Review Article

How and why systemic inflammation worsens quality of life in patients with advanced cancer

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Key Issues

- The presence of a systemic inflammatory response is associated with negative prognosis in advanced cancer, most likely through suppression of the adaptive immune response.
- Systemic inflammation is also associated with poorer global measures of quality of life in patients with advanced cancer.
- A variety of pre-clinical and clinical studies suggest that systemic inflammation has a direct role in cancer associated symptom clusters including pain and fatigue, mood, anorexia and physical function.
- Oncologic treatments commonly utilised in this patient group, including chemotherapy and radiotherapy, and their unwanted side effects and toxicities, are also associated with systemic inflammation.
- Limited evidence of interventions using anti-inflammatory agents, and some using more targeted therapies, report that attenuation of systemic inflammation leads to improvements in quality of life and related symptom clusters in patients with cancer.
- Future work should focus on targeting the systemic inflammatory response in patients with advanced cancer as an additional means of improving quality of life and associated symptom clusters.

Abstract

Introduction:

The presence of an innate host systemic inflammatory response has been reported to be a negative prognostic factor in a wide group of solid tumour types in both the operable and advanced setting, both local and distant. In addition, this host systemic inflammatory response is associated with both clinician reported patient performance status and self-reported measures of quality of life in patients with cancer.

Areas covered:

A variety of mechanisms are thought to underlie this, including the influence of the host immune response on physical symptoms such as pain and fatigue, its effect on organ systems associated with physical ability and well being such as skeletal muscle, and bone marrow. Furthermore, this innate inflammatory response is thought to have a direct negative impact on mood through its action on the central nervous system.

Expert commentary:

It is clear that the host systemic inflammatory response represents a target for intervention in terms of both improving quality of life and prognosis in patients with advanced cancer. Based on this paradigm, future research should focus both on pathways which might be targeted by novel agents, but also on whether existing anti-inflammatory drugs might be of benefit.

1 Introduction

Oncologic care in advanced cancer has been traditionally focussed on which available treatments can improve the poor prognosis in this group of patients. However, the significant burden of symptoms caused by advanced cancer, and their prognostic significance, has lead to a need to better understand the associated underlying mechanisms. It may be anticipated that this avenue of research will generate useful therapies to alleviate distress and improve quality of life in a situation in which time may be limited.

One of these key underlying mechanisms is systemic inflammation, a process so inextricably linked to cancer progression that it has been considered one of its hallmarks [1]. Indeed, systemic inflammation has been referred to as the "tip of the iceberg" [2], and the increasing evidence of its association with symptoms in patients with advanced cancer has lead to recent calls to target the systemic inflammatory response in the clinical setting [3-4].

The factors which influence quality of life in patients with advanced cancer are numerous. Furthermore, systemic inflammation has a wide-ranging impact on host biology and tumour biology, with downstream effects on quality of life (Figure 1). Similar constitutional symptoms often co-exist in so-called clusters [5]. Commonly described clusters of related symptoms include the combination of anorexia, weight loss, and decline in physical function, and the grouping of pain, fatigue, and low mood [6]. It has long been postulated that the host systemic inflammatory response has a key neuroimmunological role to play in the development of these symptom clusters [7].

The aim of the present narrative review was to examine the impact of the host systemic inflammatory response on quality of life and symptoms in patients with advanced cancer, and to review the existing evidence from related therapeutic studies.

2 The host inflammatory response to cancer

The systemic inflammatory response can be considered to be a significant mobilisation of the innate immune system, usually as a response to tissue injury or pathogens [8]. The process is regulated by a balance of cytokine production at different times; pro-inflammatory cells such as neutrophils and macrophages, and cytokines such as interleukin (IL) 1, IL 6, tumour necrosis factor (TNF) α, IGF-1, balanced by the anti-inflammatory regulatory cells and cytokines such as IL 4, and IL 10. The presence of a prolonged and inappropriate systemic inflammatory response has been reported in a variety of solid tumours and is associated with poor prognosis independent of disease stage [9-10].

