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Original Article

Recombinant human thrombopoietin prior to mobilization chemotherapy facilitates platelet recovery in autologous transplantation in patients with lymphoma: Results of a prospective randomized study

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Abstract

Background: Chemotherapy plus granulocyte colony-stimulating factor (GCSF) regimen is one of the available approaches to mobilize peripheral blood progenitor cells (PBPCs). It causes thrombocytopenia and delays leukapheresis. This study aimed to evaluate the role of recombinant human thrombopoietin (rhTPO) before mobilization chemotherapy in facilitating leukapheresis in patients with lymphoma.

Methods: In this randomized open-label phase 2 trial, patients were randomly assigned in a 1:2 ratio to receive mobilization with rhTPO plus GCSF in combination with chemotherapy (the rhTPO plus GCSF arm) or GCSF alone in combination with chemotherapy (the GCSF alone arm). The recovery of neutrophils and platelets and the amount of platelet transfusion were monitored.

Results: Thirty patients were enrolled in this study between March 2016 and August 2018. Patients in the rhTPO plus GCSF arm (n = 10) had similar platelet nadir after mobilization chemotherapy (P=0.878) and similar amount of platelet transfusion (median 0 vs. 1 unit, P=0.735) when compared with the GCSF alone arm (n = 20). On the day of leukapheresis, the median platelet count was 86 × 10^9/L (range 18−219) among patients who received rhTPO and 73 × 10^9/L (range 42−197) among those who received GCSF alone (P=0.982). After the use of rhTPO, the incidence of platelet count <75 × 10^9/L on the day of leukapheresis did not decrease significantly (30.0% vs. 50.0%, P=0.297). Platelet recovery after PBPC transfusion was more rapid in the rhTPO plus GCSF arm (median 8.0 days [95% confidence interval 2.9−13.1] to platelets ≥50 × 10^9/L vs. 11.0 days [95% confidence interval

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8.6−13.4], P=0.011). The estimated total cost of the mobilization and reconstitution phases per patient was similar between the two treatmtent groups (P=0.362 and P=0.067, respectively).

Conclusions: Our findings indicate that there was no significant clinical benefit of rhTPO use in facilitating mobilization of progenitor cells, but it may promote platelet recovery in the reconstitution phase after high-dose therapy.

Trial registration: This trial has been registered in Clinicaltrials.gov as NCT03014102.

Keywords: Recombinant human thrombopoietin; Mobilization; Lymphoma; Schedule

Introduction

High-dose chemotherapy with autologous peripheral blood stem cell transplantation (APBSCT) has become an important strategy with potential curative efficacy in various types of lymphomas.[1−4] The chemotherapy plus recombinant human granulocyte colony-stimulating factor (GCSF) regimen is one of the available approaches to mobilize peripheral blood progenitor cells (PBPCs) while minimizing the patients' disease burden before transplantation.[5,6] However, cytotoxic agents may cause thrombocytopenia, which usually occurs when mononuclear cell count has risen and leukapheresis is needed. Severe thrombocytopenia may preclude deep vein catheterization for PBPC collection and may cause delays in leukapheresis. Further, bleeding and other risks related to platelet transfusion for thrombocytopenia may further influence patient prognosis.

Recombinant human thrombopoietin (rhTPO) has been shown to regulate megakaryocyte development and platelet production.[7−9] Several clinical trials have demonstrated that rhTPO can enhance platelet recovery and relieve thrombocytopenia after myelosuppressive regimens.[10−13] In most of these studies, rhTPO was administered after the start of chemotherapy. However, Vadhan-Raj and colleagues evaluated the effect of rhTPO before the start of the doxorubicin plus ifosfamide regimen in patients with sarcoma.[10] They demonstrated the feasibility of rhTPO administered as a pre-dose before chemotherapy and suggested that rhTPO administered only after chemotherapy would not have an optimal impact on chemotherapy-induced platelet nadir.[10,14]

