RESEARCH ARTICLE

Clinical Comparison between Paclitaxel Liposome (Lipusu®) and Paclitaxel for Treatment of Patients with Metastatic Gastric Cancer

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Abstract

Aim: To compare the efficacy and safety of paclitaxel liposome (Lipusu®) with paclitaxel in combination with tegafur and oxaliplatin in treating patients with advanced gastric cancer. Materials and Methods: Patients with advanced gastric cancer receiving chemotherapy were retrospectively collected, and divided into two groups. Patients in group A received paclitaxel liposomes at a dose of 135 mg/m^2 on day 1 of each cycle, and patients in group B were given paclitaxel at the same dose with the same timing. All patients received tegafur at a dose of 500 mg mg/m^2 on days 1-5, and oxaliplatin at a dose of 80-100 mg/m^2 on day 1 for 2 cycles (each cycle was 21 d in total). Results: Fifty-eight patients could be evaluated for efficacy. The overall response rate was 47% in group A (14/30), and 46% in group B (13/28). Disease control rate was 73% in group A (22/30), and 71% in group B (20/28) (P>0.05). No significant differences were detected in hematologic and neurologic toxicities between the two groups (P>0.05). However, nausea, vomiting and hypersensitive reactions were significantly lower in group A than in group B (P<0.05). Conclusion: Paclitaxel liposomes are as effective as paclitaxel when combined with tegafur and oxaliplation in treating patients with advanced gastric cancer, but adverse reactions with paclitaxel liposomes are less common.

Keywords: Paclitaxel liposomes - pactitaxel - grast cancer - combined chemotherapy - adverse reactions

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Introduction

According to a latest estimation, stomach cancer is the third most common cause of death from cancer in males and the forth in females, with 989,600 new cancer cases and 738,000 deaths in 2010 (Jemal et al., 2011). The highest incidence rates are in Eastern Asia including China. Therefore, stomach cancer is a common disease which seriously hazard to human health (Ferlay et al., 2010). In the treatment of unresectable or metastatic gastric cancer, chemotherapy leads to a significant survival difference compared to best supportive care, and could relieve gastric cancer-related symptoms, and improve quality of life (Kucukzeybek et al., 2012). However, no standard regimen of chemotherapy has been established for patients with advanced gastric cancer. Cytotoxic agents that are considered effective in this setting include docetaxel, paclitaxel, oxaliplatin, irinotecan, 5-Fu, etc. (Kucukzeybek et al., 2012). How to increase efficacy and decrease toxicities of chemotherapy remains a focus in this area.

Paclitaxel is an alkaloid, which stabilizes microtubules and inhibits endothelial cell proliferation, motility, and tube formation (Belotti et al., 1996). It is widely used in treating a variety of carcinomas including refractory ovarian cancer, gastric cancer and non-small-cell lung cancer (NSCLC) (Drummond et al., 1999), but one problem associated with the administration of paclitaxel is its low solubility in most pharmaceutically-acceptable solvents. The paclitaxel formulation used clinically contains polyethoxylated castor oil (Cremophor EL) and dehydrated ethanol in a 1:1 (vol:vol) ratio. Cremophor EL is reported to cause toxic effects, e.g., life-threatening anaphylaxis (Szebeni et al., 1998; Van Zuylen et al., 2001). The administration of antihistamines and glucocorticoids is necessary to manage these adverse effects (Bookman et al., 1997), but these co-administered drugs have raised the possibility of additional pharmacokinetic and pharmacodynamic interactions with paclitaxel. This problem is sought to be alleviated either by synthesizing more soluble derivatives or by the administration of paclitaxel bound to more soluble formulation vehicles (Kobayashi et al., 2006). A variety of drug-delivery approaches were investigated to eliminate vehicle toxicity from paclitaxel formulations (Sharma et al., 1996; Scialli et al., 1997). Sharma and Straubinger developed a liposome-based paclitaxel formulation (Sharma et al., 1994). It provides a formulation alternative for the administration

