Original Article

Evaluation of Neuropathy and Quality of Life in Colorectal Cancer Patients Receiving FOLFOX Adjuvant Chemotherapy: A Case Series Study

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Quality of life

Background. Oxaliplatin is an essential drug used in adjuvant chemotherapy for colorectal cancer, but its side effects can affect the quality of life of patients. Numbness and tingling in the hands and feet are common adverse effects occurring in more than 90% of patients and can lead to delays or interruptions in chemotherapy. We analyzed the severity of peripheral neuropathy and its impact on patients.
Methods. In this single-center prospective study, a questionnaire survey on QoL and neuropathy was conducted on patients who received adjuvant chemotherapy (FOLFOX) from March 2022 to March 2023. The differences before chemotherapy, 7 days after chemotherapy, 2 months after chemotherapy, and 6 months after chemotherapy were compared.
Results. 12 patients were enrolled, with a median age of 65.5 years (range 44 to 75 years). We found that patient's quality of life, appetite, and anxiety levels improved over time and were statistically significant ($p = 0.005$, 0.006, and 0.003, respectively). Regarding peripheral neuropathy, there was no observed trend of improvement over time in terms of cold/hot water sensitivity, and fine motor skills ($p = 0.04$, and 0.02, respectively).
Conclusions. The peripheral neuropathy symptoms produced in patients receiving FOLFOX adjuvant chemotherapy did not show significant improvement six months after treatment completion, but significant improvement was observed in their quality of life, appetite, and anxiety. These results need to be confirmed with larger sample size studies.

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According to the statistics of the Taiwan Ministry of Health, cancer has been the leading cause of death among the Taiwanese population for the past thirty years.[1] There were at least 50,000 cancer-related deaths in 2019, of which colorectal and anal cancer ranked on top, with more than 5,700 deaths annually and on the rise.[2] In terms of cancer incidence, colorectal cancer (CRC) has topped the list for the past 11 years. Each year 15,000 people suffer from CRC in Taiwan, and it is predicted that 2.4 million new cases will be diagnosed annually worldwide by 2035.

In recent years, the awareness and vigilance about colorectal cancer has been raised through the efforts and the promotion of fecal occult blood screening programs for citizens over 50 by the National Health Service. Currently, owing to the early detection of CRC

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in Taiwan, nearly 75% of the patients with CRC have localized stage II or III tumors,[2] and it is recommended that stage III or certain stage II patients undergo adjuvant chemotherapy. The survival rate for the localized disease has thus increased over the years. As the number of patients receiving adjuvant therapy rises the adverse effects of treatment and the quality of life (QoL) of the survivors have become major issues.

Oxaliplatin is an indispensable drug in the treatment of CRC. The survival benefit of adding oxaliplatin to oral (CAPOX) or infused (FOLFOX) fluoropyrimidines for stage II and III colon cancer has been established in previous studies.[3] The addition of oxaliplatin offered a 4.5-5.1% improvement in disease-free survival (DFS) at three years compared with fluoropyrimidines alone.[4] Its adverse effects, however, are numerous and indwelling, and may include bone marrow suppression, which reduces the number of blood cells. Other adverse effects include gastrointestinal discomforts such as nausea and vomiting, hair loss, allergic reactions including itchy skin, rash, fever, chills, flushing, and difficulty breathing. Neurotoxicity leads to peripheral paresthesia and numbness of hands and feet are one of the most common side effects. Nearly 90% of patients treated with oxaliplatin experienced numbness and tingling sensations in hands and feet to some degree during or after the treatment.[5] For some, life-threatening trismus may occur, and it is important to recognize that oxaliplatin-induced neuropathy can impact QoL and survival due to delayed or interrupted chemotherapy caused by its adverse effects.

We investigate the incidence and severity of acute and chronic neurotoxicity, the effects on the QoL of patients, and the predictors of severity over time in Taiwanese CRC patients who received postoperative adjuvant chemotherapy containing oxaliplatin in a single institution.

