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ORIGINAL ARTICLE

Fatigue in patients with advanced cancer: a pilot study of an intervention with infliximab

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Abstract
Goals of work The objective of this study was to determine the effect of infliximab, an antitumor necrosis factor alpha (TNFα) antibody, on fatigue in patients with advanced cancer.
Materials and methods This was a pilot study undertaken in a specialist palliative care unit. Seventeen eligible outpatients were enrolled in this study. Infliximab 5 mg/kg was administered intravenously at baseline and if there was observable clinical benefit, every 4 weeks thereafter until clinical benefit was lost. The primary outcome measure assessing subjective functional improvement was the change in fatigue severity scale (FSS) score at 4 weeks following an infliximab infusion. Secondary outcome measures of subjective functional improvement that were assessed 4 weeks after each infliximab infusion included changes in Karnofsky performance status (KPS), hospital anxiety and depression scale (HADS) score, anxiety and depression subscores, and appetite visual analogue scale. Clinical laboratory assessments were C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), TNFα, interleukin-6, and leptin concentrations.
Main results At week 4, 9 of 14 patients improved in FSS, 3 of 15 improved in KPS, 7 of 15 improved in total HADS and the majority had modest improvements in serum CRP, ESR, or leptin concentrations. Case studies of six patients with overall improvement are described in detail. Five serious adverse events occurred; two were serious infections possibly related to treatment.
Conclusions A subgroup of patients in this small pilot study demonstrated uniform subjective/clinical benefit. We were not able to identify any predictors of this response; a larger, controlled study may reveal more information.

Keywords Advanced cancer · Hospice · Palliative care · Fatigue · Infliximab

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Introduction

Five-year survival in cancer patients has increased over the last 30 years [6] and, for many, cancer has become a chronic disease. Treatments are increasingly effective but often disrupt people's lives and may be associated with long-term physical and psychological morbidity [5]. While research has advanced the treatment of new-onset and recurrent disease, further research is needed to evaluate end-of-life issues and quality-of-life impairment in patients with advanced stages of cancer.

Weakness and fatigue are common symptoms in patients with advanced cancer. Pain, dyspnea, insomnia, and anorexia appear to be physical symptoms most predictive of fatigue [17]. Many patients with cancer who complain of fatigue are cachectic and have a poor quality of life (cachexia/asthenia syndrome). Fatigue is also seen in other advanced progressive diseases such as end-stage cardiac failure and chronic obstructive pulmonary disease. A unifying factor in these conditions is the production of inflammatory cytokines, one of which is tumor necrosis factor-alpha (TNFα) [3, 4, 13, 18].

In cancer patients, TNFα has been implicated not only in cachexia/asthenia syndrome but also in bone pain, depres-

sion, and systemic symptoms related to high bulk disease [2, 19, 20]. Anorexia may be related to TNFα production, possibly mediated by the cytokine cascade affecting secretion of the adipocyte-derived cytokine, leptin [9].

Infliximab (Remicade), a chimeric monoclonal antibody to TNFα, is approved in the United States for the treatment of Crohn's disease, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and ulcerative colitis. The safety profile of infliximab has been well documented, in both clinical studies and postmarketing experience with exposure in nearly 650,000 patients worldwide [7, 10, 14, 15]. Most notably, an increased risk of serious infection with infliximab, particularly tuberculosis (TB), has been reported, but no overall increase in mortality has been demonstrated [14]. Clinical trials and postmarketing surveillance also have shown a raised incidence of opportunistic infections, including *Listeria monocytogenes*, in patients treated with infliximab [16].

In this paper, we present the results of this investigator-initiated, pilot study of the use of infliximab in the treatment of fatigue in patients with advanced cancer. The objective of this pilot study was to determine whether infliximab, which binds TNFα, improves fatigue in patients with advanced cancer who were not receiving concurrent chemotherapy, immunotherapy, or radiotherapy.

Materials and methods

Study design

This was a small, open-label, pilot study conducted from October 2002 to September 2003. Patients were recruited from outpatient, day-time therapy clinics for specialist palliative care at the Marie Curie Hospice, Hampstead, United Kingdom. The ethics committee approved the protocol, and this study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The risks of opportunistic infections with infliximab were detailed in the patient information provided before obtaining informed consent, which patients provided before any study-specific procedures were performed. Following publication of postmarketing surveillance data showing an increased risk of *Listeria monocytogenes* infection (meningitis and septicemia) [16], the protocol was amended to revise the infliximab dosing schedule and the informed consent form was updated to include this new information.

