Sumatera Medical Journal (SUMEJ) Vol. 2, No. 3, 2019 | 117 - 122

SUMEJ
Sumatera Medical Journal

VEGF and Cervical Cancer Stage IB – IIA Response after Chemotherapy with Ifosfamide – Cisplatin

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Abstract. The aim of this study is to evaluate response of cervical cancer stage IB – IIA after neoadjuvant chemotherapy based on VEGF expression. The data were collected from 51 patients' cervical cancer stage IB – IIA parafin blocks who received chemotherapy ifosfamide – cisplatin before radical hysterectomy at General Hospital Adam Malik Medan. VEGF expression was evaluated from cervical biopsy tissue, and response therapy was evaluated based on tumor size clinically. 20 out of 51 samples with clinically complete response, and the rest are partial response. 18 out of 20 samples with clinically complete response have negative or weak VEGF expression, and 31 out of 51 samples patients were partialy response with moderate or strong VEGF expression. 23 cases with tumor size > 4 cm and 23 cases stage IIA expressed VEGF moderately or strong. Cervical cancer with tumor size < 4 cm and cervical cenncer stage IB with less expressed of VEGF have good response with chemotherapy adjuvant ifosfamide – cis platin.Keyword: ifosfamide-cisplatin, cervical cancer, VEGF

Abstrak. *Penelitian ini bertujuan untuk menilai respon kemoterapi penderita kanker serviks stadium IB – IIA berdasarkan ekspresi VEGF. Bahan dan cara kerja: data diperoleh dari 51 blok parafin penderita kanker serviks stadium IB – IIA yang mendapat kemoterapi ifosfamid – cis platin sebelum menjalani operasi histerektomi radikal di RS H.Adam Malik Medan. Ekspresi VEGF dinilai dari jaringan biopsi sebelum pengobatan, dan respon kemoterapi dinilai berdasarkan ukuran tumor secara klinis. Respon komplit dijumpai pada 20 dari 51 penderita dan sisanya dengan respon parsial. 18 kasus respon komplit tidak atau lemah mengekspresikan VEGF, sementara 31 penderita respon parsial mengekspresikan VEGF sedang atau kuat.. 23 kasus dengan ukuran tumor ≥ 4 cm dan 23 kasus stadium IIA mengekspresikan VEGF sedang atau kuat. Kemoterapi adjuvan ifosfamide – cis platin memberikan respon yang baik pada kanker serviks dengan ukuran lesi ≤ 4 cm dan stadium IB yang kurang mengekspresikan VEGF. Kata kunci: ifosfamide-cisplatin, kanker serviks, VEGF*

1. Introduction

Cervical cancer is the second commonest cancer in women after breast cancer in Indonesia. In 2012, there were 20.928 new cases and 9.498 died because of cervical cancer. (1)
Radiation and surgery are the basic treatments for cervical cancer depend on facilities, patient's condition and the disease itself. (2) (3). Unfortunately, surgery for lesion > 4 cm still gives unsatisfactory result, whereas 50%-60% cases were not reach the radicality of surgery. (4)

Mc Cann found that there are 63% cases which underwent radical hysterectomy with disease free of tumor at vaginal incision. (5) Almost 84% cases of cervical cancer stage IB- IIA with lesion > 4 cm have to be radiated for adjuvant treatment after radical hysterectomy. (6)

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https://doi.org/10.32734/sumej.v2i3.1231
Journal Homepage: http://smj.usu.ac.id

Neoadjuvant chemotherapy could decrease recurrency risk factor and increase surgical radicality, and at the end could decrease the use of radiation after radical hysterectomy for early stage cervical cancer. (7) (8)

Postponing surgery and neoadjuvant chemotherapy will still cause risk for the treatment result. Carefully choosing which neoadjuvant chemotherapy that would be benefit is essential.

Choi et al. reported that there is a close relationship between VEGF expression and chemotherapy neoadjuvant response. Cervical cancer cases with high express VEGF have less response for chemotherapy neoadjuvant. (9)

2. Methods

Data were collected at Adam Malik Hospital Medan with immunohistochemistry staining for VEGF expression from parafin block of cervical biopsy tissue from cervical cancer patients with stage IB – IIA. The staining was done at Pathology Anatomy Department on January and February 2017 for 51 parafin blocks of patients which received chemotherapy neoadjuvant from January 2014 until January 2017.

