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Safety of polyethylene glycol recombinant human granulocyte colony-stimulating factor in treating non-small cell lung cancer patients at Ⅰb stage

Bo Yan, Wei Zhang, Fang Lu, Zhong-Lin Chen, Bao-Hui Han*, Li-Yan Jiang*

Respiratory Department, Affiliated Chest Hospital of Shanghai Jiaotong University, Shanghai 200030, China

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ABSTRACT

Objective: To investigate resistance and safety of HHPG-19K in treating non-small cell lung cancer patients. **Methods:** A total of 30 cases were selected and randomly divided into 5 groups: three HHPG-19K groups of different dosage (60 μg/kg/day, 100 μg/kg/day, 200 μg/kg/day) ,positive control group (Filgrastim, namely G-CSF5 μg/kg/day) and negative control group. Safety indexes of 5 groups were observed and compared. **Results:** All patients had adverse event (100%) in three HHPG-19K groups, and increased ALP, ALT and AST were main events. The degree was mild to moderate. There was no significant difference in the incidence of adverse event between dosage groups and positive control group no difference. But the incidence of negative control group was 13%, which was significantly lower than dosage groups and positive control group. **Conclusions:** Non-small cell lung cancer patients have satisfactory tolerance to HHPG-19K, and have no resistance. Besides, dosage at 100 μg/kg is the most safe.

1. Introduction

Pegylated recombinant human granulocyte colony stimulating factor (PEG-rhG-CSF) is a new agent which modified by polyethylene glycol. The common type in clinic is Pegfilgrastim, which was approved by U.S. FDA on January 31, 2002. Clinical researches and applications for years have confirmed that Pegfilgrastim has the similar safety and efficacy to rhG-CSF[1]. With convenience and good medication compliance, it has been widely promoted in clinic. Because of the unique advantages of Pegfilgrastim, the polyethylene glycol recombinant human granulocyte colony stimulating factor-HHPG-19K has been developed by cross linking 19K PEG and *N*-terminal of G-CSF at the fixed-point by covalent amide bond. This study aims to explore resistance and safety of HHPG-19K in non-small cell lung cancer patients.

2. Materials and methods

2.1. General data

All subjects were newly diagnosed as non-small cell lung cancer by chest CT, abdominal ultrasound, overall physical examination and pathological examination. Patients with brain metastases by brain CT examination were excluded; patients with ≥5 bone metastasis in spine, long bone metaphysis and flat-shaped bone by bone ECT scan were excluded. The ages of subjects were from 41 to 70 years old, and their average age was 57 years. Majority of patients were male (*n*=25, 83.3%), and there were 5 female

*Corresponding author: Bao-Hui Han, Professor, Chief Physician, Respiratory Department, Affiliated Chest Hospital of Shanghai Jiaotong University, 241 Huaihai Road, Xuhui District, Shanghai, China.
Li-Yan Jiang, Ph.D. ,Chief Physician, Respiratory Department, Affiliated Chest Hospital of Shanghai Jiaotong University, 241 Huaihai Road, Xuhui District, Shanghai, China.
Tel: 18017321336
E-mail: yanboogg@126.com

cases (16.7%). There were 19 cases with adenocarcinoma, 2 cases with squamous cell carcinoma, 9 cases with poorly differentiated carcinoma, no other pathological types. There were 14 patients at stage Ⅲb, and 16 patients at stage Ⅳ. All patients can receive chemotherapy. There were 1 case with KPS scores 0, 1 case with 2, and the remaining 28 cases with score 1. Physical examination showed there were 8 cases with positive signs associated with tumors, and 22 cases without tumor-related positive signs. All subjects were randomly divided into 5 groups: three HHPG-19K groups of different dosage (60 μg/kg/day, 100 μg/kg/day, 200 μg/kg/day) ,positive control group (Filgrastim, namely G-CSF5 μg/kg/day) and negative control group. There was no significant differencein general information among groups (P>0.05).

2.2. Test methods

All patients in this study underwent chemotherapy (Docetaxel and cisplatin) for a course. Each patient in the HHPG-19K groups and Filgrastim positive control group received different doses of HHPG-19K or G-CSF 48 h after chemotherapy. After chemotherapy, patient in the negative control group had no other treatment which had any impact on blood tests indicators. The experiment began from the first dose group (60 μg/kg). If no dose-limiting toxicity occurred or it occurred in less than two cases, then the next dose group would start. Otherwise, the dosage would be maintained, and this dose was determined as maximum tolerance dosage (MTD). In this study MTD was 200 mg/kg. Patients in the Filgrastim positive control group received injections of Filgrastim 5 mg/kg from the 3rd day of the chemotherapy. The injection would be stopped until absolute neutrophil count reached the lowest level, and the test result was $\geqslant 5.0\times10^9$/L for successive two times, regardless of whether the lowest level is lower than 5.0×10^9/L. Patients in negative control group had no HHPG-19K or Filgrastim. If the ANC of patients was lower than 0.5×10^9/L for more than 3 days or ANC was $<1.0\times10^9$/L accompanied with T>38 ℃, then patients would receive daily subcutaneous injection of Filgrastim 5 μg/kg, until they had WBC $\geqslant 10\times10^9$/L or ANC $\geqslant 5\times10^9$/L. Otherwise, granulocyte colony stimulating factor nor t radiotherapy and/or other treatment which would affect haematological index couldn't be used during chemotherapy.

