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Side Effects during Treatment of Advanced Gastric Carcinoma by Chemotherapy Combined with CIK-cell Transfusion in Elderly People

Jingting Jiang[1]
Changping Wu[1]
Liangrong Shi[1]
Ning Xu[2]
Haifeng Deng[1]
Mingyang Lu[1]
Mei Ji[1]
Yibei Zhu[3]
Xueguang Zhang[3]

[1] Department of Tumor Biological Treatment, Third Affiliated Hospital, Suzhou University, Changzhou 213003, Jiangsu province, China.
[2] Section of Clinical Chemistry & Pharmacology, Lund University S-221 85 Lund, Sweden.
[3] Institute of Biotechnology, Key Laboratory of Clinical Immunology of Jiangsu Province, Suzhou University, Suzhou 215007, Jiangsu province, China.

Correspondence to: Changping Wu
Tel: 86-519-8618 0978
E-mail: newwcp@163.com

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CJCO http://www.cjco.cn
E-mail: 2008cocr@gmail.com
Tel (Fax):86-22-2352 2919

OBJECTIVE To study the side effects and therapeutic results of autologous cytokine-induced killer (CIK) cell treatment in elderly patients with advanced gastric cancer.
METHODS CIK cells were induced and cultured using biotechnics in vitro, and then the cells were infused back into the patients. Sixty elderly gastric cancer patients treated by chemotherapy (FOLFOX4 protocol) were followed-up. Among them, 29 patients were treated with CIK cells during application of chemotherapy. Short-term curative effects and adverse events from the CIK transfusion and chemotherapy were observed.
RESULTS Eight cases developed partial remission (PR), 9 cases moderate remission (MR), 7 cases stable disease (SD) and 5 cases progressive disease (PD). Out of a total of 29 patients who received chemotherapy combined with autologous CIK therapy, the total remission rate (PR + MR) was 58.6%. The total remission rate following chemotherapy alone was 45.2%, including 5 PR cases, 9 MR cases, 7 SD cases, and 10 PD cases. There was a relatively lower rate of severe chemotherapic toxicities in the CIK-cell transfusion group. Side effects of autologous CIK transfusion included chills (13 cases), fever (9 cases), nausea and vomiting (1 case) and general malaise (3 cases). Side effects were treated with conventional therapy resulting in their amelioration. No patients developed shock, blood capillary leakage syndrome, or abnormalities in routine blood, urine, liver and renal function tests.
CONCLUSION Adoptive immunotherapy with autologous CIK cells may decrease the clinical signs and symptoms of elderly patients who suffer from advanced gastric cancer. Adverse reactions of patients can be alleviated by conventional therapy. Autologous CIK-cell transfusion may improve endurance to chemotherapy.

KEY WORDS: gastric carcinoma, cytokine-induced killer cells, immunotherapy, adoptive, side effects.

Introduction

Gastric cancer is one of the most common causes of cancer deaths in China[1,2]. It is often diagnosed at a relatively late stage with local or long-distance metastasis[3]. The incidence of elderly people suffering from gastric cancer has increased in recent decades as life-span in China has become longer. In general, elderly patients have a lower immune response with frequent complications after an operation, resulting in a high mortality rate. In addition, both chemotherapy and radiotherapy have limitations in treating elderly patients with advanced gastric carcinoma[4,5].

It has been demonstrated that cytokine-induced killer (CIK) cells can proliferate in vitro and directly kill tumor cells, resulting in

prolonged patient life[6]. We previously reported that CIK cells in vitro possess more potent anti-tumor activity than tumor infiltrating lymphocytes (TILs)[7]. We recently reported that there were potential benefits of combining treatments with autologous CIK cells and chemotherapy in patients suffering from advanced gastric cancers (Stages III-IV) compared to patients treated with chemotherapy alone[6]. In the present study, we assessed the side effects and corresponding therapeutic results following treatment with CIK cells in combination with chemotherapy in elderly people with late-stage gastric cancer.

Materials and Methods

Treatment of patients and curative evaluation

Sixty elderly gastric cancer patients (Stages II~IV) were treated in the present study. Twenty-nine patients (21 men and 8 women, ages 60~70 years, median, 66) were treated by chemotherapy along with autologous CIK biotherapy (Group A). Thirty-one patients (24 men and 7 women, ages 58~71 years, median, 67) were treated with chemotherapy alone (Group B). All the patients received a chemotherapy protocol of FOLFOX4. Doses of the drugs were reduced for severe hematologic and non-hematologic toxicities (graded using the NCI Common Toxicity Criteria) according to a specific modified protocol. Short-term curative effects of patients were evaluated according to the objective curative effects for solid tumors proposed by the Chinese Ministry of Public Health: complete remission (CR), partial remission (PR), moderate remission (MR), stable disease (SD), progressive disease (PD), total remission = CR + PR + MR. Characteristics of the patients are listed in Table 1.

