RESEARCH ARTICLE

Further Study on Pemetrexed based chemotherapy in Treating Patients with Advanced Gastric Cancer (AGC)

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Abstract

Objective: To further observe the efficacy and safety of pemetrexed, combined with Irinotecan or oxaliplatin or cisplatin in treating patients with advanced gastric cancer as second-line or third-line chemotherapy. Methods: From September 2013 to February 2014 we recruited 50 patients with advanced gastric cancer, with stage IV disease or postoperative recurrence, or unresectable. Then treated with pemetrexed based chemotherapy. After two cycles of treatment, efficacy and toxicity were evaluated. Results: Pemetrexed based chemotherapy was used as second-line in 33 patients, RR(CR+PR) is 41.2%. And achieved 36.4% when used as third-line. Overall response rate of 50 patients treated with Pemetrexed based treatment was 38% (CR+PR). Treatment related side effects were bone marrow suppression, vomiting, hepatic dysfunction and malaise.No treatment related death occurred. Conclusions: Treatment with pemetrexed based chemotherapy is active and is well tolerated in patients with advanced gastric cancer.

Keywords: Pemetrexed based chemotherapy - advanced gastric cancer (AGC)- efficacy and safety

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Introduction

Gastric cancer is a major clinical challenge world wide, with poor overall prognosis if patients were diagnosed with advanced disease (Wei et al., 2013). In Asia, gastric cancer remains a leading cause of cancer-related deaths, with the highest incidence in Korea, Japan and China (Parkin et al., 2005). At present, the majority of patients with advanced disease are recommended to receive a palliative chemotherapy, which is a main treatment for patients with advanced gastric cancer. But for many patients, progress of the disease is unavoidable.

Pemetrexed is a multi-targeted anticancer drug, which plays a role in the process of folate metabolism. It is a new antifolate-antimetabolite. Its targets include a variety of enzymes which arised in the synthesized process of pyrimidine and purine. Previous research suggests that pemetrexed is associated with significantly inhibit thymidylate synthase (TS), dihydrofolate reductase (DHFR), and the activity of glyci-namide ribonicleotide formyltransferase (GARFT). They are important folate-dependent coenzyme. Through multitargeted inhibition of these key enzymes. Pemetrexed reduced biosynthesis of purine and thymidine, affected the synthesis of DNA and RNA in tumor cell (Calvert et al., 1999). Clinical studies suggested the drug a clear anti-tumor activity in a variety of solid tumors, including lung cancer, breast cancer, pancreatic cancer, ovarian cancer and etc (Bajetta et al., 2003). Although the clinical activity against several tumor types of adenocarcinoma, including gastric cancer, was confirmed by several clinical studies, the efficacy of pemetrexed for gastric cancer remains to be fully evaluated (Sato et al., 2012). We conducted a study to determine the efficacy and safety of pemetrexed based chemotherapy in treating patients with metastatic gastric cancer who failed to respond to first and (or) second line chemotherapy (Wei et al., 2013). In this study, we expanded sample size to further evaluate the potential efficient and safety of pemetrexed based chemotherapy in treating patients with advanced gastric cancer.

Materials and Methods

Patients

On the basis of previous studies (Wei et al., 2013), we expanded the number of patients, who received paclitaxel or docetaxel based chemotherapy in their previous treatment, and finally failed. All patients were required to be pathologically/cytologically diagnosed with gastric adenocarcinoma and received pemetrexed based chemotherapy in Jiangsu Cancer Hospital & Research Institute from September 2013 to February 2014. Eligibility criteria were as follows: 1. failed in first-line and (or) second-line chemotherapy;2. to have a score of karnofsky performance status (KPS) ≥ 70;3. to be 25 to 75 years of age; 4.to sign an informed consent before treatment;. 5.Blood test results meet the following requirements: white blood cell count > 3.0×10^9 and

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Table 1. Baseline Patient Characteristics (n = 50)

