Original Article

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Study of Oxaliplatin-based Chemotherapy-Induced Neurotoxicity in Colorectal Cancer Thai Patients

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Abstract

Oxaliplatin is known to cause neurotoxicity, especially peripheral neuropathy. To prevent such symptom, oxaliplatin is recommended to be administered in a prolonged infusion time. This was an observational study to determine the incidence of neurotoxicity in colorectal cancer Thai patients of the National Cancer Institute who received different infusion time of oxaliplatin. All patients were prospectively determined for neurotoxicity at each cycle of chemotherapy in which oxaliplatin was infused for 2-, 4-, and 6-hour per doctor's order. The severity of symptoms was graded according to the Oxaliplatin-Specific Neurotoxicity Scale. At the last cycle, patients answered the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire to evaluate quality of life. Thirty two patients were enrolled and 75% were infused for 2-hour regimen. Motor neurotoxicity and sensory alteration were presented in almost all cycles. Incidence of increasing severity was found along the increasing cycle, and it was similar among the three groups of different infusion time. The median cumulative dose of oxaliplatin in the group without symptoms, grade 1, 2 and 3 neurotoxicity were 300, 468.8, 671.9, and 1,031.3 mg/m^2, respectively (ranged from 112.5 to 937.5 mg/m^2, 162.5 to 1,012.5 mg/m^2, 150 to 975 mg/m^2, and 812.5 to 1,125 mg/m^2, respectively). Total scores of quality of life were good, higher than 70. It was concluded that oxaliplatin caused progressive neurotoxicity along the increasing cycle and there was a tendency that prolonged duration of infusion resulted in lower incidence of neurotoxicity.

Keyword: oxaliplatin, neurotoxicity, colorectal cancer, quality of life.

INTRODUCTION

Oxaliplatin is a useful drug to treat advanced colorectal cancer but it causes adverse effect on nervous system mainly as peripheral neuropathy. This neurotoxicity is a dose limiting side-effect. Two types of symptoms are reported: acute, transient neuropathy and chronic, cumulative neuropathy. Acute, transient neuropathy is characterized by the rapid onset occurs during infusion within minutes to hours or within a few days of infusion while chronic neuropathy occurs progressively with cumulative oxaliplatin dose of 780 to 850 mg/m^2. Signs and symptoms occur mainly as sensory alterations, but motor nerve defects also manifest. It is also found that cold exposure is the predisposing factor of exacerbation of acute neurotoxicity symptoms. Although oxaliplatin-induced neurotoxicity can be reversible, these neuropathic symptoms interfere with activities of daily living and contribute to unpleasant feeling of patients.[1] Various strategies are still under investigation to prevent or reduce both acute and chronic oxaliplatin-induced neuropathy. It has been reported that the prolongation of administration of oxaliplatin from 2 to 6 hours can prevent recurrence of symptoms in patients who have pharyngolaryngeal dysesthesia.[2]

Neuropathic symptoms have a harmful impact on quality of life (QOL) of patients and some studies showed the negative impact on increased pain scores along the progress of disease. There are various instruments used

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to assess QOL in cancer patients including the Functional Assessment of Cancer Therapy-General (FACT-G). FACT-G questions are divided into 4 major domains: physical, social/family, emotional, and functional well-being. It can be used with patients of any cancer types.[3]

At the National Cancer Institute (NCI), oxaliplatin-based chemotherapy is used for colorectal cancer and the recommended duration of administration is 2 hours but the prolongation is indicated in some cases due to neuropathy. Such acute neurotoxicity problems were complained by colorectal cancer patients at NCI but there was no documented incidence. This study is, therefore conducted to determine the incidence of acute neurotoxicity and to study whether prolonged oxaliplatin infusion could reduce neuropathy symptoms in Thai colorectal cancer patients. The neurologic examination and simple qualitative sensory tests are employed as assessment tools. The expected outcome of study is to find the proper duration of administration of oxaliplatin.

METHODS

Study Design and Ethical Issue

This was a prospective cohort study and approved by the Human Research Ethics Committee of National Cancer Institute (NCI) and Mahidol University Institutional Review Board (MU-IRB).