2.3. Safety evaluation

All adverse events should be recorded, which included description of adverse events and relevant symptoms, time of occurrence, severity, duration, treatment as well as the prognosis and outcomes[2]. All events were evaluated based on the grading standards of NCICTC3.0 version adverse drug reactions[3]. For these adverse reactions beyond standards, it was evaluated as following: Ⅰ degree, mild adverse events; Ⅱ degree, moderate adverse events; Ⅲ degree, severe adverse events; Ⅳ degree, a life-threatening adverse events.

3. Results

All patients had adverse event except patients in negative control group (5/6, 83.3%).There were 52 cases (37%) with degree Ⅰ, 86 cases (62%) with degree Ⅱ, and 1 case (1%) with degree Ⅲ. This case of grade Ⅲ had ALT increased gradually in the HHPG-19K 200 mg/kg group during chemotherapy, and was improved after treatment. This patient had mildly abnormal liver function before enrolled (ALT Ⅰ degree), therefore the adverse events may not be associated with the test drug. In addition to this case, other adverse events were showed in Table 1, 2.

4. Discussion

In order to explore the safety and efficacy of HHPG-19K, this study take classic leukogenic drug-Filgrastim[4] as positive control. The dosage of HHPG-19K are 60 mg/kg, 100 mg/kg and 200 mg/kg. This study based on pharmacokinetic/pharmacodynamic, preclinical toxicological, pharmacological and tolerability study of HHPG-19K human[5-7] and the study on Pegfilgrastim[8]. It is designed according to principles of tolerance test and characteristics of R & D preparations[9].

Patients with advanced lung cancer have various complications and side effects during chemotherapy. In this study, there were 29 cases (97%) with adverse events among 30 subjects. The type and severity of adverse event in dosage groups of HHPG-19K are similar to Pegfilgrastim[10]. The common adverse events of Pegfilgrastim are bone and muscle pain, fever, hypodynamia, lack of appetite, nausea, vomit and constipation *etc.* Compared with Pegfilgrastim, the incidence of HHPG-19K is lower. The bone and muscle pain of Pegfilgrastim are mainly joint and back pain, while the pain of HHPG-19K are mainly in left arm and left shoulder. The incidences of bone pain of HHPG-19K and Pegfilgrastim are both low, in this study, only 1 case in HHPG-19K 200 mg/kg dose group and Filgrastim group had bone pain. Many chemotherapy-related adverse events also occur in this study. Many patients have fatigue, lack of appetite, nausea, vomit, constipation and other adverse events during chemotherapy, but the incidence is lower than that of Pegfilgrastim test, and no alopecia occurred, which is consistent with the current status of chemotherapy in China[11]. In Pegfilgrastim test, incidence of such adverse events is much higher[12]. This may be related to the different chemotherapy drugs or different physical conditions of patients.

There was only one case in the 100 mg/kg dose group with a headache, and only one case in the 60 μg/kg dose group with skin allergies, which were transient and disappeared

Table 1

Adverse events.

