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Clinical Response in Nasopharyngeal Carcinoma with Combined Therapy of Concurrent Chemoradiotherapy and NSAIDs: Etoricoxib vs Piroxicam

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Abstract
Introduction: Many studies have shown the effects of cyclooxygenase-2 (COX-2) inhibitors as chemopreventing and radiosensitizer. The effects of these drugs on NPC is unknown. We tried to evaluate the efficacy of etoricoxib (selective) and piroxicam (non-selective) in nasopharyngeal carcinoma patients who underwent concurrent chemoradiotherapy with the aim to gain a better clinical response. **Methods & Findings**: A randomized, double blind clinical trial was conducted on NPC patients who underwent concurrent chemoradiotherapy. Total 25 subjects completed the study, they were assigned into 3 groups to receive either Etoricoxib 60 mg, Piroxicam 20 mg or placebo once daily per oral. We evaluated clinical responses in 8 subjects given Etoricoxib, 8 Piroxicam and 9 placebo. There was a significant difference in primary tumor size ($p = 0.026$), lymph node enlargement ($p = 0.024$) and tumor stage ($p = 0.024$) pre and post concurrent chemoradiotherapy in the group combined with Etoricoxib. Meanwhile, Piroxicam group showed equal results with the placebo, in which a significant difference was only found in lymph node enlargement and clinical stage but not in primary tumor size.**Conclusion**: Better clinical response is well achieved in nasopharyngeal carcinoma by combining a selective COX-2 inhibitor, Etoricoxib, with concurrent chemoradiotherapy.
Keyword: Etoricoxib, concurrent chemoradiotherapy, clinical response

1. Introduction

Nasopharyngeal carcinoma (NPC) is the most common malignancy of the head and neck cancer. There are approximately 10,000 new cases every year in Indonesia (Kurnianda *et al.* 2009). Almost 70% of newly diagnosed NPC patients present with locally advanced disease (Agulnik & Siu 2005). Early stage diagnosis is often difficult because the symptoms are not distinctive and the nasopharynx is a difficult area to examine. These conditions have cause treatment for NPC has not yet been a satisfactory.

Cyclooxygenase (COX) is the key enzyme in the biosynthetic pathway of prostaglandins (PGs). There are two isoforms of COX that have been characterized, namely COX-1 and COX-2. COX-1 is expressed constitutively in most tissues and facilitate many physiological processes, whereas COX-2, is highly expressed in various malignancies (Murono *et al.* 2001; Kyzas *et al.* 2005; Soo *et al.* 2005; Kaul et al. 2006). Overexpression of COX-2 has been reported in colon cancer, lung cancer, breast cancer, gastric cancer, esophageal cancer, and head and neck cancers. Thus suggesting that COX-2 may be involved in carcinogenesis (Kaul *et al.* 2006). COX-2 is also proposed to be a regulator of tumor angiogenesis in head and neck squamous cell carcinoma (Kyzas *et al.* 2005). In addition, overexpression of COX-2 have been shown to correlate with tumor aggressiveness and worse clinical outcome (Kyzas *et al.* 2005; Soo *et al.* 2005).

A few studies have found that COX-2 expressions are quite high in NPC specimens, there are 70.6% (Tan & Putti 2005) and 79% (Soo *et al.* 2005). Inhibition of COX-2 activity may have a therapeutic value (Kyzas *et al.* 2005).

Early stage NPC patients have a high rate of cure with radiotherapy (RT) alone, but those with distant metastatic spread has a poor prognosis (Agulnik & Siu 2005). Combined-modality treatment has produced moderate improvements in the therapeutic outcome especially in head and neck squamous cell carcinoma (HNSCC) (Choy & Milas 2003). Two randomized trials have compared concurrent chemoradiotherapy vs RT alone (Chan *et al.* 2002; Lin *et al.* 2003). Based on these trials, patients with advanced locoregional NPC benefit from concurrent chemoradiotherapy over RT alone. Moreover, a mini–review has supported the role of concurrent chemoradiotherapy followed by adjuvant chemotherapy in improving the overall survival and disease free survival for all histological types of locally advanced NPC (Agulnik & Siu 2005).

