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The relationship between the insulin-like growth factor-1 axis, weight loss, an inflammation-based score and survival in patients with inoperable non-small cell lung cancer.

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Running Title: Insulin-like growth factor-1 axis in non-small cell lung cancer.

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Abstract

Background and aims: The involvement of a systemic inflammatory response, as evidenced by the Glasgow Prognostic Score (GPS), is associated with weight loss and poor outcome in patients with non-small cell lung cancer. There is good evidence that nutritional and functional decline in patients with advanced malignant disease is associated with catabolic changes in metabolism. However, defects in anabolism may also contribute towards nutritional decline in patients with cancer. The aim of the present study was to examine the relationship between IGF-1 and IGFBP-3, performance status, mGPS and survival in patients with inoperable NSCLC.

Methods: 56 patients with inoperable NSCLC were studied. The plasma concentrations of IGF-1, IGFBP-3 and leptin were measured using ELISA and RIA.

Results: The patients were predominantly male (61%), over 60 years old (80%), with advanced (stage III or IV) disease (98%), with a BMI ≥ 20 (84%), an ECOG-ps of 0 or 1 (79%), a haemoglobin (59%) and white cell count (79%) in the reference range. On follow-up 43 patients died of their cancer. On univariate analysis, BMI ($p<0.05$), Stage ($p<0.05$), ECOG-ps ($p<0.05$), haemoglobin ($p<0.05$), white cell count ($p<0.05$) and mGPS ($p<0.05$) were associated with cancer specific survival. There was no association between age, sex, treatment, IGF-1, IGFBP-3, IGF-1:IGFBP-3 ratio, or leptin and cancer specific survival. With an increasing mGPS concentrations of haemoglobin ($p<0.005$) and IGFBP-3 ($p<0.05$) decreased. mGPS was not associated with either IGF-1($p>0.20$), or leptin ($p>0.20$).

Conclusions: In summary, the results of this study suggest that anabolism (IGF-1 axis) does not play a significant role in the relationship between nutritional and functional decline, systemic inflammation and poor survival in patients with inoperable NSCLC.

Non-standard abbreviations: GPS: Glasgow prognostic score, IGF-1: Insulin-like growth factor-1, IGFBP-3: Insulin-like growth factor binding protein –3, NSCLC: Non-small cell lung cancer

Key words: Insulin-like growth factor-1, IGF-binding protein-3, weight loss, C-reactive protein, albumin, non-small cell lung cancer.

Introduction

Non-small cell lung cancer (NSCLC) is the most common cause of cancer-related death in the world, responsible for over 600,000 deaths each year[1]. In the United Kingdom, there are over 30,000 new cases registered per year, with only 7% of these patients alive at five years[2]. Many patients present with advanced inoperable disease, have cachexia, poor performance status and poor survival[3].

Nutritional and functional decline in cancer patients is associated with disordered metabolism, particularly the development of a systemic inflammatory response[4,5]. This systemic inflammatory involvement, as evidenced by elevated circulating concentrations of C-reactive protein and hypoalbuminaemia (Glasgow Prognostic score, GPS), is a normal response to an insult which, when prolonged in cancer, becomes detrimental to the patient, being associated with cachexia, poor performance status and reduced survival in patients with a variety of common solid tumours[6-8]. These deleterious consequences have been attributed, in part, to the production of inflammatory cytokines, in particular interleukin 1-beta and interleukin-6[9-11], which exert a directly catabolic effect on skeletal muscle and other host tissues[12-13]. Indeed, Krzystek-Korpacka and colleagues[14] recently reported that the GPS was associated with increased weight loss and elevated concentrations of IL-1, IL-6, IL-8, TNF-alpha, VEGF-A and midkine concentrations.

However, although defects in anabolism may encourage and maintain this deleterious state of catabolism, few studies have addressed the relationship between the systemic inflammatory response and anabolic mediators of metabolism in patients with advanced cancer[15-17]. The insulin-like growth factor-1 (IGF-1) axis is an important regulator of anabolism, which may be deregulated in advanced cancer[15,18]. The majority of IGF-1 in human serum circulates in association with IGF-binding protein-3, which prolongs its half-life but reduces its bioactivity.