The efficacy of rhTPO in mobilization of PBPCs has been proven in three clinical trials. These results indicate that rhTPO safely and effectively augments the number of mobilized PBPCs and can reduce the required number of leukapheresis.[15−17] Two of these trials administrated rhTPO only after mobilization chemotherapy and the majority of the patients in the cohort had breast cancer.[15,16] The third trial enrolled only the patients with breast cancer and the mobilization regimen did not include chemotherapy (GCSF alone). Thus, the role of rhTPO on thrombocytopenia could not be assessed.[17]

This study was to identify the role of rhTPO before mobilization chemotherapy in attenuating thrombocytopenia and facilitating leukapheresis in patients with lymphoma. We also evaluated the hematological recovery after transplantation to estimate the quality of PBPCs mobilized with rhTPO. In addition, we analyzed the cost related to APBSCT during the mobilization and reconstitution phases.

Methods

Ethical approval

This randomized open-label phase 2 trial was conducted at the Department of Medical Oncology, Cancer Hospital, Chinese Academy of Medical Sciences in accordance with the principles of the *Declaration of Helsinki* and the Good Clinical Practice guidelines. This study was approved by the Institutional Ethics Committee (NCC2016YQ-06) and registered at Clinicaltrials.gov (NCT03014102). Written informed consent was obtained from all patients included in the study. Clinical and financial characteristics of all patients were obtained from medical records in the hospital information system.

Patients

Patients aged 18−60 years with a histologically confirmed diagnosis of lymphoma who were scheduled to undergo APBSCT were enrolled. Patients were also required to have an Eastern Cooperative Oncology Group performance status of 0−2. The exclusion criteria were abnormal liver function (aminotransferase or bilirubin levels two times the upper limit of normal) and leukopenia (white blood cell [WBC] count below 3×10^9/L). Patients were also excluded if they had a history of

thromboembolic events, coronary heart disease, stroke, arrhythmias, central nervous system metastases, or other organ system diseases or abnormalities that might predispose them to treatment-related complications.

Study design

During the mobilization phase, all patients received chemotherapy using the ifosfamide, carboplatin, and etoposide (ICE) regimen[1,6,18] combined with GCSF. The ICE regimen was administered as follows: ifosfamide 5000 mg/m^2 on day 2, carboplatin at an area under the curve of 5 (maximum dose: 800 mg) based on 12-hour creatinine clearance on day 2, and etoposide 100 mg/m^2 from days 1−3. Patients with CD20 positive lymphomas received additional intravenous rituximab (375 mg/m^2) on the day before mobilization. Daily complete blood counts were conducted during the mobilization period and the platelet and WBC counts were monitored. Lenograstim (Granocyte®) was subcutaneously administered at a fixed dose of 300 μg/d once daily to all patients, starting on the day when the WBC counts rose from the nadir after chemotherapy for the first time. Lenograstim was continued until the completion of leukapheresis.

Patients were randomly assigned in a 1:2 ratio to receive mobilization with rhTPO plus GCSF in combination with chemotherapy (the rhTPO plus GCSF arm) or GCSF alone in combination with chemotherapy (the GCSF alone arm) using opaque envelopes. Patients in the rhTPO plus GCSF arm received 15,000 IU/d of rhTPO subcutaneously on days −3, −2, and −1 before the start of the ICE regimen. Platelet transfusions were administered to all patients with platelet counts <20 × 10^9/L. Patients with platelet counts above 75 × 10^9/L underwent deep vein catheterization in the femoral vein for leukapheresis using a double-lumen catheter (Arrow International Inc., PA, USA).

PBPCs were collected as previously described.[18] Continuous leukapheresis was conducted daily with a CS-3000 Plus Blood Cell Separator (Baxter Healthcare Corp., Deerfield, IL, USA) until a target collection of at least 2 × 10^6 CD34+ cells/kg was achieved. Leukapheresis was stopped if two successive aphereses yielded a CD34+ cell dose of <0.5 × 10^6/kg, and the attempt to collect an adequate dose of CD34+ cells was deemed futile.

During the transplantation phase, patients received the carmustine, etoposide, cytarabine, and cyclophosphamide (BEAC) regimen as high-dose intravenous chemotherapy from day −7 to day −2.[19−21] PBPCs were then thawed and reinfused at 48 h after completion of high-dose chemotherapy on day 0. The recovery of neutrophils (absolute neutrophil count ≥0.5 × 10^9/L and 1.0 × 10^9/L) and platelets (platelet count ≥20 × 10^9/L, 50 × 10^9/L, and 100 × 10^9/L) was monitored after high-dose chemotherapy and PBPC infusion.

