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Chinese herbal medicine Guilu erxian jiao attenuates bone marrow suppression following chemotherapy in patients with advanced lung cancer

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ABSTRACT

In recent decades, a classic recipe in traditional Chinese medicine, Guilu erxian jiao (GEJ), has been used in the prevention and treatment of myelosuppression following cancer chemotherapy. However, the safety and efficacy of GEJ has not been studied. In the present study, we investigated the safety and efficacy of GEJ in the management of myelosuppression in a cohort of advanced lung adenocarcinoma patients who received 4 cycles of chemotherapy. Treatment with GEJ was compared to the conventional treatment with pegylated recombinant human granulocyte colony-stimulating factor (PEG-rhG-CSF). The GEJ treatment group (38 patients) was orally administered GEJ whilst the control group (25 patients) were treated with PEG-rhG-CSF during the 4 cycles of chemotherapy. We found that GEJ was as safe as the recommended treatment, PEG-rhG-CSF. GEJ patients recovered from suppressed bone marrow in a much steadier approach, compared with the highly fluctuating changes observed in PEG-rhG-CSF treatment. Our data suggests that GEJ may be a better alternative to manage cancer chemotherapy-induced myelosuppression.

1. Introduction

Myelosuppression, related to dysfunction of blood cell production, is one of the most serious side-effects of chemotherapy.[1,2] Serious myelosuppression and hematologic toxicities following chemotherapies are major reasons for mortality and morbidity, thus placing limitations on dose intensification and optimization of drug treatments for cancer patients.[3] Currently granulocyte colony-stimulating factor (G-CSF), usually administered as pegylated recombinant human G-CSF (PEG-rhG-CSF), is the recommended treatment for primary and/or secondary prophylaxis before commencement of chemotherapy regimens. However, the use of G-CSF usually posts high risk of febrile neutropenia (FN).[4] Hence, finding alternative approaches to effectively prevent and treat bone marrow suppression during chemotherapy for cancer patients is important.

A classic recipe in traditional Chinese medicine (TCM), Guilu erxian jiao (GEJ), has been used to treat anemia and related disorders in China for thousands of years.[5] In recent decades, GEJ has also been used in the prevention and treatment of myelosuppression following cancer chemotherapy. However, the safety and efficacy of GEJ has not been studied.[6,7] Therefore, in the present study, we investigated the safety and efficacy of GEJ in

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the management of myelosuppression in a cohort of advanced lung adenocarcinoma patients who received 4 cycles of chemotherapy.

2. Patients and methods

2.1. Patients and data collection

A total of 38 patients with advanced (IIIB-IV) lung adenocarcinoma admitted to the First Affiliated Hospital of Sun Yat-Sen University between January and December 2018 were included in the study. These patients were treated with 4 cycles of chemotherapy, and Chinese medicine GEJ was used to prevent and treat bone marrow suppression from the first cycle of chemotherapy. Twenty-five patients with similar diagnosis, pathology, stage of disease, demographic characteristics, and chemotherapy regimens who did not receive GEJ treatment and were treated with PEG-rhG-CSF formed the control group. The study was approved by the Human Ethic Committee of the First Affiliated Hospital of Sun Yet-sen University and all clinical data were extracted and collected according to the guidelines set out by the Committee. The study was also registered with Clinicaltrials.gov (NCT02737735).

2.2. Diagnosis

Diagnosis was made according to the 2015 NCCN Guidelines for the Diagnosis and Treatment of Non-small Cell Lung Cancer.[8] As shown below, WHO classification of toxic and side effects of anti-tumor drugs was used as the criteria for the classification of bone marrow suppression.

	0	I	II	III	IV
WBC (10^9/L)	≥4.0	3.0–3.9	2.0–2.9	1.0–1.9	<1.0
PLT (10^9/L)	100–300	75–100	50–74.9	25–49.9	<25
HGB (g/L)	≥120	100–120	80–99	6.5–7.9	<65

2.3. Inclusion and exclusion criteria

2.3.1. Inclusion criteria

Patients with stage IIIB or IV lung adenocarcinoma confirmed by histology or cytology; age> 18 years; no gender restriction; ECOG (Eastern Cooperative Oncology Group) performance status (PS) < 2 points; white blood cell count ≥1.9 × 10^9/L, neutrophil ≥1 × 10^9/L, hemoglobin ≥80g/L, platelets ≥50 × 10^9/L; Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) ≤ 2 times the normal value, bilirubin and serum creatinine (SCr) levels within the normal range; ECG and other examinations were normal; and patients agreed to complete 4 cycles of chemotherapy; and agreed to receive GEJ or G-CSF treatment.

