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• *GASTRIC CANCER* •

Long-term effects of proglumide on resection of cardiac adenocarcinoma

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Abstract

AIM: Patients with advanced stage cardiac adenocarcinoma have a very poor prognosis. Surgery is the first choice of treatment for this kind of patients. Peptide hormone gastrin is a recognized growth factor for gastric cancer, and gastrin receptor antagonist proglumide can block the effects of gastrin. The aim of this study was to investigate the actions of proglumide as an adjuvant treatment to improve the postoperative long-term survival rate of patients with cardiac adenocarcinoma.

METHODS: We performed a randomized, controlled study of gastrin receptor antagonist proglumide in 301 patients with cardiac adenocarcinoma after proximal subtotal gastrectomy. The oral dose of 0.4 g proglumide thrice daily preprandially was maintained for more than 5 years in 153 cases (proglumide treatment group). In the control group, 148 patients underwent operation only. In clinicopathologic features, there was no significant difference between the two groups (P>0.05). All patients were followed up during their lifetime, and the survival rates were analyzed combined with clinicopathologic factors by SPSS 11.5 statistical software.

RESULTS: The 1, 3, 5 and 10-year survival rate of the patients was 88.4%, 48.8%, 22.6% and 13.4%, respectively. The 1, 3, 5 and 10-year survival rate of the proglumide treatment group was 90.2%, 49.7%, 26.8% and 17.6% compared to 86.5%, 48.0%, 18.2% and 8.9% of the control group. There was a significant difference between the two groups (P = 0.0460). The patients in proglumide treatment group had no obvious side effects after administration of the drug, and no definite hepatic and renal function damage was found. According to single factor log-rank analysis, the long-term survival rate was correlated with the primary tumor position (P = 0.0205), length of the tumor (P = 0.0000), property of the operation (P = 0.0000), histopathologic grading (P = 0.0003), infiltrating degree of the tumor (P = 0.0000), influence of lymph node metastasis (P = 0.0000), clinicopathologic staging (P = 0.0000) and administration of proglumide (P = 0.0460). Cox regression analysis demonstrated the infiltrating degree of tumor (P = 0.000), influence of lymph node metastasis (P = 0.039) and the clinicopathologic staging (P = 0.003) were independent prognostic factors. Administration of proglumide (P = 0.081), length of the tumor (P = 0.304), radical status of the resection (P = 0.224) and histopathologic types (P = 0.072) were not the independent prognostic factors.

CONCLUSION: Proglumide is convenient to use with no obvious toxic side effects, and prolonged postoperative administration of proglumide as a postoperative adjuvant treatment can increase the survival rate of patients after resection of cardiac adenocarcinoma. Proglumide may provide a new effective approach of endocrinotherapy for patients with gastric cardiac cancer.

Key words: Proglumide; Cardiac adenocarcinoma

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INTRODUCTION

The optimal treatment for cardiac adenocarcinoma is surgery, but its long-term effect is still unsatisfactory[1-5]. In order to improve postoperative long-term survival rate of patients with cardiac carcinoma, from March 1990, a randomized prospective study of proglumide as adjuvant treatment for patients with cardiac adenocarcinoma after resection was conducted[6]. We observed its long-term efficacy.

MATERIALS AND METHODS

Clinical data

From March 1990 to December 1995, 457 patients with cardiac carcinoma received surgical management in the Department of Thoracic Surgery, Tumor Hospital of Shantou University Medical College. Through left thoracotomy, 395 cases had their tumor resected and then underwent subtotal gastrectomy and esophagogastric anastomosis below aortic arch, with an 86.4% resectable rate. The remaining 62 cases were only explored. Among the patients receiving resection of tumor, one case died of myocardiac infarction, 82 underwent postoperative adjuvant chemotherapy, and 11 received postoperative radiotherapy. They were all excluded from our study. Three hundred and one cases were enrolled in this study and divided into proglumide treatment group and

Table 1 Clinicopathologic characteristics of the patients

	Proglumide treated group	Control group	χ^2	*P*
n	153	148		
Sex (M/F)	115/38	122/26	2.374	0.123
Age (mean)	59.6	57.5	1.463	0.226
Location				
Cardiac	71	72	0.152	0.697
Cardiac & lower esophagus	82	76		
Tumor size				
<3 cm	17	11	1.321	0.517
3-5 cm	27	25		
>5 cm	109	112		
Margin cancer				
Not stated	132	132	0.917	0.632
Upper margin (+)	15	10		
Lower margin (+)	6	6		
Property of resection				
Radical (grade A+B)	102	91	0.877	0.349
Palliative (grade C)	51	57		
Differentiation				
High and moderate	93	84	0.774	0.856
Poor	38	40		
Undifferentiated	6	5		
Mucinous adenocarcinoma	16	19		
Depth of invasion				
Muscular layer	35	36	2.342	0.310
Tunica serosa	98	84		
Infiltration	20	28		
Lymph node metastasis				
(-)	61	62	0.127	0.721
(+)	92	86		
Stage				
I	19	11	3.120	0.374
II	43	52		
III	82	77		
IV	9	8		

control group (only surgery group). The clinicopathologic features are presented in Table 1. The radical status of resection was classified by criteria of diagnosis and management, and the staging used in the study was based on UICC1988 PTNM stage for gastric cancer[7].