There are findings suggesting that radiotherapy is also associated with overexpression of COX-2 in tumors and by inhibiting COX-2 activity in tumors, response to radiation can be improved. Selective COX-2 inhibitors in particular, enhance tumor response to radiation without substantially enhancing the radiosensitivity of normal tissues (Choy & Milas 2003). Moreover, experimental evidences support the concept of non-steroidal anti-inflammatory drugs (NSAIDs) direct antitumor effects and chemopreventive effects due to inhibition of COX-2 (Choy & Milas 2003; Steinbach *et al.* 2000).

Clinical trials combining celecoxib, chemotherapy, and radiotherapy have been conducted on few cancers such as non-small-cell lung cancer (NSCLC) (Carbone *et al.* 2002; Liao *et al.* 2003; Choy & Milas 2003), esophageal cancer (Mantravadi *et al.* 2003; Choy & Milas 2003) and cervical cancer, in which radiation is a prominent component of standard therapy, but these studies are still limited (Choy & Milas 2003).

Celecoxib is a first generation of highly selective COX-2 inhibitor. Celecoxib was associated with a significantly lower incidence of symptomatic ulcers and combined upper GI ulcer complications compare to other NSAIDs (Yuan & Hunt 2003). However, the use of Celecoxib has been restricted due to concerns that the use of Celecoxib may increase the risk of cardiovascular adverse events (Cotter 2005). Therefore, the use of other possible COX-2 inhibitor should be considered.

Etoricoxib is claimed to be equally effective as celecoxib in inhibiting COX-2. Etoricoxib is also one highly selective COX-2 inhibitor available in 55 countries in Europe, Latin America and the Asia-Pacific region including Indonesia. Its recommended dose is 60 mg once daily, which makes it easy to administer. When comparing to non-selective NSAIDs, Etoricoxib showed less perforation, gastric ulcers and bleeding (Bingham III *et al.* 2006). Thus, Etoricoxib become a choice for selective COX-2 inhibitor in this study.

To compare with non-selective COX-2 inhibitor, Piroxicam became a choice. Piroxicam belongs to a group of NSAIDs and analgetic drugs. It works very effectively for many characteristics of pain and inflammatory processes. Its recommended dose is 20 mg once daily, so it is easy to administer as well (Keleş *et al*. 2010).

Studies of combined-modality therapy of COX-2 inhibitors and radiation have provided the impuls for this clinical trial. They become the groundwork to study the role of COX-2 inhibitor in NPC with concurrent chemoradiotherapy and to assess a potential possibility of combining it with concurrent chemoradiotherapy. Administration of COX-2 inhibitor is expected to increase the effects of standard therapy by chemopreventing, radiosensitizing and hampering the progression of NPC.

2. Methods & Findings

A randomized double-blind clinical trial has been carried out in the Department of Otolaryngology-Head and Neck Surgery, in Faculty of Medicine, University of Sumatera Utara, Medan from January 2011 until March 2013.

Subjects were NPC patients who underwent concurrent chemoradiotherapy (Cisplatin 100 mg/m2 on day 1, 22, and 43 + radiotherapy $\geq$ 70 Gy (2 Gy / fraction) according to NCCN 2010. They were randomly assigned into 3 groups to receive either Etoricoxib 60 mg, Piroxicam 20 mg or placebo once daily per oral.

We assessed clinical responses, such as primary tumor size, enlarged lymph nodes and tumor stage in pre and post concurrent chemoradiotherapy 7 weeks before the administration of adjuvant chemotherapy. These responses were measured by evaluating nasopharyngeal computed tomography scan before and after the treatment.

A non parametric test was used to statistically evaluate the data in all groups pre and post treatment.

