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Review article

A REVIEW ON EFFECT OF NSAIDS ON CANCER PROGRESSION

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ABSTRACT

Early findings from biologic research suggest that the administration of NSAIDS may reduce the risk of cancer. Evidence has come from animal toxicology, experimental pharmacology, clinical medicine, and epidemiology. Preclinical and clinical studies have clearly shown a benefit of non-steroidal anti-inflammatory drug (NSAID) use in reducing cancer risk. NSAIDs are a chemically diverse family of drugs available over-the-counter or by prescription and are commonly used for the treatment of inflammation, pain, or fever. Many drugs belong to the class of drugs known as the NSAIDs. Some examples of NSAIDs include ibuprofen, mefenamic acid, celecoxib, aspirin, and diclofenac drugs have one common property, i.e., their ability to block the enzyme cyclooxygenase (COX). COX are enzymes that are involved in the synthesis of prostaglandins (PGs), which are derived from the arachidonic acid pathway. It is also found that some distinguish characteristics of NSAIDS are induced tumor cell apoptosis, down regulation of EGFR expression, protect and repair DNA damage, etc.

Key Words:- NSAIDS, Toxicology, Celecoxib, Cyclooxygenases, Prostaglandins, Apoptosis.

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INTRODUCTION

Since the 1970s, work in several disciplines (toxicology, pharmacology, clinical medicine, epidemiology) increasingly has suggested that aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) may reduce the occurrence or progression of colorectal cancers and polyps and perhaps of other gastro intestinal tumors (Rees, K., *et al.*, 2011). The potential application of these findings for chemoprevention of such cancers in a human being, now deserves serious consideration to be concentrated (Sekandarzad, M. W., *et, al.*, 2017). Recent findings from different areas of biologic research suggest that non-steroidal anti-inflammatory drugs (NSAIDs) may reduce the risk of human large bowel cancer and perhaps of cancer at other gastrointestinal sites (Huang, W.-Y., *et al.*, 2014).

Evidence has come from animal toxicology, experimental pharmacology, clinical medicine, and epidemiology (Xu, X. D., *et al.,* 2015). Preclinical and clinical studies have clearly shown a benefit of non-steroidal anti-inflammatory drug (NSAID) use in reducing cancer risk. NSAIDs and coxibs inhibit PG biosynthesis (Bansal, A., & Celeste Simon, M., 2018). One among the prostaglandins produced at high levels in the tumor microenvironment is PGE2, which is thought to play a significant role in cancer progression. Numerous experimental, epidemiologic, and clinical studies suggested that the non-steroidal anti-inflammatory drugs (NSAIDs), particularly the highly selective cyclooxygenase (COX)-2 inhibitors, have potential to act as antitumor agents (Garon, E. B., *et. al.*, 2015).

NSAIDs restore normal apoptosis in human adenomatous colorectal polyps and also in various cancer cell lines that have lost adenomatous polyposis coli gene function. NSAIDs also inhibit angiogenesis in cell culture and rodent models of angiogenesis (Corley, D. A., *et. al.*, 2003). Many epidemiologic studies have found that long-term use of NSAIDs is associated with a lower risk of colorectal cancer, adenomatous polyps, and, to some extent, low incidence for other cancers. Two NSAIDs namely Sulindac and Celecoxib, have been found to inhibit the growth of adenomatous polyps and cause regression of already existing polyps in randomized control trials of patients with existing familial adenomatous polyposis (FAP) (Lee, J. H., *et. a;*, 2013).

Nonsteroidal Antiinflamatory Drugs (NSAIDS) and There Role in Cancer

Many drugs belong to the class of drugs known as the NSAIDs. Some examples of NSAIDs include ibuprofen, Mefenamic acid, celecoxib, Aceclofenac, Aspirin, and Diclofenac. These drugs have one common and significant 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 best viewed in the interrelationships between COX, prostaglandin synthesis, and inflammation.

COX, Prostaglandin Synthesis, and Inflammation

COX are enzymes that are involved in the synthesis of prostaglandins (PGs), which are derived from the arachidonic acid pathway .These COX-derived prostaglandins belong to a group of 20-carbon lipid compounds known as eicosanoids. They are widely found in the body with many physiological functions and are known 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. First, a dioxygenase activity acts on Arachidonic acid to produce prostaglandin G2 (PGG2) and subsequently, PGG2 is reduced to prostaglandin H2 (PGH2) by a peroxidase activity. On the other hand, tissue-specific synthases helps in synthesis of prostaglandins like PGE2, PGD2, PGF2α, PGI2, and thromboxane A2 (TXA2) from PGH2. During inflammation, PGE2 augments vasodilatation and increases micro vascular permeability, which lead to the classical signs of redness and swelling.

