PO Box 2345, Beijing 100023, China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

World J Gastroenterol 2004;10(20):3070-3072
World Journal of Gastroenterology
 ISSN 1007-9327

• BRIEF REPORTS •

Clinical significance of preoperative regional intra-arterial infusion chemotherapy for advanced gastric cancer

Cheng-Wu Zhang, Shou-Chun Zou, Dun Shi, Da-Jian Zhao

Cheng-Wu Zhang, Shou-Chun Zou, Dun Shi, Da-Jian Zhao, Department of General Surgery, Zhejiang Provincial People's Hospital, Hangzhou 310014, Zhejiang Province, China
Correspondence to: Cheng-Wu Zhang, Department of General Surgery, Zhejiang Provincial People's Hospital, Hangzhou 310014, Zhejiang Province, China. zcw1989@sina.com
Telephone: +86-571-85239988
Received: 2003-10-30 **Accepted:** 2003-12-16

Abstract

AIM: Preoperative intra-arterial infusion chemotherapy could increase the radical resection rate of advanced gastric cancer, but its effect on the long-term survival has not been assessed. This study was designed to evaluate the clinical significance of preoperative intra-arterial infusion chemotherapy for advanced gastric cancer.

METHODS: Clinicopathological data of 91 patients who underwent curative resection for advanced gastric cancer were collected. Among them, 37 patients undertaken preoperative intra-arterial infusion chemotherapy were used as the interventional chemotherapy group, and the remaining 54 patients as the control group. Eleven factors including clinicopathological variables, treatment procedures and molecular biological makers that might contribute to the long-term survival rate were analyzed using Cox multivariate regression analysis.

RESULTS: The 5-year survival rate was 52.5% and 39.8%, respectively, for the interventional group and the control group ($P<0.05$). Cox multivariate regression analysis revealed that the TNM stage ($P<0.001$), preoperative intra-arterial infusion chemotherapy ($P = 0.029$) and growth pattern ($P = 0.042$) were the independent factors for the long-term survival of patients with advanced gastric cancer.

CONCLUSION: Preoperative intra-arterial infusion chemotherapy plays an important role in improving the prognosis of advanced gastric cancer.

Zhang CW, Zou SC, Shi D, Zhao DJ. Clinical significance of preoperative regional intra-arterial infusion chemotherapy for advanced gastric cancer. *World J Gastroenterol* 2004; 10 (20): 3070-3072
http://www.wjgnet.com/1007-9327/10/3070.asp

INTRODUCTION

Gastric cancer is one of the most common cancers in China. Despite recent advances in experimental researches, early diagnosis and surgical techniques, the outcome of patients with gastric carcinoma is still far from satisfaction. Surgery remains the mainstay of potentially curative treatment, but the survival rates of patients with advanced gastric cancer are poor. A number of studies have investigated whether intravenous chemotherapy after a resection could improve the survival rate, but the results were different and disputable[1,2]. Preoperative regional intra-arterial infusion chemotherapy could increase the radical resection rate of advanced gastric cancer. However, there are few reports about the influence of preoperative intra-arterial chemotherapy on the long-term survival of patients with advanced gastric carcinomas after curative resections. In the current study, we analyzed retrospectively the clinicopathologic data of 91 patients with advanced gastric cancers undergone curative surgeries during recent years. To investigate the effect of preoperative intra-arterial chemotherapy on the prognosis of advanced gastric cancer, the Cox model of proportional hazards was utilized to identify the independent variables affecting the long-term survival of patients with gastric carcinomas.

