Original Article

# Supplementation With Fish Oil Increases First-Line Chemotherapy Efficacy in Patients With Advanced Nonsmall Cell Lung Cancer

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**BACKGROUND:** Palliative chemotherapy is aimed at increasing survival and palliating symptoms. However, the response rate to first-line chemotherapy in patients with nonsmall cell lung cancer (NSCLC) is less than 30%. Experimental studies have shown that supplementation with fish oil (FO) can increase chemotherapy efficacy without negatively affecting nontarget tissue. This study evaluated whether the combination of FO and chemotherapy (carboplatin with vinorelbine or gemcitabine) provided a benefit over standard of care (SOC) on response rate and clinical benefit from chemotherapy in patients with advanced NSCLC. **METHODS:** Forty-six patients completed the study, n = 31 in the SOC group and n = 15 in the FO group (2.5 g EPA + DHA/day). Response to chemotherapy was determined by clinical examination and imaging. Response rate was defined as the sum of complete response plus partial response, and clinical benefit was defined as the sum of complete response, partial response, and stable disease divided by the number of patients. Toxicities were graded by a nurse before each chemotherapy cycle. Survival was calculated 1 year after study enrollment. **RESULTS:** Patients in the FO group had an increased response rate and greater clinical benefit compared with the SOC group (60.0% vs 25.8%, $P = .008$; 80.0% vs 41.9%, $P = .02$, respectively). The incidence of dose-limiting toxicity did not differ between groups ($P = .46$). One-year survival tended to be greater in the FO group (60.0% vs 38.7%; $P = .15$). **CONCLUSIONS:** Compared with SOC, supplementation with FO results in increased chemotherapy efficacy without affecting the toxicity profile and may contribute to increased survival. ***Cancer* 2011;000:000–000.** © *2011 American Cancer Society*

**KEYWORDS:** lung cancer, carboplatin, n-3 fatty acids, toxicity, survival, response rate.

**Lung** cancer is the leading cause of cancer related deaths in Western countries.[1] The majority of patients with lung cancers present with advanced-stage disease for which standard treatment consists of palliative chemotherapy or radiotherapy. Efficacy of chemotherapy for advanced nonsmall cell lung cancer (NSCLC) is low with large trials of different chemotherapy combinations reporting response rates below 30%.[2-4] The effectiveness of chemotherapy in advanced NSCLC has reached a plateau, with little improvement in response rates, and it has been suggested that research should focus on new approaches and novel treatments rather than different combinations of chemotherapy drugs.[5]

Experimental studies in a variety of tumor types using several different chemotherapy agents including anthracyclines, cisplatin, irinotecan, and alkylating agents have reported greater efficacy of chemotherapy when fish oil (eicosapentaenoic acid, EPA 20:5 n-3 and docosahexaenoic acid, DHA 22:6 n-3) is added to the diet or cell medium.[6-10] The mechanisms of action of these antineoplastic agents vary, suggesting that fish oil modulates chemotherapy response via diverse mechanisms (see Biondo et al[11] and Baracos et al[12] for reviews). EPA and DHA may also have antitumor effects including inhibition of angiogenesis and metastasis[12]; however, the specific mechanisms behind these effects have not been elucidated. Regardless of the exact mechanisms, these studies suggest that fish oil (FO) has potential as an effective adjuvant to chemotherapy treatment.

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Current treatment of advanced NSCLC is nonspecific and toxic, typically consisting of platinum-based regimens such as carboplatin in combination with vinorelbine or gemcitabine. Efficacy is dose-dependant and limited by gastrointestinal, hematological, and cardiac toxicities. Treatment approaches that enhance cytotoxicity of anticancer agents to tumor cells while minimizing toxicity to nontarget tissue have the potential to increase benefits of chemotherapy including disease control and survival. Increased sensitivity to chemotherapy appears to be specific to tumor tissue as evinced by lack of additional toxicity to nontumor tissues after the addition of dietary EPA and DHA.[13] There is also evidence that dietary FO enrichment may have a protective effect on nontumor tissue including minimization of gastrointestinal and hematological toxicity.[13,14] However, many experimental studies have used amounts of fish oil that are beyond concentrations achievable in humans, even with supplementation, and only 1 study in humans has been conducted.[15]

We aimed to expand upon the base of information on fish oil, chemotherapy efficacy, and treatment-related toxicity. This is the first study to evaluate the ability of fish oil to improve chemotherapy efficacy in patients with lung cancer. We hypothesized that supplementation with fish oil during first-line chemotherapy for lung cancer would increase response rates without significantly affecting chemotherapy toxicity.

