Systemic inflammation, nutritional status and survival in patients with cancer

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Purpose of the Review

There is now good evidence in humans that a chronic systemic inflammatory response results in the cardinal features of cancer cachexia, principally the progressive loss of weight (in particular lean tissue). This review examines the role of recent simple objective systemic inflammation-based scores in predicting reduction of nutritional status and survival.

Recent findings

The most common measure of the systemic inflammatory response in cancer patients has been an elevated C-reactive protein concentration. This has now been included in recent definitions of cancer cachexia. There are also recent systemic inflammation-based scores, the Glasgow Prognostic Score, Neutrophil Lymphocyte Ratio and the Platelet Lymphocyte ratio which have been shown to have prognostic value in cancer patients. These scores, in particular the Glasgow Prognostic Score, enable identification of patients who are or likely to develop cachexia, have a poor response to treatment and who are likely to have poor survival.

Summary

A chronic systemic inflammatory response is clearly implicated in the progressive nutritional and functional decline of the cancer patient and their subsequent poor outcome. Systemic inflammation-based prognostic scores not only identify patients at risk but also provide well defined therapeutic targets for future clinical trials targeting nutritional decline.

Introduction

The process of nutritional and functional decline in the patient with cancer is so common that is often accepted as part of cancer treatment and the disease itself. The clear link between weight loss, poor performance status, poor response to treatment and poor prognosis is probably due to the preferential loss of skeletal muscle. It has been suggested that the loss of adipose tissue accounts for the majority of the weight loss, but the loss of muscle for most of the morbidity and mortality [1, 2].

However, the degree of weight loss that is prognostic is not well defined and performance status is recognised to be subjective and therefore their reliability has been questioned [1, 2]. Moreover, they do not provide objective therapeutic targets. There is now good consistent evidence that the presence of a systemic inflammatory response is associated with increased weight loss, an elevated resting energy expenditure, loss of lean tissue and functional decline. Furthermore, 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 [3, 4].

Measurement of the systemic inflammatory response

The basis of the systemic response in cancer patients is not clear, it may result from a non specific response secondary to tumour hypoxia/ necrosis or local tissue damage. Nevertheless, host responses to such systemic inflammation are myriad. These include alterations in neuroendocrine metabolism including the endocrine hormones, haematopoietic changes including the interleukins, interferons and the haematopoetic growth factors and acute phase proteins [5]. The liver, in particular hepatocytes, are central to the elaboration of the systemic inflammatory response since they 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. C-reactive protein, due to 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. Recently, Marsik and coworkers [6] reported the relationship between C-reactive protein and all cause mortality in approximately 270,000 patients admitted to hospital. There was with increasing C-reactive protein concentrations from normal (<5mg/l) to highly elevated (>80mg/l) there was a 3.3 fold increase in the risk of all cause mortality. The relation of CRP to cancer death was stronger than to vascular death and there was a 22.8 fold increase in cancer mortality in those patients with highly elevated C-reactive protein concentrations (>80mg/l). Indeed, the magnitude of the increase in C-reactive protein concentrations have been shown to be associated with poorer survival in cancer patients, particularly in patients with advanced disease, independent of tumour stage [3]. There has also been some work in primary operable cancer which has shown that the systemic inflammatory response, as evidenced by an elevated C-reactive protein concentration, has prognostic value in gastro-oesophageal [7], urinary bladder [8], pancreas [9], renal [10] and non-small cell lung [11] cancers, independent of tumour stage. Also, a number of studies carried out in primary operable colorectal cancer have highlighted the independent prognostic value of an elevated C-reactive protein concentration [3].

It is of interest that in patients with cancer as C-reactive protein increases albumin falls and this relationship is similar across different tumour types [3]. Also, that albumin concentrations reflect both systemic inflammation and the amount of lean tissue [3]. Therefore, the prognostic value of the combination of an elevated C-reactive protein concentration (>10mg/l) and hypoalbuminaemia (<35g/l) was examined [12], in 161 patients with inoperable non-small cell lung cancer. On multivariate survival analysis, this

combination (HR 1.70, 95% CI 1.23–2.35, P<0.001) compared favourably with the clinical standard combination of stage and performance status (HR 1.48, 95% CI 1.12–1.95, P=0.006).

