Prevention of oxaliplatin-related neurotoxicity by \(\omega-3\) PUFAs

A double-blind randomized study of patients receiving oxaliplatin combined with capecitabine for colon cancer

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Abstract

**Background:** Peripheral neurotoxicity (PN) is a frequent side effect of oxaliplatin treatment, and also is its dose-limiting toxicity. Studies have confirmed that \(\omega-3\) polyunsaturated fatty acids (\(\omega-3\) PUFAs) had a neuroprotective effect. However, the efficacy of \(\omega-3\) PUFAs on the prevention of oxaliplatin-related neurotoxicity remains unclear. We assessed the effect of \(\omega-3\) PUFAs on the neurotoxicity in colon cancer patients treated by oxaliplatin combined with capecitabine.

**Methods:** in a randomized, double-blind, placebo-controlled study, 179 patients with colon cancer receiving oxaliplatin combined with capecitabine were recruited, and randomly assigned to take \(\omega-3\) PUFAs, 640 mg t.i.d during chemotherapy and 1 month after the end of the treatment or placebo. All patients were treated with chemotherapy for 6 treatment cycles. The incidence and severity of PN were evaluated, and the nerve conduction was measured before the onset of chemotherapy and 1 month after treatment. In addition, the quality of life was also accessed using Chinese version of European organization for research and treatment of cancer quality of life questionnaire.

**Results:** The incidence of PN in the \(\omega-3\) PUFAs group and placebo group was 52.22% and 69.66%, respectively (\(P=.017\)). In addition, there was a significant difference in the severity of PN between the 2 groups (\(P=.017\)). In terms of motor and sensory nerve conduction, the sensory action potentials amplitude of sural nerve in the \(\omega-3\) PUFAs group and placebo group after chemotherapy treatment were (15.01 ± 3.14) and (13.00 ± 3.63) \(\mu\)V respectively, suggesting there was a significant difference in the 2 groups (\(P=.000\)). In addition, the mean score of the global health-status/quality of life was obviously higher in the \(\omega-3\) PUFAs group than that in the placebo group.

**Conclusion:** \(\omega-3\) PUFAs seem to reduce the incidence and severity of oxaliplatin-related neurotoxicity, and improve the quality of patients’ life, indicating it is expected to be a potential drug for the treatment of oxaliplatin-related neurotoxicity.

**Abbreviations:** \(\omega-3\) PUFAs = \(\omega-3\) polyunsaturated fatty acids, a-SAP = sensory action potential amplitude, CRC = colorectal cancer, DHA = docosahexanoic acid, EORTC QLQ-C30 questionnaire = Chinese version of European organization for research and treatment of cancer quality of life questionnaire, EPA = eicosatetraenoic acid, PN = peripheral neurotoxicity.

**Keywords:** \(\omega-3\) polyunsaturated fatty acids, chemotherapy, colon cancer, oxaliplatin-related neurotoxicity, quality of life
1. Introduction

Global cancer statistics have reported that over 1.8 million new colorectal cancer (CRC) cases and 881,000 deaths were estimated to occur in 2018, and the incidence and mortality of CRC was 6.1% and 9.2% in all cancer cases, respectively.[1] Therefore, it is important to effectively control the development of CRC. Chemotherapy is a standard adjuvant treatment of CRC.[2] Oxaliplatin, a third generation platinum-based agent, is the principal chemotherapeutic drug for the treatment of CRC. Although oxaliplatin can significantly improve the patients’ overall survival,[3] the peripheral neurotoxicity (PN) caused by oxaliplatin is a frequent dose-limiting toxicity.[4,5] Some degree of PN occurs in nearly all patients with receiving oxaliplatin.[6] The mechanism of oxaliplatin induced neurotoxicity is unclear. Several studies have suggested that the occurrence of PN was related to the accumulation of oxaliplatin in the dorsal root ganglia.[6,7] In clinic, calcium and magnesium infusions are often used to treat oxaliplatin-related neurotoxicity,[8,9] but the curative effect does not well, and the most effective way is to suspend to use oxaliplatin.

