British Journal of Medicine & Medical Research
8(2): 123-139, 2015, Article no.BJMMR.2015.433
ISSN: 2231-0614

SCIENCEDOMAIN *international*
www.sciencedomain.org

The Role of Celecoxib as a Cox-2 Inhibitor Increasing the Radiosensitivity of Tumor Tissue

Yousef Jalalabadi[1,2], Alireza Shirazi[3], Mohammad-Reza Ghavam–Nasiri[4*], Amir Ale Davood[5] and Dariush Sardari[1]

[1]Department of Medical Radiation Engineering, Science and Research Branch, Islamic Azad University, Tehran, Iran.
[2]Department of Engineering, Kashmar Branch, Islamic Azad University, Kashmar, Iran.
[3]Department of Medical Physics and Biomedical Engineering, Faculty of Medicine, Tehran University of Medical Science, Tehran, Iran.
[4]Iranian Society of Radiation Oncology, Tehran, Iran.
[5]Department of Cancer Research, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

Authors' contributions

This work was carried out in collaboration between all authors. Author MRGN designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author YJ managed the literature searches; analyses of the study performed the spectroscopy analysis. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2015/16946
Editor(s):
(1) E. Umit Bagriacik, Department of Immunology, Gazi University, Turkey.
Reviewers:
(1) Isao Kuroda, Department of Urology, Ibaraki Medical Center, Tokyo Medical University, Japan.
(2) Xiangjiao Meng, Department of Radiation Oncology, Shandong Cancer Hospital and Institute, China.
(3) Zhiqiang Qin, Departments of Microbiology/Immunology/Parasitology, Louisiana State University Health Sciences Center, United States.
(4) Anonymous, Malaysia.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=1114&id=12&aid=8892

Review Article

Received 20th February 2015
Accepted 25th March 2015
Published 20th April 2015

ABSTRACT

One of the major causes of death in the world is cancer. Due to significant advances in molecular and cellular biology, previous approaches in cancer treatment have progressed, applying new strategies. Identification and use of chemotherapy and radiation sensitizers and their effect on the further destruction of the cancer cells have received a lot of attention in medical studies. The main objectives of this Review Article are to identify the inhibitors of the enzyme COX -2 and

**Corresponding author: Email: Ghavamnasirimr@mums.ac.ir;*

mechanisms that are known to inhibit the enzyme in order to increase the sensitivity of tumour cells to radiation. COX-2 enzyme inhibition with Celecoxib and the prevention of the restoration of this tumour have been a major challenge for researchers.

Evidence Acquisition: The mechanism by which the cells are radio sensitized can increase the initial damage, inhibiting the restoration and redistribution of the cell cycle as well as blocking in the more radio sensitized zone.

Enhanced response to treatment would be initiated by identifying enzymes that are involved in increasing tumour growth and followed by inhibiting tumour growth and restoration. COX-2 is one of the enzymes expressed highly in tumour growth. Inhibiting this enzyme will enhance the response rate of treatment followed by the death of tumour cells. High expression of COX-2 gene in tumours is more related to tumour aggressive behaviour and a worse prognosis.

Results: There are five mechanisms that the COX-2 enzyme applies to develop tumours and increase the malignant phenotype of tumour cells: 1- Apoptosis inhibition 2- Angiogenesis increase 3- Invasion rise 4- Inflammation modulation/weakened immunity, suppression 5- Procarcinogen conversion to carcinogens. Known mechanisms in increased sensitivity to radiation by Celecoxib: 1-COX-2 inhibition and subsequent reduction in PGE2 production result in increasing apoptosis and decreasing angiogenesis proliferation-2. The mechanism of COX-2 inhibition by Celecoxib has not been fully recognized. The drug inhibits the COX-2 enzyme through TNF-α signalling by nuclear transfer inhibition of growth factor. It also inhibits NF-KB transcription factor activation.

Apoptosis inhibition is one of the mechanisms implemented by COX-2 that increases tumourigenesis. Cell cycle arrest at G1-S is one of the most sensitized areas to radiation. Studies in the field of pancreatic and ovarian carcinoma cells show cell cycle arrest at G1-S; the mechanism by which this arrest happens is not fully understood.

Conclusions: Celecoxib, as a COX-2 inhibitor that affects and inhibits some enzymes and creates changes in the cell cycle process, has the role of a radiosensitizer. Celecoxib prevents cancer. Celecoxib inhibits tumour growth delay and the amount is insignificant. Simultaneous application of radio sensitzers such as celecoxib and chemo radiotherapy procedures will have a more damaging effect on the tumour cells.

Keywords: Cyclooxygenase-2; radiosensitizer; Celecoxib; radiotherapy; tumour.

1. CONTEXT

One of the major causes of death in the world is cancer. Yet no conclusive treatment has been found for cancer. At the present time and according to the type and grade of the disease, patients with cancer are classified into treatment and mitigation. A significant number of patients diagnosed with oesophageal cancer may be at a metastatic state [1].

After the initial diagnosis, only one out of every five patients with oesophageal cancer survives for three years [3]. Treatments for patients with cancer include surgery, chemotherapy, radiation therapy, and a combination of these. The superiority of concurrent chemo radiotherapy to sole radiotherapy, alternating radiotherapy, and chemotherapy has been proved [2].

Due to significant advances in molecular and cellular biology, previous approaches in cancer treatment have progressed with the application of the new strategies. Identifying medications for chemotherapy as sensitizers for cancer cells to radiotherapy are examples of improvements in the context of cancer treatment. In many cases, studies show that the sole application of radiotherapy or chemotherapy has no significant effect on cancer treatment. Studies on identifying chemicals increasing radiation effects have led to the creation of concurrent chemo radiotherapy [3].

Applying a combination of radiotherapy, chemotherapy and radiosensitizers was an attempt to enhance the toxicity potential of combined radiotherapy and chemotherapy.

In this process, when the two methods are applied concurrently, the two modalities have the same effects they have had in the absence of each other. A synergistic impact can be explained via effects interaction. In performing this experiment, radiosensitizers in tumour tissue usually target increasing or maintaining the toxicity traits of treatment modality. In this method, sensitizers increase the therapeutic index of radiotherapy, chemotherapy or a combination of both. Compounds which can be applied concurrently with radiation therapy have developed significantly.

The main objective is to identify the inhibitors of the enzyme COX -2 and mechanisms that are known to inhibit the enzyme in order to increase the sensitivity of tumour cells to radiation Celecoxib, one of the medications under study in this paper, is considered a radio sensitizer in tumour tissue. Radiation dose rates in different tissues are directly related to the number of activator enzymes. For example, in animal models, this relationship is characterized by producing PGE2 [4].

Cell restoration initiates after having received critical damage and radiotherapy. Several enzymes and proteins mobilize, and their expression increases in the cell.

In vitro experiments have shown that these inhibitors are among the factors enhancing radiation. They are considered to be suitable targets for clinical studies to evaluate the enhanced response rate to radiation therapy [5]. Taking selective inhibitors of cyclooxygenase-2 enzyme will be a potential method in improving the effectiveness of radiotherapy [6].

2. RADIOSENSITIZERS

Simultaneous application of radio sensitzers such as celecoxib and chemo radiotherapy procedures will have a more damaging effect on the tumour cells.

Accordingly, application of these materials has a greater advantage over the extra dose radiation. To improve treatment results, transforming chemicals should be injected into the pathway of radiation. A 20 to 30 per cent increase in radiation dose would highly control the tumour since most of the sensitizer enhancement ratios (SER) range between 1/2 and 1/3.

According to the dose-response curve in Fig. 2 a radiosensitizer can shift the probability of tumour control zone to the left side without much change in the probability of complications, and ultimately lead to a greater distance between the two curves.

$$\text{OER} = \frac{\text{Radiation dose required for a given level of cell killing under hypoxic conditions}}{\text{Radiation dose required for a given level of cell killing under oxygenated conditions}}$$

$$\text{SER} = \frac{\text{Radiation dose required for a given level of cell killing without sensitizer}}{\text{Radiation dose required for a given level of cell killing with sensitizer}}$$

The Oxygen Enhancement Ratio (OER) describes the potency of a sensitizer. It is the ratio of radiation dose required for a given level of cell killing under hypoxic conditions compared with the radiation dose needed in air to produce the same end point. The Sensitizer Enhancement Ratio (SER) is a similar concept that, compared with the agent radiation dose, mathematically describes the ratio of a radiation dose without a sensitizing agent [6]. The OER will depend on the oxygen concentration, whereas the SER will depend on the sensitizer concentration at the time of iradiation. Therapeutic index is defining the SER of the tumour divided by the normal tissue SER. in normal tissues with electron affinic sensitizers-oxygen-mimetic radio sentisizers- The SER is 1.0. Theoretically, SER can exceed OER. (i.e.), for radio sensitisers with reductive metabolism and toxic effect having oxygen-mimetic effect property the SER is greater than OER [7].