Characteristic	No. of patients	(%)
Age, years		
≤65	38	(76)
>65	12	(24)
Sex		
Male	37	(74)
Female	13	(26)
KPS score		
≤80	5	(2)
>80	45	(98)
Treatments for primary tumor		
None	20	(40)
Surgery	1	(2)
Surgery and adjuvant chemotherapy	29	(58)
Tumor stage		
Locally advanced	7	(14)
Metastatic	43	(86)
Number of organs involved		
1	12	(24)
‡2	38	(76)
Organs involved		
Lymph nodes	23	(46)
Liver	11	(22)
Lung	4	(8)
Peritoneum	7	(14)
Bone	3	(6)
Abdominal wall	2	(4)
Chemotherapy		
PEM (500 mg/m^2)d1+CPT-11 (150 mg/m^2)d1,8	28	(56)
PEM (500 mg/m^2)d1+DDP (60 mg/m^2)d1-5	12	(24)
PEM (500 mg/m^2)d1+OXA (100 mg/m^2)d2	10	(20)

platelet count > 150×10^9, bilirubin and transaminases < 1.5 times the upper normal limit and creatinine leval < 1.5 times the upper normal limit. Patients were excluded from this study: 1.failed to complete two cycles of chemotherapy;2.with any serious medical or psychiatric condition;3 suffer from other malignancies at the same time; 4.pregnant or lactating women. General characteristics of patients were listed in Table 1.

Methods

In this study, we use the same programs and dosage (Wei et al., 2013), but more accurate in distinguishing and observing the patients. These patients with advanced gastric cancer (AGC) were enrolled to evaluate the treatment efficiency. Before the start of chemotherapy, patients were given oral dexamethasone 4.5mg twice a day, oral multivitamin formula which contain 400 micrograms of folic acid for 5 days and Vitamin B12 20mg given intramuscularly every 9 weeks. After premedication, patients received pemetrexed (500 mg/m^2) combined with oxaliplatin (120 mg/m^2) or CPT-11 (180 mg/m^2) or Cisplatin (60 mg/m^2). Pemetrexed was injected intravenous during 15 to 20 minute and Oxaliplatin/Irinotecan in 30 minute iv on day 1 and day 8, and Cisplatin as a 3 hour iv day1-3 and day 8-9 every three weeks. Routine blood test, blood biochemistry and tumor markers were reviewed prior, during and after chemotherapy. CT scan was reviewed after two cycles of treatment to evaluate efficacy.

Table 2. Treatment Efficacy of Pemetrexed Based Chemotherapy on Second-line or Third-line

Treatment	No. of patients (%)					
	Total	CR	PR	SD	PD	RR(CR+PR)
Group A						
(Second-line)	17	0	7 (41.2)	3 (17.6)	7 (41.2)	7 (41.2)
PEM+CPT-11	9	0	4 (23.5)	1 (5.9)	4 (23.5)	4 (23.5)
PEM +DDP	4	0	1 (5.9)	2 (11.8)	1 (5.9)	1 (5.9)
PEM +OXA	4	0	2 (11.8)	0 (0)	2 (11.8)	2 (11.8)
Group B						
(Third-line)	33	0	12 (36.4)	4 (12.1)	17 (51.5)	12 (36.4)
PEM+CPT-11	19	0	7 (21.2)	2 (6.1)	10 (30.3)	7 (21.2)
PEM +DDP	8	0	3 (9.1)	2 (6.1)	3 (9.1)	3 (9.1)
PEM+OXA	6	0	2 (6.1)	0 (0)	4 (12.1)	2 (6.1)
Total(A+B)	50	0	19 (38%)	7 (14)	24 (48)	19 (38)

Table 3. Treatment Efficacy and KPS Score of all patients

Treatment	No. of patients	%
CR	0	0
PR	19	38
SD	7	14
PD	24	48
CR+PR	19	38
CR+PR+SD	26	52
KPS score (after 2 cycles)		
Increased	2	4
Stable	31	62
Decreased	17	34

*N, number of patient; CR, Complete Remission; PR, Partial response; SD, stable disease; PD, progressive disease; *Experimental group was chemotherapy combined with javanica oil emulsion injection; *KPS, score; increased, ≥10 after treatment; stable, <10; decreased, ≥10

