RESEARCH ARTICLE

Phase II Study of Pemetrexed as Second or Third Line Combined Chemotherapy in Patients with Colorectal Cancer

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Abstract

Purpose: To investigate the safety and efficacy of pemetrexed combined with chemotherapy as second or third line in patients with stage IV colorectal cancer (CRC). Patients and Methods: This trial was conducted to evaluate the effectiveness and safety of pemetrexed given to patients with recurrent or metastatic colorectal carcinoma who previously received 5-FU-based chemotherapy. All patients were required to have a histological diagnosis of colorectal adenocarcinoma with measurable metastatic disease and prior chemotherapy. Patients received pemetrexed at a dose of 500 mg/m^2 by 10 minute infusion on day 1, repeated every 21 days. Doses were modified depending on nadir counts. Combined chemotherapy included Oxaliplatin, Irinotecan and cis-platinum. Results: Thirty patients were enrolled and twenty-nine were evaluable for response. One patient did not have repeat radiological testing to determine response because he went off study after only one cycle of treatment for economic reasons. For 29 evaluable patients, 1 partial response, 6 stable disease and 22 progressive disease were recorded. Response rate was 3.45% (1/29). All responses occurred in patients receiving a starting dose of pemetrexed 500 mg/m^2. Median time to progression for all eligible patients was 2.5 months. The most common toxicities experienced were mild to moderate fever, hepatic damage, myelosuppression, nausea, vomiting, constipation, abdominal pain, diarrhea, and skin rash. Conclusion: Pemetrexed at 500 mg/m^2 given every three weeks combined with chemotherapy is associated with moderate response and good tolerability in patients with stage IV CRC.

Keywords: Pemetrexed - colorectal carcinoma - chemotherapy - phase II trial

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Introduction

Guideline based chemotherapeutic treatment (NCCN, 2012) for the management of patients with stage IV colorectal cancer are chemotherapeutic regimens contain: fluorouracil (FU)-and-oxalipatin, capeOX, irinotecan, oxalipatin, and cetuximab. Currently reported strategies for patients in this setting is to combined new regimens, eg, FOLFIRI, FOLFOX, XELOX, xeloda and irinotecan, S-1 and irinotecan, UFT/LV and irinotecan/oxalipatin and bevacizumab (Xu et al., 2011). However, which chemotherapy regimen can be more effective is not a word.

Pemetrexed at doses of 500-600 mg/m^2 has been shown to have single-agent activity comparable with that of 5-FU/LV in phase II studies, with an overall response rate in the range of 15%-17% (Cripps et al., 1999; Johnet al., 2000). Pemetrexed inhibits thymidylate synthetase (TS), dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase (GARFT), enzymes involved in purine and pyrimidine synthesis. Pemetrexed enters the cell through the reduced folate carrier mechanism and undergoes polyglutamation. The pentaglutamate moiety of pemetrexed is the predominant intracellular form and has 100-fold greater affinity for TS and GARFT than the parent drug (Shih et al., 1996). The recommended dose of Pemetrexed Disodium for Injection made in China is 500 mg/m^2 per 21 days and drip for 10 minutes. The incidence and severity of skin reactions can be reduced by taking dexamethasone in advance. Low doses of folic acid or other multivitamin containing folic acid preparation should be taken to alleviate toxicity during the using of pemetrexed.

The primary goal of our study was to test the potential benefit and safety associated with the addition of pemetrexed combined chemotherapy in the adjuvant colon cancer setting. This report summarizes the efficacy associated with the addition of pemetrexed to combination chemotherapy in patients with stage IV CRC.

Materials and Methods

Patients with histologically proven metastatic or recurrent colorectal cancer in Jiangsu Cancer Hospital & Reasearch Institution with measurable disease were

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Table 1. Patient Characteristics (n = 29 patients)

Age	
Median	57
Range	40-75
	Number of patients (%)
Sex	
Female	11 (58)
Male	18 (62)
Prior combination therapy	
Adjuvant chemotherapy	29 (100)
Radiotherapy	3 (10)
Immunotherapy	6 (21)
Metastatic site	
Abdomen	5 (17)
Colon	1 (3)
Liver	16 (55)
Lung	11 (38)
Other	2 (7)
Number of sites of disease	
1	20 (69)
2	8 (28)
3	1 (3)
Current chemotherapy	
First line	0 (0)
Second line	5 (17)
Third line	24 (83)

eligible for this study. The systemic chemotherapy of FOLFOX4 or XELOX for metastatic or recurrent disease could have been given radiation therapy may have completed but must have recovered from the acute toxic effects prior to registration; previous adjuvant chemotherapy was permitted; patients should be more than 16 years of age; additional eligibility criteria included absolute granulocytes Ssl.5 x 10^9/L, platelets >150 x 10^9/L, serum creatinine within normal limits, a bilirubin of <1.5 times the upper normal limit, AST < 2 times the upper limit of normal or > 5 times the upper limit of normal if liver metastases were documented. Minimum size of indicator lesions should be >2 x 2 cm on CT scan, and on chest X-ray or physical exam > 1 x 1 cm.

