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A Placebo-Controlled, Double Blind Trial of Infliximab for Cancer-Associated Weight Loss in Elderly and/or Poor Performance Non-Small Cell Lung Cancer Patients (N01C9)

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Abstract

PURPOSE—This study tested whether infliximab, a chimeric IgG1kappa monoclonal antibody that blocks tumor necrosis factor (TNF) alpha, improves/stabilizes weight loss in elderly and/or poor performance status patients with metastatic non-small cell lung cancer (NSCLC).

METHODS—This double-blind trial randomly assigned patients to infliximab/docetaxel (n=32) versus placebo/docetaxel (n=29). The primary endpoint was a $\geq 10\%$ weight gain.

RESULTS—Groups were balanced with respect to age, number of prior chemotherapy regimens, baseline weight loss, and performance status. No patient gained $\geq 10\%$ baseline weight, and early evidence of lack of efficacy prompted early trial closure. Appetite improvement was negligible in both arms. However, infliximab/docetaxel-treated patients developed greater fatigue and worse global quality of life scores. Other outcomes, such as tumor response rate ($<10\%$ in both groups) and overall survival, were not statistically different between groups. There were no statistically significant differences in adverse events, although one death was attributed to infliximab. Genotyping for the TNF alpha -238 and -308 polymorphisms revealed no clinical significance of these genotypes, as relevant to loss of weight or appetite.

CONCLUSIONS—This trial closed early because infliximab did not prevent or palliate cancer-associated weight loss. Infliximab was associated with increased fatigue and inferior global quality of life.

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Keywords

double blind trial; infliximab; cancer-associated weight loss; elderly patients; non-small cell lung cancer

INTRODUCTION

Weight loss predicts a poor prognosis for patients with non-small cell lung cancer (NSCLS) [1]. This weight loss is particularly problematic in elderly cancer patients who often also suffer from sarcopenia, or age-related attrition of lean tissue; they become even further compromised as a result of cancer-associated weight loss [2]. Although a handful of agents results in weight gain in cancer patients and in elderly patients [3,4], none provides compelling evidence that this weight gain translates into improved global quality of life and survival. Thus, there remains a need for testing other agents to treat weight loss and its ramifications within this group of cancer patients.

The pivotal role of tumor necrosis factor (TNF) alpha in cancer-associated weight loss has prompted further study of cytokine blockade as a potential treatment for cancer-associated weight loss. A large body of preclinical data points to this inflammatory cytokine as a key mediator of weight loss [5,6]. Most notably, Torelli and others tested a dimeric, pegylated 55-kDA TNF alpha receptor construct that inhibited TNF alpha [7]. The administration of this inhibitor resulted in weight gain and improved appetite in tumor-bearing animals, thus offering promise that TNF inhibition carries similar therapeutic value in a clinical setting.

Thus, the North Central Cancer Treatment Group (NCCTG) undertook this double-blind, placebo-controlled trial of infliximab, a chimeric IgG1kappa monoclonal antibody that blocks TNF alpha, in elderly and/or poor performance status patients with metastatic NSCLC. The purpose of this study was to evaluate whether this agent was effective in treating weight loss and its ramifications in elderly and/or poor performance patients with metastatic NSCLC.

METHODS**Overview**

Study sites within the NCCTG obtained approval from their respective Institutional Review Boards prior to opening this trial. All patients provided written informed consent.

Eligibility Criteria

All patients met the following criteria: 1) age $\geq$ 65 years, or, if younger, Eastern Cooperative Oncology Group (ECOG) performance status of 2; 2) ECOG performance score of 2 or better, if $\geq$ 65 years of age; 3) histological or cytological proof of NSCLC with no curative options; 4) life expectancy of 3 months or longer, in the judgment of the treating physician; 5) greater than 3 weeks since the completion of radiation, antineoplastic therapy, or major surgery; 6) able to complete study questionnaires alone or with assistance; and 7) willingness to have blood drawn for research purposes.

In addition, the following laboratory parameters were required for all patients within 14 days of trial registration : 1) serum creatinine ≤ 1.5 times the upper limit of normal; 2) total bilirubin within the normal range; 3) an absolute neutrophil count of $1.5 \times 10^9/\text{Liter}$ or greater; 4) platelet count of $100 \times 10^9/\text{Liter}$ or greater; and 5) liver function tests that allowed for the anticipated safe administration of docetaxel; these included an aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) $\leq$ to 2.5 times the upper limit of normal if the alkaline phosphatase was $\leq$ the upper limit of normal; or an alkaline phosphatase ≤ 4 times the upper limit of normal if the AST and/or ALT were less than the upper limit of normal.

