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RESULTS OF A PILOT STUDY OF THE EFFECTS OF CELECOXIB ON CANCER CACHEXIA IN PATIENTS WITH CANCER OF THE HEAD, NECK, AND GASTROINTESTINAL TRACT

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Abstract: *Background.* Animal models suggest that cyclooxygenase-2 (COX-2) inhibitors may be beneficial in suppressing cancer cachexia. We investigated the effect of short-course celecoxib on body composition, inflammation, and quality of life (QOL) in patients with cancer cachexia in a phase II clinical pilot trial.

Methods. Eleven cachectic patients with head and neck or gastrointestinal cancer were randomly assigned to receive placebo or celecoxib for 21 days while awaiting the initiation of cancer therapy. Body composition, resting energy expenditure, QOL, physical function, and inflammatory markers were measured on days 1 and 21.

Results. Patients receiving celecoxib experienced statistically significant increases in weight and body mass index (BMI), while patients receiving placebo experienced weight loss and a decline in BMI. Patients receiving celecoxib also had increases in QOL scores.

Conclusions. Cachectic patients receiving celecoxib gained weight, experienced increased BMI, and demonstrated improved QOL scores. Compliance was good and no adverse events were seen. ©2007 Wiley Periodicals, Inc. *Head Neck* **30:** 67–74, 2008

Keywords: cancer cachexia; body composition; quality of life; inflammation; celecoxib

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Cancer cachexia in patients with upper aerodigestive tract carcinomas produces devastating outcomes, such as increased fatigue, diminished quality of life (QOL), and decreased survival.[1] This syndrome is distinct from starvation in that it involves preferential wasting of lean body mass (LBM) while visceral proteins are preserved; elevated systemic inflammation, including increased levels of acute phase proteins and inflammatory cytokines; and elaboration of tumor-derived catabolic factors.[2] Cachexia remains difficult to treat, with few U.S. Food and Drug Administration-approved therapeutic options other than megestrol acetate, dronabinol, and oxandrolone.[2] These

agents may have serious side effects such as deep vein thrombosis and hypoadrenalism, and most of the available data regarding them is derived from cachexia due to other chronic illnesses such as acquired immunodeficiency syndrome. Also, there is also no compelling evidence that appetite stimulants or supplemental caloric intake alone will improve the performance status or QOL of patients with cancer cachexia.[3] Supplementation of diets with eicosapentaenoic acid (EPA), an ω-3 polyunsaturated fatty acid (n-3 PUFA), has shown conflicting results.[4,5]

Systemic inflammation, as evidenced by an elevated acute phase response and increased release of proinflammatory cytokines, may be the etiology of the weight loss and decreased LBM seen in cancer cachexia.[6] A recent study profiling cancer cachexia concluded that systemic inflammation, as measured by C-reactive protein (CRP) levels, may be an important target for anticachexia therapy.[7] Previous research has shown that nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase-2 (COX-2) inhibitors, may palliate cachexia in animals through the suppression of systemic inflammation.[8–10] Indeed, a recent study demonstrated that COX-2 inhibitors reversed tumor-induced wasting in mice bearing human head and neck squamous cell carcinoma and colon carcinomas.[11] Another study using murine adenocarcinoma cell lines demonstrated that a COX-2-specific inhibitor could attenuate cachexia.[12]

We report the results of a prospective, randomized, double-blind, placebo-controlled clinical pilot trial of the effect of a 21-day intervention with the COX-2 inhibitor celecoxib (Celebrex, Pfizer, New York, NY) on cancer cachexia in patients with cancer of the head, neck, and gastrointestinal tract. Outcome measures included body weight, body composition, resting energy expenditure (REE), circulating serum cytokine and CRP levels, performance status, and QOL scores. Our hypothesis was that administration of celecoxib to patients with cancer cachexia would improve body weight and body composition, improve patient QOL, and reduce systemic inflammation.

MATERIALS AND METHODS

Patient Selection and Trial Design. Patients with new or recurrent histologically confirmed carcinoma of the head and neck or gastrointestinal tract (esophagus, stomach, pancreas) were enrolled from the Otolaryngology, Head and Neck Surgery and Surgical Oncology clinics at the University of North Carolina (UNC) Hospitals (Chapel Hill, NC). Only patients with unintentional loss of greater than 5% body weight within a 6-month period prior to diagnosis and a clinical exam consistent with cachexia were enrolled. Patients with evidence of mechanical cause for weight loss were excluded, as were patients who underwent active cancer treatment within 4 weeks of entering the study. Patients on concurrent treatment that could affect weight or inflammation, such as corticosteroids, androgens, progestational agents, NSAIDs, or appetite stimulants, were excluded. Patient cancer stage was determined using clinical examinations and radiographic imaging. The protocol was designed as a window study, using the time between cancer diagnosis and the start of anticancer therapy. At no time did this study postpone any patient's cancer treatment.