## MATERIALS AND METHODS

### *Study Design*

This study was approved by the Alberta Health Services Research Ethics Board. Study accrual occurred during a 2-year period, 2007-2009. Written, informed consent was obtained from all patients. This study is part of a larger open-label trial that was focused on nutritional status during chemotherapy in which 60 NSCLC patients receiving first-line chemotherapy consented to either 1) nutritional intervention with FO or 2) standard of care (SOC, no intervention). The subset described here was chosen on the basis of treatment intent (palliative vs adjuvant) to standardize the type of chemotherapy treatment patients received. Detailed rationale, study design, and analysis of the effect of fish oil supplementation on body composition in a partly overlapping subset of these patients has been published.[16] In brief, patients with advanced lung cancer who were newly referred to the Cross Cancer Institute (Edmonton, Alberta, Canada) were given an information sheet detailing available nutritional studies. Patients indicated their interest and were approached to participate accordingly. This study was designed as an open-label trial with a contemporary control group to facilitate enrollment and study adherence. Patient interest in placebo-controlled studies is low, as this is a vulnerable patient population with an expected survival of less than 2 years.

Patients on the FO arm were offered a choice of 2 formats of supplementation: 1) 4 1-g gelatin capsules per day containing 2.2 g EPA and 240 mg DHA or 2) 7.5 mL liquid fish oil per day (2.2 g EPA and 500 mg DHA). The number of capsules or the amount of liquid remaining at the end of the study was measured to determine compliance. Capsules were provided in kind by Ocean Nutrition Canada (Dartmouth, Nova Scotia, Canada). Liquid fish oil was purchased from NutraSea (Ascenta Health, Dartmouth, Nova Scotia, Canada). These companies were not privy to the results of this study and did not influence the study conclusions.

### *Patient Eligibility*

Patients with a clinical diagnosis of stage IIIB or IV NSCLC who were chemotherapy-naive were eligible for enrollment. Stage of disease was based on the American Joint Committee on Cancer stage groupings.[17] Patients had consented to receive first-line platinum-based doublet chemotherapy of palliative intent consisting of either carboplatin with vinorelbine or carboplatin with gemcitabine. Additional criteria included ability to maintain oral intake and an Eastern Cooperative Oncology Group (ECOG) Performance Status $\leq$2 as assessed by a physician.

The majority of plasma n-6 and n-3 fatty acids are carried in phospholipids, which reflect the amount of EPA and DHA available to tissues, including tumor tissue. Because previous trials of FO supplementation have reported noncompliance[18] or cross-contamination between control and intervention arms,[19] concentrations of EPA and DHA in plasma phospholipids were analyzed in both the SOC and FO groups as a secondary measure of compliance. Blood was drawn from patients by a registered nurse before chemotherapy initiation (baseline), 1 day before each 3 week cycle of chemotherapy, and on the last day of chemotherapy treatment.

### *Anthropometric Measurements*

Height and weight were measured using a stadiometer and a medical balance-beam scale at baseline. Body mass index (BMI in $kg/m^2$) was calculated from height and weight. Self-reported weight loss in the 6 months

preceding enrollment in the study was recorded using the patient-generated subjective global assessment[20] or from patient history. Height and weight recorded by hospital staff on the same date were used for verification when available.