-3 polyunsaturated fatty acids (ω-3 PUFAs) are essential fatty acids in the human body, including eicosatetraenoic acid (EPA), and docosahexaenoic acid (DHA). Accumulated studies have shown that EPA and DHA were often used in the treatment of neurodegenerative diseases by exerting anti-oxidative, anti-inflammatory, and neurotrophic effects.[10,11] Moreover, DHA had an prevention role in treating peripheral neuropathy caused by bortezomib in patients with multiple myeloma.[12] However, little is known about the effect of ω-3 PUFAs on the treatment of oxaliplatin-related neurotoxicity. Herein, we had conducted a randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy of the ω-3 PUFAs on the treatment of neurotoxicity in patients receiving oxaliplatin combined with capecitabine.

2. Patients and methods

2.1. Patients

The protocol of this study was approved by the Medical Ethics Committee of Zhejiang Cancer Hospital (IRB-2015-216). Before the study was conducted, written informed consents of patients were obtained.

In this randomized, double-blind, placebo-controlled study, participants were recruited for the study from the department of integrated traditional Chinese and western medicine of Zhejiang Cancer Hospital from January 2017 to December 2019. The inclusion criteria will consist of: patients with stage III and IV colon cancer if they have to begin receiving oxaliplatin combined with capecitabine; ECOG score ranged from 0 to 1; not having autoimmune disease, diabetes, or renal, hepatic, cardiac, and parathyroid disorders; not having peripheral neuropathy disease; not receiving any other chemotherapeutic drugs; not taking neuroprotective drugs, such as calcium and magnesium infusions; not taking ω-3 and vitamin/mineral supplements and other nutrition medications; not allergic to fish and fish products; and without history of having other cancers. Exclusion criteria will consist of: changes chemotherapy regimen; affected by any acute disease during the study; refuses to continue chemotherapy; unwilling to continue the study; also, patients who were less than 90% compliant with treatment will be excluded. Figure 1 shows a summary of the study design.

2.2. Randomization and blinding

The randomization assignment will be performed using opaque envelopes with the numbers of the experiment groups. The participants who meet the criteria will be randomly allocated into 2 groups:

1) 640mg ω-3 PUFAs (54% DHA, 10% EPA) 3 times a day during chemotherapy and 1 month after the end of therapy or
2) placebo capsules, that were equal calorie and similar in appearance to ω-3 PUFAs capsules, and similarly administered. Noteworthy, the dose of ω-3 PUFAs was determined based on previous clinical study.[13] All capsules were produced from Zhejiang hailsiheng Co., Ltd, China. For the regimen of chemotherapy: all patients received oxaliplatin 130mg/m² combined with capecitabine 1000mg/m² every 3 weeks for 6 cycles.

For blinding, a person not involved in the study will make the randomization list, assigning participants to the ω-3 PUFAs or placebo group. ω-3 PUFAs and placebo tablets will be placed into unlabeled identical capsules. All participants and investigators will be blinded to the random assignments.

2.3. Measurements

Before the beginning of the intervention, a questionnaire about patients’ cancer history, medications, diseases, and probable supplement use will be recorded. According to previous study,[13] the neurotoxicity was measured at 1 month after the end of chemotherapy according to the classification criteria of neurotoxicity by the same neurologist.[14] Nerve conduction studies were conducted unilaterally (right side) by using a Nicolet/VIASYS Viking Quest EMG Machine based on the standard methods. The distal motor latency, peak to baseline amplitude of compound muscle action potential, and motor conduction velocity of the nerves in tibial, peroneal, and ulnar were measured as the motor nerve conduction assessment. The sensory action potential amplitude (a-SAP) and sensory conduction velocity were measured for peroneal, and ulnar nerves as the sensory nerve conduction measurements.