The aim of the present study was to examine the relationship between IGF-1, IGFBP-3, weight loss and the systemic inflammatory response in patients with inoperable non-small cell lung cancer.

Patients and Methods

Patients

      Patients presenting to a multidisciplinary oncology clinic at the Royal Infirmary between November 2003 and April 2004, with inoperable NSCLC were included in the study. All patients had cytologically or histologically confirmed disease and were staged on the basis of clinical findings, chest X-ray, and where appropriate, bronchoscopy, liver ultrasound, isotope bone scan and computerized tomography of the thorax, according to the American Thoracic Society TNM classification. Patients were excluded if they had any history of metabolic or endocrine disorders, or were on oral corticosteroid therapy. Healthy subjects were recruited from a cardiovascular risk factor clinic to form a control group.

      The study was approved by the Ethics Committee of Glasgow Royal Infirmary. All participants were informed of the purpose of the study prior to entry and gave written, informed consent.

Methods

      The body mass index (BMI), extent of weight loss and ECOG performance status were measured at the time of diagnosis. A fasting blood sample was taken at the clinic for routine laboratory analysis of white cell count and serum concentrations of haemoglobin, C-reactive protein, albumin and glucose. The inter- and intra-assay variability in each case was less than 10%. The minimal detectable concentration of C-reactive protein was 6mg/l.

      A further blood sample was taken, placed immediately on ice and centrifuged at 1000g for 15 minutes at 4°C. The plasma was then frozen at -20°C for batch analysis of circulating concentrations of IGF-1 and IGFBP-3.

      All measurements were carried out prior to treatment.

The enzyme-linked immunosorbant assay (ELISA) method was employed for quantification of IGF-1 and IGFBP-3. IGF-1 concentrations were measured using a commercial Octeia IGF-1 kit (Immunodiagnostic Systems, Boldon, UK) with a minimum detection limit of 1.9µg/L. IGFBP-3 concentrations measured using a commercial Quantikine ELISA kit (R&D Systems Europe Ltd, Abingdon, UK) with a minimum limit of detection limit of 0.04µg/L. All samples were analysed in duplicate and the mean value was calculated. The inter- and intra-assay variabilities were consistently less than 10%.

Leptin was quantified by an in-house radio-immunoassay, which has been described and validated elsewhere[19].

The GPS was constructed as previously described[7]. Briefly, patients with both an elevated C-reactive protein (>10mg/l) and hypoalbuminaemia (<35g/l) were allocated a score of 2. Patients with only one of these biochemical abnormalities were allocated a score of 1. Patients in whom neither of these abnormalities was present were allocated a score of 0. Recently, however, this has been modified based on evidence that hypoalbuminaemia, without an elevated C-reactive protein concentration, had no significant association with cancer specific survival. Therefore, patients with an elevated C-reactive protein were assigned a modified GPS score (mGPS) of 1 or 2 depending on the absence or presence of hypoalbuminaemia[20]. The rationale for the development of the GPS has been described previously[8] and the prognostic value of the combination of C-reactive protein and albumin has validated in a variety of common solid tumours[21].

Statistical Analysis

Grouping of the variables age, BMI, ECOG-ps, haemoglobin and white cell count was carried out using standard thresholds[22-24]. Survival analysis of the variables was performed using the Cox proportional hazard model. Deaths up to the end of February 2008 were

included in the analysis. Multivariate survival analysis, including all significant covariates

(P<0.05 to account for multiple comparisons) was performed using a stepwise backward

procedure to derive a final model of the variables that had a significant independent

relationship with survival. To remove a variable from the model, the corresponding P-value

had to be greater than 0.05. The relationships between the mGPS and other variables were

analysed using the Mantel–Haenszel (X^2) test for trend as appropriate. Analysis was

performed using SPSS software (SPSS Inc., Chicago, IL, USA).

Results

The characteristics of the 56 patients with inoperable NSCLC are shown in Table 1. The patients were predominantly male (61%), over 60 years old (80%) with advanced (stage III or IV) disease (98%). The majority of patients had a BMI $\geq$20 (84%), had an ECOG-ps of 0 or 1 (79%), had a haemoglobin (59%) and white cell count (79%) in the reference range.