Lower than normal muscle mass (sarcopenia) has emerged as an important predictor of chemotherapy toxicity.[21,22] Computed tomography (CT) image analysis can precisely quantify skeletal muscle.[23] To distinguish between the effect of FO and the effect of sarcopenia on toxicity, CT images taken for diagnostic purposes at the time of oncologic referral were analyzed to determine the prevalence of sarcopenia in the FO and SOC groups. Cross-sectional muscle areas ($cm^2$) were determined for 2 consecutive images taken at the third lumbar vertebrae (L3) using Slice-O-matic software V4.3 (Tomovision, Montreal, Quebec, Canada) as described previously.[23] Mean muscle area was calculated and subsequently normalized for stature ($cm^2/m^2$). Lumbar skeletal muscle area is linearly related to whole-body skeletal muscle.[24] To express data in conventional units, a regression equation was used to estimate whole-body skeletal muscle,[24] and a density of 1.04 $g/cm^3$ was used to convert muscle volume to mass.[25] Sex-specific cutpoints (males $<55.4$ $cm^2/m^2$ and females $<38.9$ $cm^2/m^2$) that were previously defined and used in advanced cancer populations[23,26] were used to classify patients as sarcopenic or nonsarcopenic.

### Tumor Response, Survival, and Toxicity Assessments

Response to chemotherapy was evaluated by a radiologist and an oncologist on the basis of clinical examination and imaging, which consisted of computed tomography, magnetic resonance imaging, or x-ray after 2 cycles of chemotherapy. If progressive disease was noted, then chemotherapy was discontinued. Otherwise, patients received an additional 2 cycles of chemotherapy followed by imaging. As 4 cycles is standard practice specifically agreed upon as Clinical Practice Guidelines by the Alberta Provincial Lung Tumor Group, response rates was defined as the sum of complete response (CR) and partial response (PR) after 4 cycles of chemotherapy divided by the number of patients. Clinical benefit was defined as the sum of CR, PR, and stable disease (SD) after 4 cycles of chemotherapy divided by the number of patients.

Toxicity was graded using the National Cancer Institute Common Toxicity Criteria, version 2.0. Patient toxicities were graded by a nurse before each cycle of chemotherapy. Dose was reduced or suspended if patients developed grade 3 or greater febrile neutropenia, or thrombocytopenia, or grade 3 or greater nonhematological toxicities, excluding alopecia or inadequately treated nausea, vomiting, and/or diarrhea. After completion of the trial, patients were followed for post-trial treatment and determination of time to death. Median follow-up was 18.5 months for all living patients. There were only 8 deaths in the FO group leaving 46.7% of patients censored, which coupled with our small sample size was too few to conduct a formal survival analysis. Instead, survival was expressed as percentage of patients surviving 1 year after enrollment in the trial (1-year survival).

### Plasma Phospholipid Fatty Acid Analysis

Blood was collected in heparin tubes and centrifuged to isolate plasma, which was immediately frozen at $-80°C$ until analysis. Plasma fatty acids were extracted using a 2:1 chloroform:methanol solution, and phospholipids were isolated on G-plates.[27] The phospholipid band was scraped, and C17:0 standard (1 mg/L) was added followed by direct methylation. Plasma phospholipid fatty acid composition was determined using automated gas liquid chromatography (Varian 3600CX Gas Chromatograph; Varian, Mississauga, Canada) as previously described.[28] Plasma phospholipid EPA and DHA were expressed as a proportion (%) of total phospholipid fatty acids.[29]

### Statistical Analysis

The primary endpoint was chemotherapy response rates. Clinical benefit, chemotherapy toxicity, and survival were secondary endpoints. Data are presented as mean $\pm$ standard deviation. Significance was determined at $P < .05$. Student *t*-test, chi-square test, or Fisher exact test were used to determine differences between SOC and FO groups where appropriate. All tests were two-sided. Logistic regression was used to determine predictors of response to treatment (PR or CR vs SD and PD) and grade 3 or 4 toxicities. Statistical analyses were performed with SPSS (version 18.0; SPSS, Chicago, Illinois).