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of paclitaxel and can confer beneficial effects on the pharmacology and toxicology of the drug. First data from a clinical phase I study using paclitaxel liposome are encouraging with respect to reducing toxic side effects (Treat et al., 2001). Lipusu® (Sike Pharmaceutical Co. Ltd., Nanjing, Jiangsu, P.R. China) is approved by the State Food and Drug Administration of China. It is the first paclitaxel liposome injection which is clinical used in China in 2006. It retained the growth-inhibitory activity of the free drug and reduced the toxicities (Chen et al., 2003; Yang et al., 2006; Kong et al., 2007). Yang et al. (2006) reported the cytotoxic effects and antitumor activities of Lipusu and concluded that Lipusu possesses the same antitumor activities in vitro and in vivo but its toxicity is lower than that of paclitaxel injection under the same dosage. Kong et al. (2007) suggested that the response rate (RR) is 39.1% in the treatment of NSCLC patients with Lipusu and cisplatin. Chen et al. (2003) compared Lipusu with conventional paclitaxel on treatments of breast cancer and NSCLC and demonstrated that both of them have similar efficacy but the former reduces the incidence of serious hypersensitive reactions significantly more than the latter. However, it is not clear whether the efficacy of paclitaxel liposome is superior to conventional paclitaxel. We hypothesize that paclitaxel liposome could be superior to conventional paclitaxel in treating patients with advanced gastric cancer.

Materials and Methods

Patient

All the patients were required to be pathologically diagnosed with gastric cancer, with Karnofsky performance status ≥ 60, aged between 18 and 75 years, predicted survival time ≥ 3 months. With adequate bone marrow (white blood cell count > 4.0×10^9 and platelet count > 100×10^9), and liver function (bilirubin and transaminases < 2 times the upper limit normal), no heart and kidney disease, and signed an informed consent before chemotherapy. Patients excluded from this study if they failed to complete two cycles of chemotherapy, with any serious medical or psychiatric condition, or other malignancies. Pregnant or lactating women are excluded from the study.

Treatment method

Eligible patients were divided into paclitaxel liposome group (Group A) or paclitaxel group (Group B).

Group A : Lipusu® (Paclitaxel liposome producted by Nanjing Sico pharmaceutical Co.) 135 mg/m^2 by intravenous infusion (iv) for > 3 h on day 1. Group B: Paclitaxel 135 mg/m^2 iv for > 3 h on day 1. Tegafur injection used by two groups is producted by Shandong Qilu pharmaceutical Co. (Each 0.5 g, Batch number: 00080222ET), 500 mg/m^2, iv, d1~5; Oxaliplatin injection used by two groups are all producted by Jiangsu AoSaikang pharmaceutical Co. (Each 50mg, Batch number: 080204), 80-100 mg/m^2, d1. Patients in Group B got premedication routinely, including oral dexamethasone 7.5 mg twice, 25mg promethazine hydrochloride injectionbefore treatment, cimetidine 400 mg,while Group A were only injected 5-10 mg dexamethasone intravenously before paclitaxel liposome.

Response Evaluation

Response evaluation with RECIST tumor chemotherapy criterion requirements was divided into complete remission (CR), partial response (PR), stability (SD), and disease progression (PD). It is defined that response rate (RR) = (CR + PR)/total, and clinical control (DCR) = (CR + PR + SD) /total (Van Zuylen et al., 2001). According to the WHO acute and subacute toxicity of anticancer drugs to identify performance and classification standard, adverse reaction is divided into 0 - IV degrees.

Statistical analysis

SPSS13.0 statistical software was used for statistical analysis. Statistically significant difference was set at $P < 0.05$. We have enough experience in conducting medical researches, and have published some results elsewhere (Huang et al., 2004; Zhou et al., 2009; Jiang et al., 2010; Yan et al., 2010; Gao et al., 2011; Huang et al., 2011; Li et al., 2011; Li et al., 2011; Li et al., 2011; Xu et al., 2011; Xu et al., 2011; Xu et al., 2011; Yan et al., 2011; Zhang et al., 2011; Gong et al., 2012; Li et al., 2012; Yu et al., 2012).

Results

Sixty-two patients meet the study criteria and entered two study groups. General characteristics of patients are shown in Table 1.

