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N(2)-L-Alanyl-L-Glutamine Dipeptide Preventing Oxaliplatin-Induced Neurotoxicity in Colorectal Cancer Patients

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Abstract

Oxaliplatin and infusional fluorouracil/leucovorin or capecitabine has emerged as important options in the adjuvant and palliative treatment of colorectal cancer. Severe Oxaliplatin induced neurotoxicity may require chemotherapy dose reduction or cessation. The incidence of oxaliplatin-induced neurotoxicity has varied from 12% - 18%. Several attempts have been proposed to prevent or treat oxaliplatin-induced neurotoxicity, but treatment of established chronic Oxaliplatin induced neurotoxicity is limited. **Purpose:** To assess the efficacy of parenteral Glutamine dipeptide (N2-L-Alanyl-L-Glutamine Dipeptide, 20 g·m/100ml, IV) for preventing of oxaliplatin induced neurotoxicity. **Patients and Methods:** A pilot study was performed. 120 patients with metastatic colorectal cancer (mCRC) entered into the study. 60 patients randomly assigned to receive IV glutamine dipeptide (20 g·m IV) day 1-2 with FOLFOX-4 to be repeated every 15 days as a first line of treatment of metastatic colorectal cancer and 60 patients assigned to receive only FOLFOX-4 (control group). Neurotoxicity symptoms and signs were evaluated before each cycle. **Results:** There were significantly fewer neurological symptoms in patients receiving glutamine dipeptide than in those who did not. A decreased percentage of grade 1-2 peripheral neuropathy was observed in the glutamine dipeptide group after two cycles (8.3% versus 20%; $P = 0.04$) and 4 cycles (13.3% vs 26.7%; $P = 0.02$). A significantly lower incidence of grade 3-4 neuropathy was noted in the glutamine dipeptide group after four and six cycles (6.7% versus 15%, $P = 0.02$ and 13.3% versus 33.3%. $P = 0.04$, respectively). The need for oxaliplatin dose reduction was significantly lower in the

glutamine dipeptide (Dipeptiven) group (10% vs 26.7%; $P = 0.02$) and there were no significant differences between two groups in response to chemotherapy among patient with mCRC (48.3% vs 50%). **Conclusion:** These data concluded that IV dipeptide glutamine significantly decreases the incidence and severity of oxaliplatin induced neurotoxicity of mCRC without any attendant side effects.

Keywords

Colorectal Cancer, Oxaliplatin, FOLFOX-4, Alanylglutamine, Neuropathy

1. Introduction

Oxaliplatin from the diaminocyclohexane platinum family, is a cytotoxic agent exerting its cytotoxic effects through the formation of DNA adducts which block both DNA replication and transcription in actively dividing cells. Since its introduction, oxaliplatin has progressively changed the management of patients with advanced colorectal cancer. Combination regimes of infusional 5-FU/leucovorin (FOLFOX) and oxaliplatin or capecitabine (XELOX) have emerged as important options in the adjuvant and palliative treatment of colorectal cancer [1]-[6]. Oxaliplatin displays a characteristic pattern of dose-limiting neurotoxicity. The incidence of oxaliplatin-induced severe neurotoxicity has varied from 12% (Multicenter International Study of Oxaliplatin/5-FU/FA in the Adjuvant Treatment of Colon Cancer, MOSAIC) to 17% (Capecitabine plus Oxaliplatin, XELOX) to 18% (Optimized 5-FU-Oxaliplatin Strategy 1, OPTIMOX1) in different clinical trials [6]-[8]. Oxaliplatin-induced neurotoxicity can be divided into two distinct syndromes; neither type has its mechanism of action fully elucidated. The acute oxaliplatin induced neuropathy may occur immediately after infusion and is characterized by cold-exacerbated paresthesias, muscle spasms, and fasciculations. These acute symptoms are reversible over the following hours and days but often return upon subsequent oxaliplatin administration; they generally do not require discontinuation of treatment [9]. The putative mechanism of action of acute oxaliplatin induced neurotoxicity (OXIN) includes altering the current of voltage-gated Na(+) channels and chelation of calcium and magnesium in response to oxalate, a metabolic by-product of oxaliplatin [10]-[12]. At a higher cumulative dose, oxaliplatin induces dose-limiting chronic sensory neuropathy occurring mainly in the distal extremities [13]. This form of neuropathy development is correlated with the cumulative dose of oxaliplatin. It may last for several months, leading to severe disturbance of neurologic function, and has a significant impact on oxaliplatin treatment. Several attempts have been proposed to prevent or treat oxaliplatin-induced neurotoxicity. Temporary interruption of oxaliplatin before limiting neurotoxicity that develops during therapy has been seen as a potential approach to avoid the problem of neuropathy associated with oxaliplatin in patients with metastatic colorectal cancer. Many neuromodulator agents such as antiepileptic drugs like carbamazepine and gabapentin, calcium-magnesium infusions, mifostine, and glutathione [14]-[17] have demonstrated some activity in the treatment and prophylaxis of