## RESULTS

### Patient Characteristics

Initial screening was performed on 204 patients. Major reasons for exclusion included ineligible for chemotherapy and participation in a clinical trial (nonstandard chemotherapy). Thirty-one patients in the SOC group and 15 patients in the FO group completed the study. Our sample size is a reflection of the inherent difficulties of conducting studies in palliative care. No patients

**Table 1.** Baseline Characteristics and Anthropometric Parameters of Patients in the Standard of Care and Fish Oil Groups

| | Standard of Care | Fish Oil |
|---|---|---|
| Total, no. | 31 | 15 |
| Women, % | 51.6 | 40.0 |
| Men, % | 48.4 | 60.0 |
| Age, y | 64 ± 1.8 | 63 ± 2.1 |
| **Stage**[a] | | |
| **III, %** | 25.8 | 20.0 |
| **IV, %** | 74.2 | 80.0 |
| BMI, kg/m$^2$ | 26.5 ± 5.4 | 26.4 ± 4.9 |
| Weight loss in preceding 6 mo, %[b] | −4.1 ± 5.8 | −6.2 ± 7.8 |
| Lumbar skeletal muscle area, cm$^2$ | 129 ± 30.7 | 140 ± 34.8 |
| Lumbar skeletal muscle index, cm$^2$/m$^2$ | 46.3 ± 8.5 | 47.0 ± 9.3 |
| Estimated whole-body SM, kg[c] | 24.5 ± 5.3 | 26.4 ± 6.0 |
| Sarcopenic, %[d] | 51.6 | 46.7 |
| ECOG PS | 1 | 1 |
| ECOG range | 0-2 | 0-2 |
| Smoking status | | |
| Never | 6.5 | 13.3 |
| Current | 22.6 | 20.0 |

BMI indicates body mass index; SM, skeletal muscle; ECOG PS, Eastern Cooperative Oncology Group performance status.
Mean ± standard deviation showed no significant differences between groups, 2-sample *t*-test and $\chi^2$-test.
[a] Based on staging from the American Joint Committee on Cancer Staging Manual, 6th edition.[17]
[b] Data not available from n = 2 in standard of care group.
[c] Derived from a regression equation.[24]
[d] Based on cutpoints for muscularity.[22]

withdrew their consent, but 13 patients in the SOC group and 7 patients in the FO group were accrued and subsequently deemed ineligible due to rapid disease progression and inability to tolerate planned chemotherapy.

Baseline characteristics and anthropometric measures of the FO and SOC group were well matched (Table 1). In addition, characteristics of these groups are comparable to those observed in the NSCLC population at our cancer center.[16,30] Although weight loss in the 6 months preceding oncology referral was common, no patients in either group were underweight (BMI < 18.5 kg/m$^2$). More than 50% of patients in each group were overweight or obese. Sarcopenia was highly prevalent in both the FO and SOC groups (46.7% vs 51.6%; $P = .75$). Reported use of over-the-counter supplements did not differ between groups ($P = .49$). The proportion of patients receiving carboplatin with vinorelbine versus carboplatin with gemcitabine did not differ between groups ($P = .75$).

**Table 2.** Plasma Phospholipid EPA and DHA in the Standard of Care and Fish Oil Groups

| | Baseline[a] | Postsupplementation[b] | *P* |
|---|---|---|---|
| | % | % | |
| **Standard of care** | | | |
| **EPA** | 0.9 ± 0.6 | 1.2 ± 0.6 | .86 |
| **DHA** | 2.3 ± 0.8 | 2.2 ± 0.6 | .80 |
| **Fish oil** | | | |
| **EPA** | 1.0 ± 0.5 | 3.6 ± 1.3 | <.001 |
| **DHA** | 2.3 ± 0.7 | 2.7 ± 1.0 | .05 |

Mean ± standard deviation, two-sample t-test.
[a] Standard of care, n = 31; fish oil, n = 15.
[b] Standard of care, n = 28; fish oil, n = 15.

Compliance to the FO supplement was more than 95%. Mean intake was 2.1 ± 0.25 g EPA and 0.29 ± 0.04 g DHA per day. No difference in plasma EPA or DHA concentration was observed between patients taking liquid fish oil or fish oil capsules ($P = .42$ and $P = .62$, respectively). In the FO group, plasma phospholipids EPA and DHA increased significantly after supplementation (Table 2). Plasma phospholipids EPA and DHA after supplementation was not available from 3 patients in the SOC group whose chemotherapy was discontinued because of toxicity, and they were lost to follow-up. There was no change in plasma phospholipids EPA or DHA from baseline to end of trial in the SOC group (Table 2). After supplementation, plasma EPA and DHA in the FO group were significantly higher than the SOC group ($P<.0001$ and $P = .04$, respectively).