This work resulted in the combination of C-reactive protein and albumin into a prognostic score (0, 1, 2). This score, now termed the Glasgow Prognostic Score (GPS), was defined as follows; patients with both an elevated C-reactive protein (>10 mg/ l) and hypoalbuminaemia (<35 g/ l) were allocated a score of 2. Patients in whom only one of these biochemical abnormalities was present were allocated a score of 1. Patients in whom neither of these abnormalities was present were allocated a score of 0. However, the score of 1 was most commonly due to an elevated C-reactive protein (33 out of 35 patients) emphasising the inflammatory basis of the GPS [12]. This inflammation based prognostic score (Table 1) has much to commend it since it has value independent of tumour stage, is simple to measure, routinely available and well standardised world-wide.

The relationship between inflammation based scores, nutritional status and survival in patients with cancer

The prognostic value of the GPS has been evaluated further in a variety of cancers including non-small cell lung cancer, breast cancer, gastro-oesophageal cancer, pancreatic cancer, renal cancer and colorectal cancer [13-26, Table 2]. These studies demonstrated that the prognostic value of the GPS was the independent of tumour stage and conventional scoring systems, superior to performance status and independent of treatment modalities. Moreover, consistent with the cachexia derivation of the systemic inflammation-based GPS [3], it was directly associated with elevated cytokine and adipokine concentrations [22, 24], biochemical disturbance [21], the loss of weight and lean tissue, loss of performance status [21, 22, 24].

More recently, the prognostic value of the neutrophil lymphocyte ratio (NLR) has been shown to have independent prognostic value in a variety of cancers including lung cancer,

gastric cancer, pancreatic cancer, colorectal cancer, colorectal liver metastases, cholangiocarcinoma and ovarian cancer [27-34, Table 3]. Also, the platelet lymphocyte ratio (PLR) has recently been shown to have independent prognostic value in patients undergoing potentially curative resection for pancreatic cancer [35, Table 3]. These studies demonstrated that the prognostic value of the NLR or the PLR was the independent of tumour stage and conventional scoring systems and independent of treatment modalities.

Recently, Leitch and coworkers [20] compared the the prognostic value of the GPS and components of the differential white cell count, including the NLR, in patients with either primary operable colorectal cancer (n=149) or synchronous unresectable liver metastases (n=84). The GPS was a superior predictor of cancer specific survival compared with white cell components of the systemic inflammatory response including the NLR.

Recent reviews on the etiology of cancer cachexia have recognised the importance of systemic inflammation and have proposed a measure of systemic inflammation (elevated C-reactive protein) in their definitions of cancer cachexia [1, 2]. However, such definitions also include highly variable clinical measures such as weight loss, fat free mass and food intake. In contrast, the GPS is a simple objective measure that reflects cachexia and reliably predicts outcome in cancer patients. Therefore, the GPS may be more suitable measure for the clinical definition of cancer cachexia..

Conclusion

Therefore, it can be concluded that markers of the systemic inflammatory response, in particular the GPS, is a reliable tumour stage independent prognostic factor in patients with cancer. Moreover, that a measure of the systemic inflammatory response (GPS) be included, in addition or in preference to the current definitions of cachexia [1, 2], with tumour staging as

part of the routine assessment of all cancer patients. As a consequence this will highlight the need not only to treat the tumour but also the systemic inflammatory response.

Further work is required to establish the value of measures of the systemic inflammatory response as stratification factors and selection criteria in randomised trials and as therapeutic targets in patients with cancer.

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References

**1. Morley JE, Thomas DR, Wilson MM. Cachexia: pathophysiology and clinical relevance. Am J Clin Nutr 2006;83:735-43.

This review formally proposes a measure of cytokine excess in the definition of clinical cancer cachexia.

**2. Fearon KC, Voss AC, Hustead DS; Cancer Cachexia Study Group. Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. Am J Clin Nutr 2006;83:1345-50.

