Association of serum folate level with toxicity of capecitabine in patients with colorectal cancers: a prospective cohort study

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KEY MESSAGES

1. A higher serum folate level is associated with a higher rate of moderate-to-severe toxicity of capecitabine in patients with colorectal cancer.
2. The safety profile of capecitabine is similar between Chinese and western populations, except for a lower rate of diarrhoea and hand-foot skin reactions in the Chinese population.
3. Future studies are needed to determine whether higher folate intake is associated with a worse toxicity profile during capecitabine treatment in cancer patients.

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Introduction

Colorectal cancer is the most common cancer in Hong Kong; over 4000 new cases were diagnosed in 2013.[1] Surgery is the only curative treatment. Adjuvant chemotherapy is indicated in stage III and high-risk stage II disease to reduce the risk of recurrence and distant metastasis after surgery. For stage IV disease, chemotherapy is the mainstay of treatment for palliation. There is a trend of replacing the chemotherapy drug 5-fluorouracil (5-FU) with an oral agent, capecitabine, which is a prodrug of 5-FU that undergoes enzymatic activation in the liver to become the active metabolite.[2] Capecitabine has been recommended in various international guidelines as a single agent or in combination with other chemotherapy agents for colorectal cancer. During capecitabine treatment, the rate of toxicity differs between western and Asian patients. A higher serum folate level has been associated with a higher rate of toxicity in western populations. We conducted a prospective study to examine the association of serum folate level with toxicity during capecitabine treatment in local Chinese patients.

Methods

A prospective cohort study design was used. We hypothesised that a higher serum folate level was associated with an increased rate of moderate-to-severe toxicity in patients who underwent capecitabine treatment for colon cancer. A total of 140 patients with a diagnosis of colorectal cancer who were scheduled to undergo capecitabine or capecitabine-oxaliplatin treatment at the Department of Clinical Oncology of the Prince of Wales Hospital were invited to participate. Informed consent was obtained from each participant before commencement of capecitabine treatment. At baseline, serum and red blood cell folate levels were assessed before commencement of chemotherapy. Patients underwent routine clinical follow-up every 3 weeks. Additional follow-up was provided to those who developed toxicity and required a dose delay. In accordance with the Common Terminology Criteria for Adverse Events 4.0,[3] the type and grade of toxicity was documented on the clinical record form at every visit. Patients were given capecitabine 1250 mg/m^2 twice daily (or 1000 mg/m^2 twice daily when combined with oxaliplatin 100 mg/m^2) for 14 days every 3 weeks. For patients with mild-to-moderate renal impairment (creatinine clearance, 30-50 mL/min), capecitabine was administered at a 25% dose reduction. Patients who developed toxicity secondary to capecitabine treatment were managed in accordance with standard departmental procedures.

Results

A total of 193 patients were recruited from October 2013 to September 2015, of whom 144 were eligible. The median age was 60 (range, 55-68) years. More than 95% of patients had an Eastern Cooperative Oncology Group performance status of 0 (asymptomatic) or 1 (symptomatic but completely ambulatory). About 70% of patients received capecitabine-based treatment. Most (57.3%) had stage III colorectal cancer, and most (74.3%) underwent capecitabine treatment in combination with other agents.

In terms of toxicity of grade 2 or higher, nausea was the most common (47.9%), followed by palmar-plantar erythrodysesthesia (25.0%) and diarrhoea (23.7%) [Table 1]. The rate of grade 3 or higher toxicities was lower than 5%, except for the rate of grade 3 diarrhoea (5.6%). There was no treatment-related death. A total of 32 (23.5%) patients required dose reduction of capecitabine.

TABLE 1. Grade and rate of capecitabine-related toxicity

Grade of toxicity	No. (%) of patients (n=144)	No. (%) patients with ≥ grade 2 toxicity
Nausea		69 (47.9)
0	35 (24.3)	
1	40 (27.8)	
2	66 (45.8)	
3	3 (2.1)	
Vomiting		18 (12.5)
0	82 (56.9)	
1	44 (30.6)	
2	13 (9.0)	
3	5 (3.5)	
Diarrhoea		35 (23.7)
0	65 (45.0)	
1	45 (31.3)	
2	26 (18.1)	
3	9 (5.6)	
Stomatitis		19 (13.2)
0	61 (42.4)	
1	64 (44.4)	
2	15 (10.4)	
3	4 (2.8)	
Skin hyperpigmentation		8 (5.5)
0	27 (18.8)	
1	109 (75.7)	
2	8 (5.5)	
Palmar-plantar erythrodysesthesia		36 (25.0)
0	49 (34.0)	
1	59 (41.0)	
2	35 (24.3)	
3	1 (0.7)	
Skin ulceration		2 (1.4)
0	129 (89.6)	
1	13 (9.0)	
2	2 (1.4)	
Neutropaenia		29 (20.1)
0	100 (69.4)	
1	14 (9.7)	
2	24 (16.7)	
3	5 (4.2)	

The mean serum folate level was 27.7 nmol/L (range, 12.8-45.4 nmol/L). When the cut-off value at the 75th percentile (33.9 nmol/L) was used, 36 (26.4%) patients belonged to the high serum folate group. The mean red blood cell folate level was 1958.4 nmol/L (range, 1183-3716 nmol/L). At the cut-off value of the 75th percentile at 2212.5 nmol/L, 36 (25.0%) patients belonged to the high red blood cell folate group (Table 2).