Eligible Patients

All new patients of NCI with colorectal cancer during August 2009 to 2010 were eligible for the study if they were treated with oxaliplatin-based chemotherapy. Other inclusion criteria were: ≥ 18 years old, creatinine clearance ≥ 60 mL/min, total serum bilirubin level < 1.5 mg/dL, baseline neutrophil count > 1,500/μL, platelets > 100,000/mm^3, and signed written informed consent. Patients with history of previous peripheral neuropathy such as diabetes mellitus, cancer of the central nervous system, HIV/AIDS, spinal injuries, alcoholism, herpes zoster infection, or receiving medicine that caused peripheral neuropathy such as stavudine, heavy metal, tacrolimus, etc., or being treated with a known drug to prevent peripheral neuropathy such as tricyclic antidepressant, vitamin B_1, B_6, B_{12} supplement, etc., or unable to communicate or refuse to participate, were excluded from the study.

Treatment

All patients received any oxaliplatin-based chemotherapy, as 2-, 4-, or 6-hour infusion, according to physician's judgement and decision.

Neurotoxicity Assessment

Neurotoxicity was firstly assessed by deep tendon reflex (DTR), and muscle weakness. A questionnaire modified from Patient Neurotoxicity Questionnaire for Oxaliplatin ($PN_{Qoxaliplatin}$) which included sensory symptoms and motor symptoms was used in addition to assess neurotoxicity. Patients whose answer was no sensory symptoms were further tested with cold-induced allodynia by painting skin with 70% alcohol pad and hyperalgesia by pinpricking finger or hand. Then the severity of neurotoxicity was graded according to the Oxaliplatin-Specific Neurotoxicity Grading Scale. Grade 1 indicates paresthesias and/ or dysesthesias of short duration with complete resolution before the next cycle, grade 2 paresthesias and/ or dysesthesias persisting between cycles without functional impairment, and grade 3 paresthesias interfering with functional impairment.

Quality of Life Assessment

FACT-G questionnaire was used to evaluate overall quality of life at the last cycle. Response scales for all subscales range from 0 "Not at all" to 4 "Very much".3 FACT-G scoring would be done according to the guideline, the higher the scores, the better the quality of life.

Statistical Analysis

Incidence of neurotoxicity was presented as number and percentage. One-way ANOVA test was used to determine the difference of FACT-G scores according to different dimensions and total scores to different duration of infusion.

RESULTS

Thirty two colorectal cancer patients were eligible for the study, receiving a total of 232 cycles of oxaliplatin-based chemotherapy. All received FOLFOX4 regimen (Oxaliplatin 85 mg/m^2 together with leucovorin 200 mg/m^2 administered separately by intravenous infusion on day 1, followed by 5-fluorouracil 400 mg/m^2 given as intravenous bolus injection and then 5-fluorouracil 600 mg/m^2 as a 22-hour intravenous infusion on day 1 and 2).[4] Number of patients decreased along the increasing number of chemotherapy cycle (Table 1), as a result of changing chemotherapy regimen or adding radiation. Finally, only 11 patients had completed the 12-cycle regimen.

Table 1. Patient's demographic data

parameter	Number of patients (%)		
	2 hour- infusion	4 hour infusion	6 hour-infusion
Number of patients			
- Cycle 1	24 (75.0)	2 (6.3)	6 (18.7)
- Cycle 2	21 (72.4)	2 (6.9)	6 (20.7)
- Cycle 3	19 (70.4)	2 (7.4)	6 (22.2)
- Cycle 4	18 (72.0)	2 (8.0)	5 (20.0)
- Cycle 5	17 (73.9)	2 (8.7)	4 (17.4)
- Cycle 6	13 (68.4)	2 (10.5)	4 (21.1)
- Cycle 7	11 (68.8)	2 (12.5)	3 (18.8)
- Cycle 8	9 (64.3)	2 (14.3)	3 (21.4)
- Cycle 9	8 (66.7)	2 (16.7)	2 (16.7)
- Cycle 10	8 (66.7)	2 (16.7)	2 (16.7)
- Cycle 11	8 (66.7)	2 (16.7)	2 (16.7)
- Cycle 12	7 (63.6)	2 (18.2)	2 (18.2)
Age (years)			
Median	57.5	41	57.5
Range	31-76	32-50	44-71
Sex			
Male (%)	16 (50.0)	1 (3.2)	4 (12.3)
Female (%)	8 (25.0)	1 (3.2)	2 (6.3)
Primary site of cancer			
Colon (%)	13 (40.6)	2 (6.3)	4 (12.5)
Rectum (%)	11 (34.4)	0 (0.0)	2 (6.3)
Number of cycles of oxaliplatin-based infusion (%)	163 (70.3)	24 (10.3)	45 (19.4)

Patient's demographic data

Patients' demographic data are presented in Table 1. More than 50 percent of patients were male, 31-76 years old. Two-hour oxaliplatin infusion was administered to 75% of patients and accounted for 163 cycles, while the 4, and 6-hour infusion groups accounted for 24, and 45 cycles of oxaliplatin-based chemotherapy, respectively.

