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Cancer and systemic inflammation: treat the tumour and treat the host

C S D Roxburgh¹ and D C McMillan^{*,1}

¹Academic Unit of Surgery, School of Medicine – University of Glasgow, Royal Infirmary, Glasgow G31 2ER, UK

Determinants of cancer progression and survival are multifactorial and host responses are increasingly appreciated to have a major role. Indeed, the development and maintenance of a systemic inflammatory response has been consistently observed to confer poorer outcome, in both early and advanced stage disease. For patients, cancer-associated symptoms are of particular importance resulting in a marked impact on day-to-day quality of life and are also associated with poorer outcome. These symptoms are now recognised to cluster with one another with anorexia, weight loss and physical function forming a recognised cluster whereas fatigue, pain and depression forming another. Importantly, it has become apparent that these symptom clusters are associated with presence of a systemic inflammatory response in the patient with cancer. Given the understanding of the above, there is now a need to intervene to moderate systemic inflammatory responses, where present. In this context the rationale for therapeutic intervention using nonselective anti-inflammatory agents is clear and compelling and likely to become a part of routine clinical practice in the near future. The published literature on therapeutic intervention using anti-inflammatory agents for cancer-associated symptoms was reviewed. There are important parallels with the development of useful treatments for the systemic inflammatory response in patients with rheumatological disease and cardiovascular disease.

Although the mechanisms determining cancer progression continue to be of intense interest to scientists and treatments to oncologists, it is the symptoms associated with cancer progression that are of most interest to patients. In particular, progressive appetite loss, weight (lean tissue) loss, fatigue and pain are extremely debilitating not only impacting on quality of life but also the response to treatment and survival. However, despite their importance, research into symptoms associated with cancer has not been given a high priority by either scientists or clinicians. For example, MacDonald (2007) pointed out that ‘the number of abstracts on all aspects of cancer nutrition totalled 15 out of 4917 papers and posters presented at the 2005 Annual Meeting of the American Society of Clinical Oncology (ASCO); in contrast there were 106 presentations on gemcitabine (Gemzar) alone. No progress on this front was evident at the 2006 ASCO meeting, when the score for nutrition was 10, gemcitabine 86’.

In recent years the importance of the inflammatory responses in determining disease progression in patients with cancer has become recognised (Hanahan and Weinberg, 2011) and has become a hot topic for scientists and clinicians with the terms

cancer and inflammation returning 1179 articles in 2002 compared with 3693 articles in 2012 (<http://www.ncbi.nlm.nih.gov/pubmed/?term=cancer+and+inflammation>). Despite the increasing interest, there remains a paucity of clinical studies showing how such new information might improve the treatment of symptoms in the cancer patient.

For a long time, there have been suspicions that cancer-associated symptoms, in particular the progressive loss of weight and lean tissue, are manifestations of a chronic ongoing systemic inflammatory response. Indeed, some early randomised clinical trial data were consistent with this concept (Lundholm *et al*, 1994; McMillan *et al*, 1999) and provoked reviews to call for further work on this hypothesis (MacDonald, 2007; McMillan, 2008).

In addition to clear associations with individuals symptoms and poorer outcome, cancer-associated systemic inflammation is likely to mitigate administration of other effective treatments. For example, the efficacy of many current chemotherapeutics are reliant on metabolic clearance by hepatic cytochrome P450 enzymes, a process which is known to be hindered by ongoing systemic inflammation, potentially resulting in treatment toxicity

*Correspondence: Professor DC McMillan; E-mail: Donald.McMillan@glasgow.ac.uk

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or failure (Kacevska *et al*, 2008). Therefore, it is logical that there should be a stratification on the basis of systemic inflammatory response measurement within randomised clinical trials of cancer therapeutics (McMillan, 2013b).

The aim of the present minireview was to examine the evidence in the last decade for the association of the systemic inflammatory response with the range of symptoms including appetite loss, weight loss, fatigue and pain and identify a rational clinical approach to moderate the systemic inflammatory response and reduce symptoms experienced in patients with cancer.

MEASUREMENT OF THE SYSTEMIC INFLAMMATORY RESPONSE

Although activation of the systemic inflammatory response involves many organ systems, the usual clinical laboratory measures of the magnitude of activation are circulating white cells and acute phase proteins (Gabay and Kushner, 1999). Over the last decade it has become clear that such measurements of an elevated systemic inflammatory response are consistently associated with poor outcome independent of tumour stage. In particular, white cell counts such as neutrophil, lymphocyte and platelet counts and acute phase proteins, such as C-reactive protein and albumin and their combinations, neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR) and Glasgow Prognostic Score (GPS) respectively have been reported repeatedly to have prognostic value (Roxburgh and McMillan, 2010; Guthrie *et al*, 2013; McMillan, 2013a). For example, over the last decade, more than 120 studies (> 60 000 patients) have examined the clinical utility of the NLR and/or the GPS to predict patient outcomes in a variety of cancers. Taken together, these systemic inflammation-based scores can be considered to represent an upregulation of the innate immune/inflammatory responses. Irrespective of this, these comprehensive and compelling data have resulted in calls for such systemic inflammation-based prognostic scores to be routinely incorporated into clinical care to improve treatment allocation and the design of randomised clinical trials (McMillan, 2013b; Douglas and McMillan, 2013).