Besides, the quality of life was accessed using Chinese version of European organization for research and treatment of cancer quality of life questionnaire (EORTC QLQ-C30 questionnaire).[15] The EORTC QLQ-C30 questionnaire has 30 items arranged into 9 scales and 6 single items. The scales are divided into 5 function scales (physical, role, cognitive, emotional, and social functions); 3 symptom scales (fatigue, nausea, or vomiting, pain) and 1 global health-status/quality of life scale. The 6 single items address specific symptoms: dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial problems. The questionnaire was officially translated into the Chinese language. The higher score of function scales and global health-status, the better the patient’s quality of life; and the higher score of symptom scales, the worse the patient’s quality of life. The questionnaire was officially translated into the Chinese language.

2.4. Statistical analysis

All data was presented as mean ± S.D. All analyses will be performed with IBM SPSS Statistics 19 (IBM Corp, Armonk, NY). The 2 groups of patients’ baseline characteristics were statistically evaluated using Chi-squared or Fisher’s test. Analysis of covariance (ANCOVA) test was used to determine the differences of nerve
conduction measurements between the 2 groups at the end of study, adjusting for baseline values and covariates. The difference of PN incidence and the severity of PN between the 2 study groups was estimated by using logistic regression and ordinal regression analysis, respectively. \( P < .05 \) was considered statistically significant.

3. Results

3.1. Patient characteristics

196 patients were enrolled in the study and randomly assigned to receive \( \omega-3 \) PUFAs \((n = 98)\) or placebo \((n = 98)\). 11 patients discontinued the study due to a critical health conditions (including grade 4 neutropenia and hand-foot syndrome, and severe liver function damage during chemotherapy) and 6 patients were unwilling to continue during the chemotherapy (lost to follow up, \( n = 17 \)). So 179 colon cancer patients completed the study, and 90 patients in the \( \omega-3 \) PUFAs group and 89 patients in the placebo group (Fig. 1). The \( \omega-3 \) PUFAs group and the placebo group were comparable for gender, age, performance scores, clinical stages, temperature, respiratory rates, pulse, systolic blood pressure, and diastolic blood pressure. There was no statistical significant difference between the 2 groups. Patient characteristics are displayed in Table 1.

3.2. Peripheral neuropathy

According to the classification criteria of neurotoxicity, the severity of PN in the patients of \( \omega-3 \) PUFAs group was as follows: 43 patients (47.8\%) did not develop PN and 47 patients (52.2\%) manifested some grade of PN: 25 patients (27.8\%) developed stage I of PN; 11 patients (12.2\%) developed stage II of PN; 6 patients (6.7\%) developed stage III of PN; and 5 patients (5.6\%) developed stage IV of PN (Table 2). In placebo group, PN was not observed in 27 patients (30.3\%), while 22 patients (24.7\%) developed stage I of PN; 11 patients...
(12.4%) developed stage II of PN; and 17 patients (19.1%) developed stage III of PN. Also, stage IV of PN was seen in 12 patients (13.5%) (Table 2). These results indicated that there was a significant difference between the ω-3 PUFAs group and the placebo group (P = 0.017).

### 3.3. Nerve conduction study parameters

The differences of quantitative values between 2 study groups were measured by using analysis of covariance adjusting baseline measurements. In the study, there was a significant difference in sural a-SAP between the ω-3 PUFAs group and the placebo group (P = 0.000) with a sharp decrease of sural a-SAP in the placebo group. Furthermore, the other differences of nerve conduction study parameters has not statistical significance between the 2 groups. (Tables 3 and 4).

### 3.4. Scale and item scores in the EORTC QLQ-C30 questionnaire

The scores of EORTC QLQ-C30 for all scales and items was shown in Table 5. In this study, the mean score of the global health-status/quality of life was obviously higher in the ω-3 PUFAs group than that in the placebo group (P = 0.032). For measurement of function scales, a significant reduction in physical function score was found in the placebo group than that in the ω-3 PUFAs group (P = 0.046). In addition, compared to the ω-3 PUFAs group, the mean score of appetite loss was higher in the placebo group (P = 0.025).