Sensitization of tumour cells to radiation can be generated through the following ways:

1. Application of oxygen-mimetic compounds
2. Deploying agents that increase DNA sensitivity to radiation
3. Using agents that interrupt DNA restoration
4. Increasing oxygen delivery to tissues by decreasing haemoglobin oxygen affinity and increasing blood oxygen carrying capacity
5. Cell cycle inhibition in the most sensitive areas of radiation

A good radiation sensitizer should have the following characteristics:

- acts selectively in tumours compared with normal tissues
- reaches tumours in adequate concentrations
- embodies predictable pharmacokinetics for timing with radiation therapy
- administers with every radiation treatment in a standard regimen
- eliminates the cell quickly
- is an electrophile
- bears minimally-owned toxicity
- enhances radiation toxicity at a minimum, and manageably
- has low lipophilicity to not pass the brain barrier and cause neuropathy
- potential mechanism range includes [8]:

    1. direct DNA damage

2. cell biochemical/molecular response alteration to radiation
3. radiation restoration decrease
4. cell death by the new mechanism

The mechanism by which the materials sensitize the cells to radiation may include initial damage, restoration inhibition and cell cycle redistribution. The halogenated pyrimidines are an example of a class of modifiers that in part enhance the radiation response by increasing damage. It has been demonstrated that the incorporation of halogenated pyrimidines into cellular DNA increases the amount of DNA damage [9] and adversely affects DNA restoration systems [10]. Extensive studies show that maximal radiation damage restoration lasts for three to six hours [11]. Agents that inhibit radiation restoration in tumours must be administered daily with radiation. Because of their lack of selectivity, most agents used to sensitize tumours also radiosensitize normal tissue. It is well accepted that cells vary in their response to radiation depending on their position in the cell cycle [12].

For instance, cells in G2/M are three-fold more sensitive to radiation than cells in late S-phase and primary G1. An agent that blocks the progression of a cell in a radiosensitive phase of the cell cycle might induce radiosensitization. Currently, several chemotherapy agents can impose a cell cycle block, leading to subsequent radiosensitization [13]. Preclinical studies show that Paclitaxel, which is evaluated in clinical chemoradiation experiments, blocks the cell cycle at G2/M phase and radiosensitizes many human tumour cell lines [14] and murine tumour models [15].

One of the major approaches in cancer therapy is the selective targeting of hypoxic cells around the centre of the tumour that (due to a lack of sufficient oxygen) is less sensitive to radiation. Compared with the tumour and normal cells, this is the major factor in the failure of treatment. Plenty of studies have been conducted for this reason to increase the sensitivity of these cells to radiation, resulting in the identification and imaging of the hypoxic zone.

Nitroimidazole sensitizers including Metronidazole [16], Misonidazole (19) Etanidazol [17], Pimonidazole, Ro-03-8799 [18], Nimorazole [19], and Pimonidazole in lower concentrations are used as markers for hypoxic cells. Halopyrimidine radiation sensitizers include: bromodeoxyuridine (BUdR) and iododeoxyuridine (IUdR) [20].

Enzymes involved in tumour growth must be identified, and for effective treatment prevented from tumour restoration and growth. COX-2 is one of the enzymes that are highly expressed in tumours, and its inhibition results in increased tumour response treatment and death.

3. Evidence Acquisition

Papers selected for this study are review papers for the years 1985 to 2010. Scholar Google search was also used to identify the articles from 2010 to 2014 depending on the scientific relevance.

Cox: Cyclooxygenase (COX) is the key enzyme required for the conversion of arachidonic acid to prostaglandins [21]. Cyclooxygenase is a key enzyme in prostaglandin synthesis and an inducible enzyme in inflammation and cancer tissues [22,23].

COX-1 exists in tissues and is reactive to the synthesis of prostaglandins, which are involved in the physiologic performance (for example, maintaining colon mucosa) and COX-2 is more involved in inflammation, cell growth, apoptosis and angiogenesis [24]. COX-2 does not exist in most normal tissues and its activity is seen in premalignant and malignant cells [25].

COX-2 plays a critical role in carcinogenesis.

COX-2 is an enzyme stimulated by the factors of growth, cytokine and mitogens and in response to inflammation, carcinogenesis, cellular proliferation and differentiation, apoptosis, angiogenesis, and metastasis discharged by the epithelial cells, which leads to the production of prostaglandins [26].

COX-2 is expressed by a number of cytokines and factors of growth and is over expressed in neoplastic diseases [27]. Celecoxib: Celecoxib (Fig. 1), known as Celebrex trademark, with a chemical formula of C17H14F3N3O2S, and molecular weight of 381.373 g/mol, is consumed orally. It has a bioavailability of 40% and a maximum absorption of three hours. Celecoxib's biological half-life is 11 hours, 57% of which is excreted through faeces and 27% by the kidneys. Celecoxib, a selective inhibitor of the cyclooxygenase-2 enzyme, has shown preventive and therapeutic properties in pre-clinical studies on animal models of cancer, including breast, colon and nasopharynx [28-30].

Celecoxib, even with doses higher than 200 mg/kg, has a minimal impact on the

inhibition of Cox-1 production [31]. In some studies, Celecoxib was used to improve treatment response to cancers such as cervical, oesophageal and breast [32]. Several epidemiological studies revealed that in patients predisposed to the risk of developing oesophageal cancer, treatment with aspirin and other non-steroidal anti-inflammatory medications (NSAIDs) such as Celecoxib is associated with a reduced risk of oesophageal cancer [33].

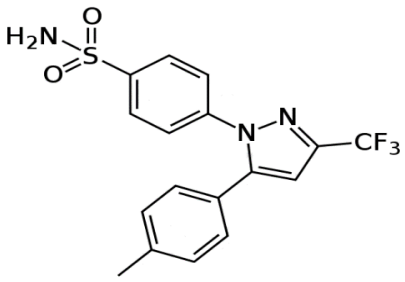

Fig. 1. Chemical structure of celecoxib

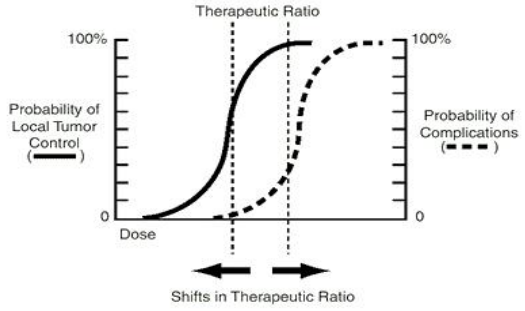

Fig. 2. Shift the probability of tumour control zone to the left side without much changes in the probability of complications and ultimately led to more distance between the two curves

Studies on carcinogen-induced tumours and genetically modified animals have revealed that non-steroidal anti-inflammatory medications (NSAIDs) and selective COX-2 inhibitors such as Celecoxib have significant suppression effects on tumours [34]. Celecoxib can safely and concurrently be taken with chest radiation if the FDA's maximum permissible dose is observed (800 mg daily) [35].

In comparison with radiation therapy, Celecoxib treatment, along with radiotherapy, reduces the tumour growth rate for 1.43 [36]. Celecoxib, as a COX-2 inhibitor, impacts on prostate specific antigen [37].

3.1 Celecoxib Inhibition Mechanism in Radiation as a COX-2 Inhibitor

In radiotherapy, the mechanism of sensitizing tumour cells by Celecoxib has not been fully discovered and further studies are required. Generally, Celecoxib as a radiation sensitizer shifts the radiation response curve to the left side [36].

Known mechanisms in increased sensitivity to radiation by Celecoxib:

- COX-2 inhibition and a subsequent reduction in PGE2 production, which results in increasing apoptosis and decreasing angiogenesis proliferation [38].
- The mechanism of COX-2 inhibition by Celecoxib has not been fully recognized.
- The drug inhibits the COX-2 enzyme through TNF-α signalling by nuclear transfer inhibition of growth factor. It also inhibits NF-KB transcription factor activation [39].
- Apoptosis inhibition is one of the mechanisms implemented by COX-2, which increases tumourigenesis [40].
- Cell cycle arrest at G1-S is one of the most sensitized areas to radiation. Studies in the field of pancreatic [41] and ovary [42] carcinoma cells show cell cycle arrest at G1-S; the mechanism by which this arrest happens is not fully understood [42].