Neurotoxicity

As shown in Figure 1, higher percentage of patients of all group had no neurotoxicity at the early cycles, but less afterwards. Grade 1 neurotoxicity (Figure 2) was detected in the 2-hour infusion group at every cycle, but not all in the 6-hour group. The highest percentage of patients with grade 1 neurotoxicity was observed after cycle 5 in all groups. Patients of the 2-hour infusion group reported grade 2 neurotoxicity since cycle 2, but the 4- and the 6-hour infusion group reported at later cycle (Figure 3). Along the advanced cycles, all groups had more patients with grade 2 neurotoxicity. Grade 3 neurotoxicity (Figure 4) was detected after cycle 9 in the 2-and the 4-hour infusion group, but not in the 6-hour infusion group.

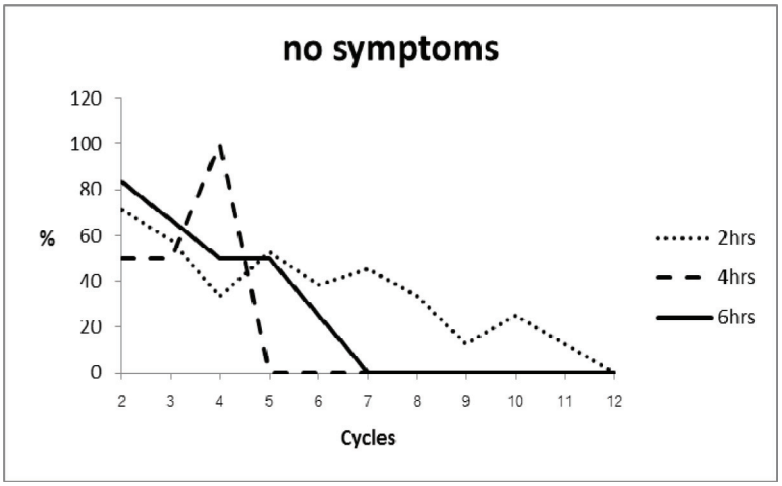

Figure 1. Percentage of patients with no neurotoxicity along the cycles of oxaliplatin infusion

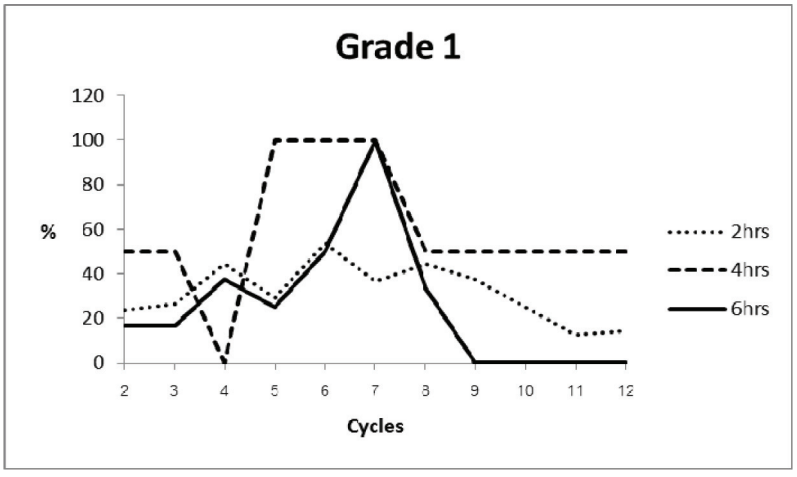

Figure 2. Percentage of patients with grade 1 neurotoxicity along the cycles of oxaliplatin infusion