oxaliplatin-induced acute neuropathy. However, randomized trials demonstrating a therapeutic or prophylactic effect of these agents on oxaliplatin's cumulative neurotoxicity are still lacking. Despite of the fact that glutamine is not considered to be an essential amino acid, it is the amino acid found in the highest concentration both in plasma (25%) as in skeletal muscle (75%) [18]. It performs many functions in which may increase its demand, for example: it is a precursor of the synthesis of nucleotides; it is an activator of the protein synthesis and it inhibits the degradation at the same time; it is an activator of glycogen synthesis; it is a metabolic substrate for rapidly replicating cells; it is an energy source for the enterocyte which is so important for maintaining the function and the integrity of the intestinal barrier, and the consumption thereof may be increased under conditions of stress [19]. Glutamine becomes a "conditionally" essential amino acid during periods of stress and in critical patients [20]. In patients with malignant diseases, marked glutamine depletion develops with time, and cachexia development is accompanied by massive depletion of glutamine in skeletal muscle. This leads to a negative impact on the function of host tissues that are dependent upon adequate stores of glutamine for optimal functioning [21]. Furthermore, the extent of normal tissue damage from chemotherapy as well as radiation may be affected by the presence of adequate tissue glutamine stores [22]. Clinically, a neuroprotective role for glutamine in patients with breast cancer receiving high-dose paclitaxel has been identified [22]. A study of circulating nerve growth factor (NGF) levels in cancer patients treated with neurotoxic chemotherapeutic agents found that peripheral neuropathy worsened as serum levels of NGF declined [23]. Moreover, the administration of NGF prevents paclitaxel-induced neuropathy in mice [24]. Because glutamine is known to upregulate NGF mRNA in an animal model [25], glutamine supplements may prevent chemotherapy-induced neuropathy via upregulating the NGF level. On the other hand, it has also been hypothesized that high systemic levels of glutamine may downregulate the conversion of glutamine to an excitatory neuropeptide, glutamate, which may also account for the reduced symptoms observed in patients receiving glutamine [26]. The administration of glutamine intravenously leads to two physical-chemical problems; the first is its low solubility in water; at 20 degrees C this is only 36 g/l, and the second problem is its low chemical stability in an aqueous solution at 22 - 24 degrees C, this being 11 days. This problem has led the industry to research two dipeptides of glutamine; L-alanyl-glutamine, and L-glycyl L-glutamine, both of which are much more soluble and much more stable. At present, on the European market there are two commercially available brands of glutamine dipeptides: Dipeptiven, by Fresenius Laboratories, Germany. A 100 ml vial which corresponds to 20 g of L-alanyl L-glutamine dipeptide (8.2 g of alanine + 13.46 g of L-glutamine, this is added to the standard amino acid solution). Glamin, Pharmacia and Upjohn Laboratory, Sweden. This is an amino acid solution with 13.4% essential and non-essential amino acids which are equivalent to 22.4 g of nitrogen/l, and which contain 30.27 g L-glycyl-L-glutamine (10.27 g of glycine + 20 g of L-glutamine). The dipeptide glutamine is endogenously split into the amino acids glutamine and alanine hereby supplying glutamine. The released amino acids flow as nutrients into their respective body pools and are metabolised according to the needs

of the organism. Many disease conditions, in which parenteral glutamine is indicated, are accompanied by a glutamine depletion, which glutamine containing infusion regimens counteract. At present there is still a controversy regarding the dosage of glutamine and its dipeptides. These facts support a possible therapeutic role for glutamine via glutamine dipeptide in the prevention of damage of normal tissues, including peripheral nerves, during chemotherapy [27]. On the basis of these considerations, a pilot study was conducted in mCRC patients to assess the efficacy of glutamine via glutamine dipeptide in preventing oxaliplatin-induced neuropathy. All were treated with the same oxaliplatin-based regimen and were randomized to receive or not to receive glutamine dipeptide (Dipeptiven, by Fresenius Laboratories, Germany).

