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

Short Title:
Manipulating colorectal cancer-related inflammation

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Abstract:

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 five-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.

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), including the cycloxygenase-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 \textit{in vitro} and \textit{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 Tumoral 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 (COX)-mediated synthesis of prostanoids, and in particular prostaglandin E2 (PGE2)(30, 31, 36, 37). Increased synthesis of PGE2 by COX-2, the inducible form of the enzyme has been shown to have several pro-tumour and immunosuppressant effects in vitro and in vivo, including an increase in tumour cell proliferation, decreased apoptosis, increased angiogenesis and increased chemo- and radio-resistance. Indeed, COX-2 is overexpressed in some but not all colorectal neoplasia, particularly those arising in the distal colon and rectum (38, 39), where its expression is associated with increased differentiation, tumour invasiveness, metastatic potential and poorer survival(30, 36, 40). Furthermore, epidemiological evidence suggests a prominent role for COX-2 inhibition, with a reduced risk of COX-2 overexpressing tumours in long-term aspirin users and a modification of their anti-tumour effects observed in patients with common COX-2 gene polymorphisms(41, 42). Similarly, an increase in tumour cell apoptosis and decrease in tumour vascularity has also been confirmed in human subjects in response to NSAID administration, mediated by a reduction in COX-2 expression and tissue PGE2(32, 43).

Aspirin, particularly at low doses employed in cardiovascular disease, is a weak inhibitor of COX-2 whereas it remains a strong inhibitor of the constitutive enzyme COX-1, particularly in anucleated cells such as platelets(44). As such, inhibition of COX-1 has also been suggested as another potential mechanism for the anti-tumour effects of NSAIDs by inhibiting platelet activation, facilitating immunosurveillance and preventing haematogenous spread. Indeed, aspirin can abrogate the increase in platelet activation demonstrated in CRC patients, even after only five days (45).

**Cyclooxygenase-independent effects**

Although many of the anti-proliferative effects of NSAIDs may be explained by their inhibitory effects on PGE2 synthesis, several COX-independent actions have also been identified (46). Similarly, many of
the effects of NSAIDs on proliferation and apoptosis have also been identified in cancer cell lines known not to express COX-2 (47). Several signal transduction pathways, including Wnt/β-catenin, nuclear factor-kappa B (NF-κB) and the phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin pathway have been identified as potential targets for the non-COX mediated effects of NSAIDs, with limited clinical evidence suggesting an NSAID-mediated effect on associated signalling and transcription pathways(47-49). Furthermore, epidemiological data again suggests these as valid targets of NSAID therapy in CRC, with increased survival with aspirin use in patients with PIK3CA mutated cancers(49), and a reduced risk of cancer with NSAIDs in patients with mutations within the NF-κB pathway(50).

**Effects on cancer-related inflammation**

The anti-inflammatory properties of aspirin and non-aspirin NSAIDs have identified them as likely candidates in the manipulation of CRC-related inflammation; indeed evidence of a NSAID-mediated attenuation of the acute phase response and weight loss in advanced cancer suggests a potential role in the management of the cancer cachexia syndrome(51). Furthermore, the chemoprophylactic effects of NSAIDs appear to be greater in patients with evidence of a systemic inflammatory response(52), although unfortunately, so do the cardiovascular risks of long-term COXIB use(53).