Adverse event	Positive control group	Negative control group	HHPG-19K 60 μg/kg	HHPG-19K 100 μg/kg	HHPG-19K 200 μg/kg	Total
Loss of appetite	3 (50%)	4 (67%)	4 (67%)	4 (67%)	1 (17%)	16 (53%)
Nausea	1 (17%)	1 (17%)	0 (0%)	0 (0%)	0 (0%)	2 (7%)
Vomit	1 (17%)	2 (33%)	1 (17%)	3 (50%)	0 (0%)	7 (23%)
Gastric discomfort	1 (17%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	2 (7%)
Constipation	0 (0%)	2 (33%)	2 (33%)	3 (50%)	1 (17%)	9 (30%)
Muscle patieats	2 (33%)	0 (0%)	4 (67%)	3 (50%)	3 (50%)	12 (40%)
Bone pain	1 (17%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	2 (7%)
Left shoulder pain	0 (0%)	0 (0%)	1 (17%)	0 (0%)	0 (0%)	1 (3%)
Cough	3 (50%)	1 (17%)	3 (50%)	1 (17%)	4 (67%)	12 (40%)
Expectoration	1 (17%)	0 (0%)	1 (17%)	1 (17%)	1 (17%)	4 (13%)
Chest distress	0 (0%)	0 (0%)	1 (17%)	1 (17%)	0 (0%)	2 (7%)
Bloody sputum	0 (0%)	1 (17%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Chest pain	0 (0%)	0 (0%)	0 (0%)	2 (33%)	0 (0%)	2 (7%)
Hypodynamia	1 (17%)	0 (0%)	0 (0%)	0 (0%)	2 (33%)	3 (10%)
Fever	3 (50%)	1 (17%)	2 (33%)	2 (33%)	4 (67%)	12 (40%)
Night sweat	0 (0%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	1 (3%)
Dizziness	0 (0%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	1 (3%)
Headache	0 (0%)	0 (0%)	1 (17%)	0 (0%)	0 (0%)	1 (3%)
Sleep disorders	0 (0%)	1 (17%)	1 (17%)	1(17%)	1 (17%)	4 (13%)
Oral ulcers	0 (0%)	0 (0%)	1 (17%)	0 (0%)	0 (0%)	1 (3%)
Oral mucositis	1 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Oral discomfort	1 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Atrial fibrillation and palpitation	0 (0%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	1 (3%)
Numbness	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	1 (3%)
Ocular discomfort	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	1 (3%)
Throat discomfort	1 (17%)	0 (0%)	0 (0%)	0 (0%)	2 (33%)	3 (10%)
Dysuria	0 (0%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	1 (3%)
Skin allergy	0 (0%)	0 (0%)	1 (17%)	0 (0%)	0 (0%)	1 (3%)
ALT increase	2 (33%)	0 (0%)	1 (17%)	0 (0%)	2 (33%)	5 (17%)
AST increase	1 (17%)	0 (0%)	1 (17%)	0 (0%)	1 (17%)	3 (10%)
ALP increase	3 (50%)	0 (0%)	1 (17%)	2 (33%)	4 (67%)	10 (33%)
Blood glucose elevation	0 (0%)	0 (0%)	2 (33%)	0 (0%)	0 (0%)	2 (7%)
DBIL increase	0 (0%)	1 (17%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Lower hemoglobin	0 (0%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	1 (3%)
PLT increase	0 (0%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	1 (3%)
PLT reduction	1 (17%)	1 (17%)	0 (0%)	0 (0%)	0 (0%)	4 (13%)
Positive urine glucose	0 (0%)	0 (0%)	2 (33%)	0 (0%)	0 (0%)	2 (7%)

Table 2

Adverse events severity classification

Grade	Positive control group	Negative control group	HHPG-19K 60 μg/kg	HHPG-19K 100 μg/kg	HHPG-19K 200 μg/kg	Total
Grade 1	10	6	12	13	5	46(33%)
Grade 2	18	11	19	21	23	92(66%)
Grade 3	0	0	0	0	1	1(1%)
Grade 4	0	0	0	0	0	0(0%)
Grade 5	0	0	0	0	0	0(0%)
Total	28(20%)	17(13%)	31(22%)	34(25%)	29(20%)	139(100%)

spontaneously without treatment. So it may be irrelevant with the test drugs. Incidence of headache is significantly lower compared with the results of healthy subjects at Ⅰ a stage, but it is consistent with the results of Pegfilgrastim test[13]. It may be related with subjects' condition[13]. In abroad, it has been reported that a few allergic reactions

occurred in patients with rhG-CSF (incidence <1/4 000)[14]. The main manifestations include rash, hives, facial swelling, difficulty breathing, tachycardia and hypotension, which mostly occurr within 30 min after administration[15,16]. As the result at Ⅰ a stage, no definite allergic reactions to HHPG-19K or Filgrastim occurred. Drug-related adverse events may be increased ALP and PLT. ALP increase have occurred in all dose groups, but the incidence was lowest in low-dose group with Ⅰ degree, which disappeared spontaneously without any treatment. Compared with the result at Ⅰa stage, there was fewer cases with ALP increased. There was only one case with PLT increases in 100 mg/kg dose group with Ⅰ degree, which was significantly reduced compared with the result at Ⅰa stage. However, the increases of ALP and PLT in this group are consistent with Pegfilgrastim test. Of all the adverse events, 34 cases may be related to HHPG-19K or Filgrastim, which include muscle patieats, bone pain, left shoulder pain, fever, ALP and PLT increases[17,18], which are consistent with the report about colony-stimulating factor[19]. There was no such event in the negative control group.

In conclusion, considering adverse events, we recommend 100 μg/kg as the optimum dose at phase Ⅰ in clinical study.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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