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Review Article

Role of NSAIDs in Cancer Prevention and Cancer Promotion

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ABSTRACT

The malignancy state is studied with the help of inflammatory reaction of non-steroidal anti-inflammatory drugs and its prevention is studied. The Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are usually given by physicians in many clinical conditions for the symptomatic treatment of pain and fever. They have anti-inflammatory properties, and these drugs have been investigated for their anticancer effects in various studies. This is because chronic inflammation has a wide connection to carcinogenesis. Anti-inflammatory drugs are also used in cancer treatment and prevention. In the past few years, research has been made that NSAIDs may lower the risk of certain types of cancer. However, there is also research that proves the contrary. NSAIDs are also known for many side effects, including some life-threatening ones.

The use of NSAIDs which includes the risk of gastric cancer and aspirin has a relation between themselves which has not been well studied. This review has been performed in a systematic way and used the analysis of published information to know the association between use of this class of drugs and the risk of gastric cancer. This review will give the relation between the role of NSAIDs in cancer prevention and cancer promotion and chronic inflammation.

Keywords: Non-steroidal anti-inflammatory drugs; Inflammation; Cancer; Pain

INTRODUCTION

Non-Steroidal Anti-inflammatory drugs (NSAIDs) are the class of drugs which help in the pain, inflammation (swallowing) and are also useful in fever. NSAIDs are one of the most used drugs for pain and inflammation because these drugs have antipyretic, analgesic, and anti-inflammatory properties [1]. They are also used as an over-the- counter medication (OTC drug) in many of the cases. Side effects depend on the specified drug but most of the time it is dependent on the risk of gastrointestinal ulcers, heart attack and Renal disease.

NSAIDs have fever relieving effect which has been well documented since the discovery and they have proven useful over the years to decrease pain and inflammatory conditions. It is particularly useful in postsurgical pain, acute and chronic orthopaedic pain [2]. NSAIDs are aspirin, ibuprofen, and naproxen, and all are available over the counter (OTC) in many countries. Paracetamol is generally not classified in an NSAID because it has very less anti-inflammatory activity. It treats pain mainly by blocking COX-2 and inhibiting endocannabinoid reuptake almost exclusively within the brain, but not in the other parts of the body [3].

NSAIDs are of two types that are non-selective and COX-Selector. Most of the NSAIDs are non-selective and COX-1 and COX-2 both activities have been inhibited. These NSAIDs inhibit platelet aggregation and increase the risk of gastrointestinal ulcers while reducing inflammation [4].

LITERATURE REVIEW

Chronic inflammation and cancer

Chronic inflammation may be responsible for causing a variety of cancer. In general, the longer the inflammation persists, the higher will be the risk of cancer. Transient infection occurred in response with Acute inflammation, the development of neoplasia, although many of the same molecular mediators are generated in both the acute and chronic inflammation are not regarded as a risk factor. Inflammatory leukocytes like neutrophils, monocytes, macrophages, and eosinophils give the

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soluble factors that can be used to mediate the development of inflammation-associated cancer, and other cells which include the cancer cells themselves. The relations between chronic inflammation and cancer was first hypothesized by Virchow more than a century ago in 1863. Virchow observed that sites of chronic inflammation were the origin of cancer and that tissue injury and the associated inflammation caused by some irritants encouraged cell proliferation [5].

We can understand between chronic inflammation and cancer by inflammatory bowel disease and colon carcinogenesis. Patients with either chronic ulcerative colitis or Crohn's disease have a five- to seven-fold increased risk of developing colorectal carcinoma [6]. Now it is widely illustrated that chronic inflammation is involved in carcinogenesis. Result of inflammation can be infectious or non-infectious in nature when the aetiology is underlying for cancer development.

The role of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) in cancer

The Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are mostly prescribed by doctors in many clinical conditions for the symptomatic treatment of pain and fever. Because of their anti-inflammatory nature, these drugs have been investigated for their anticancer effects. This is because chronic inflammation has a strong link with carcinogenesis. These anti-inflammatory drugs play a vital role in cancer treatment and prevention. Research has been made that NSAIDs may lower the risk of some types of cancer but there is also research that shows the contrary. Furthermore, NSAIDs have many side effects, including some life-threatening ones.

There are many drugs belonging to the class of drugs known as the NSAIDs. Ibuprofen, mefenamic acid, celecoxib, aspirin, and diclofenac are some examples of NSAIDs. All these drugs have one same property i.e., their ability to block the enzyme cyclooxygenase (COX) or prostaglandin endoperoxide H synthase (PGHS), even though they are very diverse in their chemical structures. The role of NSAIDs in cancer is investigated by the relation between COX, prostaglandin synthesis, and inflammation.