### 4. Discussion

Oxaliplatin is one the standard adjuvant chemotherapy drug of colon cancer, and also of the standard palliative treatment for metastases. However, peripheral sensory neurotoxicity is a common toxic effect of oxaliplatin, which is often limited the use of oxaliplatin doses and affected the efficacy of the chemotherapy treatment.[9] Oxaliplatin-related PN includes acute PN and chronic PN.[16] Acute PN often occurs during the treatment, which is characterized by rapid onset of paresthesia of peripheral nerves that are sensitive to cold stimuli, such as numbness or pain in extremities and oropharynx.[17] Chronic peripheral neuropathy is a delayed peripheral neuropathy that occurs after repeated oxaliplatin administration, and is manifested as loss of sensation and ataxia. It was estimated that most patients who received this

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**Table 1**

Comparison of clinical features between the 2 groups.

|                      | Total Number (n = 179) | ω-3 PUFAs group (n = 90) | Placebo group (n = 89) | χ² | P     |
|----------------------|------------------------|--------------------------|------------------------|----|-------|
| Gender               |                        |                          |                        | 0.005 | .943  |
| Male                 | 93 (52.0%)             | 47 (52.2%)               | 46 (51.7%)             |     |       |
| Female               | 86 (48.0%)             | 43 (47.8%)               | 43 (48.3%)             |     |       |
| Age                  |                        |                          |                        | 2.011 | .156  |
| <65                  | 85 (47.5%)             | 38 (42.2%)               | 47 (52.8%)             |     |       |
| ≥65                  | 94 (52.5%)             | 52 (57.8%)               | 42 (47.2%)             |     |       |
| ECOG score           |                        |                          |                        | 0.137 | .712  |
| 2                    | 84 (46.9%)             | 41 (45.6%)               | 43 (48.3%)             |     |       |
| 3                    | 95 (53.1%)             | 49 (54.4%)               | 46 (51.7%)             |     |       |
| Clinical stage       |                        |                          |                        | 0.148 | .700  |
| III                  | 79 (44.1%)             | 41 (45.6%)               | 38 (42.7%)             |     |       |
| IV                   | 100 (55.9%)            | 49 (54.4%)               | 51 (57.3%)             |     |       |
| BMI                  | 18.85 ± 1.69           | 18.77 ± 1.52             |             | 0.755 | .554  |
| Temperature          | 36.74 ± 0.402          | 36.77 ± 0.366            |             |     |       |
| Respiratory rates    | 18.48 ± 2.833          | 18.38 ± 2.906            |             | .824 |       |
| Pulse (Times)        | 77.778 ± 9.24          | 78.967 ± 8.090           |             | .361 |       |
| SBP (mm Hg)          | 116.778 ± 15.020       | 116.494 ± 13.869         |             | .896 |       |
| DBP (mm Hg)          | 77.378 ± 9.069         | 77.629 ± 8.790           |             | .851 |       |

ϕBP = Diastolic blood pressure, SBP = Systolic blood pressure.

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**Table 2**

Oxaliplatin-induced peripheral neuropathy in the study groups.

|                      | ω-3 PUFAs group | Placebo group | χ² | P   |
|----------------------|-----------------|---------------|----|-----|
| 0                    | 43 (47.8%)      | 27 (30.3%)    |    |     |
| I                    | 25 (27.8%)      | 22 (24.7%)    |    |     |
| II                   | 11 (12.2%)      | 11 (12.4%)    |    |     |
| III                  | 6 (6.7%)        | 17 (19.1%)    |    |     |
| IV                   | 5 (5.6%)        | 12 (13.5%)    |    |     |
| No PN                | 43 (47.8%)      | 27 (30.3%)    |    |     |
| Number of PN         | 47 (52.2%)      | 62 (69.7%)    |    |     |
| Total                | 90 (100%)       | 89 (100%)     |    |     |
| Incidence of PN      |                 |               | 5.716 | .017 |
| Severity of PN       |                 |               | 11.967 | .017 |

PN = peripheral neurotoxicity.
chemotherapeutic agent developed dose-dependent neurotoxicity. Therefore, oxaliplatin-related PN affected the patients' quality of life obviously, and it is important to prevent oxaliplatin-related neurotoxicity effectively.