Cost analysis

Data on the per-patient costs were collected from the hospital's information system. The costs of routine treatments such as antiemetics and intravenous fluids and routine procedures such as mandatory laboratory tests during the hospital stay were included in the total cost. The costs of high-dose treatment and bone marrow reconstitution were calculated only for the patients who underwent transplantation.

Statistical analyses

The primary objective was to evaluate whether the use of rhTPO before mobilization chemotherapy can reduce the incidence of grade 2 thrombocytopenia (platelet count <75 × 10^9/L) on the day of leukapheresis. The secondary objectives were to clarify whether rhTPO would accelerate platelet reconstruction after APBSCT and increase the treatment costs. All statistical analyses were performed using IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA). Due to the low number of observations, contrasts between the different treatment groups were evaluated using Fisher's exact test and Mann−Whitney U test. The Kaplan−Meier method and log-rank test were used to compare the times to hematologic recovery. A two-tailed *P*-value <0.05 was considered statistically significant.

Results

Patient characteristics

Thirty patients consented to participate in this study between March 2016 and August 2018 (Fig. 1). The patients were randomized to the rhTPO plus GCSF arm (n = 10) or to the GCSF alone arm (n = 20) and completed the mobilization phase. Two patients in the rhTPO plus GCSF arm did not meet the criteria for leukapheresis and thus, the remaining eight patients underwent APBSCT. In the GCSF alone arm, two patients did not meet the criteria for leukapheresis and thus, the remaining 18 patients underwent APBSCT.

The clinical and pathological characteristics of the study cohort are presented in Table 1. The median age at

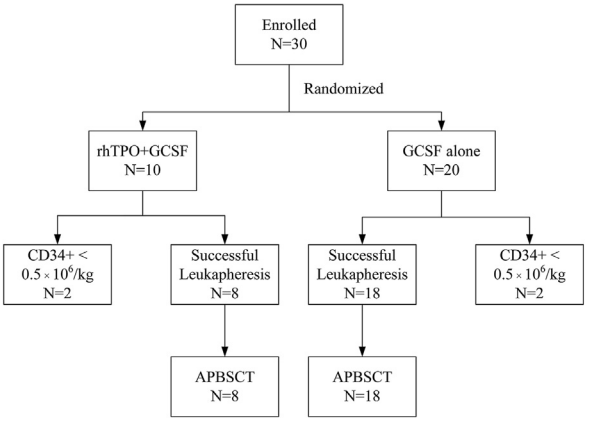

Fig. 1. Flow chart of the study cohort. GCSF: granulocyte colony-stimulating factor, rhTPO: recombinant human thrombopoietin, APBSCT: autologous peripheral blood stem cell transplantation.

enrollment was 36 years (range: 15−56 years). The study cohort consisted of 46.7% females (n = 14) and 53.3% males (n = 16). Non-Hodgkin lymphoma was diagnosed in 76.7% (n = 23) and Hodgkin lymphoma was diagnosed in 23.3% (n = 7) of the patients. Patients in the rhTPO plus GCSF arm exhibited almost similar clinicopathologic characteristics to those of patients in the GCSF alone arm (all $P > 0.05$). Notably, the previous lines of chemotherapy (P=0.121) and related thrombocytopenia (P=0.634) were similar in both arms.

Efficacy of rhTPO in treating thrombocytopenia

Patients in the rhTPO plus GCSF arm had similar platelet nadir after mobilization when compared with those from the GCSF alone arm. The amount of platelet transfusion was lower in the rhTPO plus GCSF arm, but the difference was not statistically significant (P=0.735). The median platelet nadir after the mobilization regimen was 47 × 10^9/L (range: 18−147) in the rhTPO plus GCSF arm and 49 × 10^9/L (range: 14−197) in the GCSF alone arm (P=0.878). The nadir of platelets appeared on day 15 (range: 11−24) after the start of chemotherapy in patients who had received rhTPO and on day 16 (range: 12−23) in those who had received GCSF alone (P=0.582). In this study, 4 out of 10 (40.0%) patients in the rhTPO plus GCSF arm received platelet transfusion after mobilization (median: 0 units, range: 0−4). In the GCSF alone arm, 10 out of 20 (50.0%) patients received platelet transfusion after mobilization (median: 1 unit, range: 0−4). No fever, mucositis, diarrhea, nausea, or other adverse events related to rhTPO were recorded.