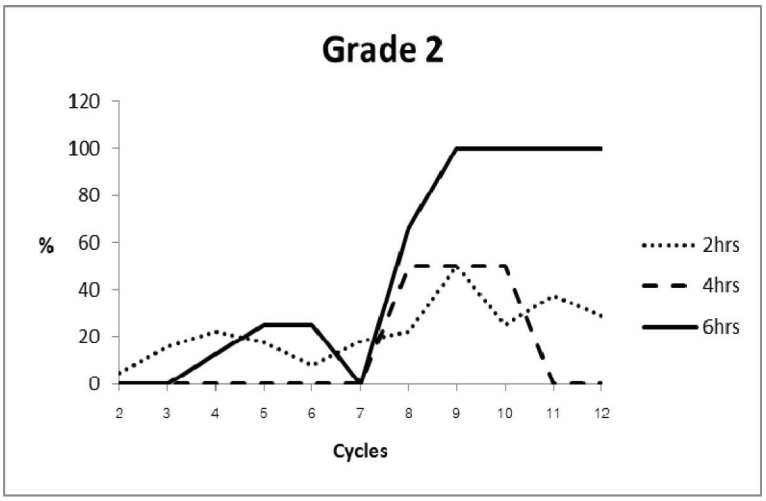

Figure 3. Percentage of patients with grade 2 neurotoxicity along the cycles of oxaliplatin infusion

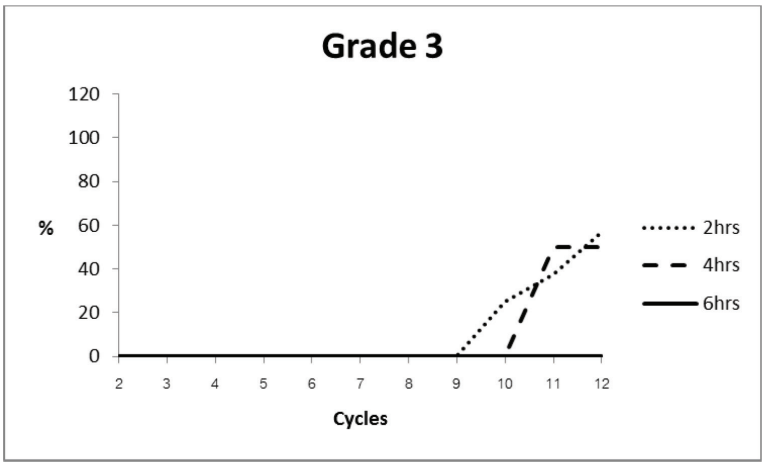

Figure 4. Percentage of patients with grade 3 neurotoxicity along the cycles of oxaliplatin infusion

Table 2 shows occurrence of any motor neurotoxicity. Difficulty in swallowing, breathing, chewing, muscle spasms, and alteration of daily living activity were detected in almost all cycles in the group of 2-hour infusion, compared to other groups. The advanced cycles resulted in more motor neurotoxicity than in the early cycles and this was observed only in the 2-hour infusion group.

Incidence of sensory alteration as shown in Table 3, was more common among patients of the 2-hour infusion group than other groups. Numbness, paresthesia, and electric shock were observed more common in all groups.

Table 2. Any incidence of motor neurotoxicity (•) among oxaliplatin infusion therapy

Cycle	2-hour					4-hour					6-hour				
	M1	M2	M3	M4	M5	M1	M2	M3	M4	M5	M1	M2	M3	M4	M5
2				•										•	
3	•		•											•	
4	•		•	•										•	
5	•	•	•	•											
6	•	•		•											
7	•	•		•										•	
8	•	•		•										•	
9	•	•	•	•		•									
10	•	•	•	•	•										
11	•	•	•	•	•					•					
12	•	•	•	•	•					•					

M1 = difficult swallow, M2 = difficult breathing, M3 = difficult chewing, M4 = muscle spasms, M5 = alteration of activity daily living

Table 3. Any incidence of sensory alteration (•) among oxaliplatin infusion therapy

Cycle	2-hour						4-hour						6-hour					
	S1	S2	S3	S4	S5	S6	S1	S2	S3	S4	S5	S6	S1	S2	S3	S4	S5	S6
2	•	•	•	•	•	•	•					•	•	•	•	•	•	
3	•	•	•	•	•		•						•	•		•	•	•
4	•	•	•	•	•	•	•							•		•		
5	•	•	•	•	•	•	•	•		•	•		•	•		•		
6	•	•	•	•	•	•				•	•	•	•	•		•		
7	•	•	•	•	•					•			•	•		•	•	•
8	•	•		•	•	•				•	•		•	•		•	•	
9	•	•	•	•	•	•					•	•	•			•	•	•
10	•	•		•	•	•	•			•	•		•				•	
11	•	•	•	•	•	•	•				•		•					
12	•	•	•	•	•	•	•	•			•		•			•	•	