**Local inflammation**

The presence of a pronounced inflammatory infiltrate at the invasive margin and within the tumour stroma is recognised as an indicator of reduced recurrence and superior survival(6). The effects of aspirin, non-selective NSAIDs and COXIBs on the tumoural inflammatory response have been investigated in a number of solid cancers, with significant anti-tumour responses identified in gastrointestinal, breast, bladder and head and neck cancers(54). A decrease in the levels of pro-tumour, immune-suppressing cytokines including PGE2, has been identified in the colorectum and in colorectal hepatic metastases, likely mediated at a gene transcription level.(32, 34, 43). Furthermore, NSAIDs have been shown to induce expression of MHC class II molecules on the surface of CRC cells(55). Such changes within the tumour milieu may in turn allow for the recruitment and propagation of a co-ordinated, effective anti-tumour lymphocytic response [Table 2]. Indeed, Lönnroth and colleagues have shown an increase in tumour infiltration of activated T-lymphocytes and a decrease in immnosuppressive regulatory T-lymphocytes ($T_{reg}$) following a short course of pre-operative indomethacin or celecoxib in patients with CRC(55). Similarly, indomethacin augmented the anti-carcinoembryonic antigen (CEA) immune response in CRC patients ex vivo through inhibition of COX-2 and $T_{reg}$ activity(56). The authors concluded that COX-2 inhibition could attenuate the inhibitory activity of $T_{reg}$ cells identified in tumour tissue and regional lymph nodes, promoting an effective anti-tumour inflammatory response. The oncological benefits of NSAID-mediated manipulation of the local inflammatory response remain to be elicited.
Systemic inflammation

Suppression of the innate and adaptive immune response has been identified in patients with CRC (57, 58), with further attenuation of systemic immunity identified following exposure to surgical stress (59, 60). Indeed, cancer-related immune suppression is thought to contribute to the risk of recurrence through failure of immunosurveillance and the ability to clear micrometastatic deposits, residual microscopic disease and tumour cells shed at the time of surgery (10, 11). The administration of NSAIDs has been shown to abrogate suppression of systemic lymphocyte and natural killer (NK) cell activity in patients undergoing major surgery (59, 60) and in patients with CRC (57, 58) [Table 3].

Nonsteroidal anti-inflammatory drugs attenuate the acute phase response in patients with advanced cancer, with a decrease in several serum markers of inflammation including C-reactive protein (CRP), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) identified in tandem with an improvement in weight and functional status (51). Furthermore, the effect of NSAIDs on reducing risk of CRC appears to be greatest in patients with evidence of systemic inflammation as measured by soluble TNF receptor-2 (sTNFR-2) but not CRP (52). Interestingly however, in a polyp prevention study utilising low dose aspirin with or without folic acid, aspirin 325mg daily did not decrease CRP but did stabilise it over a three year period whereas patients receiving placebo experienced a significant increase (61). Regardless, CRP did not predict the chemoprophylactic effects of aspirin use. Despite this, the role of NSAIDs in patients with CRC-related systemic inflammation undergoing potentially curative surgical resection remains largely unknown [Table 3]. In patients with rectal cancer, the use of celecoxib has been shown to decrease elevated circulating levels of TNFα and IL-8, potentially through a direct effect on tumour cells and NFκB activity (62). Similarly, in CRC patients with an elevated CRP, ibuprofen decreases circulating CRP, cortisol and IL-6 (63). Whether attenuation of the systemic inflammatory response by NSAIDs in CRC patients undergoing curative surgery translates into a benefit in recurrence rates and survival however remains unknown, and must be addressed by future trials of neoadjuvant and adjuvant NSAID use.

Disease progression and survival

Recent evidence has suggested a potential beneficial effect of NSAIDs on CRC progression, with as much as a 40% reduction in CRC-specific mortality with regular aspirin and NSAID use (19-23). Rothwell and co-workers suggested that the observed reduction in mortality apparent on secondary analysis of cardiovascular disease prevention trials was greater than what would be expected as a result of an NSAID-mediated decrease in cancer incidence alone (19). In addition, evidence that NSAID users are less likely to present with advanced or metastatic disease at diagnosis or follow-up further supports a direct effect on disease progression (16, 17).
Given such compelling evidence of an NSAID-mediated effect on established CRC, it is not surprising that their potential utility as adjuvant agents is currently being considered(13). Certainly, analysis of pre- and post-diagnosis NSAID usage further confirms a potential role for aspirin in addition to potentially curative surgery and adjuvant therapy, with an almost 50% reduction in cancer mortality in patients who commence regular aspirin use following diagnosis(64). Interestingly, no significant survival benefit was seen in patients continuing pre-diagnosis aspirin use, suggesting that cancers arising in these circumstances may be aspirin-resistant (64, 65).

