Research Article

Treatment Response of Platinum-Based Chemoradiation on Locally Advanced Cervical Cancer

Respons Terapi dengan Kemoradiasi Berbasis-Platinum pada Kanker Serviks Stadium Lanjut Lokal

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Abstract

Objective: To evaluate the efficacy (treatment response), toxicity, and overall survival of concomitant chemoradiation (CRT) with three-weekly cisplatin-ifosfamide compared to CRT with weekly cisplatin in advanced stage cervical cancers (stage IIB-IIIB).

Method: This is a historical cohort between 32 patients receiving CRT with three-weekly cisplatin and ifosfamide and 29 patients receiving weekly cisplatin in Gynecologic Oncology division outpatient clinic and ward, Dr. Cipto Mangunkusumo Hospital.

Results: There was no significant difference in treatment response, overall and disease-free survival. There was more gastrointestinal toxicity in the cisplatin-ifosfamide arm compared to the other arm (p=0.014), but other toxicity effects were not different.

Conclusion: Platinum based-chemoradiation has the same efficacy in terms of treatment response for locally advanced cervical cancer.

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Keywords: cisplatin, concomitant chemoradiation, ifosfamide, locally advance stage cervical cancer

Abstrak

Tujuan: *Untuk menilai efektivitas (respons terapi), toksisitas, dan kesintasan keseluruhan dari kemoradiasi dengan cisplatin-Ifosfamide tiga mingguan dibandingkan dengan cisplatin mingguan pada kanker serviks stadium lanjut lokal (stadium IIB-IIIB).*

Metode: *Studi kohort retrospektif pada 32 pasien yang ditatalaksana dengan kemoradiasi cisplatin-ifosfamide tiga mingguan dan 29 pasien dengan cisplatin mingguan menjadi subjek penelitian di poliklinik dan ruangan perawatan divisi Onkologi Ginekologi RSUPN Dr. Cipto Mangunkusumo (RSCM).*

Hasil: *Tidak terdapat perbedaan bermakna pada efektivitas (respons terapi), kesintasan keseluruhan dan kesintasan bebas penyakit pada kedua kelompok tersebut. Toksisitas gastrointestinal lebih berat ditemukan pada kelompok cisplatin-ifosfamide tiga mingguan dibandingkan cisplatin mingguan (p=0,014). Sementara, tidak terdapat perbedaan bermakna pada toksisitas genitourinaria dan hematologi pada kedua kelompok.*

Kesimpulan: *Kemoradiasi berbasis platinum memberikan efektivitas yang sama terhadap penderita kanker serviks stadium lanjut.*

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Kata kunci: *cisplatin, ifosfamide, kanker serviks stadium lanjut lokal, kemoradiasi konkomitan*

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INTRODUCTION

Cervical cancer is the third most common malignancy in women, and the seventh in the world, with approximately 528.000 new cases in 2012. According to the data from GLOBOCAN 2008, the incidence of cervical cancer in Indonesia was 13,762 cases, with as many as 7,493 deaths.[1] This high mortality rate is because most patients present with locally advanced or terminal stage. Data in RSCM from 2006-2010, showed that there were 2,297 cases of cervical cancer, with as much as 76.7% locally advanced disease (IIB to IVB).[2]

According to the National Cancer Institute (NCI), the five-year survival rate for stage IIB-IIIB cervical cancer from 1996 to 2000 was 55%, while for stage IV was 14.6%.[3] The five-year survival rate for the same stage in 2002-2008 was 56.7%, and 16.2%.[4] Data from Dharmais Cancer Hospital, Jakarta in 1996, the survival rate of cervical cancer stage I, II, III, and IV are 56.6%, 56%, 23.7%, and 0% respectively.[5] Nuranna et al reported the five-year survival rate of cervical cancer in RSCM in 2005-2006 for stage I, II, III, and IV to be 73%, 52%, 36%, and 0%, respectively; or the survival-rate of early and advanced stage to be 67 % and 41%.[6]

This low survival rate for locally advanced stages of cervical cancer and treatment advances has triggered the shift of treatment from radiation to chemoradiation.[7-11] In 1999, based on five clinical trials, the National Cancer Institute (NCI) recommends the use of cisplatin-based chemoradiation as the standard of patient care with locally advanced cervical cancer in stage IIB to IVA.[12]

