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Padjadjaran Journal of Dentistry/PdD (ISSN 1979-0201) is a new appearance of Jurnal Kedokteran Gigi / Journal of Dentistry that previously published in Bahasa Indonesia language. Padjadjaran Journal of Dentistry is published quarterly by Faculty of Dentistry Universitas Padjadjaran, Bandung-Indonesia. Corporate, Editorial, Accounting, and Circulation Office: Faculty of Dentistry Universitas Padjadjaran Bandung-Indonesia, 3rd floor Jln. Sekeloa Selatan 1 Bandung 40132 West Java, Indonesia. Tel. +62-22-2504985, Fax. +62-22-25328015, Email: jurnal.figundipad.ac.id. Subscription IDR 100,000,- per year (individual/institution), US $ 25.00 per year (foreign). Foreign air speed delivery for all PdD is $ 6.00 per issue. All prices are subject to change without notice.
# Journal of Dentistry

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Anti-tumor agent celecoxib activity toward SP-C1 tongue cancer cells invasion (in vitro)

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*Department of Pedodontics Faculty of Dentistry Universitas Padjadjaran
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ABSTRACT

Invasion is a characteristic of the occurrence of cancer and indicates the cancer cells’ capability to destroy and degrade the border between the epithelial and basal membrane to further spread into the surrounding extra-cellular matrix. The purpose of this research was to find the existence of impediment at the SP-C1 tongue cancer cell using celecoxib chemopreventive medication. The SP-C1 tongue cancer cells were treated in vitro using celecoxib medication as research subject at the following concentrations 5, 10, 25, 50, 75, 100, 125%; and 0 as control group (only DMEM growth medium treatment). Pure experimental testing was carried out for 24 and 48 hours, with observation and calculation of average number of SP-C1 tongue cancer cells. The data collected were analyzed using the ANOVA test with Newman Keuls paired range test or t test. Research results indicated that the average number of SP-C1 tongue cancer cells invasion after administration of celecoxib medication based on administration concentration and time statistically yielded significant results. The ANOVA test results was statistically significant, that is, average occurrence of the number of SP-C1 tongue cancer cells due to the use of celecoxib at certain concentrations compared to that without celecoxib was different. At celecoxib of zero (control) concentration was 24.4 with celecoxib concentration starting at 5 up to 125% experienced decline from its average 11 to become 2.3. The conclusion of the research was that the greater the celecoxib concentration administered, the greater the effect on the impediment of SP-C1 tongue cancer cell invasion.

Key words: Invasion, SP-C1 tongue cancer cell, celecoxib

ABSTRAK

Invasi merupakan karakteristik terjadinya kanker dan menunjukkan kemampuan sel kanker merusak dan mendegradasi batas antara jaringan epitel dan basal membran untuk selanjutnya menyebar ke dalam matriks ekstraseluler sekitarnya. Tujuan penelitian ini untuk mengetahui adanya hambatan pada invasi sel kanker lidah SP-C1 dengan menggunakan obat kemopreventif celecoxib. Sel kanker lidah SP-C1 pada uji invito diberi perlakuan dengan menggunakan obat celecoxib sebagai subjek penelitian pada konsentrasi 5, 10, 25, 50, 75, 100, 125, serta 0 sebagai kelompok kontrol (hanya pemberian

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media pertumbuhan DMEM). Pengujian eksperimental murni dilakukan selama 24 dan 48 jam dengan pengamatan dan perhitungan terhadap rerata jumlah invasi sel kanker lidah SP-C1 setelah pemberian beberapa konsentrasi celecoxib. Data yang diperoleh analisis menggunakan uji ANAVA dengan uji berpasangan rentang Newman Keuls atau t test. Hasil penelitian menunjukkan bahwa rerata jumlah invasi sel kanker lidah SP-C1 setelah pemberian obat celecoxib berdasarkan konsentrasi dan waktu pemberian secara statistik memberikan hasil yang signifikan. Hasil pengujian dengan ANAVA memberikan F hitung = 60,46 yang bersifat bermakna secara statistik, artinya rata-rata terjadinya jumlah invasi sel kanker lidah SP-C1 karena pemakaian celecoxib dengan konsentrasi tertentu dibandingkan tanpa celecoxib adalah berbeda. Pada Celecoxib konsentrasi noil (kontrol) adalah 24,4 dengan konsentrasi celecoxib mulai dari 5 sampai dengan 125 mengalami penurunan dari rata-ratanya 11 hingga menjadi 2,3. Kesimpulan penelitian adalah semakin besar konsentrasi celecoxib yang diberikan akan memberikan efek yang lebih besar pula terhadap hambatan invasi sel kanker lidah SP-C1.