Surprisingly, there have been few trials of aspirin or NSAIDs as adjuvant agents in CRC. Sub-analysis of a randomised trial of 5-fluorouracil and leucovorin with or without irinotecan in patients with stage III colon cancer examined the effect of aspirin and COXIBs on recurrence and survival(66). Even after controlling for treatment arm, NSAID use was associated with a 50% reduction in disease recurrence or death. Two further clinical trials of adjuvant COXIB following curative resection in patients with stage II/III disease ceased recruitment early following concerns regarding the cardiovascular safety profile of prolonged COXIBs(67, 68). The VICTOR trial, which randomised patients who had undergone surgery and adjuvant treatment for stage II/III disease to daily rofecoxib or placebo, was terminated early with only 33% of patients receiving active treatment for at least one year(67). Interestingly however, despite no significant difference in cancer-specific mortality and recurrence-free survival, a statistically significant reduction in recurrence within the first year was found with regular COXIB use. Given that most adenoma prevention trials exposed patients to at least two years of regular COXIB use, the early termination of VICTOR likely precluded the investigators from finding any significant survival benefit.

Given the observed effects on tumour biology and micro-environment, the use of NSAIDs prior to surgery in addition to standard neoadjuvant chemoradiotherapy has also been investigated. Indeed, decreased synthesis of protective prostaglandins via inhibition of COX-2 has been shown to increase tumour radiosensitivity(69). To date however, only phase II feasibility studies have shown a potential increase in tumour response and clinicopathological downstaging with the addition of COXIBs to neoadjuvant chemoradiotherapy(70). Certainly such time-restricted use may be promising and favour the risk-benefit ratio of COXIB use. Regardless, although trials of adjuvant aspirin use are currently recruiting(4), it is clear that further, adequately powered trials are required to fully ascertain the benefit of aspirin, NSAIDs and COXIBS, both in the adjuvant and neoadjuvant setting.

**Statins**

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, commonly known as statins, are primarily used in the treatment of hypercholesterolaemia and atherosclerotic cardiovascular disease and are known to have a number of pleiotropic effects on cell proliferation, angiogenesis, inflammation and endothelial cell function(71, 72). Although a reduction in the risk of several cancers has been found in epidemiological studies(73-75), the results of meta-analyses...
suggest only a modest effect if any of statins on reducing the incidence of CRC in the general population(72, 76). Despite this, the results of in vivo studies and evidence of an increased expression of HMG-CoA reductase in colon cancer, particularly tumours arising in the left colon, suggests a potential role for statins in the treatment of CRC(77).

**Direct tumoural effects**

Mevalonate, the end product of HMG-CoA reductase metabolism and its isoprenoid metabolites are required for the activation of the Ras superfamily of small GTPases by prenylation(78). In turn, these GTPases are crucial for downstream activity of several signal transduction pathways(79); inhibition of mevalonate synthesis by statins subsequently has indirect and direct effects on cell survival and growth. Such inhibition has been shown to have a pleiotropy of effects, including a reduction in cell proliferation(77, 80), induction of apoptosis(77, 80), increased susceptibility to oxidative stress(81) and inhibition of metastatic transformation and angiogenesis(82). A role for non HMG-CoA reductase-mediated pathways has also been suggested, particularly in tumours exhibiting the CpG island methylator phenotype (CIMP). CIMP-associated tumours exhibit hypermethylation of tumour suppressor gene promoter regions, including those implicated in the bone morphogenic protein (BMP) pathway(83). Statin-mediated demethylation of the BMP2 promoter region and subsequent activation of the BMP pathway has previously been shown to increase apoptosis and promote cell differentiation in cell line studies(84); indeed such an effect may suggest a pertinent role for statins in patients with CIMP-associated tumours.