Univariable analysis showed that serum folate level (not red blood cell folate level) was predictive of toxicity of grade 2 or higher (odds ratio [OR]=1.069, 95% confidence interval [CI]=1.015-1.126; P=0.011; Table 3). Multivariable analysis by logistic regression showed that both alkaline phosphatase level (OR=0.992, 95% CI=0.983-1.000; P=0.062) and serum folate level (OR=1.061, 95% CI=1.007-1.117; P=0.027) were independent predictors of grade 2 or higher toxicity (Table 3).

Discussion

We have demonstrated that serum folate level is a modest predictor of moderate-to-severe toxicity related to capecitabine-based chemotherapy. Our results are consistent with previous findings that only serum folate level (not red blood cell folate level) is associated with moderate-to-severe toxicity during a capecitabine-based regimen.[4,5] The mechanism by which serum folate levels affect 5-FU-related toxicity remains unclear. One postulation is that 5-FU relies on the presence of reduced folate to bind to one of the target enzymes, thymidine synthase, for action. High serum folate level is reflective of the recent intracellular reduced folate level in normal cells around the time of chemotherapy, which may lead to more toxicity.[4] In contrast, red blood cell folate level is more closely related to the average long-term level of folate in the cells. Hence, its level is not directly related to chemotherapy-related toxicity. This finding suggests that serum folate level, instead of red blood cell folate level, should be used in future research of 5-FU related toxicity.

This study represents the largest prospective series so far on the safety profile of capecitabine-based chemotherapy in a Chinese population. It was reassuring that capecitabine-based chemotherapy was generally tolerable in our Chinese cohort: no treatment-related deaths and <7% of toxicities of grade 3 or above were recorded.[6,7] Compared with clinical trials of capecitabine in the western population, our Chinese cohort had less severe diarrhoea (6.6% vs 10%) and palmar-planter erythrodysesthesia (<1% vs >15%). The serum folate

TABLE 2. Serum and red blood cell folate concentrations

Blood fraction	Folate concentration, nmol/L			No. (%) of patients	
	Mean ± standard deviation	Median (range)	75th percentile cut-off value	Low level	High level
Serum	27.7±9.0	26.5 (12.8-45.4)	33.9	108 (73.6)	36 (26.4)
Red blood cell	1958.4±492.0	1882.0 (1183-3716)	2212.5	108 (75.0)	36 (25.0)

TABLE 3. Univariable and multivariable analyses for predictors of toxicity of grade 2 or higher

Variable	Univariable analysis		Multivariable analysis	
	Odds ratio (95% confidence interval)	P value	Odds ratio (95% confidence interval)	P value
Age	0.956 (0.917-0.997)	0.0359	-	-
Sex (male)	0.638 (0.286-1.425)	0.2729	-	-
Eastern Cooperative Oncology Group status	0.742 (0.342-1.608)	0.4493	-	-
Body weight	0.977 (0.944-1.011)	0.1759	-	-
Tumour-node-metastasis classification	0.639 (0.134-3.050)	0.5748	-	-
Treatment: palliative	0.687 (0.296-1.598)	0.3838	-	-
Creatinine clearance	1.006 (0.988-1.024)	0.5346	-	-
Bilirubin	0.974 (0.885-1.065)	0.5288	-	-
Albumin	1.049 (0.934-1.177)	0.4211	-	-
Alanine aminotransferase	1.006 (0.980-1.032)	0.6473	-	-
Alkaline phosphatase	0.991 (0.982-0.999)	0.0298	0.992 (0.983-1.000)	0.0616
Serum folate	1.069 (1.015-1.126)	0.0109	1.061 (1.007-1.117)	0.0268
Red blood cell folate	1.001 (1.000-1.002)	0.1387	-	-

level may be a contributing factor to the geographical difference in toxicity of 5-FU.

Conclusion

There is a potentially negative effect of serum folate on capecitabine-related toxicity. Patients should be advised against taking extra vitamin supplements or making dramatic changes to their consumption of vegetables during chemotherapy.

Acknowledgement

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Ethical Approval

The study was approved by the Joint Chinese University of Hong Kong - New Territories East Cluster Clinical Research Ethics Committee (Ref. No: CRE-2013.019). Patient consent for participation was obtained.

Declaration

The authors have no conflicts of interest to disclose.

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