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

Yousef Jalalabadi¹,², Alireza Shirazi³, Mohammad-Reza Ghavam–Nasiri⁴*, Amir Ale Davood⁵ and Dariush Sardari¹

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

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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
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 sensitizers 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.

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 irradiation. Therapeutic index is defining the SER of the tumour divided by the normal tissue SER. In normal tissues with electron affinic sensitzers-oxygen-mimetic radio sensitizers- 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]:

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1. direct DNA damage
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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.

Nitroimidazoles sensitisers including Metronidazole [16], Misonidazole [17], Pimonidazole, Ro-03-8799 [18], Nimorazole [19], and Pimonidazole in lower concentrations are used as markers for hypoxic cells. Halopyrimidine radiation sensitisers 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: Cycloxygenase (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 preclinical 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].

In comparison with radiation therapy, Celecoxib have significant suppression effects on genetically modified animals have revealed that 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 tumorigenesis [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 p27kip1 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, PGE2 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
This is because expression in COX-2 inhibitor, Celecoxib, depends on the expression levels of COX-2 in cancer cells. 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. Celecoxib differently regulates cellular radio sensitivity, which is dependent on DNA-pk. It changes downstream pro-survival signalling pathways into the cell [77].

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 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

| 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  |
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 Clioq 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 Debuqueu’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 Dwark 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 56% 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, Erlotinith, 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-(Allylamo)-17-Demethoxygeldanamycyn 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 NSAIIDs 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 |
| [90]      | 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 |
| [93]      | 2006 | Prostate    | Radiotherapy + Celecoxib | Phase I clinical trial | Decreased side effects |
| [94]      | 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 radiosensitizers 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 radiosensitizers 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.

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