It is hypothesised that this effect on outcome occurs as the presence of an innate inflammatory response inhibits the more useful (in relation to anti-cancer action) local adaptive immune response [11]. This innate inflammatory response may be initiated and maintained via the production of proinflammatory mediators by the tumour cells themselves, or by the cells which make up the local immune infiltrate [12]. Increasingly, pathways related to IL 6 are being targeted in the preclinical and clinical settings as the understanding of its multiple effects, and those of the downstream Janus Activated Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) transduction pathway increases 13].

The presence and magnitude of the systemic inflammatory response has been measured and defined in numerous ways and using many individual or combined components of the innate immune response. The original and modified Glasgow Prognostic Scores (GPS) combine threshold values of C-reactive protein (CRP) (>10mg/L) and albumin <35g/L) to stratify the magnitude of the systemic inflammatory response, and have been shown to be

prognostic in a variety of solid tumours, both resectable and advanced [14-17]. Other commonly reported measures of the systemic inflammatory response combine innate and adaptive cells obtained from a differential white cell count. Similarly to the GPS, the neutrophil lymphocyte ratio (NLR) has been reported to be prognostic in a variety of solid tumours and advanced cancer [18-27], although some evidence suggests that the neutrophil component has much greater prognostic significance than that of the lymphocytes [28]. A variety of other systems based on components of the differential white cell count, including platelet lymphocyte ratio (PLR) [29], neutrophil platelet score (NPS) [30], and lymphocyte monocyte ratio (LMR) [31], have also been reported in the literature. As of yet there is no real consensus as to which of the various methods has greatest prognostic ability, although all have been reported to be prognostic individually.

3 Prognostic impact of systemic inflammation in advanced cancer

Although there is now a significant body of evidence examining the prognostic impact of the systemic inflammatory response in patients with operable cancer [9], the importance of assessing the host inflammatory response in advanced disease has been somewhat neglected in comparison. Recently there has been intense interest in the use of markers of the systemic inflammatory response as prognostic indicators in both locally advanced and metastatic disease.

This interest was further heightened by recent cohort studies reporting that inappropriate anti-cancer treatment in patients with metastatic disease does not improve quality of life or survival, has increased costs associated with end of life care, and has been

directly related to death within 30 days of initiating treatment [32-34]. These results have been further validated by a recent randomised control trial reporting longer median survival and improved quality of life in patients with metastatic non-small cell lung cancer given early palliative, when compared to those given standard oncological care [35]. Therefore, it is important to examine the criteria that may be used to effectively stratify patients as to their likely outcomes, both in terms of survival and quality of life, prior to the allocation of treatment in patients with advanced cancer.

It is against this backdrop that several recent cross-sectional studies using both singular and combined markers of the systemic inflammatory response in inoperable locally advanced and metastatic disease have been carried out. These studies have reported that markers of the systemic inflammatory response have independent prognostic value, across tumour types and geographical locations, in patients with advanced cancer [36-38]. Indeed, the mGPS has been shown in several studies to provide additional prognostic determination when combined performance status [39-40].

A recent review by Simmons and colleagues focusing on the use of a variety of validated prognostic tools used by oncologists and palliative care clinicians, concluded that such prognostic tools often consist of both subjective and objective criteria [41]. Also, that whilst the majority of the prognostic tools focused on subjective criteria, particularly performance status, only one validated prognostic tool, the GPS, was based exclusively on objective criteria. Furthermore, the authors concluded that the combination of GPS alone and performance status, had much to commend it for predicting the clinical outcome in this patient group.