2. Patient and Methods

2.1. Eligible Patients

This prospective study was carried out with the Institutional Ethics Committees approval and following the South Egypt Cancer Institute Medical Research Council Guidelines. All participants gave their written informed consent prior to entering the study. A series of 120 patients were diagnosed as metastatic colorectal cancer (100 patients with synchronous CRC metastases and 20 patients with metachronous CRC metastases) treated at the South Egypt Cancer Institute Teaching Hospital, South Egypt Cancer Institute, Assuit University, Egypt, between May 2012 and May 2015 were enrolled.

2.2. Inclusion Criteria

Patients of both gender, aged ≥18 years with histologically confirmed colorectal adenocarcinoma; stage IV according to American Joint Committee on Cancer and the Union for International Cancer Control (AJCC-UICC); 7th Edition. ECOG performance state ≤ 2, adequate hematological (evidenced by white blood cell count ≥ 4000/μl and platelet count ≥ 100,000/μl), renal (creatinine < 1.5 mg/dl) and hepatic functions (serum total bilirubin < 1.5 mg/dl). No previous therapy for metastatic diseases (adjuvant therapy was allowed if more than 6 months had transpired since its completion) was included in the study. Characteristics of enrolled patients are shown in **Table 1**.

2.3. Exclusion Criteria

Patients with pre-existing neuropathy, diabetes mellitus, alcoholic disease and central nervous system metastasis, severe renal insufficiency (creatinine clearance < 25 ml/minute), severe hepatic insufficiency, severe metabolic acidosis or known hypersensitivity to the active substances or to any of the excipients were excluded from this study.

3. Treatment Plan

3.1. Chemotherapy

All the patients were 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 infu-

sion 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 h on days 1-2, every 2 weeks. Patients were randomized to receive glutamine dipeptide (Dipeptiven, by Fresenius Laboratories, Germany, $n = 60$; glutamine dipeptide group) or not to receive glutamine dipeptide ($n = 60$; control group). In the glutamine dipeptide group, (N(2)-L-Alanyl-L-Glutamine Dipeptide, Dipeptiven, by Fresenius Laboratories, Germany) was given IV (20 g·m/100ml) on the day 1-2 of regimen.

3.2. Radiotherapy

During concurrent chemoradiation for rectal cancer, chemotherapy protocol modified from classic FOLFOX to Oxaliplatin 50 mg/m^2 day 1, 8, 22, 29 with Capecitabine 825 mg/m^2 PO bid on days 1-14 and 22-35. Clinical target volume high risk (CTV-HR) includes remaining rectum, mesorectal bed, and presacral space, CTV-standard risk includes mesorectum bed and right and left internal iliac lymph nodes, external iliac lymph nodes for T4 tumors and perineal scare in cases had abdominoperineal resection. Each CTV expanded 1 cm to form Planning target volume (PTV). Postoperative dose to PTV-HR: 54 Gy PTV-SR (Planning target volume standard risk): 45 Gy at 1.8 Gy/fraction.

3.3. Follow Up

Patients enrolled in this study were evaluated at baseline (prior to chemotherapy) and after two, four and six cycles of treatment. A detailed neurological history, complete neurological examinations were performed and CT chest and abdomen at baseline and after two, four and six cycles of treatment. Electrophysiological examinations, including nerve conduction velocity (NCV) were performed after two, four and six cycles of treatment. An experienced neurologist evaluated the data to assess possible between-group differences in electrophysiological function. Responses to chemotherapy measured by the same method of assessment and same technique used to characterize each identified and reported lesion at baseline. Assessment was done every two cycles, accordance to the Response Evaluation Criteria in Solid Tumors (RECIST). Treatment-related toxicities were evaluated on the basis of standard World Health Organization (WHO) criteria. If grade 3-4 non-neurological toxicity occurred and the doses were modified with 25% reductions for all three agents in subsequent cycles. In the case of grade 3-4 neuropathies, the oxaliplatin dose was reduced by 25% of the previous dose until recovery; in the case of intolerable neuropathies or persistent functional impairment, oxaliplatin was omitted from the regimen. The patients were followed-up until the end of May 2015; mean follow-up time from diagnosis was 32.6 months (±24.8 months).