The minimum follow-up was 48 months and the median follow-up of the survivors was 54 months. During this period, 43 (77%) died of their cancer. On univariate analysis, a low BMI ($p<0.05$), poor ECOG-ps ($p<0.05$) and low haemoglobin ($p<0.05$) were associated with cancer specific survival. In contrast, increasing TNM stage ($p<0.05$), white cell count ($p<0.05$) and mGPS ($p<0.05$) were associated with cancer specific survival. There was no association between age, sex, treatment, IGF-1, IGFBP-3, IGF-1:IGFBP-3 ratio, or leptin and cancer specific survival. On multivariate analysis of significant variables, only increasing white cell count ($p<0.05$), TNM stage ($p<0.005$) and mGPS ($p<0.001$) retained statistical significance.

The relationship between the mGPS and the clinicopathological characteristics of the patients with inoperable NSCLC are shown in Table 2). Age, sex, BMI, stage, ECOG-ps, white cell count, IGF-1, leptin and treatment were similar across the mGPS groups. With an increasing mGPS concentrations of haemoglobin ($p<0.005$) and IGFBP-3 ($p<0.05$) decreased. Also, there was a trend towards an increase in the IGF-1: IGFBP-3 ratio ($p<0.1$) as mGPS increased.

Discussion

In the present study there was no significant association between IGF-1, IGFBP-3, IGF-1:IGFBP-3 ratio, or leptin and survival. In contrast, the inflammation based prognostic score the mGPS, was independently associated with survival. Also with an increasing mGPS, IGFBP-3 concentrations were significantly decreased whereas there was no significant association with either IGF-1 or leptin. Taken together these results would suggest that anabolism (IGF-1 axis) plays a minor role in the relationship between nutritional and functional decline, systemic inflammation and poor survival in patients with inoperable NSCLC.

Recently there has been considerable speculation regarding the involvement of the IGF-1 axis in the aetiology of lean tissue loss in cancer[25,26]. IGF-1 is the downstream mediator of growth hormone (GH) action thus representing a key pathway in anabolism in health. Indeed, several studies have reported a reduction in circulating concentrations of IGF-1 in malignant disease, which may also have been be associated with nutritional decline[15,27,28]. In the present study, the median weight loss in patients was 1% which may explain why concentrations of IGF-1 were not significantly altered. The present study did not address the possibility of receptor resistance to IGF-1 action, and the possibility remains that ineffective IGF-1 action contributes towards cancer cachexia.

In the present study, the circulating concentrations of IGF-1 and IGFBP-3 of patients with inoperable NSCLC were not associated with body mass index or survival. However, when grouped according to mGPS score, levels of IGFBP-3 were significantly lower in patients with a higher mGPS. As IGFBP-3 binds to and sequesters IGF-1, reducing its bioactivity but prolonging its half-life, low concentrations of IGFBP-3 may contribute to an enhanced but short-lived action of IGF-1 in the patient. Also, Crown and co-workers[17] reported that circulating concentrations of IGF-1 and IGFBP-3 were unchanged in 30 patients

with NSCLC. They reported a negative correlation between the ratio of intact /total IGFBP-3 and the initial body weight of the cancer patients, suggesting that less IGFBP-3 proteolytic activity was associated with more weight loss, possibly by maintaining a high IGF-1 binding capacity, and reducing IGF-1 bioavailability to the tissues. However, it is possible the reduced concentrations of IGFBP-3 merely reflect the reduction in hepatic protein synthesis, following a systemic insult of this nature. IGFBP-3 is also known to inhibit cell growth independently of IGF-1 and may have a role in mediating apoptosis[29]. These results suggest that major alterations in the IGF-1 axis do not occur prior to significant weight loss or as a result of the systemic inflammatory response. Moreover, the present study questions whether IGF-1 axis has any association with prognosis in patients with inoperable NSCLC.

It is increasingly recognised that systemic inflammation is an important factor in the progressive loss of lean tissue in cancer patients[4,6,30]. In light of the above studies on the IGF-1 axis[15,17] it is possible that the increased systemic inflammation-driven demand for amino acids for increased hepatic synthesis of acute phase proteins[31], maintenance of albumin synthesis[32] and increased glucose production[33] is the main factor in the progressive loss of lean tissue in cancer patients. This is consistent with the evidence that moderation of the systemic inflammatory response is a useful approach to the management of the loss of weight and lean tissue in cancer patients[34,35].