Material and Methods

Twelve patients with stage III colorectal cancer who received adjuvant chemotherapy with a regimen of mFOLFOX6 were analyzed for neuropathy and QoL. This study was conducted by the Department of Colorectal Surgery at Cheng Hsin General Hospital, Taipei, Taiwan, between March 2022 and June 2023 and was reviewed and approved by the Institutional Review Board (IRB) of Cheng Hsin General Hospital.

Study design

The severity of adverse effects, degrees of neuropathy, and QoL were assessed during four different periods: before chemotherapy, seven days after, two months after, and six months after the last session of chemotherapy.

Inclusion and exclusion criteria

Patients were included if they were (1) ≥ 18 years of age, (2) diagnosed with stage III colorectal cancer for the first-time, and (3) received mFOLFOX6 regimen as treatment. Patients were excluded from the study if they had (1) received any prior chemotherapy, (2) had any prior nervous system disorders, and (3) were unable to comprehend and complete the questionnaire by him or herself.

Treatment regimen

The FOLFOX regimen consisted of oxaliplatin 85 mg/m^2 infusion on the first day, along with leucovorin (LV) 400 mg/m^2 followed by 5-FU bolus 400 mg/m^2. Then, a continuous 5-FU infusion of 2.4 g/m^2 was administered for 46 h. This cycle was repeated every 14 days for 12 cycles. The oxaliplatin administered in the present study was manufactured by the TTY Biopharm Company in Taiwan.

Evaluation of neuropathy and QoL

The reporting and grading of nervous system disorders that may be actuated by the treatment was done using Common Terminology Criteria for Adverse Events (CTCAE version 5) grading system. Grade 1 neuropathy was defined as asymptomatic, grade 2 was defined as interfering with function but not with activities of daily living (ADL), grade 3 was defined as interfering with ADL, and grade 4 was defined as dis-

abling ADL. Acute neuropathy was defined as any sensory or motor symptoms occurring from the beginning of the treatment to two months after treatment. Chronic neuropathy was defined as any symptoms present after six months of treatment.

Quality of life and the degrees of neuropathy were evaluated using Quality of Life (QoL-30) and Chemotherapy-Induced Peripheral Neuropathy (CIPN-20) questionnaires. Official traditional Chinese Mandarin (Taiwan) versions of both questionnaires were used with permission from EORTC. CIPN-20 assesses sensory, motor, and autonomic symptoms. Each question is scored from one (none at all) to four (most severe). QoL-30 (version 3) was used to assess the life quality and overall health status with a similar scoring system.

Statistical analysis

Statistical analyses in the present study were performed using SPSS 29.0 version (Windows 11). Paired sample t-test was performed on the mean scores of the questionnaire responses in each subcategory (sensory, motor, autonomics) of CIPN-20 and QoL-30 for different periods. Logistic regression was performed on the correlations between age, gender, exercise frequencies, and symptoms that were present six months after treatment. Mann-Whitney U test was also used for comparing the baseline characteristics and the outcome variables. Fisher's exact test was performed to determine the association between diabetes and chronic symptoms for a small sample size in our study with an alpha-level of 0.05.

Results

Patient characteristics

We enrolled a total of 12 patients — 10 females (83%) and two males (17%) with a median age of 65.5 years (range: 44-75 years). All were diagnosed with stage III colorectal cancer and had undergone surgery. All had received adjuvant chemotherapy with FOLFOX. Two patients were diabetic (16%) and none of the patients had received pre-op radiotherapy. The median body surface area (BSA) was 1.58. Eastern Cooperative Oncology Group Performance Status Scale (ECOG) was 0 at baseline (100%) for all patients. One (8.3%) patient had chemo dose reduction at the beginning of the treatment due to reduced estimated glomerular filtration rate. The above-mentioned statistics are provided in Table 1.

Incidence and severity of peripheral neuropathy

In the present study, 67% and 42% of the patients had chronic (six months after treatment) sensory and motor symptoms of grade II or above, respectively (Table 1). The average scores of severities decreased with time. This decreasing trend can be observed more prominently in the motor symptoms, while there was lower decrement in the severity of the sensory symptoms (Fig. 1). ECOG performance score was found to have worsened from 0 to 2 in chronic settings in two patients.