A meta-analysis by Lukka et al of eight randomized clinical trials have evaluated the role of cisplatin by itself or in combination with other chemotherapy agents, which was given concurrently with external radiation, in patients with locally advanced stage.[13] A systematic review from Green et al showed improvement of overall survival rate and progression-free survival, 10% and 13% respectively, favoring chemoradiation with cisplatin.[14]

The results of a meta-analysis of 18 randomized clinical trials by the American Society of Clinical Oncology, showed that there was a 6% (HR 0.81, p<0.001) increase in the overall survival rate, and an 8% increase in the Disease Free Survival (DFS) for 5 years. These advantages are also supported by other data demonstrating the improvement in local control and benefits in distant control are because of the systemic effects of chemotherapy.[15]

Available data shows that chemoradiation only increases the response rate by 20-30%[11] and the 5-year survival rate by 6%.[10] Efforts to improve the response to chemotherapy and survival rate in locally advanced cervical cancer are still continued. Attempts by using other chemotherapy or combined chemotherapy regimens with concomitant radiotherapy have been performed.

Geara, in a phase II study comparing chemoradiation with weekly cisplatin and paclitaxel in patients with locally advanced cervical cancer, found no significant clinical benefit.[16] Survival rate at two and five years in the paclitaxel group was 78% and 54%, while in the cisplatin group was 73% and 43%.[16]

Attempts to perform a combined chemotherapy regimen have been performed. Ranen Kanti, et al did not find significant differences in the use of cisplatin combination chemotherapy with weekly gemcitabine, with therapeutic response of only 67%.[17] Meanwhile, phase III clinical trials by Duen as-Gonzalez et al done in stage IIB and III cervical cancer comparing the standard cisplatin chemoradiation with cisplatin and gemcitabine, as well as two additional gemzitabin-cisplatin series found a significant increase in progression-free survival (PFS) in the third year (74.4% vs. 65.0%, p=0.029).[18]

GOG protocol 110 is a prospective, randomized; phase III study of 454 locally advanced cervical cancer patients. It found that combination of cisplatin-ifosfamide is superior to cisplatin alone (33% compared to 19%). Furthermore, these results showed superiority in terms of PFS (p=0.003), although there was no significant difference in the overall survival rate.[19] A phase II prospective study by Vrdoljak et al observed chemoradiation with cisplatin-ifosfamide regimen in 62 patients with locally advanced cervical cancer. Complete clinical response was achieved in 100% of patients, and both recurrence-free and overall survival rate was 88.7%.[20]

Due to GOG 110 study results, efforts in minimizing the effects of full-dose chemotherapy on locally advanced cervical cancer and improving therapeutic response and survival rate in locally advanced cervical cancer, the Gynecologic Oncology Division of Obstetrics and Gynecology Department, Dr. Cipto Mangunkusumo Hospital has been using chemoradiation with two chemotherapy regimens, which is weekly cisplatin and cisplatin-ifosfamide three weekly as the standard of treatment for locally advanced cervical cancer.

This study will evaluate the existing treatment regimens in terms of assessing better treatment response and survival rate, as well as toxicity profile as a part of protocol evaluation in the Gynecologic Oncology division.

METHODS

This is a historical cohort carried out in the Gynecologic Oncology outpatient clinic, radiotherapy department, and Gynecology Oncology division ward, Dr. Cipto Mangunkusumo Hospital (RSCM), from December 2013 until October 2014. The study subjects are patients who were treated using chemoradiation using cisplatin-ifosfamide and weekly cisplatin in RSCM from August 26th 2010 until June 28th 2014 who met the inclusion criteria. The total sample size in this study was 61 patients.

The inclusion criteria are stage IIB-IIIB cervical cancer patients who received chemoradiation with 3-weekly cisplatin-ifosfamide or weekly cisplatin,

with performance status based on the Eastern Cooperative Oncology Group (ECOG) criteria with score ≤2; having peripheral blood result of Hb ≥10g%, leukocyte ≥5000/mm^3, thrombocyte ≥150,000/mm^3; SGOT <27U/l, SGPT <36 U/l); and renal status of ureum <50 mg/dl, creatinin 0.60-1.20 mg/dl, CCT >68 ml/minute; had been given at least 3 series of chemotherapy; had the tumor size examined with transrectal USG; and underwent post-therapy follow up in the gynecologic oncology outpatient clinic of RSCM for at least 3 months post-therapy.