After the clinical diagnosis of cachexia was established (unintentional weight loss of more than 5% of body weight without mechanical obstruction that would interfere with oral intake), patients were enrolled into the study. Patients visited the General Clinical Research Center (GCRC) at UNC Hospitals on 2 occasions 3 weeks apart (days 1 and 21). On day 1, vital signs were recorded and blood was drawn, centrifuged, and stored at -80°C. Patients were then administered the Functional Assessment of Anorexia Cachexia Therapy (FAACT, version 4) questionnaire, a validated measure for QOL in patients with cancer cachexia.[13] Also, a physician-based score was generated for the Karnofsky Performance Scale (KPS). Body weight in kilograms was recorded with patients wearing light clothing, without shoes, on the same digital electronic scale (Scaletronics 6006, Scaletronix, White Plains, New York; calibrated monthly). Body height was measured in centimeters using a standard wall-mounted Harpenden stadiometer (Holtain, Limited, Crosswell, UK). All patients underwent body composition analysis using dual-energy X-ray absorptiometry (DEXA) and bioelectrical impedance assay (BIA) to determine LBM, fat body mass, and total body water (TBW). REE was also measured using indirect calorimetry. These analyses were all repeated on day 21.

Patients were randomized by an independent biostatistician to receive celecoxib 200 mg twice daily (bid) or placebo twice daily for 3 weeks. The placebo pills consisted of lactose, stearic acid, and

Table 1. Schedule of events.

Events	Day 1	Day 21
Eligibility/informed consent	X	
Height (cm)	X	
Weight (kg)	X	X
Body composition (DXA, BIA)	X	X
Indirect calorimetry (REE)	X	X
QOL (FAACT)	X	X
Performance status (KPS)	X	X
HCT	X	
Serum cytokine levels	X	X
CRP(μg/mL)	X	X

Abbreviations: cm, centimeters; kg, kilogram; DXA, dual-energy X-ray absorptiometry; BIA, bioelectrical impedance; REE, resting energy expenditure; QOL, quality of life; FAACT, Functional Assessment of Anorexia-Cachexia Therapy; KPS, Karnofsky Performance Scale; HCT, hematocrit; CRP, C-reactive protein.

magnesium stearate inside a gelatin capsule that was not distinguishable from the celecoxib capsule. Compliance was determined by study personnel counting the remaining pills at the end of the study for each patient. Patients were contacted by phone during the trial to inquire about adverse events. At the end of the pharmacologic intervention (day 21), each of the above assessments was repeated (Table 1). No nutritional therapy, radiation therapy, chemotherapy, or curative surgical treatment was initiated during the study period. Finally, this protocol was approved by the University of North Carolina Institutional Review Board and the Lineberger Comprehensive Cancer Center Protocol Review Committee, and all patients provided written informed consent upon entering the study.

Body Composition

Description of Body Composition Measurements. Body composition on all patients was analyzed using BIA and DEXA, the 2 commonly used techniques for this purpose. BIA was measured in all patients by a Quantum 101Q analyzer (RJL Systems, Clinton Township, MI). BIA measurements were based on the relationship between the volume, height, fat mass and fat-free mass, and impedance of the patient. Bioimpedance was measured using a 50-kHz electrical signal of a 500 A current traveling through source electrodes placed on the patient's distal metacarpals while the patient lay supine on a nonconductive surface. Also, all patients underwent DEXA testing (Discovery DEXA scanner, Hologic, software version 12.3, 1982–2006, Bedford, MA) administered by a certified radiological technologist.

Description of Measurements of Resting Energy Expenditure. REE was measured on all patients using a CPX/D Series Indirect Calorimeter (Medical Graphics Corporation, St. Paul, MN). Measurement of REE was performed for 20 minutes of steady state, as confirmed by minimal variation from the desired covariance value. Nonfasting patients were requested to remain still, in a reclining position, in a darkened room. Oxygen consumption, carbon dioxide production, and energy expenditure were measured at 30-second intervals and averaged over a 20-minute time period. The Medgraphics CPX D series was calibrated before each test with a 3 L calibration syringe and was also calibrated against 2 reference gases.