Commonly observed peripheral sensory symptoms are numbness (100%), tingling (91.7%) of hands and feet, and burning pain in the hands (75%) at any time. Motor symptoms including cramps in the feet, difficulty manipulating small objects, and difficulty in opening a jar/bottle were frequently observed (75%, 75%, and 100%, respectively).

Numbness, tingling, and pain did not show an improvement trend after six months, although no statistical significance (p = 0.14, 0.38, and 0.67, respectively) was observed. Cold sensitivity and difficulty in manipulating small objects were found to have worsened at six months after treatment (p = 0.04, 0.02, respectively). The appetite, anxiety levels, and quality of life of the patients showed improvement six months after their treatment (p = 0.005, 0.006, and 0.003, respectively). An improvement in overall health was not observed (p = 0.40).

Discussion

Oxaliplatin is a platinum-based compound with significant effects against advanced or metastatic co-

Table 1. Patient demographic

	Baseline, n = 12 (%)	Chronic	%	Mean	SD
Median age (range)	65.5 (44-75)			63.58	8.062
Gender					
Female	10 (83%)		83%		
Male	2 (17%)		17%		
Marital status					
Married	11		92%		
Single	1		8%		
Work status					
Employed	3		25%		
Unemployed	4		33%		
Retired	5		42%		
ECOG					
0	12 (100)	4 (33)			
1		6 (50)			
2		2 (17)			
Median BSA	1.58 (1.27-1.96)			1.5750	0.18486
Cancer site					
Colon	10		83%		
Rectum	2		17%		
Cancer stages					
IIIA	4		33%		
IIIB	4		33%		
IIIC	4		33%		
Severity grade					
I		4 (33)	33%		
II		8 (67)	67%		
Diabetic					
No	10		83%		
Yes	2		17%		
Cancer history					
No	12		100%		
Yes	0		0%		
Surgery history					
Yes	6		50%		
No	6		50%		
Pre-op R/T					
No	12		100%		
Yes	0		0%		
Exercise status					
Not regular	9		75%		
Regular	3		25%		
Dose reduction					
No	11		92%		
Yes	1		8%		

lorectal cancer (CRC) as well as many other cancers.[6] Oxaliplatin acts by cross-binding DNA, blocking DNA synthesis, preventing DNA replication and transcription, and causing cell death. It is typically administered with 5-fluorouracil (5-FU) and leucovorin (LV) in a combination regimen, known as FOLFOX.

Many theories have been proposed regarding the cause of peripheral neuropathy, such as the alteration of voltage-gated ion channels including Na^+, K^+, and Ca^{2+} channels in the setting of acute neuropathy.[7] For chronic neuropathy, it is theorized that the accumulated platinum compounds and their metabolites reach the nucleus and damage nuclear DNA. The resulting DNA adducts are considered key factors in the devel-