The exclusion criteria are cervical cancer patients with histopathologic findings other than squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma; received any previous therapy including surgery, radiation, or chemoradiation; suffering other severe comorbidities (uncontrolled cardiovascular disease, uncontrolled diabetes mellitus, severe psychological impairment, active peptic ulcer) or immunodeficiency/ HIV; having primary cancer in other organs (synchronous tumor); and incomplete radiation therapy.

The steps of this study are, after receiving ethical clearance; the medical records of the locally advanced cervical cancer patients (IIB-IIIB) in the gynecologic oncology outpatient clinic who underwent one of the two chemoradiation therapies were collected. The medical data was taken from patients who were diagnosed from August 2010 until November 2013. Selection of medical records corresponded to the inclusion and exclusion criteria. The demographic data, clinicopathologic data in the medical record, and data added upon patients' admission were recorded. Radiation is divided into external radiation (2.0 Gray, 5 dose/ week, 25 times) and internal radiation/brachytherapy (2 x 8.50 Gray (850 rad) or 3 x 7 Gray at point A). Meanwhile, chemotherapy was divided into weekly cisplatin regimen (40 mg/m^2 dose in 6-8 hour prior to radiation, 1 dose/week, minimal 3 times), and cisplatin-ifosfamide regimen (cisplatin 50 mg/m^2 and ifosfamide 2 gr/m^2 given with uromitexan, for 3 weeks, 4 series). Chemoradiation response was evaluated by degree of tumor regression, defined by comparison between tumor size prior to and 3-months after therapy. The patients were then evaluated every month during therapy to observe the toxicity, until 3-months after the therapy was completed. The follow-up data included recurrence, data from the last visit, patient's latest condition, which were all documented from the medical records. Patient's latest condition was inquired through telephone to determine whether the patients last condition.

The statistical analysis included descriptive analysis, bivariate analysis, and survival rate analysis with Kaplan-Meier method. All the data analysis was performed using STATA ver 10 (Stata Corporation LP., Texas, USA).

Independent variable in this study is the type of cervical cancer therapy, whereas the dependent variables are the treatment response (complete response, partial response, stable tumor, and progressive tumor), survival rate (overall survival and disease free-survival), and toxicity (gastrointestinal, genitourinary, and hematological toxicities). However, the confounding variables included age, education, parity, cervical cancer staging based on FIGO (IIB, IIIA, IIIB), tumor size, performance status, histopathologic findings, tumor differentiation, cervical cancer therapy, and radiation overall treatment time (OTT).

RESULTS

There were 61 cases that fulfilled the selection criteria, with 32 cases receiving cisplatin-ifosfamide chemoradiation and 29 cases receiving weekly-cisplatin chemoradiation.

Assesment of treatment response between the two groups was performed at 3 months after completion of radiation therapy, and done through gynecological and ultrasound examination.

From the figure above, we obtained a hazard ratio (HR) of 1.4, but it was not found to be statistically significant (p=0.71). From the DFS rate there is intersection of the curve that did not fulfill the HR assumption. It showed no statistical significance (p=0.78).

Evaluation of toxicity between radiation group and chemoradiation group was performed based on RTOG and ECOG criteria. There were gastrointestinal toxocity, genitourinary toxicity, and hematologic toxicity, which were the most common toxicities encountered and mentioned in published references.