4 Impact of systemic inflammation on global quality of life in advanced cancer

Patient recorded outcomes measures (PROMs) can be used to generate global assessments of quality of life using tools such as the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core Questionnaire (EORTC-QLC-C30) [42]. A recent large observational study in patients with a variety of advanced cancers reported a significant association between systemic inflammation, and poorer quality of life as measured by the EORTC-QLC-C30, independent of performance status [43]. In addition, an earlier cohort study by the same group of investigators reported an association between systemic inflammation, measured by the mGPS, and the presence of symptoms such as pain, anorexia, breathlessness, fatigue, and nausea in patients with advanced cancer [44]. Furthermore a cohort study in patients with malignant mesothelioma reported a significant correlation between quality of life and both CRP and NLR [45]. Although an explanation for these associations is that rising systemic inflammation is simply a result of increasing tumour load in advanced disease, there is increasing evidence that the host systemic inflammatory response drives both disease progression and the symptoms which lead to poorer quality of life. Indeed, work in preclinical models suggest that multiple symptoms associated with advanced cancer may have a common pathophysiological origin in systemic inflammation [46-47]. Furthermore, clinical studies of non-steroidal anti-inflammatory drugs have reported improvements in global quality of life in patients with advanced cancer, although many have been studied in combination with other therapeutic agents such as megestrol acetate [13]. McMillan and colleagues reported a significant improvement in quality of life, measured by the EuroQol-EQ-5D, in patients treated with the non-steroidal anti-inflammatory drug (NSAID) ibuprofen in a prospective randomised trial [48]. Maccio and colleagues reported a significant improvement in quality of life, along with a reduction in IL-6 and CRP, in patients with advanced gynaecological cancer treated with the cyclo-oxygenase (COX) 2 inhibitor

celecoxib in a prospective randomised controlled trial [49]. In addition, more targeted therapy with the JAK inhibitor ruxolitinib, in the context of myeloproliferative disease, has been reported to be associated with improved quality of life in a randomised controlled trial [50].

5 The impact of systemic inflammation on pain and fatigue in advanced cancer

Pain and fatigue have been reported to cluster in a significant proportion of patients with cancer, although the reported prevalance varies with tumour type and disease stage [6, 51-52]. Experimental models suggest that pro-inflammatory cytokines can both cause pain and lead to hypersensitivity to other stimuli. This can occur through various mechanisms, including the modulation of synaptic transmission [53], direct excitation of nociceptive pain fibres [54], and causing other sensory neuron types to switch to nociceptive fibre phenotypes, through the expression of substance P [55]. In the clinical setting, from a secondary qualitative analysis including patients from two randomised controlled trials, systemic inflammation measured by CRP has been reported to be significantly associated with patient reported measures of pain in advanced cancer [56]. A randomised controlled trial of the corticosteroid dexamethasone in patients with bone metastases reported a significant reduction in pain in patients undergoing palliative radiotherapy [57]. Although the mechanism of action of steroids in this context is not well understood, they are recognised to reduce the synthesis of pro-inflammatory cytokines such as IL 6, along with its downstream acute phase proteins, through downregulation of myeloid tissues [58]. Furthermore, a recent phase II randomised controlled trial of the JAK inhibitor ruxolitinib, in patients with metastatic pancreatic cancer, reported a significant reduction in pain intensity scores in all treated patients, and in a subgroup with a raised CRP at trial entry [59].