Patients

Patients complaining of fatigue and with an estimated survival that would allow them to participate for more than 8 weeks were asked to complete the fatigue severity scale (FSS). The FSS is a short, validated questionnaire with scores ranging from 9 to 63 where higher scores indicate greater fatigue. Patients who had an FSS score of 42 or greater (95% of the general population scored below 42 when this questionnaire was validated) [12, 17] were eligible for the study and received the comprehensive study information. After procurement of informed consent, blood samples were collected during screening.

Patients with a reversible cause of fatigue including anemia, hypercalcemia, hyponatremia, or hypothyroidism were excluded from the study. Patients were also excluded if they had major surgery, chemotherapy, or radiotherapy within 4 weeks of study entry. Based on the prescribing information for infliximab, a history of TB infection, congestive cardiac failure, or an autoimmune and/or demyelinating disease were also reasons for exclusion [14].

Study procedures

A chest X-ray was performed at the screening or baseline visits on patients who had not had a chest X-ray within 3 months of enrollment to rule out current infection or signs of previous pulmonary tuberculosis. Urine specimens were collected for routine urinalysis at these visits. At all study visits, patients completed functional self-assessment questionnaires and investigators performed clinical assessments.

The following patient self-assessment questionnaires were completed: FSS, Karnofsky performance status (KPS) [11], European Organization for Research and Treatment of Cancer 30-item Quality of Life Questionnaire (EORTC QLQ 30) [1], a 100-mm visual analogue scale (VAS) appetite questionnaire where lower values represent better appetite, and hospital anxiety and depression scale (HADS) [21].

The investigators' clinical assessments included measurement of patient body mass index (BMI), laboratory evaluations of complete blood count, renal and liver function tests, calcium concentration, tumor marker levels (if appropriate), and biomarker levels (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], TNFα, interleukin-6 [IL-6], and leptin). At week 2 and beyond, adverse events were documented. The attribution of adverse events to infliximab therapy was determined by the investigators.

Per the original protocol, infliximab 5 mg/kg was given as an intravenous infusion over 2 h, followed by a 2-h observation period at weeks 0, 2, and 4, and at every 4 weeks thereafter if improvement was demonstrated. Patients were assessed for subjective/clinical improvement in fatigue and adverse events at all dosing time points. After one patient reported a serious infection (bacterial meningitis) following the week-2 infusion, the dosing regimen was amended to infliximab 5 mg/kg at week 0, and every 4

weeks thereafter if improvement was demonstrated. Subjective and clinical assessments continued to be assessed at week 2. The first five patients were treated according to the original protocol, and the next 12 patients according to the amended protocol.

During the study, there was no change in the patients' usual care. Patients continued to have access to physiotherapy, nutritional supplements, analgesia, and other supportive care.

Treatment with infliximab was discontinued if any serious adverse events were reported, no benefit was observed, or further antineoplastic therapy was required. Serious adverse events, as defined in the International Committee on Harmonization-Good Clinical Practice guidelines (and Food and Drug Administration regulations), were reported to the Royal Free Ethics Committee, United Kingdom; the Medicines Control Agency, United Kingdom; and Centocor, Malvern, PA, USA.

Analysis

Baseline demographic and disease characteristics of this study population were described through the use of summary statistics (number, percent, mean, and standard

