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• *GASTRIC CANCER* •

Oral Xeloda plus bi-platinu two-way combined chemotherapy in treatment of advanced gastrointestinal malignancies

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Abstract

AIM: To compare the effect, adverse events, cost-effectiveness and dose intensity (DI) of oral Xeloda *vs* calcium folinate (CF)/5-FU combination chemotherapy in patients with advanced gastrointestinal malignancies, both combined with bi-platinu two-way chemotherapy.

METHODS: A total of 131 patients were enrolled and randomly selected to receive either oral Xeloda (X group) or CF/5-FU (control group). Oral Xeloda 1 000 mg/m^2 was administered twice daily from d 1 to 14 in X group, while CF 200 mg/m^2 was taken as a 2-h intravenous infusion followed by 5-FU 600 mg/m^2 intravenously for 4-6 h on d 1-5 in control group. Cisplatin and oxaliplatin were administered in the same way to both the groups: cisplatin 60-80 mg/m^2 by hyperthermic intraperitoneal administration, and oxaliplatin 130 mg/m^2 intravenously for 2 h on d 1. All the drugs were recycled every 21 d, with at least two cycles. Pyridoxine 50 mg was given t.i.d. orally for prophylaxis of the hand-foot syndrome (HFS). Then the effect, adverse events, cost-effectiveness and DI of the two groups were evaluated.

RESULTS: Hundred and fourteen cases (87.0%) finished more than two chemotherapy cycles. The overall response rate of them was 52.5% (X group) and 42.4% (control group) respectively. Tumor progression time (TTP) was 7.35 mo *vs* 5.95 mo, and 1-year survival rate was 53.1% *vs* 44.5%. There was a remarkable statistical significance of TTP and 1-year survival between the two groups. The main Xeloda-related adverse events were myelosuppression, gastrointestinal toxicity, neurotoxicity and HFS, which were mild and well tolerable. Therefore, no patients withdrew from the study due to side effects before two chemotherapy cycles were finished. Both groups finished pre-arranged DI and the relative DI was nearly 1.0. The average cost for 1 patient in one cycle was ￥9 137.35 (X group) and ￥8 961.72 (control group), or US $1 100.89 in X group and $1 079.73 in control group. To add 1% to the response rate costs ￥161.44 *vs* ￥210.37 respectively (US $19.45 *vs* $25.35). One-month prolongation of TTP costs ￥1 243.18 *vs* ￥1 506.17 (US $149.78 *vs* $181.47). Escalation of 1% of 1-year survival costs ￥172.74 *vs* ￥201.64 (US $20.75 *vs* $24.29).

CONCLUSION: Oral Xeloda combined with bi-platinu two-way combination chemotherapy is efficient and tolerable for patients with advanced gastrointestinal malignancies; meanwhile the expenditure is similar to that of CF/5-FU combined with bi-platinu chemotherapy, and will be cheaper if we are concerned about the increase of the response rate, TTP or 1-year-survival rate pharmacoeconomically.

Key words: Pharmacoeconomic; Xeloda; Advanced gastrointestinal malignancy; Hyperthermic intraperitoneal chemotherapy; Dose intensity

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INTRODUCTION

Pharmacoeconomics is a method to study the various economic costs associated with prescribing a given drug or a treatment regimen. This field of health services research and technology assessment developed in the 1960s, and it is only in the last decade that scholars have been trying to develop strong standards for its use[1]. There are four main kinds of cost analysis involved. First, the analysis of cost minimization is to find the most inexpensive treatment. Second, the cost-effectiveness analysis takes a single outcome into account, such as years of life saved, and attempts to determine the cost for each year of those additional years. The third analysis is cost utility. It is a subtype of cost-effectiveness and incorporates quality-of-life measures that focus on a patient's Quality Adjusted Life Year. The fourth is cost-benefit analysis. This analysis puts a dollar amount on additional years of life. Among the four analyses, the cost-effectiveness analysis is widely and more often used to compare the costs and clinical outcomes of competing treatment options[2]. This analysis provides an estimate of

the costs incurred to achieve a particular outcome. It is measured by dividing a therapy's total cost by its therapeutic effectiveness, which might be cure rate, remission rate, or some other end point depending on the drug and disease involved[3-5]. Oncology pharmacoeconomics differs slightly from pharmacoeconomics for drugs for other diseases. Pharmacoeconomics of anticancer drugs is to offer an effective, safe and economic regimen for patients with end-stage cancer under the precondition of limited medical cost.