MATERIALS AND METHODS

Clinicopathologic materials

The study comprised 91 patients who underwent curative resection for advanced gastric cancer from June 1984 to June 1992 at our hospital. All patients received follow-ups for 3 to 220 mo (mean time 57.1±23.8 mo) and their clinicopathologic data were well-provided. There were 69 males and 22 females,their ages ranged from 25 to 73 years with a mean age of 54.9±12.9 years. The tumor staging for each gastric cancer was evaluated according to the new TNM classification system of UICC[3], and there were 27 patients with stageII, 49 with stage III and 15 with stage IV. Of the 91 cases, 2 had well- differentiated adenocarcinomas, 48 had moderately differentiated adenocarcinomas and 41 had poorly differentiated adenocarcinomas. Thirty-one were negative for lymphatic vessel invasions and 60 were positive for lymphatic vessel invasions. For venous vessel invasion of tumor, 78 cases were negative and 13 were positive. The tumor growth pattern was defined according to Ming classification. There were 40 patients with expansive types and 51 with infiltrative types. Expressions of CD44 splice variants v6(CD44V6) and E-cadherin(E-CD) and proliferating cell nuclear antigen(PCNA) in all the 91 resected gastric carcinomous tissue specimens were detected by streptavidin-peroxidase immunohistochemistry. Of the patients, 37 patients undergone preoperative regional intra-arterial infusion chemotherapy were used as the interventional chemotherapy group and the remaining 54 patients as the control group. All the patients received systemic chemotherapy after surgeries. The clinicopathologic parameters of the two groups were analyzed and compared.

Preoperative intra-arterial infusion chemotherapy

Preoperative intra-arterial infusion chemotherapy was performed via transfemoral artery route using the Seldinger's approach before surgery. Celiac axis angiogram was initially carried out to document the visceral arterial anatomy and the arterial supply of tumor, and the digital subtraction technique was utilized in the study. According to the results of angiogram, the main blood supplying arteries of gastric cancer were detected and superselective catheterization of these arteries was performed. Then, chemotherapy drugs were administered via the placed catheter. Protocols of chemotherapy were FAP (5-FU 1.0 g+ADM 30-50 mg+DDP 40-60 mg) or FMP (5-FU 1.0 g+MMC 8-10 mg+DDP 40-60 mg). Preoperative interventional

chemotherapy was performed one or two times for each patient, and the interval time ranged from 10 to 14 d. Surgery was carried out two weeks after interventional chemotherapy. Of the 37 patients who underwent interventional chemotherapy, 31 received chemotherapy one time and 6 received two times.

Statistical analysis

The eleven variables observed including gender, age, preoperative intra-arterial infusion chemotherapy, TNM stage classification, differentiation grade, growth pattern, lymphatic vessel and venous vessel invasion, expressions of CD44V6 and E-CD, PCNA labeling index (PCNA LI), were stored in a computer, and analyses were performed using the SPSS 9.0 for Windows. Survival rates were calculated using life table method and the differences among the groups of patients were measured by Log rank test. Univariate analysis was performed first, and the variables found by univariate analysis significantly associated with survival rates were subjected to multivariate analyses using the Cox model of proportional hazards. $P<0.05$ was considered statistically significant.

RESULTS

Comparison of pathological parameters between two groups

The differences of pathological parameters were not significant between two groups ($P>0.05$, Table 1).

Comparison of immunohistochemistry results between two groups

The expressions of CD44V6 and E-CD and PCNA were not significantly different between two groups ($P>0.05$, Table 2).

Comparison of postoperative complications and survival rates between two groups

No death occurred due to surgery in this study. One wound infection and 1 pneumonic infection were found in the interventional chemotherapy group, whereas 2 pneumonic infections and 1 abdominal cavity infection occurred in the control group after surgery. The incidence of postoperative complications was not significantly different between two groups ($P>0.05$). The 5-year survival rate of the interventional chemotherapy group and the control group was 52.5% and 39.8%, respectively, and the difference between the two groups was significant ($P<0.05$).

Univariate and multivariate analyses of prognostic factors

The results of univariate analysis demonstrated that the factors including gender, age and tumor cellular differentiation grade were not associated with postoperative survival rate ($P>0.05$). The variables significantly correlated with survival rates were TNM stage, growth pattern of tumor, lymphatic vessel and venous vessel invasion, intra-arterial infusion chemotherapy, expressions of CD44V6 and E-CD, PCNA LI ($P<0.05$). These factors were subjected to multivariate analyses using the Cox model of proportional hazards. These analyses identified three independent prognostic variables which were TNM stage, preoperative interventional chemotherapy and growth pattern of tumor, according to influence strength (Table 3). The survival predicting equation ($\chi^2 = 37.63$, $P<0.001$) was obtained, it suggested the foundation of the equation be reasonable.