Studies on oesophageal carcinoma cells have shown that p21waf1/cip1 and p27kip play an important role in G1-S. Immuno fluorescence analysis revealed that 100 μM Celecoxib greatly increases the levels of these two proteins in KYSE450 cells. It was found that p21waf1/cip1 and p27kip1 proteins are involved in G1-S arrest in oesophageal carcinoma cells by Celecoxib [43].

Possible mechanisms in regulating COX-2 expression in tumour carcinogenesis are:

- High estimate of COX-2 expression by factors such as scr and ras on EGF, TGF-beta growth factors, and tumour necrosis alpha factor.
- Inactivity of tumour suppressor protein (p53), which results in COX-2 suppression. Increasing COX-2 activates free oxygen, which results in the production of free radicals and prostaglandin.
- This will result in mutation. Prostaglandin also increases tumour angiogenesis and aggressiveness [44].

One of the findings of cancer cells is the COX-2 enzyme level and its high expression. This phenomenon is not seen in normal cells and cells with low expression. By applying five mechanisms, this enzyme supports the tumours and results in the malignant phenotype tumour cells [40].

1-Aspoptosis inhibition 2- Increased angiogenesis 3- Increased invasion 4- Inflammation modulation/low immunity, suppression 5- Converting procarcinogens to carcinogens.

A potential mechanism to prevent cancer is to take chemical medications and inhibit COX-2. This is an enzyme that has a major role in synthesizing PGs from arachidonic acid [45].

4. RESULTS

4.1 The COX-2 Expression

COX-2 function is complex, and due to the cell type and experimental conditions may include different mechanisms. COX-2 may contribute to the inhibition of apoptosis, proliferation inhibition, increased angiogenesis, high adhesion and invasion, as well as inflammation regulation. However, the molecular events that occur due to the presence of COX-2 in ESCC remain totally unknown [46].

Table 1 shows studies on COX-2 expression in different types of cancer and in most cases represents that expression is high and positive.

Activation of the COX-2 enzyme and its high expression in various cancers may be caused by the excessive proliferation of tumour cells. Requirements for more angiogenesis in replicating and transporting oxygen and nutrients to the cell have been proved somewhat by studies on oesophageal cancer [47].

Studies show that high expression of the COX-2 gene is related to more aggressive tumour behaviour, worse prognosis and tumour aggressiveness [48].

Since COX is a key enzyme in synthesizing prostaglandins from arachidonic acid, the high expression of prostaglandins indicates the activation of COX-2 enzyme.

Studies suggest that levels of PGE2 (a major product of prostaglandin synthesis by COX-1 and COX-2) in human and animal tumours are higher than its levels in normal tissues [49].

Chemotherapy and radiotherapy as primary treatments have increased COX-2, PGE 2 in lung, prostate and rectal carcinoma cancers, all *in* vivo and in vitro [50]. The role of prostaglandins derived from COX-2 in human carcinogenesis is supported by retrospective and epidemiological studies stating that regular use of NSAIDs may reduce the incidence of human cancers (especially breast, colon and lung cancer) [51]. High expression of the COX-2 gene is related to more aggressive tumour behaviour, worse prognosis and tumour aggressiveness [48].

Over expression of COX-2 is sufficient to cause tumour genesis in animal models, and removing the COX-2 gene suppressed tumour progression in mice predisposed to intestinal neoplasia [52]. COX-2 expression could be upgraded at an early stage of epidermoid carcinoma cancer. Inhibiting COX-2 from proliferating cancer cells and tumours in hairless mice was effective [43].

4.2 COX-2 Inhibitors

Depending on cell types and inhibitors, the effects of COX-2 inhibitors vary in different tumour cells [53]. The protective impact of NSAIDs in some cancers such as colon cancer in animals has revealed that there is an inverse relationship between using NSAIDs and oesophagus and colon cancer [54].

Evidence indicates that the inhibition of colon cancer by NSAIDs is due to the changes in the metabolism of arachidonic acid by the COX enzymes [55,56]. Several clinical studies revealed that selective inhibition of COX-2 alters cancer progression [57]. Treatment with COX-2 inhibitors in an animal model and Barrett's oesophagus reduced adenocarcinoma [58]. Taking a COX-2 inhibitor improves not only tumour responses to treatment but also the side effects in patients undergoing chemotherapy or radiotherapy [29]. To increase the radiotherapy and chemotherapy response rate some medications, including inhibitors and cyclooxygenase–2 enzymes, are being studied Studies on cyclooxygenase-2 inhibitor enzymes such as Celecoxib have shown that these medications possess anti-tumour and anti-angiogenesis features [28,29]. Cyclooxygenase-2 inhibitors such as Celecoxib may play an important role in the treatment of nasopharyngeal

Table 1. COX-2 expression in different types of cancer

Reference	Year	Cox-2 expression	Cancer type
[54]	1999	Positive	Esophagus
[60]	1999	Positive	Stomach
[61]	1999	Positive	Esophagus
[28]	2000	Very high	Head and neck
[62]	2000	Very high	Esophagus
[63]	2001	High	Colon, Lung
[64]	2001	90%	Colorectal
[64]	2001	40%	Colon
[65]	2001	High	Bladder
[48]	2001	High	Lung
[66]	2002	High	breast
[67]	2002	Positive	breast
[68]	2002	High	Lung
[59]	2002	Very high	Head and neck
[44]	2003	70%	Esophagus
[69]	2003	High	Esophagus
[70]	2005	Very high	Head and neck
[29]	2006	Very high	Head and neck
[43]	2006	90%	Esophagus
[71]	2009	High	prostate
[72]	2010	High	brain
[73]	2014	71%	pancreatic

carcinoma through the inhibition of cell proliferation and angiogenesis, reduction of distant metastasis, and induction of apoptosis [28,29,57,59].

Studies have shown that Celecoxib, as a selective COX-2 inhibitor, can prevent cancer. On the other hand, in premalignant lesions and mouth cancer, the COX-2 expression rate increases. These studies support the hypothesis that COX-2 regulation is very complex and is influenced by internal and external factors, including levels of antioxidants and formation of oxidative stress [74].

Celecoxib blocks cancer cell growth in the head and neck. It stops DNA-dependent kinase catalyst proteins as well as KU70 expression. These both stop restoration of DNA double-stranded breaks. Celecoxib also blocks the active NF-kB and radiation-induced NF-kB in head and neck cancer cells (HN5) [75]. In cells with high expression of COX-2, Celecoxib with radiation makes no change to the G2-M phase stop. More blocks are for radiation-induced G2-M in cells with low expression of COX-2. An improvement in the radiation-induced effects of Celecoxib depends on the expression levels of COX-2 in cancer cells. It also depends on the type of cancer cell. This is because expression in some cancer cells is high and in some is low [76]. Celecoxib differently regulates cellular radio sensitivity, which is dependent on DNA-pk. It changes downstream pro-survival signalling pathways into the cell [77].

Celecoxib increases ki67 levels in prostate tumour tissue, which is the sign of more proliferation [71].

Applying flow cytometry in PGE2 production is strongly suppressed by Celecoxib (NS-398). It was stifled after 48 hours of treatment when compared to the control group for KYSE450 and KYSE510 cells. Treatment with Celecoxib in 100 μM concentrations showed significant cell proliferation (KYSE450 and KYSE510 cells), while at the lower concentrations (10 μM and 1 μM and 0.1 μM) it had no effect on blocking proliferation [43]. Celecoxib significantly inhibited G1-S in the cell cycle, but had no effect on the G2-M transition phase. Blocking of the cell cycle at the G1-S point by Celecoxib inhibits oesophageal carcinoma cell growth (KYSE450 and KYSE510 cells).