2.3.2. Exclusion criteria

Patients participating in other clinical trials; pregnant and lactating women; women of childbearing age who do not agree to use contraception during the experiment; patients with severe pneumonia, tuberculosis, pulmonary abscess, myocarditis, and other malignant tumors; patients with severely impaired heart, liver, and kidney function (Heart function grades 3 to 4, ALT and/or AST more than 2 times the normal upper limit, SCr exceeded the normal upper limit); patients with mental illness and unable to cooperate; patients without obtained informed consent; patients with Grade IV bone marrow suppression after any cycle of chemotherapy; patients who the investigator determined not appropriate for the trial.

2.4. Treatment

Chemotherapy was given to the patients according to the NCCN Guidelines for the Diagnosis and Treatment of Non-Small Cell Lung Cancer (Chinese version). The G-CSF group was given PEG-rhG-CSF subcutaneously 48 hours after the commencement of each cycle of chemotherapy; the GEJ group received GEJ orally at a dose of 10 g twice daily 48 hours after each cycle of chemotherapy for 14 days. GEJ was prepared traditionally using tortoise shell gum, antler gum, red ginseng, and wolfberry boiled for 2 hours at a ratio of 32: 16: 6: 3. All Chinese herbal medicines used in this study were provided by the Guangzhou Chinese Herbal Medicine Company (Guangzhou, China).

2.5. Safety assessment

Number of participants with adverse events (AE) and dose limiting toxicities of GEJ were assessed according to CTCAE v4.0.

2.6. Analysis of liver and kidney function, and routine blood count

Serum ALT, AST, direct, indirect and total bilirubin (TBil), and SCr were determined before the commencement of chemotherapy and again the third week of the 4th cycle of chemotherapy by hospital standard enzymatic procedures using an automated bioanalyzer (Hitachi, Tokyo, Japan). Routine blood counts (red blood cells (RBC), hemoglobin (HGB), while blood cells (WBC), and platelets (PLT)) were conducted using a hospital automated bioanalyzer.

2.7. Statistical analysis

Data analysis was performed using SPSS 22.0 software. Chi-square test was used for gender and disease staging analysis. One-way ANOVA was used for analysis of HGB, WBC, and PLT counts in different groups. $P < 0.05$ was considered statistically significant.

Table 1
Comparison of baseline information from 2 groups.

Group	N	M/F	Age	IIIB (%)	IV (%)	Smoking Index
GEJ Group	38	2.78	56.04 ± 9.5	47.1	52.9	150 (0–2500)
G-CSF Group	25	3.54	57.37 ± 10.8	52.5	47.5	400 (0–2400)

Note: $P > 0.05$.

Table 2
Toxicity of GEJ measured as liver and kidney functions at the end of treatment.

Items	Unit	GEJ Group	G-CSF Group	F	P value
ALT	U/L	31.2 ± 7.6	33.7 ± 11.2	0.945	0.335
AST	U/L	40.6 ± 11.4	39.8 ± 10.6	0.075	0.785
TBil	Hmol/L	22.5 ± 9.0	21.6 ± 7.4	0.164	0.687
SCr	Hmol/L	96.2 ± 18.7	97.4 ± 20.6	0.058	0.810

Note: Data were presented as mean ± SE. Analysis of variance was used to compare the difference between groups. ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, TBil: Total bilirubin, SCr: Serum creatinine.