Patients were deemed ineligible if they had any one of the following: 1) adrenal corticosteroids, androgens, progestational agents, or other appetite stimulants (inhaled or optical steroids were allowed; also short term use of dexamethasone around the time of chemotherapy was acceptable) within the past month, currently, or planned; 2) malabsorption, intractable vomiting, or mechanical obstruction of the gastrointestinal tract; 5) symptomatic or untreated brain metastases; 3) infection or debilitating illness that would make the administration of chemotherapy too risky in the opinion of the treating oncologist; 4) grade 2 or worse peripheral neuropathy; 5) parenteral nutrition or enteral nutrition administered through a feeding tube; 6) prior radiation to 25% or more of the bone marrow cavity; 7) prior malignancy with the exception of basal or squamous cell carcinoma of the skin or a more invasive cancer effectively treated 5 or more years ago; 8) pregnant, nursing, or of child-bearing potential and unwilling to employ contraception; 9) history of tuberculosis or a positive tuberculosis skin test; 10) clinical evidence of congestive heart failure or a previous history of heart failure; or 11) edema or ascites.

Stratification and Randomization

Stratification was conducted with a minimization algorithm that balanced the marginal distributions. The following stratification factors were utilized: 1) patient-reported weight loss in the preceding 6 months: 0 *versus* $< 5\%$ *versus* $\geq 5\%$; 2) number of prior chemotherapy regimens for metastatic disease: 0 *versus* 1 *versus* > 1 ; 3) male *versus* female; and 4) the prognostic index: good *versus* bad *versus* unsure [8].

Therapy

All patients were randomly assigned in a double-blinded fashion to one of two treatment arms, both of which included docetaxel: 1) infliximab 5 mg/kg/day intravenously on day 1 weeks 1, 3, and 5 during the first 8 week cycle followed by day 1 on weeks 1 and 5 of every 8-week cycle thereafter *versus* 2) an identical placebo prescribed in a similar fashion. This dose of infliximab was chosen based on its proven efficacy in other disease settings and earlier safety data in cancer patients [9,10].

Docetaxel was administered to all patients in both groups at 36 mg/m²/day intravenously every 7 days for 6 consecutive weeks if toxicity checks and blood counts permitted with weeks 7 and 8 off. The length of the treatment cycle was 8 weeks.

Follow-Up

Patients were monitored throughout the study but were formally assessed at one-month intervals. The latter required the healthcare provider to undertake a history, physical examination, weight measurement, and toxicity check that included grading adverse events by means of the Common Terminology Criteria, version 2. Patient-completed questionnaires and diaries to capture interim information on weekly weight, appetite, patient-reported adverse events, and quality of life were gathered at these monthly assessments. These questionnaires included the NCCTG Anorexia/Weight Loss questionnaire, the Brief Fatigue Inventory (BFI), and the Functional Assessment of Anorexia/Cachexia (FAACT). Tumor measurements were undertaken at baseline and every 2 months.

Dose Modifications, Holding Therapy, and Stopping Therapy

Infusion reactions with either infliximab or docetaxel were to be managed with maximal supportive care. Severe reactions required complete cessation of drug administration and discontinuation of protocol therapy.

In the event the absolute neutrophil count was less than 1.5×10^9 /Liter or the platelet count less than 100×10^9 /Liter, both docetaxel and infliximab were held until blood counts increased above this threshold. Thereafter, infliximab was given at full dose, and docetaxel at a 25% reduction of the most recently-prescribed dose.

Infliximab was held for any infection and was only to be restarted after resolution. Any grade 3 adverse event directly attributable to infliximab required that this agent be stopped, no further therapy be given per protocol, and the patient be monitored.

Grade 3 or 4 diarrhea required that docetaxel be held until symptoms returned to baseline. This chemotherapy agent was then re-prescribed with a 25% dose reduction. In the event of grade 2 diarrhea, docetaxel was to be held until symptoms approached baseline, and the patient was then to be retreated at the previous dose. Docetaxel was not to be given if the bilirubin exceeded the normal range, and all other non-hematologic adverse events required that docetaxel be held until resolution and then restarted with a 25% dose reduction.