### *Chemotherapy Response*

The response rates and clinical benefit were approximately 2-fold greater in the FO group compared with the SOC group (Table 3). The proportion of patients in the FO and SOC group who had a CR, SD, PR, or PD is shown in Table 3. Logistic regression demonstrated that plasma phospholipid EPA concentration after supplementation was a significant predictor of response to chemotherapy independent of age, sex, BMI, presence of sarcopenia, performance score, and weight loss history (hazard ratio [HR], 1.8; 95% CI, 1.1 to 2.5; $P = .03$). There were no other significant predictors of response to treatment.

Compared with the FO group, a greater percentage of patients in the SOC group had progressive disease after 2 cycles of chemotherapy. Consequently, more patients in the FO group completed all planned chemotherapy (86.7% vs 54.8%, $P = .03$). On average, patients in the FO group completed an additional 3 weeks of

**Table 3.** Chemotherapy Outcomes and Survival in the Standard of Care and Fish Oil Groups

| | Standard of Care[a] | Fish Oil[b] | *P* |
|---|---|---|---|
| Response rate, no. (%) | 8 (25.8) | 9 (60.0) | .008 |
| Clinical benefit, no. (%) | 13 (41.9) | 12 (80.0) | .02 |
| Complete response, no. (%) | 1 (3.2) | 1 (6.7) | |
| Partial response, no. (%) | 7 (22.6) | 9 (60.0) | |
| Stable disease, no. (%) | 5 (16.1) | 2 (13.3) | |
| Progressive disease, no. (%) | 18 (58.1) | 3 (20.0) | |
| Number of chemotherapy cycles received | 3.0 ± 1.4 | 3.9 ± 0.9 | .02 |
| Time on chemotherapy, d | 60.3 ± 31.1 | 78.9 ± 23.5 | .05 |
| 1-Year survival (%) | 38.7 | 60.0 | .15 |

Mean ± standard deviation, two-sample t-test and $\chi^2$-test.
[a] n = 31.
[b] n = 15.

chemotherapy (1 cycle) compared with patients in the SOC group (Table 3).

Despite the wide variation in overall survival (1-30 months), 1-year survival in the FO group appeared to be greater than in the SOC group (Table 3). The median number of post-trial lines of therapy was 1 in both cohorts. The most common post-trial therapy was erlotinib (55% of SOC and 53% of FO group). Thirty-five percent of patients in the SOC group and 27% patients in the FO did not receive any further treatment ($P = .40$).

### *Chemotherapy Toxicity*

FO supplementation was well-tolerated with no reported adverse events. The most commonly reported chemotherapy-related grade 1 and 2 toxicities were neutropenia followed by nausea, vomiting, and thrombocytopenia. The overall incidence of any grade 3 or 4 toxicity was 22.6% in the SOC group versus 13.3% in the FO group ($P = .46$). Grades 3 and 4 toxicities included nausea, vomiting, hand-foot syndrome, neutropenia, constipation, and gastritis. One patient in each group discontinued treatment because of fatigue and increased symptom burden. Hematological toxicity resulted in treatment discontinuation in 2 patients in the SOC group. In the SOC group, a further 2 patients discontinued chemotherapy because of gastritis and hand-foot syndrome. The total incidence of grade 3 or 4 toxicity resulting in discontinuation of planned chemotherapy did not differ between groups (16.1% vs 6.7%, $P = .52$). Logistic regression did not reveal any significant predictors of grade 3 or 4 toxicity.