3. Results

Fifty-seven patients received concurrent chemoradiotherapy and participated in this study, but eventually 32 subjects drop out because patients chose alternative treatment, economic reason, etc. Total 25 subjects who completed the study were grouped into 8 subjects of Etoricoxib, 8 Piroxicam and 9 placebo as described in Table 1.

Characteristics	Placebo n (%)	Piroxicam n (%)	Etoricoxib n (%)
Age (years)			
≤ 20	1 (11,2)	0 (0,0)	0 (0,0)
21-40	2 (22,2)	2 (25,0)	2 (25,0)
41-60	4 (44,4)	5 (62,5)	6 (75,0)
>60	2 (22,2)	1 (12,5)	0 (0,0)
Gender			
Male	6 (66,7)	6 (75,0)	7 (87,5)
Female	3 (33,3)	2 (25,0)	1(12,5)
Type of histopathology			
Squamous cell carcinoma	5 (55,6)	7 (87,5)	3 (37,5)
Undifferentiated carcinoma	4 (44,4)	1 (12,5)	5 (62,5)

Table 1. Distribution of nasopharyngeal carcinoma based on age, gender and type of histopathology

NPC patients in this study were mostly found in the age group of 41-60 years and we found a male

predominance with a ratio of 3.2:1 compare to female. Based on the type of histopathology, most common nasopharyngeal carcinoma was squamous cell carcinoma (Table 1).

Table 2. Comparison of primary tumor size in pre and post concurrent chemoradiotherapy treated with placebo, piroxicam or etoricoxib in nasopharyngeal carcinoma.

Intervention	Primary tumor size	Concurrent chemoradiotherapy		*P*
		Pre	Post	
Placebo	T0	0	0	$p = 0.317$
	T1	2	3	
	T2	3	3	
	T3	2	3	
	T4	2	0	
Piroxicam	T0	0	1	$p = 0.279$
	T1	3	3	
	T2	1	0	
	T3	1	3	
	T4	3	1	
Etoricoxib	T0	0	0	$p = 0.026$
	T1	1	6	
	T2	3	1	
	T3	2	1	
	T4	2	0	

In table 2, a nonparametric test showed a significant difference of the size of the primary tumor pre and post concurrent chemoradiotherapy in the Etoricoxib group ($p < 0.05$).

Table 3. Comparison of the size of lymph nodes in pre and post concurrent chemoradiotherapy treated with placebo, piroxicam or etoricoxib in nasopharyngeal carcinoma.

Intervention	Size of lymph node	Concurrent chemoradiotherapy		*p*
		Pre	Post	
Placebo	N0	0	0	$p = 0.014$
	N1	1	5	
	N2	3	4	
	N3	5	0	
Piroxicam	N0	3	4	$p = 0.046$
	N1	1	2	
	N2	2	1	
	N3	2	1	
Etoricoxib	N0	0	2	$p = 0.024$
	N1	1	3	
	N2	3	2	
	N3	4	1	

As in Table 3, a nonparametric test showed a significant difference of size of lymph nodes pre and post concurrent chemoradiotherapy in all intervention groups ($p < 0.05$).

Table 4. Comparison of clinical stage in pre and post concurrent chemoradiotherapy treated with placebo, piroxicam or etoricoxib in nasopharyngeal carcinoma.

Intervention	Clinical stage	Concurrent chemoradiotherapy		*p*
		Pre	Post	
Placebo	0	0	0	$p = 0.038$
	1	0	0	
	2	1	3	
	3	3	6	
	4	5	0	
Piroxicam	0	0	1	$p = 0,024$
	1	0	1	
	2	1	2	
	3	2	2	
	4	5	2	
Etoricoxib	0	0	0	$p = 0.024$
	1	0	1	
	2	0	3	
	3	3	3	
	4	5	1	

Table 4 showed there is also a significant difference in clinical stage pre and post concurrent chemoradiotherapy in all intervention groups ($p < 0, 05$).

4. Discussion

Nasopharyngeal carcinoma (NPC) is a rare malignancy in most part of the world. It mainly affects people from Southern China. The highest incidence of the disease is also reported in other population of South East Asian countries, especially among admixture of the Chinese population (Kumar 2003).

