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The Difference Level of Kynurenic Acid as Pain Biomarker Serum based on the Origin Cancer

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Abstract:-
Background: The prevalence of chronic pain ranges from 30-50% in patients. A comprehensive pain scale assessment must be carried out because of the high rate of morbidity, opioid dependence, and failure of conventional treatment. Objective pain measurement is expected to improve the quality of chronic pain management for malignancy. This study is aim to explore the kynurenic acid level serum in different type of cancer based on its origin, thus we can further evaluate the pain of cancer therapy based on its origin.

Methods: This is a literature review study using electronic database between the years 2011 to 2021. We used Pubmed, Google Scholar, Web of Science databases and analyzed the datas in to comprehensive resumes.

Results: Twenty-five articles, identified from 140 abstracts, were included in this review. From the articles we explored kynurenic acid was found in the serum of cancer patients in the range from 21.3 to 250 nM depending on the type of cancer. It is increasing in some kind of cancer, except for primary cervical cancer than healthy people. The level of this biomarker for example colon adenocarcinoma (37.52 nmol/L, lung Adenocarcinoma (107.1 nmol/L), and multiple myeloma (59.23 nmol/L). Kynurenic acid can be a plasma biomarkers of inflammation and kynurenine pathway activity are independent predictors of cancer mortality and the latter can be used as progostotic factors.

Conclusion: Kynurenic acid level was different in every cancer origin. It is hypothesized that the biological behaviour of type of cancer alter the action of kynurenine metabolic pathway.

Keywords:- *Kynurenic Acid, Pain, Biomarker, Cancer.*

I. INTRODUCTION

Pain is an unpleasant sensory and emotional experience with either the presence or potential for tissue damage that involves an objective component and subjective components (Gelman, 2018; Haefeli M,2018; Australian and New Zealand College of Anesthetists, 2016). Acute pain is the initial phase of nociceptive sensation because tissue injury can then develop but will subside within a few weeks. If this acute pain cascade fails, it will develop into chronic pain (Meissner, 2018). By involving the psychological and physical aspects of the sufferer, chronic pain greatly affects the patient's condition including anxiety, fear, behaviour changes, and sleep disturbances. Meanwhile, from the physical aspect, pain affects morbidity and mortality (Vadivelu N, 2017).

Chronic pain is constant or intermittent that persists over a period of time causing activities limitation of daily living, dependence on opioids, anxiety and depression. The prevalence of chronic pain ranges from 8% to 60% in the world (Dahlhamer J, 2018). Associated with the incidence of chronic pain, patients with cancer have complaints that are exacerbated by chronic pain including impaired physical and psychological function, giving rise to problems that can worsen their quality of life (Australian and New Zealand College of Anaesthetists, 2015). Patients with cancer with chronic pain are complex conditions that require a comprehensive assessment of pain. Identification of the multidimensional aspects of cancer pain in each individual is the key to developing the most effective therapeutic strategy so as to optimize quality of life to prevent further complications (Lawlor P, 2018; Rodriguez C, 2019).

The importance of pain management as part of routine cancer care has been widely emphasized by WHO. The prevalence of cancer patients ranges from 30-50% in patients with chronic pain undergoing active therapy for solid tumor and about 70-90% in advanced disease. Prospective studies show 90% of patients obtain adequate analgesia with simple drug therapy, but this success is not found in routine practice which ultimately requires opioids (Gelman D, 2018).

The use of opioids and the failure of conventional treatment make chronic pain need more objective measurements so that its management can be more effective and increase understanding of the identification of chronic pain pathophysiology. Several studies have found several biomarkers that are thought to measure chronic pain more objectively than subjectively through pain scores (Amirdelfan K, 2020; Gunn J, 2020). In Amirdelfan K's study, it was found that methylmalonic acid, xanthurenic acid, pyroglutamic acid, kinurenic acid, hydroxymethylglutarate were significant biomarkers for assessing pain ($p<0.005$) (Amirdelfan K, 2020).

Meanwhile, in Gunn J's study, it was found that among the biomarkers assessed, quinolinic acid (29%) and kinurenic acid (27%) were the most common abnormal

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biomarkers of the 17,834 patients studied. Both are detectable biomarkers of chronic inflammation mediated by pro-inflammatory cytokines (Gunn J, 2020). Kynurenic acid is a cytokine that has been widely tested for biomarkers of depression. In a recent study, these biomarkers demonstrated the significance of the inflammatory process. The inflammatory reaction is a mechanism for the formation of pain. The kynurenic acid pathway shows how these cytokines play a role in chronic pain processes and quinolinic acid itself its metabolites also have a role in chronic inflammatory processes. This is supported by the latest research on pain, the kynurenic pathway is related to the amino acid tryptophan which in the process plays a role in producing significant cytokines in chronic pain events (Walczak K, 2020).

The aim of this article review is to explore the kynurenic acid level serum in different type of cancer based on its origin, thus we can further evaluate the pain of cancer therapy based on its origin.

