RESEARCH ARTICLE

A Clinical Study on Juheli (Recombinant Human Interleukin - 11) in the Second Prevention of Chemotherapy Induced Thrombocytopenia

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Abstract

Objective: to investigate the effect and side effects of recombinant human interleukin - 11 (rhIL - 11, in Chinese Juheli, produced by Qi Lu Biotechnology CO., LTD) in the second prevention of chemotherapy induced thrombocytopenia (CIT). Methods: Cancer patients with CIT were recruited and were treated with rhIL - 11 (treatment phase, TP), and in the following cycle, all these patients administered with rhIL - 11 24 hours immediately after chemotherapy (preventive treatment phase, PTP). Duration and severity of thrombocytopenia between two phases were compared. Results: for patients in TP or PTP, nadir values of platelet were (29.28±20.08)×10^9/L and (45.24±19.66)×10^9/L, duration of thrombocytopenia in TP and PTP was (11.52±4.33) and (8.20±+2.77)days, recovery time was (19.40±3.89)and (13.44±3.02)days, duration of rhIL - 11 administration was 10.68±2.46)and (6.28±1.77)days, number of patients needing platelet infusion was 16and4 respectively, all differences were statistically significant (*p* value were 0.007, 0.002, 0.000, 0.000, 0.034 respectively). For TP and PTP, number of patients with hemorrhage was 8 and 4, duration of bleeding was (5.00±0.82) and (4.50 ± 0.71) days respectively, with no statistically significant difference. Adverse reactions mainly included fever, edema, arrhythmia, joint pain, fatigue, skin rash, headache, dizziness, etc., all were not statistically significant between TP and PTP. Conclusion: rhIL - 11 could be well tolerated and is effective that could reduce the duration, severity of CIT, platelet transfusion, and incidence of bleeding, as well as shorten the recovery time, duration of rhIL - 11 administration. Thus, rhIL - 11 could be commended in the second prevention of CIT for patients with cancer.

Keywords: Recombinant human interleukin - 11 - second prevention - chemotherapy induced thrombocytopenia

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Introduction

Cancer and its treatment, especitally myelosuppressive chemotherapy are frequently accompanied by anemia, neutropenia, and thrombocytopenia, as well as some combination of these conditions. These complications are associated with the potential to produce life threatening neutropenia, anemia, and thrombocytopenia, and could potentially increase the morbidity. These conditions also could compromise therapeutic dosing of chemotherapy which impacts survival as well as quality of life. The introduction of recombinant growth factors could minimize or prevent the development of treatment-induced anemia and neutropenia, but the management of chemotherapy-induced thrombocytopenia (CIT) remains a major challenge. Several guidelines recommend dose reduction in case of CIT, although full dose, on time chemotherapy could lead to reduced tumor burden and better overall survival (1a-3a). Thus, patients with CIT will experience potentially life threatening complications, delay in treatment, poorer outcomes and increases of health care resources (Elting et al., 2001). At present, platelet transfusions remain the "gold-standard" for the management of severe CIT, but there are many issues and possible complications associated with platelet transfusions (Clarke et al., 1996). Consequently, medical oncologists are engaged in development of an urgent method that could ameliorate CIT.

Recombinant human interleukin-11 (rHuIL-11) was the first thrombocytopoietic cytokine (Demetri et al., 2000), a protein product of bone marrow stromal cells (Teramura et al., 1996). RHuIL-11 could enhance the growth of early hematopoietic progenitor cells, and stimulate both megakaryocytopoiesis and erythropoiesis. Administration of recombinant IL-11 to myelosuppressed animals accelerates the recovery of multilineage blood

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Table 1. Patient Characteristics