Fatigue is a common symptom in patients with advanced cancer and may relate to other common problems in this group of patients, such as physical function, or the presence of anaemia, both discussed in more detail below. However, it is also possible that systemic inflammation has a more direct influence on fatigue. A meta-analysis of studies, including over 1000 patients with cancer, reported a significant association between circulating pro-inflammatory cytokines and reported fatigue, in particular IL 6 and IL 1ra [60]. In observational studies of patients with advanced cancer, CRP has also been reported to be associated with self reported fatigue [44, 61]. Conversely, in a single observational study, patients with ovarian cancer who reported an improvement in fatigue, at follow up, after surgery and chemotherapy, were found to have had a decrease in circulating IL 6 when compared to that before treatment [62]. Previous literature reviews have comprehensively reported the mechanisms currently proposed, through both pre-clinical and clinical research, to directly link cancer related inflammation to fatigue, including dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, direct effects on the central nervous system (CNS) by circulating cytokines on neurons and supporting glial cells, and alterations in synaptic neurotransmission, in particular that of serotonin, dopamine, and norepinephrine [63-65]. Exercise is believed to generate an overall anti-inflammatory effect, with the production of small quantities of IL 6 by skeletal muscle during activity inducing a longer lasting stimulation of production of anti-inflammatory cytokines such as IL 10 [66]. What limited evidence exists on the topic reports that exercise based activities can reduce the degree of fatigue suffered by patients with advanced cancer [67]. Whether this effect occurs through the modulation of systemic inflammation or has more direct central effects remains unclear. The same randomized controlled trial of the COX 2 inhibitor celecoxib in patients with advanced gynaecological cancers which reported an improvement in quality of life and a significant reduction in IL 6 and CRP, also reported significantly lower patient reported

fatigue (MFSI-SF) in the treatment group [49]. In addition, a small randomized controlled trial of dexamethasone, in patients with advanced cancer reported a significant reduction in fatigue measured on the Functional Assessment of Chronic Illness-Fatigue (FACIT-F) scale [68]. Furthermore, patients with advanced cancer treated with etanercept, a tumour necrosis factor alpha (TNF α) inhibitor, alongside a conventional cytotoxic drug in the context of a small dose escalation study, reported significantly less fatigue than those treated with the cytotoxic agent alone [69].

6 Systemic inflammation, mood, and psychological symptoms in advanced cancer

That mood disturbance should be considered in a symptom cluster along with pain and fatigue is not universally agreed [70], as reports of the prevalence of depression alongside pain and fatigue vary [71]. It is however increasingly recognised that systemic inflammation has an impact on both the central nervous system and higher brain functions, including cognition and mood, in a variety of diseases, both of the nervous system itself, and also in relation to psychological symptoms in systemic non-cancer diseases [72]. The same is true of patients with advanced cancer.

Preclinical studies of ovarian cancer have demonstrated anhedonic type behaviours in murine models associated with considerable systemic inflammation [73]. In a small cross-sectional study, cancer patients diagnosed with major depressive disorder were been shown to have higher circulating levels of IL 6 [74]. A significant association has been reported between CRP and self-reported emotional and social function in patients with advanced cancer [44]. In addition, a significant association between systemic inflammation measured

by the GPS, and both depression and anxiety, measured using the Hospital Anxiety and Depression Scale (HADS), has been reported in a cohort of patients with metastatic lung cancer [75]. Perhaps some additional evidence pointing toward a causal relationship between systemic inflammation and depression can be found in the widely reported phenomenon of cancer patients treated with pro-inflammatory interferon, who have been found to have an increased risk of significant psychiatric symptoms [76-77]. In an effort to examine the underlying pathophysiology in patients with cancer, an observational study using proton magnetic resonance spectroscopy to assess the cerebral metabolic status of patients with lung cancer prior to systemic therapy found a significant association with circulating levels of IL 6 and TNF α and neurotransmitter concentrations [78].

The literature in non malignant diseases involving systemic inflammation may shed some light as to potential therapeutic agents and targets in patients with advanced cancer. Patients with rheumatoid arthritis treated using a short course of high dose corticosteroid in a cohort study reported a significant reduction in depression and anxiety [79]. In both rheumatoid arthritis and Crohn's disease, the use of anti-TNF therapy has been reported to be associated with significant improvement in mood during observational studies utilising neuroimaging techniques [80-81]. In randomised controlled trials, inhibition of IL 6 using the monoclonal antibody sirukumab has been reported to be associated with improvement in self reported emotional well-being in patients with rheumatoid arthritis [82], and systemic lupus erythematosus [83]. However, to the author's knowledge no study examining the impact of attenuation of the systemic inflammatory response on depression or mood, in patients with cancer, has been attempted.

