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Original Article

Efficacy and safety of recombinant human interlerukin-11 in the treatment of chemotherapy-induced thrombocytopenia in acute lymphoblastic leukemia

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Abstract: Background: In order to investigate the efficacy and safety of recombinant human interleukin-11 (rhIL-11) in the treatment of chemotherapy-induced thrombocytopenia in acute lymphoblastic leukemia. Methods: we conducted a multicenter, randomized, parallel contrast trial of rhIL-11 in 120 patients, of which, 104 patients were eligible for this study. Forty-six patients received rhIL-11 at 50 μg/kg subcutaneously daily beginning at 24 h after the chemotherapy ended and continuing for 10 days or until platelet counts reaching $\geq 80\times10^9$/L after nadir. Fifty-eight patients in the control group received the same chemotherapy regimen without rhIL-11. Platelet counts were monitored every other day and symptoms of bleeding or infection were recorded. Results: Only 4/46 patients (8.70%) who received rhIL-11 required platelet transfusion versus 14/58 control patients (24.10%, $P < 0.05$). rhIL-11-treated patients received fewer platelet transfusions than control patients (mean of 7.2 transfusions vs. 11.7 transfusions, P=0.05). The incidence of grade-4 thrombocytopenia was lower in rhIL-11-treated patients (6.5%) than in the control group (20.7%). rhIL-11-treated patients achieved higher platelet counts than the control group after nadir. Conclusions: rhIL-11 at 50 μg/kg/day beginning at 24 h after the end of chemotherapy was safe and effective for treating chemotherapy-induced thrombocytopenia with mild and manageable side events.

Keywords: Recombinant human interleukin-11, acute lymphoblastic leukemia, chemotherapy, thrombocytopenia, children

Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignancy in children. The current curative treatment for ALL requires intensive chemotherapy, which leads to chemotherapy-induced thrombocytopenia. Thrombocytopenia has become a dose-limiting factor in chemotherapeutic regimens and is also life-threatening. Although platelet transfusion can prevent bleeding, thrombocytopenia remains a common life-threatening factor after chemotherapy due to the insufficient supply and short life span of platelets. Concerns about the potential transmission of infectious agents and allergic reaction to platelet transfusion motivate the search for safe and effective drugs that promote platelet growth.

Recombinant human interleukin-11 (rh-IL11) is a growth factor that increases platelet counts by stimulating the growth of primitive hematopoietic stem cells and the proliferation of megakaryocytic progenitor cells. Administration of rh-IL11 to adults has been reported [1], but prospective multicenter clinical trials in children are lacking. We therefore sought to evaluate the safety and efficacy of rhIL-11 at 50 μg/kg/day for the treatment of chemotherapy-induced thrombocytopenia. We hypothesized that this exposure would reduce the need for platelet transfusions in ALL patients who received

Table 1. Clinical characteristics of patients at baseline

Characteristics		rhIL-11-treated group (n=46)	Control group (n=58)	*P* value
Age in years, mean (range)		5 (1-13)	5 (1-18)	0.813
Sex	Male, n (%)	31 (67.4%)	36 (62.1%)	0.361
	Female, n %	15 (32.6%)	22 (37.9%)	
Height in cm, mean (range)		108 (76-165)	109.5 (68-163)	0.962
Weight in kg, mean (range)		19 (9-63)	18.25 (8-89.5)	0.772
Laboratory tests, mean (range)	Platelet count ($\times10^9$/L)	115.05 (14-477)	171 (7-746)	0.165
	RBC count ($\times10^{12}$/L)	2.70 (1.79-3.95)	2.63 (1.64-4.57)	0.785
	WBC count ($\times10^9$/L)	2.35 (0.60-9.30)	2.95 (0.60-8.40)	0.241
	Neutrophils ($\times10^9$/L)	1.49 (0.31-8.17)	1.74 (0.20-62.10)	0.411
	Hemoglobin (g/L)	78.5 (8.90-128.0)	83.0 (53.2-129.0)	0.153
	ALT (IU/L)	23.0 (5.0-338.0)	18.0 (7.0-204.0)	0.355
	AST (IU/L)	23.55 (8.0-221.0)	18.0 (6.0-149.0)	0.193
	GGT (IU/L)	20.0 (13.0-152.0)	23.5 (3.0-119.0)	0.899
	Total bilirubin (μmol/L)	9.5 (4.0-48.6)	9.8 (4.7-30.2)	0.890
Chemotherapy regimen	Regimen 1, n (%)	32 (69.6%)	39 (67.2%)	0.485
	Regimen 2, n (%)	14 (30.4%)	19 (32.8%)	
Chemotherapy remission, n (%)		46 (100%)	57 (100%)	-

Abbreviations: RBC, red blood cells; WBC, white blood cells; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase.

cyclophosphamide-arabinoside-thiopurine (CAT) chemotherapy.

