RESEARCH ARTICLE

A Predictive Model for Evaluating Responsiveness to Pemetrexed Treatment in Patients with Advanced Colorectal Cancer

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Abstract

Purpose: To highlight the potential factors that could predict the response rate of patients with metastatic colorectal cancer (mCRC) treated with pemetrexed combined chemotherapy after first- or second-line chemotherapy using the FOLFOX regimen. Materials and Methods: Between January 2007 and July 2014, 54 patients diagnosed and pathologically-confirmed with advanced colorectal cancer in Jiangsu Cancer Hospital and Research Institute, were enrolled. They received pemetrexed at a dose of 500mg/m^2 by 10 minute infusion on day 1, repeated every 3 weeks. Doses were modified depending on nadir counts of blood cells. Combined chemotherapeutic agents included irinotecan, lobaplatin, carboplatin, oxaliplatin, gemcitabine, cis-platinum or bevacizumab. Multiple variables (age, sex, hemoglobin, platinum drugs combined, metastasis sites, LDH, ALP, CEA>40 ug/ml) reported earlier were selected.We used logistic regression analysis to evaluate relationships between these and tumor response. Results: On multivariable analysis, we found that age was significant in predicting the responsiveness to pemetrexed ($p<0.05$) combined with oxaliplatin. We did not find any other factors which were significantly associated with the response rate to chemotherapy with pemetrexed and irinotecan. Conclusions: By multivariate analysis, we found that age had significant impact on the responsiveness of pemetrexed when combined with oxaliplatin. Additional research based on genomic properties of host and tumors are needed to clarify markers for better selection of patients who could benefit from pemetrexed combined chemotherapy.

Keywords: Pemetrexed - predictive factors - combined chemotherapy metastatic colorectal cancer (mCRC)

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Introduction

Colorectal cancer is the third most commonly cancer in males and the second in females, with over 1.2 million new cancer cases and 608, 700 deaths estimated to occurred in 2008 (Jemal et al., 2011). Approximately half of all patients will develop metastatic cancer (D.M.Parkin et al., 2005). On many occasions, disease is too advanced and only palliative therapy could be considered. Doublets such as irinotecan plus infusional 5-FU/LV (FOLFIRI) or oxaliplatin plus infusional 5-FU/LV (FOLFOX) prolonged median survival to more than 20 months (de Gramont et al., 2000; Douillard et al., 2000; Goldberg et al., 2004; Kohne et al., 2005). Nevertheless, many patients still failed to treatment due to tumor recurrence and metastasis, and 5-year survival rate still less than 10%.

Pemetrexed is a new anticancer drug. Three enzymes - thymidine nucleoside Acid synthetase (thymidylate synthetase, TS), dihydrofolate reductase Glycinamide called formyltransferase DHFR) and Amino acid RNA nucleoside acyltransferase (dihydrofolate reductase, ARFT), are involved in terminating cell cycle in S phase, thus inhibit the growth of tumor cells (Jones et al., 2002). Combinations of pemetrexed with agents, eg. gemcitabine or platinum compounds are currently under investigation and demonstrated *in vitro* and in clinical setting with some promising results in several chemo-resistant tumors (Giovannetti et al., 2004; Scagliotti et al., 2008), including colorectal cancer (Atkins et al., 2005). Pemetrexed 500-600mg/m^2 administered every three weeks showed single-agent activity as first-line treatment for advanced CRC in two phase II trials (Cripps et al., 1999; John et al., 2000). The objective responses rates were 15% in one study (John et al., 2000) and 17% in another (Cripps et al., 1999) and the median overall survival time was 16.2 and 15.1 months, respectively. The main toxicities of pemetrexed were reported to be myelosuppression, and mucositis, with neutropenia being the primary dose-limiting toxicity (Louvet et al., 2004). Supplement of vitamin B12 and folic acid may lower plasma homocysteine and improve the toxicity of pemetrexed.

We designed this study and tried to identify independent factors that could predict the responsiveness of pemetrexed in treating patients with advanced colorectal.

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Materials and Methods

Patients

Patients eligible for this study were diagnosed with pathologically-confirmed mCRC, who progressed after first or second line chemotherapy with FOLFOX. Further inclusion criteria were: Chinese; at least 18 years old; Karnofsky performance status (KPS)>=70; life expectancy over 9 weeks; at least one detectable metastatic lesion; adequate hematological, hepatic and renal functions. Exclusion criteria included: pregnant or breast-feeding women; unwillingness or inability to take vitamin B12 or folic acid. All patients provided informed consent before chemotherapy.