Written informed consent was required from all patients before chemotherapy.

The patients were staged by physical examination, CT scans and chest X-rays, which were obtained within two weeks of study entry to serve as baseline evaluation. Therapy consisted of pemetrexed as a 15-20 minute intravenous infusion(iv) and Oxaliplatin/Irinotecan as a 30 minute iv on day 1 and day 8 every three weeks. The starting dose of pemetrexed was 500 mg/m^2. Premedication of pemetrexed consists: 400 μg of folic acid was given orally daily and 1000 μg of vitamin B12 was given intramuscularly every 9 weeks starting 7 days prior to the first dose and until 3 weeks after the last dose of pemetrexed; 4.5 mg of dexamethasone was given orally every 12 h on the day before, day of and the day after all doses of pemetrexed. Antiemetics were given before chemotherapy on day 1. Colony-stimulating factors were not used prophylactically. All toxicities were graded according to National Cancer Institute Common Toxicity Criteria (version 2.0) (National Cancer Institute, 1998).

Evaluation of response was performed after every two courses of treatment. Complete response was defined as disappearance of all clinical and radiological evidence of tumour determined by two observations not less than four weeks apart. The patients must have been free of all tumour-related symptoms. Partial response was defined as a 50% or greater decrease in the overall sum of measurable lesions determined by two observations no less than four weeks apart. No simultaneous increase in the size of any lesion or the appearance of any new lesion may have occurred. Stable disease was defined as disease less than a partial response that is less than 50% decrease in the overall sum of measurable lesions or progression less than progressive disease documented to be present for at least six weeks after the start of therapy. Progressive disease was defined as an unequivocal increase of at least 25% in the overall sum of measurable lesions as compared to baseline. The appearance of new lesions would constitute progressive disease. Response duration was measured from the time the measurement criteria were first met until disease progression.The distribution of time to progression and survival time was estimated using the Kaplan–Meier method. We have enough experience in conducting medical researches, and have published some results elsewhere (Huang et al., 2004; Zhou et al., 2009; Jiang et al., 2010; Yan et al., 2010; Gao et al., 2011; Huang et al., 2011; Li et al., 2011; Li et al., 2011; Li et al., 2011; Xu et al., 2011; Xu et al., 2011; Xu et al., 2011; Yan et al., 2011; Zhang et al., 2011; Gong et al., 2012; Li et al., 2012; Yu et al., 2012).

Table 2. Response of Pemetrexed in Combined Chemotherapy in Stage IV CRC (n = 29 patients)

	Number of patients (%)	median duration in months(range)
Complete response (CR)	0	--
Partial response (PR)	1 (3.45)	10-10
Stable disease (SD)	6 (20.7)	4 (3-8)
Progressive disease (PD)	22 (75.9)	

Response rate = 3.45% (1/29)

Results

From January 2011 to December 2012, 30 patients were recruited and twenty-nine were evaluable for response. One patient did not have repeat radiological testing to determine response because he went off study after only one cycle of treatment due to economic reasons. Patient characteristics are listed in Table 1. Liver was the predominant site of metastasis (16 patients). Twenty patients had one site of disease, eight had two sites of disease, and one patient had three sites. All patients had prior adjuvant chemotherapy and three patients had prior radiotherapy.

Response

One patient achieved partial response. The response rate was 3.45%(1/29). All responses were confirmed by independent radiologic review. Site of disease in responding patient was: liver. Response duration was 10 months (Table 2).

Six patients had stable disease and twenty-two had

Table 3. Toxicity of Pemetrexed in Combined Chemotherapy in Stage IV CRC

	Grade 1(%)	Grade 2(%)	Grade 3(%)	Grade 4(%)
Hematologic toxicity				
Granulocytes	0	5(17.2)	4(13.8)	1(3.4)
Hgb	5(17.2)	4(13.8)	3(10.3)	--
Platelets	7(24.1)	--	--	2(6.9)
WBC	0	5(17.2)	4(13.8)	1(3.4)
Non-hematologic toxicity				
Hepatic damage	0	10(34.5)	3(10.3)	--
Vomiting	11(37.9)	6(20.7)	1(3.4)	--
Constipation	0	4(13.8)	--	--
Abdominal pain	4(13.8)	6(20.7)	1(3.4)	--
Diarrhea	0	4(13.8)	2(6.9)	--
Skin rash	0	0	2(6.9)	--

progressive disease. The median time to progression of the whole group was 2.5 months (range 0.5-10 months) and the median overall survival was 9.1 months (range 1.5-18 months).

