

rhTPO combined with chemotherapy and G-CSF for autologous peripheral blood stem cells in patients with refractory/relapsed non-Hodgkin's lymphoma

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Objective: The mobilization and collection of sufficient autologous peripheral blood stem cells (APBSCs) are important for the fast and sustained reconstruction of hematopoietic function after autologous transplantation. This study aims to evaluate the mobilization effect and safety of thrombopoietin (TPO) combined with chemotherapy + G-CSF for APBSCs in patients with refractory/relapsed non-Hodgkin's lymphoma.

Methods: A total of 78 patients were included in the present study. After receiving mobilization chemotherapy, all patients were randomly divided into two groups: TPO group (n=40), patients were given subcutaneous injection of rhTPO + G-CSF, and control group (n=38), patients were given subcutaneous injection of G-CSF. The primary endpoint was the total number of obtained CD34+ cells. The secondary endpoints were the mono-nuclear cell count, the proportion of target and minimum mobilization, the engraftment time of neutrophils and platelets after APBSCT, the number of platelet and red blood cell infusions, the incidence of infectious fever and fever duration, and TPO-related side effects in patients.

Results: TPO participation significantly increased the total CD34+ cell count. A higher proportion of patients in the TPO group achieved the minimum and target CD34+ cells, when compared to the control group. TPO-related adverse events were not observed in either of these groups. In addition, there were no significant differences in engraftment time, the number of platelet and red blood cell transfusions, the incidence of infectious fever, and fever duration between these two groups.

Conclusion: TPO combined with chemotherapy + G-CSF can safely and effectively enhance the mobilization effect for APBSCs in patients with refractory/relapsed non-Hodgkin's lymphoma.

Keywords: recombinant human thrombopoietin, mobilization, non-Hodgkin's

Introduction

Autologous peripheral blood stem cell transplantation (APBSCT) has been widely used in the treatment of hematologic and solid tumours and autoimmune diseases, and has achieved significant efficacy, especially for non-Hodgkin's lymphoma (NHL).¹ The mobilization and collection of sufficient peripheral blood stem cells is a prerequisite to ensure the fast and sustained reconstruction of hematopoietic function after autologous transplantation in patients. In general, when the collected CD34+ cell count is greater than 5×10^6 cells/kg, the successful engraftment of neutrophils and platelets can be guaranteed in almost patients. In contrast, transplanted CD34+ cells of less than $1-2 \times 10^6$ cells/kg may cause

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delayed hematopoietic recovery or engraftment failure. Therefore, the collection of 2×10^6 CD34+ cells/kg is considered the minimal cell threshold for autologous stem cell transplantation.² Mobilization efficacy is influenced by many factors, including the disease type, patient age, disease stage, previous chemotherapy and treatment course, previous history of radiotherapy, mobilization program, and determination of whether the tumour cells have invaded the bone marrow.³ In particular, the number and intensity of previous chemotherapy and radiotherapy have the greatest impact on the mobilization effect of autologous stem cells. For most patients with refractory/relapsed NHL, mobilization efficacy may be poor due to multiple previous cytotoxic therapies. As reported in literature, nearly 30% of patients lose their chance for autologous stem cell transplantation, because the number of mobilized stem cells could not reach the minimum threshold (2×10^6 cells/kg).^{4,5} Therefore, the optimization of the mobilization program to increase the number of collected hematopoietic stem cells has important clinical significance.

For lymphoma patients, the commonly used standard mobilization regimen is chemotherapy combined with cytokines. These chemotherapy regimens include high-dose cyclophosphamide (CTX) and high doses of etoposide, ESHAP (a combination of etoposide, solu-medrone, high-dose Ara C, and cisplatin) and DHAP (a combination of dexamethasone, high-dose Ara C and cisplatin), with granulocyte colony stimulating factor (G-CSF) commonly used as the cytokine.^{6,7} Thrombopoietin (TPO) is one of the cytokinins, and is a plasma glycoprotein. TPO can affect the proliferation and maturation of megakaryocytes and release platelets in blood, which is the major physiological factor involved in the regulation of platelet levels in the circulatory system.⁸ It has been reported that recombinant human thrombopoietin (rhTPO) can enhance the mobilization of peripheral blood progenitor cells (PBPCs) in cancer patients.⁹ A recent cohort study also revealed that rhTPO augments the efficacy of intermediate-dose cyclophosphamide and G-CSF in the mobilization of peripheral blood stem cells in patients with multiple myeloma.¹⁰ Furthermore, a study has confirmed that the mobilization program of rhTPO combined with G-CSF and chemotherapy could improve the mobilization efficacy of peripheral blood stem cells in breast cancer patients.¹¹

Therefore, it is speculated that rhTPO can effectively improve the mobilization efficacy of peripheral blood stem cells in refractory/relapsed lymphoma. The present prospective, multi-center and randomized controlled clinical

study was conducted to evaluate the efficacy and safety of rhTPO in mobilizing peripheral blood stem cells in patients with relapsed/refractory lymphoma.

