

Cyclooxygenase-2 (COX-2) expression in lymphoma in north-west of Iran

Zohreh Sanaat^{*1}, Seyed-Mohammad Tavangar², Jalil Vaez Gharamaleki³, Iraj Aswadi Kermani⁴, Jamal Eivazi Ziae⁵, Alireza Nikanfar⁶, Ali Esfahani⁷, Seyyed Hadi Chavoshi⁸, Bevrani H⁹, Farideh Akbari¹⁰

¹Associate professor of hematology & oncology, Hematology & oncology Research Center, Tabriz University of Medical Science, Tabriz, Iran.

²Seyed-Mohammad Tavangar, Professor of pathology, pathology department, shariati hospital, Tehran University of Medical Science, Tehran, Iran.

³Jalil Vaez Gharamaleki, Professor of hematology and oncology, Hematology and Oncology Research Center, Tabriz University of Medical Science, Tabriz, Iran.

⁴Iraj Aswadi Kermani, Professor of hematology and oncology, Hematology and Oncology Research Center, Tabriz University of Medical Science, Tabriz, Iran.

⁵Jamal Eivazi Ziae, Associate Professor of hematology and oncology, Hematology and Oncology Research Center, Tabriz University of Medical Science, Tabriz, Iran.

⁶Alireza Nikanfar, Associate professor of hematology and oncology, Hematology and Oncology Research Center, Tabriz University of Medical Science, Tabriz, Iran.

⁷Ali Esfahani Assistant professor of hematology and oncology, Hematology and Oncology Research Center, Tabriz University of Medical Science, Tabriz, Iran.

⁸Seyyed Hadi Chavoshi Assistant professor of hematology and oncology, Hematology and Oncology Research Center, Tabriz University of Medical Science, Tabriz, Iran.

⁹Assistant professor of statistic, Faculty of Mathematic, Tabriz University of Medical Science, Tabriz, Iran.

¹⁰Internist, Hematology and Oncology Research Center, Tabriz University of Medical Science, Tabriz, Iran.

***Corresponding author:** Zohreh Sanaat, Associate professor of hematology & oncology, Hematology & oncology Research Center, Tabriz University of Medical Science, Tabriz, Iran.

Tel: 00984113343811-13

Fax: 00984113343844

Abstract

Background: Lymphomas are a group of malignancies affecting B, T and NK cells. COX-2 enzyme is one of the known inflammatory factors which increase in the inflammation process. Increase in COX-2 expression inhibits apoptosis and increases tumor cells invasion and angiogenesis. Increase in the COX-2 gene expression is seen in a group of cancers. Specific COX-2 inhibition also can be beneficial in some cancers through apoptosis stimulation.

Materials & Methods: In a descriptive-analytic study, COX-2 expression degree was evaluated in patients with non-Hodgkin lymphoma. Patients' cases were used to study the following variables: gender, age, lymphoma type, and stage of the disease, the degree of the disease, existence of B symptom, extranodal involvement, and response to treatment, death, and LDH levels. Paraffin-embedded tissue blocks from 153 cases of non-Hodgkin and Hodgkin lymphoma were selected for immunohistochemical staining for COX-2 expression.

Results: COX-2 level were reported positive in four (4.7%), patients with non-Hodgkin lymphoma and four (5.7%), patients with Hodgkin lymphoma. During the seven year follow-up, 15 patients were suffering from the disease relapse and 9 patients died during this period. There were no significant relation between others quantitative and qualitative variables and COX-2 expression. Also, There was no relation between COX-2 and type of lymphoma (P=0.476).

Conclusion: According to our results, there was no relation between cox-2 expression and type of lymphoma. We recommend more patients are needed for more assess cox-2 expression. On the other hand, in our study most of the patients had Azari Race, may be, have an effect in our results.

Keywords: COX-2, non-Hodgkin lymphoma, Hodgkin lymphoma

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Introduction

Lymphomas are a group of malignancies in B, T and NK cells.¹ Chronic inflammation can be associated with cancer emergence.² Rudolf Virchow for the first time reported that there was chronic inflammation in the cancer emergence sites. This enzyme increases in the inflammations.³

Inflammation is one of the important factors in the cancer phenomenon.² COX-2 plays an important role in the tumor growth, malignant cells proliferation which is followed by increased in angiogenesis, invasion and metastasis. There is a close relation between COX-2 and EGFR.⁴ There are two known COX types including COX-1 and COX-2. COX-1 is produced in many different situations whereas COX-2 is produced in inflammation and cancer. COX-2 mRNA is not seen in the tissues normally but it can increase following response to inflammation or mitogenic stimuli such as growth factor cytokines, oncogenes and several chemical factors. Increase in COX-2 expression inhibits apoptosis and increases tumor cell invasion and angiogenesis. Stimulation for activating COX-2 gene may have an important role in the emergence of cancer.²⁻⁵ The increase in COX-2 expression can be seen in a group of cancers including pancreas, stomach, prostate, lung, colorectal, head and neck, breast and bladder. Specific inhibition of COX-2 can also be useful in some cancers by apoptosis stimulation.²⁻⁵

The aim of this study is to evaluate COX-2 expression degree in the patients with lymphoma (4-5). Considering the fatality and malignancy of lymphoma disease, COX-2 expression can be used as a prognostic factor; or even NSAIDs targeting COX-2 inhibition and increasing apoptosis and anti-angiogenesis activities can be used.