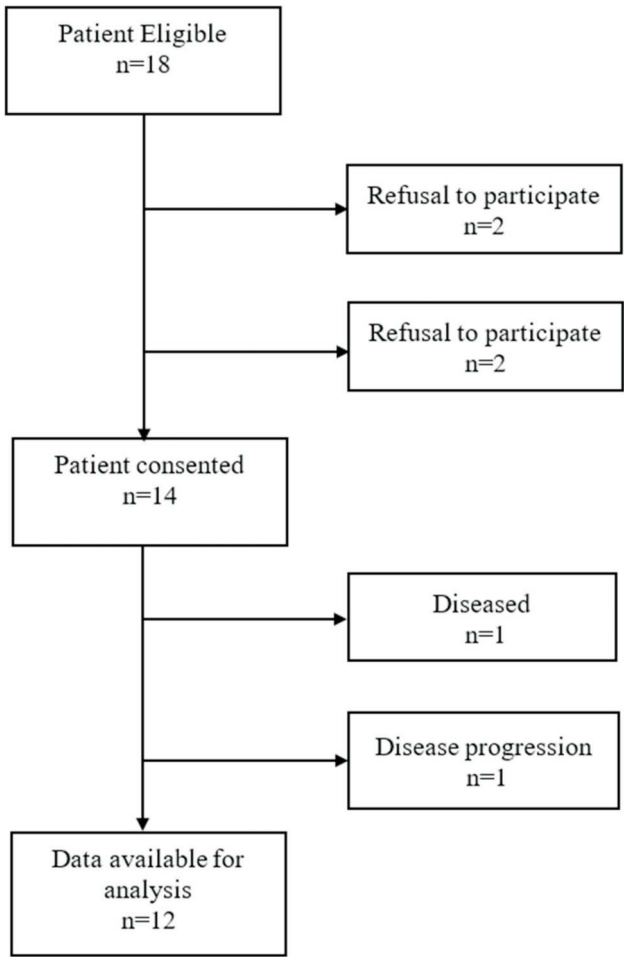

Fig. 1. Patient selection.

opment of chronic neuropathy.[8] However, many of these studies are based on animal models and are limited in numbers. A definite and accurate answer for such adverse effects and preventive methods is yet to be found.

In our study, neuropathy following adjuvant chemotherapy containing oxaliplatin was present in a significant portion of patients six months after the completion of treatment. The high incidence (91%) of any grade neuropathy is in line with two Taiwanese studies[9,10] and one French/Italian study (92%).[16] However, reports from the United States (U.S.) showed 70 to 78% of incidence in neuropathy.[6] This may be associated with the higher percentage of patients requiring

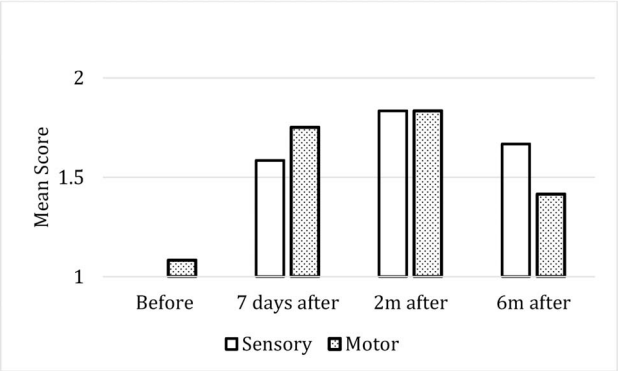

Fig. 2. Mean scores (CTCAE v5.0) of symptom severity throughout time.

Table 2. Number and percentage of patients reporting any or severe symptoms on a EORTC QLQ-CIPN20 questionnaire at follow up

		Any time				Chronic			
		n	Any grade %	n	Severe %	n	Any grade %	n	Severe %
Q1	Tingling fingers/hands	11	91.7%	7	58.3%	7	58.3%	2	16.7%
Q2	Tingling toes/feet	11	91.7%	5	41.7%	7	58.3%	2	16.7%
Q3	Numbness fingers/hands	12	100.0%	6	50.0%	11	91.7%	3	25.0%
Q4	Numbness toes/feet	12	100.0%	5	41.7%	10	83.3%	3	25.0%
Q5	Shooting/burning pain fingers/hands	9	75.0%	1	8.3%	4	33.3%	1	8.3%
Q6	Shooting/burning pain toes/feet	8	66.7%	1	8.3%	4	33.3%	1	8.3%
Q7	Cramps in hands	4	33.3%	1	8.3%	2	16.7%	1	8.3%
Q8	Cramps in feet	9	75.0%	1	8.3%	6	50.0%	1	8.3%
Q9	Impaired standing or walking	6	50.0%	2	16.7%	6	50.0%	2	16.7%
Q10	Difficulty distinguishing hot from cold	4	33.3%	1	8.3%	4	33.3%	0	0.0%
Q11	Problems holding pen/writing	8	66.7%	1	8.3%	8	66.7%	0	0.0%
Q12	Difficulty manipulating small objects	9	75.0%	2	16.7%	6	50.0%	0	0.0%
Q13	Difficulty opening jar/bottle	12	100.0%	4	33.3%	11	91.7%	3	25.0%
Q14	Difficulty walking due to drop feet	5	41.7%	2	16.7%	2	16.7%	0	0.0%
Q15	Difficulty climbing stairs or getting up	5	41.7%	1	8.3%	5	41.7%	0	0.0%