Efficacy Observation

There are 32 patients in group A and 30 in group B. However each group has 2 patients who cannot complete at least 2 cycles of chemotherapy and dropped out. Other cases are eligible for evaluating RR, which was conducted

Table 1. General Characteristics of Gastric Cancer Patients in Two Groups

Variable	Paclitaxel (n=30)	Paclitaxel liposome (n=32)
Median age (years)	56 (42~74)	54 (40~72)
Sex		
Male	22	24
Female	8	8
Primary tumor site		
Cardiac	10	9
Stomach	20	23
Pathological types		
Adenocarcinoma	26	27
Squamous cell carcinomas	1	2
Other	3	3

Table 2. The Response Rate of Patients with Advanced Gastric Cancer in Two Groups

Group	n	CR	PR	SD	PD	RR/%	DCR/%
Paclitaxel	28	0	13	7	8	46	71
Paclitaxel liposome	30	0	14	8	8	47	73

CR, complete remission; PR, partial response; SD, stability; PD, disease progression; RR, response rate; DCR, clinical control

Table 3. Adverse Reactions in Patients with Gastric Cancer in Two Groups

Adverse reactions	Paclitaxel (n=28)					Paclitaxel liposome (n=30)				
	I	II	III	IV	Incidence rates/%	I	II	III	IV	Incidence rates/%
Leukocytopenia	8	4	2	1	54	8	5	2	0	50
Thrombocytopenia	3	2	0	0	18	4	1	0	0	17
Hemoglobin reduction	4	3	1	0	29	3	4	1	0	27
Nausea and vomiting	8	4	2	0	50	4	2	1	0	23
Rash	7	0	0	0	25	1	0	0	0	3
Baldness	9	2	1	0	43	8	2	1	0	37
Dyspnoea	4	1	0	0	18	0	0	0	0	0
Myalgia	15	3	1	0	68	3	0	0	0	10
Liver dysfunction	3	1	0	0	14	2	1	0	0	10
Renal function abnormality	1	0	0	0	4	1	0	0	0	3
Peripheral neuritis	7	2	0	0	32	1	0	0	0	3
Diarrhea	2	1	0	0	11	1	1	0	0	7

after 4 cycles of chemotherapy. RR of group A and B were 47% and 46% respectively. No significant difference in RR was detected in two groups ($P > 0.05$), as shown in Table 2.

Toxicity Assessment

In 2 groups, main adverse reactions are hematologic and gastrointestinal, and nervous system toxicities ($P > 0.05$). The difference of incidence in alopecia, diarrhea and constipation between two groups is not statistically significant ($P > 0.05$), but the incidence of nausea and vomiting, rash, shortness of breath, muscle pain and peripheral neuritis in group A is lower than those in group B, with statistically significant difference ($P < 0.05$) (Table 3).

Discussion

Paclitaxel is a broad-spectrum plant kind of anti-cancer drugs. Through combination with cellular microtubules beta, it is reported to promote the microtubule polymerization, suppress the depolymerization and block mitosis, and further to inhibit tumor growth (Szebeni et al., 1998). In recent years, clinical studies suggested that paclitaxel has significant curative effect for a variety of solid tumors. But ordinary paclitaxel is almost insoluble in water, paclitaxel formulation used clinically contains Cremophor EL. Cremophor EL is associated with toxic effects, e.g., life-threatening anaphylaxis (Szebeni et al., 1998; Van Zuylen et al., 2001). Premedication with antihistamines and glucocorticoids is necessary (Bookman et al., 1997). Study in recent years suggested that, liposomes as a drug carrier could improve the histocompatibility and cellular affinity, improve the stability of paclitaxel, and reduce toxicity (Kobayashi et al., 2006).

This study suggested that the RR of paclitaxel liposome combined with tegafur and oxaliplatin be slightly superior to conventional paclitaxel in treating patients with advanced gastric cancer. The incidence of allergy, nausea and vomiting, rash, muscle pain in paclitaxel liposome group was lower than that in conventional paclitaxel group. In this study, RR of paclitaxel liposome and conventional paclitaxel was 47% and 46%. No statistically significant difference was detected between two groups, and this result is consistent with previous studies (Sharma et al., 1994; Sharma et al., 1996; Scialli et al., 1997). Before paclitaxel, patients should take premedication. But patients do not need strong premedication before paclitaxel liposome. Thus the latter is proper for patients who can not tolerate heavy dose of hormone.

In conclusion, paclitaxel liposome is as effective as conventional paclitaxel when combined with tegafur and oxaliplation in treating patients with advanced gastric cancer, and adverse reactions of paclitaxel liposome are less common.

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