Table 1. Distribution of the Clinicopathologic Characteristics Based on Type of Chemoradiation

Clinicopathologic characteristics		Cisplatin-Ifosfamide (n=32)		Weekly Cisplatin (n=29)		Total		p-value
		n	%	n	%	n	%	
Performance status	0	19	59.4	21	72.4	40	65.6	0.487
	1	13	40.6	4	13.8	17	27.9	
	2	0	0,0	4	13.8	4	6.5	
Stage	IIB	9	28.1	8	27.6	17	27.9	0.863
	IIIA	1	3.1	1	3.4	2	3.3	
	IIIB	22	68.8	20	69.0	42	68.8	
Tumor size	<4 cm	10	31.25	12	41.4	22	36.1	0.370
	>4 cm	22	68.75	17	58.6	39	63.9	
Histopathology type	Squamous cell carcinoma	23	71.9	18	62.1	41	67.2	0.700
	Adenocarcinoma	7	21.9	9	31.0	16	26.2	
	Adenosquamous Carcinoma	2	6.2	2	6.9	4	6.6	
Degree of Differentiation	Well	7	21.9	8	27.6	15	24.6	0.831
	Moderate	18	56.2	16	55.2	34	55.7	
	Poor	7	21.9	5	17.2	12	19.7	
OTT*	<62 days	13	40.6	17	58.6	30	49.2	0.160
	>62 days	19	59.4	12	41.4	31	50.8	
Total		**32**	**100**	**29**	**100**	**61**	**100**	

[a] *Pearson chi-square test*
**OTT/Overall Treatment Time: Total period of radiation therapy from the first external radiation to the last internal radiation.*

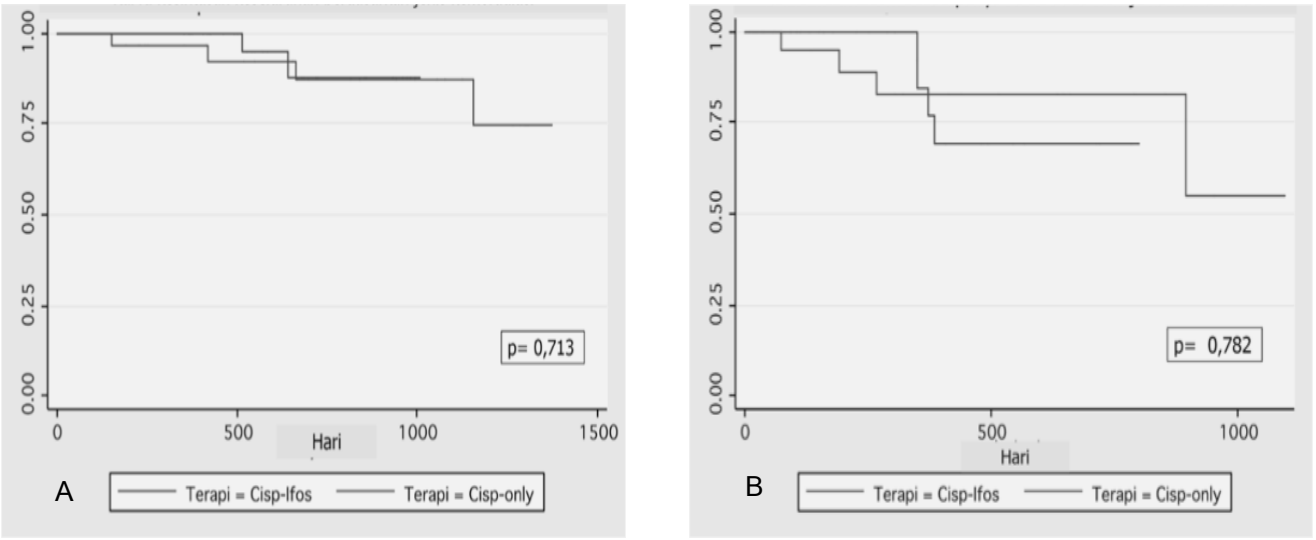

Figure 1. Overall Survival (A) and Disease-Free Survival (B) Rate based on Type of Chemoradiation.

Table 2. Comparison of Treatment Response According to Type of Chemotherapy

Treatment Response	Cisplatin-Ifosfamide n (%)	Weekly Cisplatin n(%)	Total n(%)
Complete response	30 (93.8)	26 (89.7)	56 (91.8)
Partial response	2 (6.2)	1 (3.4)	3 (4.9)
Stable tumor	0 (0)	0 (0)	0 (0)
Progressive tumor	0 (0)	2 (6.9)	2 (3.3)
Total	32 (100)	29 (100)	61 (100)

