RESEARCH COMMUNICATION

Ubenimex capsule Improves General Performance and Chemotherapy related Toxicity in Advanced Gastric Cancer Cases

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Abstract

Objective: To evaluate the effect of ubenimex capsule on general performance and chemotherapy related toxicity in patients with advanced gastric cancer undergoing chemotherapy. Methods: Patients with advanced gastric cancer were randomly divided into two groups: with or without ubenimex. All received the following regimen for 2 cycles: docetaxel 40mg/m^2 intravenous infusion on days 1 and 8, cisplatin 15mg/m^2 and tegafur 600mg/m^2 intravenous infusion from days 1 to 5. Oral ubenimex capsule at 30mg daily was continued for 8 weeks from the start of chemotherapy. Study targets included Karnofsky performance status (KPS), body weight, leukocytes, hemoglobin, variation of several immunologic index prior,during and after chemotherapy. Results: Sixty-three patients were recruited into this study, 32 randomly entered into the ubenimex capsule and 31 into the control group. KPS score and body weight after chemotherapy were more stable in the treatment group (P <0.05), and myelosuppression, including reduction of leukocytes, hemoglobin and platelets, was milder (P <0.05). T lymphocytes (CD3 +), T assisted- induced lymphocytes (CD3 +, CD4 +), T suppressor and NK cells (CD16 +, CD56 +) all increased after ubenimex capsule intake, while decreasing in the control group (P <0.05). Conclusion: Ubenimex capsule could improve general performance and reduce chemotherapy related toxicity in patients with advanced gastric cancer.

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Introduction

Ubenimex is a dipeptide produced by *Streptomyces orivoleticuli* (Umezawa et al., 1976), with the ability to inhibit aminopeptidase activity (Suda et al., 1976; Leuhauseng et al., 1983), enhance functions of immunocompetent cells (Umezawa et al.,1976; Ishizuka et al., 1980; Shizuka et al., 1981; Shorlemmer et al., 1983; Noma et al., 1984) and induce apoptosis (Constam et al., 1995). The aim of this study was to evaluate the effects of ubenimex capsule on general performance and toxicity of chemotherapy in patients with advanced gastric cancer.

Patients and Methods

Patients

To be included in the study, patients had to have histologically confirmed advanced gastric cancer, stage III-IV by TNM staging classification,with no contraindication on chemotherapy, no autoimmune disease or history of immunologic treatment.

Chemotherapy

All eligible patients were assigned to receive two cycles of chemotherapy as follows: 40mg/m^2 docetaxel on days 1 and 8; 15mg/m^2 cisplatin from day 1 to day 5; and 600 mg/m^2 tegafur from day 1 to day 5.The premedication of docetaxel were documented elsewhere (Zhou JN et al., 2009). The treatment group received oral ubenimex capsule (Zhejiang Apeloa Kangyu Pharmaceutical Co.,Ltd) 30mg daily and continued 8 weeks from the start of chemotherapy.The remaining therapies for two groups were basically the same.

Evaluations and observations

All patients underwent weekly evaluations that included an assessment on karnofsky performance status(KPS),body weight, toxicity of chemotherapy and an assessment on immunocompetent cells. An increased KPS score ≥ 10 after treatment was defined as improvement, <10 defined as stable, KPS score decreased ≥ 10 after treatment defined as reduced. For body weight, increased ≥ 1.0 kg after treatment was defined as improvement,decreased ≥ 1.0kg defined as reduced, increased or decreased <1.0kg defined as stable. Chemotherapy related toxicities were assessed and graded according to WHO criteria (Miller et al., 1991).

Statistical analysis

Continuous variables were summarized by descriptive

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Table 1. KPS Scores, Body Weight Changes and Results for Toxicity and Immune Cell Populations