	Number of patients	Gender		Chemotherapy				
		Male	Female	Adjuvant	Palliative	Agent	Dosage (mg/m^2)	Usage
None small cell lung cancer	8	4	4	6	2	Paclitaxel	135	d1
						Cisplatin	25	Qd*3
	6	6	0	2	4	Paclitaxel	135	d1
						Carboplatin	AUC=5	d1
	6	4	2	2	4	Gemcitabin	1000	d1, 8
						Cisplatin	25	Qd*3
Small cell lung cancer	10	8	2	4	6	Etopside	100	Qd*3
						Cisplatin	25	Qd*3
Breast cancer	8	0	8	0	8	Gemcitabin	1000	d1, 8
						Cisplatin	25	Qd*3
	8	0	8	0	8	Paclitaxel	70	d1, 8
						Gemcitabin	1000	d1, 8
Gastric cancer	14	8	6	10	4	Oxalipaltin	130	d1
						TS-1	40-60	Bid*14
Esophageal cancer	8	4	4	0	8	Paclitaxel	135	d1
						Nedaplatin	80	d1
	6	6	0	6	0	5-Fu	750	Qd*5
						Cisplatin	25	Qd*3
Pancreatic cancer	10	8	2	6	4	Gemcitabin	1000	d1, 8
						Oxalipaltin	130	d1
Galll baldder cancer	6	6	0	4	2	Gemcitabin	1000	d1, 8
						Cisplatin	25	Qd*3
Cervical cancer	6	-	6	2	4	Paclitaxel	135	d1
						Cisplatin	25	Qd*3
Ovary cancer	4	-	4	0	4	Paclitaxel	175	d1
						Carboplatin	AUC=5	d1

elements, including platelets.

Thus, it is licensed for the prevention of severe CIT and the reduction of the need for platelet transfusion following myelosuppressive chemotherapy in cancer patients who are at high risk of severe CIT. However, rHuIL-11 has significant side effects and demonstrates only modest efficacy. Therefore, optimizing the management of CIT remains a significant unmet need for patients with this condition (Demetri et al., 2000). And, few study is conducted to confirm the effectiveness of rhIL - 11 in the second prevention of CIT.

On this background, it is hypothesized that rhIL - 11 could be effective in the second prevention of CIT.

Materials and Methods

Patients recruited in this study were required to be pathologically/ cytologically diagnosed with cancer in Tai Xing Hospital from June 2015 to April 2013, to sign an informed consent before treatment; to expose to long term chemotherapy and supportive care; to have a score of Karnofsky Performance Status (KPS) ≥ 60 with expectancy life span more than 3 moths; to be classified with no contraindications for chemotherapy; to have a routine blood test and confirmed thrombocytopenia (blood platelet less than 75 * 10^9 / L) after chemotherapy, and normal hematopoietic function as evidenced by white blood cell count 3000/ul, normal hepatic function test (aspartate aminotransaminase and alanine aminotransferase less than 1.5 times of the upper limit of normal values), renal function test (serum total bilirubin<1.5mg/dl and creatinine<1.5mg/dl). Exclusion criteria included history of alcoholic intoxication, diabetes, and patients who were pregnant or nursing. Chemotherapy was administered according to NCCN guideline. All patients were injected subcutaneously with recombinant human interleukin - 11 (rhIL - 11, in Chinese Juheli, produced by Qi Lu Biotechnology CO., LTD) at a dosage of 50ug/kg/day, after the first cycle of chemotherapy when throbocytopenia was confirmed till the blood platelet count no less than 100 * 10^9/L (treatment phase, TP), and 24 hours immediately after thefollowing cycle, all these patients administered with rhIL - 11 till the blood platelet count no less than 100 * 10^9 /L (preventive treatment phase, PTP). After TP and PTP were attempted, safety and effectiveness were evaluated. We have enough experience in conducting medical researches, and have published some cancer related results elsewhere (Chen et al., 2014; Chen et al., 2014; Cao et al., 2014; Cui et al., 2014; Huang et al., 2014; Huang et al., 2014; Ji et al., 2014; Liu et al., 2014; Liu et al., 2014; Lu et al., 2014; Qian et al., Tian et al., 2014; 2014; Xiao et al., 2014; Xiao et al., 2014; Xu et al., 2014; Xu et al., 2014; Xu et al., 2014; Xu et al., 2014; Wang et al., 2014; Wu et al., 2014; Cui et al., 2015; Huang et al., 2015; Huang et al., 2015; Li et al., 2015; Liu et al., 2015; Liu et al., 2015; Qian et al., 2015; Shen et al., 2015; Shi et al., 2015; Sun et al., 2015; Xu et al., 2015; Xu et al., 2015; Xu et al., 2015; Xu et al., 2015; Wang et al., 2015; Wu et al., 2015; Wu et al., 2015; Yang et al., 2015; Zhou et al., 2015)