Pearson chi-square test; p = 0.290

Table 3. Distribution of Toxicity Based on Type of Chemoradiation

Toxicity		Therapy				Total n (%)	p-value
		Cisplatin-Ifosfamide		Weekly Cisplatin			
		n	%	n	%		
Gastrointestinal							
	Degree 0	-	-	-	-	-	
	Degree 1	10	31.3	11	37.9	21 (35)	
	Degree 2	22	68.7	18	62.1	40 (65)	0.014
	Degree 3	-	-	-	-		
	Total	32	100	29	100	61 (100)	
Genitourinary							
	Degree 0	-	-	-	-		
	Degree 1	29	90.6	26	89.7	55 (90.2)	
	Degree 2	3	9.4	3	10.3	6 (9.8)	0.337
	Degree 3	-	-	-	-		
	Total	32	100	29	100	61 (100)	
Hematologic							
	Degree 0	-	-	-	-	-	
	Degree 1	12	37.5	13	44.8	25 (41)	
	Degree 2	14	43.8	14	48.3	28 (45.9)	0.331
	Degree 3	6	18.7	2	6.9	8 (13.1)	
	Total	32	100	29	100	61 (100)	

DISCUSSION

This study is a historical cohort study on locally advanced cervical cancer (Stage IIB, IIIA, and IIIB) in the Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, RSCM. In the period of December 2013 to October 2014, we obtained 61 samples that meet the inclusion criteria and completed follow-up for up to three months after completing treatment, which consisted of 32 cases who received chemoradiation therapy with three-weekly cisplatin-ifosfamide, and 29 cases who received chemoradiation therapy with weekly cisplatin. These patients received chemoradiation treatment between August 26, 2010 to June 28, 2014.

This study has limitations because the sample size is relatively small, and employed historical cohort as research design so that there was no randomization in sample collection. The advantages of this research is that the treatment response was assessed for three months after finishing radiation treatment and monitoring was continued afterward with minimal period of monitoring of up to three years.

Of the 61 subjects in the study, we obtained an age range of 35-66 years old, with a mean of 49 years old. Similar results were obtained in phase II multicenter clinical study conducted by Kato et al in 2009 in China, Philippines, and Vietnam; where the mean age was 48.5 years old.[18]

Cornain et al reported that the incidence of cervical cancer at age over 50 years old is two times higher (13.9/100,000) than at under 50 years (6.7/100,000), and the highest distribution is in the 45-49 years old group.[21] Research conducted by Aziz MF in RSCM in 2001 stated a risk of developing cervical cancer over the age of 50 years to be higher than that of those under the age of 50 years with an OR of 2.53 (95% CI 1.27 to 5.05).[22] Nuranna et al in 2011 have reported the distribution of characteristics of cervical cancer in the Division of Gynecologic Oncology RSCM, with the highest frequency being in the 35-64 year age group which constituttes 87.3% of cases.[2] Gunawan et al in 2012, found that more than 50% of patients with cervical cancer aged 46-68 years.[23] Moreover, Nuranna et al in 2014 in Dr. Cipto Mangunkusumo found 66.2% of cervical cancer patients were aged 30-49 years and 33.1% were aged >50 years.[6]

Range of parity of the sample in this study is 0 to 8, with a mean of 3.29 ± 1.7 children. The highest frequency is in the parity >2 group (60.1%), while in the parity 1-2 was 36.1%. MF Aziz in his research reported cervical cancer cases with parity ≥6 was up to 78 cases (75%), compared to the parity 0-1, which was 49 cases (25%).[22] In this study, the largest proportion of cervical cancer cases belonged to the 40-60 years old age group, with equal education level of elementary, junior high, or high school, which was 34.4%, 31.2%, and 34.4%.

