ORIGINAL ARTICLE

The relationship between an inflammation-based prognostic score (Glasgow Prognostic Score) and changes in serum biochemical variables in patients with advanced lung and gastrointestinal cancer

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Background: The Glasgow Prognostic Score (GPS), an inflammation-based prognostic score formed from standard thresholds of C reactive protein (CRP) and albumin, has prognostic value in patients with advanced cancer. Little is known about the general biochemical disturbance associated with the systemic inflammatory response in cancer.

Aim: To examine the relationship between the GPS and blood biochemistry in patients with advanced lung and gastrointestinal cancer.

Methods: The GPS (albumin <35 g/l = 1 and CRP >10 mg/l = 1 combined to form a prognostic score of 0 (normal) and 1 or 2 (abnormal)) and a variety of biochemical variables were examined in patients ($n=50$) with advanced lung or gastrointestinal cancer and in a healthy control group ($n=13$).

Results: The GPS was normal in all the controls, but abnormal in 78% of the cancer group. Serum levels of sodium, chloride, creatine kinase, zinc and vitamin D were lower in the cancer group (all $p<0.01$), whereas levels of calcium, copper (both $p<0.05$), alkaline phosphatase, γ -glutamyl transferase (both $p<0.001$) and lactate dehydrogenase ($p<0.10$) were raised. In the patient group, with increasing GPS, there was a median reduction in Karnofsky Performance Status (25%), haemoglobin (22%), sodium (3%), zinc (15%) and survival (93%, all $p<0.05$) and a median increase in white cell count (129%), alkaline phosphatase (217%), γ -glutamyl transferase (371%) and lactate dehydrogenase (130%, all $p<0.05$). CRP levels were strongly and similarly correlated with alkaline phosphatase and γ -glutamyl transferase, accounting for more than 25% of the variation in their activities.

Conclusion: Several correlations were seen between biochemical variables and increasing GPS. In particular, chronic activation of the systemic inflammatory response in cancer was associated with increase in γ -glutamyl transferase and alkaline phosphatase activity in patients with advanced lung and gastrointestinal cancer.

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Progressive malignant disease is often associated with a complex biochemical and metabolic disturbance, which results in the syndrome of cancer cachexia. Some biochemical abnormalities in patients with advanced cancer are related to tumour burden whereas others appear not to be. For example, tumour volume in patients with colorectal liver metastases has been reported to be correlated with increased transaminase activity and bilirubin. By contrast, other biochemical variables such as albumin are more closely associated with a systemic inflammatory response as evidenced by raised circulating levels of C reactive protein (CRP).¹

Increasing evidence that CRP has prognostic value, independent of stage and performance status (both Karnofsky and Eastern Cooperative Oncology Group), is observed in patients with advanced cancer.^{2–5} Recently, a cumulative score (Glasgow Prognostic Score, GPS) formed from the combination of standard thresholds of CRP and albumin has been shown to have additional prognostic value in patients with advanced lung^{6,7} and gastrointestinal cancer.⁸ Stage and performance status in these patients may have less prognostic value as they reflect the patient's status at a specific point in time. By contrast, the GPS, based as it is on hypoalbuminaemia and the presence of an ongoing systemic inflammatory response, reflects current nutritional status and also predicts continuing nutritional decline of the patient.^{9–11} It has also been suggested that the GPS may be useful as a framework for identifying

inflammation-derived symptoms in patients with advanced cancer.¹²

Little is known about the general biochemical disturbance associated with the systemic inflammatory response in cancer. Therefore, our study examined the relationship between the GPS and blood biochemistry in patients with advanced lung and gastrointestinal cancer.

MATERIALS AND METHODS

Patients

Patients with a firm clinical or histological diagnosis that was not amenable to curative treatment were recruited from two palliative care centres and an associated hospital—Strathcarron Hospice (Denny), Marie Curie Hospice (Glasgow) and Stobhill Hospital NHS Trust (Glasgow). Patients were identified as suitable for the study by medical or nursing staff in the wards at each centre, the respiratory/oncology outpatient clinic, the hospice day centres or by the hospice community specialist palliative care nurses. Patients were excluded from the study if they had received surgery, chemotherapy or radiotherapy within the previous month or had an active connective tissue disease.