Toxicity Evaluation

The incidence rates of toxicity in this study were assessed on baseline and respectively after TP and PTP,

Table 2. Difference between TP and PTP

	TP	PTP	t/x^2	*p*
Nadir of platelet (10^9/L)	29.28±20.08	45.24±19.66	-2.840	0.007
Duration of CIT (d)	11.52±4.33	8.20±+2.77	3.229	0.002
Recovery time of CIT (d)	19.40±3.89	13.44±3.02	6.051	< 0.001
Platelet Transfusion (times)	16 (16.00)	4 (4.00)	4.500	0.034
rhIL-11 administered (days)	10.68±2.46	6.28±1.77	7.258	< 0.001
Bleeding (number)	8 (8.00)	4 (4.00)	0.758	0.384
During of bleeding (day)	5.00±0.82	4.50±0.71	0.730	0.506

TP=treatment phase; PTP=preventive treatment phase

Table 3. Toxicities between groups in TP and PTP

	TP	PTP	x^2	*p* value
Fever	12	10	0.117	0.733
Edema	8	6	0.166	0.684
Tachycardia	12	10	0.177	0.733
Muscle pain	8	10	0.136	0.713
Fatigue	6	6	0.000	1.000
Skin rash	6	4	0.222	0.637
Headache and dizziness	10	8	0.136	0.713

TP=treatment phase; PTP=preventive treatment phase

the grade of toxicities was determined according to The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; version 3).

Results

Clinical characteristics of patients: 100 patients were recuited (male 54, female 46) and aged 21 to 58 (41.0 ± 4.0) years. Non-small cell lung cancer was diagnosed in 20 patients and received chemotherapy that included paclitaxel/cisplatin (or carboplatin) or gemcitabine/ cisplatin. Small cell lung cancer were confirmed in 10 patients and received etoposide/cisplatin. Sixteen patients with breast cancer were treated with gemcitabine/cisplatin or gemcitabine/paclitaxel. Fourteen patients with gastric cancer were treated with TS-1/oxaliplatin. Another 14 patients with esophageal carcinoma were treated with fluorouracil/ cisplatin or paclitaxel/cisplatin. Ten patients with pancreatic cancer were treated with gemcitabine/ oxaliplatin. Cervical cancer was diagnosed in 6 patients and these patients were treated with paclitaxel/cisplatin. Six patients with gallbladder cancer were treated with gemcitabine/cisplatin. Four patients with ovarian cancer were treated with paclitaxel/carboplatin (Table 1).

Treatment efficacy: Duration and severity of thrombocytopenia between two phases were compared. Results: for patients in TP or PTP, nadir values of platelet were (29.28±20.08)×10^9/L and (45.24±19.66)×10^9/L, duration of thrombocytopenia in TP and PTP was (11.52±4.33)and (8.20±+2.77)days, recovery time was (19.40±3.89)and (13.44±3.02)days, duration of rhIL - 11 administration was 10.68±2.46)and (6.28±1.77)days, number of patients needing platelet infusion was 16and4 respectively, all differences were statistically significant (*p* value were 0.007, 0.002, 0.000, 0.000, 0.034 respectively). For TP and PTP, number of patients with hemorrhage was 8 and 4, duration of bleeding was (5.00±0.82) and (4.50 ± 0.71) days respectively, with no statistically significant difference (Table 2).

Side effects: Adverse reactions mainly included fever, edema, arrhythmia, joint pain, fatigue, skin rash, headache, dizziness, etc., all were not statistically significant between TP and PTP (Table 3).

Discussion

Platelets are anuclear cell particles that are released into the bloodstream by megakaryocytes located in the bone marrow. The differentiation of megakaryocytes is regulated by an intricate interaction of specific cytokines and growth factors (Kaplan et al., 2006). Bone marrow stromal elements are also critical to the differentiation and release of platelets. Cancer chemotherapy often depletes the stem and progenitor cells involved in platelet proliferation, which is called CIT and leads to a diminution of platelets and temporary interruption of platelet production. CIT will be lasting until stromal elements and megakaryocytes regenerate.