Treatment

All patients received 500mg/m^2 pemetrexed as a 10 minute intravenous infusion combined with other chemotherapeutics in the treatment and repeated every 3 weeks. Cycles were stopped when disease progressed, unacceptable toxicity, and investigator or patient decision. Folic acid oral supplementation of 400ug was given daily beginning 1 to 2 weeks prior day 1 of cycle1 and continuing daily until 3 weeks after the last pemetrexed dose. Vitamin B12 1000ug was given intramuscularly 1 or 2 days prior to the first pemetrexed dose and repeated every 9 weeks until 3 weeks after the last dose. Dexamethasone (4.5 mg) was administered orally every 12h on the day before, the day of and the day after each dose of pemetrexed.

Assessments

Disease status was assessed at baseline by a complete medical history and physical examination with abdominal computed tomography (CT) scans and chest X-ray. Performance status (PS) was measured and complete blood chemistry and hematology were monitored routinely. Clinical items including toxicities and vital signs, performance status (PS), blood counts, and chemistry profile were recorded on special forms at regular intervals during follow-up. All toxicities were evaluated according to the National Cancer Institute criteria (version 3.0). CT-scans and CEA levels were performed every 4 cycles to evaluate response, then 30 days after chemotherapy and repeated every 3 months for two years.

Statistical Analysis

We established the associations between responsiveness of pemetrexed and characteristics of patients. Potential predictors explored included age, gender, hemoglobin, chemotherapeutics combined, CEA, LDH, ALP and sites of metastasis. The primary objective was to identify the factors associated with response to PEM. All variables were included in multivariable logistic regression model with pemetrexed responsiveness as the dependent variable. Stata version 8.0 (StatSoft Inc., Tulsa, OK) was used to analyze data. We have enough experience in conducting medical researches, and have published some results elsewhere (Cao et al., 2013; Chen et al., 2013; Huang et al., 2013; Wei et al., 2013; Wu et al., 2013; Yang et al., 2013; Gong et al., 2014; Lu et al., 2014; Xiao et al., 2014; Xu et al., 2014).

Table 1. Patient Characteristics (N=54)

			N (%)
Age , years	Median	57	
	Range	33-80	
Gender	Male		35 (64.8%)
	Female		19 (35.2%)
Metastatic sites	Lymph nodes		3 (5.6%)
	Bone		3 (5.6%)
	Liver		22 (40.7%)
	Lung		25 (46.3%)
	Peritoneum		13 (24.1%)
	Brain		3 (5.6%)
	Renal		1 (1.9%)
	Pancreas		1 (1.9%)
	Spleen		1 (1.9%)
	Other (mediastinum, pelvic)		12 (22.2%)
Number of target lesions	1		26 (48.2%)
	2		23 (42.6%)
	3		2 (3.7%)
	4 or more		3(5.56%)
Chemotherapeutic agents combined			
	DDP		7(12.96%)
	OXA		9(16.67%)
	CBP		7(12.96%)
	LBP		13(24.07%)
	GEM		1(1.85%)
	CPT-11		20(37.74%)
	Bevacizumab		3(5.56%)

Results

Fifty-four patients were entered in the study from Jiangsu Cancer Hospital and Research Institute between 01/2007 and 07/2014. All patients with mCRC, who progressed after first or second line chemotherapy, accepted pemetrexed combined chemotherapy for two cycles. The overall response rate (CR+PR) was 5.56% (3/54).

Patient Characteristics

Baseline characteristics of patients are summarized in (Table 1). The majority of the patients were male (64.8%) and the median age was 57 years (range: 33 to 80 years). The majority of patients (42.6%) had two or more synchronous metastatic sites. Liver (40.7%) and lung (46.3%) were the most common sites of metastases. All patients were previously treated with a FOLFOX regimen before or after metastatic disease. In combined

Table 2. Multivariate Analysis on Predictive Factors Associated with Responsiveness of Pemetrexed and Oxaliplatin Combined Chemotherapy

	P value	OR	95%CI
Age	0.048	11.4	1.0-126.5
Gender	0.705	1.3	0.3-5.7
Hb	0.314	0.4	0.1-2.2
CEA (>40)	0.360	2.4	0.4-15.2
LDH	0.199	2.7	0.6-12.2
ALP	0.471	0.5	0.1-3.2
OXA combined	0.468	2.1	0.3-15.9
Liver metastasis	0.269	0.4	0.9-1.9
Lung metastasis	0.653	1.4	0.3-6.6
Peritoneum metastasis	0.645	1.5	0.3-15.9