S1 = numbness, S2 = pain, S3 = burning, S4 = paresthesia, S5 = electric shock, S6 = change in sense of touch

Cumulative dose ofoxaliplatin

The median cumulative dose of oxaliplatin given to those with no symptoms, grade 1, 2 and 3 neurotoxicity were 300, 468.8, 671.9, and 1,031.3 mg/m^2, respectively (ranged from 112.5 to 937.5 mg/m^2, 162.5 to 1,012.5 mg/m^2, 150 to 975 mg/m^2, and 812.5 to 1,125 mg/m^2, respectively). Figure 5 shows plots between the cumulative dose at the first detected neurotoxicity of any grade and the three grading. It was found that the cumulative dose of no symptoms was higher in the 6-hour infusion than the 2- and the 4-hour infusion. At grade 1, 2, and 3 neurotoxicity, the cumulative dose that caused neurotoxicity was highest in the 4-hour infusion group followed by the 2- and the 6-hour infusion group. The graphs of cumulative dose of neurotoxicity in the 4-hour infusion group was steeper than the 2- and 6-hour infusion group.

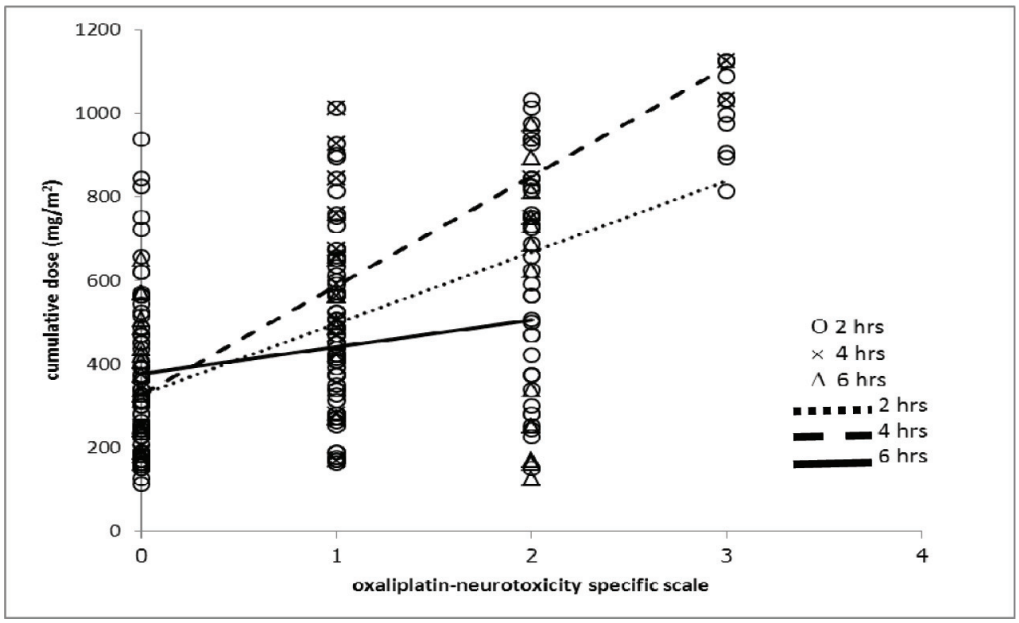

Figure 5. Graph showing trend of grading severity (no symptom, grade1, grade 2, and grade 3) of neurotoxicity along with cumulative dose among three groups of oxaliplatin infusion

Quality of life

Thirty patients (93.8%) participated in the QOL assessment. Each dimension and total score of each group are illustrated in Table 4. There was no statistically significant difference in scores at each dimension as well as in total scores. The total scores of quality of life from all dimensions were higher than 70, indicating good quality of life.

Table 4. Quality of life scores of patients with oxaliplatin infusion therapy

Parameters	Duration of infusion				p-value
	2 hours	4 hours	6 hours	All	
Number of patients (%)	22 (73.3)	2 (6.7)	6 (20.0)	30 (100.0)	-
Mean scores (range)					
PWB	22.0 (8.0-28.0)	20.5 (18.0-23.0)	23.2 (19.0-28.0)	22.1 (8.0-28.0)	0.730
SWB	20.4 (10.5-28.0)	17.4 (11.7-23.0)	20.6 (15.2-23.3)	20.3 (10.5-28.0)	0.682
EWB	20.0 (14.0-24.0)	19.5 (18.0-21.0)	19.7 (11.0-23.0)	19.9 (11.0-24.0)	0.968
FWB	18.5 (11.0-28.0)	15.5 (12.0-19.0)	19.2 (15.0-23.0)	18.4 (11.0-28.0)	0.704
Total	80.9 (59.7-106.0)	72.8 (67.7-78.0)	82.6 (61.2-92.3)	80.7 (59.7-106.0)	0.662

PWB = physical well-being, SWB = social well-being, EWB = emotional well-being, FBW = functional well-being.