While p21waf1/cip1andp27kip1 plays a significant role in G1-S, immunofluorescent analysis showed that Celecoxib, at a concentration of 100 μM, greatly increases the levels of these two proteins in KYSE450 cells. It was found that p21waf1/cip1 and p27kip1 proteins have a role in G1-S Celecoxib-mediated

arrest in oesophageal carcinoma cells. Concentrations between 0.1 to 1 μM of Celecoxib affect the suppression of PGE2 secretion. They have no effect on cell growth. The fact that Celecoxib, at a concentration higher than 100 μM, will stop cell growth shows that, except for COX-2, there might be other factors involved [43]. Studies have shown that the cytochrome C pathway is the cause of Celecoxib apoptosis. In this way, cytochrome C is released from mitochondria and by activating caspase 3 and caspase 9 splits poly ADP-ribose polymerase (PARP). Moreover, the effect of NS398 was inhibited by caspase Z-DEVD-FMK inhibitor and prostaglandin E2.In contrast, BCL-2, bax, c-Myc, Fas and Fas-ligand showed minor changes. In total, the data suggest that induction of apoptosis by NS398 is associated with the expression of COX-2. This occurs through the cytochrome C-dependent pathway following by the activation of caspase 9, caspase 3 Clioz PARP (144). Factors such as asbcl-2, MAKs/ras, caspase-3, Par-4 are pro-and anti-apoptotic [78]. Applying angiogenesis and blocking tumour growth cause high expression of COX-2, which in turn contributes to growth factors such as VDEG, PDGF, and bFGF and matrix metalloproteinases (MMPs) [40]. Compared to the group receiving only carcinogens, prescribing topical 2500ppm Celecoxib can enhance total antioxidant levels. It seems that a reduction in the amount of antioxidants in this group reduces the formation of tumours and increases tumour cell mortality. Studies have also revealed that mice treated only with Celecoxib had higher antioxidant levels than the other groups under study, indicating a selective effect of the COX-2 inhibitor in the antioxidant system. Topical administration of Celecoxib can be applied as an adjunctive treatment in patients with oral premalignant lesions with lower levels of antioxidants [79]. Various studies show that selective COX-2 inhibitors play a critical role in improving the antioxidant system .Prescribing 2500ppm topical Celecoxib in the presence of carcinogens reduces tumour formation and increases bcl-2 expression as tumour suppressor genes. It also increases the level of tumour cell apoptosis [74]. Celecoxib has antagonistic effects on anti-apoptotic proteins such as MCL-1 and Surviving [80]. The maximum dose permissible and tolerable for Celecoxib along with Erlotinib in advanced lung cancer was 600mg to be taken twice daily [81]. Cardiovascular complications are one of the common side effects of Celecoxib. Celecoxib has increasing does-related effects and is directly related to death by cardiovascular diseases, myocardial infarction, stroke, and heart failure [82]. Celecoxib alone slightly inhibits tumour growth and restoration. Taking Celecoxib, chemotherapy and radiotherapy lead to a synergistic effect. Compared to the case in which no Celecoxib is used, it can significantly inhibit tumour growth and restoration. Fig. 3, is an example of such a synergistic effect [83].

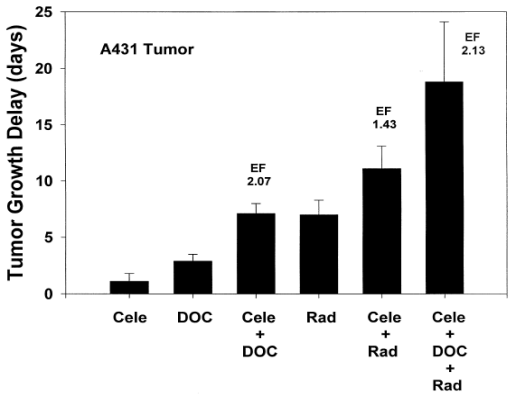

Fig. 3. Effect of Celecoxib on growth delay of tumour treated with docetaxel and 10Gy radiotherapy. (Reprinted from Ref (1))

4.3 Clinical Chronological Studies (1990 to 2013 on Various Types of Cancer)

In Jakobson's study (reported in 2007) patients with rectal cancer received chemo radiotherapy with Celecoxib, but the study was terminated due to the occurrence of maculopapular rashes (in 49% of patients). The Celecoxib dose was 400mg qid [84]. In Debucquoy's study, reported from Belgium in 2009, patients received pre-operative chemo radiotherapy (total dose of 45 Gy/25f + 400 mg Celecoxib twice/day). The tumour response rate was evaluated according to Dwork grading: 61% in the Celecoxib group and 35% in the placebo group showed a good response (grade 3=good regression and grade 4=complete pathological response). T & N down staging, which was assessed by EUS or MRI before surgery, was 72% and 59% in Celecoxib and the placebo group, respectively. The complete pathological response rate was 39% in Celecoxib and 29% in the placebo group [85]. In a study investigating the processing of cyclooxygenase-2 in squamous carcinoma cells of the head and neck, the expression of this enzyme dramatically increased in malignant cells compared to normal cells. In this study, the application of cyclooxygenase-2 inhibitors was associated with a significant decrease in cell

growth and increased apoptotic programmed death [59].

Another study has investigated micro vessel density in biopsies obtained from squamous carcinoma of the nasopharynx. Applying COX-2 inhibitors, micro vessel density was dramatically reduced compared to previous levels. This study revealed that Celecoxib reduces angiogenesis and can induce changes in the transcription of tumour cells [29]. Administration of cyclooxygenase-2 inhibitors in another study was associated with a remarkable decrease in vascular permeability and in acute and chronic inflammation [86]. In the second phase of a study at Princess Margaret Hospital, Celecoxib side effects were investigated while 31 patients with advanced carcinoma of the cervix were treated by chemo radiotherapy. All patients received 400 mg oral Celecoxib during the course of treatment (chemo radiotherapy) twice daily also having had the drug two weeks before radiotherapy. The most common acute grade three side effects include hematologic 12.9% and gastrointestinal 16.1%. These side effects mostly results from chemotherapy. 12.9% the patients had Chronic side effects (G.3) and complications including fistula .25 patients (81%) had complete response. Scientists in this study concluded that the addition of Celecoxib to concurrent chemo radiation can be associated with an acceptable rate of acute complications and an unacceptable rate of chronic complications and does not increase the complete response rate [83]. In another second phase study, the effect of Celecoxib with concurrent pre-operation chemo radiotherapy was investigated in 31 patients with oesophageal carcinoma. All patients received 75 mg platin for each M2 of their body on day 29 and during days 1 to 4, and 29-32. They also received 1000 mg/m2 of 1-5 fluorouracils with 50Gy radiations.

From the first day until surgery, all patients received 200 mg oral Celecoxib twice daily. The dose concerned was increased to 400 mg until the disease progressed, and the procedure continued for a maximum of five years. Surgery was performed four to six weeks after completion of concurrent chemo radiotherapy. The primary objective of this study was to find a pathological complete response rate. Secondary objectives included response rate, complications, overall survival, and the relationship between cyclooxygenase-2 expression and pathological complete response rate. A total of 58% of patients developed grade 3 complications and 19% experienced grade 4 side effects, including hematologic, gastrointestinal, mucosa, nausea and vomiting. Seven patients died of post-operative complications, including pulmonary embolism, pneumonia and progressive disease. Researchers concluded that adding concurrent Celecoxib to chemo radiotherapy is well tolerated. In this study the pathologic complete response rate was 22% similar to those obtained in other studies using pre-operative concurrent chemo radiotherapy. Moreover, researchers recommended that for overall survival, long-term follow-up is needed to evaluate the effect of a maintenance dose of Celecoxib [32]. Overall in terms of one-year survival for recurrent head and neck cancers, concurrent application of Celecoxib and Erlotinib recurrently followed by radiation and active regimen had positive clinical results [87]. Concurrent application of Celecoxib and Erlotinib can further enhance the anti-tumour activity of radiation therapy. Compared with single-factor or two-factor approaches, concurrent Celecoxib, Erlotinithe, and irradiation are the most effective regimens for reducing colony existence, increasing apoptosis, and inhibiting tumour growth *in vivo* studies. Simultaneous treatment by Celecoxib and Erlotinib along with radiation or without radiation helps multiple proteins' survival including: COX-2, p-STAT3, p-AKT, p-EGFR, p-ERK1/2 and PGE2. A combination of Erlotinib, Celecoxib, and IR is a promising approach to overcome resistance to the combined inhibition of EGFR and IR [88]. Concurrent application of Celecoxib and 17-(Allylamino)-17-Demethoxygeldanamycin by radiation therapy in a series of colon cancer cell lines has had good synergistic results in controlling tumour growth [89]. The expression of 31 genes before and during the Celecoxib course has been studied for patients with cervical cancer. Twice a reduction has been experienced during application with seven genes including: (CD58, JARIC1C, TRIP6, KCNAB1, WFS1, FAM54B, NKG7) [107]. Patients' survival with rectal carcinoma and high COX-2 expression treated by surgery was not different in patients receiving surgery and radiotherapy [50]. By inducing apoptosis and inhibiting cell proliferation and angiogenesis, COX-2 selective inhibitors suppress the growth of human prostate cancer cells *in vitro* and *in vivo*. Treatment by NSAIDs results in an increase in cell cycle-dependent kinase inhibitors, which in turn lead to cell accumulation in G0/G1 [108]. Medications including NS-398, Nimesulide and CAY10404 cause apoptosis with no effect on cell cycle distribution in colon cancer cells [109]. A clinical

trial is underway on the effect of Celecoxib on COX-2 expression after radiotherapy, its impact on pathological response to surgical specimens, its relationship between Celecoxib dose and radiation dose, COX-2 expression response to treatment, and survival rates.