Separation of peripheral blood mononuclear cells (PBMCs) and induction of CIK cells

Patients' peripheral blood (50~100 ml) was collected with heparin as an anticoagulant. PBMCs were isolated by Ficoll-Conray density gradient centrifugation as described previously[8]. Viability of PBMCs was assessed by trypan blue exclusion. PBMCs 2.0×10^6/ml were plated into six-well dishes (Nunc, Denmark) and cultured with the Medium I containing RPMI 1640 medium in the presence of human interferon-gamma (IFN-γ, 1.0×10^6 U/L, Shanghai Fosun Pharma Co., China), recombinant human interleukin 2 (IL-2, 5.0×10^5 U/L, Shangdong Quangang Pharmaceutical Co., China), 10% inactivated human serum, 25 mM HEPES, 2 mM L-glutamine, penicillin (100 U/ml) and streptomycin (100 μg/ml). The cells were incubated in a humidified atmosphere under 5% CO_2 at 37℃. After 24 hr monoclonal antibodies (MAb) against CD3 (100 μg /L, Antibody Diagnostic Inc., USA) and IL-1α (1.0×10^5 U/L, Promega) were added. After another 48 hr of culture, the supernatants were aspired and the cells cultured in Medium II (Medium I in absence of INF-γ). The medium was then changed every third day. CIK cells were identified and sorted by flow cytometry (FACS, Beckman-Coulter) at days 1, 7, 14, 21, 28 and 35. The cytotoxic activity of CIK cells was determined by co-incubation of the CIK cells with the NK-sensitive K562 cell line (ATCC, USA) as described previously[8]. Before infusion into the patients, the CIK cells were washed twice with 0.9% NaCl and re-suspended in 100 ml 0.9% NaCl containing 1% human albumin. The CIK cells (1.0×10^9 cells) were transfused into the patient within one hour for biotherapy 5 days after each chemotherapy treatment. Curative effects were evaluated and all side effects were recorded after each treatment.

Statistical analysis

The data were processed by SPSS 13.0. The curative and side effects of the two groups were compared by the Fisher's exact test.

Results

Curative and side effects of the treatments

Improvement of both appetite and physical strength occurred in 25 cases in Group A and 13 cases in Group B ($P < 0.05$), In Group A and Group B 20 and 18 cases had pain remissions, and 14 and 10 cases improved their sleeping respectively. In Group A, 8 cases showed partial remission (PR), 9 cases developed moderate remission (MR), 7 cases stable disease (SD), and 5 cases showed progressive disease (PD). The total remission was 58.6%. In Group B, 7 cases reached PR, 8 cases MR, 7 cases SD, and 9 cases PD. The total remission was 48.4% (Table 1).

The toxicity of chemotherapy was evaluated in all treated patients and for all cycles. The most prevalent toxicities were hematologic, including neutropenia and leukopenia. Nausea, vomiting, diarrhea and neuropathy were the most common non-hematologic toxicities. Grade 3 and 4 leukopenia, neutropenia and diarrhea occurred at a slightly higher rate in Group B. Among the 217 chemotherapy cycles, there were 51 grade 3 and 4 adverse events in Group B , but there were only 37 severe events out of 239 cycles in group A ($P < 0.05$). There were 6 patients with neutropenia fever in Group B, which was higher than a single patient in Group A. Because of severe adverse events13 patients could not continue chemotherapy in Group B, and only 4 patients in Group A stopped therapy ($P < 0.05$) (Table 2).

All side effects, for the CIK-treated patients, including chill, fever, dizziness and headache, nausea and vomiting, malaise, shock, rash, were recorded. Blood and urine routine tests and hepatic and renal functions were also determined every week. There were 13 cases

Table 1. Curative effects in both treatment groups.

Group	Stages	Cases	CR	PR	MR	SD	PD	Remission rate (%)	Total remission rate (%)
Chemotherapy plus CIK									58.6
	II	6	0	3	1	1	1	66.7	
	III	14	0	4	5	4	1	64.2	
	IV	9	0	1	3	2	3	44.4	
Chemotherapy alone									48.4
	II	6	0	3	1	1	1	66.7	
	III	16	0	4	4	5	4	50.0	
	IV	9	0	0	3	1	4	33.3	

Table 2. Differences among severe toxicities from chemotherapy between the 2 groups.