The main limitations of the present study were that small numbers of patients were studied and only baseline measurements were included in the analysis. Furthermore, the patient recruitment from an outpatient clinic may have biased the population towards those with less weight loss and a better performance status since those patients with more weight loss and poorer performance status are less likely to attend such clinics. Therefore, longitudinal measurements of the relationship between weight loss, IGF-1, IGF-BP3 and the systemic inflammatory response during the progression of the disease would have been of

interest to corroborate the cross sectional results. Nevertheless, the present baseline data, at

diagnosis and with mature survival follow-up, are important as they have clinical relevance

since they identify patients who may benefit from early nutritional or therapeutic intervention.

In summary, the results of this study suggest that anabolism (IGF-1 axis) does not play

a significant role in the relationship between nutritional and functional decline, systemic

inflammation and poor survival in patients with inoperable NSCLC.

Conflict of interest

There is no conflict of interest to declare.

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Table 1. Prognostic factors of patients with NSCLC.

	Patients (n= 56)	Hazard ratio (95% CI)	P- value
Age (<60/ ≥60 years)	11/ 45	0.792 (0.38-1.66)	0.536
Sex (M/F)	34 / 22	1.13 (0.61-2.08)	0.704
BMI (≥20/ <20)	47/ 9	2.33 (1.07-5.08)	0.034
Stage (II/ III/ IV)	1/ 29/ 26	1.81 (1.02-3.20)	0.042
ECOG-ps (0/ 1/ 2)	20/ 24/ 12	1.62 (1.07-2.44)	0.021
Haemoglobin (≥12/ <12 g/dl)	33/ 22	1.87 (1.01-3.46)	0.047
White cell count (≤11/ >11 10^9/l)	44/ 12	2.42 (1.21-4.87)	0.013
IGF-I (μg/L) tertiles	102.01 (16.00-310.00)*	1.35 (0.93-1.95)	0.116
IGFBP-3 (ng/mL) tertiles	2147.38 (58.92-4881.09)*	1.27 (0.87-1.87)	0.215
IGF-I:IGFBP-3 tertiles	0.04 (0.02-0.27)*	1.02 (0.71-1.47)	0.913
Leptin (ug/l) tertiles	8.35 (1.00-103.00)*	0.78 (0.54-1.13)	0.194
Treatment (active/ palliative)	46/ 10	0.93 (0.41-2.09)	0.862
mGPS (0/ 1/ 2)	19/ 31/ 6	2.10 (1.30- 3.40)	0.002

*Median (range)

Table 2. Characteristics of patients with NSCLC grouped according to mGPS.

	mGPS 0 (n=19)	mGPS 1 (n=31)	mGPS 2 (n=6)	P- value
Age (<60/ ≥60 years)	3/ 16	7/ 24	1/ 5	0.768
Sex (M/ F)	12/ 7	17/ 14	5/ 1	0.699
BMI (≥20/ <20)	17/ 2	26/ 5	4/ 2	0.229
Stage (II/ III/ IV)	0/ 8/ 11	1/ 18/ 12	0/ 3/ 3	0.383
ECOG-ps (0/ 1/ 2)	9/ 8/ 2	9/ 14/ 8	2/ 2/ 2	0.143
Haemoglobin (≥12/ <12 g/dl)	16/ 3	16/ 14	1/ 5	0.002
White cell count (≤11/ >11 10^9/l)	15/ 4	26/ 5	3/ 3	0.358
IGF-I (ug/L) tertiles	7/ 9/ 3	10/ 7/ 14	1/ 4/ 1	0.292
IGFBP-3 (ng/mL) tertiles	2/ 8/ 9	13/ 11/ 7	3/ 1/ 2	0.035
IGF-I:IGFBP-3 tertiles	10/ 5/ 4	5/ 12/ 14	3/ 2/ 1	0.271
Leptin (ug/l) tertiles	6/ 6/ 6	7/ 12/ 12	5/ 0/ 0	0.174
Treatment (active/ palliative)	16/ 3	25/ 6	5/ 1	0.859