7 The impact of systemic inflammation on anorexia, physical function, and weight loss in advanced cancer

Disease progression in cancer is often associated with the gradual process of involuntary loss of appetite, weight, muscle mass, and physical function, an entity known as cancer cachexia [84]. Cancer cachexia and anorexia are recognised to be poor prognostic factors in a variety of tumours [85]. Definitions of cancer cachexia have traditionally focused on loss of weight or changes in body mass index (BMI), however as the overall weight of the world's population increases, measures of body composition have been recognised to be more useful [86]. Some have called for future definitions of cancer cachexia to be based on what is thought to be one of the key underlying mechanisms, systemic inflammation [87]. Several longitudinal studies in cancer cachexia have reported that the presence of systemic inflammation was associated with both a lower quantity and quality of skeletal muscle at the outset, and accelerated loss of lean tissue through the study period [88-90]. Further recent observational evidence suggests that systemic inflammation may be a key underlying mechanism driving this catabolic process [91].

Several clinical trials of anti-inflammatory agents have demonstrated some benefit to patients in terms of physical function. In a prospective, controlled clinical trial, Lundholm and colleagues reported a significant improvement in performance status in patients treated with the NSAID indomethacin, when compared to placebo, however did not demonstrate any improvement in another common objective measure of physical function, hand-grip strength [92]. In a small prospective study, Cercetti and colleagues reported that patients with

advanced lung cancer treated with a combination of fish oil and celecoxib had a significantly improved hand-grip strength and lower serum CRP when compared to patients given fish oil and placebo [93]. In a prospective randomised trial, Maddedu and colleagues reported a significant improvement in physical activity measured by the 6 minute walk test and an improvement in performance status, after treatment with celecoxib, when compared to baseline [94]. This was accompanied by a reduction in systemic inflammation measured by the GPS, however the treatment effect did no extend to other measures of physical function including hand-grip strength, daily step count, and metabolic equivalents (METs). Indeed, glucocorticoids, non-selective immunomodulators, are commonly used to treat patients with cancer cachexia, and there is some evidence that non-steroidal anti-inflammatory drugs used in patients with cancer cachexia may reduce weight loss [95]. Furthermore, pre-clinical studies of tocilizumab, a monoclonal antibody which targets the IL-6 receptor, in animal models of lung cancer, reported a reduction in the loss of lean tissue and weight in treated animals [96].

8 Systemic inflammation and anaemia in advanced cancer

Anaemia is often associated with distressing symptoms such as fatigue, breathlessness, and reduced physical ability in patients with advanced cancer. In colorectal cancer in particular, anaemia has been reported to be present preoperatively in as many as 80% of patients with locally advanced disease where it is traditionally associated with iron deficiency secondary to frank or occult gastrointestinal blood loss [97]. However, anaemia is also prevalent in other solid tumour types, even those not typically associated with blood loss, overt or otherwise. In

those patients without haematological malignancy or direct invasion of the bone marrow, anaemia is thought to relate to the host systemic inflammatory response. Indeed, systemic inflammation is associated with functional iron deficiency (FID), a state in which iron is inadequately incorporated into erythroid precursors despite sufficient iron stores, and a major component of the anaemia of chronic disease [98]. This process is mediated by the inhibition of the iron transport protein ferroportin due to the action of IL 6 on hepcidin, a key regulator of iron homeostasis [99]. In a large cross-sectional study, even a modest inflammatory response was shown to have an impact on commonly utilised serum measures of iron status, and a highly significant impact at levels of inflammation commonly found in patients with advanced cancer [100]. This anaemia of inflammation is resistant to simple treatment measures, such as iron replacement therapy, itself associated with not inconsiderable side effects [101].