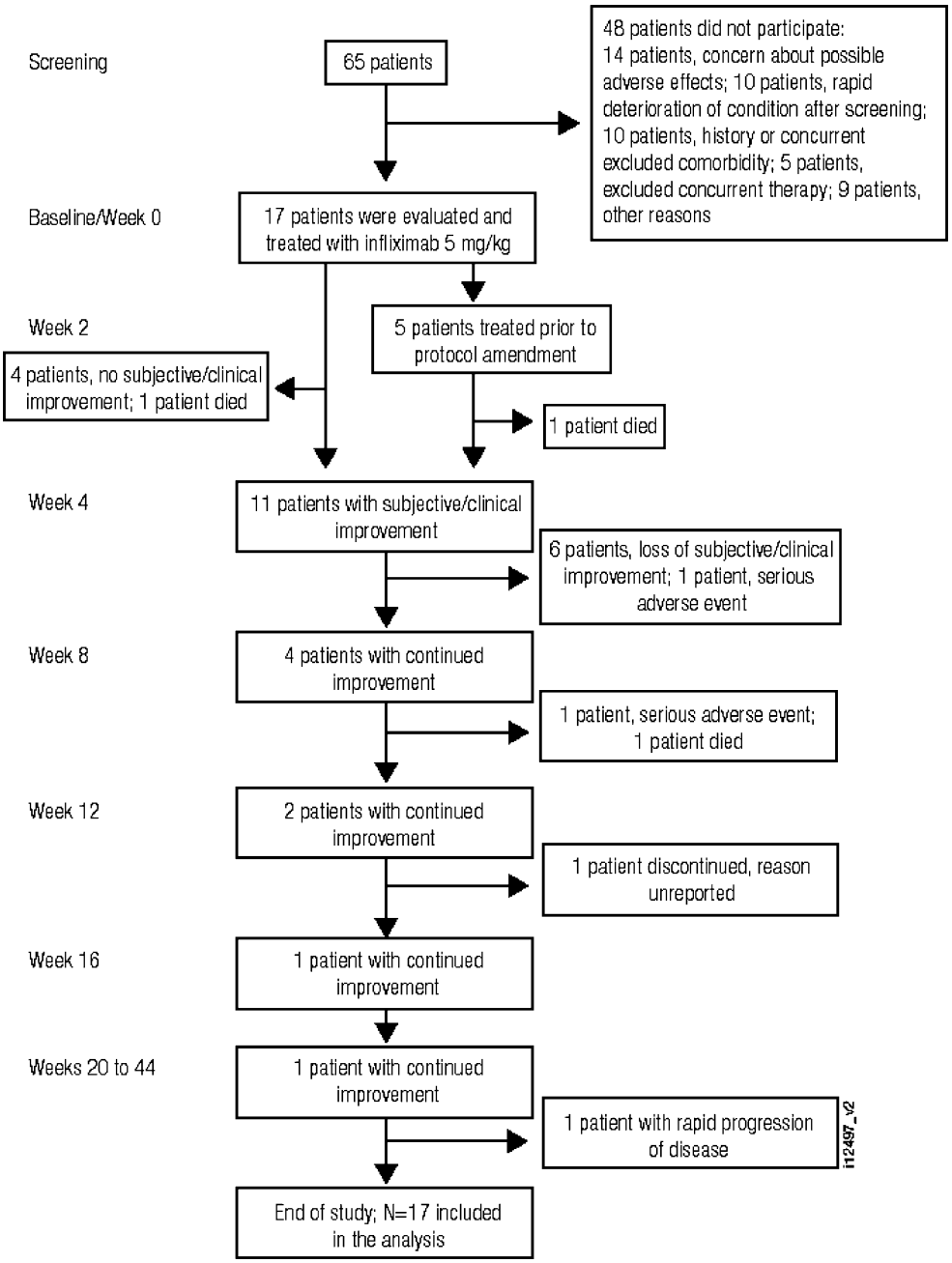

Fig. 1 Flow diagram of the prospective, open-label, pilot study

Table 1 Patient demographics and baseline characteristics

Characteristic	*N*=17
Gender, *n* (%)	
Male	13 (76.5)
Female	4 (23.5)
Age (years), mean (±SD)	63.5 (11.86)
Cancer diagnosis, *n* (%)	
Renal cell carcinoma	4 (23.5)
Non-small cell carcinoma	4 (23.5)
Breast carcinoma	2 (11.8)
Cervical carcinoma	1 (5.9)
Gastric carcinoma	1 (5.9)
Colorectal carcinoma	1 (5.9)
Esophageal carcinoma	1 (5.9)
Prostate carcinoma	1 (5.9)
Small-cell lung carcinoma	1 (5.9)
Squamous cell carcinoma of tonsil	1 (5.9)

deviation). Scatter plot diagrams for selected subjective and clinical assessments were constructed to visually examine the effect of the initial infliximab infusion at the first decision point for continued treatment (week 4). These figures illustrate the change in subjective or clinical assessments at week 4 relative to the baseline value. For all clinical and self-reported subjective assessments illustrated, decreasing values/scores indicate therapeutic benefit. For the investigator-assessed KPS, increasing values indicate therapeutic benefit. Brief case summaries are presented for six patients who responded to infliximab therapy. No formal statistical analyses were performed because of the small sample size.

Results

Sixty-five patients were screened, 17 of whom were enrolled and treated (Fig. 1). Demographic and baseline characteristics are presented in Table 1.