The aim of the current randomized, double-blind, placebo-controlled study was to confirm the efficacy of ω-3 PUFAs in prophylaxis against oxaliplatin induced PN. According to our knowledge, this is the first time to confirm the efficacy of ω-3 in

| Table 3                                                                                      |
|------------------------------------------------------------------------------------------------|
| Motor nerve conduction measurements.                                                         |
| Group                                        | Pre-chemotherapy | Post-chemotherapy | P     |
|-----------------------------------------------|------------------|-------------------|-------|
| Tibial nerve                                 |                  |                   |       |
| DML (ms) ω-3 PUFAs                          | 16.75 (1.93)     | 17.90 (2.33)      | .001  |
| Placebo                                      | 16.62 (2.34)     | 17.23 (2.33)      | .037  |
| P                                            | .646             | .079              |       |
| a-CMAP (m/s) ω-3 PUFAs                      | 11.20 (1.84)     | 11.63 (2.50)      | .092  |
| Placebo                                      | 11.68 (2.49)     | 11.34 (2.56)      | .372  |
| P                                            | .061             | .447              |       |
| MCV (m/s) ω-3 PUFAs                         | 46.92 (5.63)     | 46.47 (5.70)      | .595  |
| Placebo                                      | 46.66 (5.60)     | 46.59 (5.48)      | .745  |
| P                                            | .939             | .884              |       |
| Peroneal nerve                               |                  |                   |       |
| DML (ms) ω-3 PUFAs                          | 15.61 (2.46)     | 15.607 (1.972)    | .99   |
| Placebo                                      | 15.71 (2.73)     | 15.658 (2.25)     | .881  |
| P                                            | .791             | .872              |       |
| a-CMAP (m/s) ω-3 PUFAs                      | 8.25 (2.96)      | 8.06 (2.63)       | .658  |
| Placebo                                      | 7.90 (2.83)      | 7.88 (2.73)       | .948  |
| P                                            | .54              | .655              |       |
| MCV (m/s) ω-3 PUFAs                         | 47.61 (7.20)     | 46.98 (6.71)      | .558  |
| Placebo                                      | 47.27 (6.50)     | 46.01 (7.77)      | .245  |
| P                                            | .939             | .375              |       |
| Ulnar nerve                                  |                  |                   |       |
| DML (ms) ω-3 PUFAs                          | 11.65 (4.46)     | 11.94 (4.20)      | .655  |
| Placebo                                      | 12.27 (4.21)     | 12.44 (4.18)      | .782  |
| P                                            | .343             | .424              |       |
| a-CMAP (m/s) ω-3 PUFAs                      | 17.18 (4.81)     | 17.29 (4.01)      | .873  |
| Placebo                                      | 17.30 (4.17)     | 17.39 (4.08)      | .886  |
| P                                            | .858             | .864              |       |
| MCV (m/s) ω-3 PUFAs                         | 54.16 (11.11)    | 52.50 (10.38)     | .303  |
| Placebo                                      | 52.78 (12.31)    | 52.32 (11.27)     | .667  |
| P                                            | .434             | .309              |       |
| ω-3 = ω-3 PUFAs                              |                  |                   |       |
| SCV (m/s)                                    | 14.97 (4.08)     | 13.00 (3.63)      | .001  |
| Placebo                                      | 14.97 (4.08)     | 13.00 (3.63)      | .001  |
| P                                            | .732             | .000             |
| SCV (m/s)                                    | 50.89 (10.82)    | 50.75 (11.74)     | .932  |
| Placebo                                      | 50.96 (9.31)     | 51.06 (9.58)      | .942  |
| P                                            | .967             | .844              |       |
| a-CMAP (m/s)                                 | 36.90 (9.31)     | 32.23 (9.75)      | .001  |
| Placebo                                      | 34.76 (12.4)     | 29.36 (12.02)     | .004  |
| P                                            | .92              | .08               |       |
| SCV (m/s)                                    | 52.41 (10.47)    | 52.10 (9.85)      | .835  |
| Placebo                                      | 51.48 (11.64)    | 51.51 (10.84)     | .984  |
| P                                            | .573             | .707              |       |
| a-SAP = amplitude of compound muscle action |                  |                   |       |
| potential, DML = distal motor latency, MCV  |
| = motor conduction velocity.                 |
| One month after the cessation of chemotherapy.                                              |
| P value is reported based on the analysis of covariance.                                    |

