Original Article

Use of N(2)-L-Alanyl-L-Glutamine Dipeptide in Stage III Colon Cancer Patients with Oxaliplatin-based Chemotherapy, Benefit or Harm?

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Key Words
Stage III colon cancer;
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Purpose. Oxaliplatin plays an important role in adjuvant chemotherapy but its toxicity often results in dose reduction or discontinuance. We evaluated the clinical benefits or harm of parenteral glutamine dipeptide (N2-LAlanyl-L-Glutamine Dipeptide, 20 g · m/100 ml, IV) for stage III colon cancer patients receiving oxaliplatin-based chemotherapy.

Methods. Between January 2015 and December 2017, 74 stage III colon cancer patients who received FOLFOX-4 as adjuvant chemotherapy were enrolled and their data analyzed retrospectively. Among these patients, 31 had received IV glutamine dipeptide (20 g · m IV) days 1-2 with FOLFOX-4 repeated every 15 days (glutamine dipeptide group), and 43 patients received only FOLFOX-4 (control group). Main measures were neurotoxicity symptoms and signs before each cycle, non-neurological toxicities and events (dosage reduction, disease recurrence or progression) and clinicopathologic features, neurotoxicity, disease recurrence, and prognosis.

Results. Patients receiving glutamine dipeptide had significantly fewer neurologic symptoms than controls, including significantly lower incidence of grade 1-2 neuropathy after four and six cycles (6.45% vs. 32.56%, $p = 0.0113$; 6.45% vs. 51.16%, $p < 0.001$ respectively). No significant differences were found between groups in nausea, vomiting, neutropenia, and thrombocytopenia. Compared to controls, patients with intravenous glutamine dipeptide had less mucositis (3.23% verse 20.93%, $p = 0.0382$), a lower percentage of incomplete FOLFOX courses ($p = 0.0204$) and no increased recurrence rates or impaired prognosis. No significant differences were found in overall, disease-free, and cancer-specific survival between groups.

Conclusion. Supplemental IV glutamine dipeptide significantly decreases the incidence and severity of oxaliplatin-induced neurotoxicity in stage III colon cancer.

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Oxaliplatin is a cytotoxic agent that blocks DNA synthesis and replication. Since its introduction in the early 2000s, it has played an important role in the management of patients with advanced colorectal

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cancer. One of the major regimens in adjuvant and palliative treatment of colorectal cancer is the combination regimen of intravenous 5-FU/leucovorin and oxaliplatin (FOLFOX).[1-5] Oxaliplatin toxicity results from inhibiting DNA synthesis such as replication and transcription. These mechanisms also influence the health and function of normal cells, which may result in neurotoxicity, neutropenia, and thrombocytopenia. Oxaliplatin displays a characteristic pattern of dose-limiting neurotoxicity. The rate of neurotoxicity was recorded in more than 90% of patients who received oxaliplatin, and this neurotoxicity can persist even 2-3 years after cessation of oxaliplatin;[6] these side effects often result in prolonged infusion times, treatment delay, dose reduction, treatment cessation and functional impairment.

Several neuroprotective agents such as thiols, neurotrophic factors, anticonvulsants and antioxidants have been tested for prevention of oxaliplatin-induced toxicity. Glutamine dipeptide is a non-essential amino acid. Glutamine is found in the highest concentration in human plasma and skeletal muscle and it is also reported that the supply of glutamine will influence functioning of the gastrointestinal system and immune system.[7-9] A randomized double-blind placebo-controlled trial performed in 1995 disclosed evidence that glutathione is effective for the prevention of cisplatin-induced neuropathy.[10] Oral glutamine was also reported to be an effective agent for significantly reducing the incidence and severity of peripheral neuropathy of metastatic colorectal cancer patients receiving oxaliplatin.[11] The present study aimed to evaluate the clinical benefits or harm of using supplemental glutamine dipeptide in patients with stage III colon cancer treated with oxaliplatin-based chemotherapy.