On the day of leukapheresis, patients who had received rhTPO plus GCSF tended to have higher platelet counts than those of patients in the GCSF alone arm. The median platelet count on the day of leukapheresis was 86 × 10^9/L (range: 18−219) among patients who had received rhTPO and 73 × 10^9/L (range: 42−197) among patients who had received GCSF alone (P=0.982). On the day of leukapheresis, 3 out of 10 patients (30.0%) in the rhTPO plus GCSF arm and 10 out of 20 patients (50.0%) in the GCSF alone arm exhibited platelet counts ≤75 × 10^9/L and required platelet infusion to ensure the safety of catheterization (P=0.297).

Post-transplantation hematologic recovery

The median collection yield per leukapheresis was 3.24 × 10^6 CD34+ cells/kg (range: 0.72−12.41) in the rhTPO plus GCSF arm and 3.00 × 10^6 CD34+ cells/kg (range: 0.41−17.13) in the GCSF alone arm (P=0.710, Fig. 2C). The circulating volume (P = 0.600) and the total CD34+ cell count (P = 0.696) per patient were similar between the groups (Supplementary Fig. 1). The addition of rhTPO during the mobilization stage did not influence the time to neutrophil recovery (Fig. 2B, all $P > 0.05$), while platelet recovery was more rapid in the rhTPO plus GCSF arm during the transplantation stage. Notably, patients who had received rhTPO in the mobilization phase seemed to require a median of 3.0 days less for platelet recovery to 50 × 10^9/L than those in the GCSF alone arm (P=0.011, Fig. 2A). All patients received ≥1 platelet transfusions during the post-transplantation period and the median number of platelet transfusions was not significantly different between the treatment groups (P=0.148, Fig. 2C).

Cost analysis

The consumer price index in 2016 increased by 2.0% over the previous year in China. The estimated median total cost of the mobilization and collection phases per patient was ¥31,900 (range: 22,141−51,315) in the rhTPO plus GCSF arm and ¥35,083 (range: 19,592−75,880) in the GCSF alone arm (P=0.382). No significant difference was observed in the costs of platelet transfusion, antibiotics, and use of GCSF between the groups during mobilization (all $P > 0.05$, Fig. 3A). Among the patients who had completed transplantation, the median total cost of transplantation was also similar between the groups (¥59,860 [range: 48,687−73,125] in the rhTPO plus

Table 1
Characteristics of patients in the cohort.

Characteristics	Total	rhTPO+GCSF N = 10	GCSF alone N = 20	*P*-value
Age at mobilization (years)				0.421
Median	36	28	37	
Range	15−56	16−52	15−56	
Gender				1.000
Female	14 (46.7)	5 (50.0)	9 (45.0)	
Male	16 (53.3)	5 (50.0)	11 (55.0)	
Primary diagnosis				0.853
DLBCL	14 (46.7)	5 (50.0)	9 (45.0)	
T cell lymphoma	5 (16.7)	1 (10.0)	4 (20.0)	
Mantle cell lymphoma	1 (3.3)	0	1 (5.0)	
Burkitt lymphoma	1 (3.3)	0	1 (5.0)	
NK/T cell lymphoma	2 (6.7)	1 (10.0)	1 (5.0)	
Hodgkin lymphoma	7 (23.3)	3 (30.0)	4 (20.0)	
Disease stage at primary diagnosis				1.000
III	1 (3.3)	0	1 (5.0)	
IV	29 (96.7)	10 (100.0)	19 (95.0)	
Previous lines of chemotherapy				0.245
1	15 (50.0)	3 (30.0)	12 (60.0)	
2	15 (50.0)	7 (70.0)	8 (40.0)	
Previous thrombocytopenia				0.634
Never	21 (70.0)	8 (80.0)	13 (65.0)	
Grade 1	1 (3.3)	0	1 (5.0)	
Grade 2	6 (20.0)	1 (10.0)	5 (25.0)	
Grade 3	2 (6.7)	1 (10.0)	1 (5.0)	

Data are presented as number (%) unless specified otherwise.
rhTPO: recombinant human thrombopoietin, GCSF: granulocyte colony-stimulating factor; DLBCL: Diffuse large B cell lymphoma, NK: natural killer.