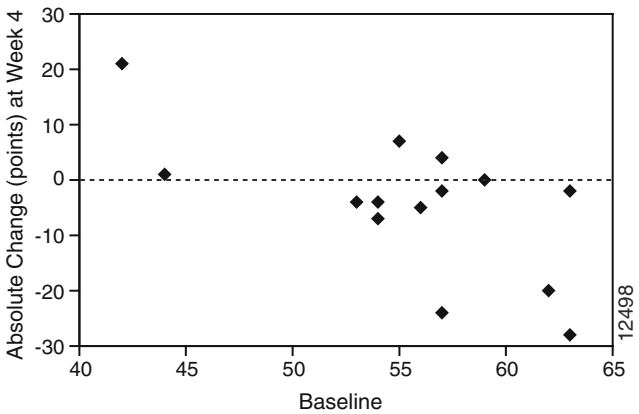

Fig. 2 Fatigue severity score: change from baseline at week 4

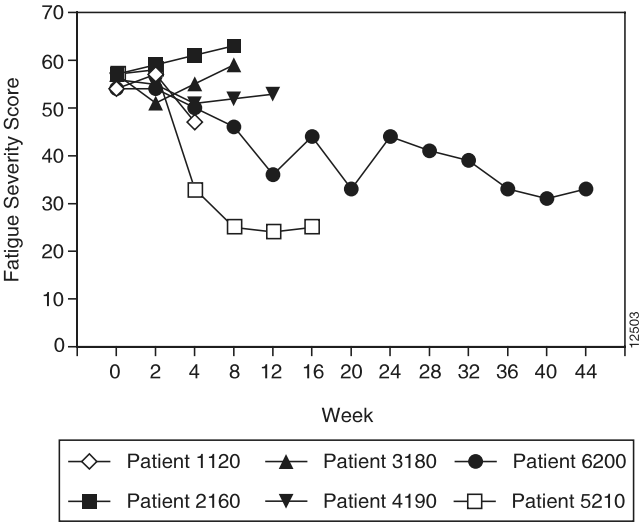

Fig. 3 Fatigue severity scores over time in patients with uniform subjective and clinical assessments

Of the 65 patients who were screened, 48 (73.8%) did not participate in the study. Possible adverse events or a rapidly deteriorating condition were reasons provided for nearly half of the 48 patients who chose not to participate.

Subjective functional assessments

Overall, there was variable improvement in FSS scores from baseline (Table 2) at week 4; however, most patients had some improvement in their FSS score (Fig. 2). In particular, there was improvement in FSS scores over time with repeated infliximab infusions in four patients (Fig. 3). One additional patient showed improvement in their FSS scores, but had an increase in FSS score at the final assessment and one patient had a slight increase over time.

Similarly, KPS scores as assessed by the investigators showed a decrease at week 4 in one patient and remained

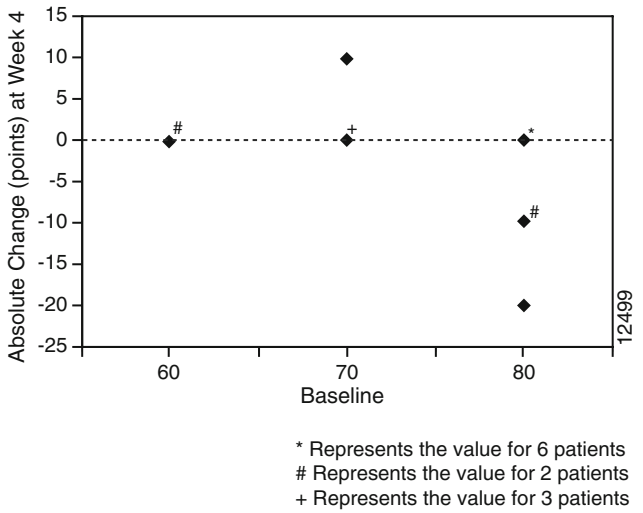

Fig. 4 Karnofsky performance status: change from baseline at week 4

Table 2 Baseline subjective and clinical assessments

Assessment	*N*=17
Subjective, mean (±SD)	
Fatigue severity scale	55.9 (5.90)
Karnofsky performance status	74.1 (7.12)
HADS total	13.9 (6.92)
Depression	6.9 (4.01)
Anxiety	7.1 (3.88)
Clinical, mean (±SD)	
Weight (kg)	64.9 (13.11)
Mid-arm muscle circumference (mm)	241.8 (30.98)
Body mass index (kg/m^2)	22.3 (4.54)
TNFα (pg/ml)	7.6 (6.90)
IL-6 (pg/ml)	38.5 (70.66)
CRP (mg/l)	65.6 (109.22)
ESR (mm/h), *n*=15	52.2 (35.02)
Leptin (ng/ml)	11.2 (16.95)

HADS Hospital anxiety and depression scale, *TNFα* tumor necrosis factor-alpha, *IL-6* interleukin-6, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate

unchanged in 11 patients (Fig. 4). Only three patients had a lower KPS score at week 4 than at baseline.

The HADS total scores remained relatively stable from baseline (Table 2) to week 4; however, the anxiety subscale showed the most variability of the two subscales (Fig. 5a to c) with respect to this self-reported assessment.

Case summaries

Six patients showed uniform subjective functional and clinical benefit (Tables 3 and 4, respectively) with repeated infliximab infusions. All six patients were dosed according to the amended protocol. Case summaries for these patients are presented.

