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An inflammation-based prognostic score and its role in the nutrition-based management of patients with cancer

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Progressive involuntary weight loss, in particular the loss of lean tissue, is common in patients with advanced cancer and has long been recognised to result in a deterioration in performance status and quality of life, increased morbidity and mortality. The aetiology of such weight loss or cachexia is complex and involves both tumour and host responses. Thus, identification of patients who are or are likely to become cachectic has been problematic. In addition to a reduction in appetite and increased satiety leading to poor dietary intake, there is now increasing clinical evidence that the activation of a chronic ongoing systemic inflammatory response is one of the earliest and most important contributory factors to cachexia. Such findings help to explain the failure of simple nutritional programmes to reverse weight loss adequately in patients with cancer. In the present paper the development of an inflammation-based score is described, which is derived from the acute-phase proteins C-reactive protein and albumin and is termed the Glasgow prognostic score (GPS). Its value as a predictor of survival, independent of tumour stage, performance status and treatment (active or palliative), has been shown in a variety of advanced common solid tumours. The nature of the relationship between the GPS, appetite, body composition, performance status and quality of life of the patient with advanced cancer will be described. Recently, it has become evident that the systemic inflammatory response is also present in a smaller proportion of patients with primary operable cancer and is also predictive of disease progression and poor survival. The role of GPS in clinical decision making will be discussed.

Cancer: Nutrition: Prognosis: Inflammation-based score

Cancer is the leading cause of death worldwide among individuals aged 35–64 years and globally is responsible for $>0.5 \times 10^6$ deaths annually. In the UK approximately one in three contract the disease in their life time and one in four of the population die from cancer[1].

Although much research is devoted to finding a cure for cancer, for the majority of patients with cancer the disease will progress either locally or become metastatic. Thus, anticipated survival is a major factor to be taken into consideration when deciding whether active intervention or palliation is appropriate.

Establishing the tumour stage of the patient has assumed paramount importance in the treatment of cancer.

However, it is becoming increasingly recognised that the information that tumour stage provides on disease progression is inadequate. In particular, it is well recognised that predicting life expectancy of patients with advanced cancer is difficult and clinicians often overestimate survival[2,3]. Current methods of assessing the suitability of such patients for treatment are usually based on host factors such as weight loss or performance status, since cancer patients who lose weight and have reduced performance status have a poorer prognosis than those who remain weight stable independent of tumour stage and anticancer therapies such as chemotherapy or radiotherapy treatment[4–6].

The clear link between weight loss, poor performance status and poor prognosis[7–9] is probably a result of the preferential loss of skeletal muscle[10–12]. It has been suggested that the loss of adipose tissue accounts for the majority of the weight loss, but the loss of muscle accounts for most of the morbidity and mortality[13,14].

However, the extent of weight loss that is prognostic is not well defined[15,16] and performance status is recognised to be subjective[17] and therefore their reliability has been questioned.

Aetiology of weight loss and reduced performance status

It is of interest that although the majority of patients with advanced cancer lose weight and have a poorer performance status, the extent varies according to tumour type. Patients with lung and gastrointestinal cancers tend to lose considerable amounts of weight and have reduced performance status early on in their illness.

Given that weight loss and reduced performance status are such an important problem in patients with cancer in terms of morbidity and mortality, the reversal of this process would seem to be a priority. However, the definitive method of treating these symptoms, i.e. removal of the tumour, is not an option in the majority of patients.

Weight loss results from an energy imbalance between energy intake and energy expenditure. This negative energy balance may, thus, be related to a reduced food intake, increased energy expenditure or a combination of both.

There have been many studies that have investigated the energy expenditure in patients with lung and gastrointestinal cancers[18–21]. Most studies have found an increased energy expenditure in patients with cancer who are losing weight, in contrast with the body's normal response to starvation that produces a reduced metabolic rate.

It has been reported that an elevated resting energy expenditure in patients with pancreatic cancer is associated with the presence of a systemic inflammatory response, as evidenced by an elevated C-reactive protein concentration[21]. Similar results have been reported in other tumour types associated with weight loss, including lung cancer[22,23].