II. METHODS

This is a literature review study using electronic database between the years 2011 to 2021. We used Pubmed, Google Scholar, Web of Science databases and analyzed the datas in to comprehensive resumes.

III. RESULTS

We identified 25 articles from 140 abstracts. Those 25 articles were explored on this section.

Kinurenic Acid as an objective parameter of chronic cancer pain

Given the importance of tryptophan metabolism and the kynurenine pathway in driving the inflammatory response, it is not surprising that the kynurenine pathway has recently emerged as an important factor in the pathogenesis of various types of cancer. In addition, tryptophan metabolism is also important for cell proliferation and immunoregulation. It remains unclear whether the kynurenine pathway in cancer is activated by disease biology (eg inflammatory processes) or simply by associated stress. However, its role in tumorigenesis deserves special attention and has been highlighted by several findings (Sforzini L, 2019).

Evidence suggests that IDO activity may support tumor modulation of the immune system. (Gostner J.M, 2015). There are two types of IDO enzymes, IDO1 and IDO2, which convert tryptophan to kynurenine, with different levels of activity. IDO2 is less expressed and has weaker enzymatic activity than IDO1. IDO1 activity is closely related to two key inflammatory cytokines, interferon-gamma (IFN-gamma) and interleukin 6 (IL-6), whose functions in inflammation and cancer are widely known although not fully understood.

Apart from having a common anti-tumor effect, the activity of IDO is also a pro-tumorigenic factor. IFN-gamma activates IDO1 expression, which in turn activates IL-6, creating a network in which IDO1 acts like a negative feedback loop on IFN-gamma, and partially regulates IL-6. Being a regulatory interface between IFN-gamma and IL-6, IDO1 promotes a pro-inflammatory response that plays a role in neovascularization cancer, by increasing the development of new blood vessels (Prendergast G.C, 2017).

More importantly, this enzyme appears to promote tumor development, by acting predominantly on regulatory T cells (Tregs), CD8+ cytotoxic effector (Teff) T cells, and natural killer (NK) cells, these lymphocytes exert protective activity by reducing tumor progression and inhibiting tumor growth. enhance antitumor immunity, but kynurenine can suppress CD8+ and NK T cells and bias Treg differentiation (Miller AH, 2008).

This activity was shown to be reversible by administration of a therapeutic enzyme, Pegylated kynureninase, which converts kynurenine to an immunologically inert compound, with an associated increase in CD8+ lymphocyte proliferation, which in turn increases tumor infiltration (Triplett T.A, 2018).

Although poorly studied, IDO2 has been found to be overexpressed in several human tumors, to functionally allow IDO1-dependent Treg suppression and to support B-cell-mediated autoantibody production that is important in the development of certain cancers, such as squamous cell carcinoma. Together, the IDO1 and IDO2 genes are variably upregulated in neoplastic cells as well as in stromal, endothelial, and innate immune cells of the tumor microenvironment and in tumor-draining lymph nodes (Prendergast GC, 2017) .

Data are also available on another tryptophan catabolizing enzyme, Tryptophan-2,3-Dioxygenase (TDO), which is constitutively expressed in the liver and responsible for metabolizing dietary tryptophan. TDO is also activated during cancer. From recent findings, the level of expression of the TDO2 gene, the gene encoding TDO, correlates with poorer breast cancer clinical outcome. Taken together, these findings suggest that novel pharmacological agents can target IDO (1 and 2) and TDO (Greene L, 2018).

Dysregulation of the kinurenin pathway in cancer may also increase malignancy by production of NAD+, which may directly affect several cellular functions. Furthermore, NAD+ can activate the aryl hydrocarbon receptor (AhR) transcription factor and consequently regulate gene expression (Bostian A.C.L and Eoff R.l., 2016).

An interesting study by Schroecksnadel et al in 146 patients suffering from various types of malignancies (mainly gastrointestinal tumors, haematological malignancies, gynecological neoplasms, and lung cancer). Fifty-four sub-groups were depressed and had to take antidepressant medication. Increased tryptophan degradation, measured by lower tryptophan levels and increased kynurenine concentration and K/T ratio, was

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associated with decreased quality of life (QoL), assessed by self-reported scores (from 1 to 5) (Schroecksnadel K, 2007).

These results emphasize the role of immune-mediated tryptophan degradation in cancer-induced decline in quality of life, but, surprisingly, quality of life is not significantly associated with depression. Nonetheless, this study did not directly measure depression or antidepressant drug status in relation to the kynurenine pathway, leaving some questions are open for future research (Schroecksnadel K, 2007).

Finally, plasma biomarkers of inflammation and kynurenine pathway activity are independent predictors of cancer mortality and the latter can be used as progostotic factors. In particular, even in the early stages of cancer, SSI activity is enhanced and that activity, in most studies, has been associated with a poorer prognosis. Moreover, IDO activation may be associated with the development of cancer-associated fatigue and thus with debilitating consequences (Kim S, 2015; Sforzini L, 2019).