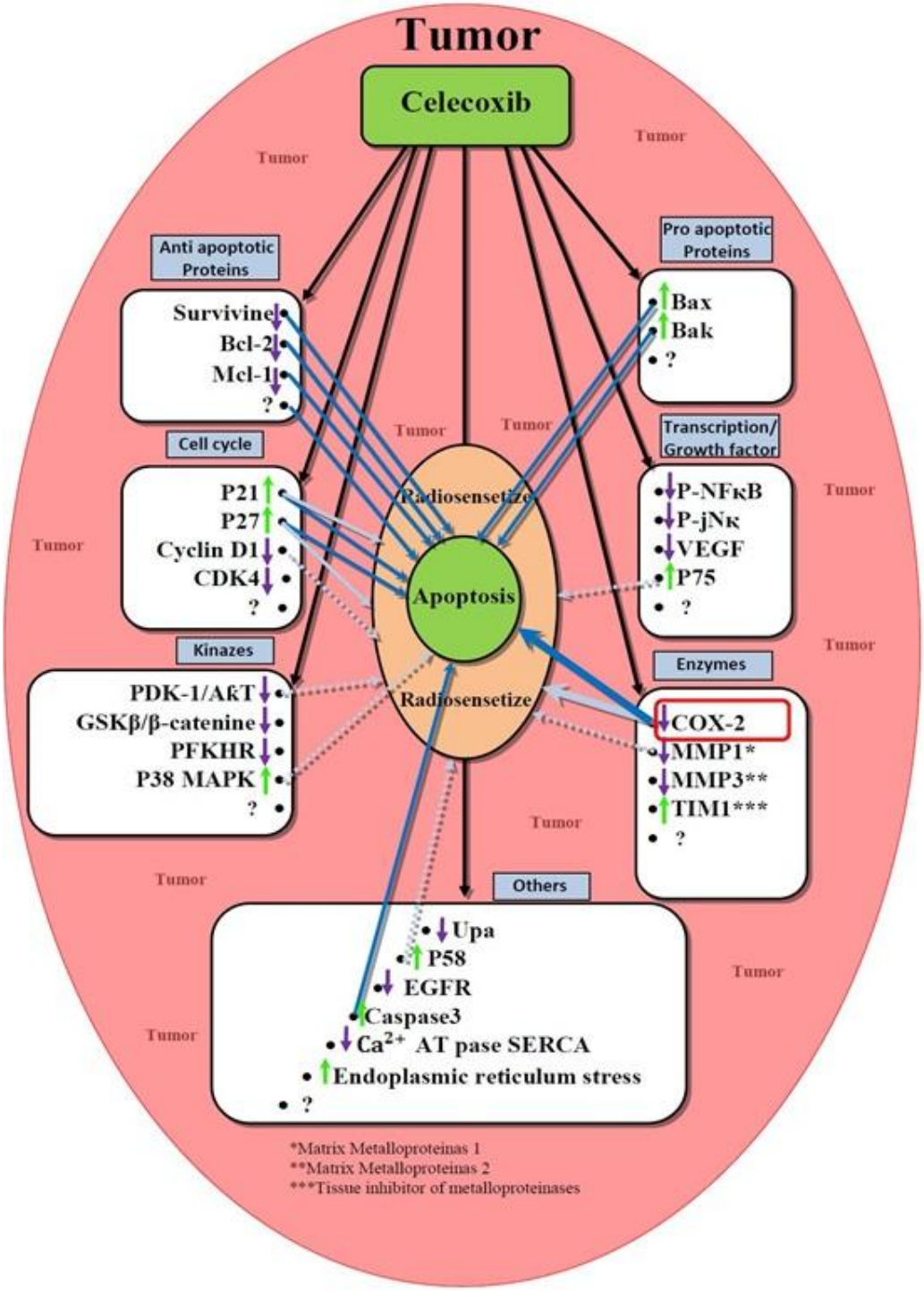

Fig. 4. Graphical abstract for review

Table 2. Results of the application of Celecoxib in different cancers

Reference	Year	Cancer type	Treatment	Environment	Treatment result
[90]	2000	Prostate	Celecoxib**+** Radiotherapy	*in vitro*	Up-regulation of COX-2 ,elevated PGE2 level after irradiation
[30]	2000	Colon	Celecoxib	*in vitro*	Decreased volume and number of colon polyps
[90]	2000	Lung, Prostate	Celecoxib	*in vitro*	Induction of apoptosis by blocking Akt activation independently of Bcl-2
[90]	2000	Lung	Celecoxib	*in vitro*	Increased cell death and apoptosis
[90]	2003	Lung, Prostate	Celecoxib	*in vitro*	Growth inhibition
[90]	2004	Lung, Prostate	Celecoxib**+** Radiotherapy	*in vitro*	Bax- independent proapoptotic effect of Celecoxib
[90]	2005	Lung	Celecoxib**+** COL-3/Docetaxel	*in vitro*	Augmentation of chemotherapeutic drug induced apoptosis by activation of caspase 3 and 9
[91]	2006	Lung	Radiotherapy**+**Celecoxib**+** gefitinib	Phase I clinical trial	Improved treatment response due to the synergistic effect
[92]	2006	colorectal	Celecoxib	Phase I clinical trial	Preventing the formation of scattered colorectal adenoma
[90]	2006	Prostate	Radiotherapy **+** Celecoxib	Phase I clinical trial	Decreased side effects
[93]	2006	breast	Celecoxib	Phase I clinical trial	Decreased risk of breast cancer
[94]	2007	Lung	Celecoxib	Phase I clinical trial	Decreased risk of lung cancer
[4]	2008	Lung	Radiotherapy**+** Celecoxib	*in vivo*	Delaying the growth of tumour and decreasing lung metastases
[4]	2008	Lung	Celecoxiboral	*in vivo*	Inhibiting the growth of lung tumour
[95]	2010	brain	Radiotherapy**+**Celecoxib**+** thalidomide**+**isotretinoin	Phase I clinical trial	Improved treatment response compared to radiotherapy alone
[96]	2011	colon	celecoxib-loaded hydroxyapatite -chitosan nanocomposite	*in vitro*	showed significant antiproliferation, apoptosis
[96]	2011	colon	celecoxib-loaded hydroxyapatite -chitosan nanocomposite	*in vivo*	demonstrated significantly greater inhibition of tumour growth following treatment
[97]	2012	breast	celecoxib + luteolin	*in vitro*	provided superior inhibition of breast cancer cell growth
[98]	2012	colorectal	celecoxib	*in vitro*	celecoxib reduces the growth and metastatic potential of colorectal carcinoma
[99]	2013	gastric	celecoxib	*in vitro*	Celecoxib was able to cell apoptosis rate
[100]	2013	prostate	celecoxib	*in vitro*	reduces the growth of prostate cancer cell lines
[101]	2013	Lung	Celecoxib+ 5-FU	*in vitro*	The results suggest that Celbx can enhanced the anticancer activity of 5-FU by stronger inhibition of cancer cell growth
[102]	2013	colon	Celecoxib+ 5-FU	*in vitro*	Increase of cyclooxygenase-2 inhibition with celecoxib combined with 5-FU enhances tumour cell apoptosis
[103]	2013	Lung	Celecoxib+ sorafenib	In vitro, *in vivo*	increased the induction of apoptosis and decreased the expression of inhibitor of apoptosis genes
[104]	2013	Cervical	Chemoradiotherapy + Celecoxib	Phase I clinical trial	Improved treatment response compared to Chemoradiotherapy alone
[105]	2014	Rectal	Celecoxib +chemoradiotherapy	Phase I clinical trial	Improved treatment response
[106]	2014	Brain	Celecoxib +chemotherapy	*in vivo*	Improved treatment response

5. CONCLUSIONS

Chemical modifiers are substances that increase responses to treatment and survival in different pathways in treated patients with cancer. Radiosensitizers are one of these chemical modifiers. The mechanism concerned is not yet fully understood. However, the results show the effectiveness of these substances directly or indirectly during and after radiation by damaging the cancer cells. This impact can move toward greater damage or can inhibit cell restoration, resulting in cell mortality. In general, radiosensitizers should affect those events that are generated after radiation, should kill more cancer cells and should inhibit restoration by radiation. Studies indicate that after radiation some events occur in the cell and many enzymes are activated to restore the damage.