Table 3 Independent prognostic variables identified by Cox proportional hazard model

Variables	SE	Wald	df	Sig	R	Exp(B)
TNM stage	0.1220	16.3113	1	0.0001	0.1753	1.6304
Interventional chemotherapy	0.2501	4.7491	1	0.0285	0.0681	1.6981
Growth pattern	0.2607	4.0105	1	0.0417	0.0711	1.6953

DISCUSSION

Preoperative chemotherapy was initiated in the 1980s as an auxiliary therapy for malignant neoplasms[4]. It has been considered that preoperative chemotherapy could reduce activities of tumor cells, contract volumes of tumors, decrease iatrogenic diffusion of tumor cells during surgery, and improve curative resections for tumors. It was reported that serum concentration of chemotherapy drugs in abdominal organs by local intra-arterial infusion was nearly ten times as high as by systemic chemotherapy[5]. Kosaka *et al*.[6] investigated the therapeutic efficacy of intra-arterial infusion chemotherapy for advanced gastric cancer, and found that the response rate of tumors to intra-arterial infusion chemotherapy was significantly higher than that to systemic infusion chemotherapy. Liu[7] reported that the overall response rate to preoperative interventional chemotherapy was 72.8% for gastric carcinomas, and it was revealed that preoperative intra-arterial infusion chemotherapy exerted its effect by introducing apoptosis of cancer cells, restraining tumor cell proliferation and promoting pathological necrosis of tumors[8]. Tao *et al.* also demonstrated that preoperative regional artery chemotherapy showed inhibitory actions on growth of gastric cancer cells mainly through inhibiting proliferation and inducing the apoptosis of tumor cells[9]. Our previous study also showed that preoperative intra-arterial infusion chemotherapy could dramatically improve the rate of radical resection for gastric cancer. However, the

Table 1 Comparison of pathological parameters between two groups

Groups	TNM stage			Differentiation grade			Growth pattern		Lymphatic vessel invasion		Venous vessel invasion	
	II	III	IV	Well	Moderately	Poorly	Expensiv	Infiltrative	Negative	Positive	Negative	Positive
Interveytional	11	12	6	1	19	17	15	22	14	23	32	5
Control	16	29	9	1	29	24	25	29	17	37	46	8
	$P>0.05$			$P>0.05$			$P>0.05$		$P>0.05$		$P>0.05$	

Table 2 Comparison of immunohistochemistry results between two groups

Groups	Expression of CD44V6				Expression of E-CD				PCNA LI (%)
	-	+	++	+++	-	+	++	+++	
Interventional	8	14	5	10	11	13	9	4	63.8±17.6
Control	16	12	8	18	17	18	13	6	64.7±18.0
	$P>0.05$				$P>0.05$				$P>0.05$

influence of preoperative intra-arterial infusion chemotherapy on the prognosis of patients with gastric cancer has been controversial. Masuyama *et al.*[10] concluded that preoperative intra-arterial infusion chemotherapy might prevent local and lymph node metastases, but it could not improve the survival of gastric cancer patients. Whereas Shchepotin *et al.*[11] reported superselective intra-arterial chemotherapy conferred a highly significant survival advantage compared to control or systemic intravenous chemotherapy for advanced nonresectable gastric cancer. This study demonstrated that the 5-year survival rate of preoperative interventional chemotherapy group was significantly higher than that of the control group, and there was no statistical difference between the incidences of postoperative complications of the two groups. It is suggested that preoperative intra-arterial infusion chemotherapy is both effective and safe for patients with advanced gastric cancer.

