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Review

Inflammation and cancer: What a surgical oncologist should know

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ABSTRACT

Chronic inflammation is an aberrantly prolonged form of a protective response to a loss of tissue homeostasis and it is involved in several steps of the carcinogenesis process. As a result, many cancers are inflammation-related. The systemic inflammatory response is associated with survival in advanced and localized cancers. Two categories of scores have been proposed to monitor the systemic inflammatory response, those derived from protein measurement and those based on counting inflammatory cells. This review aims to provide a critical appraisal of these 2 categories of surrogate markers. The 3 scale modified Glasgow prognostic score (mGPS) is based on the combination of C-reactive protein and albumin and is graded 0 to 2. It has been validated worldwide showing an independent prognostic value in patients with cancer in a variety of tumour types and tumour stages. Leukocytes-based scores are mainly neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR). Elevated NLR and/or PLR and lower LMR seem to be associated with decreased survival, but the studies about these markers are very heterogeneous. The main limit is the variety of thresholds used to dichotomize patients, so that reproducibility and reliability of leukocytes-based scores can be questioned. Hence, there is no sufficient evidence to support their use in clinical practice. Comprehensive management of patients with operable and advanced cancer should integrate the host systemic inflammatory response by calculating the mGPS. It could be a helpful tool to tailor patients' management.

Introduction

Carcinogenesis is a multi-step process during which cells undergo several changes. This will result in excessive proliferation, followed by escape surveillance by the immune system and metastases [1]. The generation of cancer cells is caused by various genomic changes, mainly due to acquired somatic mutations and environmental factors. Genetic and epigenetic changes cause alterations in oncogenes and in tumour suppressor genes, which are the two broad categories of genes that are involved in carcinogenesis.

Deoxyribonucleic acid (DNA) damage is considered to be the primary cause of cancer [2]. In sporadic cancers, a deficiency in DNA repair is frequently due to epigenetic alterations that reduce or silence gene expression. Thus, various exogenous carcinogenic agents have been identified, such as tobacco smoke for lung cancer or helicobacter infection for gastric cancer. One commonality of carcinogenic agents is chronic inflammation, which is defined by an aberrantly prolonged form of a protective response to a loss of tissue homeostasis [3]. Examples of inflammation-related cancers are shown in Table 1. Virchow was the first to observe a link between inflammation and tumour growth in 1881 [4], describing leukocyte infiltrates within tumours. In 2011, inflammation has been considered as a hallmark of cancer [5]. Hallmarks of cancer are common traits that govern the transformation of normal cells to cancer cells. Six hallmarks were proposed in 2000 [6]: (1) self-sufficiency in growth signals, (2) insensitivity to anti-growth signals, (3) evading apoptosis, (4) limitless replicative potential, (5) sustained angiogenesis, and (6) tissue invasion and metastasis. Four new hallmarks were proposed in 2011 [5]: (1) abnormal metabolic pathways, (2) evading the immune system, (3) genome instability, and (4) inflammation.

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Table 1
Examples of inflammation-related cancers.

Cause of inflammation	Associated cancer
Inflammatory bowel disease	Colorectal cancer
Reflux esophagitis and Barrett's metaplasia	Oesogastric cancers
Helicobactesr pylori	Gastric cancer
Tobacco-induced bronchitis	Lung cancer
Asbestos	Mesothelioma
Hepatitis B and C	Hepatocellular carcinoma
Human papillomavirus	Cervical cancer

This review aims to summarise the data about GPS and leukocytes-based ratios as routinely measurable surrogate markers of cancer-related inflammation, as well as highlighting potential limitations of their use.

Inflammation and carcinogenesis

Numerous mediators and immune cells are involved in inflammation, particularly cytokines and chemokines [7,8]. The Interleukin-6/NF-κB/signal transducer and activator of transcription 3 (STAT3) signalling cascade is broadly implicated in inflammation. Major mediators of inflammation are listed in Table 2.

Several inflammation-related mechanisms detailed above have been identified in the carcinogenic pathway: genomic instability, promotion of proliferation and survival, immunomodulation of the tumour microenvironment, and facilitation of metastatic spread.

