MINI REVIEW

Inflammatory Markers in Pancreatic Cancer Back to the Basics

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INTRODUCTION

Although implementation of standardized protocols in the perioperative setting of patients undergoing pancreatoduodenectomy, has improved surgical outcomes, little progress has been made in terms of long time survival in these patients. Increased accuracy of preoperative diagnosis, improved surgical technique and acquired experience along with implementation of enhanced recovery programs, have driven pancreatic surgery to a new era. Moreover neo- and adjuvant chemoradiotherapy, supported by genetics and better understanding of pancreatic cancer pathology have become cornerstones in improving survival. However progression is very slow for such an uprising disease, mainly due to our lack of knowledge regarding its basic characteristics, giving room for massive research in molecular biology and primary genetics field. Still the question remains: are we forgetting something?

Inflammation and Cancer

Up to 20% of cancer is related with chronic inflammation. It is well established the strong connection between persistent helicobacter pylori infection and gastric cancer, while infections with hepatitis B or C raise the possibilities of hepatocellurar carcinoma. Moreover tobacco smoke acts as a trigger of chronic inflammation promoting different types of cancer. Despite its action as a part of normal host defense, inflammatory response has an advert role in tumor genesis, where tumorigenic pathogens sabotage host immunity, establishing infections leading to chronic low-grade inflammation. Thus, cancer-related inflammation includes inflammatory cells and mediators, playing a significant role in tumor repair and remodeling along with angiogenesis and metastasis. Following tumor development, inflammation remains a strong factor in cancer's proliferation. Inflammatory cells and mediators can be found in the majority, if not in all, cases of solid tumors [1, 2].

Host leucocytes can be found all over the tumor's microenvironment. Tumor- associated macrophages (TAM) deriving from monocytic precursors when activated can produce growth and protease enzymes, stimulating tumor proliferation and invasion. Tumor associated dendritic cells (TADC) have an immature phenotype, localized in the invasive edge of tumors such the papillary thyroid carcinoma, reflecting lack of effective maturation signals and resulting to immunosuppression. T cells and especially the presence of CD8 cytotoxic T cells and CD4 helper T cells have been associated with worse outcome in breast cancer and cancer associated with cancer. On the other hand natural killer cells (NK) which lack of protumorigenic role, seem to be rare in the same tumor environment [3].

Furthermore, the role of proinflammatory cytokines on tumor progression is well established nowadays. Tumor necrosis factor (TNF) has a predominant role, through its actions of both tissue destruction and recovery. In a malignant setting, TNF can act as an endogenous promoter, inducing angiogenetic factors and serving as a leader in stromal development and tissue remodeling. Its harmful effect has been established in studies made on breast cancer, prostate cancer and in blood malignancies like leukaemia and lymphoma. Inflammatory chemokines like interleukin 8 (IL-8) is known to be secreted by a plethora of solid tumors. IL-8 is strongly inducible by hypoxia, is associated with the tumorigenic and metastatic potential of pancreatic cancer and induces proliferation and migration of malignant cells. Moreover hypoxia, a situation common in many solid tumors, apart from IL-8 induction leads to necrotic cell death at the tumor's core, a consequent release of proinflammatory mediators, enhancement of inflammatory response and neoangiogenesis, driving cancer cells in new pathways of progression [1, 2, 3].

These inflammation mediators use a variety of mechanisms in order to maintain or evolve tumor's environment. First of all they can induce DNA damage by producing NO, an agent that can oxidize DNA leading to mutations and damage to DNA repair proteins, resulting in genomic instability. In addition tumor suppressor p53 mutations, presumably caused by oxidative damage due

to a cytokine called migration inhibitory factor, can lead to the inactivation or bypass of this protein, which in turn can give rise to cell proliferation and metastasis. Moreover TAM, IL-8 and TNF can stimulate vascular endothelial growth factor (VEGF), produce tumor growth factor (TGF) and by direct or indirect ways influence microvascular endothelial cells resulting to angiogenesis. Last but not least, chemokines and TNF can induce protease production, necessary for tumor growth, along with using their molecular tools and migrating ability for lymphovascular dissemination [1, 2, 3].

