·肿瘤介入 Tumor intervention·

Intra-arterial chrono-chemotherapy for liver metastasis arised from colorectal cancer

HUANG Jin-hua[1,2], ZHANG Liang[1,2], WU Pei-hong[1,2], FAN Wei-jun[1,2], ZHANG Fu-jun[1,2], GU Yang-kui[1,2], ZHAO Ming[1,2] and CHENG Ying-sheng[3]

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1.State Key Laboratory of Oncology in South China, Guangzhou, Guangdong 510060, P, R. China 2. Department of Medical Imaging and Interventional Therapy, Cancer Center, Sun Yat-Sen University, Guangzhou ,Guangdong 510060, P, R. China 3.Department of Radiology, Sixth People's Hospital, Shanghai Jiao Tong University, Shanghai 200233, P, R. China.

【Abstract】 Objective To evaluate the toxic effects and efficacy of the intra-arterial chrono-chemotherapy on patients with liver metastasis arised from colorectal cancer. **Methods** Chemotherapy of 42 patients were randomly divided into group A (n = 20) with continuously constant arterial infusion, and group B (n = 22) with arterial chrono-modulated infusion. And the toxic effects and efficacy of two groups were compared. **Results** A significant difference was found in the toxic effects of digestive system between the two groups. The treatment response was similar in the two groups. **Conclusions** Intra-arterial chrono-chemotherapy may decrease the toxic effects and improve the life quality of these patients. (J Intervent Radiol, 2006, 15: 487-490)

【Key words】 Liver metastasis; Colorectal cancer; Chrono-chemotherapy; Intra-arterial infusion

Introduction

Colorectal cancer has a tendency to involve the liver. Unfortunately, for the patients with liver metastasis surgical resection rate is very low, and so chemotherapy becomes a primary treatment method. Some authors have reported that systemic chemotherapy via the chrono-modulated infusion can decrease the toxic effects of the anticancer drugs because of the effect of circadian rhythms[1], and if chemotherapy via the arterial infusion, the local concentration of the drugs in tumor tissue can be increased to 7 – 10 times of the concentration of systemic chemotherapy and resulted in a better efficacy than systemic chemotherapy[2,3]. However, the study of the combination of both methods mentioned above has not yet been reported. In this paper, a randomized prospective clinical trial was designed to evaluate the toxic effects and efficacy of the arterial chrono-chemotherapy and the result of 42 patients was reported.

Authors setting: 510060 Cancer Center, Sun Yat-Sen University, Guangzhou, Guangdong

Corresponding author: WU Pei-hong

Methods

General information 42 patients, 19 males and 23 females ranging form 27 to 71year of age (average 49.4), with liver metastasis alone arised from colorectal cancer were studied. All the primary lesions of 42 cases had been removed and adenocarcinoma was confirmed pathologically. None of the liver lesions had received any other treatment before this therapy. Liver function of all the patients was under 2.5N (< = I degree, according to the criteria of WHO). 42 patients were randomly divided into group A (n = 20) with continuously constant arterial infusion and group B (n = 22) with arterial chrono-modulated infusion. The characteristics of two groups were shown in Table 1.

Interventional procedure Using Seldinger's technique, the catheter was inserted into the proper

hepatic artery if the lesions located in both the right and left lobes. If the lesions located in the right or left lobes of the liver, catheter should be selected into the right or left hepatic arteries. The gastroduodenal artery was sometimes embolized if necessary. Portal catheter system (PCS) was implanted under the subcutis of the right inguinal ligament.

Table1 Baseline characteristics of two groups

Characteristic		Group A (n = 20)	Group B (n = 22)
median age(year)		47.2	53.4
sex	F	12(60%)	11(50%)
	M	8(40%)	11(50%)
Primary tumour			
	colon	14(70%)	16(72.7%)
	rectum	6(30%)	6(27.3%)
Number of liver metastatasis			
	≤2cm	3(15%)	4(18.2%)
	>2cm	17(85%)	18(81.8%)
Location of metastasis			
	Right lobe	6	5
	Left lobe	2	1
	Both lobes	12	16

Chemotherapy regimen Every patient was arranged to receive two treatment courses and then received further chemotherapy or radio-frequency ablation, according to the patient's response to the treatment. Anticancer drugs was administered through an ambulatory multichannel programmable pump which was devised to avoid chemical interactions of drugs. Daily doses included fluorouracil (or 5-Fu) 600 mg/m^2, folinic acid (or CF) 300 mg/m^2, and oxaliplatin (or LOHP) 20 mg/m^2. Drugs were delivered by constant-rate infusion or chronomodulated infusion in 24 hours and repeated for 5 consecutive days in each course. Next course could be performed after a 21-day interval if necessary. In group B, 5-Fu was infused via arterial PCS from 22:00 h to 10:00 h with the peak flow rates at 04:00 h, and LOHP was infused via arterial PCS from 10:00 h to 22:00 h with the peak flow rates at 16:00 h (figs.2-4). But, chronomodu-lated infusion of CF was via vein with the same rate as that of 5-FU. In the group A, the constant-rate infusion of 5-FU and LOHP were also performed by arterial PCS and the constant-rate infusion of CF was via vein too.