Results

From September 2013 to February 2014, we recruited 52 patients (39 males and 13 females) with advanced gastric cancer. Who were all with adenocarcinom gastric cancer and failed in first-line and (or) second-line paclitaxel or docetaxel or fluorouracil based chemotherapy. Patients with stage IV disease or patients with postoperative recurrence, or unresectable were recruited . At last, we excluded 2 male patients, due to economic reasons and eventually got 50 useful cases of date. And their mean age is 57.2 years. Of all the 50 patients, 17patients received pemetrexed based combination therapy as second line, 33 as third line. And in these 50 patients, 28 patients recepted PEM and CPT-11 combined chemotherapy, 12 patients recepted PEM and DDP combined chemotherapy, and 10 patients recepted PEM and OXA combined chemotherapy. The efficiency of Second-line treatment as grouple A or third-line treatment as grouple B are listed in Table 2.

Efficacy evaluation

Before the chemotherapy, all patients received physical examination, routine blood test, including blood biochemical examination. Treatment efficacy was evaluated according to RECIST criteria (Response Evaluation Criteria In Solid Tumor) (Sohaib, 2012) after

Table 4. Toxicity

Toxicity	YES (%)	NO (%)
Bone marrow suppression	46 (92)	4 (8)
I	9 (18)	
II	21 (42)	
III	10 (20)	
IV	6 (12)	
Vomiting	22 (44)	28 (56)
Diarrhea	2 (4)	48 (96)
Hepatic dysfunction	18 (36)	32 (64)
Malaise	27 (54)	23 (46)
Skin rash	0 (0)	50 (100)

two cycles of chemotherapy. Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) was separately defined. Quality of life was designated increasing if the KPS score increased by 10 after treatment, decreasing if the score decreased by 10 and otherwise. After completed two cycles of chemotherapy, 50 patients were evaluated as in Table 3.

When the pemetrexed based chemotherapy used as second-line treatment in 17patients in group A, 9 patients received the combined chemotherapy of PEM and CPT-11 and got its CR+PR as 23.5%, 4 patients received the PEM +DDP combined chemotherapy and their CR+PR was 5.9%, and another 4 patients accepted PEM +OXA combined chemotherapy, got the rate of 11.8% as CP+PR. The total effective rate (CR+PR) of these 17 patients received pemetrexed in second-line treatment is 41.2%. In group B, 33 patients accepted pemetrexed based chemotherapy as third-line treatment. Eventually, 19 patients with PEM and CPT-11 combined chemotherapy got the rate of CR+PR as 21.2%, and 8 patients with PEM and DDP combined chemotherapy got 9.1%, and 6.1% in 6 patients used PEM combined with OXA. The total effective rate (CR+PR) of these 33 patients received pemetrexed as third-line drug is 36.4%.

Overall, 19 patients (38%) achieved PR, while 7 patients (14%) remained stable, no CR. 28 patients received pemetrexed combined with CPT-11, 12 patients with DDP and 10 with OXA (Table 1).

In this study, before and after two cycles of treatment, KPS score of every patients were evaluated. 2 patients (4%) increased, and 31 patients keep stable.

Toxicity

All Patients were assessed the grade of toxicities according to WHO criteria (De Angelis, 2004). During chemotherapy, all adverse reactions were documented as in Table 4.

The main adverse drug reactions is bone marrow suppression, occurred in 92% of patients, but no patients developed grade III or IV. Among them, 6 patients reach 4 grade, with the rate of 8%.22 patients vomited, and the rate is 44%. There are 36% patients with hepatic dysfunction, and these 18 patients all returned to normal after treated accordingly. while no skin rash occurred. And 2 patients died after the study due to electrolyte imbalance or cardiac failure which were not considered as related to pemetrexed.

Discussion

Most patients with effective first-line chemotherapy will eventually have progression and need second-line or even third-line treatment (Liu et al., 2013). At present, no standard therapy is established as a second-line or third-line chemotherapy.

We found that the efficacy of pemetrexed combined chemotherapy in this study is optimistic. Overall, of the 50 enrolled patients, no CR, but 19 PR and24 SD were recorded. In group A, 17 patients received pemetrexed as second-line treatment and total effective rate (RR) is 41.2%. In group B, 33 patients received pemetrexed as third-line chemotheraphy and RR is 36.4%. Thus, pemetrexed based chemotherapy used as a second-line therapy could achieve a better result than used as third-line.