The patients in proglumide treatment group continuously took 0.4 g of proglumide, thrice daily, 15 min preprandially, for 5 years or more. All patients in the two studied groups took compound vitamin B_{co} and vitamin E as well. The patients received no additional chemotherapy, radiotherapy, immunotherapy, or traditional Chinese medicine in our study.

Follow-up and statistical analysis

All the patients were followed up during their lifetime, and the follow-up rate was 95.3%. The patients who failed to receive follow-up were assumed to have died as they could not be contacted before the deadline. The patients followed up as outpatients received hepatic and renal function test regularly. Statistical analysis was performed using SPSS 11.5 software, and survival rate was calculated by Kaplan-Meier method. Single factor analysis was carried out using log-rank time sequence test, and multiple factors analysis was made using Cox proportional hazard model.

RESULTS

The overall 1-, 3-, 5- and 10-year survival rate was 88.4%, 48.8%, 22.6%, 13.4%, respectively. The patients in proglumide treatment group had no obvious side effects after administration of the drug, and no definite hepatic and renal function damage was found in followed patients. The 1-, 3-, 5- and 10-year survival rate in proglumide treatment group was 90.2%, 49.7%, 26.8% and 17.6% compared to 86.5%, 48.0%, 18.2% and 8.9% in the control group ($P = 0.0460$).

According to single factor log-rank analysis, the location of the disease ($P = 0.0205$), the length of tumor ($P = 0.0000$), radical status of resection ($P = 0.0000$), histopathological types ($P = 0.0003$), infiltrating depth ($P = 0.0000$), clinicopathologic staging ($P = 0.0000$) were all significant prognostic factors. However, the age, gender and residual end carcinoma were not associated with prognosis.

Cox regress multiple factor analysis also showed that infiltrating depth ($P = 0.0000$), lymph node involved status ($P = 0.039$) and clinicopathologic staging ($P = 0.003$) were independent prognostic factors. The length of tumor ($P = 0.304$), radical status of resection ($P = 0.224$), histopathologic types ($P = 0.072$) and administration of proglumide ($P = 0.081$) were regarded as independent prognostic factors.

DISCUSSION

Cardiac carcinoma is a common tumor in our country. Its main treatment is still surgical resection by far, the 5-year survival rate of surgical resection was just 17.6% to 25.1%[1,5]. The 5-year survival rate of palliative resection was 8.0%[5,8]. Moreover, because of the physical and anatomical characteristics of cardia, it is difficult to make early diagnosis of the disease, resulting in the limited efficacy of radical treatment.

When cardiac tumor infiltrated less than one-third of lesser curvature, proximal gastrectomy was mainly performed for cardiac carcinoma[9]. The acidic function of residual stomach apparently decreased after operation, leading to a massive secretion of gastrin from G-cells in mucosa of gastric antrum. The sustained increase of circulating gastrin was found after truncal vagotomy and removal of vagus nerve around proximal stomach, resulting in elevation of gastrin in baseline and postprandial level about twice higher than that before operation[10]. Serum gastrin concentration in empty stomach after resection of cardiac carcinoma was 2.9 times as high as that before operation, and the postprandial peak value was 2.3 times as high as that before operation[11]. At the same time, it was reported that some gastric cancer cells secreted gastrin[12-14]. It has been confirmed that there are gastrin receptors upon the membranes of gastric carcinoma cells[12-16]. Furthermore, the positive rate of high-affinity and high-content gastrin receptors in cancer of gastric body and fungus was higher than that in cancer of gastric antrum[17], and advanced gastric carcinoma was easier to express high-affinity and high-content gastrin receptors than early and moderate gastric cancer[18].

In the course of the development and growth of gastric cancer, gastrin played a role in promoting proliferation of tumor cells[19-21]. After the combination of gastrin and its receptors, the flow of intracellular Ca^{2+} was triggered, activating cyclic-AMP and cyclic-AMP-depended protein kinase system, regulating the expression of early genes, such as *c-fos* and

c-jun[22-24] associated with cell differentiation through the conduction of intracellular information so as to enhance the growth of gastric tumor cells, inhibit cell apoptosis[22] and exert its biological effects of carcinogenesis and tumor promotion. This is likely to be another reason why the survival rate of patients with cardiac carcinoma is hard to improve.

Proglumide, an antagonist of gastrin receptors, could completely block the proliferation of tumor cells caused by exogenous gastrin[25]. It has been shown *in vitro* that proglumide can completely inhibit growth of cancer cells, MKN_{45}[25-27]. Animal experimental studies *in vivo* also demonstrated that proglumide could block the growth of xeno-transplanted gastric cancer, make the tumor size much smaller, tumor weight much lighter, average DNA content and S-phase fraction of gastric cancer cells much lower[25,28-30]. Furthermore, it was also able to induce apoptosis to exert anti-tumor actions[25]. Unlike chemotherapy or radiotherapy which could eliminate tumors directly, proglumide restrained the growth of gastric cancer with positive gastrin receptors and could be used as an adjuvant endocrine therapy after operation[25,29]. Nevertheless, there were few reports using proglumide in clinical therapy. Harrison *et al*, treated patients with advanced stage gastric carcinoma by proglumide, and achieved a prolonged survival time. We used proglulmide as an adjuvant therapy after operation and achieved a better efficacy[6], which was probably related with the high positive rate of high-affinity and high-content gastric receptors.

In conclusion, proglumide can be utilized as an alternative adjuvant therapy. Along with the development of more specific antagonists of gastrin receptors, a more efficient endocrine therapy for patients with cardiac adenocarcinoma will be available.

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