBSCs were cryopreserved at -80℃ without programme control for 2.0~6.5 months. The cell recovery rate was 88.5±6.9%. Trypan blue exclusion rate was 91.7±4.9%. The back perfusion volume of MNCs, $CD34^+$ cells and CFU-GM yields were 5.27±2.46×10^8/kg, 6.88 ±3.63×10^6/kg, and 2.59 ±2.37×10^5/kg, respectively.

V Hematopoietic Reconstitution After Transplantation

IV degree myelosuppression was seen in 47 cases of autologous PBSCT. WBC decreased to zero in all of the recipients. This condition lasted for 6.39±2.43 days. The lowest level of blood platelets was (24.12±11.37)×10^9L^{-1}. The hematopoietic functions in all patients achieved satisfying reconstruction in bone marrow puncture examination

3 to 4 weeks after transplantation. No hematopoietic function disorders were seen after the follow-up. None of the 47 patients died of procedure-related complications during transplantation.

Discussion

Since 1992, Sheridan initially reported that peripheral blood stem cells could be successfully mobilized with G-CSF followed by autologous PBSCT [16]. Autologous PBSCT has been used to treat malignant tumors, especially malignant blood diseases. $CD34^+$ cells are regarded as a marker for early-stage multipotential hematopoietic stem cells. These cells account for about 1.5% of the total normal human bone marrow mononuclear cells in the body. They are rarely found within peripheral blood cells [17, 18]. Bone marrow stem cells mobilized by drugs are able to induce their proliferation and release them into peripheral blood, where the stem cells are collected for transplantation. PBSCs mobilization is required to obtain enough $CD34^+$ cells and reduce PBSCs harvesting times [19, 20]. The mobilization efficiency is closely related to the selection of high-efficiency, low-toxicity regimen, the timing of mobilization and harvesting as well [21, 22]. If it is efficient, this could reduce harvesting times and pain associated with the procedure.

In this study, 50 patients with leukemia and lymphomas were treated with high-dose arabinosylcytosin and mitoxantrone, followed by G-CSF/GM-CSF per day. The MAG regimen was used for the mobilization of autologous PBSCs. G-CSF and GM-CSF were given subcutaneously when WBC increased after the remission of myelosuppression caused by chemotherapy. This could increase the release of $CD34^+$ cells in circulation. At the same time, harvesting of larger volumes can be performed to obtain sufficient levels of $CD34^+$ cells. T lymphocytes are important for immunity and transplantation. They play a crucial role during the recovery of the immune system after autologous PBSCT. T lymphocytes are determined by FACS. These results showed that the proportion of T lymphocytes in patients could be decreased and reversed with or without G-CSF.

Levels of $CD34^+$ increased by 33-fold in 50 patients before mobilization (0.054±0.032%) and before the first PBSCs harvest (1.77±0.79%). In two successive harvestings, the volumes of MNCs, $CD34^+$ cells, and CFU-GM obtained were $5.84\pm2.41\times10^8$/kg, $7.48\pm3.40\times10^6$/kg, and $2.89\pm2.56\times10^5$/kg, respectively. The indexes required by autologous PBSCT hematopoietic function recovery were $2\sim3\times10^8$/kg, 2.0×10^6/kg, 1.0×10^5/kg for MNC, $CD34^+$ cells, and CFU-GM, respectively [23, 24]. The increase of PBSCs after chemotherapy is associated with the degree of myelosuppression by chemotherapy [24, 25]. Patients' receiving MA chemotherapy displayed stronger myelosuppressive effects. After the remission of myelosuppression, $CD34^+$ cells are able to enter the division pool, amplify and differentiate. These processes can be enhanced by the addition of G-CSF and GM-CSF. G-CSF and GM-CSF have a synergistic effect on the proliferation of hematopoietic stem /progenitor cells [1, 2]. A rapid increase in WBC levels after these treatments can lead to a larger harvest of MNCs. Levels of $CD34^+$ cells and CFU-GM in patients (n=27) administered C-CSF plus GM-CSF combination group were significantly higher than those receiving G-CSF alone (n=23). These observations suggest that MA chemotherapy, when combined with G-CSF alone or G-CSF plus GM-CSF, can safely and effectively mobilize autologous PBSCs, while G-CSF plus GM-CSF is superior to G-CSF alone. The delay of giving hematopoietic factors can lead to synchronous effects during mobilization [26, 27].

The dexamethasone administered preferentially to mobilized patients should also stimulate hematopoiesis in synergy with HGF. The role of glucocorticoids, especially dexamethasone, on the proliferation of hematopoietic progenitors has been suggested *in vitro* [28]. Hematopoietic factors were given upon increases in WBC counts to synchronize the mobilization of CFU-GM into the peripheral blood. Currently, harvesting should be started when WBC counts are recovered to $1.0\times10^9L^{-1}$ or $2.5\times10^9L^{-1}$, and separation performed when WBC recovers to $4.0\sim5.0\times10^9L^{-1}$ [29, 30]. Therefore, our observations suggest that it may be advantageous to start separation when WBC counts doubled and when the percentage of $CD34^+$ cells is >1%. Large-volume leukapheresis (LVL) differs from standard leukapheresis by increased blood flow and an altered anticoagulation regimen. LVL is an important method to improve the production rate of stem cells and decrease the times of harvesting over the past years.

CS 3000 plus blood cell separator can separate the patients' blood under large-volume circulation. It can also increase the operating time to increase the harvesting volume of PBSCs. At the same time, large-volume harvesting can also affect mobilization [31-33]. The findings of this study showed that trebling TBV could obtain the threshold dosage required by transplantation and that the hematopoietic function recovered after transplantation. Many factors can impact autologous PBSCs mobilization and their effects on harvesting efficacy. In a number of cases of this study (2 cases of AML), the MNCs and $CD34^+$ cells did not reach the threshold during two successive harvestings. This may be due to an older patient population and severe myelosuppression. The peripheral hemogram of the AML patient recovered very slowly after MAG regimen mobilization, and the CFU-GM did not rebound. Levels of $CD34^+$ cells can decrease with each successive chemotherapy leading to a poor quantity and quality of the hematopoietic stem cells and thereafter failing mobilization and transplantation.

Autologous PBSCs of all the 50 patients in this group were cryopreserved at -80°C without programme control. After thawing, there was a recovery in the cell activity and a higher recovery rate. After PBSC-supported large-dose chemotherapy with transplantation as a pretreatment, all the cells were back infused into the patients once or twice. Autologous PBSCT obtained quick hematopoietic reconstitution. Neutrophil levels increased up to $0.5\times10^9L^{-1}$ on day 15.6±3.9 post-transplantation. Levels of blood platelets also increased to $2.0\times10^{10}L^{-1}$ on day (18.7±6.4) post-transplantation. No death occurred during transplantation. However, the long-term disease-free survival rate after transplantation remains to be determined.

Ethical Approval

The study was approved by the Ethics Committee of the hospital.

Consent

Written informed consent was obtained from all patients.

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