This paper formally proposes a measure of the systemic inflammatory response, an elevated C-reactive protein concentration, in the definition of clinical cancer cachexia.

**3. McMillan DC. An inflammation-based prognostic score and its role in the nutrition-based management of patients with cancer. Proc Nutr Soc. 2008;67:257-62.

This review describes the rationale and development of the first systemic inflammation-based prognostic score for patients with cancer.

*4. Gridelli C, Gallo C, Ceribelli A, et al. Factorial phase III randomised trial of rofecoxib and prolonged constant infusion of gemcitabine in advanced non-small-cell lung cancer: the GEmcitabine-COxib in NSCLC (GECO) study. Lancet Oncol. 2007;8:500-12.

A recent study confirming the benefits of anti-inflammatory treatment in patients with advanced cancer.

5. Gabay C, Kushner I Acute-phase proteins and other systemic responses to inflammation. N Engl J Med. 1999;340:448-54.

**6. Marsik C, Kazemi-Shirazi L, Schickbauer T, et al. C-reactive protein and all-cause mortality in a large hospital-based cohort. Clin Chem. 2008;54:343-9.

This study examines the relationship between the magnitude of admission C-reactive protein and cancer and non-cancer survival in approximately 270,000 patients.

7. Crumley AB, McMillan DC, McKernan M, et al. An elevated C-reactive protein concentration, prior to surgery, predicts poor cancer-specific survival in patients undergoing resection for gastro-oesophageal cancer. Br J Cancer. 2006;94:1568-71.

8. Hilmy M, Bartlett JM, Underwood MA, et al. The relationship between the systemic inflammatory response and survival in patients with transitional cell carcinoma of the urinary bladder. Br J Cancer 2005;92: 625– 627.

9. Jamieson NB, Glen P, McMillan DC, et al. Systemic inflammatory response predicts outcome in patients undergoing resection for ductal adenocarcinoma head of pancreas. Br J Cancer 2005;92: 21–23

10. Karakiewicz PI, Hutterer GC, Trinh QD, et al. C-reactive protein is an informative predictor of renal cell carcinoma-specific mortality: a European study of 313 patients. Cancer. 2007;110:1241-7.
11. Hara M, Matsuzaki Y, Shimuzu T, et al. Preoperative serum C-reactive protein level in non-small cell lung cancer. Anticancer Res. 2007;27:3001-4.
12. Forrest LM, McMillan DC, McArdle CS, et al. Evaluation of cumulative prognostic scores based on the systemic inflammatory response in patients with inoperable non-small-cell lung cancer. Br J Cancer 2003; 89: 1028–1030.
13. Forrest LM, McMillan DC, McArdle CS et al. Comparison of an inflammation-based prognostic score (GPS) with performance status (ECOG) in patients receiving platinum-based chemotherapy for inoperable non-small-cell lung cancer. Br J Cancer 2004;90: 1704–1706.
14. Al Murri AM, Bartlett JM, Canney PA, et al. Evaluation of an inflammation-based prognostic score (GPS) in patients with metastatic breast cancer. Br J Cancer 2006;94: 227–230.
*15. Crumley AB, McMillan DC, McKernan M, et al. Evaluation of an inflammation-based prognostic score in patients with inoperable gastro-oesophageal cancer. Br J Cancer 2006;94: 637–641.
A large study with mature follow-up showing the prognostic value of the GPS in patients with advanced gastro-oesophageal cancer.
16. Crumley AB, Stuart RC, McKernan M, et al. (2007) Comparison of an inflammation-based prognostic score (GPS) with performance status (ECOG-ps) in patients receiving palliative chemotherapy for gastroesophageal cancer. J Gastroenterol Hepatol. 2007;Jul 20; [Epub ahead of print]
17. Glen P, Jamieson NB, McMillan DC, et al. Evaluation of an inflammation-based prognostic score in patients with inoperable pancreatic cancer. Pancreatology 2006;6: 450 – 453
18. Ramsey S, Lamb GW, Aitchison M, et al Evaluation of an inflammation-based prognostic score in patients with metastatic renal cancer. Cancer 2007;109: 205–212.
*19. McMillan DC, Crozier JE, Canna K, et al. Evaluation of an inflammation-based prognostic score (GPS) in patients undergoing resection for colon and rectal cancer. Int J Colorectal Dis. 2007;22:881-6.
A large study with mature follow-up reporting the prognostic value of the GPS in patients with primary operable colorectal cancer cancer.

