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Correlation between HIF-1α and CD44 with Radiotherapy Response in Stage IIB-IIIB Cervical Squamous Cell Carcinoma

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Abstract: ***Cervical cancer is the fourth most commonly malignancy in women worldwide and one of the most common malignancies in Indonesian women. Radiotherapy is one of the therapeutic modalities of cervical carcinoma. On the other hand, radioresistance can cause failure in this treatment. Under certain circumstances, reoxygenation can ensure the successfulness of radiotherapy. HIF-1α and CD44 are proteins markers that play role in hypoxia condition and stemness of cancer cells which has correlation with radiotherapy resistance. The aim of this study is to find the correlation between HIF-1α and CD44 immunoexpression with radiotherapy response in stage IIB-IIIB cervical squamous cell carcinoma. A retrospective case control analysis design has been used in this study, using secondary data of patientsstage IIB-IIIB cervical squamous cell carcinoma at the Department of Anatomical Pathology of Dr Hasan Sadikin Hospital, Bandung. There are 64 samples consist of 32 radiotherapy sensitive cases and 32 radiotherapy resistant cases. Immunohistochemical staining of HIF-1α and CD44 were performed to all samples. The result of this study shows a statistically significant correlation between HIF-1α (p=0.0001) and CD44 (p=0.011) immunoexpression with radiotherapy response respectively, with Odd Ratio (OR) 27.35 and 4.78 respectively. In conclusion, radiotherapy response in Cervical squamous cell carcinoma is influenced by hypoxia condition and stem cell status. Immunoexpression of HIF-1α and CD44 can be used to predict radiotherapy response. Increase of HIF-1 α and CD44 immunoexpression has a positive correlation with the possibility of radiotherapy resistance.***

Keywords: CD44, HIF-1α, Cervical Squamous cell carcinoma, Radiotherapy

1. Introduction

Cervical cancer in general according to Globocan (2012) is the fourth leading cancer in women, and the seventh of overall cancer worldwide.[1] In developing countries, including Indonesia, cervical cancer is reported as the second leading cause of death in women with high mortality rate (59%).[2] Moreover in 2013, according to Pusdatin (Center for Data and Information) Ministry of Health Republic of Indonesia, cervical cancer is claimed as the highest incidence of cancer occupied by women.[3]Squamous cell carcinoma is one of the types of cervical cancer which composed of squamous cells with various degree of differentiation.[4]

The five-years survival rate of cervical cancer patients is generally varies depending on the stage of the disease, i.e, 97-100% in stage IA, 84% in stage IB, 65-73% in stage II, then continue to decrease to 36% in stage III, and lastly < 15% in stage IV.[5]

Cervical cancer treatment at early stage is done by surgery, whereas radiation therapy is applied at all stages with the mass of the tumor still localized in the pelvis. Especially in patients with advanced stages of cancer, radiation therapy is recommended as the primary therapy, while in high-risk patients such as comorbid or obese patients, radiation therapy may be given as adjuvant therapy to reduce the risk of recurrence after surgery. Radiation therapy is a very effective therapy in stage IB1 of cervical cancer, with systemic and local controls reaching 98% and 95% respectively, and the disease-free survival rate is reaching 90%. However, maintaining high percentage of local control is still become a major constraint in locally advanced stage IB2-IIIB cervical cancer, due to high rate of local recurrence (60% to 70%). The rate of patient's 5-year survival ranged from 40% to 50%, and it continue to decrease along with the cancer progression, 5-15% in stage III and stage IV cervical cancer.[6]In Indonesia, cervical cancer management with radiotherapy or chemoradiation is considered as the main therapy for stage IIB-IIIB cervical cancer, according to cervical cancer management guidelines issued by The Ministry of Health, Republic of Indonesia. Cervical cancer stage is stipulated based on clinical staging, which is staging corresponding to pre-treatment primary tumor clinical examination. Currently, cervical cancer stage is determined by International Federation of Obstetricians and Gynecologist (FIGO) 2000. Hence, this research was conducted to early-detect the radiotherapy response on cervical squamous cell carcinoma patients that had underwent biopsy procedure.

There are several factors that can alter the radiosensitivity in cervical cancer such as apoptotic protein mutation (bcl-2, bax, and p53); tumor DNA damage that caused by free radical formed by COX by product in inflammation reaction; angiogenesis which can be detected by VEGF and EFGR expression; hypoxia conditions which can be assessed by examination of oxygen levels by using electrodes and with hypoxic markers HIF-1α; and temperature.[7]

Hypoxia inducible factor-1α (HIF-1α) is a transcription factor that regulates cell biology in hypoxia condition, and tumor cells are known to activate this condition other than physiological hypoxia.[8] Cancer stem cells (CSC) are also contribute to cancer invasiveness. Biomarker stem cell CD44 is a transmembrane receptor protein which also categorized as adhesion molecule group is involved in cell-cell and cell-matrix interaction. Several studies have mentioned that CD44 and HA interaction can elicit various