Characteristic of NPC in this study are most common found in the age group of 41-60 years, with male predominance in which male to female ratio was 3.2:1. This finding is consistent with other studies which showed the highest proportion of NPC in 41-60 years of age group with a range of 25-50% of the population (Liu *et al.* 2010; Pua et al. 2008). It is known that DNA repair mechanisms are less efficient and more error-prone as the age increases. An example of a study to introduce DNA damage is using human peripheral blood lymphocytes irradiated with ultraviolet (UV). The study showed a decline of UV damage repair to 25% over 40 years. Not only the repair become less efficient, it also makes more errors and mutations. Thus, NPC is more likely to be found at that age (Gorbunova *et al.* 2007).

Studies in other countries also showed that NPC was mostly found in men. This is allegedly due to living habits, and working conditions that caused men expose to carcinogen more often than women. Fumes, smoke and chemical exposure may increase risk of NPC 2-4 times, while formaldehyde exposure increases the risk 2-4 times (Chang & Adami 2006). There has been an increase incidence rate and mortality due to NPC in miners, blacksmiths, bread makers, farmers and wood cutter (Turkoz *et al.* 2011).

In this study, squamous cell carcinoma was the most common type of histopathology in the patients, found in 15 subjects (60%). While undifferentiated carcinoma was the least common, found in 10 subjects (40%).

Wei *et al*. (2011) cited from Cao *et al*. (2006) stated that 97.6% of 1.142 cases of NPC in Guangdong consist of non keratinizing squamous cell carcinoma, 1.7% consist of undifferentiated carcinoma and 0.5% consist of keratinizing squamous cell carcinoma.

A different report by Alabi *et al*. (2010) in Nigeria that found the most common type of NPC was undifferentiated carcinoma (70%), keratinizing squamous cell carcinoma (20%), non-keratinizing squamous cell carcinoma (10%).

Non keratinizing squamous cell carcinoma and undifferentiated carcinoma are the most common type of NPC in endemic areas such as South China, South East Asia, and North Africa. Meanwhile, keratinizing squamous cell carcinoma is the most common NPC found in Europe with poor prognosis (Licitra *et al.* 2003; Guigay *et al.* 2006). It is consistent with this study, in which squamous cell carcinoma was found in 15 subjects (60%).

Nasopharyngeal carcinoma is a very radiosensitive tumor. Radical external radiotherapy is the mainstay of treatment. Nasopharyngeal carcinoma is also more chemosensitive than head and neck cancer at other site. It makes concurrent chemoradiotherapy become a standard treatment for NPC patients with advanced tumor and node stage (Chan et al. 2002).

Improvements in radiotherapy treatment will likely depend on increasing the sensitivity of tumor cells to radiation and reducing the effects of irradiation on normal tissues (Rosen *et al.* 2000). Cell exposure to radiation induces expression of genes whose products are involved in internal signaling pathways that either promote cell survival or trigger cell death, and it is the balance between these gene expressions that determines the immediate fate of the irradiated cell. The radiation exposure is associated with an increase in eicosanoid production such as prostaglandins and thromboxanes—prostaglandin E1 (PGE1), prostaglandin E2 (PGE2), prostaglandin F2α (PGF2α), PGI2 which is a vasodilator and inhibitor of platelet aggregation, thromboxane A2 (TXA2) -a platelet aggregator and vasoconstrictor, and TXB2— can be detectable in most tissues and persist for several days or weeks (Choy & Milas 2003).

Prostaglandin H (PGH) synthase and prostaglandin endoperoxide synthase, which is also known as cyclooxygenase, is the rate-limiting enzyme in the conversion of membrane-derived arachidonic acid to prostaglandin H2 (PGH2). PGH2 is the common precursor that isomerases convert into the various prostaglandins and TXA2. Cyclooxygenase consist of two forms, COX-1 and COX-2. NSAIDs inhibit the activities of both COX-1 and COX-2, whereas selective COX-2 inhibitors only inhibit COX-2 activity (Choy & Milas 2003).