If any treatment needed to be held beyond three weeks or if more than 3 dose reductions occurred, the patient was removed from protocol therapy and monitored. If a patient manifested stable disease after 4-6 months of protocol therapy, the treating oncologist could stop both the docetaxel and the infliximab and proceed to monitoring.

Genotyping

Patients were to have a blood draw for genotyping of select functional TNF alpha polymorphisms. Buffy coats were prepared and shipped on ice directly to the Mayo Clinic in Rochester, Minnesota. They were then stored at -70 degrees centigrade until the time of DNA isolation and genotyping. Genomic DNA was extracted from buffy coat preparations using the EASY DNA Kit (Invitrogen, Carlsbad, California, USA) according to the manufacturer's instructions. Tumor necrosis factor alpha -238 A/G and tumor necrosis factor alpha -308 G/A alleles were detected by polymerase chain reaction (PCR) restriction fragment length polymorphism assays.

The primers were as follows:

F238 (5'-AAACAGACCACAGACCTGGTC-3') and

R238 (5' CTCACACTCCCCATCCTCCCGGATC-3');

F308 (5'AGGCAATAGGTTTTGAGGGCCAT3') and

R308 (5' TCCTCCCTGCTCCGATTCCG3')

One hundred nanograms of genomic DNA were amplified in a total volume of 50 microliters containing 0.2 μ M each primer, 0.5 units platinum Taq DNA polymerase (Invitrogen, Carlsbad, California, USA), 200 μ M of each dNTP, and PCR reaction buffer (Invitrogen, Carlsbad, California, USA) for one cycle at 94°C for 5 minutes followed by 35 cycles at 94°C for 1 minute, 60°C for 1 minute and 72°C for 1 minute plus 72°C for 5 minutes and then 4°C. The PCR products were digested at 37°C with *Bam*HI and with *Nco*I (all from New England Biolabs, Ipswich, Massachusetts, USA), followed by 4% agarose gel electrophoresis to detect tumor necrosis alpha -238 A/G and tumor necrosis factor alpha 308 G/A alleles, respectively. Each PCR run included a “blank” to which no DNA had been added to ensure that there had been no sample contaminations.

Statistical Analyses

The primary analysis was to compare the percentage of patients in each study arm with a non-fluid weight gain of $\geq 10\%$ of baseline weight. The sample size within this report provided 80% power to detect a 34% difference in the percentage of patients who gained $\geq 10\%$ of their baseline weight at any point while on the study using a chi-squared test with a two-tailed alternative and a 5% type I error rate, assuming that the inferior group had no more than 20% of patients who gained $\geq 10\%$ of their baseline weight. Patients who developed edema had their weight data censored starting immediately after the detection of edema. Appetite changes were based on patient-reported questionnaire data and were analyzed similarly; analyses were undertaken for other quality of life assessments, such as fatigue and global quality of life, and were analyzed with Wilcoxon rank sum tests. Additionally, differences in confirmed tumor response rates (complete or partial responses on two consecutive evaluations at least 8 weeks apart) were compared between arms by means of a chi-squared test. Adverse event grades were compared between groups by means of Wilcoxon rank sum tests. Kaplan-Meier survival curves were constructed for each patient group and compared with a log rank test. Correlations between changes in weight and genotype were explored by means of chi square analyses. Kaplan Meier curves of time to $\geq 5\%$ weight loss were constructed for each patient group and compared with a log-rank test.

RESULTS

Baseline and Descriptive Data

The NCCTG Data Monitoring Committee terminated this study early because of slow accrual and lack of efficacy after a total of 61 eligible patients were recruited between October 2002 and October 2005. This cohort does not include 3 patients who received no study agent, and 3 deemed ineligible.

Patients treated with infliximab/docetaxel (n=32) and placebo/docetaxel (n=29) were similar in baseline characteristics (Table 1).

Follow-Up

Only one patient stopped therapy on protocol because of stable disease; this patient had received infliximab. Otherwise, 14 infliximab/docetaxel and 7 placebo/docetaxel patients declined further therapy and/or suffered severe adverse events. These events included on-study deaths, not all of which were attributable to therapy, in 4 infliximab/docetaxel patients. Fifteen infliximab/docetaxel and 20 placebo/docetaxel patients stopped therapy because of cancer progression. The remaining 4 patients stopped therapy for less easily categorized reasons.