GCSF arm and ¥52,689 [range: 41,803−75,635] in the GCSF alone arm, P=0.070). No significant difference was observed in the costs of platelet transfusion, antibiotics, and use of GCSF between the groups during transplantation (all $P > 0.05$, Fig. 3B).

Discussion

In this randomized controlled phase 2 study, we observed that rhTPO helped in mobilization and leukapheresis by reducing the platelet transfusion required during the mobilization phase and by increasing the platelet count on the day of leukapheresis, thereby facilitating deep vein catheterization. To the best of our knowledge, this is the first study to evaluate the role of rhTPO before mobilization chemotherapy in lymphoma patients planning to undergo APBSCT.

The ability of rhTPO to enhance the mobilization of PBPCs has been evaluated mostly in patients with advanced breast cancer.[15−17] Researchers have found that rhTPO used after chemotherapy during the mobilization phase can reduce the number of required leukaphereses and allow more patients to meet the minimal cell yield requirements to receive APBSCT.[15,16] In our study, the median CD34+ yield on the first day of leukapheresis was higher in the rhTPO plus GCSF arm than in the GCSF alone arm in patients with lymphoma. This finding could be explained by the biological nature of rhTPO, which is a potent stimulator of megakaryocytopoiesis and hematopoietic progenitor cells.[22]

Our results revealed that the addition of rhTPO in the mobilization phase did not influence the time to neutrophil recovery in the reconstitution phase. Transplantation of rhTPO-mobilized PBPCs was effective in supporting the patients following high-dose chemotherapy with the BEAC regimen. However, we observed that platelet recovery in the reconstitution phase was more rapid in patients who had received rhTPO during mobilization. This may be related to the kinetics of its biological effects in stimulating progenitor cell production in the bone marrow.[22] Several studies have reported a delayed effect of rhTPO in stimulating platelet production. Moreover, the timing of rhTPO administration may be important for optimal biological activity.[9,10,22] The small number of patients in both treatment groups precluded us from deriving a definitive conclusion from our study. Before the start of the study, the sample size