In general, one of the critical mechanisms of modifiers is to prevent or inhibit the restoration activity of these enzymes. Another mechanism is to cause more effective destruction of major targets with radiation; for example, to weaken strands in DNA molecules and create greater destruction by radiation. Therefore, a thorough understanding of what happens inside the cells after radiation, what enzymes are activated for restoration to occur, and in which pathways these enzymes are transmitted and synthesized is of great importance.

Celecoxib is a COX-2 inhibitor that affects and inhibits some enzymes and creates changes in the cell cycle process through the role of radiosensitizer. It destroys more cancer cells during and after radiation therapy.

Fig. 4 above which bears the major significance of the present study deserves special attention because it indicates the effects of Celecoxib on different parameters in normal cell and tumour. This process leads to the inhibition of abnormal growth-rate through tumour apoptosis. Concurrent application of celecoxib and radiotherapy will bring about radiosentization which is very important in tumour growth inhibition. Solid arrows indicate a known/confirmed relationship and dotted arrows show that there is a probable relationship which should be studied and tested more.

6. FURTHER STUDIES

Further studies are recommended as follows: investigation of the concerned changes in living cells after radiation, identification of all of the enzymes activated for restoration, and complete identification of different stages in synthesis. Materials that inhibit enzymes are to be tested first in vitro and then in vivo, and if they have the features of an ideal sensitizer they can be used clinically to witness an increase in clinical response to treatment, resulting in a radiation dose reduction with acceptable and good clinical and pathological response. Further studies, similar to the laboratory and clinical results in Tables 1 and 2. Above of this review, can be followed on other types of cancer cells with Celecoxib or other similar medications as well as new combinations of different doses of this drug.

The present researchers believe that following questions and challenges deserve special attention in.

6.1 Future Studies

Question one: Are there enzymes other than cox-2 which support the tumour cells?

Question two: Are there radiosentisizers other than celecoxib which inhibit cox-2 as well?

Challenge one: what is the most effective combination of several treatment procedures?

Challenge two: what is the most effective sequence of several treatment procedures?

Challenge three: what is the most effective stage in which radiosentisizers are to be combined with radiotherapy procedure?

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Layke JC, Lopez PP. Esophageal cancer: a review and update. Am Fam Physician. 2006;73(12):2187-94.
2. Agulnik M, Siu L. nasopharyngeal carcinoma: current and future directions. British Journal of Cancer. 2005;92(5):799-806.
3. Skipper HE, Chapman JB, Bell M. The anti-leukemic action of combinations of certain known anti-leukemic agents. Cancer Research. 1951;11(2):109-112.

4. Park W, et al. Antitumor enhancement of celecoxib, a selective Cyclooxygenase-2 inhibitor, in a Lewis lung carcinoma expressing Cyclooxygenase-2. Journal of Experimental & Clinical Cancer Research: CR. 2008;27(1):66.
5. Milas L. Cyclooxygenase-2 (COX-2) enzyme inhibitors and radiotherapy: preclinical basis. American Journal of Clinical Oncology. 2003;26(4):S66-S69.
6. Skarsgard L. et al. Radiosensitization of hypoxic cells at low doses. International Journal of Radiation Oncology Biology Physics. 1986;12(7):1075-1078.
7. Laderoute KR, et al. The production of strand breaks in dna in the presence of the hydroxylamine of sr-2508 (1-[< i> N</i>-(2-hydroxyethyl) acetamido] 2-nitroimidazole) at neutral pH. International Journal of Radiation Oncology Biology Physics. 1986;12(7):1215-1218.
8. Herscher LL, et al. Principles of chemoradiation: theoretical and practical considerations. Oncology (Williston Park, NY). 1999;13(10 Suppl 5):11-22.
9. Kinsella TJ, et al., Enhancement of X ray induced DNA damage by pre-treatment with halogenated pyrimidine analogs. International Journal of Radiation Oncology Biology Physics. 1987; 13(5):733-739.
10. Wang Y, Pantelias G, Iliakis G. Mechanism of radiosensitization by halogenated pyrimidines: the contribution of excess DNA and chromosome damage in BrdU radiosensitization may be minimal in plateau-phase cells. International Journal of Radiation Biology. 1994;66(2):133-142.
11. Gordon Steel G, et al. The dose-rate effect in human tumour cells. Radiotherapy and Oncology. 1987;9(4):299-310.
12. Terasima T, Tolmach L. X-ray sensitivity and DNA synthesis in synchronous populations of HeLa cells. Science. 1963;140(3566):490-492.
13. Sinclair WK. Hydroxyurea revisited: a decade of clinical effects studies. International Journal of Radiation Oncology Biology Physics. 1981;7(5):631-637.
14. Liebmann J, et al. In vitro studies of Taxol as a radiation sensitizer in human tumor cells. Journal of the National Cancer Institute. 1994;86(6):441-446.
15. Milas L, et al. Therapeutic potential of paclitaxel-radiation treatment of a murine ovarian carcinoma. Radiotherapy and Oncology. 1996;40(2):163-170.
16. Urtasun R, et al. Radiation and high-dose metronidazole in supratentorial glioblastomas. New England Journal of Medicine. 1976;294(25):1364-1367.
17. Brown J, Yu N. The optimum time for irradiation relative to tumour concentration of hypoxic cell sensitizers. The British Journal of Radiology. 1980;53(633):915-916.
18. Chaplin DJ, Horsman MR. Tumor blood flow changes induced by chemical modifiers of radiation response. International Journal of Radiation Oncology Biology Physics. 1992; 22(3):459-462.
19. Overgaard J, et al. Nimorazole as a hypoxic radiosensitizer in the treatment of supraglottic larynx and pharynx carcinoma. First report from the Danish Head and Neck Cancer Study (DAHANCA) protocol 5-85. Radiotherapy and Oncology. 1991;20:143-149.
20. McGinn CJ, Shewach DS, Lawrence TS. Radiosensitizing nucleosides. Journal of the National Cancer Institute. 1996;88(17):1193-1203.
21. Soslow RA, et al. COX-2 is expressed in human pulmonary, colonic, and mammary tumors. Cancer. 2000;89(12):2637-2645.
22. Fu JY, et al. The induction and suppression of prostaglandin H2 synthase (cyclooxygenase) in human monocytes. Journal of Biological Chemistry. 1990;265(28):16737-16740.
23. O'banion M. Cyclooxygenase-2: molecular biology, pharmacology, and neurobiology. Critical Reviews in Neurobiology. 1998;13(1):45-82.
24. Zimmermann KC, et al. Constitutive cyclooxygenase-2 expression in healthy human and rabbit gastric mucosa. Molecular Pharmacology. 1998;54(3):536-540.
25. Nieder C, Milas L, Ang K. Modification of radiation response. Springer; 2007.
26. Gallo O, et al. Cyclooxygenase-2 pathway correlates with VEGF expression in head and neck cancer. Implications for tumor angiogenesis and metastasis. Neoplasia. 2001;3(1):53-61.
27. Herschman HR. Primary response genes induced by growth factors and tumor promoters. Annual Review of Biochemistry. 1991;60(1):281-319.