The chemotherapy regiment is a combination of ifosfamide and cisplatin intra venously that given for three weeks. 2000 mg/m_2 ifosfamide was given at day 1,3 and 5, and 50 mg/m_2 cis-platin at day 1. Mesna dose was 20% of ifosfamide dose at day 1,3 and 5. While day 2,4 and 6 mesna dose was 50% of ifosfamide dose. After three cycles chemotherapy all patients underwent radical hysterectomy.

VEGF expression detected using Vascular Endothlial Growth Factor (VEGF) anti body, clone VG1, mouse anti human. VEGF expression interpretted by two patologists. The parafin block sliced 3-4 micrometer, heated at 37_oC and 60_oC. Deparafinization thrice with xylol and rehidrated with alcohol 90% and 80%. Then rinse with water and blocking endogen peroxiside and washed with phosphate buffered saline. After added with anti body primer, it washed again with phosphate buffered saline. Labelled with trekavidin-horseradish peroxydase, chromogen 3,3'-diaminobenzadine and counter staining with hematocyclin.

3. RESULTS.

From January 2014 until January 2017 period, there were 75 cervical cancer patients stage IB – IIA which treated with neoadjuvant chemotherapy. Unfortunately only 51 parafin blocks can be evaluated for VEGF expression.

Table.1. Clinicopathology characteristic and treatment response

Age	**Complete Response**	**Partial Response**	**N**
≤ 40 year	1	4	5
> 40 year	19	27	46
Lesion size			
≤ 4 cm	19	9	28
> 4 cm	1	22	23
Hystology			
Squamous cell carsinoma	20	26	46
Adenocarsinoma	0	5	5
Differentiation			
Well	11	13	24
Moderate	7	10	17
Poor	2	8	10
Stage			
IB	15	14	29
IIA	5	17	22

The responses of treatment were evaluated after three cycles neoadjuvant chemotherapy. Response was evaluated for tumor size clinically. 20 out of 51 cases with complete responses, while 31 cases with partial responses. In our center, the reason to give neodjuvant chemotherapy are to reach the surgical radicality, and long waiting list for surgery. All patients were given neoadjuvant chemotherapy. Partial response results were more often for cases with tumor size > 4 cm, stage IIA and poor differentiation.

Table.2.VEGF expression for tumor size, stage and treatment response.

Tumor size	**Negative**	**Weak**	**Moderate**	**Strong**	**p**
≤ 4 cm	4	14	10	0	0.005
> 4 cm	0	0	18	5	
Stage					
IB	4	11	14	0	0.005
IIA	0	3	14	5	
Treatment resonse					
Complete	4	14	2	0	0.005
Partial	0	0	26	5	

There are strong relationship between VEGF expression, tumor size and stage. Partial response result was more often for tumor size > 4 cm, stage IIA with strong VEGF expresion.

4. DISCUSSION.

In this study, patient's age were correspond with data from Information Centre on HPV and Globocan 2012, where the most cervical cancer patients were found at age more than 40 years old. (1) (10)

When tumor size increases, many of its cells will fall in hypoxia condition. These hypoxic cells will activate antiapoptosis mediator for cell survival. In the other hand, hypoxia condition will activate HIF-1α and finally activate VEGF. But chemotherapy response were decreased in this case. (11) (12)

In this study, VEGF expression was interpretted by two patologists, and the kappa test is 85.5%. Based on this kappa test where the two interpretter are equal, we used data from the first interpretter.

From table 2, description of negative and weak VEGF expression which only found in tumor with ≤ 4 cm size. The same condition was found for tumor with partial response. VEGF expression was not correlated with hystology type and differentiation.

For tumor growth, angiogenesis process is very important. When the tumor cells are increasing, because of hypoxia condition, it will activate HIF-1α and induced neovasculazation. This new vascular walls is different from normal vascular wall, which is fragile, more permiable and twisted

in appearance. With this vascular characteristic, it will inhibit distribution of chemotherapy agent and decrease the chemotherapy response. (12) (13) (14)

In this study we found that cervical cancer with strong VEGF expression showed good chemotherapy response.

5. CONCLUSION.

Ifosfamide and cis-platin as neoadjuvant chemotherapy treatment for cervical cancer stage IB – IIA especially with large tumor size can shrink the tumor mass and make the radicality result of surgery become easier. Completed responses result more often in cervical cancer stage IB and tumor size < 4 cm whereas they express VEGF less.

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