**20. Leitch EF, Chakrabarti M, Crozier JE, et al. Comparison of the prognostic value of selected markers of the systemic inflammatory response in patients with colorectal cancer. Br J Cancer 2007;97:1266-70.
This study compares the prognostic value of selected markers of the systemic inflammatory response including GPS and NLR
21. Brown DJ, Milroy R, Preston T, et al. 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. J Clin Pathol.2007; 60:705-8.
22. Krzystek-Korpacka M, Matusiewicz M, Diakowska D, et al. Acute-phase response proteins are related to cachexia and accelerated angiogenesis in gastroesophageal cancers. Clin Chem Lab Med. 2008;46:359-64.
23. Kobayashi T, Teruya M, Kishiki T, et al. Inflammation-based prognostic score, prior to neoadjuvant chemoradiotherapy, predicts postoperative outcome in patients with esophageal squamous cell carcinoma. Surgery. 2008;144:729-35.
24. Kerem M, Ferahkose Z, Yilmaz UT, et al. Adipokines and ghrelin in gastric cancer cachexia. World J Gastroenterol. 2008;14:3633-41.
**25. Ishizuka M, Nagata H, Takagi K, et al. Inflammation-based prognostic score is a novel predictor of postoperative outcome in patients with colorectal cancer. Ann Surg. 2007;246:1047-51.
A large study with mature follow-up validating the prognostic value of the GPS in patients with operable colorectal cancer.
26. Read JA, Choy ST, Beale PJ, et al. Evaluation of nutritional and inflammatory status of advanced colorectal cancer patients and its correlation with survival. Nutr Cancer. 2006;55:78-85.
27. Sharma R, Zucknick M, London R, et al. Systemic inflammatory response predicts prognosis in patients with advanced-stage colorectal cancer. Clin Colorectal Cancer. 2008;7:331-7.
*28. Sharma R, Hook J, Kumar M, et al. Evaluation of an inflammation-based prognostic score in patients with advanced ovarian cancer. Eur J Cancer. 2008;44:251-6.
Comprehensive evaluation of the GPS in patients with ovarian cancer
*29. Yamanaka T, Matsumoto S, Teramukai S, et al. The baseline ratio of neutrophils to lymphocytes is associated with patient prognosis in advanced gastric cancer. Oncology. 2007;73:215-20

A large study with mature follow-up reporting the prognostic value of the NLR in patients with advanced gastric cancer.
30. Walsh SR, Cook EJ, Goulder F, et al. Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. J Surg Oncol. 2005;91:181-4.
**31. Malik HZ, Prasad KR, Halazun KJ, et al. Preoperative prognostic score for predicting survival after hepatic resection for colorectal liver metastases. Ann Surg. 2007;246:806-14.
A large study with mature follow-up reporting the prognostic value of various markers of the systemic inflammatory response in patients with colorectal liver metastases.
32. Halazun KJ, Aldoori A, Malik HZ, et al. Elevated preoperative neutrophil to lymphocyte ratio predicts survival following hepatic resection for colorectal liver metastases. Eur J Surg Oncol. 2008;34:55-60.
33. Gomez D, Morris-Stiff G, Toogood GJ, et al. Impact of systemic inflammation on outcome following resection for intrahepatic cholangiocarcinoma. J Surg Oncol. 2008;97:513-8.
34. Cho H, Hur HW, Kim SW, et al. Pre-treatment neutrophil to lymphocyte ratio is elevated in epithelial ovarian cancer and predicts survival after treatment. Cancer Immunol Immunother. 2009;58:15-23
35. Smith RA, Bosonnet L, Raraty M, et al. Preoperative platelet-lymphocyte ratio is an independent significant prognostic marker in resected pancreatic ductal adenocarcinoma. Am J Surg. 2008 Jul 16. [Epub ahead of print]