28. Alshafie GA, et al. Chemotherapeutic evaluation of Celecoxib, a cyclooxygenase-2 inhibitor, in a rat mammary tumor model. Oncology Reports. 2000;7(6):1377-1458.
29. Soo RA, et al. Celecoxib reduces microvessel density in patients treated with nasopharyngeal carcinoma and induces changes in gene expression. Annals of Oncology. 2006;17(11):1625-1630.
30. Steinbach G, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. New England Journal of Medicine. 2000;342(26):1946-1952.
31. Futaki N, et al. NS-398, a new anti-inflammatory agent, selectively inhibits prostaglandin G/H synthase/ cyclooxygenase (COX-2) activity in vitro. Prostaglandins. 1994;47(1):55-59.
32. Govindan R, et al. Cisplatin, fluorouracil, celecoxib, and RT in resectable esophageal cancer: preliminary results. Oncology (Williston Park, NY). 2004;18(14 Suppl 14):18-21.
33. Funkhouser EM, Sharp GB. Aspirin and reduced risk of esophageal carcinoma. Cancer. 1995;76(7):1116-1119.
34. Yamamoto K, et al. Inhibitory effects of selective cyclooxygenase-2 inhibitors, nimesulide and etodolac, on the development of squamous cell dysplasias and carcinomas of the tongue in rats initiated with 4-nitroquinoline 1-oxide. Cancer Letters. 2003;199(2):121-129.
35. Liao Z, et al. A phase I clinical trial of thoracic radiotherapy and concurrent celecoxib for patients with unfavorable performance status inoperable/ unresectable non–small cell lung cancer. Clinical Cancer Research. 2005;11(9):3342-3348.
36. Nakata E, et al. Potentiation of tumor response to radiation or chemoradiation by selective cyclooxygenase-2 enzyme inhibitors. International Journal of Radiation Oncology Biology Physics. 2004;58(2):369-375.
37. Pruthi RS, et al. Phase II trial of celecoxib in prostate-specific antigen recurrent prostate cancer after definitive radiation therapy or radical prostatectomy. Clinical Cancer Research. 2006;12(7):2172-2177.
38. Davis TW, et al. Synergy between celecoxib and radiotherapy results from inhibition of cyclooxygenase-2-derived prostaglandin E2, a survival factor for tumor and associated vasculature. Cancer Research. 2004;64(1):279-285.
39. Funakoshi-Tago M, et al. Celecoxib potently inhibits TNFα-induced nuclear translocation and activation of NF-κB. Biochemical Pharmacology. 2008;76(5): 662-671.
40. Dempke W, et al. Cyclooxygenase-2: a novel target for cancer chemotherapy? Journal of Cancer Research and Clinical Oncology. 2001;127(7):411-417.
41. Yip-Schneider MT, et al. Cell cycle effects of nonsteroidal anti-inflammatory drugs and enhanced growth inhibition in combination with gemcitabine in pancreatic carcinoma cells. Journal of Pharmacology and Experimental Therapeutics. 2001; 298(3):976-985.
42. Denkert C, et al. Induction of G0/G1 cell cycle arrest in ovarian carcinoma cells by the anti-inflammatory drug NS-398, but not by COX-2-specific RNA interference. Oncogene. 2003;22(54):8653-8661.
43. Zhi H, et al. Significance of COX-2 expression in human esophageal squamous cell carcinoma. Carcinogenesis. 2006;27(6):1214-1221.
44. Zhang W, et al. Immunohistochemical analysis of cyclooxygenase-2 expression in premalignant and malignant esophageal glandular and squamous lesions in Cixian, China. Cancer Detection and Prevention. 2003;27(4):243-249.
45. Dannenberg AJ, Subbaramaiah K. Targeting cyclooxygenase-2 in human neoplasia-Rationale and promise. Cancer cell. 2003;4(6):431-436.
46. Trifan O, Hla T. Cyclooxygenase-2 modulates cellular growth and promotes tumorigenesis. Journal of Cellular and Molecular Medicine. 2003;7(3):207-222.
47. Masferrer JL, et al. Antiangiogenic and antitumor activities of cyclooxygenase-2 inhibitors. Cancer Research. 2000;60(5):1306-1311.
48. Khuri FR, et al. Cyclooxygenase-2 overexpression is a marker of poor prognosis in stage I non-small cell lung cancer. Clinical Cancer Research. 2001;7(4):861-867.
49. Rigas B, Goldman I, Levine L. Altered eicosanoid levels in human colon cancer. Journal of Laboratory and Clinical Medicine. 1993;122(5):518-523.
50. de Heer P, et al. Cyclooxygenase 2 expression in rectal cancer is of prognostic significance in patients receiving

preoperative radiotherapy. Clinical cancer research. 2007;13(10):2955-2960.
51. Schreinemachers DM, Everson RB, Aspirin use and lung, colon, and breast cancer incidence in a prospective study. Epidemiology. 1994;5(2):138-146.
52. Oshima M, et al, Suppression of Intestinal Polyposis in< i> Apc</i>< sup> Δ716</sup> Knockout Mice by Inhibition of Cyclooxygenase 2 (COX-2). Cell. 1996;87(5):803-809.
53. FODERÀ D, et al. Induction of Apoptosis and Inhibition of Cell Growth in Human Hepatocellular Carcinoma Cells by COX-2 Inhibitors. Annals of the New York Academy of Sciences. 2004;1028(1):440-449.
54. Ratnasinghe D, et al. Expression of cyclooxygenase-2 in human squamous cell carcinoma of the esophagus; an immunohistochemical survey. Anticancer Research. 1998;19(1A):171-174.
55. Marnett LJ. Aspirin and the potential role of prostaglandins in colon cancer. Cancer Research. 1992;52(20):5575-5589.
56. Smith WL. Prostanoid biosynthesis and mechanisms of action. Am J Physiol. 1992. 263(2 Pt 2): p. F181-F191.
57. Choy H, Milas L. Enhancing radiotherapy with cyclooxygenase-2 enzyme inhibitors: a rational advance? Journal of the National Cancer Institute. 2003;95(19):1440-1452.
58. Buttar NS, et al. Chemoprevention of esophageal adenocarcinoma by COX-2 inhibitors in an animal model of Barrett's esophagus. Gastroenterology. 2002;122(4):1101-1112.
59. Lee DW, et al. Increased cyclooxygenase-2 expression in human squamous cell carcinomas of the head and neck and inhibition of proliferation by nonsteroidal anti-inflammatory drugs. Anticancer Research. 2001;22(4):2089-2096.
60. Murata H, et al. Cyclooxygenase-2 overexpression enhances lymphatic invasion and metastasis in human gastric carcinoma. The American Journal of Gastroenterology. 1999;94(2):451-455.
61. Zimmermann KC, et al. Cyclooxygenase-2 expression in human esophageal carcinoma. Cancer Research. 1999;59(1):198-204.
62. Shamma A, et al, Up-regulation of cyclooxygenase-2 in squamous carcinogenesis of the esophagus. Clinical Cancer Research. 2000;6(4):1229-1238.
63. Shiotani H, et al. Increased expression of cyclooxygenase-2 protein in 4-nitroquinoline-1-oxide-induced rat tongue carcinomas and chemopreventive efficacy of a specific inhibitor, nimesulide. Cancer Research. 2001;61(4):1451-1456.
64. Sheng H, et al. Prostaglandin E2 increases growth and motility of colorectal carcinoma cells. Journal of Biological Chemistry. 2001;276(21):18075-18081.
65. Shirahama T, Sakakura C. Over expression of cyclooxygenase-2 in squamous cell carcinoma of the urinary bladder. Clinical Cancer Research. 2001;7(3):558-561.
66. Ristimäki A, et al. Prognostic significance of elevated cyclooxygenase-2 expression in breast cancer. Cancer Research. 2002;62(3):632-635.
67. Half E, et al. Cyclooxygenase-2 expression in human breast cancers and adjacent ductal carcinoma in situ. Cancer Research. 2002.62(6):1676-1681.
68. Hastürk S, et al. Expression of cyclooxygenase-1 and cyclooxygenase□2 in bronchial epithelium and nonsmall cell lung carcinoma. Cancer. 2002;94(4):1023-1031.
69. Yu HP, et al. Cyclooxygenase-2 expression in squamous dysplasia and squamous cell carcinoma of the esophagus. Cancer Letters. 2003;198(2):193-201.
70. Yao M, et al. Effects of nonselective cyclooxygenase inhibition with low-dose ibuprofen on tumor growth, angiogenesis, metastasis, and survival in a mouse model of colorectal cancer. Clinical Cancer Research. 2005;11(4):1618-1628.
71. Antonarakis ES, et al. Phase II, randomized, placebo-controlled trial of neoadjuvant celecoxib in men with clinically localized prostate cancer: evaluation of drug-specific biomarkers. Journal of Clinical Oncology. 2009;27(30):4986-4993.
72. Schrage Y, et al. COX-2 expression in chondrosarcoma: a role for celecoxib treatment? European Journal of Cancer. 2010;46(3):616-624.
73. Pomianowska E, et al. COX-2 overexpression in resected pancreatic head adenocarcinomas correlates with favourable prognosis. BMC Cancer. 2014;14(1):458.
74. Sohrabi, M., et al., Effect of dietary and topical Celecoxib on expression of bcl-2,