Patient 1120, a 49-year-old patient with metastatic colon carcinoma, underwent a right hemicolectomy in August 2002 followed by first- and second-line chemotherapy that was discontinued in June 2003. His disease was progressive clinically and on computed tomography (CT) imaging; fatigue was a major symptom. Following the first dose of infliximab, there was subjective improvement in fatigue and levels of activity, with a 13% drop in FSS score (54 to 47). Of note, there was a decrease in TNFα and leptin levels despite a worsened appetite. The patient's disease progressed rapidly (with increased carcinoembryonic antigen from week 0 to week 4, and rising CRP and IL-6 levels). Given the history of cancer that was unresponsive to first- and second-line chemotherapy, it was believed that this was not as a result of infliximab therapy. In particular, the patient developed jaundice due to liver metastases and was admitted to the hospice. He died 35 days after his

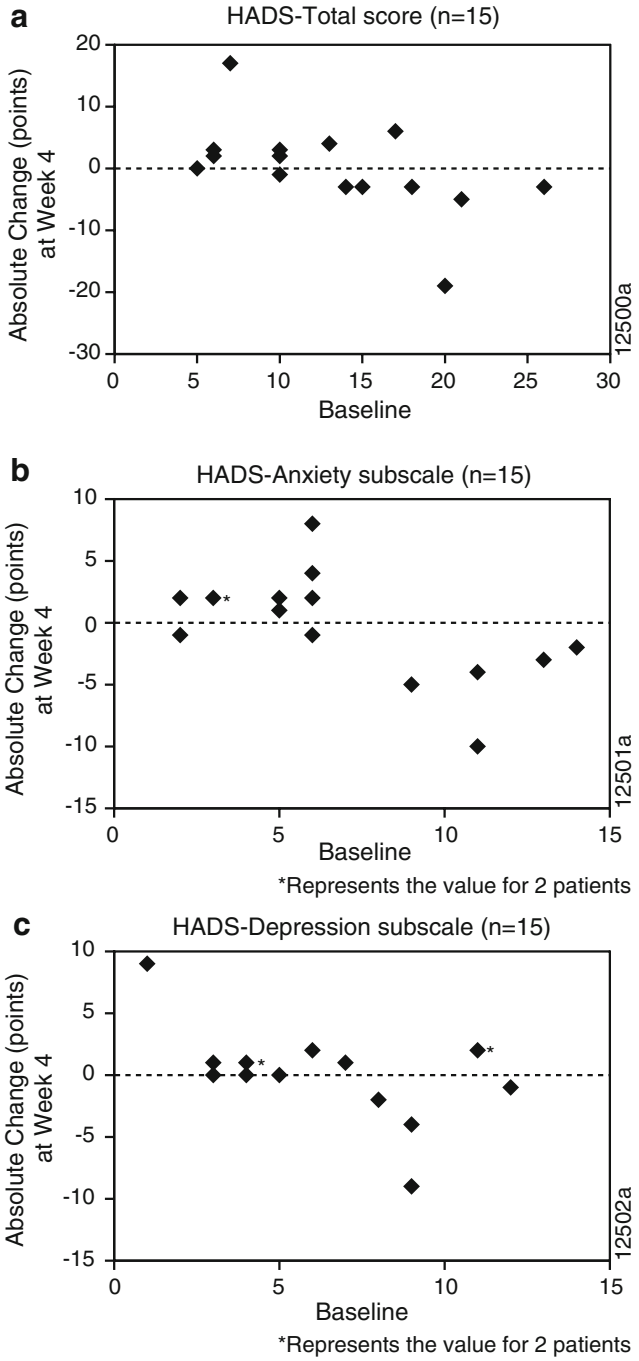

Fig. 5 Hospital anxiety and depression scale total score and anxiety and depression subscore: change from baseline at week 4

second dose of infliximab. At week 8, the patient was too ill to provide consent to have more blood tests performed.

Patient 2160, a 70-year-old patient with metastatic renal cell carcinoma, was treated with a right nephrectomy more than 15 years previously. Medical history indicated that the patient had angina and a myocardial infarction (treated with thrombolysis). The patient developed lung metastases (biopsy proven) and received interferon alpha from January

Table 3 Listing of subjective functional assessments

	Week 0	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44
Patient 1120													
FSS	54	57	47										
KPS	80	80	80										
VAS appetite (mm)	5	4	64										
Patient 2160													
FSS	57	59	61	63									
KPS	80	80	80	80									
VAS appetite (mm)	55	53	23	32									
Patient 3180													
FSS	57	51	55	59									
KPS	70	80	80	70									
VAS appetite (mm)	67	61	48	79									
Patient 4190													
FSS	56	55	51	52	53								
KPS	80	80	80	80	60								
VAS appetite (mm)	23	8	10	24	78								
Patient 5210													
FSS	57	58	33	25	24	25							
KPS	80	70	80	80	80	80							
VAS appetite (mm)	65	97	24	32	11	15							
Patient 6200													
FSS	54	54	50	46	36	44	33	44	41	39	33	31	33
KPS	70	70	70	70	80	70	70	70	80	80	80	80	80
VAS appetite (mm)	78	17	83	20	15	15	10	12	23	11	7	2	3