Of further interest, statin therapy has been shown to augment the activity of a number of chemotherapeutic agents, even in resistant cell lines(78, 85, 86). The activity of epidermal growth factor receptor inhibitors, including cetuximab, also appears to be potentiated in vitro and in vivo, even in cell lines with known KRAS mutations and resistance(87). Furthermore, statin therapy may also increase the likelihood of pathological complete response following neoadjuvant chemoradiotherapy(85, 88).

**Effects on cancer-related inflammation**

Cardiovascular disease prevention trials have identified a clear anti-inflammatory effect of statins, with down-regulation of pro-inflammatory cytokines and increased cardiovascular risk reduction in patients with elevated serum inflammatory markers(89). Furthermore, favourable effects on organ rejection following heart and renal transplant suggest a potent immunomodulatory effect, potentially through a direct effect on MHC class II expression and subsequent T-cell activation(90). Similar effects on the inflammatory response may also be expected in patients with CRC, and certainly evidence from clinical trials of a 90% reduction in risk of inflammatory bowel disease-related CRC is compelling(91).
**Local inflammation**

To date, no clinical evidence exists to support the role of statins in influencing the local inflammatory response in CRC, although pre-clinical data suggests a direct inhibitory effect on NF-κB activation, with subsequent down-regulation of COX-2 and pro-inflammatory cytokine expression(92-94). A cohort study of patients undergoing radical prostatectomy found that statin use was associated with a reduced tumour inflammatory infiltrate(95); in contrast to CRC, however, a minimal local inflammatory response is associated with reduced recurrence and improved survival. Whether similar effects on the tumour inflammatory infiltrate in CRC can be expected remains to be seen.

**Systemic inflammation**

Despite a clear benefit on the systemic inflammatory response in cardiovascular disease and in patients following transplant, the clinical application of these effects in CRC is less clear [Table 3]. In an interventional study of patients undergoing curative CRC resection, Malicki and co-workers found a significant reduction in pre-operative serum IL-6 in patients receiving statins(96). In contrast however, a recent study of the systemic inflammatory response to neoadjuvant chemoradiotherapy in patients with oesophageal and rectal cancer found that concomitant statin use did not attenuate the serum inflammatory response or treatment-associated symptoms(97). Further clarification of the effects of statins on cancer-related systemic inflammation is required, and such measures should be incorporated into future studies of the chemotherapeutic benefits of statins.

**Disease progression and survival**

Despite an unclear effect on the incidence of CRC, statins may influence the progression of established disease, with regular statin use being associated with earlier stage at diagnosis in three case-control studies(73, 98, 99). Siddiqui and co-workers, in a case-control study of 326 male users with CRC and regular statin use of at least three years, found a lower mean stage and lower frequency of metastases (28.4% vs. 38.8%, p<0.01) at presentation, with a higher prevalence of right-sided tumours in statin users(99). Furthermore, statin users had superior five-year survival (37% vs. 33%, p=0.03). Coogan and colleagues also found a significant reduction in the risk of stage IV CRC (odds ratio 0.18, 95% CI 0.05-0.62) with regular use of statins for at least 3 months(98). Similarly, a modest reduction of stage III/IV CRC was also observed by Poynter et al, however this failed to reach statistical significance (odds ratio 0.90, 95% CI 0.54 to 1.50). In contrast however, despite finding a reduced risk of CRC with statin use, a recent case-control study with prescription data linkage from Scotland found no difference in stage at diagnosis or survival(75), although the study was underpowered to identify any significant survival benefit. Of more interest, a prospective observational study of statin use within a randomised trial of adjuvant chemotherapy in stage III colon cancer found no survival benefit with statin use, irrespective of duration of use or presence of KRAS mutations(100). These conflicting results may in part be explained by population-based genetic
variation in HMG-CoA reductase, as the presence of single nucleotide polymorphisms have previously been shown to modify the protective effect of statins on risk of CRC(101).