Groups	Chemotherapy plus CIK	Chemotherapy alone	*P* value
Chemotherapy cycle	239	217	-
Leucopenia (grade 3 and 4)	10	18	0.068
Neutropenia (grade 3 and 4)	17	22	0.249
Diarrhea (grade 3 and 4)	6	8	0.589
Other grade 3 and 4 toxicities	4	3	0.553
Total grade 3 and 4 events	37	51	0.030
Patients with neutropenia fever	1	6	0.088
Patients unable to endure further chemotherapy due to toxicities	4	12	0.045

Table 3. Side effects after chemotherapy plus CIK cell transfusion (total cases = 29).

	Chills	Fever	Dizziness & headache	Nausea & vomiting	Malaise	Shock	Rash	Blood & urine routine	Liver & kidney function
With	13	9	3	1	3	0	0	0	0
Without	16	20	26	28	26	29	29	29	29

Table 4. Infections after chemotherapy plus CIK-cell transfusion (total cases = 29).

	Injection site	Upper respiratory tract infection symptoms	Eye symptoms	Neck lymph node swelling and pain
With	1	3	2	0
Without	28	26	27	29

with chills, 9 cases had fever, 1 case with nausea and vomiting, and 3 cases showed general malaise (Table 3). In addition, 1 case had slight infection at the injection site, 3 cases had symptoms of an upper respiratory tract infection, and 2 cases had eye symptoms (Table 4).

Side effects of CIK-cell treatment

All side effects were treated accordingly. In brief, narcotic drugs were used when pain was serious. The following drugs were used when required: meperidine (25~50 mg/2 h) during an onset of pain. Physical cooling method and/or Mezolin (12.5 mg/6 h orally) to decrease patient fever, or Mezolin suppositories (50 mg) were also used. For nausea and vomiting, we offered patients a quiet and comfortable environment, and an antivomiting drug (metoclopramide, 20 mg/12 h orally). For general malaise, the patients were provided with additional rest time, and lorazepam (0.5 mg/12 h orally) or vitamin B6 (10 mg/12 h orally). Compazine (10 mg/4 h i.v.) was properly administered in order to reduce the symptoms. No patients developed shock, blood capillary leakage syndrome, rash or abnormalities in routine blood, urine, liver and renal function tests.

Discussion

In the present study we investigated the clinical responses of chemotherapy together with CIK-cell infusion in elderly patients suffering from advanced gastric cancer. It was demonstrated that transfusion of autologous CIK cells in the chemotherapeutic-treated patients had potential benefits. The short-term curative effects and the

quality of life were moderately improved. After therapy, most patients had an improvement in their appetite, physical strength, sleeping, pain remission, etc. There were no severe side effects noted. All moderate side effects disappeared after allopathic treatments, indicating that CIK-cell transfusion together with chemotherapy is a relatively safe therapy in elderly patients, and that it is better than chemotherapy alone. In addition, the patients treated by autologous CIK cells had relatively lower grade 3 and grade 4 adverse events from chemotherapy, and fewer patients ceased chemotherapy due to severe toxicities, furthermore suggesting that CIK-cell therapy may improve patient endurance to chemotherapy.

Gastric cancer in China is often diagnosed at a relatively advanced stage when metastases have occurred[3]. A series of treatments such as surgical resection combined with chemotherapy[9,10], radiotherapy[4,11], thermotherapy[12,13] and/or traditional Chinese medicine[14,15] have been introduced, but the 5-year survival rate of advanced gastric cancer patients remains very poor. In addition, both chemotherapy and radiotherapy may cause a series of side effects, such as bone marrow depression, severe nausea and vomiting, peripheral neuritis, diarrhea, alopecia and skin pigmentation[16]. Moreover, the immune responses and the general condition in elderly patients are relatively weak, and sometimes they suffer from other chronic diseases, i.e., cardiovascular diseases, hyperlipedemia and diabetes, leading to intolerance to an operation and other therapies. In addition, multiple complications may develop.

It had been suggested that cellular immunotherapy that regulates directly or indirectly the biological interaction between the host and the tumor is another choice to increase survival time[17]. Autologous CIK cells are one of the promising cellular immunotherapies[18], which may also obliterate the micro long distance metastasis. Although we decided not to divide the patients randomly, most patients treated with chemotherapy plus CIK cells had a better QOL, and their 2-year life span was longer than the patients treated by chemotherapy alone. However, the 5-year life span was not different between the groups.

It is concluded that chemotherapy combined with CIK-cell transfusion has potential benefits for elderly patients suffering from late-stage gastric cancer. CIK cell transfusion has no severe side effects, and some slight side effects can be eliminated by moderate treatment.

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