DISCUSSION

In this study, neurotoxicity incidence occurred in all patients. The upward trend was found for grade 1, 2 and 3 neurotoxicity along the increasing cycle of oxaliplatin in fusion. These were measured and graded by the oxaliplatin-specific neurotoxicity scale. Although other electrophysiological examinations such as nerve conduction velocity (NCV) and electromyography (EMG) give more precise results, they were not routinely used in the management of patients who suffered from chemotherapy-induced peripheral neurotoxicity.[5] Kautio *et al*[6] assessed chemotherapy-induced peripheral neuropathy using oxaliplatin-specific scale and found similar results, preferably with prolonged administration of oxaliplatin, no matter which measure was used. Our study used both measures and found corresponding results between the two measures. However, oxaliplatin-specific scale was used in the study conducted by Petrioli *et al*.[2] where the results also showed preferably prolonged administration of oxaliplatin. It should be concluded that both measures were good enough to detect neurotoxicity but oxaliplatin-specific scale was better because it was more sensitive in detecting the reversibility of neuropathic symptoms from the previous cycle.

Painting skin with 70% alcohol pad and pinpricking fingers or hands were used in our study as test agents to detect incidence of cold-induced allodynia and hyperalgesia in patients who firstly reported no sensory change. None reported cold-induced allodynia but about 9% of tested patients had hyperalgesia. One might argue that these two tests were not good enough, however, they were used in clinical practice in our study as quick screening test,[7] and it was aimed only to confirm the reported sensory symptoms.

There was higher incidence of acute neurotoxicity of oxaliplatin among the 2-hour infusion, compared to those after the 4- and 6-hour infusion in our study. This occurrence might be explained by the fact that the 4- and 6-hour infusion resulted in lower peak level of oxaliplatin than after the 2-hour infusion and might accordingly reduce nerve excitability.

Our study demonstrated impairment of sensory symptoms in all patients but time of occurrence varied. The incidence of sensory symptoms was higher along the increasing cycle. This would be explained by the long contact of oxaliplatin that caused irritation to vessels.[8] The sensory complaints noted here were numbness and electric shock that occurred in almost all patients at almost all cycles.

The motor impairment due to oxaliplatin, especially difficult swallow and muscle spasm, was mostly detected in patients of 2-hour infusion group. The incidence was higher along the increasing cycle, similar to the impairment of sensory symptoms. This would be explained by chelation of oxalate with calcium ions and caused neuronal hyperexcitability, resulting in repetitively discharging without stimulation and some peripheral nerves resulting in muscle tetany.[1,9]

We found the median cumulative dose of oxaliplatin was stepped-up approximately 1.5 times at each grade of neurotoxicity, i.e. 300 mg/m^2 for no symptoms, 468.8 mg/m^2 for grade 1 symptoms, 671.9 mg/m2 for grade 2 symptoms, and 1,031.3 mg/m^2 for grade 3 symptoms. This suggested one to avoid increasing the dose 1.5 times of the previous cumulative dose if grade 1 symptom had already occurred. However, we have to balance with the therapeutic outcome that might decline if the given dose was lower than the suggested one. The curve of cumulative dose among the three infusion groups was not as good a prediction of the increasing order of cumulative dose along the prolong infusion time. It may be due to the effect of small sample size among the 4- and 6-hour infusion groups.

In our study, FACT-G was used to measure quality of life in colorectal cancer patients receiving oxaliplatin-based chemotherapy. For the same reason of small sample size, there was no statistically significant

difference in total scores, social well-being, emotional well-being, and functional well-being among the 3 groups of different duration of oxaliplatin infusion.

CONCLUSION

Neurotoxicity occurred in all patients with oxaliplatin-based chemotherapy with an upward trend of incidence along the increasing cycle. Although rather small sample size, our study demonstrated the prolonged infusion time of oxaliplatin had tendency to lower neurotoxicity. In addition, there was no statistically significant difference in quality of life scores among the 3 groups of different duration of infusion.

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