COX, prostaglandin synthesis, and inflammation

COX are the enzymes which are involved in the synthesis of prostaglandins (PGs), which are formed from the arachidonic acid pathway. These COX-derived prostaglandins are a group of 20-carbon lipid compounds known as eicosanoids. Eicosanoids are mostly found in the body and have physiological functions and are called mediators of inflammation. The synthesis of prostaglandin begins with the enzymatic action of phospholipase A2 (PLA2) on membrane phospholipids, which produces arachidonic acid (AA). AA is then metabolized to prostaglandins by COX in two steps. The dioxygenase interacts with AA to yield prostaglandin G2 and successively it was reduced to prostaglandin H2 by the work of peroxidase. On the other hand, tissue-specific synthases help synthesize PGE2, PGD2 PGF2α, PGI2, and thromboxane A2 (TXA2) from PGH2.

At the time of inflammation, PGE2 augments vasodilatation and increases microvascular permeability, which are the classical signs of redness and swelling. It also acts on the neurons of the sensory nervous system and gives rise to pain experienced during the inflammatory process . On the other hand, PGI2 is a potent vasodilator and an inhibitor of platelet aggregation . It is mainly produced by vascular, endothelial, and smooth muscle cells and is involved in the regulation of cardiovascular homeostasis, whereas PGD2 is the major eicosanoid synthesized in the central nervous system and peripheral tissues, which appears to play a role in both inflammation and homeostasis. The research has shown that PGD2 is formed as the predominant prostanoid by activated mast cells and plays a role in the initiation of type I acute allergic responses mediated by immunoglobulin E (IgE). Another prostaglandin, PDF2α, is formed in the female reproductive system predominated from COX-1. Other than its processing in ovulation, parturition initiation and uterine contraction, PGF2α has been found at sites of inflammation such as in the synovial fluid collected from the joints of patients with rheumatoid arthritis, psoriatic arthritis, osteoarthritis, and reactive arthritis.

Characterization of NSAIDs on the lines of COX reaction and specificity

The drugs are popular targets in cancer prevention because of their inhibiting property of NSAIDs on COX, in view of the close relationship between chronic inflammation and cancer. COX-1 and COX-2 are the two subtypes of COX. COX-1 and COX-2 are employed in the PG synthesis. Prostaglandins produced by COX-1 play a role in platelet function and gastrointestinal cytoprotection, whereas those produced by COX-2 are involved in pain and inflammation. The different functions of the COX isoforms explains the side effects of various NSAIDs and also helps in differentiation in the therapeutic effects. There are several ways to categorize NSAIDs. Most convenient method of classification is based on the kinetics of their interaction with COX-1 or COX-2. Such interactions can be (i) freely reversible, time-dependent, (ii) slowly reversible, and (iii) irreversible. The firmness of purpose of the IC50 (i.e., concentration at which 50% of COX activity is inhibited) of COX-1 and COX-2, followed by the assessment of the ratio for COX-1 IC50 and COX-2 IC50, can be used to reduce the preferential COX selectivity of these drugs. The drug inhibits COX-1 and COX-2 to a similar extent which is indicated by a ratio. A ratio >1 indicates that the drug is preferentially selective toward COX-2, whereas a ratio <1 indicates that the drug is more selective for COX-1. For example, COX-1/COX-2 ratios for naproxen and ibuprofen have been reported to be 0.49 and 0.56, respectively, while NSAIDs that have a ratio >1 include acetaminophen (1.6), meloxicam , diclofenac (24.4), celecoxib (32), and etoricoxib (162).

Targeting inflammation in cancer

Due to the relation between chronic inflammation and cancer, there is a very big reason for researchers to target inflammation in cancer prevention and treating. Many targets which has explored in combating inflammation relevant to cancer include fibroblast growth factor (FGF) and its receptor and COX, NF-

kB, cytokines/chemokines and their receptors as also as vascular endothelial growth factor.

As NSAIDs are well-known COX inhibitors, they are inevitably a popular anticancer anti-inflammatory candidate in cancer therapy and prevention. Some of the products of COX activity (e.g., prostaglandin E2) are involved in tumorigenesis that is why Inhibiting COX is a good strategy. Prostaglandin E2 (PGE2) was shown to be increased in cancer cells and is capable of stimulating cancer cell proliferation and invasion. The COX-2/PGE2 signalling pathway has been reported to play a crucial role in colorectal tumorigenesis. Research suggests that an increase in the expression of COX-2 and PGE2 supports colorectal cancer cell survival especially in a glucose-deprived tumour microenvironment.

Role of NSAIDs in cancer prevention

NSAIDs play a vital role in cancer prevention. NSAIDs decrease the risk of cancer. There is a lot of research that gives evidence of antitumor effects in NSAIDs. In this the discussion will be on the role of NSAIDs in chemoprevention. There are also some inventions that show a major difference between aspirin and non-aspirin NSAIDs.

Evidence from *in vivo* and *in vitro*

Many experimental studies have been made that show the mechanisms of anticancer effects of NSAIDs either using animal models cell lines. Many nonaspirin NSAIDs have been shown to exert their cancer-protective effects. One other study has made that ibuprofen-inhibited cell proliferation in mouse and human colorectal cells. A 40%-82% tumor growth inhibition and a reduction in liver metastases in mice with colorectal cancer were also observed in the same study.