Gastrointestinal cancer ranks the top of the morbidity and mortality of the cancer in China. The general chemotherapy usually has little effect on the end-stage patients with little opportunity to resect because of implantation in cavity, local recurrence after operation, or metastasis of lymph node or viscera. From December 2001 to April 2004, 131 end-stage cases of carcinoma of stomach and colorectum in our department were admitted for the new combination chemotherapy. Among them, 51 cases received the regimen of oral Xeloda with bi-platinu (oxaliplatin and cisplatin) in two ways (intravenous and intraperitoneal administration), the other cases received the regimen of calcium folinate (CF)/5-FU with bi-platinu in the same two ways as the former. The cost-effectiveness and quality-of-life index effect of this new chemotherapy regimen were compared with another chemotherapy. The dosage intensity of these two chemotherapy regimens were also compared.

MATERIALS AND METHODS

Patients

A total of 131 cases of advanced gastrointestinal cancer with 80 men and 51 women, mean age being 57.6 years ranging from 33 to 83 years were included. There were 61 cases of gastric carcinoma and 70 cases of colorectal cancer. All the patients were in stage IV by clinical assessment, which was confirmed by biopsy. About 83.7% of patients had received one combination chemotherapy at least, but no chemotherapy was administered to them within a month. Karnofsky performance status of all these patients measured at baseline was $\geqslant$60, and the anticipative survival time was $\geqslant$3 mo with observable objective index of the focus. They were randomly divided into two groups, Xeloda and control group (abbreviated as X group and C group, respectively). The main clinical characteristics of the two groups are listed in Table 1.

Table 1 Clinical characteristics of stage IV gastrointestinal cancer

Clinical characteristics	Gastric cancer		Colorectal cancer	
	X group	C group	X group	C group
Male / female	21 / 11	17 / 12	19 / 16	23 / 12
Age: mean (range / yr)	63.6 (36–83)	61.0 (33–80)	62.9 (45–75)	60.8 (34–74)
Recurrence (%)	14 (43.8)	14 (48.3)	8 (22.9)	9 (25.7)
Metastasis				
Liver (%)	17 (53.1)	16 (55.2)	21 (60.0)	22 (62.9)
Lung (%)	8 (25.0)	7 (24.1)	11 (31.4)	10 (28.6)
Celiac lymph node (%)	21 (65.6)	21 (72.4)	14 (40.0)	15 (42.9)
Others (%)	8 (25.0)	9 (31.0)	12 (34.3)	10 (28.6)
Previous chemotherapy	23 (71.9)	22 (75.9)	17 (48.6)	19 (54.3)

Drugs

Xeloda® was supplied as white film-coated tablets containing 500 mg capecitabine manufactured by Roche Pharmaceutical Ltd. CF and oxaliplatin were purchased from Jiangshu Henrui Pharmaceutical Co. Ltd, packed in 100 or 50 mg per vial and 20 mg of cisplatin in a vial was supplied by Shandong Qilu Pharmaceutical Factory. 5-FU was packed in 250 mg per ampule and manufactured by Shanghai Pharmaceutical Factory.

Treatment regimen

Oral Xeloda 1 000 mg/m^2 was administered twice daily from d 1 to 14 in X group, while CF 200 mg/m^2 was taken as a 2-h intravenous infusion followed by 5-FU 600 mg/m^2 intravenous infusion for 4-6 h on d 1-5 in C group. Cisplatin and oxaliplatin were given in the same way to both the groups: cisplatin 60-80 mg/m^2 hyperthermic intraperitoneal abdominal administration, and oxaliplatin 130 mg/m^2 intravenous infusion for 2 h on d 1. All the drugs were recycled every 21 d, with at least two cycles. Granisetron 40 μg/kg was given by intravenation before intravenous or intraperitoneal chemotherapy. Pyridoxine (vitamin B6) 50 mg was given t.i.d. orally for prophylaxis of the hand-foot syndrome (HFS).