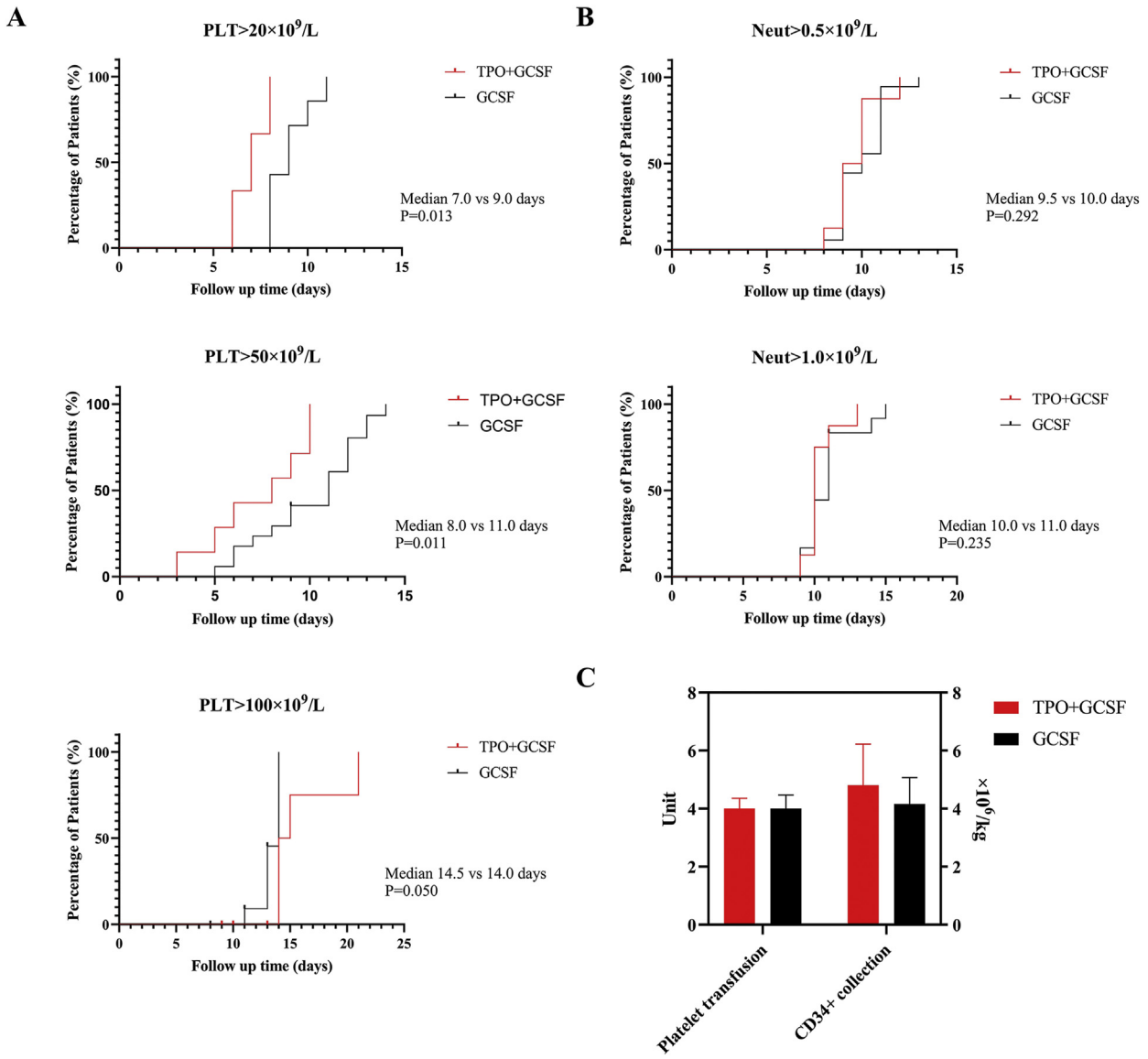

Fig. 2. Hematologic recovery in the transplantation stage. The addition of rhTPO in the mobilization phase did not influence the time to neutrophil recovery (B), while platelet recovery was more rapid in the rhTPO plus GCSF arm (A). The mean CD34+ cell collection yield per leukapheresis and the median number of platelet transfusions were not significantly different between the groups (C). GCSF: granulocyte colony-stimulating factor, rhTPO: recombinant human thrombopoietin.

was directly determined by comprehensive consideration of objective factors such as study cost and time period. On the day of leukapheresis, 3 out of 10 patients (30.0%) in the rhTPO plus GCSF arm and 10 out of 20 patients (50.0%) in the GCSF alone arm exhibited platelet count $<75 \times 10^9$/L ($P = 0.297$). Suppose the probability of type I error is 0.05, and the post-hoc power is 16.8%.

We observed that the total cost of the mobilization phase for patients in the rhTPO plus GCSF arm was similar to that for patients in the GCSF alone arm. This is a logical finding, since rhTPO utilization reduces the amount of platelet transfusion, which in turn, reduces the cost of blood products. In addition, the risks associated with platelet transfusion such as thrombotic events, infection, sepsis, or organ failure could also be reduced