Expression of COX-2 can be observed in epithelial cells of the cancer and especially in invading vascular tumor. This suggests that COX-2 and not COX-1, is formed in malignant epithelial and also expressed in cells undergoing angiogenic response to cancer (Leahy *et al.* 2000). Overexpression of COX-2 in cells was said to be resistant to apoptosis, an important mechanism of cell death induced by irradiation. This is due to an increase in the level of important anti-apoptotic protein Bcl-2 in epithelial cells. Clinically, overexpression of COX-2 has been related with treatment failure in neck cancer radiotherapy (Nix et al. 2004).

Administration of COX-2 inhibitors in NPC patients cause a decrease of angiogenesis (Soo et al. 2005). Angiogenesis are needed for tumor growth and metastasis (Leahy et al. 2000).

Use of NSAIDs, celecoxib, had been reported in which this cyclooxygenase-2 inhibitor leads to a significant reduction in the number of colorectal polyps (Steinbach *et al.* 2000). Clinical trials combining celecoxib, chemotherapy, and radiotherapy are also being conducted in cancers such as cervical cancer and non–small-cell lung cancer (NSCLC), in which radiation is a prominent component of standard therapy (Carbone *et al.* 2002; Liao *et al.* 2003; Choy & Milas 2003).

No reports were identified using COX-2 inhibitors as combined therapy in tumors, moreover, in nasopharyngeal carcinoma with concurrent chemoradiotherapy. In this study, we assessed clinical response in patients treated with combined therapy of COX-2 inhibitors and concurrent chemotherapy.

A non-parametric test on primary tumor size pre and post concurrent chemoradiotherapy (table 2), showed a significant difference in the etoricoxib group ($p = 0.026$), while the placebo ($p = 0.317$) and piroxicam ($p = 0.279$) group did not show any significant difference.

This is possible mainly because tumor cells and cells of the neovascular endothelium express COX-2. Meanwhile, exposure of radiation increases this expression and stimulates the rapid re-growth of the tumor. Suppression of the COX-2 activity blocks prostaglandin synthesis and prevents the stimulation of tumor growth and angiogenesis, thus increasing the sensitivity of the tumor to radiation (Choy & Milas 2003).

Principally, ionizing radiation affect the effects of oxygen containing free radicals in lipid membranes and membrane transport that can cause edema. Ionizing radiation activates cytoplasmic phospholipase A2 that stimulates arachidonic acid from the membrane phospholipids, which then produce eicosanoids through cyclooxygenase and lipoxygenase pathway. Irradiated cells produce various eicosanoids including PGE2 (Choy & Milas 2003). PGE2 stimulates proliferation through EGFR and MAPK. PGE2 can also stimulate NFκB that will also stimulate the formation of Bcl-2, a gene that plays role in anti-apoptotis (Koontongkaew & Leelahavanichkul 2012). This might explain why the combination of concurrent chemoradiotherapy and placebo did not reveal any significant differences. After the administration of concurrent chemoradiotherapy, various factors that contribute to tumorigenesis are also stimulated.

Etoricoxib is a highly selective COX-2 inhibitor (Martina *et al.* 2005). This may be the reason why when combined with concurrent chemoradiotherapy, there was a significant decrease of the primary tumor size compared to those combined with placebo or piroxicam. Moreover, in a study about the use of COX-2 inhibitor in head and neck cancer (oral cavity, oropharynx, larynx/hypopharynx and other sites eg: sinonasal and temporal bone) treatment, there were no difference found in survival and recurrence in patients who used non-selective COX-2 inhibitors compared to non-users (Gillespie *et al.* 2007).

In table 3, non parametric test on the size of cervical lymph nodes pre and post concurrent chemoradiotherapy showed significant difference in all treatment groups, either placebo ($p = 0.014$), etoricoxib

(p = 0.024) and piroxicam (p = 0.024).