Effectiveness and side effects

The short-term effect is classified into four grades as complete remission (CR), part remission (PR), no-change (NC) and progress of disease (PD) by the evaluation standard of short-term effect introduced by WHO[6]. The responsible effective rate (RR) is prescribed to CR+PR (%). There are two other indexes, TTP (time of tumor progress) and 1-year survival rate, which have been adopted to evaluate the mid-term effect. Side effects were added up by standard grade, also introduced by WHO[7] in both the groups regardless of the kind of disease. The classification HFS was graded according to the criteria of WHO[8]: I-dysesthesia/paresthesia, tingling in the hands and feet; II- discomfort in holding objects and upon walking, painless swelling or erythema; III-painful erythema and swelling of palms and soles, periungual erythema and swelling; IV- desquamation, ulceration, blistering, severe pain.

Dose intensity estimation

Two indexes of dose intensity (DI) were calculated by the following formula: DI = total dosage (mg/m^2)/duration of treatment (weeks), relative DI = actual DI/standard DI[9].

Costs estimation

The costs evaluated consisted of two parts, the direct medical cost and the indirect one[5]. The cost of drugs (chemical drug, GM-CSF or G-CSF, the drug to ameliorate gastrointestinal side effect, and so on), hospital stays, the required medical staff, laboratory and diagnostic tests were included in the direct medical cost. The part indirect cost contained the material loss because of the absence of the patients and their relatives from work. Two periods of treatment were added up, then the average cost per patient in one cycle was obtained. The cost of therapy was expressed in Chinese currency (Ren-Min-Bi, ¥) and in US dollars

Table 2 Different chemotherapeutic effect of gastrointestinal cancers

Therapeutic effect	Gastric cancer		Colorectal cancer		Total	
	X group	C group	X group	C group	X group	C group
n	24	25	31	34	55	59
CR (*n*)	1	1	1	0	2	1
PR (*n*)	13	10	14	14	27	24
NC (*n*)	5	10	12	14	17	24
PD (*n*)	5	4	4	6	9	10
CR+PR (*n*)	14	11	17	14	29	25
(%)	58.3	44.0	54.8	41.2	52.7	42.4
TTP (mo)	7.0±1.3[a]	5.4±0.9	7.8±1.9[a]	6.7±2.0	7.4±1.7[a]	6.0±1.5
1-yr survival (%)	41.7[a]	36.0	64.5[a]	52.9	53.1[a]	44.5

[a]$P<0.05$ *vs* C group.

Table 3 Chemotherapeutic side effects of gastrointestinal cancers (*n*)

Side effects	X group (*n* = 55)				C group (*n* = 59)			
	I	II	III	IV	I	II	III	IV
Leukopenia	21	8	5	0	20	8	4	0
Thrombocytopenia	10	5	1	0	13	4	2	0
Nausea	15	19	10	2	16	20	11	2
Vomiting	11	11	4	1	14	12	3	2
Diarrhea	7	9	3	0	5	6	2	0
HFS	32	2	1	0	8	2	0	0
Neurotoxicity	12	11	0	0	14	12	1	0

(US $). The rate of exchange between them was 1:8.3.

Cost-effectiveness analysis

Based on the total costs, the expenses that add to 1% of the response rate (costs/total efficient rate), one-month prolongation of TTP (costs/TTP) and the escalation of 1% of 1 year (costs/1-year survival rate) were calculated, respectively.

Statistical analysis

All data are expressed as mean±SD, except as otherwise stated. Parameters were compared by using *t* test, or χ^2 test.

RESULTS

Effect

In 131 cases, 17 patients (13.0%) terminated treatment after one cycle because of disease progression, refusal to continue chemotherapy or other reasons. Fifty-eight cases (44.3%) finished two or three cycles of chemotherapy, 33 patients (25.2%) finished four or five cycles of chemotherapy, the other 23 cases (17.6%) finished six or more cycles of chemotherapy. The average number of completed chemotherapy cycles was 2.6. These 114 who finished more than two chemotherapy cycles were analyzed. For both the short-term and mid-term effect, the X group was better than C group. But there was no statistical difference in the short-term effect. Short-term effect of gastric cancer group was superior to that of colorectal cancer group, whereas mid-term effect of the former was inferior to that of the latter (Table 2).