bax, c-erb-B2 and Ki67 in carcinogen-induced tongue carcinoma in rat. Pakistan Journal of Biological Sciences: PJBS. 2009;12(10):750-757.
75. Raju U, et al. Inhibition of DNA repair as a mechanism of enhanced radioresponse of head and neck carcinoma cells by a selective cyclooxygenase-2 inhibitor, celecoxib. International Journal of Radiation Oncology Biology Physics. 2005;63(2):520-528.
76. Shin YK, et al. Radiosensitivity Enhancement by Celecoxib, a Cyclooxygenase (COX)-2 Selective Inhibitor, via COX-2–Dependent Cell Cycle Regulation on Human Cancer Cells Expressing Differential COX-2 Levels. Cancer Research. 2005;65(20):9501-9509.
77. Kodym E, et al. DNA-PKcs–Dependent Modulation of Cellular Radiosensitivity by a Selective Cyclooxygenase-2 Inhibitor. International Journal of Radiation Oncology Biology Physics. 2007; 69(1):187-193.
78. Li M, Wu X, Xu XC. Induction of apoptosis by cyclo-oxygenase-2 inhibitor NS398 through a cytochrome C-dependent pathway in esophageal cancer cells. International Journal of Cancer. 2001;93(2):218-223.
79. Arbabi KF, Mesgari AM, Akbari N. Evaluation the effect of topical and systemic celecoxib on serum antioxidant in induction of tongue neoplasm in rat. Zahedan Journal of Research in Medical Sciences (tabib-e-shargh); 2010.
80. Jendrossek V. Targeting apoptosis pathways by Celecoxib in cancer. Cancer Letters. 2013;332(2):313-324.
81. Reckamp KL, et al. A Phase I Trial to Determine the Optimal Biological Dose of Celecoxib when Combined with Erlotinib in Advanced Non–Small Cell Lung Cancer. Clinical Cancer Research. 2006; 12(11):3381-3388.
82. Solomon SD, et al. Cardiovascular Risk of Celecoxib in 6 Randomized Placebo-Controlled Trials the Cross Trial Safety Analysis. Circulation. 2008;117(16):2104-2113.
83. Herrera FG, et al. A prospective phase I–II trial of the cyclooxygenase-2 inhibitor celecoxib in patients with carcinoma of the cervix with biomarker assessment of the tumor microenvironment. International Journal of Radiation Oncology Biology Physics. 2007;67(1):97-103.
84. Jakobsen A, et al. A COX-2 inhibitor combined with chemoradiation of locally advanced rectal cancer: a phase II trial. International Journal of Colorectal Disease. 2008;23(3):251-255.
85. Debucquoy A, et al. Double blind randomized phase II study with radiation+ 5-fluorouracil±celecoxib for resectable rectal cancer. Radiotherapy and Oncology. 2009;93(2):273-278.
86. Suleyman H, et al. Anti-inflammatory effects of selective COX-2 inhibitors. Pharmacological Reports. 2004;56(6):775-780.
87. Kao J, et al. Phase 1 trial of concurrent erlotinib, celecoxib, and reirradiation for recurrent head and neck cancer. Cancer. 2011;117(14):3173-3181.
88. Fu S, et al. Combined inhibition of epidermal growth factor receptor and cyclooxygenase-2 as a novel approach to enhance radiotherapy. Journal of cell Science & Therapy. 2011;1(2).
89. Kim YM, Pyo H. Cooperative enhancement of radiosensitivity after combined treatment of 17-(allylamino)-17-demethoxygeldanamycin and celecoxib in human lung and colon cancer cell lines. DNA and Cell Biology. 2012;31(1):15-29.
90. Ganswindt U, et al. Combination of celecoxib with percutaneous radiotherapy in patients with localised prostate cancer–a phase I study. Radiat Oncol. 2006;1(9).
91. Park JS, et al. Radiosensitivity enhancement by combined treatment of celecoxib and gefitinib on human lung cancer cells. Clinical Cancer Research. 2006;12(16):4989-4999.
92. Bertagnolli MM, et al. Celecoxib for the prevention of sporadic colorectal adenomas. New England Journal of Medicine. 2006;355(9):873-884.
93. Harris RE, Beebe-Donk J, Alshafie GA. Reduction in the risk of human breast cancer by selective cyclooxygenase-2 (COX-2) inhibitors. BMC Cancer. 2006;6(1):27.
94. Harris RE, Beebe-Donk J, Alshafie GA. Reduced risk of human lung cancer by selective cyclooxygenase 2 (COX-2) blockade: results of a case control study. International Journal of Biological Sciences. 2007;3(5):328.
95. Gilbert MR, et al. A phase I factorial design study of dose-dense temozolomide alone and in combination with thalidomide, isotretinoin, and/or celecoxib as

postchemoradiation adjuvant therapy for newly diagnosed glioblastoma. Neuro-Oncology. 2010;1167-1172.
96. Venkatesan P, et al. The potential of celecoxib-loaded hydroxyapatite-chitosan nanocomposite for the treatment of colon cancer. Biomaterials. 2011;32(15):3794-3806.
97. Jeon YW, Suh YJ. Synergistic apoptotic effect of celecoxib and luteolin on breast cancer cells. Oncology Reports. 2013; 29(2):819-825.
98. Ninomiya I, et al. Antitumor and anti-metastatic effects of cyclooxygenase-2 inhibition by celecoxib on human colorectal carcinoma xenografts in nude mouse rectum. Oncology Reports. 2012; 28(3):777-784.
99. Wang YJ, et al. Effects of celecoxib on cycle kinetics of gastric cancer cells and protein expression of cytochrome C and caspase-9. Asian Pac J Cancer Prev. 2013;14(4):2343-7.
100. Katkoori V, et al. Selective COX-2 inhibitor (celecoxib) decreases cellular growth in prostate cancer cell lines independent of p53. Biotechnic & Histochemistry. 2013;88(1):38-46.
101. Jastrzebska E, et al. A microfluidic system to study the cytotoxic effect of drugs: the combined effect of celecoxib and 5-fluorouracil on normal and cancer cells. Microchimica Acta. 2013;180(9-10):895-901.
102. Zhang DQ, et al. Increase of cyclooxygenase-2 inhibition with celecoxib combined with 5-FU enhances tumor cell apoptosis and antitumor efficacy in a subcutaneous implantation tumor model of human colon cancer. World J Surg Oncol. 2013;11(16).
103. Zhang H, Li Z, Wang K. Combining sorafenib with celecoxib synergistically inhibits tumor growth of non-small cell lung cancer cells in vitro and in vivo. Oncology Reports. 2014;31(4):1954-1960.
104. Doll CM, et al. COX-2 expression and survival in patients with locally advanced cervical cancer treated with chemoradiotherapy and celecoxib: a quantitative immunohistochemical analysis of RTOG C0128. International Journal of Gynecological Cancer. 2013;23(1):176-183.
105. Wang LW, et al. Celecoxib plus chemoradiotherapy for locally advanced rectal cancer: A phase II TCOG study. Journal of Surgical Oncology. 2014;109(6):580-585.
106. Vera M, et al. New celecoxib multiparticulate systems to improve glioblastoma treatment. International Journal of Pharmaceutics. 2014;473(1):518-527.
107. Weidhaas JB, et al. Changes in gene expression predicting local control in cervical cancer: results from Radiation Therapy Oncology Group 0128. Clinical Cancer Research. 2009;15(12):4199-4206.
108. Toyoshima T, et al. Inhibitor of cyclooxygenase-2 induces cell-cycle arrest in the epithelial cancer cell line via up-regulation of cyclin dependent kinase inhibitor p21. British Journal of Cancer. 2002;86(7):1150-1156.
109. Sun Y, et al. Cyclooxygenase-2 overexpression reduces apoptotic susceptibility by inhibiting the cytochrome c-dependent apoptotic pathway in human colon cancer cells. Cancer Research. 2002;62(21):6323-6328.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=1114&id=12&aid=8892