Materials and methods

Patients

The age of these 78 patients included in the present study ranged within 18–60 years old. These patients had refractory/recurrent NHL, and experienced failure of first-line chemotherapy. The initial diagnosis was confirmed by pathological biopsy and immunohistochemical staining. The Eastern Cooperative Oncology Group (ECOG) performance status scale was 0 or 1, showing normal organ function. The exclusion criteria were as follows: liver dysfunction (alanine aminotransferase or bilirubin greater than two times the normal upper limit); renal dysfunction (creatinine or urea higher than 1.5 times the normal upper limit); cardiac dysfunction (cardiac insufficiency over level II); respiratory failure; history of venous thrombosis; ischemic heart disease; stroke; arrhythmias, uncontrolled hypertension, or diabetes; severe diabetic retinopathy; previous treatment with high-dose chemotherapy, followed by autologous stem cell transplantation; the administration of cytokines other than G-CSF within three weeks prior to mobilization; uncontrolled active infection; rhTPO allergies; pregnant or lactating women; severe acute or chronic mental illness. This study was conducted in accordance with the declaration of Helsinki and approved by the Institutional Review Board of Shanghai General Hospital, and is registered under the Chinese Clinical Trial Registry (Trial registry number: ChiCTR-IIR-17010787). All patients provided a signed informed consent.

Study design

The present study was a prospective, multi-center and randomized controlled study. A total of 78 cases of NHL were enrolled from Shanghai General Hospital, Fudan University Affiliated Zhongshan Hospital, Shanghai Jiaotong University Affiliated Ruijin Hospital, and Shanghai Jiaotong University Affiliated Xinhua Hospital from July 2010 to July 2015. All patients received CTX and etoposide chemotherapy, with a detailed regimen of intravenous CTX (2.0 g/m^2) on day one and two, and VP16 (200 mg/m^2) on day one. All patients were randomly divided into two groups: TPO group and control group. For patients in the control group, $7.5 \text{ } \mu\text{g/kg}$ of G-CSF (Filgrastin, Kirin Do., Japan) was subcutaneously injected from day four to the

end of the stem cell collection. For patients in the TPO group, 15,000 U of rhTPO (Shenyang Sunshine Pharmaceutical Co. Ltd., China) was subcutaneously injected daily from day four to the end of the stem cell collection in addition to G-CSF. When the peripheral blood white blood cell count was $\geq 10 \times 10^9$ cells/L, mononuclear cells (MNCs) were collected from the peripheral blood using a cell separator (COBESpectra, USA), and the total blood volume processed for each patient varied between 10 L and 15 L. Flow cytometry was used for CD34+ cell counting. The collection was stopped when the number of CD34+ cells reached 5×10^6 cells/kg. The collection was performed for no more than three times. The mobilization was considered a failure when the collected CD34+ cells in any of the three attempts did not reach 2×10^6 cells/kg.

The collected peripheral blood MNCs were placed in an immortalization solution containing 10% dimethyl sulfoxide (DMSO) and phenol for cryopreservation at -80°C . According to CTC 3.0, the type, incidence, severity and duration of adverse events, as well as the correlation with TPO, were evaluated. The primary endpoint of the mobilization phase was the total CD34+ cell count. The secondary endpoints included the total mononuclear cell count, the number of days from mobilization to stem cell collection, the “optimal” rate (the proportion of patients with CD34+ cells $> 5 \times 10^6$ cells/kg) and “minimum” rate (the proportion of patients with CD34+ cells $> 2 \times 10^6$ cells/kg) of collection, and TPO-related side effects.