$REE_{predicted}$ was derived from the Harris-Benedict equation.[14] The equation for men was adapted from Bauer et al[15] and is shown later. There is an agreement between the mean $REE_{measured}$ and $REE_{predicted}$ for patients with cancer cachexia at the group level when using this equation.[15] This equation was converted into kcal/day for use in our analysis:

$$\begin{aligned}\text{REE (for men, in KJ/day)} &= [57.5 \times (\text{weight in kg})] \\ &+ [20.9 \times (\text{height in cm})] \\ &- [28.3 \times (\text{age in years})] + 278.[15]\end{aligned}$$

Patients with an $REE_{measured}$ more than 110% of the $REE_{predicted}$ were considered hypermetabolic, based on data demonstrating that 95% of healthy, elderly individuals have an $REE_{measured}$ within 10% of their $REE_{predicted}$.[16]

Measurement of Systemic Inflammation. Multiplex analysis of serum cytokine levels was performed using a Luminex 100 analyzer (R&D Systems, Minneapolis, MN) running on Bio-Plex software (Bio-Rad Laboratories, Hercules, CA). Data were analyzed using BeadView software version 5.0 (Upstate, Charlottesville, VA). Analysis of inflammatory cytokines included interleukin-1β (IL-1β), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), tumor necrosis factor-α (TNF-α), and interferon-γ (INF-γ). IL-6 levels were confirmed with a highly sensitive colorimetric sandwich enzyme linked immunosorbent assay (ELISA) (Quantikine HS, R&D Systems; results shown as "IL-6HS"). CRP was measured using a BN-II nephelometer (Dade-Behring, Deerfield, IL).

Table 2. Baseline patient characteristics.

Characteristic	All patients ($n = 11$)	Celecoxib-treated patients ($n = 4$)	Placebo-treated patients ($n = 7$)	p value*
Sex (M:F)	11:0	4:0	7:0	
Age, y				
Mean	59.1	55.3	61.3	.36
SD	9.9	8.5	10.5	
Height, cm				
Mean	176.5	172.7	178.7	.11
SD	5.9	1.2	6.5	
Weight, kg				
Mean	69.1	70.6	68.2	.80
SD	13.9	17.4	13.0	
BMI, kg/m^2				
Mean	22.2	23.7	21.3	.70
SD	4.3	5.7	3.6	
Hematocrit, %				
Mean	37.1	37.5	36.9	.86
SD	5.0	4.2	5.8	
CRP, μg/ml				
Mean	12.8	15.2	11.4	.14
SD	15.9	20.5	14.2	
LBM, kg				
Mean	53	54	52	.63
SD	8	9	8	
$REE_{measured}$, kcal/day				
Mean	1691	1790	1649	.42
SD	261	301	255	
$REE_{predicted}$, kcal/day				
Mean	1499	1525	1484	.78
SD	218	223	233	
$REE_{measured}/REE_{predicted}$	113%	117%	111%	
FAACT Score				
Mean	98	86	104	.16
SD	18	8	19	
KPS Score				
Mean	76	85	71	.13
SD	14	13	14	
Tumor Site				.91
Head&Neck	3	1	2	
GI	8	3	5	
Tumor Stage				.70
I	0	0	0	
II	0	0	0	
III	2	1	1	
IV	9	3	6	

Abbreviations: M, male; F, female; BMI, body mass index; m, meters; CRP, C-reactive protein; LBM, lean body mass; REE, resting energy expenditure; FAACT, Functional Assessment of Anorexia-Cachexia Therapy; KPS, Karnofsky Performance Scale; GI, gastrointestinal.
Values are means (± standard deviation (SD)), unless otherwise specified in table.
**One-way analysis of variance.*

Quality of Life Assessment. QOL was measured using the FAACT (version 4) questionnaire. This self-administered questionnaire was designed to measure both general aspects of QOL and specific cachexia concerns using a unique subscale that provides information not captured by more generic chronic illness questionnaires.[13]

Physician-Assessed Performance Status. Patients were assessed by their attending surgical oncologist for level of physical function and activities of daily living using the standard KPS.

Statistical Methods for Phase II Trial. The statistical objectives of the study were to analyze for statistically significant differences in mean preintervention to postintervention changes between treatment groups for each measurement category. These included weight, body mass index (BMI), body composition parameters, FAACT and KPS

Table 3. Changes in body composition and resting energy expenditure.