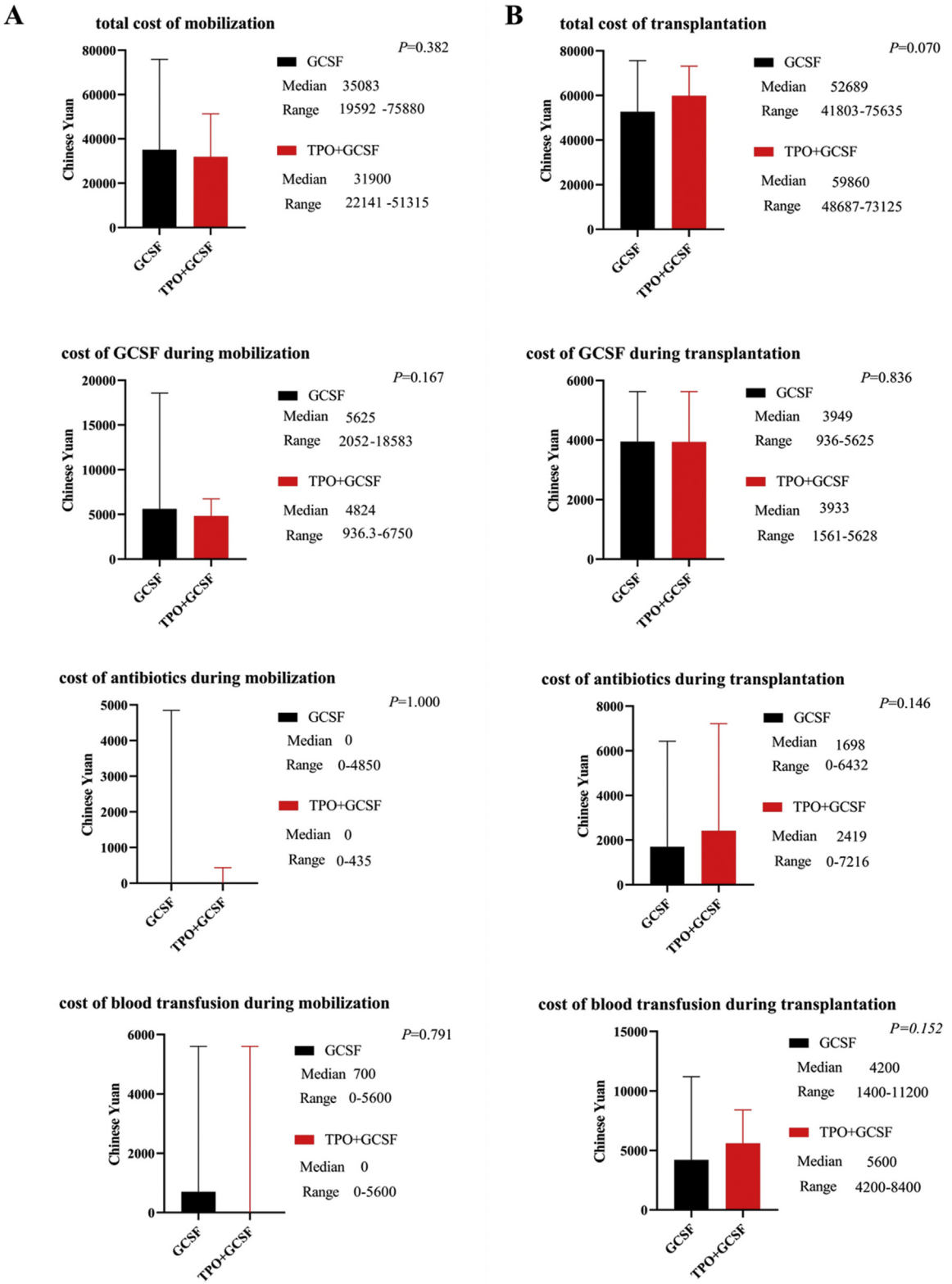

Fig. 3. Treatment cost during the mobilization (A) and transplantation (B) stages. The total treatment cost as well as the costs of platelet transfusion, antibiotics, and GCSF were almost similar between the groups.

indirectly after the utilization of rhTPO.[23,24] rhTPO may not be widely available in some regions of the world. In these areas, platelet transfusions may be more versatile.

In conclusion, our findings indicated that there was no significant clinical benefit of rhTPO use in facilitating mobilization of progenitor cells, but platelet recovery after high-dose therapy was faster than that in the GCSF alone arm. Further studies are required to evaluate the optimal schedule and timing of rhTPO in larger cohorts of patients with lymphoma.

Data availability statement

Data supporting our findings in this study are available upon request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cdtm.2021.05.003.

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