Group		Ubenimex	Control	P value
KPS scores	Improvement	2	1	
	Stable	21	11	
	Reduced	9	19	<0.05
	Stable rate (%)	65.6	35.5	<0.05
Body weights	Improvement	1	0	
	Stable	22	11	
	Reduced	9	20	<0.05
	Stable rate (%)	68.8	35.5	<0.05
Leukopenia ($\times 10^9$/L)		2.76±1.14	3.82±1.62	<0.05
Anemia (g/L)		9.26±5.78	16.2±7.32	<0.05
Thrombocytopenia ($\times 10^9$/L)		21.3±10.2	43.5±14.8	<0.05
T lymphocytes(CD3 +)				
Before treatment		65.2±21.3	64.9±20.4	
After treatment		70.6±22.5	52.2±18.6	
Change		+5.4±2.1	+12.7±4.3	<0.05
T assisted-induced lymphocytes (CD3+, CD4+)				
Before treatment		40.7±16.2	41.1±17.1	
After treatment		46.3±17.6	31.7±15.3	
Change		+5.6±1.9	+9.4±3.8	<0.05
T suppression, killing lymphocytes (CD3+, CD8+)				
Before treatment		22.1±8.4	23.7±7.9	
After treatment		23.3±8.9	24.4±9.7	
Change		+1.2±0.5	+0.7±0.3	<0.05
Natural killer cell(NK cell) (CD16+,CD56+)				
Before treatment		9.2±4.7	9.6±4.9	
After treatment		12.3±6.5	4.5±2.1	
Change		+3.1±1.4	-5.1±2.3	<0.05

Improvement: KPS score increase≥ 10 after treatment, stable :<10, reduced:decreased ≥ 10. Improvement: body weight increased ≥1.0 kg after treatment, reduced:decreased ≥1.0kg, stable:increased or decreased 1.0kg

statistics, categorical variables by frequency.Count data by Chi-square test; measurement data as mean ± standard deviation.P <0.05 was considered statistically significant.

The study data were analyzed through the STATA 8.0 software(Stata Corporation, 4905 Lakeway Drive College Station, Texas 77845 USA).

Results

Sixty-three patients, men 34 and women 29, were enrolled into this study,with age ranging from 45-81. All patients were randomly assigned to receive either ubenimex or placebo. Thirty-two patients entered into treatment group, 31 into the control group. No significant differences in terms of clinical characteristics were detected between two groups.

KPS score and body weight remained stable after chemotherapy in 65.6% and 68.8% of patients who assigned to treatment group compared with 35.5% and 35.5% in the control group (P <0.05) (see Table 1). Reduction of leukocytes, hemoglobin and platelet after chemotherapy in treatment group was less common than that in control group (P <0.05). T lymphocytes (CD3 +), T assisted, induced lymphocyte (CD3 +, CD4 +), T suppressor, NK cells (CD16 +, CD56 +) increased after chemotherapy in the treatment group, while decreasing in control group, with statistical signifcance between the two groups (P <0.05).

Discussion

In this study, we used KPS score and body weight to evaluate general performance of patients receiving chemotherapy. In ubenimex treatment group, both rates of KPS score and body weight declined only 28.1%, stable rate were 65.6% and 68.8% after chemotherapy compared with prior chemotherapy;while in control group, KPS score and body weight decreased significantly, rates of declining were up to 61.3% and 64.5%, both stable rates were only 35.5%,which suggested that ubenimex could decrease the possibility of deterioration of general performance for patients receiving chemotherapy.

Myelosuppression is a major concern when subjecting cancer patients to chemotherapy.However, myelosuppression, including reduction of leukocytes, hemoglobin and platelet, was mild in our treatment group when compared with control (P <0.05). On contrast, changes in T suppression and killing lymphocyte (CD3 +, CD8 +) between treatment and control groups indicated no statistically significant difference. T lymphocytes (CD3 +), T assisted, induced lymphocyte (CD3 +, CD4 +), T suppressor and NK cells (CD16 +, CD56 +) increased after ubenimex intake while decreased in control group(P <0.05), indicated that ubenimex could somehow ameliorate myelosuppression and affect immunologic index of patients.

Possible mechanism of our findings could be attributed to the fact that ubenimex is an effective immunomodulator (Umezawa et al., 1976), with a direct stimulating effect on lymphocytes (and monocytes) via its fixation on cell surface leucine-aminopeptidase, and an indirect effect on monocytes (and lymphocytes) via aminopeptidase B inhibition of tuftsin catabolism (Mathe 1991). Ubenimex can not only promote T cell proliferation and promote cell secretion of interleukin -1(IL-1), IL -2, interferon and other cytokines, but also activate monocytes / macrophages, inducing tumor cell apoptosis, exhibits anti-tumor effects (Ozono et al., 1990; Ino et al., 1996; Lin et al., 2002).

In summary, our study suggests that ubenimex capsule has the ability of improving general performance of patients during chemotherapy, improving the immunologic index of cancer patients, as well as reducing myelosuppression of chemotherapy.

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