Abbreviations: CRP, C reactive protein; GPS, Glasgow Prognostic Score; KPS, Karnofsky Performance Status

Table 1 Characteristics and inflammatory variables of healthy controls and patients with advanced lung and gastrointestinal cancer

	Healthy controls (n = 13)	Patients with cancer (n = 50)	p Value
Sex (m:f)	6:7	30:20	0.369
Age (years)	65 (46–74)	64 (38–81)	0.878
BMI	25.2 (22.0–28.9)	21.4 (14.8–33.3)	0.002
KPS	100 (90–100)	70 (30–100)	<0.001
Haemoglobin (g/dl)	14.4 (12.3–16.1)	12.3 (9.1–16.3)	0.001
White cell count (10 ⁹ /l)	6.0 (4.1–7.7)	10.2 (5.0–27.2)	<0.001
Platelets (10 ⁹ /l)	223 (178–317)	295 (78–682)	0.020
CRP (mg/l)	<10 (<10–<10)	49 (<10–214)	<0.001
≤10 or >10 mg/l	13/ 0	11/ 39	<0.001
Albumin (g/l)	44 (41–47)	39 (23–45)	<0.001
≥35 or <35 g/l	13/ 0	37/ 13	0.033
GPS 0	13	11	
1	0	26	
2	0	13	<0.001

BMI, body mass index; CRP, C reactive protein; GPS, Glasgow Prognostic Score; KPS, Karnofsky Performance Status. Values are in median (range).

A group of age-matched and sex-matched healthy volunteers were recruited as a control group from Strathcarron Hospice and also through personal contacts at the University of Glasgow.

The study was approved by the local ethics committees of the participating units. All patients and controls were aware of the purpose of the study and gave written, informed consent.

Methods

Blood samples were taken from patients and volunteers. Although neither patients nor volunteers had undergone a fast, the samples were not taken during the immediate post-prandial period. Glucose, urea, sodium, potassium, chloride, bicarbonate, creatinine, calcium, phosphate, albumin, alkaline phosphatase, aspartate transaminase, alanine transaminase, γ -glutamyl transferase, lactate dehydrogenase, creatine kinase and CRP levels were assayed on an Olympus AU5200 analyser (Olympus Optical, Tokyo, Japan) using Olympus reagents. Intra-assay and interassay coefficients of variation were better than 5% and 10%, respectively. The calcium concentrations were adjusted for albumin, with the normal albumin concentration considered to be 44—that is, adjusted calcium = measured calcium + ((44 – measured albumin) $\times$ 0.02).

Magnesium, zinc and copper levels were measured by atomic absorption spectrophotometry on a Perkin-Elmer 1100B analyser (Perkin-Elmer, Norwalk, Connecticut, USA). Intra-assay and interassay coefficients of variation were better than 10%.

White cell and platelet counts and haemoglobin levels were measured using the Sysmex method on a SYSMEX NE 8000 analyser (TOA Medical Electronics Co., Kobe, Japan). Intra-assay and interassay coefficients of variation were better than 10%.

The serum 25-hydroxycholecalciferol (the main circulating metabolite of vitamin D) level was assayed by an Equilibrium Radio-Immunoassay procedure using an Incstar ¹²⁵I-RIA Kit (Diasorin, Stillwater, Minnesota, USA) and a Packard Cobra 5005 γ counter (Packard Instrument Co., Meriden, Connecticut, USA). Intra-assay and interassay coefficients of variation were better than 10%.

The Karnofsky Performance Status (KPS) was used as an observer-rated measure of functional ability and assessed by a single investigator (DJFB).

The Glasgow Prognostic Score (GPS) was formed from albumin and CRP as previously described.^{6,7} Briefly, hypoalbuminaemia

(<35 g/l = 1) and a raised CRP (>10 mg/l = 1) were combined to form a prognostic score (0, 1 and 2).

Statistics

Data are presented as medians, with ranges. Where appropriate, group comparisons were made using contingency table analysis (χ^2) and the Mann-Whitney U test. Associations with biochemical variables were analysed using Spearman's rank correlation coefficient. Analysis was carried out with SPSS software (SPSS, Chicago, Illinois, USA).

RESULTS

A total of 13 healthy controls and 50 patients with advanced cancer (38 lung and 12 gastrointestinal) participated in the study (table 1).

Most patients had metastatic disease. The controls and patients with cancer were similar in terms of sex and age. The patients with cancer had a significantly lower body mass index (BMI (weight (kg)/(height (m)²)); $p < 0.01$), lower albumin and haemoglobin levels and a poorer KPS ($p \leq 0.001$) compared with the control group. By contrast, the patients with cancer had higher white cell counts ($p < 0.001$), higher platelet counts ($p < 0.05$) and higher CRP levels ($p < 0.001$). As a result, the cumulative prognostic score of CRP and hypoalbuminaemia (GPS) was markedly raised in the patients with cancer. All patients who had hypoalbuminaemia ($n = 13$) had a raised CRP level.