Patients and Methods

Patients

Between January 2015 and December 2017, a total of 237 patients were diagnosed as colorectal cancer at Chi-Mei Hospital, Tainan, Taiwan. Among patients with a pathologic diagnosis of stage III colonic adenocarcinoma, 74 who had received adjuvant chemotherapy with FOLFOX-4 in our division of colorectal surgery were enrolled and their data were analyzed retrospectively. All patients had been treated with the standard FOLFOX-4 consisting of 2-hour intravenous infusion of oxaliplatin (85 mg/m^2) on day 1, and 2-hour intravenous drip infusion of calcium folinate (200 mg/m^2) on days 1-2, followed by intravenous injection of 5-FU (400 mg/m^2) and continuous infusion of 5-FU (600 mg/m^2) lasting 22 hours on days 1-2, every 2 weeks. A total of 31 patients received glutamine dipeptide (N(2)-L-Alanyl-L-Glutamine Dipeptide (Dipeptiven, Fresenius Laboratories, Germany), which was given IV (20 g · m/100 ml) on days 1-2 of the regimen. The remaining 43 patients who received only FOLFOX-4 served as the control group.

Main measures

Patients enrolled in this study were evaluated at baseline (prior to chemotherapy) and after two, four and six cycles of treatment. Events such as dose reduction, treatment cessation, side effects of chemotherapy, disease recurrence, and mortality were all recorded. We then analyzed the demographic and clinicopathologic characteristics, including age, gender, pre-OP carcinoembryonic antigen (CEA) level, histological differentiation, pathologic stage, duration of follow-up, recurrence, and prognosis. A detailed neurological history and complete neurological examinations were performed and recorded. Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria (NCI-CTC), except for neurologic toxicity, that was graded according to the Lévis scale. Blood test results and non-neurological toxicity were checked and recorded at the out-patient department after each chemotherapy cycle. If grade 3-4 non-neurological toxicity occurred, the doses were modified with at least 15% reductions of all three agents in subsequent cycles. In the case of grade 3-4 neuropathies, the oxaliplatin dose was reduced by at least 15% of the previous dose until recovery; in the case of intolerable neuropathies or persistent functional impairment,

oxaliplatin was discontinued from the regimen. The patients were followed-up until the end of March 2019; mean follow-up time from diagnosis was 25.12 months (±6.99 months). All data in this study were obtained from the Cancer Registry Database, the Cancer Center of Chi-Mei Hospital, and patients' medical records.

Statistical analysis

Continuous data are represented as the mean and standard deviation, and comparisons between the groups were made using a two-sample t-test. Categorical data are presented as count and percentage and compared using a chi-square or Fisher's exact test, as indicated. The survival curves are presented using the Kaplan-Meier method with the log-rank test for comparing differences between the two groups. All data were analyzed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). The Kaplan-Meier curves were plotted using STATA (version 12; Stata Corp., College Station, TX, USA). Statistical significance was set as $p < 0.05$.

Results

Patients' demographic and clinicopathologic characteristics

From 2015 to 2017, 237 patients were diagnosed as stage III colon cancer after surgical intervention in Chi-Mei hospital. Of these, 74 patients received adjuvant chemotherapy with FOLFOX-4 in our division of colorectal surgery and were enrolled in this study, 43 who received only FOLFOX-4 (control group) and 31 who also received glutamine dipeptide (glutamine dipeptide group). The profiles of enrolled patients are shown in Table 1. No significant differences were found between groups in age, pre-OP serum CEA, histological differentiation, or pathology stage. Significantly fewer neurological symptoms were found in patients receiving glutamine dipeptide than in those who did not (Table 1).