dose reduction (30%) and withdrawal (33%) in the U.S.[7] While was no withdrawal and a lower rate of dosage adjustment in the present study. A major factor attributed to the high incidence of neuropathy are the smaller sample size and a higher percentage of female patients in our report, where according to Wang et al., females are at greater risk for severe oxaliplatin induced neuropathy.[7] We also found that most of our patients experienced mild grade of neuropathy in the acute period (Fig. 3), while only a percentage of patients experienced severe grade neuropathy. Hence the lower rate of dosage adjustment and withdrawal in our study.

Our results showed that the most common neuropathy symptoms at any time are numbness and tingling of feet/toes (100% and 91%), which is in line with previous reports.[11,12] Shooting/burning pain fingers/hands (75%) and difficulty opening a jar/bottle (100%) are higher than previous reports. This may be associated with the small sample size in our study. For chronic persisting symptoms of any grade, numbness in the fingers/hands, numbness in the toes/feet, and difficulty opening a jar/bottle are found to be most common. It is worth mentioning that these symptoms also persisted to the chronic setting and were severe in higher grades. Similar results were seen in Nordic studies.[12] The ECOG performance of two patients in our study had worsened from 0 to 2 at the end of their treatment. One of the patients developed Bell's palsy and depression at the end of the treatment, while no definite risk factor was found in the other patient for the worsening of the ECOG score. In a previous study by L. M. Soveri et al., ECOG > 1 was found to be a predictor of the presence of long-term neuropathy and poor QoL;[11] therefore, the worsening of the ECOG scores in these two patients may have some influence on the high incidence of chronic neuropathy in our series.

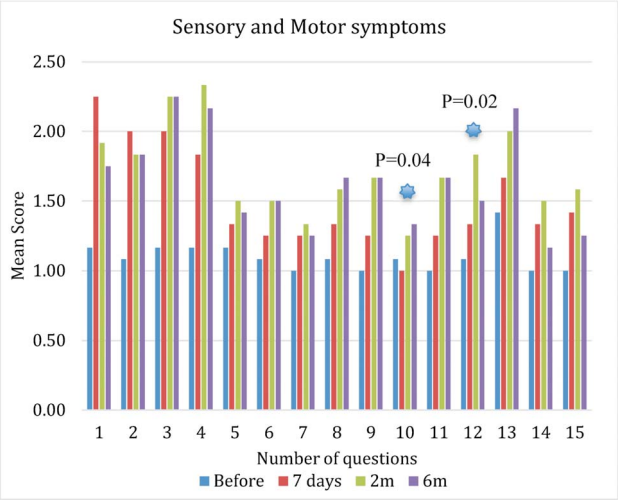

Fig. 3. Mean score of symptoms (CIPN-20) throughout time.

Further statistical analysis of the questionnaires revealed that the mean scores for appetite, anxiety, and quality of life improved with time. This result can also be observed in another study.[13] However, mixed signals were observed in the category of sensory symptoms of neuropathy over time. There was a trend of improvement in the tingling of hands/feet over time, but this trend was not observed in numbness and pain of hands/feet further follow-up studies with a larger sample size may show a different trend. Briani et al. conducted a similar study where they found that the persistence of oxaliplatin-induced peripheral neuropathy (OXAIPN) beyond two years after finishing chemotherapy is common. In such cases, though the improvement of symptoms is commonly observed, chronic neuropathy may still last for the lifetime of most of the patients.[14]

There are several strengths in our study. The major strength being that all assessments of adverse effects and quality of life were conducted during face-to-face interviews, and our QoL, sensory, and motor symptoms questionnaires were all filled out by the patients in person, which may provide more authentic information on the condition of the patients as op-