It also acts on the nerve terminals 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. Research has shown that PGD2 is produced as the predominant prostanoid by activated mast cells and plays a very important role in the initiation of type I acute allergic responses mediated by immunoglobulin E (IgE).

Another prostaglandin, PDF2*α*, is derived from COX-1 in the female reproductive system predominantly. Other than its involvement in ovulation, uterine contraction, and parturition initiation, PGF2_ 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. It is worth mentioning that platelets are also involved as active players in the inflammatory processes as a result of COX's activity on prostaglandin synthesis. Although platelets were once primarily recognized as a key player in hemostasis, its role in inflammation and cancer has been increasingly described in the published literature. TXA2 is a PGH2-derived substance produced by activated platelets, which exerts a potent vasoconstrictor effect and a stimulatory effect on platelet aggregation.

However, other than its hemostatic role, TXA2 has been shown to be involved in inflammation and linked to allergic reactions, modulation of acquired immunity, angiogenesis, and cancer cell metastasis. Platelets' influence on tumor genesis may involve (I)increase of tumor cell survival by forming platelet aggregates surrounding tumor cells, (ii) increased tumor cell adhesion to the endothelium that leads to tumor cell arrest and extravagation, and (iii) production of lipid products such as TXA2 which increases tumor vascularization and dissemination of tumor cells into the bloodstream . A past research has reported platelet-induced overexpression of COX-2 in human colon carcinoma cells, whereas increased COX-2-dependent PGE2 synthesis has been linked to tumorigenesis by mechanisms such as suppression of dendritic, natural killer, and T-cells and type-1 immunity, as well as promotion of type-2 immunity that in turn promotes tumor immune evasion. In addition, PGE2 was

demonstrated to promote colorectal cancer stem cell expansion and metastasis.

Chronic Inflammation and Cancer

In order to understand clearly the role of NSAIDs in cancer, one must examine the link between chronic inflammation and carcinogenesis. The relationship between chronic inflammations and cancer was first hypothesized by Virchow more than a century ago in 1863. He observed that sites of chronic inflammation were the primary origin of cancer and that tissue injury and the associated inflammation caused by some irritants encouraged cell proliferation. Many molecular targets and signaling pathways in apoptosis, cell proliferation, and angiogenesis are common to both inflammation and carcinogenesis. Dysregulation of these signaling pathways during chronic inflammation often leads to aberrant expression of pro-inflammatory genes, which play a role in malignant transformation. Many cytokines act like a double-edged sword in tumor development, depending on the tumor microenvironment. Some of these cytokines, which exert antitumor effects, may induce cell transformation and malignancy during chronic inflammation. Some examples of cytokines that are involved in inflammation and the tumor microenvironment include tumor-necrosis factor-α (TNF-α), interleukin-6 (IL- 6), transforming growth factor ß (TGF-β), and interleukin- 10 (IL-10) .The link between cancer and chronic inflammation is further strengthened by the fact that many cancer cells express cytokines and chemokines, as well as their receptors, all of which are important in cell proliferation, angiogenesis, cell migration, and metastasis .

In addition to cytokines, other pro inflammatory molecules such as inducible nitric oxide synthase (iNOS), reactive oxygen species (ROS), and other nuclear factor kappa-light-chain enhancer of activated B cells (NF-kB) are also up regulated in chronic inflammation. It is now widely accepted that chronic inflammation is involved in carcinogenesis. The underlying etiology for cancer development as a result of inflammation it may be either infectious or noninfectious in nature.

Classification of NSAIDS

NSAIDs are a chemically diverse family of drugs available over-the-counter or by prescription and are commonly used for the treatment of inflammation, pain, or fever. Their anti-inflammatory activity is attributed to the inhibition of COX enzymes that catalyze the conversion of arachidonic acid into prostaglandinH2, the precursor for the synthesis of prostaglandins (PG), prostacyclin, and thromboxane A2—collectively referred to as eicosanoids. The three major PG products of COX activity, PGE2, PGD2, and PGF2a, promote inflammation, pain, and fever.