Side effects

To 114 patients who finished more than two chemotherapy cycles, the side effects were observed and summed up when the second cycle ended (Table 3). In X group, the rates of leukopenia, thrombocytopenia, nausea, vomiting, diarrhea and neurotoxicity above grade II were 23.6%, 10.9%, 56.4%, 29.1%, 21.8%, and 20.0%, respectively. In C group, the rates were 20.3%, 10.2%, 55.9%, 28.8%, 13.6%, and 22.0%, respectively. No statistical difference was revealed between the two groups.

The occurrence of HFS that appeared in X group was higher than that of C group (63.6% *vs* 16.9%, $P<0.05$), but 97.1% of HFS episodes were grade 1 or 2. No patient withdrew from the study, and none required dose modification due to side effects before two chemotherapy cycles were finished.

Dose intensity

Relative DI mg/(m^2×week) cannot be achieved due to the delay in the treatment (including side effect and noncompliance), which means that the actual DI is lower than standard DI. There was no statistical difference in relative DI between the two groups (Table 4).

Table 4 Chemotherapeutic DI of gastrointestinal cancers, mg/(m^2·wk)

DI	X group			C group			
	Oxal[1]	DDP[1]	Xeloda	Oxal[1]	DDP[1]	CF	5-FU
Standard	43.3	40.0	9 333.3	43.3	40.0	333.3	1 000.0
Actual	40.7	38.3	8 662.7	41.3	38.7	322.7	966.7
Relative	0.94	0.96	0.93	0.95	0.97	0.97	0.97

[1]Oxal – oxaliplatin; DDP – cisplatin.

Costs and cost-effectiveness

There was a statistical difference in the average hospitalization

Table 5 The average cost per patient of two groups (mean±SD, ￥, US $)

Group	Hospitalization(d)	Cost of drug		Other cost		Total cost	
		￥	US $	￥	US $	￥	US $
X	5.94±3.11[a]	7 887.33±140.92[a]	950.28±16.98[a]	1 250.02±101.43[a]	150.60±12.22[a]	9 137.35±121.18	1 100.89±14.60
C	9.37±2.73	6 108.97±205.44	736.02±24.75	2 852.75±217.73	343.70±26.23	8 961.72±211.59	1 079.73±25.50

[a]P<0.05 *vs* C group.

Table 6 Comparison of cost-effectiveness of two groups

Group	Costs / efficient		Costs / TTP		Costs / 1-year survival	
	￥	US $	￥	US $	￥	US $
X	161.44±2.14[a]	19.45±0.26[a]	1 243.18±16.49[a]	149.78±1.99[a]	172.24±2.28[a]	20.75±0.27[a]
C	210.37±4.97	25.35±0.60	1 506.17±35.56	181.47±4.28	201.61±4.76	24.29±0.57

[a]P<0.05 *vs* C group.

time between the two groups (P<0.05, Table 5). The drug costs of X group was higher than that of C group, but other costs (the costs of hospitalization, cancer clinic care and others) were adverse, so there was no difference in the total costs between the two groups. The cost-effectiveness ratio obtained from X group was more satisfactory than that of C group no matter what the cost of percentage response rate, per TTP and per life-year survival (Table 6).

DISCUSSION

The morbidity caused by gastric and colorectal carcinoma are respectively the first and the fourth in China[10,11]. It is difficult to cure the patients at the end stage without a chance for operation or with recurrence and metastasis. 5-FU is a basic drug for gastrointestinal cancer, but its effective rate is only 10-20%. Increasing the dosage, intravenous injection continually or in combination with intensifier can enhance the effect of 5-FU, whereas its side effects and medical costs will increase too. For example, increasing the dosage can result in higher incidence of stomatitis and extremity syndrome, and intravenous injection continually or in combination with intensifier leads to more severe phlebitis, and all of which raise the cost. The regimen of 5-FU combined with CF and levamisole has stood the dominant status in treating tumor of the digestive system for more than 20 years[12,13]. Recently, oxaliplatin combined with 5-FU and CF has become the most frequent and effective chemical therapy for patients with colorectal cancer, and also has been used to treat gastric cancer[14-17].