Weight

No patient in either arm achieved the primary endpoint of 10% or greater weight gain (Figure 1). In evaluating weight stability, a 5% or greater weight decline was observed in 5 (21%) infliximab/docetaxel patients and in 10 (38%) placebo/docetaxel patients ($p=0.17$). Similarly, time to 5% or greater weight decline was not statistically different between study arms ($p=0.11$).

Anorexia, Fatigue, and Global Quality of Life

The NCCTG Anorexia/Weight Loss Questionnaire found no significant differences in appetite over time between the two treatment groups (data not shown). Similar negative findings were seen with the FAACT (data not shown).

The Brief Fatigue Inventory (BFI) observed more fatigue among patients who received infliximab/docetaxel. Averaged responses to the nine questions on the BFI showed descriptively higher scores, or greater fatigue, throughout the study period (Figure 2).

In terms of global quality of life, the Functional Assessment of Cancer Therapy-General (FACT-G), contained in the FAACT, showed no clinically or statistically significant differences between groups over time for emotional and social well-being. However, infliximab/docetaxel-treated patients had lower levels of functional and physical well-being (Figure 3).

Tumor Response and Survival

One patient treated with infliximab/docetaxel had a confirmed tumor response (3.7%), as did 2 treated with placebo/docetaxel (8.3%); ($p=0.48$). In comparing overall rates of response and stable disease, there were no statistically significant differences between groups.

Neither was survival statistically different between the two groups. Median survival among the infliximab/docetaxel-treated patients was 189 days and among the placebo/docetaxel patients 169 days ($p=0.88$) (Figure 4). Progression-free survival was also not statistically different between groups.

Adverse Events

Adverse events, as summarized by maximum grade for each event per patient post-baseline, were not statistically different between groups (Table 2). Infliximab was not associated with higher infection rates nor with higher rates of heart failure symptoms.

However, there was one treatment-related death from pneumonitis on the infliximab-docetaxel arm. There were also 11 grade 4 adverse events on the infliximab/docetaxel arm and 2 on the infliximab/placebo arm. These events included dyspnea, fatigue, hypotension, hypoxia, cardiac ischemia/infarction, thrombosis, melena, and muscle weakness. Despite these notable adverse events, there was no statistically significant difference between groups to suggest worse overall toxicity based on study arm and the maximum grade of any adverse event per patient ($p=0.11$).

Tumor Necrosis Factor Polymorphisms

Genetic polymorphisms of the TNF alpha gene at positions -238 and -308 were assessed in 52 and 51 patients, respectively. The TNF alpha -238 A/A, G/A and G/G genotypes were observed in 2, 4, and 46 patients, respectively. The TNF alpha -308 A/A, G/A, and G/G genotypes were observed in 3, 14, and 34 patients, respectively.

Hardy Weinberg equilibrium was assessed, and marker frequencies did not reach a statistically significant difference from what was expected. Clinical correlative studies showed no association between these genotypes and $\geq 5\%$ weight loss or change in appetite.

DISCUSSION

This study was undertaken to determine whether infliximab improves outcomes in elderly and/or poor performance status NSCLC patients with weight loss or at risk for it. Several outcomes -- including weight, appetite, quality of life, tumor response, and survival -- were not positively impacted. Admittedly, early study closure for slow accrual and lack of efficacy detracted from our ability to powerfully assess all the study endpoints. Nevertheless, lack of efficacy on the weight endpoint, coupled with the negative effects of infliximab on fatigue and global quality of life, all suggest that this agent, when prescribed in this manner, does not help patients suffering from cancer-associated weight loss.

Indeed, this study is not the first to report such findings. First, Wiedenmann and others tested infliximab in 89 patients with unresectable exocrine pancreas cancer [11]. In this three-arm, placebo-controlled trial, infliximab was tested at 3 mg/kg and at 5 mg/kg. All patients also received gemcitabine. This study observed no statistically significant augmentation of lean body mass, as measured by bioelectrical impedance; and other secondary endpoints, such as survival, progression-free survival, and the 6-minute walk were not statistically different between study arms. Second, another NCCTG study had tested another inhibitor of TNF alpha, etanercept, for cancer-associated weight loss [12]. Focusing on 63 patients with a variety of cancer types, this study observed that etanercept did not result in a statistically significant improvement in weight compared to placebo, and other study endpoints, such as

survival, were not favorably impacted. In effect, the negative findings from the current study corroborate those from the trials that preceded it.