Vane was the first to show that aspirin inhibits inflammation by suppressing PG synthesis, whereas COX inhibition was later shown to be responsible for this effect, Aside from their role in inflammation, eicosanoids are critically important for the homeostatic maintenance of the gastrointestinal mucosa, blood clotting, regulation of blood flow, and kidney function. Two distinct isoforms of COX, COX-1 and COX-2, have been reported.COX-1 is constitutively expressed in most tissues, whereas COX-2 is induced by inflammatory stimuli, mitogens, or growth factors, and is generally associated with pathologic processes. Conventional NSAIDs, such as aspirin, ibuprofen, sulindac, and indomethacin, inhibit both COX-1 and COX-2, although aspirin has a unique mechanism involving irreversible acetylation of a serine residue in the catalytic domain of both enzymes. The recognition that COX-2 is the main mediator of inflammation lead to the development of a new class of inhibitors with COX-2 selectivity (coxibs) to bypass gastrointestinal and renal toxicities associated with nonselective NSAIDs.

Association between NSAIDs and Cancer Distant Metastasis

Eleven studies involving 247,826 patients and more than 40,000 events reported on the risk estimates for cancer distant metastasis in patients exposed to NSAIDs before or after diagnosis. Among the eleven studies, ten studies reported the negative association between NSAIDs and cancer metastasis, although the results from two studies were not statistically significant. The remained study found positive relationship between NSAIDs and cancer metastasis with statistically significance. Overall, compared with the reference group, cancer patients taking NSAIDs showed a significantly reduced risk for metastasis development (RR: 0.623, 95% CI 0.515–0.753, $p < 0.001$).

Association between NSAIDs and Cancer LN Metastasis

We subsequently investigated the relationship between NSAIDs and lymph node metastasis. Six studies involving 110735 participants and approximately 20,000 patients with LN metastasis were recruited in this analysis. All of these studies (predominantly breast cancer and prostate cancer clinical trials) focused on the relationship between pre-diagnostic use of NSAIDs and LN metastasis. Four of these studies found an association between pre-diagnosis use of NSAIDs and a reduced risk of LN metastasis, although only one study reported statistically significant results. However, compared with the referent group, the risk of LN metastasis slightly decreased in the pre-diagnostic NSAID use group (RR = 0.949, 95% CI 0.914–0.985, $p = 0.006$, $I2 = 36.3\%$).

Role of COX-2 in Cancer Progression

COX-2 is known to produce prostaglandins that regulate tumor-associated angiogenesis, modulate the immune system, regulate cell migration/invasion, and also inhibit apoptosis, all of which promote cancer progression. Other byproducts of the COX-2 pathway, such as Malondialdehyde, directly form DNA adducts resulting in mutations that could initiate carcinogenesis. All of these effects stimulate tumor progression and help to explain the pro -neoplastic role of COX-2 (10, 21). One of the major prostaglandin products of the COX-2 pathway in the gastrointestinal tumor microenvironment is PGE2.

NSAID VS Placebo

All studies considered aspirin or other traditional NSAIDs. There were no studies relating to COX-2 inhibitors. All publications studied single doses of analgesic agents and were performed before 1991. All studies demonstrated analgesic superiority of NSAIDs when compared with placebo (one study only showed advantage with higher doses of aspirin). NSAIDs and doses that demonstrated superior outcomes to placebo were ketorolac 10 mg p.o., ketorolac 10 mg i.m., ketorolac 30 mg i.m., ketorolac 90 mg i.m., ketoprofen 100 mg p.o., ketoprofen 300 mg p.o., aspirin 1000 mg p.o., aspirin 650 mg p.o., and mefenamic acid 250 mg p.o. Adverse effects appeared comparable between NSAID and placebo groups.

NSAID VS NSAIDS

Some publications identified comparing different NSAIDs; only two were published in the past 20 yr.A single study related to COX-2 inhibitors was identified. Most findings reported no significant differences amongst the NSAIDs investigated; however, the largest sample size used, involved 60 participants in each arm, raising the question of whether these studies are powered appropriately to detect efficacy differences between drugs with the same mechanism of action. The one study that reported a difference in pain relief and patient preference, found ketoprofen 400 mg significantly superior to both ketoprofen 100 mg and aspirin 1g. However, the maximum licenced daily dose for ketoprofen is 300 mg, making the clinical relevance of this finding uncertain. Most publications failed to identify a significant difference between adverse events associated with different NSAIDs. One study found significantly greater gastrointestinal side-effects requiring antacid therapy in those taking aspirin compared with piroxicam.