The highest number of cervical cancer cases is in stage IIIB with 42 cases (68.9%), while stage IIB had 17 cases (27.9%) and there were only 2 cases of stage IIIA cancer (3.28%). Similar findings were observed on multicenter clinical investigations conducted by Kato et al.[18] Negi R et al supported this study with similar proportion of cases; 34 cases of stage IIB (38%), 54 cases of stage IIIB (60.7%), and only 1 case of stage IIIA (1.1%).[24] Gunawan et al in Dr. Cipto Mangunkusumo in 2012 obtained 16 cases of stage IIIB and 15 cases of stage IIB.[23]

Tumor size <4 cm was found in 22 cases (36.1%), 10 cases in the group of cisplatin-ifosfamide and 12 patients in weekly cisplatin, whereas tumor size >4 cm was found in 22 cases (68.8%) in the cisplatin-ifosfamide group, and 17 cases (58.6%) in the weekly cisplatin group. Rose PG et al also found a similar distribution of tumor diameter, tumors ≤40 mm with 76 cases (14.7%) and >40 mm with 440 cases (85.3%) in locally advanced cervical cancer.[10] Kong et al found 215 cases with tumor size >4 cm and 40 cases with size <4 cm.[25] Gunawan et al also observed that the more common tumor diameter is >4 cm for 28 cases, compared to the size of <4 cm with only 4 cases.[23] Another study conducted by Nuranna et al in 2014 found that 74.4% of cases had tumor size >4 cm, and only 25.3% had tumor size <4 cm. These study findings support a similar characteristic in terms of tumor size.[6]

Median ECOG performance status of the patient is 0 and 1. There were only four subjects with ECOG 2 (13.8%) in the group of weekly cisplatin. Similar distribution was found in the study conducted by Kato et al in the Philippines and Vietnam, where they found a score of 0 in 12 cases and 10 cases.[18] Restriction of ECOG score <2 was done in order to avoid bias in the results of treatment response due to patient's physical condition.

The most commonly encountered histopathologic type is squamous cell carcinoma with 41 cases (67.2%), followed by adenocarcinoma consisting of 16 cases (26.2%), and 4 cases (6.6%) of adenosquamous type. This finding is consistent with another study by Nuranna et al in 2011 in RSCM found that the most common histopathologic type of cervical cancer is squamous cell carcinoma with 1322 cases (70.2%) and 285 adenocarcinoma cases (15%).[2] Sakata et al in Japan (2008) also reported 231 cases of squamous cell carcinoma (94.2%) and 11 cases of adenocarcinoma (4.9%), while for adenosquamous was not encountered among the 226 cases.[26] Rose et al encountered the same results, with 472 cases of squamous cell carcinoma (89.7%), while there were only 18 cases of adenocarcinoma (3.4%).[10] Kanti et al obtained the distribution of squamous cell carcinoma to be 56 cases (86.5%), 4 cases of adenosquamous (5.9%), and 5 cases of adenocarcinoma (7.6%) of a total of 67 cases.[17] Kong et al showed similar results, namely squamous cell carcinoma for 238 cases, followed by adenocarcinoma and adenosquamous carcinoma at 9 cases.[25] Another study in 2014 by Nuranna et al, found 71.6% squamous cell carcinoma, followed by 11.9% adenocarcinoma and

13.6% adenosquamous, which was concordant with the other studies.[6]

The degree of differentiation holds a role in predicting the prognosis of cervical cancer. In general, a poorer differentiation may indicate a worse prognosis.[27] In this study, 34 cases (55.74%) were moderately differentiated, 15 cases (24.59%) were well differentiated, and 12 cases (19.67%) were poorly differentiated. Similar to our results, the study by Gunawan et al found that 23 cases (71.88%) were moderately differentiated, then 7 cases (21.87%) with well differentiation, and 2 cases (6.25%) with poor differentiation.[23] Nuranna et al in 2014 showed moderate differentiation made up 55.2%, 20.6% were well-differentiated, and 16.6% with poor-differentiation.[6]

Evaluation of the confounding demographic and clinicopathologic variables such as age, performance status, stage, tumor size, histopathologic type, degree of differentiation, and OTT radiation in both treatment groups showed no statistical significance. This result showed that there was an equal distribution of confounding variables in both groups of chemoradiation types. Thus, the effect of confounding variable can be eliminated.

In our study, treatment response was assessed three months after treatment in either groups with adjuvant concurrent chemoradiation of 40 mg/m^2/week cisplatin or chemoradiation with cisplatin-ifosfamide three-weekly. According to the operational definition, treatment response can be divided into complete response, partial response, stable tumors, and progressive tumors. In the group of cisplatin-ifosfamide, as many as 30 patients had a complete response (93.8%), and 2 patients had partial response (6.2%). This result is worse compared to the study by Vrdoljak et al, who achieved 100% complete response. Meanwhile in the group receiving cisplatin alone, as many as 26 patients achieved complete response (89.7%), 1 patient had partial response (3.4%), and 2 patients had progressive tumor (6.9%). There was a total of 5 patients (8.2%) who did not achieve complete response consisting of 3 cases (4.9%) who had partial response and 2 cases (3.3%) who had progressive tumor.