Efficacy evaluation and statistical analysis The toxic effects including nausea, vomiting, mucositis, diarrhea, liver function damage, bone marrow depression, neuritis and skin toxicity ect. were observed and recorded, and divided into five grades according to the criteria of WHO. CT and MRI were used to evaluate the tumor response to the therapy after two courses of treatment, and the results were defined according to the WHO criteria. All data were statistically analyzed by SAS software with χ^2 test or flash exact test.

Results

The toxic effects of 84 courses of the two groups were assessed as seen in Table 2. The difference on the toxic effect of the digestive system, such as nausea, vomiting and mucositis etc were statistically significant ($P < 0.05$). However, the other toxic effects of two groups were found no significant difference statistically.

In addition, 40% of the 20 patients in group A and 40.9% of the 22 patients in group B had an objective response to chemotherapy (partial remission of the liver metastasis), but there was no significant difference statistically ($P = 0.9522$).

Discussion

Hepatic arterial infusion of chemotherapeutic agents can shrink the size of liver metastatic lesions providing a chance for surgical or radio frequency ablation therapy, and combinative use of the 5-FU, CF and LOHP was the first regimen for the liver metastasis arising from the colorectal carcinoma with an objective response rate from 24% to 48%[4-6]. In our study, the objective response rate of 42 patients was 40% - 41%. Levi and his colleagues[7-11]reported that more than 1500 patients with metastatic colorectal cancer treated by this regimen (5-FU, CF, and LOHP), and the toxic effects of chronotherapy group were obviously lower than those of the control group. The study of Levi et al. evidenced that in chrono-chemotherapy tolerance of body to anticancer drugs

Table2 Toxic effects in 84 course of two groups

Toxic effects	Group A(n = 40)*	Group B(n = 44)*	P Value
Nausea and vomiting			
Grade 0, Ⅰ or Ⅱ△	33(82.5%)	44(100%)	
Grade Ⅲ or Ⅳ△	7(17.5%)	0(0%)	P = 0.0123
Mucositis			
Grade 0, Ⅰ or Ⅱ	31(77.5%)	43(97.7%)	
Grade Ⅲ or Ⅳ	9(22.5%)	1(2.3%)	P = 0.0117
Diarrhea			
Grade 0, Ⅰ or Ⅱ	38(95%)	44(100%)	
Grade Ⅲ or Ⅳ	2(5%)	0(0%)	P = 0.4326
Liver function damage			
Grade 0, Ⅰ or Ⅱ	38(95%)	43(97.7%)	
Grade Ⅲ or Ⅳ	2(5%)	1(2.3%)	P = 0.9330
Bone marrow depression			
Grade 0	36(90%)	42(95.5%)	
Grade Ⅰ or Ⅱ	4(10%)	2(4.5%)	P = 0.5855
Grade Ⅲ or Ⅳ	0	0	
Neuritis	0	0	
Skin toxicity	0	0	
Kidney toxicity	0	0	

* n was indicated as the number of chemotherapic courses.

△ Grade 0, Ⅰ or Ⅱ was indicated as the absent, mild or moderate toxic effects separately. Grade Ⅲ or Ⅳ was indicated as the degree of severe effects.

changed with the circadian rhythm, and so the doses could be added without increasing toxicity if being administered in high tolerance periods. On the basis of these evidences, combined chronochemotherapy with arterial infusion was used in this study, in order to reduce the toxicity of chemotherapeutical agents and improve the life quality of patients.

The anticancer mechanism of 5-FU is to inhibit thymidylic acid synthase, decrease the content of thymidylic acid and result in inhibition of DNA synthesis, which ultimately leads to cell death. DPD enzyme is a catabolic rate-limiting enzyme of 5-FU, whose activation level will affect the toxicity of anticancer drugs like 5-FU to body. Infusing 5-FU at night (22:00 h–10:00 h) with a peak at 03:00 h-05:00 h, which is coincident with the peak period of activity of DPD in the cells of bone marrow and gastrointestinal mucosa, so that the toxic effects of 5-FU can be reduced[12]. In this study, the incidences of nausea, vomiting and mucositis in chrono-chemotherapy group were obviously lower than those of continuous infusion group, and no severe diarrhea was found.