Neurotoxicity, non-neurologic toxicity and dose reduction

The results of neurotoxicity, non-neurological

Table 1. Demographic and clinicopathologic profiles of enrolled patients

N(%)	FOLFOX + glutamine (N = 31)	FOLFOX (N = 43)	*p* value
Gender			0.6376
Male	19 (61.29)	24 (55.81)	
Female	12 (38.71)	19 (44.19)	
Age (years)			
Means ± SD	63.16 ± 14.93	60.23 ± 10.38	0.3514
Pre-OP CEA			
Median (Q1, Q3)	3.20 (2.10, 5.40)	3.70 (1.20, 7.80)	0.8229
Histological differentiation			0.1658
Well differentiation	7 (22.58)	3 (6.98)	
Moderate differentiation	21 (67.74)	35 (81.40)	
Poor differentiation	3 (9.68)	5 (11.63)	
Pathology T status			0.2384
1	0 (0.00)	3 (6.98)	
2	3 (9.68)	1 (2.33)	
3	22 (70.97)	27 (62.79)	
4	6 (27.91)	12 (27.91)	
Pathology N status			0.6862
1	21 (67.74)	31 (72.09)	
2	10 (32.26)	12 (27.91)	
Pathology stage			0.9336
IIIA	3 (9.68)	3 (6.98)	
IIIB	21 (67.74)	29 (67.44)	
IIIC	7 (22.58)	11 (25.58)	

toxicities and dose reduction are revealed in Tables 2 and 3. Regarding oxaliplatin-induced neurotoxicity, the percentage of grade 0 sensory neuropathy was similar in both groups after 2 cycles (93.55% versus 93.02%). After 4 cycles of chemotherapy, a lower rate of grade 1-2 and grade 3-4 sensory neuropathy was observed in the glutamine dipeptide group. An even more significant lower rate of grade 1-2 and grade 3-4 sensory neuropathy was found in the glutamine dipeptide group after 6 cycles of chemotherapy. After patients had completed 6 cycles of chemotherapy, more than 87% of patients in the glutamine dipeptide group were recorded as grade 0 sensory neuropathy. In non-neurological toxicities of FOLFOX with and without glutamine dipeptide, no significant differences were found in nausea, vomiting, neutropenia and thrombocytopenia between groups. Compared to controls in the non-glutamine supplement group, patients who received intravenous glutamine dipeptide had less mucositis (3.23% vs. 20.93%, $p = 0.0382$). The percentage of oxaliplatin dose reduction was not significantly difference between the two groups during the treatment periods (16.13% vs. 11.63%; $p = 0.7330$). During the whole course of chemotherapy, patients with intravenous glutamine dipeptide also had lower rates of incomplete FOLFOX treatment (3.23% vs. 23.26%, $p = 0.0204$) (Tables 2 and 3).

Impact of glutamine dipeptide on response to oxaliplatin-based chemotherapy, tumor recurrence and survival

Supplemental intravenous glutamine dipeptide delivered with oxaliplatin-based chemotherapy did not increase recurrence rates or impaired prognosis (Table 4). The glutamine dipeptide group had a 2-year overall survival rate, disease-free survival rate and cancer-specific survival of 100%, 86.9% and 100%, respectively. The corresponding rates in the FOLFOX-only control group were 95.4%, 79.3% and 95.4% (Figs. 1-3). No significant differences were found in overall, disease-free, and cancer-specific survival between the two groups (Table 4).

Discussion

In the present study, patients receiving glutamine dipeptide had significantly fewer neurologic symptoms than controls who had received FOLFOX only. Grade 1-2 neuropathy was significantly lower after four and six cycles in patients receiving supplemental glutamine dipeptide. After patients had completed 6 cycles of chemotherapy¡Amore than 87% of patients in the glutamine dipeptide group were recorded as grade 0 sensory neuropathy. Compared to controls,

Table 2. Incidence of oxaliplatin-induced neurotoxicity by group

All patients	FOLFOX + glutamine (N = 31)	FOLFOX (N = 43)	*p* value
Neuropathy after 2 cycle			0.4451
Grade 0	29 (93.55)	40 (93.02)	
Grade 1-2	1 (3.23)	3 (6.98)	
Grade 3-4	1 (3.23)	0 (0.00)	
Neuropathy after 4 cycle			0.0113
Grade 0	28 (90.32)	27 (62.79)	
Grade 1-2	2 (6.45)	14 (32.56)	
Grade 3-4	1 (3.23)	2 (4.65)	
Neuropathy after 6 cycle			< .0001
Grade 0	27 (87.10)	16 (37.21)	
Grade 1-2	2 (6.45)	22 (51.16)	
Grade 3-4	2 (6.45)	5 (11.63)	