Xeloda (capecitabine) is a novel, oral, selectively tumor-activated fluoropyrimidine carbamate and absorbed by small intestine in antetype term. It can be activated and transformed to 5-FU by thymidine phosphorylase that has high competence in tumor. So the concentration of 5-FU in tumor tissue is much higher than that in normal tissue and its systemic side effect is lower[18-21]. Xeloda has already been used to treat advanced gastrointestinal cancer with much better result. If combined with oxaliplatin, there will be good results.

The heat-chemical therapy of abdominal cavity includes heat and chemical drug treatments. This therapy has many advantages. It can increase the concentration, the contact surface and the time of the drug in abdominal cavity by perfusing heat drug into abdominal cavity, which is in favor of prolonging action time and killing of cancer cell. A part of the drug can be absorbed by the peritoneum and come into the liver *via* portal vein, which can prevent and eliminate metastatic focus in liver. Its heat effect (40-45 ℃) can reduce the pH value in and around the tumor, which will result not only in metabolic disturbance of the tumor, but also the amelioration of the function of the cellular immunity. Furthermore, the heat can kill the tumor cell directly by cytotoxic effect[22-24]. Considering those advantages, the oral Xeloda combined with bi-platinu two-way heat-chemical therapeutic regimen was adopted to treat 55 patients with advanced gastrointestinal cancer and this regimen was compared with another regimen, 5-FU/CF combined with bi-platinu two-way heat-chemical therapeutic regimen simultaneously. Our results revealed that the effect, 1 year survival and TTP of the former were much better than the latter, and that there was little difference in primary side effect, such as the reaction of the alimentary system and nervous system, bone marrow depression and extremity syndrome between the two groups.

There is a relationship between the dose and effect for cancer chemotherapy. Following the increasing dosage, the effect will be improved, but the side effect and expenses will be increased. So a balance between effect, side effect and expense is needed. Pharmacoeconomics and the study of DI are the new hot points in cancer chemotherapy. To choose the optimal regimen and distribute the limited medical cost, the cost-effectiveness and quality-of-life index effect of oral Xeloda were investigated and compared with CF/5-FU combination chemotherapy in patients with advanced gastrointestinal malignancies, both combined with bi-platinu two-way chemotherapy. Generally, the expenses of the treatment include the direct medical and non-medical fees and indirect medical fee. The average cost for a patient in one cycle was ￥9 137.35 in X group. This cost was a little higher than that in control group (￥8961.72). But the cost-effectiveness analysis is more important, because the elongation of survival time and increasing the survival rate should be emphasized in addition to the effective rate[25]. The costs of Xeloda group and the cost of unit effect were fewer than C group. Because Xeloda was administered in

lower dosage (1 000 mg/m^2 twice daily) in our study, not 1 250 mg/m^2 twice daily as recommended, the incidence of grade 3 or 4 of HFS was reduced. Pyridoxine being given at a high dose from the beginning may be useful for the prophylaxis of the occurrence of HFS[7,26]. For other minor side effects of the two regimens, all patients having accomplished the treatment on time, would mean the relative DI of two groups is close to one. However, the shorter intermission of Xeloda group (about 7 d) leads to the stronger of the actual DI [8 662.7 mg/(m^2·wk)] which probably is another reason for the better effect of Xeloda group than control group. The DI is an index to evaluate the drug or regimen. The analysis of relation between DI and effect will help to improve the effect of the chemical therapy by increasing the dosage of unit time or decreasing intermission of chemical therapy[27-29].

In summary, oral capecitabine can mimic continuous infusion of 5-FU and avoid the inconvenience, complications, and additional costs associated with intravenous chemotherapy. The regimen of oral Xeloda with bi-platinu in two ways (intravenous and intraperitoneal administration) to treat the advanced gastrointestinal cancer has better short-term and long-term effect. It is an effective, safe and economic regimen for patients, even for the old. For ideal pharmacoeconomics, satisfying DI and good compliance, this regimen has a good prospect in the future.

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