Measure	Celecoxib ($n = 4$)	Placebo ($n = 7$)	p value*
Weight, kg			
Mean	+1.0	−1.3	.05
SD	1.3	1.7	
ΔBMI, kg/m^2			
Mean	+0.3	−0.6	.05
SD	0.5	0.7	
ΔLBM%			
Mean	+0.3	0.0	.82
SD	2.8	1.6	
ΔFM%			
Mean	−0.2	−0.5	.74
SD	1.0	1.2	
ΔTBW%			
Mean	+1.1	+1.2	.94
SD	1.4	3.2	
$REE_{measured}$, kcal/day			
Mean	+6.3	−219.3	.42
SD	436.7	364.9	
$REE_{predicted}$, kcal/day			
Mean	+14.4	−19.3	.04
SD	18.6	24.6	

Abbreviations: kg, kilograms; Δ, change; BMI, body mass index; m, meters; LBM, lean body mass; FM, fat mass; TBW, total body water; REE, resting energy expenditure.
**One-way analysis of variance.*

scores, and serum cytokine and CRP levels. One-way analysis of variance (ANOVA) was used for all comparisons, although the Wilcoxon sum rank test was used where appropriate. Statistical significance was established at $p < .05$.

RESULTS

Patient Characteristics. Eleven patients were randomly assigned to the treatment or placebo group. All patients but 1 completed the trial. All data were analyzed with per protocol analysis. All the patients had newly diagnosed cancer and began anticancer therapy after this clinical trial. None of the patients had incurable or known metastatic disease at the time of this trial. Characteristics of the study population confirm previous observations of patients with cancer cachexia (Table 2).[7] All patients in this study had anemia (mean hematocrit, 37.1% ± 5.0%). The mean CRP level was elevated (mean CRP, 12.8 ± 15.9 μg/mL). BMI values were reduced (mean BMI, 22 ± 4 kg/m^2) as was the LBM (mean LBM, 53 ± 8 kg). The patients had reduced performance status and QOL scores (mean KPS score, 76 ± 14, mean FAACT score, 99 ± 18).

Only male patients were enrolled in this study. This reflects a predominance of male patients available for recruitment in our hospital during the study. Also, the uneven treatment groups in this study resulted from batched randomization and early closure of the study due the planned departure of the study coordinator. Despite this, there were no statistically significant differences in baseline characteristics between study groups (Table 2).

Adverse Events and Compliance. There were no reported toxicities or adverse events in this study. Compliance was good, with 74% of the study drug (mean = 31 of 42 pills) consumed in the treatment group and 88% of the study drug (mean = 37 of 42 pills) consumed in the placebo group ($p = .11$).

Effect of Celecoxib on Body Composition. During the study period, the experimental group experienced increases in body weight (mean change, +1.0 kg) and BMI (mean change, +0.31 kg/m^2), while the placebo group lost weight (mean change, −1.3 kg) and experienced decreased BMI (mean change, −0.56 kg/m^2) (Table 3). Mean changes in BMI were significantly different between groups ($p = .05$). The percent LBM increased slightly

Table 4. Change in serum cytokine and CRP levels.

Analyte	Baseline ($n = 11$)	Celecoxib ($n = 4$)	Placebo ($n = 7$)	p value*
IL-6 (pg/ml)				
Mean	7.6	−3.2	0.1	.18
SD	6.4	5.3	1.4	
IL-6HS (pg/ml)				
Mean	15.8	−8.8	−0.3	.24
SD	26.9			
IL-1ß (pg/ml)				
Mean	0.1	0.0	−0.0	.89
SD	0.1	0.0	0.1	
IL-2 (pg/ml)				
Mean	0.2	−0.1	0.0	.63
SD	0.2	0.2	0.3	
IL-8 (pg/ml)				
Mean	33.7	−11.0	+14.6	.19
SD	25.9	12.0	33.5	
TNF-α (pg/ml)				
Mean	5.0	−0.0	+0.6	.65
SD	1.1	1.9	2.1	
IFN-γ (pg/ml)				
Mean	1.5	0.1	0.0	.69
SD	0.1	0.2	0.1	
CRP (μg/ml)				
Mean	12.8	0.8	1.6	.80
SD	15.9	2.7	6.0	

Abbreviations: IL, interleukin; TNF-α, tumor necrosis factor alpha; IFN-γ, interferon gamma; CRP, C-reactive protein.
**One-way analysis of variance.*