It is therefore of interest that the presence of a systemic inflammatory response has also been shown to be associated with a reduction in the body cell mass (lean tissue) as measured by total body K[12,24].

Further evidence of the central importance of the systemic inflammatory response is that the use of anti-inflammatory agents is associated with moderation of weight loss and the maintenance of performance status and quality of life in patients with advanced cancer[25–27].

Development of a systemic-inflammation-based score

There are a myriad of systemic responses to inflammation in human subjects resulting from infection, tissue injury, immunological disorders or cancer. These responses
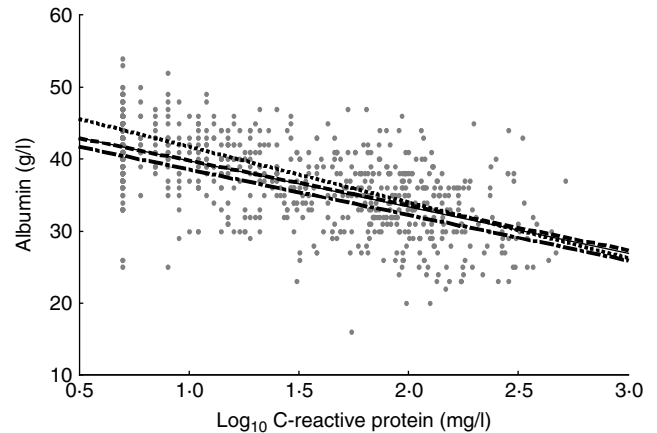

Fig. 1. Relationship between C-reactive protein and albumin in a variety of common solid tumours. (····), Colo-rectal cancer; (——), gastric cancer or breast cancer; (—·—), bronchogenic cancer. (From McMillan *et al.*[30].)

involve alterations in neuroendocrine metabolism (including the endocrine hormones), haematopoietic changes (including the IL, interferons and the haematopoietic growth factors), changes in protein and energy metabolism (including loss of muscle protein) and acute-phase proteins[28]. The liver is central to the elaboration of the systemic inflammatory response. Hepatocytes are stimulated to synthesise and release into the systemic circulation a variety of acute-phase proteins, such as C-reactive protein, which initiate or sustain the systemic inflammatory response.

The systemic inflammatory response, manifested by elevation of C-reactive protein, may simply reflect a non-specific inflammatory response secondary to tumour hypoxia and necrosis or local tissue damage because apoptosis is a relatively 'clean' form of cell death in that it does not elicit an inflammatory immune response. These features are distinct from cells undergoing necrosis as a result of acute cell damage or 'accidental' cell death[29].

In patients with cancer there is evidence of the stereotypical acute-phase protein response of C-reactive protein increasing and albumin falling, and this relationship is similar across different tumour types[30] (Fig. 1). C-reactive protein, because of its sensitivity, specificity and reproducibility of analysis in hospital laboratories, is most commonly used to assess the magnitude (whether acute or chronic) of the systemic inflammatory response[28,31]. Indeed, the magnitude of the increase in C-reactive protein concentrations has been shown to be associated with poorer survival in patients with cancer, particularly in patients with advanced disease[32–35].

It has been shown that in patients diagnosed with inoperable non-small-cell lung cancer and followed to death (*n* 106) there is, with increasing C-reactive protein concentrations from normal (<10 mg/l) to elevated (11–100 mg/l) and to highly-elevated (>100 mg/l), an increasing proportion of patients with >5% weight loss, poorer performance status and more fatigue[36]. Also, the more elevated the C-reactive protein concentration the

Table 1. Cumulative prognostic scores and survival in patients with inoperable non-small-cell lung cancer (n 161); univariate survival analysis (from Forrest et al.[38])