3.4. Statistical Analysis

Statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL). Data were described as frequencies (percentages). Differences in distributions between the variables examined were analyzed by chi-square test. In this study, we primarily focused on oxaliplatin-induced neuropathy because this neuropathy may result in severe

disturbance of neurologic function and have a significant impact on oxaliplatin treatment. The difference in clinicopathological characteristics, including the development of neuropathy, response to chemotherapy, non-neurological toxicity. All analyses were performed on a microcomputer using the SPSS software package for Windows. Statistical difference was defined as $P < 0.05$.

4. Results

Statistical analysis showed that all of the pretreatment parameters were well balanced between the two groups of patients. As shown in Tables 1-3, there was no significant differences between-group in age, gender, performance status, location of primary

Table 1. Characteristics of enrolled patients.

Characteristic	FOLFOX	FOLFOX + Dipeptiven	*P*
All patient rolled	60	60	
Age (years)			
>50	22	26	NS
<50	38	34	
Gender			
Male	33	39	NS
Female	27	21	
Performances status			
0	21	18	NS
1 - 2	39	42	
Site of primary tumor			
Colon	44	47	NS
Rectum	16	13	
Histological differentiation			
Grade I-II	32	26	NS
Grade II-IV	28	34	
Site of metastases			
Liver only	27	24	
Liver and others	25	28	NS
Others	8	8	
Surgical procedures			
Radical surgery (n = 20)	**11**	**9**	
Rt hemicolectomy	4	3	
Lt hemicolectomy	2	2	NS
Extended Rt hemicolectomy	2	2	
Extended Lt hemicolectomy	1	1	
Low ant resect. of Dixon	2	1	
Palliative surgery(n = 10)	**5**	**5**	
Hartman's operation	1	2	NS
Colostomy	2	1	
Bypass	1	0	
Ileostomy	1	2	
Serum CEA level			
>5	32	37	NS
<5	28	23	

CEA: carcinoemberyonic antigen.

Table 2. Incidence of oxaloplatin induced neurotoxicity in different group.

All patients	FOLFOX + dipeptide glutamine (%)	FOLFOX (%)	*P*
After 2 cycles			
Grade 0	55 (91.7)	47 (78.3)	
Grade 1-2	5 (8.3)	12 (20)	0.05
Grade 3-4	0 (0)	1 (1.7)	
After 4 cycles			
Grade 0	48 (80)	35 (85.3%)	
Grade 1-2	8 (13.3)	16 (26.7)	0.02
Grade 3-4	4 (6.7)	9 (15)	
After 6 cycles			
Grade 0	40 (66.7)	24 (40)	
Grade 1-2	12 (20)	18 (30)	0.04
Grade 3-4	8 (13.3)	20 (33.3)	

Neurotoxicity was defined by the national cancer institute common toxic criteria.

Table 3. Electrophysiological examination after 2 cycles in different group.

Nerve	Differences	FOLFOX + Dipeptiven	FOLFOX	*P* (NS)
		Median ± SD	Median ± SD	
Median	Distance of latency	3.4 ± 0.2	3.4 ± 0.3	0.09
	Conduction velocity	45 ± 2	43 ± 3	0.08
Ulnar	Distance of latency	3.3 ± 0.4	3.5 ± 2	0.08
	Conduction velocity	44 ± 3	42 ± 4	0.07
Sural	Distance of latency	3.4 ± 1	3.6 ± 1	0.09
	Conduction velocity	46 ± 2	43 ± 4	0.09