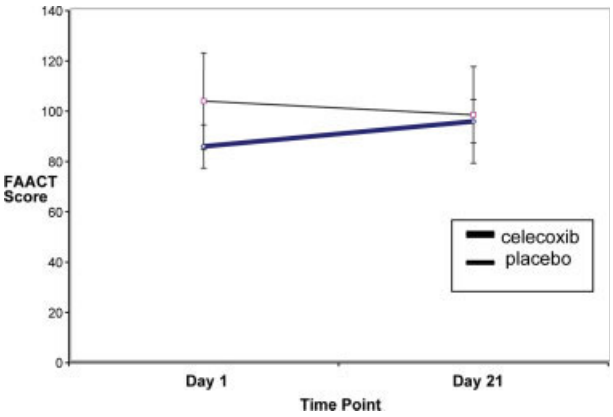

FIGURE 1. Changes in FAACT score. FAACT, Functional Assessment of Anorexia/Cachexia Therapy. Values are changes from the mean. Comparisons between groups were made using 1-way analysis of variance. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

(mean change, +0.3%) in the celecoxib group, while it slightly decreased in the placebo group (mean change, 0.0%) but this was not statistically significant ($p = .82$). The TBW increased in the treatment group but this was not significantly different from the placebo group ($p = .3$). The changes in percent TBW and percent fat body mass were similar between the celecoxib and placebo groups ($p = .94$ and .74, respectively).

Effect of Celecoxib on Resting Energy Expenditure. At the initiation of the study, all patients were hypermetabolic, as defined by an $REE_{measured}$ that is 110% or more of the $REE_{predicted}$ using the Harris-Benedict equation (Table 2).[15] Treatment with celecoxib for 21 days did not reduce $REE_{measured}$. Interestingly, $REE_{measured}$ decreased in the placebo group even as these patients lost weight (Table 3).

Results of Serum Cytokine and C-Reactive Protein Analysis. Observed changes in circulating proinflammatory cytokine levels were not statistically different between treatment and control groups (Table 4). The group receiving celecoxib demonstrated moderately decreased IL-6 levels after 21 days of treatment, but this was not statistically significant ($p = .18$). Measures of CRP did not change materially in either group over the time course of this study ($p = .80$).

Effect on Quality of Life and Performance Status Scores. Patients' baseline QOL scores on the FAACT questionnaire are shown in Table 2. The group receiving celecoxib had a significantly greater mean change in QOL score than the placebo group, which actually had a mean decrease in QOL score ($p = .05$) (Figure 1). KPS scores did not change significantly between groups ($p = .61$).

DISCUSSION

This study represents a relatively homogenous cohort of patients with cachectic cancer comprehensively evaluated during a defined period of time prior to therapeutic intervention. All patients were seen with cachexia at the time of their diagnosis of cancer. None had metastatic disease and none were considered for palliative therapy. In this regard, this population's characteristics may represent cancer cachexia in its early stages, prior to anticancer therapy. Baseline BMI values for this study population were reduced on average (22 ± 4 kg/m^2) as compared with healthy controls drawn from the general population in a study by Pichard and Kyle (25 ± 3 kg/m^2).[17] Patients also had lower mean LBM on entry to the study (53 ± 8 kg) when compared with this population of healthy controls (59 ± 7 kg).[17] In the current study, all patients were found to have advanced cancer (stage III or IV). All had reduced hematocrit values and many had elevated CRP levels, consistent with most definitions of cancer cachexia. This study population had REE values approximately 113% of predicted, confirming that they were hypermetabolic at the beginning of the study. QOL and performance scores were also relatively low in this patient population, confirming observations that cachectic patients are often debilitated.

Important findings in this pilot study suggest that COX-2-inhibiting NSAIDs such as celecoxib may help increase patient weight and improve both BMI and QOL in the absence of protein or nutritional supplements. Although a statistically significant increase in LBM was not seen in the treatment group, a true gain in LBM was unlikely in the absence of protein and nutritional supplementation. However, the weight gain in the treatment group in this study compares favorably with the weight gain seen in a recent 8 week trial of a protein and energy dense oral nutritional supplement (0.5 kg).[18] Another 8-week trial of 2 g of EPA also had comparable weight gain (1.2 kg), but it was not significantly different from the placebo group and there were many more adverse events than seen in this study.[5] This indicates that inflammatory suppression may induce weight gains but may not be sufficient to produce major changes in LBM.