Materials & Methods:

This descriptive-analytic study was conducted in the hematology and oncology clinic of Tabriz Shahid Ghazi Tabatabaei medical educational center from 2004 to 2010. Patients with lymphoma who had pathology reports of non-Hodgkin or Hodgkin lymphoma were selected. Patients' cases were used to study the following variables: gender, age, lymphoma type, stage of the disease (Ann Arbor Staging

System), the grade of the disease (WHO classification), existence of B symptom, extranodal involvement, and response to treatment, death and LDH levels. Immunohistochemistry approach was used to evaluate COX-2 expression. Informed consents were obtained from all patients. The immunohistochemistry tests were covered by the approved project of hematology-oncology research Center of Tabriz University of Medical Science.

Immunohistochemistry method

Samples were cut to 3 micrometer thick sections of formalin fixed, paraffin –embedded tissue samples were deparaffinized, rehydrated through a series of graded alcohols and blinked for endogenous peroxidase (3% H₂O₂) and avidin/biotin. Antigen retrieval was carried out in a microwave oven with peroxidase blocking reagent for 5 min. Primary monoclonal antibody for COX-2 (1/600 dilution-DAKO) was applied to the section. After washing they were incubated for 20 min with biotinylated horse antimouse IgG immunoglobulin (DAKO) and for 30 min with strept avidin peroxidase reagent. The sections were counterstained with Maters hematoxylin and then cover slipped. Later 3 cellular sections were selected and evaluated using X20 lens of a microscope attached to the computer and finally the degree of positivity for COX-2 in tumoral cells was reported. Quality control was performed by using positive colon cancer samples.

SPSS 13 software, Chi-square, T-test, Mann-Whitney Test, Fisher's exact test were used for statistical analyses. P<0.005 was considered significant.

Results

In this study, 153 patients with lymphoma were included. 105 patients (68.6%) were male and 48 (31.4%) female. Age ranged from 13 to 78 years, with a median age of 40±17 years. 71 cases (46.4%) had B symptom. The stage could be determined in 153 patients: 53 patients had in stage I, 53 in stage II, 40 in stage III and 7 in stage IV. 24 patients (15.7%) had extranodal lymphoma. In non-Hodgkin lymphoma, based on the histology, 21 patients (24.6%) were indolent, 55 (64.7%) aggressive and 9 (10.6%) very aggressive. LDH level were 151-

1237(414±294).COX-2 level were reported positive in four (4.7%), patients with non-Hodgkin lymphoma and four (5.7%), patients with Hodgkin lymphoma. During the seven year follow-up, 15 patients were suffering from the disease relapse and 9 patients died during this period. There were no significant relation between others quantitative and qualitative variables and COX-2 expression. Also, There was no relation between COX-2 and type of lymphoma (P=0.476).

Discussion

Inflammation is one of the important factors in the cancer phenomenon.² COX-2 plays an important role in the tumor growth, malignant cells proliferation followed by increase in angiogenesis, invasion and metastasis. There is a close relation between COX-2 and EGFR.⁵ In arachidonic acid cycle, cyclooxygenase COX-2 plays an important role in the production of prostaglandins.

The number of studied on lymphoma is relatively limited as compared with solid tumors. In the study of Li et al, COX-2 expression degree was significantly higher in the patients with lymphoma compared to the normal tissues.⁸ In the study of Paydas S et al focused on the comparison of COX-2 expression degree in the patients with non-Hodgkin lymphoma, it was reported that 56% of the patients with non-Hodgkin lymphoma possessed COX-2 and there was no significant difference regarding COX-2 expression between different clinical types.⁵ In our study, 8 of 145 patients with lymphoma were COX-2 positive.

In the study of Hazar B, the difference between the mean age of the lymphoma patients who were COX-2 positive and COX-2 negative patients was not significant (p=0.660).⁴ In our study, their difference was not significant (p=0.483).

In the study of Li B et al, the degree of positive COX-2 expression was significantly higher in the relapsed NHL.⁹ In our study 15 patient experienced relapse in who COX-2 was negative. In the study of Sugita Y, COX-2 was reported positive in the 22 patients from the 26 patients with neurological system lymphoma.¹⁰ In the study of Mohammad et al and Wun T et al, COX-2 expression was significantly higher

in the malignant lymphoid tissues compared to the normal tissues.¹¹⁻¹² In a study carried out by Thum MJ, it has been confirmed that the COX-2 expression increases in the malignant lymphoid tissues significantly but usage of NSAIDs in treating malignant tumors is not yet confirmed.¹³ According to our results, there was no relation between cox-2 expression and type of lymphoma. Although we recommend, more patients are needed for more assess cox-2 expression. On the other hand, most of the patients in our study had azari race, perhaps that have effect in our results.

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