Study about oral squamous cell carcinoma by Morita *et al.* (2012) suggested that COX-2 overexpression may cause lymphangiogenesis of tumor and lymph node metastasis. Inactivation of COX-2 by administration of COX-2 inhibitors may suppress this lymphangiogenesis and lymph node metastasis (Yu *et al.* 2012).

A study that compared concurrent chemoradiotherapy vs radiotherapy alone in nasopharyngeal carcinoma found a complete remission rate of cervical lymph nodes in NPC patients after 1,6, and 12 months of chemoradiotherapy were 91.5%, 94.9% and 98.3% consecutively [10]. Yu *et al.* (2012) has also found that there was a statistically significant difference remission of cervical lymph nodes in advanced stage NPC patients who received concurrent chemoradiotherapy.

VEGF-C which is a part of VEGF and together with VEGF-D is responsible for tumor lymphangiogenesis and lymph node metastasis. The implication of COX-2 in lymphangiogenesis is possible due to COX-2 which is a pleiotropic enzyme mediate various cellular functions. A recent study in lung adenocarcinoma showed an increase expression of VEGF-C by COX-2 through HER-2/Neu pathway (Kyzas *et al*. 2005).

In this study, administration of a combined COX-2 inhibitor, either etoricoxib or piroxicam, with concurrent chemoradiotherapy showed significant difference in lymph node size.

This study has also found that NPC patients may benefit from this combined treatment, which is demonstrated by reducing clinical stage pre and post concurrent chemoradiotherapy in all intervention groups, placebo (p = 0.038), etoricoxib (p = 0.024) and piroxicam (p = 0.024) (Table 4).

Overexpression of COX-2 is associated with carcinogenesis, growth and development of head and neck squamous cell carcinoma through many pathways (Kyzas *et al.* 2005; Gallo *et al*. 2001). Thus, increase of COX-2 is associated with poorer staging and prognosis (Kyzas *et al*. 2005).

Inhibition of COX-2 expression by administrating COX-2 inhibitor showed the evidence of antitumor and antiangiogenesis effect (Gallo et al 2001).

In a study of expression COX-2 protein in radioresistant laryngeal cancer, selective COX-2 inhibitor, enhance the effect of radiotherapy preferentially in human cells with overexpressed COX-2. With the use of COX-2 inhibitors, clinicians can increase the sensitivity of radiotherapy in laryngeal cancer. It can reduce the failure of radiotherapy (Nix et al. 2004).

Yu *et al.* (2013) showed that concurrent chemoradiotherapy can increase the overall survival rate and local control rate in nasopharyngeal carcinoma patients.

COX-2 inhibitor in animal clinical trial showed antitumor activity against tumor. In a clinical trial on rat and human colon cancer, COX-2 inhibitor is associated with inhibition of tumor growth and reduction of metastases development in the lung compared to those who were not given any treatment (Choy & Milas 2003).

In this study there was a significant difference in clinical stage pre and post concurrent chemoradiotherapy with a combination of either Etoricoxib, Piroxicam or placebo. This is may be due to decrease of primary tumor and lymph node size in all intervention groups.

5. Conclusion

This study showed significant improvement in primary tumor size, lymph nodes and clinical stages both clinically and statistically when combined with a selective COX-2 inhibitor pre and post concurrent chemoradiotherapy. Meanwhile, the administration of piroxicam, a non selective COX-2 inhibitor, and placebo only showed significant differences in size of lymph nodes and clinical stage ($p < 0.05$). It did not reveal any significant difference in primary tumor size ($p > 0,05$). This suggests that a combination of etoricoxib, selective COX-2 inhibitor, on concurrent chemoradiotherapy has advantages compared to piroxicam, non selective COX-2 inhibitor, or concurrent chemoradiotherapy alone.

Therefore, selective COX-2 inhibitor, etoricoxib should be considered as an additional therapy to the concurrent chemoradiotherapy in patients with nasopharyngeal carcinoma for a better therapeutic effect.

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