**Kata kunci:** Invasi, sel kanker lidah SP-C1, celecoxib

**INTRODUCTION**

Cancer is an abnormal rapid growth of cells, uncontrolled, and there are no clear borders with sound tissues and also have some traits such as anaplasia, invasion, metastatic and rapid growth acceleration. The disease characterized by disorders or failure of multiplication control mechanism in multicellular organism so that uncontrollable behavioral change occurred. The change caused by genetic transformation, especially in genes that regulate cell growth, such as protooncogenes and tumor suppressor genes. The transformed cells continuously proliferate and suppress the normal cells growth.

Squamous cell carcinoma in tongue is a malignancy that originated from oral epithelial mucosa and mostly epidermoid carcinoma. Tongue squamous cell carcinoma accounted for 25 to 50% of all cancers in oral cavity. Out of 441 tongue squamous cell carcinoma reported by Ash and Millar, 25% occurred in women and 75% founded in men with mean age of 63 years old. According to the NCI's SEER statistic (National Cancer Institute Surveillance Epidemiology and End Results) of the U.S. National Institutes of Health Cancer it was assumed 9,800 men and women (6,930 men and 2,870 women) diagnosed tongue cancer. Tongue squamous cell carcinoma had a poor prognosis, so that early diagnose of this disease is important particularly if it was metastatic to a remote area (such as neck and cervical). Tongue carcinoma frequently observed concomitant with another disease such as syphilis and premalignant lesions as leukopiakia, erythroplasia while according to Frazell and Lucas study, the tongue cancer cases occurred at tongue dorsum was only 4%, but it was more malignant (Undifferentiated epidermoid carcinoma).

Tongue squamous cell carcinoma occurred because of lost control of cell cycles, which is the control cell survival, and control cell motility. The pathogenesis of squamous cell carcinoma is a gradual process, that occurred because of disturbances in growth control function (protooncogenes and tumor suppressor genes) so an increasing growth factors production occur and the cell surface receptors, accelerate the intercellular signal transduction and increasing the transcription factors production. Lethal trait of cancer is the ability to invade the surrounding structures, and metastasize to a distant sites of the body.

Tongue cancer cell SP-C1 is a tongue cancer cell that isolated from cancer patient lymphoidin. The SP-C1 tongue cancer cell originated from the squamous cell carcinoma moderately differentiated and had not yet invaded the local muscle tissues. This cancer cell characterized by: (1) rapid invasion and metastatic activity; (2) mostly found in human cells; (3) recurrence rate is high even though a radical mode of therapy had been carried out; (4) survival rate is low. This cancer also accounted as a hard to be cured disease and easily metastasized to cervical lymphonoid with high malignancy level.

Prior to invasion process, the squamous cell carcinoma developed locally in the cancer origin epithelial, and had not yet penetrate the basal
membrane, this condition known as carcinoma in situ. But because of the invasive cancer growth pattern, they went out of their origin tissue, to influence the adjacent organ surface function.  

Squamous cell carcinoma will invade the underlying structure, and metastasize based on their malignancy level. Invasion is a characteristic of a cancer. Invasion showed the ability of cancer cell to destroy or degrade the border of epithelial tissues and basal membrane.  

The invasion process occurred as it infiltrate into the border tissue, impair the basal membrane, extracellular matrix and destroy the tissue structure even organ function. Cancer cell metastatic activity occurred because of the epithelial cell migration. The epithelial cell migration is a very essential for many physiological and pathological processes. Migration of carcinoma cell involved the molecular mechanism similar to the physiological migration. Cell behavioral change occurred as a result of the impaired molecular signal and different ability of tumor cells in respond to this signal. The tumor cell invasion involving the bonding process of receptor and ligand and interaction between proteins and enzymes of basal membrane.  

Two important facts regarding the NonSteroid Anti Inflammatory Drugs (NSAIDs) usage in radiotherapy of cancer disease treatment. First, on preventive side (cancer preventive) that eventually resulted in long term effect. Second, on curative side of cancer. Celecoxib is a kind of NSAIDs while in use not only act as an analgesic, antipyretic and antiinflammatory therapeutic agents but also act in cancer prevention measure. Celecoxib (NSAID group) can retard the proliferation process and inhibit the invasion of cancer cells and also causes death to cancer cells (in some percentage). Celecoxib as an anti-cancer agent has an important role in cell cycle intervention.  

METHODS  

In this study, an observation toward several concentrations of celecoxib used to obtain data regarding the inhibition of SP C1 tongue cancer cell Supri’s clone invasion using the Boyden Chamber Assay measurement device. In period of 24 hours and 48 hours observation and counting the alive cancer cells amount done eventually, in order to obtain the numbers of cancer cells survived from invasion inhibition after celecoxib applied, with each concentration of 5, 10, 25, 50, 75, 100, 125%, and as comparison there also been a control group with growth medium applied (DMEM).  