FSS=Fatigue severity score, KPS=Karnofsky performance status, VAS=Visual analogue scale

to June 2003 with disease progression noted on CT imaging. The patient's major symptoms were fatigue and dyspnea. Following infliximab therapy, this patient reported increased energy and motivation; however, this improvement was not reflected by a decrease in the FSS score, although, the patient's CRP level decreased initially. The patient's appetite improved and the leptin level decreased. The patient was hospitalized for a myocardial infarction and died 30 days after his third dose of infliximab.

Patient 3180, a 48-year-old patient with renal cell carcinoma, was treated with a right nephrectomy in December 2000. The patient became jaundiced due to a porta hepatis mass, and in November 2002, was found to have right renal bed and lung metastases. Interferon therapy was initiated and the disease progressed. The patient's major symptoms were fatigue, anorexia, and weight loss. Following the first dose of infliximab, activity levels and appetite improved. A weight gain of 1 kg was noted at week 2. This improvement was not maintained at week 8 as reflected in the patient's worsening FSS score, CRP level, and VAS appetite measurement. The decreases observed at week 4 in IL-6 and leptin levels were noteworthy.

Patient 4190, a 42-year-old patient, with metastatic breast carcinoma was originally treated with right breast local excision in December 1997 (estrogen receptor-/progesterone receptor-positive, axillary nodes-negative) followed by radiotherapy. This patient subsequently developed lung and bone metastases and received radiotherapy to her sternum in April 1998 followed by first-, second-, and third-line chemotherapy and hormonal therapy. The patient had been having monthly intravenous bisphosphonate therapy for 2 years prior to study entry. The patient's primary symptoms were fatigue, shortness of breath on exertion, and loss of appetite. Following the first dose of infliximab, the patient reported having more "energy" and being able to drive again. At week 4, the patient had gained 2 kg resulting from an improved appetite and was resuming previous activities; although, the patient's FSS score improved by only 5 points. At week 8, activity levels were maintained and, the patient reported feeling much improved. Following the patient's third

Table 4 Listing of clinical assessments

	Week 0	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44
Patient 1120													
BMI	22.2	22.2	21.9										
TNFα	6.9	–	0.5										
IL-6	20.9	–	217.7										
CRP	100	–	308										
Leptin	3.4	–	0.7										
CEA	4402	–	8557										
Patient 2160													
BMI	24.6	24	24.9	24.7									
TNFα	13.3	–	2.67	4.7									
IL-6	41.4	–	55	26.5									
CRP	49	–	15	76									
Leptin	8.5	–	3.9	5.8									
Patient 3180													
BMI	22.2	22.6	22.2	21.1									
TNFα	15.6	–	4.1	4.7									
IL-6	15.2	–	3.8	19.7									
CRP	24	–	16	45									
Leptin	3.2	–	1.8	0.6									
Patient 4190													
BMI	27.6	27.2	27.9	27	–								
TNFα	2.5	–	8.9	1.6	5.1								
IL-6	0.8	–	0	0	1.8								
CRP	7	–	7	10	8								
Leptin	35.8	–	28	28	13.2								
Patient 5210													
BMI	15.4	15.1	15.6	15.6	15.4	15.1							
TNFα	2.5	–	1.8	1.6	0	0							
IL-6	18.5	–	8.2	6.2	4.7	4.8							
CRP	6	–	4	11	12	18							
Leptin	0.1	–	0.1	0.1	0.1	0.1							
Patient 6200													
BMI	30.4	30.4	30	30.4	30.4	29.4	29.4	29.4	29	29	28.6	28	28.7
TNFα	2.5	–	8.9	0	0	0	1.4	0	–	–	–	–	–
IL-6	0.8	–	0	0	60.5	17.9	13.5	12.8	–	–	–	–	–
CRP	147	–	6	6	112	10	64	18	62	29	55	26	21
Leptin	18	–	22.5	20.2	14.8	13.7	–	–	–	–	–	–	–

BMI = mg/kg^2, TNFα = pg/ml, IL-6 = pg/ml, CRP = mg/l, Leptin = ng/ml
BMI = body mass index, TNFα = tumor necrosis factor alpha, IL-6 = interleukin -6, CRP = C-reactive protein

dose of infliximab, she developed *Listeria monocytogenes* septicemia, and at week 12, was withdrawn from the study.