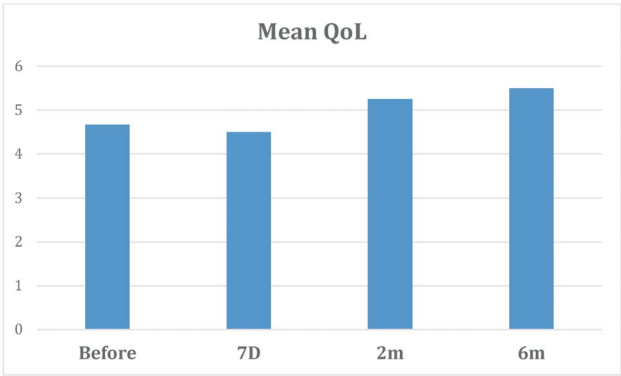

Fig 4. Mean QoL over time.

posed to a telephonic interview. This probably reflected in the higher incidence of OXAIPN in our study compared to previously published reports.[13] Lastly, our report is one of the few studies in the Asia-Pacific region that provides an insight into the quality of life of colorectal cancer patients during a long-term follow-up after the completion of FOLFOX treatment.

Our study has some limitations, with the most significant one being the number of patients. Our sample size is much smaller than anticipated. This may be correlated to the fact that our patients were mostly recruited during the COVID-19 pandemic period, where the number of diagnosed CRC patients had decreased largely due to preventive and safety measures. Similar phenomena were observed throughout many medical facilities around the globe.[15] Another limitation is that our follow-up time is shorter (six months) than in one previously published report. In the study by L. M. Soveri et al.,[11] the median follow-up time is 4.2 years. However, in contrast to the previous study,[11] which was performed in Europe, our series recruited Asian patients. Finally, our study may be at risk of selection bias as those who are bed-ridden or cannot comprehend and answer the questionnaires by themselves were excluded from the study. This may have affected the validity of our analysis as patients who have worse baseline conditions were precluded from the study.

In conclusion, our study showed that peripheral neuropathy is present in most of the patients receiving FOLFOX and may persist throughout and even six months after the treatment. While common symptoms such as numbness, tingling, and cold sensitivity did not show a trend of improvement at six months after treatment, overall quality of life, degrees of appetite, and levels of anxiety have shown to be in recovery at six months after treatment. This article provides a perspective for health care providers to explain the influence of FOLFOX on the quality of life. The high incidence of chronic peripheral neuropathy in this study can help guide physicians to conduct early evaluation and intervention in clinical practice. However, further research, larger sample sizes, and longer follow-ups are needed to provide more concrete evidence and conclusion.

Financial Support Disclosure

None to disclose.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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原　著

大腸直腸癌病患接受術後輔助性化療所引起之周邊神經副作用與日常生活品質之臨床案例研究

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背景　Oxaliplatin 是大腸癌術後化療重要藥物之一，其副作用可能引響病患生活品質。末稍感覺異常，手腳麻木，是為常見副作用，約九成病患因此副作用影響病患生活品質，導致化療延遲或中斷。在這篇研究中主要目的為分析第三期大腸直腸癌病患術後接受含有 Oxaliplatin 化療後產生的周邊神經副作用嚴重程度以及對生活品質的影響。

方法　在此單一中心研究，在 2022 年 3 月至 2023 年 3 月，針對接受術後輔助性化療 (FOLFOX) 的病患進行紙本問卷調查及副作用程度評估。並比較於化療前，化療完成後七天、兩個月、和六個月的差異。

結果　共招募了 12 患者。患者年齡在 44 歲至 75 歲之間，年齡中位數為 65.5 歲。我們發現病患在生活品質、食慾及焦慮程度上可隨時間改善，並具有統計上顯著差異 (p = 0.005，0.006 和 0.003)。但在周邊神經病變的副作用方面，冷/熱水敏感性及精細運動受損，並未觀察到在化療完成後六個月有顯著改善的現象 (p = 0.04 和 0.02)。

結論　在接受 FOLFOX 化療的病患身上產生的周邊神經症狀在治療完成後六個月並未出現明顯的改善，但在生活品質、食慾、焦慮程度上則觀察到顯著的改善。此結果可能需更大的樣本數試驗來進行驗證。

關鍵詞　大腸直腸癌、化療、神經病變、生活品質、Oxaliplatin。