COX inhibitors have been used in other studies, often as palliative treatment and combined with other agents. In a retrospective study of unselected weight-losing patients with cancer, the use of the long-term COX inhibitor (indomethacin) were associated with a decrease in CRP and erythrocyte sedimentation rate levels, suggesting that it does reduce systemic inflammation.[9] When indomethacin (50 mg twice daily) was given with erythropoietin (15–40,000 units per week) and total parental nutrition to patients with solid tumors that were predominantly gastrointestinal, there was no significant increase in body weight or LBM. There was prolonged survival in the experimental group but it is difficult to determine which treatment intervention was responsible for this.[10] In a randomized clinical trial of weight-losing patients with gastrointestinal cancer, ibuprofen taken with megestrol acetate increased body weight by 2.3 kg after 12 weeks. It is unclear which agent is responsible for the weight gain since megestrol acetate alone caused weight loss.[19]

In large, population-based studies, the short-term (<180 days) use of celecoxib has not been shown to increase the risk of cardiovascular disease as compared with ibuprofen.[20] In a Canadian study, NSAID-naïve patients greater than 66 years of age showed no increase in risk of acute myocardial infarction in the first 30 days of celecoxib use when compared with controls not taking NSAIDs.[21] Therefore, patients treated with a very short (21-day) course of moderate-dose (400 mg per day) celecoxib do not appear to be at increased risk for cardiovascular events. Indeed, no adverse events were seen in this study.

This study demonstrated improved QOL scores in the group receiving celecoxib. However, these improvements were not paralleled by improved physical function as measured by the KPS scale. This may be due to the fact that the FAACT questionnaire is derived from the patient, while the KPS is derived from the physician's perception of the patient.

Changes in body composition in this study were not statistically significant. Although it is well validated for the measurement of body composition, DEXA scanning is subject to error.[22] DEXA measurements are based on the assumption that hydration of fat-free mass remains constant at 73%. Hydration, however, can be variable in certain disease states including cachexia.[22,23] Physiological changes due to cachexia may alter body composition and distort DEXA's assumption that hydration and density are in a constant relationship.

A number of previous studies have emphasized the relationship of cancer cachexia-induced weight loss with increased REE and inflammation.[8,10] The current study did not confirm this. Although the patients in this study were hypermetabolic at baseline, patients with weight gain during this study tended to have increased REE, while patients with weight loss had decreased REE. This suggests that cancer cachexia may not simply be a disease of hypermetabolism. The current study also does not confirm previous findings of reduced REE in patients with pancreatic cancer after a 7-day course of ibuprofen, a COX inhibitor.[24] It is consistent with a study of patients with esophageal cancer in which thalidomide treatment was associated with a gain in LBM (1.2 kg) and an increase in REE.[25] Further investigation of the association between weight loss, REE, and COX inhibitors should utilize homogeneous patient populations undergoing selective anticachexia treatment in the absence of anticancer therapy. The current study suggests that short term reversal of cancer cachexia is achievable without directly affecting REE. In this study, inflammatory cytokine and CRP measurements demonstrated a decrease in IL-6 in the group receiving celecoxib. However, this trend was not statistically significant. Neither CRP nor any other cytokine showed significant reductions in the celecoxib group. This finding is also consistent with a recent large, multi-institutional trial in which serum concentrations of IL-1β, TNF-α, and IL6 did not correlate with changes in weight in patients with cancer cachexia.[26] One explanation for this is that changes in inflammation affecting end organs may not be accurately reflected by changes in levels of circulating serum cytokines or other inflammatory markers. Longer periods of anti-inflammatory therapy might be necessary to see systemic changes in inflammation.

There is a growing consensus that cancer cachexia may be due, in large part, to an inappropriate inflammatory response. Targeting this inflammation as part of a multimodal therapeutic approach makes theoretical sense. The results of this pilot study are consistent with prior animal and human experiments and should stimulate larger clinical trials investigating the role of COX-2 inhibitors in the treatment of cancer cachexia. Indeed, more studies are needed to confirm the findings of this pilot study. Future research may involve short-term, moderate-dose celecoxib

therapy combined with a protein-dense, EPA-containing nutritional supplement. Finding the right combination of agents in multimodal therapy will be challenging due to the conflicting data arising from the use of EPA in treating cancer cachexia. Extending the length of the trial and measuring energy expenditure using physical activity meters should also be considered.

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