## DISCUSSION

The goal of palliative chemotherapy is to improve symptoms and survival. However, more than 65% of advanced NSCLC cases do not respond to first-line chemotherapy,[2-4] and 1-year survival rates are low. This is the first study to show that the addition of approximately 2.5 g of EPA plus DHA per day significantly increases the response rates to first-line chemotherapy compared with SOC without affecting the toxicity profile. In addition, supplementation with FO has the potential to increase survival as a greater proportion of patients in the FO group were surviving at time of censorship.

The response rates observed in this study represents an approximately 2-fold-increase over the SOC group, and only 3 patients in the FO group did not experience clinical benefit from chemotherapy. Comparatively, one-third of patients in the SOC group responded to treatment, which falls within the range of response rates reported in large randomized trials of first-line combination chemotherapy regimens.[2-4] Our finding is concordant with a previous study in an animal model of lung cancer, which showed that the combination of cisplatin chemotherapy and dietary FO resulted in slower tumor growth and a lower metastatic load.[10] In humans, a positive correlation between chemotherapy efficacy and breast tissue n-3 fatty acid concentration in patients with breast cancer has been reported.[31] The same researchers followed up this study with a trial examining the ability of supplementation with DHA to improve response rates in patients with advanced breast cancer[15] and found that despite the poor prognosis of the patient population, the response rates was comparable to previous trials for standard first-line chemotherapy.

Only one-third of patients with nonoperable stage III and IV NSCLC survive 1 year after first-line platinum-based treatment.[4,32,33] Comparably, approximately two-thirds of patients in the FO group were surviving 1 year post-trial. Although the difference in 1-year survival only tended toward significance between the FO and SOC groups, this may be a reflection of our small sample size.

The observed increase in survival may be due to the increased response rates and decreased tumor burden. Bougnoux et al[15] reported a similar increase in survival in advanced breast cancer patients supplemented with DHA. In addition, higher plasma phospholipid EPA and DHA concentrations, as observed in the FO group, have been shown to be predictive of increased survival in patients with advanced cancer.[34] A further study by Gogos et al[35] demonstrated increased survival in patients with generalized malignancy when provided with fish oil versus placebo. Although we were unable to calculate overall survival because of the large number of censored patients, we continue to follow the study patients to determine the effect of FO on overall survival.

Toxicities from carboplatin are cumulative, with few patients receiving more than 4 cycles. Although patients in the FO group received more cycles of chemotherapy than the SOC group, the prevalence of grade 3 and 4 hematological and nonhematological toxicities did not differ. These results are consistent with animal studies demonstrating a protective effect on host tissue despite increased tumor response.[36-38] In addition, a protective effect of high plasma DHA concentrations on hematological toxicities was observed in patients with advanced breast cancer receiving anthracycline therapy.[15] Taken together, these studies show that supplementation with fish oil does not result in higher chemotherapy sensitivity in nontarget tissue.

Platinum-based chemotherapy for NSCLC is the standard worldwide, and a 30% increase over the typically observed response rates that we report in this study could have a large impact. In Canada alone, an estimated 24,000 people will be diagnosed with lung cancer each year,[1] among which 75%-80% are deemed incurable, and two-thirds will receive palliative chemotherapy. Fish oil supplementation may represent a safe and nontoxic approach to improve current standard of care in patients with lung cancer. Nonetheless, we acknowledge that our results require verification in larger randomized controlled trials, as our study was designed as a pilot study with a limited sample size. However, the observed difference in response rates between the FO and SOC groups was striking, even with a small number of patients.

Although this study was open-label, our results are most likely due to an effect of FO and not due to group selection bias because the baseline characteristics of the SOC and FO group were well-matched and representative of our local NSCLC population. As well, the response rates and 1-year survival in the SOC group were comparable to those typically observed in chemotherapy trials. Our study was not designed to investigate underlying mechanisms, and we are aware that our results do not ensure causality. However, the interaction between FO and carboplatin-based chemotherapy holds promise for improving the treatment of lung cancer patients.

## CONCLUSION

The addition of fish oil to standard first-line platinum based chemotherapy may increase response rates and clinical benefit in patients with advanced NSCLC without affecting treatment toxicity. Additional randomized trials are warranted to confirm these findings.

## CONFLICT OF INTEREST DISCLOSURES

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