Table 3. Multivariate Analysis of Predictive Factors Associated with Responsiveness to Pemetrexed in Combined Chemotherapy with Irinotecan

	P value	OR	95%CI
Age	0.064	9.8	0.9-109.8
Gender	0.787	1.2	0.3-5.3
Hb	0.450	0.6	0.1-2.6
CEA (>40)	0.402	2.2	0.3-14.2
LDH	0.337	2.1	0.5-10.0
ALP	0.486	0.5	0.1-3.3
CPT-11 combined	0.621	0.7	0.2-3.0
Liver metastasis	0.343	0.5	0.1-2.2
Lung metastasis	0.601	1.5	0.3-7.0
Peritoneum metastasis	0.629	1.5	0.3-8

chemotherapy, irinotecan (37.74%) was the most frequently used chemotherapeutic agent.

Predictive factors

We put these potential factors into the multivariable logistic regression model to analye the responsiveness of pemetrexed combined chemotherapies contained oxaliplatin or irinotecan, respectively. In Table 3, we found age was significatantly related to the responsiveness of pemetrexed, and could significantly predict the responsiveness of pemetrexed ($p<0.05$) by multivariable analysis. And it suggests when age <=57 years, the response rate was higher than those over 57 years.

Discussion

This study assessed factors that could predict potential responsiveness of pemetrexed combined chemotherapy in patients with mCRC, with the purpose for tailoring anticancer treatment in patients with colorectal cancer according to individual molecular and clinical features, and futher improving response rates. In multivariable analysis, we found age, sex, LDH, CEA (>40), oxaliplatin combined, lung metastasis and peritoneum metastasis are more relevant to the responsiveness of pemetrexed. While only age has statistical significance, no other factors were statistically significant.

The clinical benefit of second- or third-line therapy in patients with progressive disease remains unsatisfactory. So the choice of a second- or third-line therapy in patients with mCRC should be careful. Pemetrexed has more molecular targets than 5-FU and has shown activity against mesothelioma, (Jackman et al., 2009) non-small-cell lung cancer (Manegold et al., 2009). An important attribute of pemetrexed is the lower toxicities and relative high efficacy (Calvert AH et al., 2004). Recent study reported that pemetrexed alone in neoadjuvant chemotherapy of rectal cancer had a better objective response rate and disease control rate (Derwinger K et al., 2011).

However, we consider it is important to further clarify patients who could benefit from pemetrexed. Pemetrexed is a multitargeted antifolate (Cripps et al., 1999; John et al., 2000; Hanauske et al., 2001; de Gramont et al., 2002; Hochster et al., 2004; Louvet et al., 2004), could involve in folate metabolism, including TS, dihydrofolate reductase, glycinamide ribonucleotide formyltransferase, and aminoimidazole carboxamide formyl transferase. Pemetrexed could also interfere the metabolism of hemoglobin. While hemoglobin, age and gender reflect the general condition of a patient, so we included gender, age, LDH, ALP, CEA in logistic regression model. In addition, cancer metastasis especially liver metastasis is considered to associate with metabolism of chemotherapeutic agents. So we also put liver metastasis into the logistic regression model. As the number of lung and peritoneum metastasis were risk factors for PS, we hypothesis that these factors may also influence the responsiveness of pemetrexed. The National Surgical Adjuvant Breast and Bowel Project phase II trial of pemetrexed plus oxaliplatin in 54 first-line patients with ACRC achieved a 29.6% confirmed RR, median time to progression of 5.3 months, and median survival of 12.3 months (Louvet et al., 2004; Hochster et al., 2004; Atkins et al., 2005). FOLFIRI-2 regimen (leucovorin, fluorouracil, irinotecan, and hydroxyurea) induced an objective response rate of 17%, a median PFS of 4.1 months, and a median survival of 9.7 months in 29 patients refractory to 5-FU and oxaliplatin (Mabro et al., 2003). FOLFIRI-3, in which irinotecan is administered as two infusions (half dose before 5-FU and half dose at the end of the 5-FU infusion), induced a response rate of 23% in 65 mCRC patients pretreated with FOLFOX, a median progression-free survival of 4.7 months, and a median survival of 10.5 months (Mabro et al., 2006). Considering that oxaliplatin and irinotecan were frequently used in the treatment of colorectal cancer, we conducted the multivariate regression analysis separately.

In conclusion, by multivariate analysis, we found that age had significant impact on the responsiveness of pemetrexed when combined with oxaliplatin. Additional researches based on genomic properties of host and tumor are needed to clarify markers for better selection of patients who could benefit from pemetrexed combined chemotherapy.

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