Patients with a collected cell number that reached the minimum cell number threshold (2×10^6 CD34+ cells/kg) for transplantation received the subsequent high-dose chemotherapy and autologous stem cell reinfusion. The BEAM regimen was used for conditioning (BCNC 300 mg/m^2 , d-6; etoposide 150 mg/m^2 , d-5-d-2; cytarabine 300 mg/m^2 , d-5-d-2; melphalan 140 mg/m^2 , d-1). At 48 hrs after the end of the pre-treatment, PBPC reinfusion was performed. In order to promote hematopoietic recovery, G-CSF ($5\text{ }\mu\text{g/kg/d}$) was subcutaneously injected when neutrophils were less than 0.5×10^9 cells/L, and until these were higher than 2×10^9 cells/L. No other cytokine types, including GM-CSF, IL-11, or TPO, were used. Patients with platelet counts $< 20 \times 10^9$ platelets/L or a tendency for bleeding were given platelet transfusions, while patients with hemoglobin (HB) of $< 80\text{ g/L}$ or severe symptoms of anemia were given red blood cell transfusions. All blood products were irradiated with 2.5 GY to inactivate the lymphocytes. The endpoints of the hematopoietic reconstitution phase were as follows:

time of platelet engraftment (defined as platelet count $> 20 \times 10^9$ platelets/L for seven consecutive days without platelet transfusion), time of neutrophil engraftment (defined as the absolute value of neutrophils $> 0.5 \times 10^9$ cells/L for three consecutive days), the number of platelet and red blood cell transfusions, and the proportion of patients with infectious fever and fever duration.

Statistical analysis

Statistical analysis software SAS 9.13 was used for the computation. All statistical tests were performed using two-sided tests. Differences with P -values ≤ 0.05 were considered statistically significant. For the comparison of demographic and clinical data between groups, Fisher's exact test was used for binary data or unordered multi-category data, two-sample rank sum test was used for ranked data or measurement data that are not normally distributed, and a Student's t -test was used for normally distributed data.

Results

Patient information

These 78 NHL patients were randomly divided into two groups: TPO group ($n=40$) and control group ($n=38$) (Table 1). The diagnoses of patients in the TPO group were as follows: diffuse large B-cell lymphoma (DLBCL, $n=32$), mantle cell lymphoma (MCL, $n=4$), follicular lymphoma (FL, $n=2$), and peripheral T-cell lymphoma (PTCL, $n=2$). The diagnoses of patients in the control group were as follows: DLBCL ($n=33$), MCL ($n=3$), FL ($n=1$), and Burkitt lymphoma ($n=1$). These two groups of patients had no significant differences in age, gender, clinical stage, disease status prior to mobilization, the determination of whether they received radiotherapy, bone marrow invasion, the number of courses of previous chemotherapy, and the number of different diagnoses. In the control group, five patients were considered to have failed stem cell mobilization, because the collected CD34+ cells did not meet the standard ($< 2 \times 10^6$ CD34+ cells/kg). Therefore, these patients did not receive the subsequent high-dose chemotherapy + autologous stem cell transplantation.

Mobilization efficacy of TPO

TPO participation did not significantly increase the mononuclear cell count, when compared to controls (6.89 vs 6.35×10^8 cells/kg, $P > 0.05$; Table 2). However, the total

Table 1 Patient characteristics

	TPO(n=40)	Control(n=38)	P-value
Mediam (range) Age	39(17–61)	41(18–62)	0.62
Gender (male:female)	27:13	25:13	0.98
Disease stage n (%)			0.53
I	0	0	
II	4(10%)	3(7.9%)	
III	16(40%)	17(44.7%)	
IV	20(50%)	18(47.4%)	
Disease status n (%)			0.63
CR	16(40%)	14(36.8%)	
PR	16(40%)	18(47.4%)	
PD	8(20%)	6(15.8%)	
Mediam (range)course of Prior chemotherapy	9(4–22)	8(5–16)	0.17
Prior radiotherapy n(%)	10(25%)	7(18.4%)	0.35
BM involvement n(%)	3(7.5%)	4(10.5%)	0.25

Abbreviation: TPO, Thrombopoietin.