It is clear that the benefit of statins in the treatment of CRC has not yet been defined and that further clinical trials are required. Recruitment for the National Surgical Adjuvant Breast and Bowel Project: Statin Polyp Prevention Trial is currently underway with the aim of investigating the effects of rosuvastatin on polyph/cancer recurrence and metachronous cancer development in patients who have undergone resection for stage I/II colon cancer(102). This and further trials may in time define the role statins may play in treatment of CRC.

**H2RAs**

Since early reports of a survival advantage in patients with gastric cancer(103), there has been interest in the potential use of H2RAs in the treatment of CRC. Aside from potentially beneficial effects on the local and immune responses, pre-clinical data suggests direct anti-tumour effects, including inhibition of histamine as a growth factor and inhibition of tumour-endothelial cell adhesion and motility. Furthermore, prolonged H2RA use has been shown to increase the systemic bioavailability of 5-fluourouracil(104).

**Direct tumoural effects**

Histamine acts as an autocrine tumour growth factor and has been shown to increase CRC cell proliferation and growth in vitro and in vivo(105). Indeed, expression of histamine and histidine decarboxylase, the enzyme responsible for histamine synthesis, is increased in CRC when compared to normal colorectal mucosa(106, 107); increasing expression has been associated with the presence of nodal and distant metastases as well as increased microvessel density, suggesting a potential role in the transformation to invasive and metastatic disease. Furthermore, histamine has also been shown to increase expression of COX-2 and PGE2 as well as vascular endothelial growth factor in cell lines constitutively expressing COX-2(106). Celecoxib has been shown to abrogate the histamine-induced increase in vascular endothelial growth factor expression, suggesting that at least some of the pro-tumour effects of histamine may be mediated by COX-2 and prostaglandin activity(106).

Although several histamine receptors have been identified with H2 and H4 receptor stimulation both being implicated in tumour growth(106), only H2 receptors appear to be preserved in CRC tissue with loss of H1 and H4 receptors when compared to normal mucosa(108). The use of H2RAs in both cell line and animal studies has been associated with a decrease in histamine-induced tumour growth, proliferation and increase in apoptosis in vitro(105, 109). The use of H2RAs may also reduce the metastatic potential of colorectal tumour cells by inhibition of E-selectin expression, endothelial cell adhesion and a decrease in tumour microvessel density(106, 110).
Effects on cancer-related inflammation

**Local inflammation**

Activation of histamine receptor-2 on regulatory T-lymphocytes inhibits the cell-mediated immune response\(^{111}\). Amelioration of this immunosuppressant effect by H2RA use has been shown to subsequently increase tumour infiltration of activated lymphocytes [Table 2]. Adams and co-workers, using quantitative assessments of peri-tumoural lymphocytic infiltration such as the presence of a Crohn’s-like reaction or Jass criteria, found an increased conspicuous lymphocytic infiltration with peri-operative cimetidine use\(^{112, 113}\). Qualitative assessment of the lymphocytic infiltrate using immunohistochemistry have been equivocal, with one study suggesting that H2RA use increases tumour infiltration of CD3+ T-lymphocytes, particularly in patients with late stage disease\(^9\), whereas another study examining the dose-response of cimetidine suggested that H2RAs may exert their effects through other, non-CD3+ cellular components\(^{114}\). Interestingly, Kapoor et al. found that pre-operative use of the H2RA famotidine led to a significant increase in tumour lymphocyte infiltration in colon cancer rather than rectal cancer, with the largest effect seen in those patients with a normal pre-operative CEA\(^{115}\).

**Systemic inflammation**

Histamine attenuates the systemic immune response in patients with CRC. Similarly, the exaggerated post-operative immune suppression experienced in patients with CRC is in part mediated by histamine release\(^9\). The use of H2RAs has been shown to abrogate tumour-associated systemic immune suppression [Table 3], with restoration of circulating levels and activity of T-lymphocyte and NK cell subsets\(^{116}\), potentially via augmentation of IL-2 and interferon activity. Furthermore, peri-operative H2RA use restores normal cell-mediated immunity following surgery\(^{9, 117}\). Although shown to decrease post-operative CRP in patients without cancer \(^{118}\), the effects of H2RA use on systemic cytokine profiles and biomarkers of the systemic inflammatory response in patients with CRC remains unknown.