RELATIONSHIP BETWEEN SYSTEMIC INFLAMMATORY RESPONSE, SYMPTOM CLUSTERS AND SURVIVAL

Symptoms associated with cancer are commonly regarded as natural sequelae to the progression of cancer, that is, due to the tumour burden. However, it has long been recognised that progressive involuntary loss of appetite, weight and physical function are features of advanced disease and aggressive types of tumour such as lung and pancreatic cancer, independent of the tumour stage. Similarly, fatigue, pain and depression are all features of advanced disease. Indeed, in the last decade it has become clear that the common symptoms such as appetite loss, weight loss, physical functioning and fatigue and pain are independently associated with survival in patients with advanced disease (Trajkovic-Vidakovic *et al*, 2012; Laird *et al*, 2013a).

Also, there is now a great deal of evidence, at least in animal models, of the role of pro-inflammatory cytokines in producing sickness behaviour that recapitulates many of the symptoms seen in patients with cancer (Illi *et al*, 2012). Finally, consistent with this concept is that symptoms in patients with cancer rarely exist in isolation but most occur in clusters, three or more symptoms that are related to each other (Kirkova *et al*, 2010). In particular, there are multiple reports that appetite loss, weight loss and physical function are a symptom cluster (Solheim *et al*, 2013a) and that fatigue, pain and depression are another (Laird *et al*, 2011) in patients with cancer. These symptom clusters may be considered to

represent in part a neurological response to upregulation of the innate immune response (Dantzer, 2004). Observations that advanced disease and aggressive tumours, such as lung and pancreatic cancer, are associated with a greater activation of the systemic inflammatory response compared with tumours in which symptom clusters are rarely seen, such as breast cancer (Proctor *et al*, 2010), are consistent with this concept.

Recently in a large international cohort of advanced cancer patients ($n = 1466$), Laird *et al* (2013b) reported that C-reactive protein was significantly associated with all of the function components of the EORTC QLQ-C30 including cognitive, physical, role, emotional and social. There was also a significant association with appetite loss, pain and fatigue. However, it remains to be clearly established that reduction of markers of the systemic inflammatory response will be accompanied by a clinically relevant improvement in symptoms and survival.

Conclusion. The importance of treating cancer-associated symptoms has recently been highlighted to oncologists with evidence that the administration of routine chemotherapy protocols are associated with a significant 30-day mortality (NCEPOD, Systemic Anti-Cancer Therapy: For better, for worse?; <http://www.ncepod.org.uk/2008sact.htm>). Furthermore, that early referral to palliative care for symptom control was associated with not only an improvement in quality of life but also an improvement in survival compared with standard care in patients with advanced non-small cell lung cancer (Temel *et al*, 2010).

The above literature shows a clear association between the systemic inflammatory response and cancer-associated symptoms (see Figure 1 and also in more detail Saligan and Kim, 2012). Given that activation of the systemic inflammatory response for most patients is chronic and unremitting, this raises the issue of how might it be moderated to ameliorate symptoms in the patient with cancer.

TREATMENT OF CANCER-ASSOCIATED SYMPTOMS IN PATIENTS WITH ANTI-INFLAMMATORY AGENTS

Owing to the myriad effects of the systemic inflammatory response in patients with cancer and the established anti-cancer treatments, it is likely that those anti-inflammatory agents most likely to make their way into routine clinical practice in the short term (5–10 years) will be those agents that have a broad brush

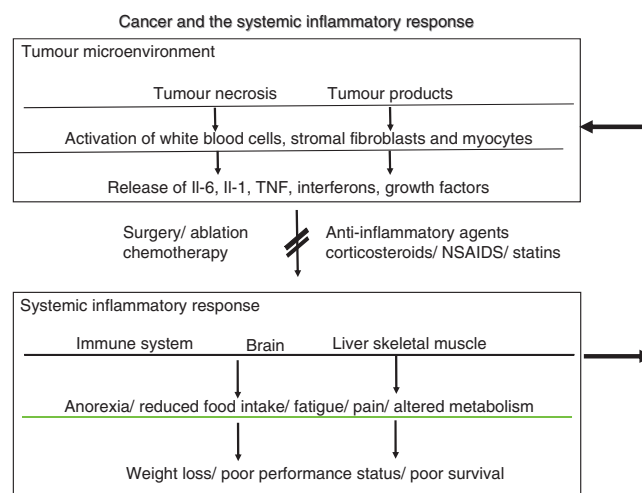


Figure 1. The relationship between the tumour microenvironment and the host systemic inflammatory response: treat the tumour and treat the host.

anti-inflammatory action and have a low or well-documented side-effect profile and readily used alongside standard cancer treatments (some currently used due to comorbid disease). The use of such anti-inflammatory agents will be guided by measures of the systemic inflammatory response as described above.