Genomic instability is a characteristic of most cancer cells. Genomic instability is caused by increased DNA damages and by altered DNA repair mechanisms. Inflammation may have a prominent role in genomic instability by inducing somatic mutations. These mutations might be caused by several mechanisms: cytokines introducing mutations in proto-oncogene TP53 [9], reactive oxygen species and reactive nitrogen species causing DNA alterations [10], microbiota changes with increased genotoxic capabilities [11], or indirectly by increased susceptibility to mutagenesis [12]. For example, mismatch repair (MMR) proteins are part of the DNA repair machinery. In case of mutation of MMR gene(s) (MSH2, MLH1, MSH6 and PMS2), the risk of colorectal cancer is increased. Loss of MMR proteins expression is mainly observed in hereditary Lynch Syndrome. Beside gene mutation, loss of MLH1 expression can also be caused by inflammation-induced hypermethylation of MLH promoter [13].

Cell proliferation and survival, as well as migration and cellular differentiation are mediated by growth factor receptor tyrosine kinases (RTK) [14]. Cancer cells enable continuous activation of signalling cascades of these RTK by several mechanisms (derailed endocytosis, inhibition of negative feedback…) [15,16]. Activation of transcription factors NF-κB/STAT3 pathway is frequently observed in inflammation-induced carcinogenesis [17,18]. Beside aberrant downstream pathway activation, tumour cell proliferation is increased by local anti-inflammatory cytokines, produced in response of tissue damage caused by chronic inflammation [19].

The microenvironment plays an important role in tumour development. Cancer cells can modulate the inflammatory response of the host and so its antitumour immune response by way of soluble mediators, especially cytokines. Interactions between tumour cells and immune cells induce tumour-specific local immune tolerance (due to manipulation of T regulatory cells by tumour cells) and suppression of antitumour T cell response (blockade of T effectors cells) [7].

Inflammatory mediators are involved in several steps of the metastatic process. The first step of metastasis, called epithelial–mesenchymal transition (EMT), is a change in cell characteristics which enables migration [20]. EMT is enhanced by activation of the NF-κB/STAT3 pathway and by production of inflammatory cytokines [21]. Then, the extra-cellular matrix (ECM) is modified, notably by inflammatory mediators, to enable intravasation of cancer cells into blood vessels and lymphatics [22]. Finally, cancer cells extravasate, induced by chemokines (a family of proinflammatory mediators) [10].

Inflammatory scores

Cancer-related inflammation includes modulation of inflammatory cells and mediators such as cytokines and chemokines. Systemic levels of cytokines and chemokines are not routinely measured, contrary to the direct changes they trigger, providing a direct surrogate marker of expression. Several prognostic scores based on shifts in these cellular populations have been proposed, including the modified Glasgow Prognostic Score (mGPS), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR).

Glasgow Prognostic Score (GPS)

The systemic inflammatory response is increased by cancer. It can be easily assessed by measuring concentrations of CRP and albumin. CRP is an activator of innate immunity (macrophage, complement) and a modulator of adaptive immunity (lymphocytes) [23]. Laboratory measurement of CRP is sensitive, specific and reproducible at low cost. Increase in CRP concentrations has been shown to be associated with poorer survival in patients with cancer, particularly in patients with advanced disease [24] [25], but also with primary operable cancer [26].

The three scale GPS was originally developed, from the combination of C-reactive protein and albumin, in a cohort of patients with advanced non-small cell lung cancer [27]. Scoring system of the GPS

Table 2
Major mediators of inflammation.

Mediators	Source(s)	Main action(s)
Cell-derived		
Cytokines (TNF, IL-1, IL-6, IL-22…)	Macrophages, endothelial cells, T lymphocytes	Responsible for the systemic effects of inflammation Recruitment of neutrophils and monocytes
Chemokines	Leukocytes, activated macrophages	Chemotaxis
Reactive oxygen species	Leukocytes	Tissue damage
Nitric oxide	Macrophages, endothelial cells	Recruitment of leukocytes
Leukotrienes	Leukocytes	Chemotaxis, vascular permeability
Plasma-derived		
Complement	Plasma (produced in liver)	Chemotaxis, other immune functions
Kinins	Plasma (produced in liver)	Vascular permeability
Proteases of the coagulation system and the fibrinolysis system	Plasma (produced in liver)	Recruitment of leukocytes, induce production of chemokines and nitric oxide

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