Circulating levels of sodium ($p < 0.01$), chloride ($p < 0.001$), creatinine kinase ($p < 0.001$), zinc ($p < 0.001$) and vitamin D ($p < 0.01$) were lower, whereas calcium ($p < 0.05$), copper ($p < 0.05$), alkaline phosphatase ($p < 0.001$), γ -glutamyl transferase ($p < 0.001$) and lactate dehydrogenase ($p < 0.10$) were higher in the patients with cancer (table 2).

Patients with cancer were grouped according to the Glasgow Prognostic Score (0, 1, 2; table 3). All but 5 (10%) of the patients died during follow-up. Age, sex and BMI were similar in the GPS groups. Significant reductions were observed in KPS ($p < 0.01$), haemoglobin ($p < 0.05$), sodium ($p < 0.01$), zinc ($p < 0.01$) and survival ($p < 0.01$) with an increasing GPS. By contrast, an increase was seen in white cell count ($p < 0.01$), alkaline phosphatase ($p < 0.01$), γ -glutamyl transferase ($p < 0.05$) and lactate dehydrogenase ($p < 0.05$).

KPS was correlated with albumin ($r_s = 0.61$; $p < 0.001$) and CRP ($r_s = -0.42$; $p = 0.002$); haemoglobin was correlated with albumin ($r_s = 0.49$; $p < 0.001$) and CRP ($r_s = -0.41$; $p = 0.003$);

Table 2 Biochemical variables of healthy controls and patients with advanced lung and gastrointestinal cancer

	Healthy controls (n = 13)	Patients with cancer (n = 50)	p Value
Glucose (mmol/l)	6.2 (4.4–11.0)	6.2 (3.7–28.2)	0.641
Sodium (mmol/l)	139 (137–144)	137 (123–145)	0.004
Potassium (mmol/l)	4.4 (3.6–4.8)	4.4 (3.3–5.1)	0.864
Bicarbonate (mmol/l)	24.0 (22.0–27.0)	24.5 (19.0–30.0)	0.891
Chloride (mmol/l)	105 (100–106)	100 (88–110)	<0.001
Urea (mmol/l)	5.8 (4.3–17.7)	6.2 (2.0–17.6)	0.773
Creatinine (μmol/l)	91 (74–323)	87 (62–161)	0.333
Calcium (mmol/l)	2.31 (2.23–2.52)	2.38 (2.18–3.29)	0.024
Phosphate (mmol/l)	1.06 (0.77–1.60)	1.13 (0.56–1.59)	0.135
Bilirubin (μmol/l)	7 (7–14)	7 (2–171)	0.391
Alkaline phosphatase (U/l)	158 (108–197)	300 (106–2152)	<0.001
Aspartate transaminase (U/l)	19 (14–25)	18 (6–218)	0.341
Alanine transaminase (U/l)	18 (5–45)	22 (5–122)	0.168
γ-Glutamyl transferase (U/l)	14 (6–34)	65 (12–692)	<0.001
Lactate dehydrogenase (U/l)	352 (291–419)	408 (244–4074)	0.072
Creatine kinase (U/l)	105 (38–199)	35 (10–318)	<0.001
Magnesium (mmol/l)	0.83 (0.69–1.03)	0.87 (0.58–1.02)	0.640
Zinc (μmol/l)	12.4 (9.1–15.5)	9.6 (4.7–14.8)	<0.001
Copper (μmol/l)	18.2 (11.4–27.5)	21.2 (10.8–37.5)	0.020
Vitamin D (nmol/l)	35.0 (22.0–82.0)	21.0 (6.0–128)	0.002

Values are in median (range).

white cell count was correlated with albumin ($r_s = -0.41$; $p = 0.003$) and CRP ($r_s = 0.32$; $p = 0.027$); sodium was correlated with CRP ($r_s = -0.42$; $p = 0.003$) but not with albumin ($r_s = 0.26$; $p = 0.072$); zinc was similarly correlated with CRP ($r_s = -0.46$; $p = 0.002$) and albumin ($r_s = 0.40$; $p = 0.007$).

Alkaline phosphatase was correlated with CRP ($r_s = 0.52$; $p < 0.001$) and albumin ($r_s = -0.47$; $p = 0.001$); γ-glutamyl transferase was correlated with CRP ($r_s = 0.51$; $p < 0.001$) and albumin ($r_s = -0.34$; $p = 0.016$); lactate dehydrogenase was correlated with CRP ($r_s = 0.41$; $p = 0.003$) but not with albumin ($r_s = -0.17$; $p = 0.232$). Alkaline phosphatase was correlated with γ-glutamyl transferase ($r_s = 0.67$; $p < 0.001$) and lactate dehydrogenase ($r_s = 0.31$; $p = 0.032$); γ-glutamyl transferase was correlated with lactate dehydrogenase ($r_s = 0.39$; $p = 0.005$).