In addition, reduced glutamylcysteinyl glycine is an important triple peptid, which exists in most mammal animal's tissues. It participates in a variety of physiologic reactions, and serves as a reductant. It can also reverse the cytotoxicity made by some drugs such as alkylating agent and platinum derivatives. Smaaland et al [13] after a research on ten healthy persons found that the content of GSH (reduced glutathione hormone) changed with the circadian rhythm and its content in bone marrow cells was as follows: peak value at 08:30 h (activity phase), trough value at 20:30 h (rest phase). The experience in recent 20 years of chrono-chemotherapy combined 5-FU, CF with LOHP in EORTC center showed that peripheral sensory neuropathy induced by LOHP decreased to half[7,14]. But, such changes were not observed in our study.

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·病例报告　Case report·

门静脉支架置入术一例

陈家焱，马桂香，于　江，姬广翠

【关键词】 支架术;门静脉
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Stenting for portal vein one case report *CHEN Jia-ying, MA Gui-xiang, YU Jiang, JI Guang-cui. Siyang County Hospital of Jiangsu Province 223700, China* (J Intervent Radiol, 2006, 15: 490)

【Key words】 Stenting;Portal vein

患者 男,70 岁。食欲不振,消瘦伴右上腹隐痛 1 个月余,来本院就诊。彩超:肝左叶见 6.1 cm × 5.3 cm 实性低回声,界欠清,门静脉径宽 1.9 cm,主干内见一约 4.9 cm × 1.9 cm 实性低回声。诊断:肝癌伴门脉癌栓形成。CT 平扫:肝左叶局部低密度区,界欠清,增强扫描,肝脏左叶增大,内见一约 6.0 cm × 5.0 cm 低密度区,CT 值 + 68HU,延长扫描左叶低密度影仍在,CT 值+48HU,门脉主干癌栓形成。肝、肾功能、血常规等各项检查均无介入手术禁忌证。在造影室消毒、铺巾,局麻后先采用 Seldinger 技术经右侧股动脉穿刺插管成功,选择性将导管置肝固有动脉造影,见有明显肿瘤血管染色。再经皮经肝肝内门静脉右支穿刺成功(图 1),将导丝越过癌栓段,交换导管将导管置门静脉主干汇合处造影,见门静脉主干一长约 4.5 cm × 3.0 cm 大小癌栓(图 2),将 10 mm × 70 mm 记忆合金支架准确定位后释放成功,再次造影证实通畅(图 3)。再经导管行肝动脉化疗栓塞术,见有明显碘油沉积。术后经保肝、保护胃黏膜及预防感染治疗 5 d 好转出院。一个半月后再次行肝动脉化疗栓塞术,随访 5 个月仍生存,生活质量明显提高。8 个月后死于肿瘤广泛转移。

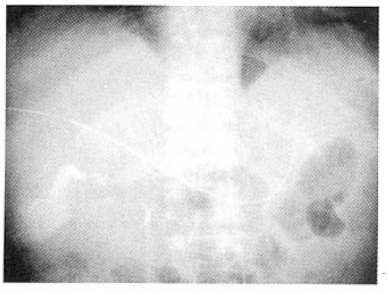

图 1　经皮经肝穿刺,导丝进入门静脉

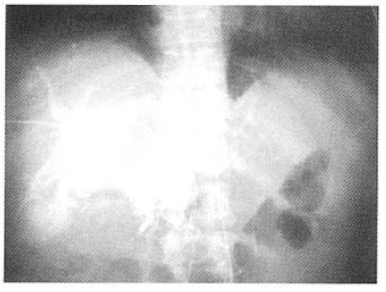

图 2　门静脉造影见巨大癌栓

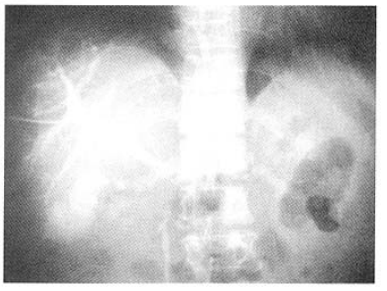

图 3　放入支架后造影,门静脉通畅

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作者单位:223700　江苏省泗阳县人民医院放射科
通讯作者:陈家焱