**Survival**

The first reports of a survival advantage for H2RAs in patients with CRC were in the early 1990s, when Adams and co-workers reported a non-significant increase in 3-year survival with peri-operative cimetidine in patients with Dukes A to C CRC (3-year survival 93% vs. 59%, p=0.17)\(^{112}\). In 1995, Matsumoto and co-workers reported the survival analysis of a multicentre, randomised controlled trial of the effects of cimetidine on adjuvant 5-fluorouracil-induced appetite loss and oesophagitis\(^{119}\). Interestingly, they found a significant increase in survival for both colonic and rectal cancers at almost 4 years. A 10-year analysis from the same patient cohort further confirmed...
increased survival and reduced risk of recurrence with cimetidine, with greatest benefit seen in Dukes C patients(110).

Further studies of differing doses and types of H2RAs given either prior to surgery or as adjuvant treatment have only shown a non-significant trend towards improved survival(114, 115, 120, 121), particularly in patients with Dukes C cancers(120). Subgroup analyses have identified potential patient groups who may be more likely to benefit from H2RA treatment, such as those with microsatellite instability (MSI) low tumours or tumours with a low peritumoural lymphocytic infiltrate(114). MSI-low tumours are less likely to have a pronounced lymphocytic infiltrate(122). As such patients with MSI-low tumours may represent a subgroup of CRC patients likely to benefit from H2RA use, however no large scale studies have examined these relationships and therefore this area merits further investigation. In addition, patients who did not receive peri-operative blood transfusion or develop post-operative infectious complications have similarly been identified as groups who may benefit oncologically(121). Differences in type and dose of drug used as well as inclusion of patients with metastatic disease at enrolment may have precluded finding significant results in these studies. The consistency of trend towards improved survival however does suggest that further, standardised studies are required. A recent Cochrane Collaboration review of H2RAs as adjuvant treatment for resected CRC found overall a significant improvement in survival for cimetidine only (combined hazard ratio (HR) 0.53; 95% confidence interval (CI) 0.32 to 0.87)(123). Given that most of the included trials were performed before the routine use of diagnostic cross-sectional imaging, total mesenteric excision surgery and contemporary chemoradiotherapy regimes, the authors advised caution regarding the applicability of these trials and advised the need for further studies incorporating current “best practice” treatment.

**Conclusion**

Increasing appreciation of the role of host-tumour factors has allowed for better identification and prognostication of patients deemed at high risk, regardless of pathological staging. Indeed, assessment of the local and systemic inflammatory responses should be incorporated in to the routine staging of patients with CRC(7, 124).

Even though measurement of the host inflammatory response allows for greater risk stratification, the appropriate management of such patients remains unknown. Although more intense surveillance may be beneficial, oncological management is impaired by the systemic inflammatory response(13). Certainly it is clear that optimal management should attempt to manipulate the inflammatory response.

In spite of convincing epidemiological evidence, the role of statins, H2RAs and particularly NSAIDs in the management of patients with CRC has yet to be defined. Although shown to have a direct effect not only on tumour biology but also on the host systemic and local inflammatory response, most
evidence has arisen from pre-clinical investigations of CRC in vitro and in vivo. The few clinical investigations reviewed above have been limited in their clinical applicability, and the long-term oncological outcomes have not yet been fully explored.

The use of these agents is an attractive option not only because of their low cost, but also due to their relatively well-defined long-term safety profiles. Clinical trials of adjuvant aspirin and statins in CRC are currently recruiting. It is clear however, that further studies are required to identify the role of anti-inflammatory agents in the management of patients with CRC, and particularly those patients identified at high risk due to the presence of an “unfavourable” inflammatory profile.

Conflict of interest statement

All authors disclose no conflict of interest.
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