Toxicity

Overall 4 of 29 patients at 500 mg/m^2 experienced grade 3 granulocytopenia (Table 3), one grade 4 granulocytopenia and only two grade 4 thrombocytopenia. The most common non-hematologic toxicities were hepatic damage, myelosuppression, nausea, vomiting, constipation, abdominal pain, diarrhea, and skin rash. (Table 3). 13 cases of transient elevations of liver enzymes and 2 cases of grade 2 skin rash occurred in this study. The rash was erythematous, swollen and pruritus. It commonly involved the face and trunk to make lying in bed painful. The use of dexamethasone 4.5 mg twice daily for three days starting one day prior to receiving pemetrexed seem to reduce the frequency and severity of the rash in patients who received this in subsequent cycles. No neurological, renal and ototoxic adverse reaction was recorded

Discussion

The standard treatment for metastatic colorectal cancer has remained 5-FU or 5-FU combinations. Response rates to 5-FU alone are less than 20% and while combination regimens with biochemical modulating agents (i.e., leucovorin) have improved response rate, survival has not been affected. Now, multiple other agents are available for treatment of metastatic colorectal cancer. These agents include UFT, capecitabine, CPT-11, oxaliplatin and raltitrexed. All have predictable toxicities with very similar response rates and survival. Based on phase II data, UFT gave a response rate of 30% (95% CI: 14%-46%) with a median time to progression of 7.4 months and a median survival time of 14.2 months (Nogue et al., 1996). Capecitabine had very similar response rates with 7 of 36 patients on continuous treatment, 9 of 32 on intermittent treatment and 8 of 33 patients on intermittent treatment with leucovorin. Median times to progression were 17, 30 and 24 weeks, respectively. A good safety profile was also noted (Findlay et al., 1997).

Oxaliplatin, still an investigational drug, has a response rate of 57% and a progression-free survival of 39.6 weeks (De Gramont et al., 1998) when combined with 5-FU and leucovorin. Despite the limited availability of preclinical data, the association of pemetrexed (500 mg/m^2) and oxaliplatin (120 mg/m^2), every 21 days for 6 cycles, was studied as first-line therapy in a phase II trial, reporting a clinical response rate of 29.6% in patients with metastatic adenocarcinoma of the colon or rectum (Atkins et al., 2005).

Irinotecan is another new agent available for treatment in metastatic colorectal cancer (Conti et al., 1996). Prospective, randomized trials in colorectal cancer have just recently been completed. Irinotecan gave a response rate of 22% and a statistically improved difference in response when compared to best supportive care in patients who had failed 5-FU based chemotherapy (Cunningham et al., 1998).

This phase II study of pemetrexed in this population has documented a response rate of 3.45% and a median time to progression of 2.5 months. Only one response was seen in 29 patients who started at 500 mg/m^2 dosage. The grade 3 and 4 toxicities were unpredictable in that they could occur after any course and were not dose related. The clinical significance of a grade 3 skin rash is unknown, but the rash certainly affected patients symptomatically and cosmetically. Use of prophylactic dexamethasone decreased the frequency and severity of this problem. The median survival of these patients was 9.1 months which is longer than the expected survival of 8 months. However, the importance of this observation is difficult to interpret given the small sample size, selected nature of the patients included in this trial and the fact that a significant proportion went on to have chemotherapy with irinotecan and/or raltitrexed.

The toxicities seen in this phase II trial and their often unpredictable nature are similar to those seen with methotrexate and other antifolates with the spectrum of skin rash, diarrhea, neutropenia and thrombocytopenia. Addition of folic acid and vitamin B12 significantly reduced the toxicity of pemetrexed, especially hematologic toxicity and gastrointestinal toxicity. The count of leukocyte and platelet returned to normal after the treatment of colony-stimulating factor, interleukin 11 and recombinant human thrombopoietin. Pemetrexed is the expected agent for use in high risk patients, especially elderly or poor performance status patients (Sudoh et al., 2008). Digestive tract reaction ranged from 1 to 2 could be alleviated by symptomatic treatment. By hepatoprotective drugs, transaminase could return to normal. Only 2 patients had rash with pruritus, rash subsided gradually after symptomatic treatment of the antipruritic and anti allergic.

We feel that the activity of pemetrexed in combining chemotherapy in this population is unlikely to bring an advantage in terms of efficacy. While it causes minimal toxic effects during the chemotherapy. To patients with stage IV CRC who were invalid with first-line treatment, pemetrexed with combination chemotherapy could slow down the progression of disease to certain extent without strong toxicities. Therefore, future studies modification of administration schedules for the combination of pemetrexed and platinum/irinotecan are needed in a larger patient population to evaluate the efficacy and tolerability

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