RESULT  

Based on observation data (Table 1 and 2), it can be described as follows: generally the result and the counting of tongue cancer cell SP C1 in 24 hours group in polycarbonate membrane under the light microscope, there was a significant change in SP C1 cancer cell inhibition, from the concentration 5 to 125%. Instead, compared to the control group of 24 hours (mean 95) and 48 hours showed an increasing invasion numbers of SP C1.
Table 2. Cell invasion comparison based on period and drug concentrations

<table>
<thead>
<tr>
<th>Time (A)</th>
<th>0%</th>
<th>5%</th>
<th>10%</th>
<th>25%</th>
<th>50%</th>
<th>75%</th>
<th>100%</th>
<th>125%</th>
<th>F count</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hour</td>
<td>Mean</td>
<td>95.5</td>
<td>57.0</td>
<td>39.67</td>
<td>24.0</td>
<td>31.33</td>
<td>17.67</td>
<td>14.33</td>
<td>11.31</td>
<td>311.91D</td>
</tr>
<tr>
<td></td>
<td>(SD)</td>
<td>(1.0)</td>
<td>(7.3)</td>
<td>(0.577)</td>
<td>(1.0)</td>
<td>(2.082)</td>
<td>(0.577)</td>
<td>(1.528)</td>
<td>(2.082)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>94.96</td>
<td>52.95</td>
<td>39.40</td>
<td>23.25</td>
<td>19.23</td>
<td>17.18</td>
<td>13.16</td>
<td>9.13</td>
<td>311.91D</td>
</tr>
<tr>
<td>48 hour</td>
<td>Mean</td>
<td>100</td>
<td>31.33</td>
<td>25.67</td>
<td>21.0</td>
<td>19.33</td>
<td>17.0</td>
<td>13.0</td>
<td>6.67</td>
<td>1204.22D</td>
</tr>
<tr>
<td></td>
<td>(SD)</td>
<td>(2.646)</td>
<td>(1.155)</td>
<td>(1.528)</td>
<td>(1.0)</td>
<td>(0.577)</td>
<td>(1.0)</td>
<td>(2.0)</td>
<td>(0.577)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>96.103</td>
<td>30.32</td>
<td>24.27</td>
<td>20.22</td>
<td>19.20</td>
<td>16.18</td>
<td>11.15</td>
<td>6.7</td>
<td>1204.22D</td>
</tr>
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</table>

Long time cancer cells after counting the data in 48 hours period (100). Counting the control group cancer cells, in comparison of control in 24 hours (95), to the control in 48 hours (100) showed an increasing amount for 5%. This pointed out that cancer cells without treatment of celecoxib would return as an increasing number of SP-C1 cancer cells amount (there was an invasion of cancer cells). Observation on cancer cells amount in concentration of celecoxib 5, 10, 25, 50, 75, 100, 125% in 24 hours period (57; 39.5; 24; 21.3; 17.67; 14.3; 11.3) showed a decreasing result and after observation in 48 hours (31.3; 25.7; 21; 19.3; 17; 13; 6.7). This suggested that there was an inhibition toward the SP-C1 tongue cancer cells after application of celecoxib medium.

**DISCUSSION**

Basically oral cancer occurred because of abnormal genome, caused by impaired genes that regulate the cell differentiation. The genes that regulate cell growth and differentiation known as protooncogene and tumor suppressor genes, and can be found in every chromosome abundantly. Impaired protooncogenes that undergo changes so that it could eventually be a cancer known as oncogenes. 13

Understanding of the carcinogenesis process is a strategic development in cancer disease treatment. Cancer therapy approach using the chemopreventive agents is more promising than any other conventional anti-cancer drugs. Chemopreventive agents defined as a compound that inhibit and suppress the carcinogenesis process in human cells so that cancer growth could be prevented. 14

Chemopreventive agents development based on the cell cycle regulation including the growth hormone receptors and protein kinase, angiogenesis inhibition, cyclooxygenase-2 (COX-2) enzyme inhibition, and apoptotic induction. Chemopreventive agents specifically targeted to an activity through the molecular mechanisms. The abnormality of cell cycle and apoptotic regulation, COX-2 enzyme increase, and angiogenesis process only occurred at cells invaded by cancer even though only on several cases angiogenesis observed in the heart. 14

Celecoxib (NSAID group) could inhibit the cancer cell proliferation and invasion and also killed the cancer cells (at some percentages). Celecoxib as an anti-cancer agents played a role in intervention toward the cell cycle. Cyclooxygenase enzyme (COX) that is a target of Non-Steroid Anti-Inflammatory Drugs (NSAID) could be found in two isomorph, which is COX-1 and COX-2. Both enzyme catalyzed the reaction and resulted the same product, prostaglandin, but with different biological functions. 15

Statistical analysis using the ANOVA showed a significant value, which means that the cancer cells invasion event toward the celecoxib in several concentration is different compared to the group without celecoxib treatment. The control celecoxib group was 97.50 and the concentration with celecoxib concentration of 5 μM to 125 μM had a mean value change from 44.17 to 9.00.

