Cancer Treatment Reviews 40 (2014) 68–77

Contents lists available at SciVerse ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Anti-Tumour Treatment

The impact of anti-inflammatory agents on the outcome of patients with colorectal cancer

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ARTICLE INFO

Article history:
Received 4 March 2013
Received in revised form 21 May 2013
Accepted 23 May 2013

Keywords:
Colorectal cancer
Inflammation
Immune response
NSAID
Aspirin
Statin
Histamine

SUMMARY

Although there is increasing appreciation of the role of the host inflammatory response in determining outcome in patients in colorectal cancer, there has been little concerted effort to favourably manipulate cancer-associated inflammation, either alone or in combination with current oncological treatment. Epidemiological and cardiovascular disease studies have identified aspirin, other nonsteroidal anti-inflammatory drugs and statins as potential chemotherapeutic agents which may manipulate the host inflammatory response to the benefit of the patient with cancer. Similarly, evidence of a chemotherapeutic effect of histamine-2 receptor antagonists, again mediated by an immunomodulatory effect, has previously led to increased interest in their use in gastrointestinal cancer. Extensive pre-clinical data and a limited number of clinical investigations have proposed a direct effect of these agents on tumour biology, with an anti-tumour effect on several of the hallmarks of cancer, including proliferative capacity, evasion from apoptosis and cell cycle regulation, and invasive capability of tumour cells. Furthermore, clinical evidence has suggested a pertinent role in down-regulating the systemic inflammatory response whilst favourably influencing the local inflammatory response within the tumour microenvironment. Despite such compelling results, the clinical applicability of nonsteroidal anti-inflammatory drugs, statins and histamine-2 receptor antagonists has not been fully realised, particularly in patients identified at high risk on the basis of inflammatory parameters. In the present review, we examine the potential role that these agents may play in improving survival and reducing recurrence in patients with potentially curative colorectal cancer, and in particular focus on their effects on the local and systemic inflammatory response.

Introduction

Colorectal cancer (CRC) is the second most common cause of cancer-related death in Western Europe and North America. In the UK, 41,000 new cases are diagnosed each year with over 16,000 deaths.[1] Despite advances in surgical and adjuvant treatment over the past two decades, survival remains poor, with a 5-year survival of approximately 50% in patients undergoing resection with curative intent.[2] Since the establishment of 5-fluorouracil and platinum-based regimes, few new chemotherapeutic agents have shown any significant survival benefit.[3] Similarly, biological agents, such as bevacizumab and cetuximab have proven to be of only modest benefit, and only in the palliation of metastatic disease.[4] As such, there remains a need to identify potential adjuvant and neo-adjuvant agents in patients with CRC.

Inflammation has been implicated in the pathogenesis of many adult malignancies and is now recognised as the seventh "hallmark" of cancer.[5] Furthermore, the host inflammatory response to CRC influences disease recurrence and survival. A pronounced local inflammatory response with intra- and peri-tumoural lymphocytic infiltration is a stage-independent predictor of increased survival.[6] Conversely, up-regulation of the systemic inflammatory response has been shown to be a predictor of recurrence and reduced survival in several cancers including CRC.[7]

Impaired cell-mediated immunity is common in cancer patients.[8] Particularly in patients undergoing surgical resection of CRC, that is recognised to attenuate post-operative cell-mediated immunity[9], this may be an important mechanism by which disseminated or shed tumour cells evade effective immunosurveillance and establish *de novo* metastases.[10–12] Furthermore, the presence of a systemic inflammatory response has been associated with a poorer response to chemotherapeutic agents and an increased risk of toxicity.[13]

It is clear that manipulation of the host inflammatory response, particularly in those patients with an "unfavourable" inflammatory profile, presents an intriguing concept. Despite this, few agents have been examined in the clinical setting for their potential effects on CRC-associated inflammation, particularly in the context of contemporary surgical and oncological treatment of high-risk disease.

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http://dx.doi.org/10.1016/j.ctrv.2013.05.006

Table 1
Direct tumoural, local and systemic inflammatory effects of nonsteroidal anti-inflammatory drugs, statins and H2 receptor antagonists in colorectal cancer.