Patient 5210, a 54-year-old patient, had squamous cell carcinoma of the left tonsil (T4). The patient's cancer had been treated with radical chemoradiation followed by 10 fractions of radiotherapy to a right neck recurrence. Poor appetite and fatigue were the major symptoms experienced by the patient. At week 4, there was clear subjective improvement in activity with less fatigue and improved appetite reflected in improved FSS and VAS appetite scores. Also of note, IL-6 and leptin levels declined. The patient maintained this improvement through week 16, but developed a new right-sided neck mass and was withdrawn from the study in anticipation of chemotherapy.

Patient 6200, a 71-year-old patient, had non-small cell lung carcinoma that was diagnosed in October 2002. The patient received 12 fractions of radiotherapy to a right lung mass that were completed in January 2003, followed by two cycles of chemotherapy through June 2003, during which he had progressive disease. Fatigue, shortness of breath, sweats, and loss of appetite were the major symptoms experienced by the patient. Fatigue was reduced following infliximab treatment, corresponding with a decrease in his FSS score. Appetite also improved. Of note, the CRP level decreased after the first infliximab dose. This decrease in CRP was maintained with some variation attributed to several intermittent chest infections which all responded to oral antibiotics. The patient

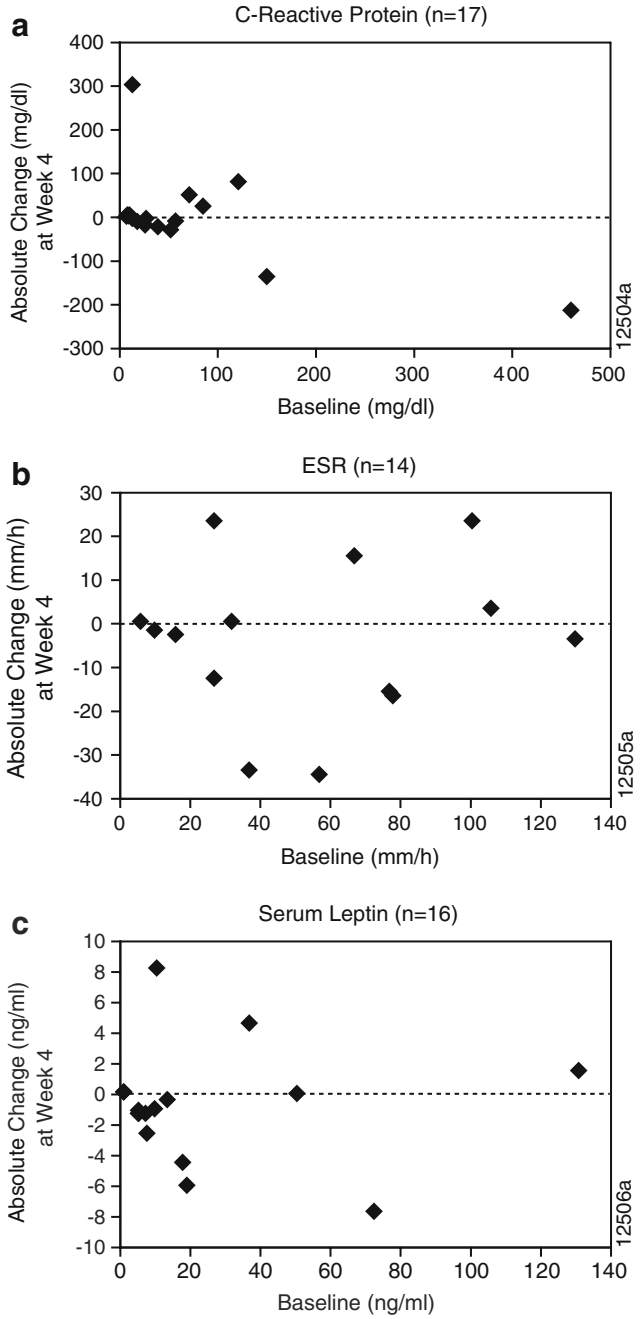

Fig. 6 C-reactive protein, erythrocyte sedimentation rate, and leptin: change from baseline at week 4

maintained improvement for 60 weeks and had received 16 infliximab doses before developing progressive disease with bone metastases and laryngeal nerve palsy, at which point the patient was withdrawn from the study.

Clinical laboratory assessments

While no formal statistical tests were performed, most patients appeared to have modest improvements in their serum CRP, ESR, or leptin levels at week 4 (Fig. 6a to c) following an infusion of infliximab 5 mg/kg at week 0.