Among the prognostic factors of gastric cancer, the influence of clinical modalities on the prognosis of patients has been the focus of studies on gastric cancer. It has been proved that the most important prognostic variable for gastric cancer is curative resection of tumor[12]. In the current study, all patients underwent curative resections of tumors. Furthermore, the clinicopathologic parameters of the two groups were not significantly different. This makes it possible to evaluate the effect of other therapeutic modalities on the prognosis of patients with advanced gastric cancers. As is shown in this article, among the seven variables significantly associated with the survival of patients with gastric cancer by univariate analysis, TNM stage was the most important independent prognostic factor by multivariate analyses using the Cox model of proportional hazards. It was consistent with previous reports[13]. The results of our study also revealed that preoperative intra-arterial infusion chemotherapy and growth pattern of tumors were the independent prognostic variables affecting long-term survival of gastric cancer patients, suggesting that preoperative intra-arterial infusion chemotherapy is of great importance in improving the prognosis of patients with advanced gastric cancers after undergoing curative resections.

In summary, the results of the present study revealed that preoperative intra-arterial infusion chemotherapy was one of the independent prognostic variables of patients with advanced gastric cancer. Therefore, preoperative intra-arterial infusion chemotherapy in combination with curative resection would have important clinical values in improving the prognosis of patients with advanced gastric carcinoma.

REFERENCES

1 **Hermans J**, Bonenkamp JJ, Boon MC, Bunt AM, Ohyama S, Sasako M, Van de Velde CJ. Adjuvant therapy after curative resection for gastric cancer: meta-analysis of randomized trials. *J Clin Oncol* 1993; **11:** 1441-1447

2 **Janunger KG,** Hafstrom L, Nygren P, Glimelius B. A systematic overview of chemotherapy effects in gastric cancer. *Acta Oncol* 2001; **40**: 309-326

3 **Yoo CH**, Noh SH, Kim Y, Min JS. Comparison of prognostic significance of nodal staging between old (4th edition) and new (5th edition) UICC TNM classification for gastric carcinoma. *World J Surg* 1999; **23**: 492-497

4 **Leong T**, Michael M, Foo K, Thompson A, Lim Joon D, Weih L, Ngan S, Thomas R, Zalcberg J. Adjuvant and neoadjuvant therapy for gastric cancer using epirubicin / cisplatin / 5-fluorouracil (ECF) and alternative regimens before and after chemoradiation. *Br J Cancer* 2003; **89**: 1433-1438

5 **Tokairin Y,** Maruyama M, Baba H, Yoshida T, Kure N, Nagahama T, Ebuchi M. Pharmacokinetics of "subselective" arterial infusion chemotherapy. *Gan To Kagaku Ryoho* 2001; **28:** 1795-1798

6 **Kosaka T**, Ueshige N, Sugaya J, Nakano Y, Akiyama T, Tomita F, Saito H, Kita I, Takashima S. Evaluation of intra-arterial infusion chemotherapy for advanced gastric cancer. *Gan To Kagaku Ryoho* 1998; **25:** 1288-1291

7 **Liu FK.** The interventional therapy for advanced gastric cancer before and after operation. *Zhongguo Shiyong Waike Zazhi* 2001; **21**: 403

8 **Dong XC**, Li B, Li YP. Effect of preoperative intra-arterial chemotherapy on apoptosis and p53 expression of gastric cancer. *Aizheng* 2002; **21**: 1078-1080

9 **Tao HQ,** Zou SC. Effect of preoperative regional artery chemotherapy on proliferation and apoptosis of gastric carcinoma cells. *World J Gastroenterol* 2002; **8:** 451-454

10 **Masuyama M,** Taniguchi H, Takeuchi K, Miyata K, Koyama H, Tanaka H, Higashida T, Koishi Y, Mugitani T, Yamaguchi T. Recurrence and survival rate of advanced gastric cancer after preoperative EAP-II intra-arterial infusion therapy. *Gan To Kagaku Ryoho* 1994; **21:** 2253-2255

11 **Shchepotin IB,** Chorny V, Hanfelt J, Evans SR. Palliative superselective intra-arterial chemotherapy for advanced nonresectable gastric cancer. *J Gastrointest Surg* 1999; **3**: 426-431

12 **Allgayer H,** Heiss MM, Schildberg FW. Prognostic factors in gastric cancer. *Br J Surg* 1997; **84:** 1651-1664

13 **Hermanek P**, Wittekind C. News of TNM and its use for classification of gastric cancer. *World J Surg* 1995; **19:** 491-495

Edited by Wang XL and Xu FM