Table 2 Results of PBPC collection

	TPO(n=40)	Control(n=38)	P-value
Total MNC cell($\times 10^6$ /kg)	6.89(4.2–17.9)	6.35(3.8–12.1)	0.33
Total CD34+ cell($\times 10^6$ /kg)	6.35(2.3–22.7)	3.3(0.5–16.2)	0.0054
Patients meeting successful target($>2 \times 10^6$ CD34+ cells/kg)(%)	100%	86%	0.035
Patients meeting optimal target($>5 \times 10^6$ CD34+ cells/kg)(%)	72.9%	41.3%	0.021
Median day to apheresis(d)	11(8–14)	11(7–15)	0.79
Number of apheresis	2 (1–3)	2 (1–3)	0.84

Notes: 100% and 86% (the red values) represent the percentage of patients meeting successful target ($>2 \times 10^6$ CD34+ cells/kg) in TPO group and Control group, respectively. $p < 0.05$. The difference between the two groups was statistically significant. 72.9% and 41.3% (red values) represent the percentage of Patients meeting optimal target ($>5 \times 10^6$ CD34+ cells/kg) in TPO group and Control group, respectively. $p < 0.05$. The difference between the two groups was statistically significant.

Abbreviation: PBPC, peripheral blood progenitor cells.

number of CD34+ cells in the TPO group was nearly twice of that in the control group (6.35 vs 3.3×10^6 cells/kg, $P < 0.01$). Furthermore, there was no mobilization failure cases in the TPO group, because the CD34+ cells collected from all patients met the minimal threshold ($>2 \times 10^6$ cells/kg), while five patients (14%) in the control group failed to meet this standard. The TPO group had a greater advantage in the optimal rate ($>5 \times 10^6$ CD34+ cells/kg) in the mobilization (72.9% vs 41.3%, $P < 0.05$). The days from the beginning of mobilization to stem cell collection were not significantly different, with 11 days in both groups. The numbers of apheresis were also not significantly different between the two groups. The total number of patients in the TPO group who received 8–14 injections had a median value of 11. The cost of the TPO mobilization cycle ranged within 8,504–14,882 yuan, with a median value of 11,693 yuan (equivalent to 1,131–1,984 euros,

with a median value of 1,558). Furthermore, TPO-related side effects were not observed during the mobilization.

Impact of TPO on hematopoietic reconstitution after autologous transplantation

The addition of TPO in the mobilization program had no effect on neutrophil engraftment time, with a median of 12 days in both groups (Table 3). The platelet engraftment time was slightly shorter in the TPO group, when compared to the control group, but the difference was not statistically significant (12 vs 14, $P > 0.05$). During the autologous transplantation phase, the TPO and control groups received a median of three and four times of platelet transfusions, respectively, and both groups received a median of four times of red blood cell transfusions. Furthermore, the

Table 3 Results of hematopoietic reconstitution

	TPO (n=40)	Control (n=33)	P-value
Neutrophil engraftment(d)	12(8–15)	12(8–14)	0.48
Platelet engraftment(d)	12(11–17)	14(10–16)	0.27
Platelet transfusion events	3(2–5)	4(3–6)	0.088
Red blood cell transfusion events	4(2–6)	4(2–8)	0.332
Patients with infectious fevers	42%	48%	0.93
Fever durations(d)	4(0–6)	3(0–5)	0.882

Abbreviation: TPO, Thrombopoietin.

proportion of patients with infectious fever was 42% and 48%, respectively, and the median day of fever was four days and three days, respectively, which was not significantly different.

Discussion

A successful APBSCT requires the infusion of the minimum amount of hematopoietic stem cells to ensure the completion of continuous hematopoietic reconstruction within a certain amount of time after high-dose chemotherapy. Several studies have shown that the number of hematopoietic stem cells infused and engraftment time are clearly correlated.^{12–14} The objective of the mobilization process is to collect a sufficient number of stem cells (i.e. a sufficient number of CD34+ cells), which is correlated to rapid hematopoietic recovery. At present, 2×10^6 CD34+ cells/kg has generally been considered the minimum threshold, and cases with a value lower than this standard may not achieve a fully sustained hematopoietic recovery. However, since the use of $\geq 5 \times 10^6$ CD34+ cells/kg was correlated to faster neutrophil and platelet recovery with little difference between patients, this number was considered the optimal target for autologous HSCT.¹⁵