Drug/Class	Direct tumour effects	Effects on local inflammatory response	Effects on systemic inflammatory response
NSAID	↑ • Differentiation • Apoptosis • Cellular adhesion • Radiosensitivity • Susceptibility to oxidative stress ↓ • Proliferation • Angiogenesis • Motility/migration	↑ • MHC class II expression • Anti-tumour cytokines • Inflammatory infiltrate • Th1/M1 response ↓ • Pro-tumour cytokines • COX-2 expression • T_{reg} activity	↑ • Lymphocyte and NK cell activity ↓ • Platelet activation • Serum acute phase proteins
Statin	↑ • Apoptosis • Cell cycle arrest • Susceptibility to oxidative stress • Differentiation ↓ • Proliferation • Angiogenesis	Unknown effect on inflammatory infiltrate ↓ • NOS expression • COX-2 expression	↓ • Circulating cytokines
H2 receptor antagonist	↑ • Cellular adhesion ↓ • Proliferation • Angiogenesis	↑ • Inflammatory infiltrate • Anti-tumour cytokine ↓ • T_{reg} activity	↑ • Lymphocyte and NK cell activity

↑ increased activity or expression in response to drug, ↓ decreased activity or expression in response to drug.

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), including the cyclooxygenase-2 inhibitors (COXIBs), have been identified as potential chemotherapeutic drugs which may favourably manipulate the inflammatory response in CRC. Despite convincing evidence from epidemiological studies and cardiovascular secondary prevention trials of a chemoprophylactic effect in reducing CRC incidence and mortality,[14,15] it is relatively recently that a potential benefit in patients with established CRC has been realised, with NSAID users less likely to present with advanced or metastatic disease at diagnosis or follow-up.[16,17] Indeed, emerging evidence of as much as a 40% reduction in mortality in patients undergoing curative treatment makes the concept of the use of NSAIDs as adjuvant treatment in high risk disease more compelling,[13,18–23] where potential survival benefits may outweigh the risks which have so far abrogated their use in CRC prevention.[24]

Similarly, statins and histamine-2 receptor antagonists (H2RAs) have also been identified as drugs with a potential benefit in improving survival and reducing risk of recurrence in patients with established CRC. A direct effect on tumour biology has been proposed through manipulation of several key signalling pathways, with a resultant effect on several of the key hallmarks of carcinogenesis, including proliferative and anti-apoptotic capacity as well tumour-mediated angiogenesis and invasiveness.[25] Furthermore, these drugs have also been identified as potential agents capable of manipulating the host systemic and local inflammatory response to CRC [Table 1]. Although the use of such agents to manipulate the tumoural and inflammatory microenvironment in CRC as well as the systemic inflammatory response presents an attractive concept, most evidence to date arises from *in vitro* and *in vivo* investigations, with little confirmation from clinical studies. In particular, there has been no attempt to stratify the use of anti-inflammatory agents and subsequent benefit in CRC patients according to the presence of a systemic inflammatory response. The present review examines the clinical evidence supporting the use of NSAIDs, statins and H2RAs in influencing the tumour microenvironment and host inflammatory response in CRC and focuses on their utility in improving survival in patients with potentially curative disease.

Aspirin, NSAIDs and COX-2 inhibitors

Early evidence of a prophylactic effect of aspirin and NSAIDs in CRC originally arose out of studies of hereditary cancer syndromes. The use of NSAIDs decreases the number and size of colonic polyps in patients with familial adenomatous polyposis; similarly, aspirin has also been found to confer a protective effect on the colorectum in patients with Lynch syndrome.[26,27] Over the past two decades, increasing evidence from epidemiological studies has identified a potential role in the prophylaxis of sporadic CRC, with an approximate 30% risk reduction with aspirin and non-aspirin NSAIDS and a potentially greater reduction with COXIB use.[28,29] In general, a duration-dependent increase in risk reduction has been observed, with the greatest benefit seen after at least 10 years of continuous use. Similarly, cessation of regular use results in a return to normal population risk for subsequent CRC development. Furthermore, secondary analyses of cardiovascular secondary prevention trials have found a significant benefit with aspirin doses commonly employed for cardiovascular disease prevention, rather than doses commonly associated with analgesic use.[19] Despite such convincing evidence, concerns regarding the safety profile of NSAIDs have discouraged their use as prophylactic agents in the general population, at least until the optimal target population is identified.[24]

Direct tumoural effects

The direct cellular effects of aspirin and other NSAIDs have been under close scrutiny since their anti-tumour effects were first appreciated, and have been reviewed extensively elsewhere. In general, pre-clinical investigations have found an increase in tumour cell apoptosis in association with a decrease in cell proliferation, angiogenesis and metastatic potential.[30,31] Although limited, mechanistic studies in patients with CRC have again suggested similar effects, with an NSAID-mediated decrease in primary and metastatic tumour blood flow and microvessel density even with short courses of NSAIDs.[32,33] Of further interest, NSAID administration has also been shown to facilitate tumour cell differentiation, with a loss of cancer cell stemness and down-regulation of gene expression associated with increased metabolic turnover and resistance to oxidative stress.[34,35]

Cyclooxygenase-dependent effects

Several potential mechanistic pathways have been implicated in the anti-tumour effects of aspirin and other NSAIDs. The most studied mechanism is their inhibitory effect on cyclooxygenase