Similarly, Evidence has also revealed the anticancer effects of aspirin. Xiang et al. demonstrated the antiproliferative and antiapoptotic effects exerted by aspirin on HeLa cells. There is a change observe that cervical cancer cells in terms of decrease of ErbB2 expression and subsequently mode of action of the antiapoptotic effects was due to its inhibition on the activation of extracellular signal-regulated kinase (ERK) and AKT. The demonstrated analysis are shown to be focusing on the aspirin with the small effect on the human hepatocellular carcinoma, this also results in the cells cycle decline and the growth restriction and when both drugs are mutually taken antitumor activity in a acute way seemed in nude mice with a HepG2 cell xenograft.

Evidence from epidemiologic studies

The studies of the protection or the prevention of the cancer related disease is co-related to the evidence of pharmacological effects of aspirin and non-aspirin NSAIDs. It is also concluded that the effect or the investigational approach to the gastrointestinal tract cancer and digestive cancer could be studied along with the digestive and colorectal cancer. It was found that the risk for gastric cancer was reduced in regular NSAID users (OR 0.3; 95% CI: 0.1-0.6). The analysis of the cases and the control studies were observed. The 10,280 cases and 102,800 controls established that the chances or the possibilities of the colorectal cancer risk was observed to be reduced by 27% when we employed the low dose aspirin (OR=0.73; 95% CI: 0.54 to 0.99) and subsequently high intensity aspirin use of that dosage form also exhibited the reduction in the disease factor with high COX-2 selectivity.

The studies revealed that the cancers developed from GIT and breast cancer, and other than that NSAIDs were useful in minimizing the risk of cancers from the reproductive system in males and females. Then the prostate cancer reduction from NSAIDs and the case and control studies i.e. 819and 879 respectively which resulted in the decrease in the prostate cancer risk (OR=0.77, 95% CI: 0.61-0.98) for drugs inhibiting COX-2 (OR=0.48, 95% CI: 0.28-0.79). Reduce effect of prostate cancer in the case of men was studied when we have used non aspirin NSAIDs (OR = 0.49, 95% CI: 0.27-0.89) with the history of prostatitis (OR=0.21, 95% CI: 0.07-0.59).In the same study, aspirin use was slightly and negatively associated with prostate cancer (OR = 0.86, 95% CI: 0.65–1.14); however, such association was not statistically significant.

Role of NSAIDs in cancer promotion

The comparative studies have been made on the prevention of the risk of cancer through NSAIDs. But the studies based on the NSAIDs role in the promotion or the increase of the relative risk of the cancer have been more statutory based on the origin, the studies depicted that the increased risk of renal cancer and the NSAIDs use has been followed by several studies including 77,525 women for 16 years and 49,403 men for 20 years and 333 renal cell carcinoma cases were documented. Subsequently the dose response relation was plotted between non aspirin NSAIDs use and renal cancer risk.

Although earlier studies reported that the use of NSAIDs reduces the risk of endometrial cancer, the role of NSAIDs in endometrial cancer remains unclear as there are some conflicting findings in this area of research. The most recent research has marked the evidence of relationship or interaction among the NSAIDs and the endometrial cancer death rate and regular occurrence with the help of an association (HR=1.66, 95% CI: 1.21 to 2.30) amidst NSAIDs.

The study of the NSAIDs and aspirin that demonstrated that both are of the category that lowers prostate specific antigen levels and helps in reducing pain and also results in the delay of treatment and symptom identification and thereby the risk should be reduced and should be carefully evaluated before publishing literature. It suggested that not conclusive evidence could be discovered relating epidemiologic study and there is a scope of study of the mechanism and investigation in the effect of NSAID in cancer.

CONCLUSION

Innumerous results or inference could be taken out from this content. First of all several analyses on the employment of NSAIDs in cancer that consist of aspirin and not aspirin and it demonstrate the regular or the irregular evaluation in the terms of drugs in cancer with the constant lookout at the increase or the decrease of the certain parts of cancer and the associated

reporting. These studies are originative in nature with the laboratory evaluation of the NSAIDs and cancer studies and the pharmacological mode of action of NSAIDs in terms of protective effects and it could be concluded that there is some scope for the improvement of the study of increase and decrease of the cancer risk. Originative studies are preferred but not conclusive in the terms of study of the research and it is also pretty evident that the NSAIDs dose depends on the type of cancer with the increase or decrease in cancer and it came out in a study that NSAIDs also differ between the subunits of the molecules as same in breast cancer.

Lastly, NSAIDs are associated with other non-cancerous, serious complications such as myocardial infarction, gastrointestinal bleeding, and renal failure. This is demonstrated that NSAIDs in the cancer treatment firstly need to be carefully observed and the prevention and the balance should be looked out for in the risk assessment and the advantages of the drug in relation to the findings, not fully evaluated the mode of action and the serious chronic damage to life.

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