Patients and methods

Patients

All children's guardians provided written informed consent to participate in this study. This study was approved by the ethics committees of the lead hospital and the participating hospitals and registered at ClinicalTrials.gov (ID: NCT02314273). Newly diagnosed ALL patients that younger than 18 years were eligible. Patients were required to have adequate renal (creatinine ≤120 μmol/L), hepatic (total bilirubin ≤34 μmol/L), and cardiac (normal ejection fraction) functions after induction therapy. Patients were also required to lack severe uncontrolled infection and a history of drug allergy, for example allergy to asparaginase. Additional exclusion criteria included ineligibility after reassessment, administration of other potential thrombopoietic agents, violation of the clinical trial, severe side effects, and the patient willing to withdraw from the trial.

Treatment plan

We conducted a prospective, multicenter, randomized, parallel contrast study. Patients were centrally randomized into a rhIL-11 treatment group (n=46) and a control group (n=58). After induction therapy, each patient was treated with CAT chemotherapy: 1000 mg/m^2 cyclophosphamide intravenously on day 1, 75~100 mg/m^2 cytosine arabinoside for 7 or 8 days, and 50~60 mg/m^2 6-mercaptopurine orally on days 1-14 (regime 1) or 75 mg/m^2 6-mercaptopurine orally on days 1-7 (regime 2). rhIL-11-treated patients received rhIL-11 at 50 μg/kg/day (Topmega; Amoytop Biotech Co, Amoy, Fujian province, China) subcutaneously daily beginning at 24 h after the end of chemotherapy and continuing for 10 days or until platelet counts were ≥80×10^9/L after nadir without platelet transfusions. The control group did not receive rhIL-11. All other supportive care and patient management was the same for the two groups.

Assessment

Peripheral blood counts were monitored every other day after the completion of chemotherapy. Platelet counts, platelet transfusions, duration of infection, and hemorrhagic tendency were monitored until the next cycle of chemotherapy. Remission status was assessed after bone-marrow recovery and liver function was tested before the next cycle of chemotherapy.

Table 2. Clinical outcomes in the rhIL-11-treated group and the control group

Evaluation	rhIL11-treated group (n=46)	Control group (n=58)	*P* value
Platelet transfusions required, n (%)	4 (8.7%)	14 (24.10%)	0.033
Cases of grade-4 thrombocytopenia, n (%)	3 (6.5%)	12 (20.7%)	0.036
Recovery time from grade-4 thrombocytopenia in days, mean (range)	3 (3-7)	5 (3-9)	0.695
Hemorrhagic cases, n (%)	4 (8.7%)	3 (5.2%)	0.372

Table 3. Adverse events

Adverse events	rhIL-11 treated group (n=46)		Control group (n=58)
	Not associated with rhIL-11	Difficult to judge	
Fever, n	2	2	0
Infection, n	1	2	2

Adverse events were assessed and scored. Safety was assessed by charting adverse events and abnormal laboratory data and comparing these data between groups. The relationship between adverse events and the drug was evaluated. Effectiveness was assessed by monitoring platelet counts, platelet transfusions, infections, hemorrhagic tendency and remission status.

Statistical analysis

Quantitative data were summarized using means or medians (range) as appropriate. Enumeration data were described using frequencies. Proportions were compared using the two-tailed χ^2 test or Fisher's exact test as appropriate. The number of platelet transfusions was compared between groups with the Mann-Whitney test.

Results

One hundred twenty patients were enrolled between August 2011 and April 2014 from five hospitals (Shanghai Children's Medical Center affiliated with Shanghai Jiaotong University School of Medicine, Children's Hospital of Fudan University, Nanjing Children's Hospital, Children's Hospital of Suzhou University and Beijing Children's Hospital, all in China). Subsequently, 16 patients were determined to be ineligible and excluded from the study. Thus, there were 46 patients in the rhIL-11-treated group (31 males, 15 females) and 58 patients in the control group (36 males, 22 females). The mean patient age was 5 years (range 1 year to 18 years). The groups were well matched in terms of age, sex, chemotherapy regimens, and other parameters (**Table 1**).