The Role of Inflammatory Markers on Pancreatic Cancer Outcome

Several prognostic factors based on systematic inflammatory response have been explored, in order to correlate their expression with the outcomes of surgery for pancreatic neoplasms. C - reactive protein (CRP) is an acute phase protein produced by the hepatocytes mainly under the control of circulating Intrleukin 6 (IL 6). Elevated CRP in cases of resectable or even advanced pancreatic cancer has an advert effect on survival. It is estimated that elevated CRP reflects a more aggressive tumor or a high tumor burden along with increased tissue necrosis. CRP has been combined with several other factors in order to evaluate its correlation with pancreatic cancer outcomes [4]. The modified Glasgow prognostic score (mGPS) is a combination of CRP and albumin, whereas CRP in combination with white cell count are producing the prognostic index (PI) [5].

The mGPS has been validated in series of studies providing solid evidence on its predictive evidence irrespective of the tumor site. Especially in pancreatic cancer this score has been shown to influence survival independently from other tumor related parameters such as stage and lymph node count. Moreover in studies examining the role of mGPS in pancreatic cancer survival, no long time (>48 months) survivor could be identified in cases of elevated preoperative score. Advocators of this score suggest that the combination of CRP and albumin reflect both the induced inflammatory response and the progressive nutritional decline of the patient with pancreatic cancer, providing a more accurate survival prognostic tool [6].

Another prognostic score widely used in predicting cancer related survival is the neutrophil/leucocyte ratio (NLR) and the platelet/leucocyte ratio (PLR). Elevated neutrophils and subsequent lymphocytopenia predisposes to impaired immune response, mediated response to therapy and increased circulation of VEGF. Moreover recent studies have associated NLR with circulating cytokines. Elevated circulating cytokines along with increased peritumoural infiltration with macrophages have been found in cases of elevated NLR. In patients with pancreatic cancer, NLR can predict overall survival and disease free survival, while in the same time can become a useful tool in the follow up period, having also a predictive value on recurrence rates. Finally NLR has been associated with worse tumor characteristics such as poor differentiation and poorer patient performance status [5, 7].

PLR, PI and the Onodera's prognostic nutritional index (PNI) have also been used as a prognostic tool. Platelet count may serve as an additional index of the inflammatory response caused by the pancreatic malignancies. *In vitro* studies have shown that antiplatelet agents may inhibit the invasive potential of pancreatic cancer cells. Furthermore nutritional status plays a significant role in postoperative outcomes, especially in pancreatic cancer, a disease that produces profound cachexia and weight loss. Impaired nutrition can contribute to tumor development mainly due to impaired host immunity. Both scores have been found of been strongly related with overall survival in patients with resectable pancreatic cancer [8, 9].

Implications for Practice and Research

Cyclooxygenase 2 (COX-2) is involved in the synthesis of prostaglandins and is frequently expressed by cancerous cells. COX-2 produced prostaglandins promote cellular processes in cancer proliferation including, angiogenesis, mitogenesis and metastasis. Moreover, these prostaglandins contribute in cancer related cachexia and anorexia and hold a predominant role in the "vicious circle" of inflammation and cancer immunosuppression. Various studies have analyzed the role of COX-2 inhibitors in the chemoprevention of cancers. Ibuprofen, aspirin and celecoxib have been found to reduce the risk of breast cancer, colon cancer, prostate cancer and lung cancer. In addition COX-2 inhibitors have been found to reverse weight loss, ameliorate cancer cachexia and improve quality of life [10, 11].

TNF inhibitors on the other hand, have an increased effect on immune response supported by good clinical evidence. They can inhibit chemokine production, prevent leucocyte infiltration, reduce angiogenesis and improve bone marrow function. As with COX-2 inhibitors, they can prevent or even reverse cachexia. Studies on patients already on TNF antagonists for inflammatory bowel disease can provide useful information about their potentials in cancer chemoprevention [1].

Information upon inflammatory status can be useful in stratifying patients for different treatment options. Patients with elevated inflammatory scores can be delayed from surgery until score improvement or in order to be treated with regulators of the immune response like anti-inflammatory agents. In addition patients with elevated CRP seem to respond poorly in gemcitabine based chemotherapy. This fact can further stratify patients in order to receive more effective regiments, driving pancreatic cancer towards a new era of personalized treatment [4].

One must bear in mind, that shifting pancreatic cancer therapy towards cheaper and simpler treatment modalities hinders significant obstacles, mainly raised by physicians and medical industry. Nevertheless, when dealing with a cancer with such a complex biology, we should not forget that multimodal management, based on the basics of human function, is essential.

Conflict of Interest

Authors declare to have no conflict of interest.

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