Table 1. An inflammation-based prognostic score, the Glasgow Prognostic Score [3]

Biochemical Characteristics	Score
C-reactive protein ≤10mg/l and albumin ≥35g/l	0
C-reactive protein ≤10mg/l and albumin <35g/l	0
C-reactive protein >10mg/l	1
C-reactive protein >10mg/l and albumin <35g/l	2

Table 2. Systemic inflammatory response, as evidenced by the GPS, as a prognostic factor in patients with cancer [14-27].

Study	Tumour type	n	HR (p-value)	Comments
Forrest et al., [13]*	Lung	109	1.70 (0.001)	GPS independent of stage/ treatment and superior to ECOG-ps
Al Murri et al., [14]*	Breast	96	2.26 (<0.001)	GPS independent of stage/ treatment
Crumley et al., [15]*	Gastro-oesophageal	258	1.51 (<0.001)	GPS independent of stage/ treatment
Crumley et al., [16]*	Gastro-oesophageal	65	1.65 (<0.05)	GPS independent of stage/ treatment and superior to ECOG-ps
Glen et al., [17]*	Pancreas	187	1.72 (<0.001)	GPS independent of stage
Ramsey et al., [18]*	Renal	119	2.35 (<0.001)	GPS independent of scoring systems
McMillan et al., [19]*	Colorectal	316	1.74 (<0.001)	GPS independent of stage/ treatment
Leitch et al., [20]*	Colorectal	233	2.08 (<0.001)	GPS superior to WCC/ lymphocytes
Brown et al., [21]*	Lung and colorectal	50	Not reported	GPS associated with weight loss, poor performance status and biochemical disturbance
K-Korpacka et al., [22]	Gastro-oesophageal	96	Not reported	GPS associated with weight loss, transferrin, IL-1, IL-6, IL-8, TNF, VEGF-A and midkine concentrations
Kobayashi et al., [23]	Oesophageal	48	Not reported	GPS independent of stage/ treatment and associated with toxicity
Kerem et al., [24]	Gastric	60	Not reported	GPS associated with weight loss, ghrelin, resistin, adiponectin and leptin
Ishizuka et al., [25]	Colorectal	315	1.53 (p<0.01)	GPS independent of stage/ treatment
Read et al., [26]	Colorectal	84	2.27 (p<0.05)	GPS independent of stage/ treatment
Sharma et al., [27]	Colorectal	84	Not reported	GPS independent of stage/ treatment and associated with toxicity
Sharma et al., [28]	Ovarian	154	1.68 (<0.01)	GPS independent of stage/ treatment

* studies from the Glasgow group, HR hazard ratio for incremental change of GPS.

Table 3. Systemic inflammatory response, as evidenced by the Neutrophil Lymphocyte Ratio and Platelet Lymphocyte Ratio, as a prognostic factor in patients with cancer [28-35]

Study	**Tumour type**	**n**	**HR (p-value)**	**Comments**
Yamanaka et al., [29]*	Gastric	1220	1.52 (<0.001)	NLR independent of stage/ treatment
Walsh et al., [30]*	Colorectal	230	Not reported	NLR predicted cancer survival
Malik et al., [31]*	Colorectal liver	687	1.73 (<0.001)	NLR independent of stage/ treatment
Halazun et al., [32]*	Colorectal liver	440	2.26 (<0.001)	NLR independent of stage/ treatment
Gomez et al., [33]*	Cholangiocarcinoma	27	1.78 (<0.01)	NLR independent of stage/ treatment
Cho et al., [34]*	Ovarian	192	8.42 (<0.05)	NLR independent of stage/ treatment
Smith et al., [35]**	Pancreatic	110	1.004 (p<0.01)	PLR independent of stage/ treatment

* Neutrophil Lymphocyte Ratio prognostic studies, ** Platelet Lymphocyte Ratio prognostic studies, HR hazard ratio for incremental change of NLR or PLR..