DISCUSSION

In this study, compared with controls, the presence of advanced cancer was associated with a pronounced systemic inflammatory response (higher CRP levels and white cell and platelet counts) and a cluster of biochemical abnormalities including enzymes (higher alkaline phosphatase, γ-glutamyl transferase, lactate dehydrogenase and lower creatine kinase activities), trace elements and vitamins (lower zinc and vitamin D, and higher copper levels) and lower sodium and chloride, and higher calcium levels. These results suggest that the blood biochemistry is markedly different in patients with advanced cancer. This confirms previous findings in patients with cancer.^{13–15}

When patients with cancer were grouped according to an inflammation-based prognostic score (GPS), a consistent increase in enzyme activities was seen. In particular, CRP levels

Table 3 Relationship between the systemic inflammatory response (GPS), biochemical variables and survival in patients with advanced lung and gastrointestinal cancer

	GPS 0 (n = 11)	GPS 1 (n = 26)	GPS 2 (n = 13)
Sex (m:f)	6:5	17:9	7:6
Age (years)	63 (51–74)	63 (38–80)	69 (51–81)
BMI	19.8 (15.8–31.0)	23.3 (16.6–33.3)	19.9 (14.8–29.9)
KPS	80 (60–100)	70 (40–90)*	60 (30–80)†
Haemoglobin (g/dl)	14.3 (10.4–16.3)	12.3 (9.6–15.2)	11.1 (9.1–14.2)*
White cell count (10 ⁹ /l)	8.1 (5.5–12.7)	10.6 (5.0–27.2)	10.4 (6.5–17.6)†
Platelets (10 ⁹ /l)	285 (158–347)	326 (152–682)	284 (78–598)
Sodium (mmol/l)	139 (135–145)	136 (123–144)*	135 (132–140)†
Chloride (mmol/l)	103 (97–109)	98 (88–110)*	100 (93–105)
Calcium (mmol/l)	2.35 (2.19–2.50)	2.41 (2.18–3.29)	2.36 (2.28–2.58)
Alkaline phosphatase (U/l)	242 (106–310)	301 (130–1144)	526 (141–2152)†
γ-Glutamyl transferase (U/l)	48 (21–256)	71 (12–357)	178 (14–692)*
Lactate dehydrogenase (U/l)	332 (269–466)	425 (244–1348)*	433 (276–4074)*
Creatine kinase (U/l)	38 (24–100)	30 (10–205)	28 (13–318)
Zinc (μmol/l)	11.0 (8.2–13.7)	9.5 (5.7–14.8)	9.4 (4.7–11.0)†
Copper (μmol/l)	19.6 (17.2–23.8)	23.4 (11.3–37.5)	20.5 (10.8–36.7)
Vitamin D (nmol/l)	26.0 (14.0–55.0)	19.5 (6.0–128.0)	19.5 (6.0–48.0)
Cancer type (lung:gastrointestinal)	9:2	20:6	9:4
Survival (months)	15.4 (6.6–24.2)	4.0 (2.3–5.6)	1.0 (0.5–1.4)†

BMI, body mass index; GPS, Glasgow Prognostic Score; KPS, Karnofsky Performance Status.

Values are in median (range).

* $p < 0.05$; † $p < 0.01$ compared with GPS 0.

were strongly and similarly correlated with alkaline phosphatase and γ -glutamyl transferase, accounting for more than 25% of the variation in their activities. Given that these enzymes are primarily synthesised and function intracellularly, this raises the question of whether this association with increased acute-phase protein production reflects enzyme induction by liver tissue or increased cellular permeability. Increased cell permeability would be consistent with the correlation between albumin concentration and the activities of alkaline phosphatase and γ -glutamyl transferase, although weaker than with CRP.

The increase of γ -glutamyl transferase activity by a systemic inflammatory response may also be important for regulating enzyme activity in the liver. It has recently been reported that cytochrome P450 activity is reduced in the systemic inflammatory response in patients with advanced cancer.¹⁶ This mechanism may account for the observation that a raised GPS is associated with a poor tolerance to chemotherapy in patients with inoperable lung cancer.⁷ Irrespective of this, the results of this study indicate that, along with its prognostic value, the GPS is associated with a cluster of biochemical changes and therefore measurement of the GPS may identify those patients with abnormal biochemical variables, in which the systemic inflammatory response has a role.

In summary, the presence of cancer and the activation of the acute-phase protein response are associated with an increase in γ -glutamyl transferase and alkaline phosphatase activity in patients with advanced lung and gastrointestinal cancer.

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