Corticosteroids. Corticosteroids are known to reduce the systemic inflammatory response, at least in the short term and are frequently prescribed in advanced cancer for symptom control. For example, a survey from the USA reported that 33% oncologists prescribe steroids in the end-of-life care (www.nccn.org, 2013). Moreover, they have been subject to at least six controlled trials accounting for more than 1000 patients and have been shown to improve appetite and quality of life if only for a limited time of a few weeks. A recent placebo-controlled trial demonstrated that dexamethasone 4 mg per day administered to advanced cancer patients for just two weeks resulted in significant improvements in cancer-related symptoms (weight loss, anxiety, fatigue, pain, nausea, anorexia and depression, Yennurajalingam *et al*, 2013). However, unlike other chronic inflammatory diseases, for example, rheumatoid arthritis, as these drugs have been given empirically in cancer and not specifically tailored to moderate the systemic inflammatory response (e.g., C-reactive protein, GPS, NLR or PLR), it is not clear which corticosteroid should be used nor the amount and timing of the dosage for optimal and continued reduction of the systemic inflammatory response.

Non-steroidal anti-inflammatory drugs (NSAIDs). Aspirin and other NSAIDs inhibit the enzyme cyclooxygenase and the production of prostaglandins that result in inflammatory responses and pain. These are used extensively in the populations of the western world. There has been a longstanding interest in the use of NSAIDs in the treatment of cancer-associated symptoms (Lundholm *et al*, 1994; McMillan *et al*, 1999). More recently, there has been further work that supports the routine use of NSAIDs in treating the most troublesome symptoms associated with cancer (Madeddu *et al*, 2012). Solheim *et al* (2013b) in a recent systematic review (including 13 controlled trials of NSAIDs in advanced cancer), reported that 11 studies reported a slowing of weight loss with 4 studies demonstrating a reduction in measures of systemic inflammation. There was also evidence that NSAIDs may improve physical function and patient-reported quality of life and reduce markers of the systemic inflammatory response.

Together with well-defined systemic inflammatory response parameters, the broad-spectrum anti-inflammatory properties of NSAIDs along with their relatively mild side-effect profiles in patients, make them good agents for the manipulation of cancer-associated inflammation with or without gastro-protection. Furthermore, with recent studies demonstrating positive survival outcomes with aspirin use following surgery for colorectal cancer dependent on tumour molecular phenotypes (Liao *et al*, 2012) and similar work in breast cancer, the role of aspirin/NSAID treatment looks set to expand to early-stage disease. However, it is not clear which NSAID should be used nor the amount and timing of the dosage for optimal and continued reduction of the systemic inflammatory response.

Statins. Statins are HMG-CoA reductase inhibitors that have had a major beneficial impact on the natural history of coronary artery disease in humans. Beyond their cholesterol-lowering properties, statins exhibit important anti-inflammatory activities (Jain and Ridker, 2005). For example, in randomised clinical trials, moderation of the systemic inflammatory response using a statin has been clearly associated with improved outcomes (Ridker *et al*, 2008). Furthermore, favourable effects on organ rejection following heart and renal transplant confirm an important immunomodulatory effect. Also, similar to NSAIDs, long-term statin use before

cancer diagnosis is associated with significantly lower-stage tumours and better long-term survival (e.g., Ng *et al*, 2011).

CONCLUSION

From the above, therapeutic intervention using nonselective anti-inflammatory agents has considerable potential to ameliorate the symptoms associated with cancer and therefore the potential to improve the quality and quantity of life in these patients. Indeed, when commenting on the role of NSAIDs in cancer cachexia Christoffersen (2013) recently stated, 'It is hard to avoid noting the striking contrast between the enormous efforts and resources spent on developing novel and very expensive drugs targeted at signalling pathways, many of which have turned out to have only marginal effects, and the lack of good studies trying out the effects of relatively cheap drugs.'

The current evidence base is such that, in the absence of definitive mechanisms, the clinical use of the nonselective anti-inflammatory agents discussed above should be considered in patients with cancer-associated symptoms and who have a measurement of an elevated systemic inflammatory response. There will remain concerns about the well-documented side effects of routine use of nonselective anti-inflammatory agents, in particular NSAIDs. However, these should be considered against the severity of the symptoms and poor outcome associated with a chronic systemic inflammatory state. Furthermore, the effectiveness of their use is now readily monitored. Therefore, it can be readily envisaged that, with monitoring of their anti-inflammatory effect and potential side effects, such anti-inflammatory agents can be used alongside standard anti-tumour treatment hence the title of the present review. Such work should stimulate a new era of randomised controlled trials of broad-spectrum anti-inflammatory agents to provide definitive clinical protocols to improve the quantity and quality of life of the patient with cancer.

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