Safety

Five serious adverse events occurred during this study (Table 5). Two of which were infections that occurred in women with metastatic breast carcinoma, and were considered by the investigators to be related to infliximab therapy. One of the serious infections occurred in a 61-year-old woman with an 8-year history of breast carcinoma with widespread bone metastases and chest wall recurrence. This patient died 6 days after her second infliximab dose (given at week 2) and a postmortem examination revealed bacterial meningitis due to a gram-positive coccus. The second serious infection occurred in a 42-year-old woman with a 6-year history of breast carcinoma with bone and pulmonary metastases. This patient developed septicemia due to *Listeria monocytogenes* following her fourth infliximab dose. Infliximab therapy was discontinued, and the patient was hospitalized and successfully treated with intravenous antibiotics.

Three other serious adverse events were considered to be unrelated to infliximab therapy, but related either to disease progression or comorbidities (Table 5). One patient experienced a nonserious infusion reaction, manifested by flushing and bronchospasm. The infusion was discontinued and intravenous antihistamine, hydrocortisone, and nebulized salbutamol were administered, leading to full recovery. This patient was successfully retreated with infliximab 13 days later following prophylactic paracetamol, chlorpheniramine, and hydrocortisone.

Discussion

The results of this study did not show an overall improvement in fatigue in patients with end-stage cancer in a hospice setting. It is interesting to note, however, that consistent improvement in subjective and clinical assessments was observed in a small cohort of patients (6 of 17,

Table 5 Serious adverse events and relationship to study medication

Diagnosis	Serious adverse event	Relationship
Squamous cell carcinoma of cervix	Bowel obstruction[a]	No
Metastatic breast carcinoma	Bacterial meningitis (gram-positive coccus)[a]	Possibly
Metastatic colorectal carcinoma	Jaundice and general deterioration	No
Metastatic renal cell carcinoma	Myocardial infarction	No
Metastatic breast carcinoma	*Listeria* septicemia	Yes

[a] The patient received an infliximab dose at week 2.

35%) who received infliximab. While there was no apparent association between clinical and subjective assessments in patients treated with infliximab, these findings provide us with useful data for further discussion. The presence of fatigue and the level of serum TNFα at baseline were not directly related, which demonstrates that the mechanism of cancer-related fatigue is more complex than the production of TNFα alone. As expected, we found low leptin levels in cachectic patients since leptin is produced in adipose tissue and those patients who were cachectic had low or undetectable leptin levels.

Six patients appeared to have uniform subjective and clinical benefit, with one particularly striking example. This prototypic patient had a history of non-small cell lung carcinoma that was progressive through chemotherapy, suggesting a poor prognosis. However, the patient remained clinically and radiologically stable for 16 months during which infliximab 5 mg/kg was administered every 4 weeks. The patient had a low baseline TNFα level. However, the markedly increased baseline CRP level decreased dramatically upon initiation of infliximab therapy. It is not possible to say whether infliximab acted to mitigate symptoms or slow the progression of end-stage cancer in this particular patient, but studies are currently underway to evaluate this possibility. What remains unknown is whether the absolute level of serum TNFα correlates with symptoms or whether there is an individual variation in sensitivity. It is worth noting that the enzyme-linked immunosorbent assay used to measure TNFα concentrations measures not only unbound TNFα, but also antibody-bound TNFα.

Our study was an interventional pilot study with the primary aim of determining whether infliximab could improve fatigue in patients with advanced cancer. Translational research, such as this, is unusual in palliative care and we have demonstrated that it is possible to carry out such work. We have also shown that prospective interventional studies are acceptable to palliative care patients and that there is a group of patients willing to participate in such studies.

There are several limitations to our study. Our sample size was too small to perform formal statistical analyses, and thus, the results are entirely descriptive in nature. Although we enrolled 17 patients into this study, we did not achieve our target of 30 patients over a 12-month recruitment period. The design of this pilot study did not include a control group; thus, we do not know the comparative value that our results may have on disease progression. Despite the open-label, exploratory nature of this study, we recommend that future studies use a control group. However, we acknowledge that given the clinical scenario of rapidly progressive disease, a genuine control population is difficult to recruit and ethically challenging. Had it been possible to recruit patients earlier in their disease course, there would be potential for a longer follow-up period. Furthermore, it remains unknown whether or not significant debilitation in patients could have been delayed if symptoms were treated more aggressively earlier in their disease course.

We did document observable clinical benefit in a small subset of patients. As observed in other patient populations treated with infliximab, physicians must remain vigilant for the occurrence of signs and symptoms of infection. Our study did not reveal any clinical or biochemical features predictive of response to infliximab, but the possibility remains that such characteristics could be determined, with further investigation.

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