Over a long period of time, platelet transfusions are the most effective methods to control bleeding and CIT (McCullough et al., 2000). However, a number of issues, eg., availability, cost, refractoriness, transfusion reactions and disease transmission related to platelet transfusion support alternate strategies to reduce or eliminate it (McCullough et al., 2000). Besides, several experimental agents targeted to prevent CIT involved in the differentiation and production of platelets (Jenkins et al., 2007). Currently, the only agent commercially available for prevention of thrombocytopenia is IL-11, but the toxicity profile seems to be concerned when it is widespread introducted into clinical practice.

In previous studies on administration of rhIL - 11 for patients with advanced breast cancer who received aggressive doses of combined chemotherapy, it was suggested a dose dependent increase in bone marrow progenitor cells, megakaryocytes, cycling megakaryocytes, and mean platelet counts, and decreased the anticipated incidence of severe CIT were associated with this administration(Orazi et al., 1996; Gordon et al., 1996). The efficacy of rHuIL-11 (25 μg/kg and 50 μg/ kg) to prevent the need for platelet transfusions in cancer patients with CIT was evaluated. The marginal activity of IL-11 to decrease the risks of thrombocytopenia was confirmed in a randomized, placebo-controlled study of rHuIL-11 to prevent CIT for patients with breast cancer and treated with dose-intensive chemotherapy (Isaacs et al., 1997). IL-11 associated toxicities reported in these studies included fatigue, anemia, myalgias, arthralgias,

cardiovascular events, dependent edema, and fluid retention with weight gain (Gordon et al., 1996; Isaacs et al., 1997).

The efficacy of rHuIL-11 in preventing the need for platelet transfusions, compared with placebo, was invesgigated in 93 cancer patients receiving chemotherapy who had previously documented a need for platelet transfusion (Tepler et al., 1996). These patients had required platelet transfusions in the chemotherapy cycle immediately preceding entry into the study. Among the patients receiving placebo along with the chemotherapy, 96% again experienced thrombocytopenia requiring platelet transfusion. In contrast, a 50-μg/kg dose of rHuIL-11 modestly reduced the platelet transfusion requirements to 70% ($p < 0.05$) (Tepler et al., 1996). Based on these results, as well as the lack of any other available therapies besides transfusional support, the FDA approved rHuIL-11 for the treatment of CIT. Treatment-associated toxicities from the randomized study were the same as those reported in prior studies and confirmed that the use of IL-11 is frequently associated with unacceptably severe side effects. These IL-11-induced toxicities included a low incidence of atrial arrhythmias and syncope, as well as more common problems with edema and fluid retention. Despite these results with conventional chemotherapy regimens, a randomized trial of rHuIL-11 in the autologous bone marrow transplantation setting failed to demonstrate significant efficacy in decreasing platelet transfusion requirements (Vredenburgh et al., 1998). And further, few study is conducted to confirm the effectiveness of rhIL - 11 in the second prevention of CIT

In this study, our purpose is to investigate the effect and side effects of rhIL - 11 in the second prevention of CIT. We recruited Cancer patients with CIT. rhIL - 11 was administered when thrombocytopenia less than 75 * 10^9 / L, and in the following cycle, all these patients were treated with rhIL - 11 24 hours immediately after PTP. As a result, it was suggested that for patients in TP or PTP, nadir values of platelet were (29.28±20.08)×10^9/L and (45.24±19.66)×10^9/L, duration of thrombocytopenia in TP and PTP was (11.52±4.33)and (8.20±+2.77)days, recovery time was (19.40±3.89)and (13.44±3.02)days, duration of rhIL - 11 administration was 10.68±2.46)and (6.28±1.77)days, number of patients needing platelet infusion was 16and4 respectively, all differences were statistically significant (p value were 0.007, 0.002, 0.000, 0.000, 0.034 respectively). For TP and PTP, number of patients with hemorrhage was 8 and 4, duration of bleeding was (5.00±0.82) and (4.50 ± 0.71) days respectively, with no statistically significant difference. Adverse reactions mainly included fever, edema, arrhythmia, joint pain, fatigue, skin rash, headache, dizziness, etc., all were not statistically significant between TP and PTP. In conclusion, our current study suggested that rhIL - 11 could be well tolerated and is effective that could reduce the duration, severity of thrombocytopenia, platelet transfusion, and incidence of bleeding, as well as shorten the recovery time, and duration of rhIL - 11 administration. Thus, rhIL - 11 could be commended in the second prevention of CIT for patients with cancer.

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