The evidence for targeting inflammation to treat anaemia in cancer is very limited, however, studies performed in non-cancer diseases involving systemic inflammation may be considered. The inhibition of IL 6 by tocilizumab in animal models of rheumatoid arthritis has been reported to be associated with reductions in serum hepcidin and a corresponding improvement in anaemia [102]. The use of tocilizumab in a cohort of patients with Castleman's disease, in which IL 6 plays a key role, has been reported to be associated with a reduction in circulating hepcidin and normalisation of serum measures of iron status [103]. In addition, the use of anti-TNF therapy within a prospective open label clinical trial has been reported to be associated with improvement of anaemia in patients with rheumatoid arthritis [104]. In the context of cancer, corticosteroids are commonly used in the treatment of haematological malignancy there is very little evidence with regard to the therapeutic use of anti-inflammatory drugs in the anaemia associated with solid tumours. Shuster and colleagues reported in abstract form that a monoclonal antibody targeting IL 6

(clazakizumab) was associated with the reversal of existing anaemia in patients with non-small cell lung cancer [105]. To the author's knowledge no other study examining the impact of attenuation of the systemic inflammatory response on anaemia in patients with solid tumours, has been attempted.

9 The association between oncologic treatments, systemic inflammation and quality of life in patients with advanced cancer

In addition to the tumour-host relationship, it is also recognised that oncologic therapies given to patients with advanced cancer have an impact on, and may indeed act via, the systemic inflammatory response. In particular, commonly reported toxicities caused by chemotherapy and radiotherapy have been reported to be inflammatory in nature, suggesting that modulation of the immune system is also a key mechanism by which these modalities have their therapeutic actions [106-108]. Furthermore, there is growing evidence to suggest that the systemic inflammatory response is also a key mediator of the negative symptoms associated with such treatments [109]. Pre-clinical models have suggested that the administration of cytotoxic agents induces IL 6 and is associated with the development of illness behaviours in mice [110]. Several common cytotoxic agents have been shown to be associated with pro-inflammatory cytokine production and alterations in the activity and presence of natural killer (NK) cells, myeloid derived cells, and T cell subpopulations in patients with cancer [111-113]. An observational study in patients with advanced lung cancer undergoing chemoradiotherapy demonstrated a dose dependent rise in pro-inflammatory cytokines, including IL 6, IL 10 and TNF, which correlated with symptoms such as pain, fatigue and anorexia [114]. If indeed systemic inflammation is a key player in the development of unwanted symptoms due to oncologic treatments then targeting the systemic

inflammatory response may represent a further therapeutic option in their palliation [46, 115]. However, little evidence in this context exists and further study is warranted.

10 Summary and areas for future work

There is at present a limited evidence base linking quality of life and related symptom clusters to the presence of systemic inflammation in patients with advanced cancer. The wide ranging nature and quality of this small volume of existing evidence prevented the use of strict inclusion and exclusion criteria within the context of the present narrative review. However, the evidence that does exist points toward systemic inflammation as an potentially important mediator underpinning symptoms and quality of life in this group of patients. Despite this, there are relatively few studies of interventions targeting the systemic inflammatory response in this context. Perhaps one concern regards the ethics of clinical trials for symptom control in patients with advanced cancer. It is of interest then, that a small qualitative study exploring the experience of patients recruited to trials investigating treatments for symptom control, reported that being involved in such studies as a positive experience along with an improvement of overall well being independent of improvement in other symptoms [116]. This would suggest that future research into the association between systemic inflammation, quality of life and symptoms clusters, with a view to the development of new therapeutic strategies, is to be encouraged. In any case the severity and prevalence of symptoms associated with advanced cancer clearly generate a clinical need for additional

symptomatic treatments, and the current evidence suggests that targeting systemic inflammation may yet prove fruitful.

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11 Figures and Legends

Figure 1: A simple conceptual framework for the effect of inflammation on quality of life in patients with advanced cancer.