Two cases of partial response belonged to the cisplatin-ifosfamide group, and 1 case in the weekly cisplatin group. All cases with progressive tumors were from the weekly cisplatin group. Although no significant difference were found in the results of this response assessment, result of progressive tumor needs special attention because it represents an unresponsive condition.

Radiation protocols used in this study was 50 Gray external radiation and 2 x 8.50 Gray (850 rad) or 3 x 7 Gray for internal radiation. The duration of radiation was similar between both study groups. Similarly, Negi et al used a total dose of 81 Gray to point A with OTT anticipated to be 7 to 10 weeks.[24] Vrdoljak et al employed external radiation dose of 45 Gray plus 2x30 Gray internal radiation.[20] Kong et al employed 45 Gray external radiation in 25 fractions over 4-5 weeks with internal radiation of 30 Gray in 5 fractions at 1-week intervals.[25] This varying results may due to retrospective study. If any future prospective study is to be conducted, the type of radiation and radiation scheme employed should be determined in detail so that the radiation dose will be consistent.[20]

In this study, the median OTT was 63 days. In the group of cisplatin-ifosfamide, average OTT is 69 days, while the average for weekly cisplatin is 59 days. OTT for radiation is divided into two categories, OTT <62 days and >62 days. There were no significant differences in the distribution of radiation OTT in both study groups. Although radiation OTT variable in this study is a confounding variable, assessment of treatment response in both groups showed no significant difference (p=0.61). We should also consider that in the group with OTT <62 days, there were two cases that underwent progressive tumors, while in the group of more than 62 days there were three cases with partial response.

In a study conducted by GOG 85, GOG 120 and RTOG 90-01 the median OTT were 64, 63 and 58 days, respectively.[10,11,28] Unlike the GOG 85 and RTOG 90-01 study, in this trial the median OTT was similar with GOG 120, which was 63 days. Rose et al obtained results of median OTT being 63 days in the chemoradiation with cisplatin group, 65 days in the chemoradiation using cisplatin + fluorouracil + hydroxyurea group, and 62 days in the chemoradiation with hydroxyurea group.[10]

From the data obtained, survival analysis was performed to evaluate the OS and DFS. DFS was assessed from 8 cases that experience recurrence among the 56 cases. Recurrence was diagnosed on physical examination, histopathologic, and imaging data found in the medical record. There were 8 cases of recurrence, in both treatment groups.

There was no local recurrence in both groups. There were 4 cases of regional recurrence in both treatment groups, also 4 groups of recurrence with distant metastases to lungs and liver as target organs.

Two-years survival rate of cisplatin-ifosfamide was 89.4%, while for cisplatin alone was 86.5%. Vrdoljak et al reported DFS and OS of 88.7% at a median follow-up of 4 years.[20]

The survival curve showed that there was a hazard ratio of 1.4 in the sense that at any time there was a probability of death of 1.4 times in the cisplatin-ifosfamide compared to the cisplatin alone group. However, this difference was not proven to be statistically significant (p=0.71).

In terms of disease-free survival rate, in the cisplatin-ifosfamide group was 87.1% in the first year, while it was 82.7% in the cisplatin group. However, in the second year, cisplatin-ifosfamide DFS dropped to 68.8%, while cisplatin alone was maintained at 82.7%. (p=0.78). The presence of disease-free survival rate curve intersection occurred because of the design of retrospective study, causing no further monitoring protocol, instead relying solely on data contained in the medical record. Apart from the problem of data validity, this picture can be seen from the medical records of the two-year recurrence and after treatment monitoring.