Only 4/46 rhIL-11-treated patients (8.70%) underwent platelet transfusion versus 14/58 control patients (24.10%; P<0.05), which indicates that rhIL-11 can prevent the need for platelet transfusion for chemotherapy-induced thrombocytopenia. rhIL-11-treated patients received fewer platelet transfusions than control patients (mean of 0.72 unit transfusions *vs*. 1.17 unit transfusions, P=0.05). Grade-4 thrombocytopenia occurred in only 3/46 patients in the rhIL-11-treated group (6.5%) versus 12/58 patients in the control group (20.7%; P<0.05; **Table 2**), demonstrating that rhIL-11 can decrease the incidence of grade-4 thrombocytopenia due to chemotherapy.

Patients treated with rhIL-11- achieved higher platelet counts than the control group after nadir. However, the time to platelet recovery, defined as the number of days from the first day after nadir (platelet count of 20×10^9/L) to the day of a platelet count up to 50×10^9/L, was not significantly lower in patients with grade 4 thrombocytopenia who received rhIL-11 (3 days in the rhIL-11-treated group vs. 5 days in the control group; P>0.05; **Table 2**).

Regarding hemorrhagic tendency, 4/46 rhIL-11-treated patients (8.70%) experienced mild mucosal hemorrhage, as 3/58 control patients did (5.20%; **Table 2**). Only one patient in the control group had a visceral hemorrhage.

Ten adverse events were recorded in this study, eight in the rhIL-11-treated group and two in the control group (P>0.05; **Table 3**). The most common adverse events were fever and infection,

which were mild, easily managed, and reversible after supportive care. All patients completed the study. No adverse events were considered to be associated with rhIL-11 (**Table 3**).

Discussion

Trials have been performed all over the world to test the efficacy of rhIL-11 in reducing the need for platelet transfusion for cancer patients treated with chemotherapy [2, 3]; however, no trials have been reported for children. In a multicenter, randomized, placebo-controlled clinical trial of rhIL-11 in 93 patients diagnosed with solid tumors and treated with chemotherapy, Tepler et al. showed that 50 μg/kg/day rhIL-11 significantly reduced the number of platelet transfusions compared with 25 μg/kg/day rhIL-11 or placebo [2].

Childhood ALL is a curable disease; 70~80% of pediatric patients with ALL are cured after state-of-the-art chemotherapy and supportive treatment. However, chemotherapy-induced thrombocytopenia may lead to severe hemorrhagic events that are a major source of mortality. Although platelet transfusions may decrease the risk of hemorrhagic complications, insufficient platelet supply and the high cost of transfusion prevent effective usage. RhIL-11 was previously demonstrated to induce the proliferation and maturation of megakaryocytic progenitor cells in vitro and to increase platelet counts in animal species [4, 5]. rhIL-11 may therefore prevent the need for platelet transfusion and promote the recovery of platelet numbers [6].

CAT chemotherapy is a common consolidation regime for the treatment of ALL, whose main adverse event is myelosuppression. Platelet counts usually reach their nadir at 4-7 days after the completion of chemotherapy, but then recover gradually. Thrombocytopenia may increase the risk of visceral hemorrhage, especially cerebral hemorrhage, thus interrupting the continuation of chemotherapy. Wang et al. demonstrated that administering rhIL-11 beginning at 24 h after chemotherapy may reduce the need for platelet transfusion and enhance patient tolerance to chemotherapy [1].

Here, rhIL-11 treatment reduced the frequency of platelet transfusion and decreased the incidence of grade-4 thrombocytopenia (**Table 2**). The administration of rhIL-11 was generally well tolerated in this trial; of the 10 adverse events, none was confirmed to be due to rhIL-11 treatment (**Table 3**). The most common adverse events were fever and infection (**Table 3**), which were mild, easily managed, and reversible after supportive care. No patients withdrew from the study.

In summary, 50 μg/kg/day rhIL-11 administered at 24 h after the end of chemotherapy was safe and effective for chemotherapy-induced thrombocytopenia in pediatric patients with ALL. Since rhIL-11 is not expensive, this treatment modality merits further investigation.

Disclosure of conflict of interest

None.

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