Table 3. Non-neurological toxicities of FOLFOX with/without glutamine dipeptide

N(%)	FOLFOX + glutamine (N = 31)	FOLFOX (N = 43)	*p* value
Non neurological toxicities			
Nausea	3 (9.68)	5 (11.63)	> 0.9999
Vomiting	2 (6.45)	7 (16.28)	0.2883
Mucositis	1 (3.23)	9 (20.93)	0.0382
Neutropenia	14 (45.16)	18 (41.86)	0.7773
Thrombocytopenia	7 (22.58)	10 (23.26)	0.9457
Oxaliplatin dose reduction			
Yes	5 (16.13)	5 (11.63)	0.7330
No	26 (83.87)	38 (88.37)	
Incomplete C/T			
Yes	1 (3.23)	10 (23.26)	0.0204
No	30 (96.77)	33 (76.74)	

Table 4. Recurrence and survival

N (%)	FOLFOX + glutamine (N = 31)	FOLFOX (N = 43)	*p* value
Follow-up (months)			
Means ± SD	23.52 ± 7.39	26.27 ± 6.54	0.0957
Recurrence			
Yes	4 (12.90)	9 (20.93)	0.3706
Overall survival rate, mean (95% CI)			
1 year	1.000 (-, -)	1.000 (-, -)	-
2 year	1.000 (-, -)	0.954 (0.827, 0.988)	-
Disease-free survival rate, mean (95% CI)			
1 year	0.903 (0.729, 0.968)	0.930 (0.799, 0.977)	0.6814
2 year	0.869 (0.688, 0.949)	0.793 (0.623, 0.893)	0.4022
Cancer-specific survival rate, mean (95% CI)			
1 year	1.000 (-, -)	1.000 (-, -)	-
2 year	1.000 (-, -)	0.954 (0.827, 0.988)	-

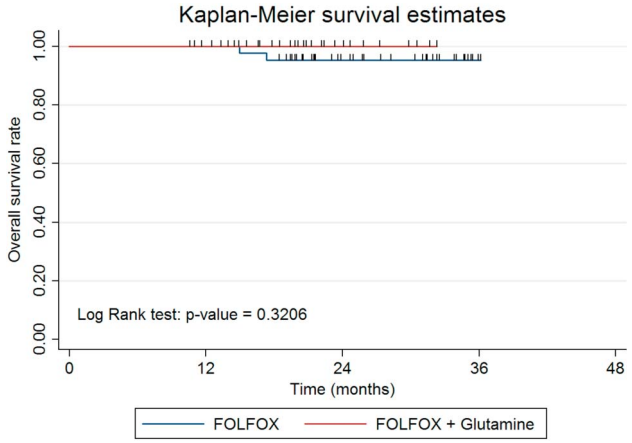

Fig. 1. Kaplan-Meier estimates of overall survival rate for patients with stage III colon cancer.

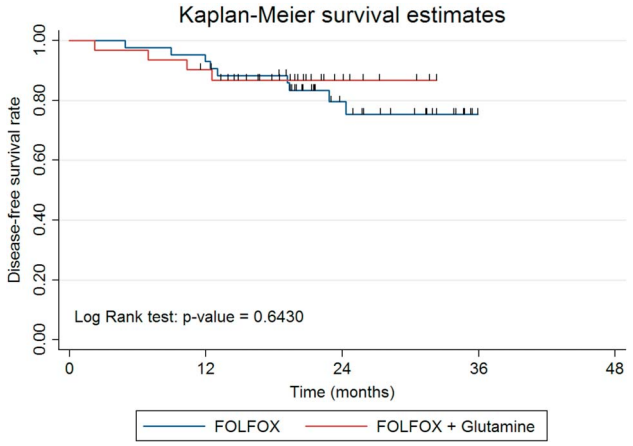

Fig. 2. Kaplan-Meier estimates of disease-free survival rate for patients with stage III colon cancer.