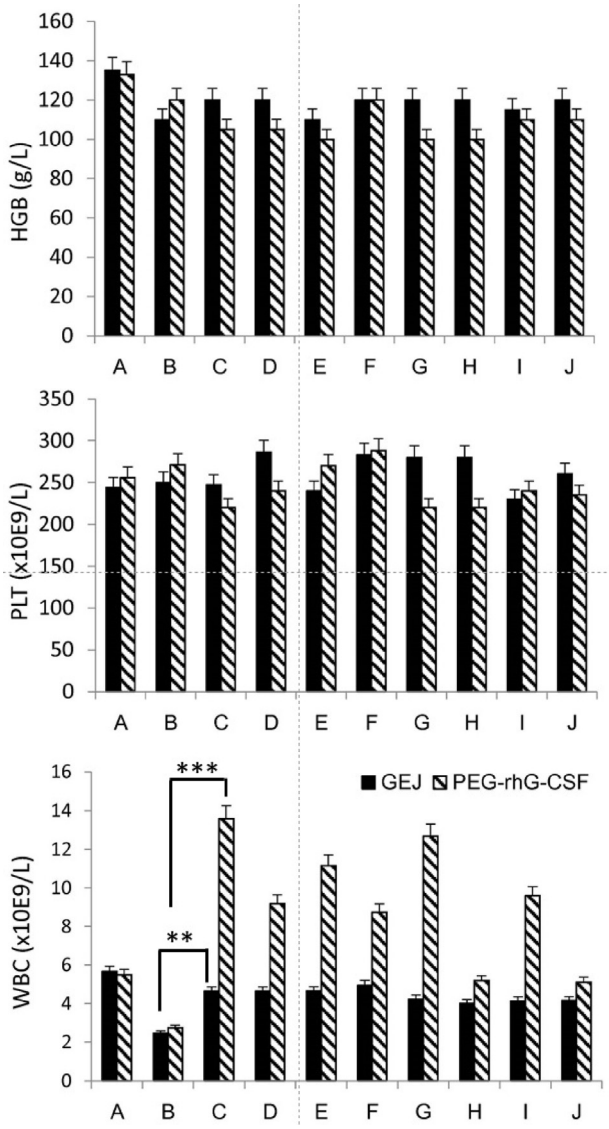

Fig. 1. Hematological profiles (white blood cells, hemoglobin, and platelet) at various timepoints following treatments. **A**: Before chemotherapy; **B**: on completion of 1st cycle of chemotherapy; **C**: 1 week after 1st cycle of chemotherapy; **D**: before 2nd cycle of chemotherapy; **E**: On completion of 2nd cycle of chemotherapy; **F**: before 3rd cycle of chemotherapy; **G**: One week after 3rd cycle of chemotherapy; **H**: Before 4th cycle of chemotherapy; **I**: One week after 4th cycle of chemotherapy; **J**: Three weeks after 4th cycle of chemotherapy. $^{**}P < 0.01$, $^{***}P < 0.001$.

3. Results and discussion

3.1. Baseline information of the patients

There was no statistical difference in the indexes between the two groups, GEJ and G-CSF (Table 1). From the table, the sex ratio and age of onset of these groups are similar to the overall incidence of lung cancer, indicating that these two groups of cases are comparable.

3.2. Safety profile of GEJ

During the course of this study, following continuous administration of GEJ for 4 cycles of chemotherapy, no observed AE/toxic reaction was found associated with the use of GEJ (Table 2). Also shown in Table 2, there was no significant difference in liver and kidney functions between the GEJ group and the G-CSF group.

3.3. Hematological profile following treatment

As shown in Fig. 1, there was no significant difference between the GEJ group and the G-CSF group in HGB and PLT. Following chemotherapy, WBC decreased significantly after 1 cycle of chemotherapy ($P < 0.01$); WBC increased significantly after treatment with GEJ or G-CSF ($P < 0.01$ or 0.001). The magnitude of increase in WBC in the G-SCF group is much more significant than that in GEJ group at multiple time points (C, D, E, F,G and I, $p < 0.001$ in all comparisons), indicating that G-CSF at the recommended dosage stimulated bone marrow much stronger that by GEJ treatment. In the GEJ treatment group, WBC counts significantly increased after GEJ treatment achieving WBC levels similar to WBC counts taken prior to chemotherapy ($p < 0.01$). Thereafter, the GEJ patient group maintained WBC stability, from one week after the first cycle of chemotherapy to the end of the study (from C to J, Fig. 1).

In summary, our data showed that the safety profile of oral GEJ is identical to that of PEG-rhG-CSF given subcutaneously. There was no indication, in this study, that long term use of herbal medicine causes impairment of liver and kidney. Both GEJ and G-CSF effectively increased WBC in lung adenocarcinoma patients receiving a standard 4 cycles of chemotherapy. In the group treated with GEJ, WBC increase was much steadier, compared to the highly fluctuating changes observed in the G-CSF group. Our findings suggest that GEJ may be a better alternative to treat myelosuppression in patients receiving cancer chemotherapy. Treating patients with GEJ may help in the prevention of bone marrow failure due to excessive stimulation and mobilization of bone marrow as observed in patients receiving PEG-rhG-CSF. Thus, further research is warranted to investigate the underlying mechanism of GEJ as an alternative therapy to treat chemotherapy-induced myelosuppression.

CRediT author statement

Baoguo Sun, Yiguang Lin, Yan Chen, Hongjie Chen: Conceptualization, Methodology, Software; **Yan Chen, Hongjie Chen, Yue Li**: Data curation, Writing- Original draft preparation. **Zexiong Chen, Yingzi Wu, Xianqin Qu**: Visualization, Investigation, Software, Validation; **Baoguo Sun**: Supervision; **Yiguang Lin, Eileen McGowan:** Writing- Reviewing and Editing.

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Conflict of interest

The authors declare no conflicts of interest in this work.

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