Despite such negative findings, it is important to acknowledge that TNF alpha may nonetheless be a mediator of cancer-associated weight loss, as suggested by the following two comments. First, as alluded to earlier, a sizable literature strongly suggests that this cytokine is a key mediator of cancer-associated weight loss [4,5,6]. This trial's negative findings may perhaps be explained by the fact that a cascade of cytokines, including TNF alpha, likely mediates cancer-associated weight loss and that the redundant role of these cytokines offsets for the inhibition of only one [13]. Secondly, the dose of infliximab may have been an issue. Although we had utilized an infliximab dose that is commonly used in the treatment of rheumatoid arthritis, treating cancer-associated weight loss may require a much higher (or lower) dose to achieve a therapeutic response and reverse weight loss. In short, although this study did not observe therapeutic benefit with infliximab, the results of this study cannot necessarily negate previously-reported evidence that TNF alpha is a key mediator of cancer-associated weight loss. Further study of other clinical interventions as well as basic mechanisms relevant to cancer-associated weight loss remains warranted.

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Figure 1.
This “bug plot” shows the percent change in weight from baseline.

Figure 2.

Patients in the infliximab/docetaxel group had higher levels of fatigue, as suggested by average patient-reported scores from the Brief Fatigue Inventory. The dark line represents scores from the infliximab/docetaxel group, the interrupted line represents scores from the placebo/docetaxel group, and bars show 95% confidence intervals.

Figure 3. Patients who received infliximab/docetaxel had worse global quality of life scores, as suggested by worse total FACT-G scores. The dark line represents scores from the infliximab/docetaxel group, the interrupted line represents scores from the placebo/docetaxel group, and bars show 95% confidence intervals.

Figure 4.
Kaplan Meir curves did not reveal statistically significant differences in survival between groups.

Table 1

Baseline Characteristics*

Characteristic	Patients on Infliximab/ Docetaxel N=32	Patients on Placebo/Docetaxel N=29	P-Value
Age, median in years (range)**	71 (59, 86)	75 (59, 83)	0.18
Gender			
Male (%)	27 (84)	20 (69)	0.15
Female (%)	5 (16)	9 (31)	
Performance Status			
0	7 (22)	5 (17)	0.08
1	20 (63)	12 (41)	
2	5 (16)	12 (41)	
Number of Prior Chemotherapy Regimens			
0	17 (53)	20 (69)	0.38
1	10 (31)	7 (24)	
>1	5 (16)	2 (7)	
Patient-Reported Weight Loss in the Preceding 6 Months			
0%	14 (44)	12 (41)	0.88
<5%	5 (16)	6 (21)	
>= 5%	13 (41)	11 (38)	
Prognostic Index			
Good	11 (34)	6 (21)	0.31
Bad	1 (3)	3 (10)	
Unsure	20 (63)	20 (69)	

* Numbers in parentheses denote percentages unless otherwise noted and may not sum to 100% because of rounding.

** P-value for age is based on a Wilcoxon rank sum test. All others are based on chi-square tests.

Table 2

Maximum Select Adverse Events

ADVERSE EVENT and GRADE*	% INFLIXIMAN/DOCETAXEL N=32	% PLACEBO/DOCETAXEL N=29	P-VALUE
Anemia			
2	3	10	0.35
3	3	3	
Constipation			
2	13	7	0.84
3	0	3	
Dyspnea			
2	3	0	0.36
Fatigue			
1	28	31	0.73
2	38	28	
3	22	38	
4	6	0	
Hypotension			
2	0	10	0.29
4	3	0	
Infection			
2	6	3	0.75
3	3	3	
Cardiac Ischemia/Infarction			
3	3	0	0.18
4	3	0	
Neutropenia			
1	22	14	0.49
2	13	14	
3	6	3	
Abdominal pain			
2	3	0	0.36
Chest pain			
2	6	0	0.65
3	0	1	
Pneumonitis			
3	9	3	0.20
5	3	0	

ADVERSE EVENT and GRADE*	% INFLIXIMAN/DOCETAXEL N=32	% PLACEBO/DOCETAXEL N=29	P-VALUE
Rash			
2	0	10	0.07
Thrombocytopenia			
1	16	14	0.57
3	3	0	
Thrombosis			
4	6	0	0.18
Transfusion of Red Blood Cells			
2	3	0	0.10
3	3	0	
4	3	0	
Vomiting			
1	13	10	0.39
2	6	3	
3	3	0	

* Grade refers to Common Terminology Criteria, version 2.0; if grade is not listed, then no events of this grade occurred.