tumor, histological differentiation, sites of distant metastasis, or serum carcinoembryonic antigen (CEA). There were significantly fewer neurological symptoms in patients receiving glutamine dipeptide than in those who did not. The percentage of grade 1-2 sensory neuropathy was significantly lower in glutamine dipeptide group than in the control group after 2 cycle (8.3% versus 20%; $P = 0.04$) and 4 cycles of treatment (13.3 vs 26.7). Moreover, the percentage of grade 3-4 sensory neuropathy was lower in glutamine dipeptide group after four cycles of treatment (6.7% versus 15%; $P = 0.02$) and remained so after six cycles (13.3% versus 33.3%; $P = 0.04$). Electrophysiological examinations were carried out, as nerve conduction studies are useful in objectively assessing peripheral neuropathy is of extreme interest. In the current study, we found that distance of latency and conduction velocities of peripheral sensory were frequently deteriorated in both groups of patients. However, there was statistical difference between groups in the incidence of abnormalities concluded from electrophysiological examinations after 4 and 6 cycles of treatment ($P = 0.05$) (Tables 4-6). As glutamine dipeptide supplementation significantly reduced the incidence and severity of oxaliplatin induced neurotoxicity and neurotoxicity is one of the major dose-limiting toxicities of oxaliplatin, the percentage of patients needing oxaliplatin dose reduction was significantly lower in the group receiving glutamine dipeptide during the treatment periods (10% versus 26.7%; $P = 0.02$). Another important issue was the impact of supplemental glutamine

Table 4. Electrophysiological examination after 4 cycles in different group.

Nerve		FOLFOX + Dipeptiven	FOLFOX	*P*
		Median ± SD	Median ± SD	
Median	Distance of latency	3.4 ± 0.4	3.6 ± 0.5	0.05
	Conduction velocity	45 ± 6	40 ± 6	0.05
Ulnar	Distance of latency	3.4 ± 0.5	3.5 ± 1.1	0.03
	Conduction velocity	43 ± 6	42 ± 8	0.05
Sural	Distance of latency	3.5 ± 3	3.7 ± 1.2	0.04
	Conduction velocity	45 ± 6	41 ± 8	0.04

Table 5. Electrophysiological examination after 6 cycles in different group.

Nerve		FOLFOX + Dipeptiven	FOLFOX	*P*
		Median ± SD	Median ± SD	
Median	Distance of latency	3.4 ± 0.8	3.6 ± 0.7	0.02
	Conduction velocity	45 ± 6	39 ± 9	0.05
Ulnar	Distance of latency	3.3 ± 0.9	3.5 ± 1.5	0.03
	Conduction velocity	44 ± 6	42 ± 9	0.05
Sural	Distance of latency	3.5 ± 4	3.7 ± 1.2	0.002
	Conduction velocity	46 ± 6	41 ± 9	0.04

Table 6. Non neurological toxicities of FOFOX with and without dipeptiven.

	FOLFOX + Dipeptide glutamine	FOLFOX (%)	*P*
Non neurological toxicities			
Nausea	8 (13.3)	7 (11.7)	NS
Vomiting	7 (11.7)	9 (15)	NS
Mucositis	4 (6.7)	12 (20)	0.04*
Diarrhea	6 (10)	12 (20)	0.03*
Alopecia	10 (16.7)	9 (15)	NS
Hand foot syndrome	6 (10)	8 (13.3)	NS
Neutropenia	5 (8.3)	7 (11.7)	NS
Febrile neutropenia	3 (5)	4 (6.7)	NS
Anemia	6 (10)	5 (8.3)	NS
Thrombocytopenia	3 (5)	4 (6.7)	NS
Oxaliplatin dose reduction			
Yes	6 (10)	16 (26.7)	0.02
No	54 (90)	44 (73.3)	

dipeptide on the response to oxaliplatin-based chemotherapy as well as survival, there were no significant differences between-group in the response to chemotherapy (48.3% versus 50%; $P = 0.8$) and in the median survival time (17.3 months versus 18.6 months; $P = 0.79$) (Table 7 and Figure 1). There were significant difference between-groups in incidence of mucositis (6.7% versus 20%; $P = 0.05$) and diarrhea (10 vs 20, $P = 0.02$) but no statistical differences in other gastrointestinal and hematological toxicities.

Table 7. Response to chemotherapy among metastatic CRC.