NSAID VS OPIOIDS

Studies identified comparing NSAIDs with opioids. Sample sizes were again small (Most n¼100). Only one study conducted in the past 20 year was identified. Facilitating interpretation by combining data is extremely difficult. Although oral morphine equivalence would theoretically allow such comparisons, other factors not least heterogeneity in study design, duration of follow-up, and outcome measures render this a challenging and potentially futile exercise. The findings of these studies vary considerably. Of the eight studies detailed in, outcome measures favored the opioid treatment arm in two studies, the NSAID treatment arm in three studies, and no significant difference in the remaining three. No two studies compared the same two agents. A total of five NSAIDs and four opioid analgesics were utilized in these eight studies. One additional publication mentions unpublished data, for which the methodology and specifics cannot be fully interrogated.

NSAID WITH OPIODS

A total of five identified studies compared NSAIDs against NSAIDs combined with an opioid, and are detailed in none of these studies involved COX-2 inhibitors, nor were conducted in the past 20yr. Only two of these studies considered use of these agents beyond a single dose. Two publications reported that the combination of NSAID plus opioid resulted in either superior analgesic efficacy or fewer patients withdrawing because of inadequate analgesia. However, only one of these studies report that their findings were statistically significant. The remaining three studies failed to show any significant difference in analgesic efficacy between the two groups. Although three studies report a greater incidence of adverse effects associated with the combination treatments, only one performed statistical analysis and concluded that the difference was not significant. One further publication details a randomized controlled trial of 342 patients assigned to three treatment arms (diclofenac with morphine, celecoxib with morphine, and both diclofenac and celecoxib with morphine). The dose of NSAID remained constant, whereas opioid dose was titrated over the four week study period. A 50% reduction in visual analogue scale (VAS) scores across all three groups was reported. This reduction was greater in the group taking both diclofenac and celecoxib in combination with morphine ($P<0.05$).

Advances in Antitumour Effects of NSAIDS

Aspirin is used in primary tumor prevention

A great number of large epidemiological studies found that long-term use of low-dose aspirin (75–300 mg/daily) can effectively inhibit a variety of cancer incidence, malignant cancer metastasis rate, and provide patients with a high survival rate. At the same time, the risk of esophageal cancer, gastric cancer, cholangio carcinoma and breast cancer in the aspirin group was significantly decreased. Rothwell et al15 analyzed five large randomized clinical trials which examined the effects of aspirin (75 mg/daily or more) on tumors. The results of the analysis showed that aspirin could reduce

the incidence of distant metastases by 36% and reduce the risk of cancer-specific mortality by 50% compared with the control group. For patients with adenocarcinoma, the risk of morbidity can be reduced by 46%. In patients with no metastatic adenocarcinoma at the time of initial diagnosis, the use of aspirin in the subsequent long-term observation can reduce the associated cancer metastasis rate by 70%.

It is also found that some distinguish characteristics of NSAIDs are induced tumor cell apoptosis, down regulation of EGFR expression, protect and repair DNA damage etc.

CONCLUSION

Based on a large amount of clinical data NSAIDs has been gradually extended to clinical cancer treatment. The National Comprehensive Cancer Network colorectal cancer guide (2017 version) established the role of NSAIDs in the secondary prevention of cancer. However, taking into account the side effects of long-term use of NSAIDs, the large-scale use of NSAIDs as a cancer chemical prophylaxis have the need to weigh up the pros and cons for individual patients. The US "Guidelines for the use of Preventive Drugs" clearly state that daily intake of "low-dose" aspirin which is one of the prominent NSAIDs has anticancer effect. In future studies need to focus on molecular classification of NSAIDs and choose population accordingly for study and also dose of NSAIDs to be choose wisely in order to achieve the anticancer benefits. Further research work should focus on exploring the relationship between cancer and role of different types of NSAIDs, clarifying the role of them in tumorigenesis and development, evaluating which stage of NSAIDs intervention could give more benefits, proposing potential molecular mechanisms and various new ideas for NSAIDs in clinical cancer prevention and treatment.

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