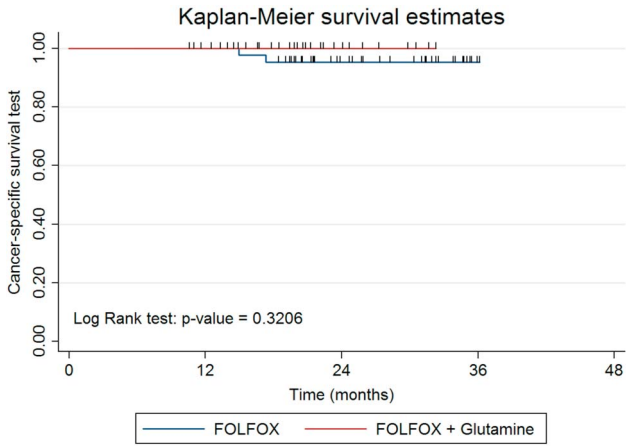

Fig. 3. Kaplan-Meier estimates of cancer-specific survival rate for patients with stage III colon cancer.

patients with intravenous glutamine dipeptide also had less mucositis, a lower percentage of incomplete FOLFOX courses ($p = 0.0204$) and no increased recurrence rates or impaired prognosis. However, no significant between-group differences were found in overall, disease-free, and cancer-specific survival.

Since its introduction in 2004, oxaliplatin with a fluoropyrimidine has been standard adjuvant chemotherapy in patients with stage III colon cancer. Severe oxaliplatin-induced peripheral neurotoxicity may result in dose reduction or treatment cessation. Although various preventative measures have been evaluated for their ability to decrease the incidence of oxaliplatin-induced neurotoxicity, the efficacy of these measures, even though promising, is not universally accepted. Many studies have demonstrated that glutamine supplementation has a potential role in preventing chemotherapy-induced side effects, including the detrimental and sometimes fatal neurotoxic effects.[12-16] Study results support a possible therapeutic role for glutamine supplementation via glutamine

dipeptide in the prevention of oxaliplatin-induced neurotoxicity.[14]

Glutamine is an α-amino acid and is the most abundant non-essential amino acid in the plasma and amino acid pool. Ehrensvard et al.[17] first described the importance of glutamine to cell survival and proliferation. At the most basic level, glutamine acts as an important energy source in human cells and tissues and a high rate of glutamine uptake is characteristic of rapidly dividing cells such as enterocytes, fibroblasts, and lymphocytes.[18,19] Furthermore, this nutrient is considered as an essential amino acid conditionally and its requirement increases in catabolic diseases, especially including cancers.[20-22] Also, glutamine depletion among patients with colorectal cancer has been found to lead to suppression of the T-cell response. Therefore, the immune system cannot destroy the cancer cells in this situation.[23,24] In addition, this nutrient has been suggested to improve the immune system through the proliferation of lymphocytes and macrophages.[25] While the antioxidant properties of this amino acid play a beneficial role in protecting the structure and function of the gastrointestinal tract, it can also be a favored option for reducing complications of colorectal cancer treatment and preventing gastrointestinal adverse events.[26-28] In the present study, supplementation with glutamine dipeptide significantly reduced the incidence and severity of peripheral neuropathy as well as the need to discontinue oxaliplatin in stage III colon cancer patients receiving oxaliplatin-based chemotherapy. These findings of the present study agree with those of previous studies.[4,9,11,29-31] The reported properties may increase the therapeutic index of oxaliplatin.

In the present study, the main causes of FOLFOX cessation in the FOLFOX-only group are intolerable neurotoxicity and fatigue. Some patients refuse to receive further chemotherapy because of nausea, vomiting, or other personal reasons but the main reasons for discontinuance among patients in the FOLFOX + glutamine group are fatigue and poor appetite. In contrast, almost all patients in the FOLFOX-only group who had incomplete FOLFOX treatment had symptoms of neurotoxicity. This suggests that if patients' neurotoxic symptoms can be alleviated, then more patients will have the opportunity to complete 12 courses of chemotherapy without ceasing treatment due to neurotoxic symptoms.