Kong et al also found no significant difference in progression-free survival (PFS) rate and on the overall survival rate in the chemoradiation group compared with weekly chemoradiation to be 74.6% vs 64.3% and 78% vs. 73% (p=0.7105 and p=0.237).[25] While Roy found the 16-month DFS rate of 83% in the cisplatin chemoradiation with gemcitabine compared to 73% in weekly cisplatin.[29] Based on this DFS rate, other types of regimen were found to not be better than cisplatin-ifosfamide.

In this study, the incidence of degrees 0 acute toxicity was not found in terms of gastrointestinal, genitourinary, and hematology toxicities. Proven gastrointestinal toxicity was significantly different (p=0.014). Distribution shows that the most common degree of gastrointestinal toxicity was grade 2, complaining of nausea and vomiting which required antiemetic or abdominal pain which required analgesics, diarrhea that required treatment, rectal and abdominal pain requiring analgesics. There were 22 cases (68.7%) in the cisplatin-ifosfamide therapy group and 18 cases (62.1%) in the cisplatin group who experienced toxicity degree 2. A total of 21 cases (35%) were spread evenly in both treatment groups who experienced toxicity grade 1 in the form of nausea and abdominal discomfort which did not require any treatment, or increased frequency of bowel, or anal sore that did not require medication.

Kong et al also found that gastrointestinal toxicity is more common in monthly compared to weekly chemoradiation, 6 cases compared to 22 cases.[25] This toxicity included diarrhea (4 cases on monthly chemoradiation and 2 cases on weekly chemoradiation), nausea (17 cases in the monthly chemoradiation and 2 cases in weekly chemoradiation), and vomiting (11 cases on monthly chemoradiation and 7 cases on weekly chemoradiation).

In genitourinary toxicity, the highest degree of toxicity was grade 2 in the form of urinary frequency/nocturia less than every 1 hour, dysuria, urgency and bladder spasms that require treatment. There were three cases in each treatment group with grade 2 toxicity (9.4% and 10.3%). While 52 cases (90.2%) experienced grade 1 toxicity in the form of urination two times more often than usual, dysuria, or who did not require emergency treatment (90.6% in cisplatin-ifosfamide and 90.2% in cisplatin alone). There was no significant difference in terms of genitourinary toxicity (p=0.337).

Hematologic toxicity grade 3 in the form of anemia with hemoglobin level reaching 6.5-8 g/dl, or leukopenia (2000-3500 leukocytes/μl), or thrombocytopenia (platelet 50,000-100,000/μl) occurred in 18.7% of cases in the cisplatin-ifosfamide group and 6.9% of cases in the cisplatin alone group. While toxicity level 1 and 2 were distributed evenly in the two treatment groups. There were no significant differences between the two treatment groups in terms of hematologic toxicity (p=0.331).

Kong et al showed that the toxicity of monthly chemoradiation was greater than weekly chemoradiation, with 22 cases compared to 12 cases. A total of 7 cases on a monthly chemoradiation were anemic, more than that found in weekly chemoradiation, which were only 3 cases.[25] Likewise, leukopenia on monthly chemoradiation amounted to 11 cases, while weekly chemoradiation only had 7 cases. Thrombocytopenia in monthly chemoradiation consists of 4 cases, more than weekly chemoradiation with only 2 cases.

Major acute toxicity can be seen in hematologic and gastrointestinal toxicity. There were no treatment-related deaths. None of the patients stopped the chemotherapy by request or due to its toxicity. Overall, these three toxicity effects were treatable with appropriate therapy according to patient's complaints, thus preventing incomplete therapy.

CONCLUSION

Chemoradiation with three-weekly cisplatin-ifosfamide and weekly cisplatin have the same efficacy in patients with locally advanced cervical cancer, but weekly cisplatin chemoradiation is more tolerable. Our historical cohort design may bring about selection bias, that may affect the results of the study even though it had been minimized by performing confounding variables equality test. In addition, this study used a long period of monitoring time and closed data that may affect the validity of the results.

Nevertheless, the treatment of locally advanced stage cervical cancer in consideration of control of local recurrence, regional and distant recurrence remains an issue, thus allowing another potential therapy combination. It is suggested to conduct a multicenter randomized trial of prospective cohort to investigate new chemotherapy regimens assessing effects of particular radiosensitizer and the effects of chemotherapy in cervical cancer in order to improve the survival and quality of life of patients with locally advanced cervical cancer.

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