In our previous study (Wei et al., 2013), 23 patients were recruited from Jun 2011 to May 2013, and finally 3 patients (1 as second-line and 1 as third-line) achieved PR with a rate of 13%, while 5 patients (22%) remained stable with no CR. RR of our former study was 13% (Wei et al., 2013). Compared with this former study, we expanded the number of patients to 50. The current research suggests pemetrexed based chemotherapy is effitive in treating patients with advanced gastric cancer and especially when used as second-line treatment, RR is higher than that used as third-line treatment. So we hypothesize the early use of pemetrexed based chemotherapy on patients with advanced gastric cancer could have better efficacy.

When treating patients with gastric cancer, cisplatin, irinotecan and oxaliplatin as a single agent were suggested to be effective (Liu et al., 2013). However, in a phase II trial, pemetrexed demonstrated a promising response rate of 21% as a single agent in treating 36 patients with advanced gastric cancer (Bajetta et al., 2003). Beers et al (1983) treated 18 gastric cancer patients with cisplatin 75-120mg/m2 infusion 6 hours for 3 weeks, and the effective rate was 21%, with a median of 12 weeks. Leichman et al (1991) reported that cisplatin 75-120mg/m2 infusion, 3 weeks in the treatment of 129 patients (114 patients with previous treatment), achieved CR in 6 patients, PR in 19 patients, and the effective rate was 19%. Because no cross-resistance exists between oxaliplatin and cisplatin, when patients developed resistant to cisplatin, the administration of oxaliplatin could be considered. The effective rate of CPT-11 as a monotherapy in treating patients with gastric cancer is 23%.

Some previous researches on cisplatin, irinotecan and oxaliplatin combined second-line or third-line chemotherapy also suggest particular response rate in treating advanced gastric cancer (AGC). Between November 2006 to May 2009, a phase II study was conducted to evaluate the efficacy and safety of the combined administration of irinotecan plus cisplatin as second line therapy for advanced or recurrent gastric cancer. It is reported that 18 patients were enrolled, 2 CR, 1 PR and 7 SD were identified, RR was 16.7%. (Yasushi et al., 2013). In another study, mXELOX was administered in 49 patients as second-line therapy. RR was 39.1% among 46 evaluated patients: 3 CR (6.5%) and 15 PR

(32.6%) (Kuo et al., 2014) . In a Korean phase II study, 50 patients with advanced gastric cancer were treated with pemetrexed and cisplatin, 13 PR and an overall RR of 26% (95%CI, 14.6-40.3%) were reported (Yeul et al., 2008). Compared with other combination chemotherapy, it is suggested that pemetrexed based chemotherapy could be similarly effective. Pemetrexed based chemotherapy is associated with a mild toxic effects and is easy to be tolerated by patient (Wu et al., 2013). A phase II study was conducted to assess the toxicity profile of pemetrexed in 32 patients, 8 experienced grade IV neutropenia and 1 grade IV thrombocytopenia. The most common nonhematologic toxicities were diarrhea, fatigue, mucositis, nausea and vomiting, skin rash, and reversible abnormalities in liver function. There was no case of nonhematologic grade 4 toxicity (Celio et al., 2008). As mentioned above, in the Korean phase II study, 50 patients were also evaluable for toxicity. The most frequent toxicities were neutropenia in 49% of patients (25% of cycles) and anorexia in 10% of patients (4% of cycles) (Yeul et al., 2008). In this study, among 50 enrolled patients, the main toxicities of pemetrexed based chemotherapy were bone marrow suppression and vomiting, 92% of patients were bone marrow suppression, and 44% of patients vomited, 36% of patients with hepatic dysfunction and their hepatic enzymes all returned to normal after accepted treatment. No skin rash was observed. We found the toxicity profile of pemetrexed based chemotherapy is acceptable.

In conclusions, our research suggests that pemetrexed based chemotherapy is effective in treating patients with advanced gastic cancer, especially as second-line chemotheraphy. Toxicities were acceptable. However, randomized study should be conducted to further evaluate the efficacy and to compare with other agents.

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