Combinations compared	n			Cumulative scores	Survival (months)		HR	95% CI	P
					Median	95% CI			
CRP and stage		CRP (mg/l)	Stage						
	14	≤10	III	0	18·2	14·5, 21·9			
	15		IV	1	10·4	7·9, 12·8			
	43	>10	III	1	8·9	5·5, 12·3	1·73	1·23, 2·33	<0·001
	89		IV	2	6·1	3·4, 8·7			
CRP and ECOG*		CRP (mg/l)	ECOG*						
	23	≤10	0–1	0	17·9	15·5, 20·3			
	6		2–4	1					
	68	>10	0–1	1	9·0	4·3, 13·6	1·79	1·37, 2·35	<0·001
	64		2–4	2	4·2	2·2, 6·2			
CRP and albumin		CRP (mg/l)	Albumin (g/l)						
	27	≤10	≥35	0	17·0	11·4, 22·6			
	2		<35	1					
	99	>10	≥35	1	8·9	6·3, 11·4	2·00	1·47, 2·70	<0·001
	33		<35	2	3·9	0·8, 7·1			
Stage and ECOG*		Stage	ECOG*						
	40	III	0–1	0	16·1	9·5, 22·6			
	17		2–4	1	9·7	3·5, 15·8			
	51	IV	0–1	1	10·4	5·8, 14·9	1·73	1·33, 2·24	<0·001
	53		2–4	2	3·6	1·7, 5·6			

CRP, C-reactive protein; HR, hazard ratio.
*Eastern Cooperative Oncology Group performance status, which assesses the well-being of patients with cancer and their ability to perform ordinary tasks[37].

lower the albumin concentrations and the poorer the cancer-specific survival, independent of tumour stage.

In order to examine how the prognostic value of an elevated C-reactive protein concentration (>10 mg/l) might be used clinically, the prognostic value of the combinations of C-reactive protein and stage, C-reactive protein and performance status (Eastern Cooperative Oncology Group performance status, which assesses the well-being of patients with cancer and their ability to perform ordinary tasks[37]), C-reactive protein and albumin (<35 g/l) together with stage and performance status were compared in 161 patients with inoperable non-small-cell lung cancer[38] (Table 1). On multivariate analysis, when the three scores based on the combinations of the systemic inflammatory response and stage, performance status and albumin were compared with the combination of stage and performance status, only the score based on the combination of the systemic inflammatory response and albumin (HR 1·70 (95% CI 1·23, 2·35); P<0·001) and the score based on stage and performance status (HR 1·48 (95% CI 1·12, 1·95); P = 0·006) were found to retain independent significance.

The combination of C-reactive protein and albumin into a score (0, 1, 2) has much to commend it, since it has independent prognostic value, is simple to measure, routinely available and well standardised. This score now termed the Glasgow prognostic score (GPS) has been defined as follows: patients with both an elevated C-reactive protein (>10 mg/l) and hypoalbuminaemia (<35 g/l) are allocated a score of 2; patients in whom only one of these biochemical abnormalities is present are allocated a score of 1; patients in whom neither of these abnormalities is present are allocated a score of 0. However, in the clinical study the score of 1 was most commonly found to be a result of an elevated C-reactive protein (thirty-three of thirty-five patients), emphasising the inflammatory basis of the GPS[38].

Application of a systemic-inflammation-based score in patients with advanced cancer

The prognostic value of the GPS was then evaluated further in a variety of advanced cancers including non-small-cell lung[39], breast[40], gastro-oesophageal[41,42], pancreatic[43], renal[44] and colo-rectal[45] cancers. These studies (Table 2) have demonstrated that the prognostic value of the GPS is independent of tumour stage (all studies) and conventional scoring systems[44], superior to performance status[39,42] and superior to other markers of the systemic inflammatory response such as leucocyte or lymphocyte counts[39,40,42,44,45].

Having established a scoring system (the GPS) based on the systemic inflammation-driven loss of weight, lean tissue and performance status, it was of interest to examine its relationship with the general biochemical disturbance of patients with advanced cancer[46]. The GPS was found to be normal in all the controls (n 13), but abnormal in 78% of the group with lung and gastrointestinal cancer (n 50). In addition to lower BMI and poorer performance status, serum concentrations of Na, chloride, creatine kinase, Zn and vitamin D were found to be lower in the group with cancer, whereas concentrations of Ca, Cu, alkaline phosphatase and γ-glutamyl transferase were raised. In the

Table 2. Systemic inflammatory response, as evidenced by the Glasgow prognostic score (GPS), as a prognostic factor in advanced inoperable cancer