In their study of women with breast cancer, Lyon and colleagues (Lyon D.E, 2011) found a significant difference in tryptophan degradation, expressed in enhanced SSI activity, between patients with early-stage breast cancer and healthy controls. One important consideration of the authors is that this could be relevant to the development of neuropsychiatric symptoms, including depression. Since it is very clear that tryptophan metabolism is critical in both depression and cancer, the assumption that in patients with various types of cancer the development of depression may be associated with immune activation, particularly in immune-mediated activation of SSI, has received increasing attention. However, this hypothesis remains unclear. In Table 1, we have briefly summarized the cancer types in which alterations in the kynurenine pathway have been demonstrated, along with depression prevalence rates, assessed through diagnostic interviews or by self-reported questionnaires. (Sforzini L, 2019; Lyon D.E, 2011).

IV. DISCUSSION

Kynurenic acid in the body

Pain neurotransmitters are expressed in the liver along with IDO-1 or IL-1β mRNA which has an inflammatory function. This suggests that IDO-1 is involved in the formation of pain in the inflammatory process. Kynurenine 3-monoxygenase (KMO) is another enzyme that plays a role in the tryptophan metabolic pathway that is relevant for depression and pain. One study found that depression-like behavior in mice was mediated by activating NMDA receptors with increased levels of quinolonic acid. A subsequent study showed that mice exhibiting a depressant trait of lipopolysaccharide discharge with a genetic deletion of the KMO enzyme did not exhibit depressive behavior. A similar principle behind the interaction of quinolinic acid and NMDA receptors with respect to the occurrence of pain and depression can also be accepted with other NMDA receptor antagonists such as kinurenic acid which reduces neuropathic pain (Jovanovic, 2020).

From this mechanism, the activity of the kynurenine pathway is said to be a plasma biomarker of inflammation that can be used as an independent predictor of cancer mortality and can also be used as a prognostic factor (Sforzini, 2019).

In a systematic review conducted by Walczak et., al in 2020, it was found that serum kynurenic acid levels in patients with primary cervical cancer (250 nmol/L) were lower than healthy people (500 nmol/L) while other cancers were found to be higher than healthy people. However, from the article, it appears that serum kynurenic acid levels in patients with cervical cancer are relatively higher than other types of cancer. As in colon adenocarcinoma (37.52 nmol/L, Lung Adeno Ca (107.1 nmol/L), and multiple myeloma (59.23 nmol/L).

Kynurenic acid variation in cancer

Kynurenic acid was found in the serum of cancer patients in the range from 21.3 to 250 nM depending on the type of cancer (Golyski J, 2013; Walczak K, 2019). Kynurenic acid was increasing in the serum of colon adenocarcinoma patients. Sagan found that serum kynurenic acid has different level in lung cancer based on histopathology type. Kynurenic acid is one of metabolite from kynurenine pathway which induce immunosuppression and facilitate escape of tumor cells from immune surveillances. It is estimated that the biological behaviour of type of lung cancer alter the action of kynurenine metabolic pathway. The level of kynurenic acid in the adenocarcinoma (107.1 ± 62.8 pmol/ml) was significantly higher than in squamous cell lung cancer (82.1 ± 47.6 pmol/ml), $p=0.027$. These results showed that elevated serum kynurenic acid level correlate with the biological behaviour of invasiveness and aggressive cell of adenocarcinoma cancer (Sagan D, 2012). It is concluded that there is a potent role of kynurenic acid as a marker for non-invasive discrimination between N0 and N+ patients in non-small cell lung cancer (NSCLC) (Walczak K, 2020).

Additionally, an increased kynurenic acid concentration was observed in bone marrow plasma of monoclonal gammopathy of undermined significance (MGUS) and multiple myeloma (MM) patients. Interestingly, the kynurenic acid level in the bone marrow plasma of MGUS patients was signifcantly higher than in the MM group. It is found that in patients with primary cervical cancer has more than twofold decrease of serum kynurenic acid concentration in comparison to a healthy patient. A similar efect was noted for patients diagnosed with glioblastoma. Kynurenic acid concentration in plasma from glioblastoma patients was signifcantly lower than in plasma from healthy volunteers. However, the reason for this phenomenon has not been clarifed. Cancer can change the route of kynurenine pathway in which it produce more nicotinamide adenine dinucleotide (NAD+) as a supply energy for metabolic processes. It was showed by the increasing activation of kynurenine pathway (kynurenic acid/tryptophan ratio) with the decreasing in the concentration of neuroactive metabolites in glioblastoma patient compared to healthy patients (Walczak K, 2020).

V. CONCLUSION

Kynurenic acid level was different in every cancer origin. It is hypothesized that the biological behaviour of type of cancer alter the action of kynurenine metabolic pathway. Thus, further research is needed to compare the level of kynurenic acid in some types of cancer.

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