Response criteria	FOLFOX + dipeptide glutamine	FOLFOX	*P*-value
Complete remission	3	4	NS
Partial remission	26	26	NS
Stationary disease	16	12	NS
Progressive disease	15	18	NS

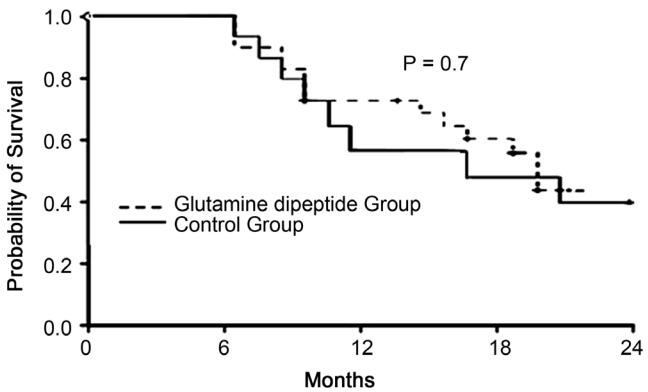

Figure 1. Survival curves of metastatic colorectal cancer patients receiving glutamine dipeptide or not receiving glutamine dipeptide supplementation during oxaliplatin treatments ($P = 0.07$).

5. Discussion

Addition Oxaliplatin to fluorouracil and capecitabine has become an integral component of chemotherapeutic regimens in adjuvant and palliative treatment of CRC cancer [3]-[6]. However, up to 30% of patients experience dose-limiting neurotoxicity proved by moderate motor and sensory symptoms, even though they are still actively responding to this drug [28]. Severe oxaliplatin-induced peripheral neurotoxicity may require dose reduction or cessation this early discontinuation or dose reduction due to neurotoxicity are undesirable. Although various preventative measures have been tested to decrease the incidence of oxaliplatin induced neurotoxicity, the promising efficacy of these measures, are not universally accepted. Many studies have proven that glutamine supplementation is has potentially effective role in preventing chemotherapy induced side effects [29]-[33]. These facts support a possible therapeutic role for glutamine supplementation via glutamine dipeptide in the prevention of oxaliplatin induced neurotoxicity [31]. In the current study, supplementation with glutamine dipeptide significantly reduced the incidence and severity of peripheral neuropathy as well as the need for dose reduction of oxaliplatin in these patients. These properties may increase the therapeutic index of oxaliplatin. Our clinical finding matched with results of studies conducted by Cascinu *et al.* [17], and Wei-Shu Wang *et al.*, [34]. Electrophysiological study show that, sensory nerve conduction affected significantly after oxaliplatin-based treatment, the severity of clinical sensory neuropathy does not always correlate with findings of nerve conduction studies. For example, it has been reported that the symptoms of oxaliplatin-induced neurotoxicity could be remarkably reduced after discon-

tinuation of oxaliplatin treatment; however, abnormalities of sensory nerve conduction were shown to persist [35]. In the current study, we noticed an inconsistency between the electrophysiological findings and the subjective results reported by patients and assessed by physicians. There is statistically significant difference between-groups were seen in electrophysiological studies of patients receiving glutamine dipeptide supplements or not ($P < 0.05$). The current result is mismatched with result of Wei-Shu Wang [36] because both studies a non-placebo controlled unblinded study with a relatively small sample size; patient and physician bias may have played a role in this inconsistency. Although the role of glutamine in tumor growth is a controversy [36]-[40], however in the current study, no difference between-group was found in the response to chemotherapy (52.4% versus 47.8%; $P = 0.9$) or survival ($P = 0.79$). As a result to lower the incidence and severity of Oxaliplatin induced peripheral neuropathy, glutamine dipeptide supplements also improve ADL (activities of daily living)(consistent mainly with fine motor coordination) for patients who received glutamine dipeptide supplementation 15% (9 cases), compared with 38.3% (23 cases) of those who did not ($P = 0.02$). Improving ADL is considered a very important indicator of outcome in patients receiving glutamine dipeptide. In addition of improving oxaliplatin induced neuropathy, glutamine dipeptide significantly reducing the incidence of gastrointestinal diarrhea (10% (6 cases) versus 20% (12 cases), $P = 0.03$), and mucositis (6.7% (n = 4) versus 20% (n = 12), $P = 0.04$). Hematological toxicities show no significant differences between both groups.

6. Conclusion

Our data concluded that supplementation of glutamine via glutamine dipeptide has a potential neuroprotective effect in mCRC patients treated with oxaliplatin, and may therefore improve the therapeutic index. Larger placebo-controlled, randomized studies are necessary to confirm the application of glutamine dipeptide as a protective agent against oxaliplatin-induced neuropathy.

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