| Table 4                                                                                      |
|---------------------------------------------------------------------------------------------|
| Sensory nerve conduction measurements.                                                       |
| Group                                        | Pre-chemotherapy | Post-chemotherapy | P-value |
|-----------------------------------------------|------------------|-------------------|---------|
| Sural nerve                                  |                  |                   |         |
| a-SAP (µV) ω-3 PUFAs                        | 14.78 (3.21)     | 15.01 (3.14)      | .638    |
| Placebo                                      | 14.97 (4.08)     | 15.00 (3.63)      | .001    |
| P                                            | .732             | .000              |
| SCV (m/s) ω-3 PUFAs                         | 50.89 (10.82)    | 50.75 (11.74)     | .932    |
| Placebo                                      | 50.96 (9.31)     | 51.06 (9.58)      | .942    |
| P                                            | .967             | .844              |
| Ulnar nerve                                  |                  |                   |         |
| a-SAP (µV) ω-3 PUFAs                        | 36.90 (9.31)     | 32.23 (9.75)      | .001    |
| Placebo                                      | 34.76 (12.4)     | 29.36 (12.02)     | .004    |
| P                                            | .92              | .08               |
| SCV (m/s) ω-3 PUFAs                         | 52.41 (10.47)    | 52.10 (9.85)      | .835    |
| Placebo                                      | 51.48 (11.64)    | 51.51 (10.84)     | .984    |
| P                                            | .573             | .707              |
| a-SAP = sensory action potential amplitude, SCV = sensory conduction velocity. |
| One month after the cessation of chemotherapy.                                              |
| P value is reported based on the analysis of covariance.                                    |
The incidence of PN in diabetic neuropathy. In addition, a combined EPA and DHA oral administration accelerated nerve regeneration and prevented neuropathic pain though its anti-neuroinflammatory activity in mice with peripheral nerve injury. Also, accumulating evidence has shown that ω-3 PUFAs alleviated neuropathic pain by suppressing neuroinflammation and oxidative stress. In addition, study also reported fish oil treatment can provide some neuroprotective effects against cisplatin-induced peripheral neuropathy.

Meanwhile, a combined EPA and DHA oral administration accelerated nerve regeneration and prevented neuropathic pain though its anti-neuroinflammatory activity in mice with peripheral nerve injury.

Additionally, relatively small sample size and single-center study were another possible limitations of the current trial.

5. Conclusion

This double-blind, randomized study illustrated that ω-3 PUFAs may be potential neuroprotective agent for treatment of oxaliplatin-related neurotoxicity. Another double-blind, multicenter, placebo-controlled randomized clinical study is needed to confirm these results. Moreover, we will further measure the incidence and severity of PN and quality of life at 6 months or 1 year after the end of chemotherapy as indicators of long-term efficacy of ω-3 PUFAs. Besides, the mechanism of ω-3 PUFAs on the prevention of oxaliplatin-related neurotoxicity should be further studied.

Author contributions

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