Study	Tumour type	n	Comments
Forrest et al.[39]	Lung	109	GPS superior to ECOG*
Al Murri et al.[40]	Breast	96	GPS independent of stage and treatment
Crumley et al.[41]	Gastro-oesophageal	258	GPS independent of stage and treatment
Glen et al.[43]	Pancreatic	187	GPS independent of stage
Ramsey et al.[44]	Renal	119	GPS independent of scoring systems
Crumley et al.[42]	Gastro-oesophageal	65	GPS superior to ECOG*
Leitch et al.[45]	Colo-rectal	84	GPS superior to WCC and lymphocytes

WCC, leucocyte count.
*Eastern Cooperative Oncology Group performance status, which assesses the well-being of patients with cancer and their ability to perform ordinary tasks[37].

Table 3. Systemic inflammatory response, as evidenced by C-reactive protein (CRP), as a prognostic factor in primary operable cancer

Study	Tumour type	n	Comments
McMillan et al.[55]	Colo-rectal	36	Post-op CRP stage independent
Nozoe et al.[56]	Colo-rectal	120	Pre-op CRP stage independent
Nielsen et al.[57]	Colo-rectal	456	Pre-op CRP stage independent
Wigmore et al.[63]	Colo-rectal	202	Pre- and post-op CRP not stage independent
McMillan et al.[58]	Colo-rectal	174	Pre- and post-op CRP stage independent
Chung et al.[64]	Colo-rectal	172	Pre-op CRP not stage independent
Nikiteas et al.[59]	Colo-rectal	74	Pre-op CRP stage independent
Crozier et al.[60]	Colo-rectal	222	Pre-op CRP stage and treatment independent
Wong et al.[61]	Colo-rectal, liver	170	Pre-op CRP stage independent
McMillan et al.[62]	Colo-rectal	316	GPS independent of stage and treatment

Pre-op, pre-operative; post-op, post-operative; GPS, Glasgow prognostic score.

patient group, with increasing GPS a median reduction was found in Karnofsky performance status[47] (25%), Hb (22%), Na(3%), Zn (15%) and survival (93%) and a median increase in leucocyte count (129%), alkaline phosphatase (217%), γ-glutamyl transferase (371%) and lactate dehydrogenase (130%). C-reactive protein concentrations were found to be strongly and similarly correlated with alkaline phosphatase and γ-glutamyl transferase, accounting for >25% of the variation in their activities. Thus, it would appear that chronic activation of the systemic inflammatory response in cancer is associated with important aspects of the general biochemical disturbance in patients with advanced cancer[46].

Thus, it is concluded that the combination of an elevated C-reactive protein concentration and hypoalbuminaemia (the GPS) is a tumour stage and performance status independent prognostic factor in patients with advanced inoperable cancer.

Application of a systemic-inflammation-based score in patients with primary cancer

There has also been some work in primary operable cancer that has shown that the systemic inflammatory response, as evidenced by an elevated C-reactive protein concentration, has prognostic value in gastro-oesophageal[48, 49], urinary bladder[50], pancreatic[51], renal[52,53] and non-small-cell lung[54] cancers, independent of tumour stage (Table 3). Also, a number of studies carried out in primary operable colo-rectal cancer have highlighted the independent prognostic value of an elevated C-reactive

protein concentration[55–62], with only two studies failing to observe such a relationship[63,64].

Recently, the prognostic value of the GPS has been examined in patients with either primary operable colo-rectal cancer (n 149) or synchronous unresectable liver metastases (n 84)[65]. The GPS was found to be a superior predictor of cancer-specific survival compared with leucocyte components of the systemic inflammatory response.

Thus, it is concluded that markers of the systemic inflammatory response, in particular C-reactive protein, are independently associated with survival in patients with primary operable cancer. The combination of an elevated C-reactive protein concentration and hypoalbuminaemia (the GPS) is a tumour stage- and treatment-independent prognostic factor in patients with primary operable colo-rectal cancer.

In summary, it is believed that a measure of the systemic inflammatory response, such as the GPS, should be included together with tumour stage as part of the assessment of the patient with cancer. As a consequence, this approach will highlight the need not only to treat the tumour but also the systemic inflammatory response.

Acknowledgements

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