The mechanism of oxaliplatin-induced neurotoxicity has not been clearly understood. Animal research has disclosed that oxaliplatin may interact with the voltage-gated sodium channel. One of the metabolites of oxaliplatin is oxalate, which was shown to influence voltage-gated sodium channels from the pathway involving calcium ions.[32,33] These mechanisms may be the main cause of acute neurotoxity. In the chronic view, axon loss and atrophy on dorsal root ganglion cells were considered to be other possible causes.[34] Oxaliplatin accumulation in the dorsal root ganglion cells is also thought to be a contributing factor.[35] Glutamine penetrates the neuron cells and acts as a neurotrophic factor,[36] which may help to explain why glutamine supplementation with oxaliplatin treatment reduces neurotoxic side effects.

Although the role of glutamine in tumor growth remains controversial,[37-41] no significant between-group differences were found in the cancer recurrence rate, overall survival, disease-free survival and cancer-specific survival in the present study.

Our study has a few limitations, including that it was retrospective and not a randomized control trial, therefore selection bias exists. The sample size was also relatively small and larger placebo-controlled, randomized studies are necessary to confirm glutamine dipeptide as a protective agent against oxaliplatin-induced neuropathy. We also did not perform electrophysiological study in our series to provide objective data about nerve injury. Additionally, most patients in the glutamine dipeptide group had relatively short-term follow-up and longer follow-up would be necessary in subsequent studies.

Conclusion

In patients with stage III colon cancer receiving oxaliplatin adjuvant chemotherapy, glutamine dipeptide reduces the incidence and severity of peripheral neuropathy as well as the need for cessation of oxaliplatin treatment. In short-term follow-up, no signifi-

cant adverse effects are noted on tumor recurrence and prognosis when giving glutamine dipeptide to patients with stage III colon cancer.

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原　著

第三期大腸癌病患接受奧沙利鉑基底化療合併使用雙胜肽丙氨醯谷氨酸治療是否對治療有所助益？

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目的　在患有第三期大腸癌的患者中，奧沙利鉑在化療中扮演重要作用。但奧沙利鉑的毒性如神經毒性，嗜中性白血球低下症或血小板減少症可能導致治療過程中劑量減少甚至暫停化療。在先前的論文中報導了雙胜胺可預防神經毒性。本研究旨在討論雙胜胺對第三期結腸癌患者的臨床益處或危害。

方法　2015 年至 2017 年期間，奇美醫院大腸直腸外科共有 74 名患者診斷為第三期結腸癌患者接受 FOLFOX-4 治療。31 位患者於每次 15 天的化療週期中有合併使用雙胜胺，另外 43 位則否。神經毒性症狀於每次化療週期前評估。其它毒性相關如化療劑量減少，疾病復發和進展等事件亦被記載。我們統計分析兩組間的臨床病理結果，神經毒性與非神經毒性，疾病復發或進展，及預後。

結果　有使用雙胜胺之組別有著較低的神經症狀。經過 4 次及 6 次的 FOLFOX 治療後，雙胜胺組有較低的第一或二級神經症狀發生率。經過 6 個週期的治療後，雙胜胺組仍可有高達 87% 病人維持沒有神經症狀。在非神經毒性症狀如噁心、嘔吐、嗜中性白血球低下症或血小板減少症方面，兩組沒有顯著差異。與對照組相比，靜脈注射雙胜胺的患者粘膜炎發生率較低 (3.23%, 20.93%, $p = 0.0382$)。在整個化療過程中，靜脈注射雙胜胺組較能完成 12 次的 FOLFOX 療程記錄 ($p = 0.0204$)。以奧沙利鉑為基礎的化療，補充靜脈注射雙胜胺也不會增加癌症復發率和預後受損。兩組之間的總體存活率、，無疾病存活率和癌症特異性存活率無顯著差異。

結論　在接受奧沙利鉑基底輔助化療的第三期結腸癌患者中，補充靜脈注射雙胜胺可以有效降低神經症狀發生率及嚴重程度。

關鍵詞　第三期大腸癌、奧沙利鉑、FOLFOX-4、丙氨醯谷氨酸、神經病變。