Analysis of period of time using ANOVA also resulted a significant value, this showed that time factor influenced majorly in celecoxib as an anti-invasion drugs effectivity: the longer time the lower or there would be a decreased cancer cells invasion based on the mean of cancer cells invasion (35.04) in 24 hours while in the 48 hours it mean value was 29.250.

The result of this study correspond with Lucille et al. 16 study which suggest that celecoxib
10 µM inhibits the cells invasion or migration through matrix collagen type I about 40% in 24 hours. The zymography result concluded that in existence of celecoxib with concentration of 10 µM the activity of MMP-2 and MMP-8 enzyme decreased about 30-40%. This in vitro study also showed that there is inhibition in proliferation and invasion of squamous cell carcinoma by the specific inhibitor of COX-2, where the celecoxib resulted an anti-cancer effect through various mechanism of cellular and molecular. This study also tested 10 groups of NSAID available toward oral cancer cells and resulted that celecoxib and sulindac sulfide (Clinoril sulfide) were very effective in killing and inhibiting the cancer cells growth. Study regarding the two drugs, celecoxib and sulindac sulfide suggested that celecoxib proved as more effective, inhibited up to 60 percent of oral cancer cells.

CONCLUSION

The celecoxib drug inhibits the SP-C1 tongue cancer cells invasion in several concentrations, this showed in decreased numbers of tongue cancer cells after the drug with several concentrations applied from the lowest (5) to the highest (125). While in the control group (without celecoxib application) still showed an increased numbers of tongue cancer cells invasion.

REFERENCES

as agents of change is clear from even a brief consideration of the nature and conditions of dentist-patient relationship. Most people will go to a particular dentist regularly over a period of time subsequently establishing a relationship between them. Thus, this makes interaction and exchange of information between them easier as they have prestige, respect, authority and liking of their patients. Their role in the smoking cessation program is very important as they are well placed to recognize smokers and identify the impact of tobacco use in the mouth. This may range from recognizing smoker’s palate, through a diagnosis of periodontal disease to the management of potentially sinister white, red or speckled lesions.

The dental practice setting provides a unique opportunity to assist tobacco users in achieving tobacco abstinence. Widespread acceptance of interventions to tackle nicotine addiction in the dental setting has been lacking and limitations in primary care resources have curtailed further efforts. Compared to other health care providers, dentists can more accurately estimate patient’s tobacco use however they are less consistent with and supportive of intervention, less likely to report having strong knowledge or skill levels regarding tobacco cessation, and more likely to perceive barriers to tobacco intervention.

According to Albert et al., national surveys reveal only 25 percent of dental hygienists provide tobacco cessation counseling (TCC). Warnakulasuriya reviewed two previous decades of tobacco cessation activities among dental care providers and concluded that the most significant barrier to TCC by providers remains the lack of tobacco cessation education during formative years of training.

More than 40% of dentists do not routinely ask about tobacco use and 60% do not routinely advise tobacco users to quit. While 61.5% of dentists believe their patients do not expect tobacco cessation services, 58.5% of their patients felt such services should be provided. Barriers to providing tobacco cessation service include concern for patient resistance, lack of knowledge, lack of time, lack of financial reimbursement and a concern for poor co-ordination of care between dentistry and tobacco cessation services. However, 85% perceived that discussing smoking habits is part of their job.

Nicotine Addiction Research & Collaborating Centre (NARCC)

The uniqueness of dentists playing a more interventional role therefore cannot be argued. The role of psychiatrists to support the effort therefore becomes all the more important. In realizing the above, two leading universities in Malaysia, University Malaya and Universiti Kebangsaan Malaysia, have teamed up to set up the Nicotine Addiction Research & Collaborating Centre (NARCC) under the University Malaya Centre of Addiction Sciences (UMCAS) in December 2008. This group will attempt to address the problems faced by dentists in setting up a TCC in their respective sites. The team conducts workshops throughout the country and provide expert consultation to attract dentists of all walks of life to fight against this growing menace to society. The positive outcome of such collaborative efforts hoped to be realized in the years ahead.

CONCLUSION

The potential influence of dentists as agents of change is clear from even a brief consideration of the nature and conditions of dentist-patient relationship. The dental practice setting provides a unique opportunity to assist tobacco users in achieving tobacco abstinence. The role of psychiatrists to support the effort therefore becomes all the more important.

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Encouraging dentists as agents of change in the fight against tobacco in Malaysia (Amer Siddiq, AM et al)