Although chemotherapy plus G-CSF was effective for stem cell mobilization in most patients, a considerable number of patients still failed the mobilization. The most common cause of mobilization failure was previous chemotherapy with bone marrow toxicity.^{16,17} Recently, the deepening understanding of the biology of stem cell mobilization has enabled the application of many new strategies to improve the quantity and quality of production of stem cells, and reduce the risk of mobilization failure.¹⁸ Plerixafor is the most well-studied mobilization synergist, and is thereby the most widely applied. As an antagonist

for chemokine receptors, plerixafor combined with G-CSF is approved by the Food and Drug Administration (FDA) for PBSC mobilization in patients with NHL and multiple myeloma (MM), who failed the mobilization, or are predicted to have poor mobilization. In patients who failed the mobilization, 60% of NHL cases and 71% of MM cases have achieved successful re-mobilization using plerixafor.^{19–21} However, plerixafor is not yet commercially available in China, and its high price is expected to limit its wide application. Therefore, for patients with poor predicted mobilization efficacy (especially patients with refractory/relapsed NHL), the design of an alternative, efficient and inexpensive mobilization program has become a hotspot of APBSCT research, with the aim of increasing the number of collected hematopoietic stem cells, reducing the failure rate of mobilization, and ensuring that more patients have the opportunity for autologous transplantation.

The rhTPO is a full-length glycosylated thrombopoietin prepared from Chinese hamster by recombinant DNA technology, which has a pharmacological effect similar to endogenous TPO. Both in vitro and in vivo experiments have confirmed that rhTPO not only effectively enhances platelet levels, but also stimulates the growth of hematopoietic progenitor cells to increase their pluripotency.²² Animal experiments have also confirmed that the synergy of TPO and G-CSF greatly shortens the time for platelet, red blood cell and neutrophil generation, and speeds up the recovery of erythroid and megakaryocytic precursor cells in the bone marrow.²³ Somlo et al observed for the first time that rhTPO combined with G-CSF for mobilization in breast cancer significantly increased the number of collected CD34+ cells and shortened the platelet and neutrophil engraftment time during the autologous transplantation process, while reducing the amount of red blood cell and platelet transfusions.¹¹ The study conducted by Linker et al, which comprised of 134 patients with hematological malignancies, indicated that rhTPO participation in the mobilization reduced the number of collections.⁹ The cases included in the present study were all refractory/relapsed NHL patients, and most of them previously received many rounds of repeated cytotoxic chemotherapy, and were considered as a high-risk group with failure in mobilization. It was found that rhTPO was an effective mobilization enhancer that could significantly improve the mobilization effect for peripheral blood stem cells in relapsed/refractory NHL patients when combined with chemotherapy and G-CSF, resulting in an increase in CD34+ cell yield by nearly 50%. Furthermore,

the participation of rhTPO allowed a greater proportion of patients to achieve the target collection value. It was particularly important that all patients in the TPO group reached the minimum acquisition threshold, with no mobilization failure cases. All the patients in this group successfully underwent the subsequent high-dose chemotherapy and autologous stem cell transplantation, and the hematopoietic cells were successfully engrafted in all patients, with no cases of delayed engraftment or engraftment failure. In addition, TPO exhibited good safety, and no TPO-related adverse events occurred during the mobilization, such as excessive platelet increase or a thrombotic event.

The time of hematopoietic reconstitution after transplantation is significantly correlated with the number of CD34+ cell infusions. In the present study, although the number of collected CD34+ cells was higher in the TPO group at the transplant stage, the cases in the TPO group did not show a significant advantage in shortening the neutrophil and platelet engraftment time. The possible explanations for this observation are that five patients in the control group failed the mobilization and did not enter the autologous transplantation stage, which “optimized” the control group data, and the size of the included samples was relatively small. Therefore, future studies with a larger number of samples would be conducive to obtain a more objective conclusion. Also, it is important to evaluate the long-term safety of TPO therapy in further investigations, in which the TPO-related adverse events such as secondary carcinogenesis need to be monitored. In conclusion, the present study revealed that the participation of rhTPO, as a synergist of the mobilization of peripheral blood stem cells based on chemotherapy + G-CSF in refractory/relapsed NHL patients, significantly improved mobilization efficacy and safety. High quality mobilization can ensure post-transplantation hematopoietic reconstruction, which is expected to be used to some extent in patients with mobilization failure or a poor predicted mobilization result, as an alternative to plerixafor in China. This approach is worth promoting in clinical application.

Ethical approval

The present study was approved by the Institutional Review Board of Shanghai General Hospital, and is registered under the Chinese Clinical Trial Registry (Trial registry number: ChiCTR-IIR-17010787).

Informed consent

All patients provided a signed informed consent form.

Disclosure

The authors declare that they have no conflicts of interest in this work.

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