COMPARISON OF RESPONSE OF CHEMOTHERAPY BY CISPLATIN AND 5-FU VERSUS CISPLATIN AND PACLITAXEL IN RECURRENT CARCINOMA OF UTERINE CERVIX

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Abstract:

This quasi-experimental study was done from January, 2008 to December, 2008 at Onclogy Department of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Radiotherapy Department of Dhaka Medical College Hospital (DMCH), Dhaka and National Institute of Cancer Research and Hospital (NIRCH), Dhaka. Total 60 patients were enrolled. Among them 30 patients received Cisplatin & 5-FU as group A and next 30 patients received Cisplatin & Paclitaxel as group B. The objective of the study was to compare the response of chemotherapy regiment of Cisplatin-5FU (group-A) with Cisplatin-Paclitaxel (group-B) in recurrent cervical cancer. After completion of the treatment, response was assessed in terms of toxicities, improvement of symptoms and clinical tumour regression. Tumour response in terms of symptoms improvement, P/V bleeding, P/V discharge, foul smelling discharge and complain of pain, was found to be high in Group B than Group A and was statistically significant ($p < 0.05$) at the end of 5th and 6th cycle chemotherapy. About chemotherapy toxicities, the symptoms of nausea and vomiting was high among the Group-B patients, than Group-A patients & the difference was statistically significant ($p< 0.05$). The proportion of diarrhea episodes was higher in Group-A patient than Group-B and the difference was statistically significant ($p<0.05$).Alopecia and fever was high among Group B patient than Group A patient and the difference was statistically very highly significant ($p<0.001$) Tumour response seen by P/V and P/S examinations, it was found that after 3rd follow-up, a statistical significant difference was found ($p<0.05$) between Group-A & Group-B with proportion of complete regression of tumour was found to be higher among the Group-B patients than Group-A. By Pap's test at 1st follow-up, complete regression of tumour was found higher in group B than group A patients and the mean difference was statistically significant ($p < 0.05$). In 2nd and 3rd follow-up, patients got complete response in Group B was higher than Group A and but the difference was not statistically significant ($p > 0.05$). There is a significant success in terms of symptom improvement, tumour regression in palliative treatment for recurrent cervical cancer with Cisplatin-Paclitaxel (group-B) regiment over Cisplatin-5FU (group-A) regimen.

(Bang. Onc. J. 2009; 4 (2) : 63-71)

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Introduction:

Carcinoma of uterine cervix is the most common form of cancer that affects women virtually in all developing countries, and is the second most common form of cancer world-wide, with more than 471,000 cases per year[1]. According to World Health Organization (WHO) 2003 cervical cancer is the second most common cancer of women world wide with more than 470,000 new cases per year of about 230,000 deaths every year, more than 80% occurring in developing countries[2]. The uterine cervix is the most common site of cancer in Indian women and accounts for 20% of all malignant tumors in the female[3]. An annual report of 2005 of National Institute of Cancer Research and Hospital, a hospital based cancer registry shows carcinoma of cervix is at the top of the list of common female cancer in Bangladesh [4]. The high prevalence of cervical cancer in developing countries is probably related to early marriage and early starting of sexual activity, multiparity, low socio-economic condition and poor hygiene. Cervical cancer is a preventable disease as cervix is an easily approachable organ and its aetiological factors can be regulated. Most of the cervical carcinoma can be prevented by proper screening [5]. Despite improvement in overall survival, recurrent cervical cancer remains essentially incurable. Chemotherapy was traditionally used for the palliative management of advanced or recurrent diseased

after surgery or radiotherapy. Combination of Cisplatin and 5-FU become a gold-standard regimen due to its cheap price and acceptability in clinical response. Combination of Cisplatin and Paclitaxel also shows encouraging clinical response. Combination chemotherapy with Cisplatin with 5-FU and Cisplatin and Paclitaxel has attracted significant interest and deserve further discussion. Identification of new agents with activity in cervical cancer is, therefore, a high priority.

Methodology:
Diagnosed patients of recurrent cervical cancer and study place were selected first purposively, and then simple random sampling technique was adopted in every step of sampling.

Inusion criteria:
A histologicaly confirmed recurrent cervical cancer cases who previously received definitive treatment for the primary disease.

a. Patient without distant metastasis and without obstructive feature.
b. Performance status scale up to 60 (karnofsky performance scale)
c. Minimum laboratory criteria:
   i) Haemoglobin more than 10 gm/dl or >60%
   ii) Granulocyte count more than or equal to 4000 /cu mm of blood.
   iii) Platelet count of more than or equal to 100000 /mm. of blood
   iv) Serum bilirubin level <1.5 mg/dl
   v) SGPT/AST level no more than four times of upper limit of normal
   vi) Serum creatinine level <1.5 mg/dl.
   vii) Blood urea <50 mg/dl

Pretreatment evaluation:
Following procedures were followed to evaluate the patient's condition before treatment

- Complete clinical history, performance status, General and Systemic examinations.
- Per-vaginal examinations
- Per speculum examinations
- Per rectal examinations
- Bimanual examination (recto-vaginal, abdomino-vaginal) paying particular attention to detect the extension of lesion
- Complete blood picture including T.C, D.C., Hb%, ESR & total platelet count
- Liver function test
- Renal function test
- Chest X-Ray (P/A & lateral view)
- Ultra-sonography of whole abdomen
- Others on need basis

Chemotherapy regimen:

Cisplatin-5FU regimen (Group A):

Cisplatin: 75 mg/m^2 I.V. on day 1 (or 20mg/ m^2 divided dose day 1 to 3) [21].

5-FU: 1000 mg/m^2 I.V. continuous infusion on day 2-5 (or 500mg/m^2 divided dose day 2 to 4) [21].

Cisplatin-Paclitaxel regimen (Group B):
Cisplatin: 75 mg/m^2 I.V. on day 1(or 20mg/ m^2 divided dose day 2 to 4) [21].

Paclitaxel: 135 mg/m2 I.V over 24 hours on day 1 (or 3 hour infusion on day 1).

Response criteria and assessment of treatment response:
Treatment response was assessed in the light of WHO guideline of response criteria.

Patients were declared to have complete response (CR) when all miserable disease disappears (by P/V, P/S, P/R, Pap's smear, USG), partial response (PR) were declared for presence of residual disease, progressive disease (PD) means appearance of new lesions and stable disease (SD) means no change of disease.

Toxicity of treatment evaluated according to common toxicity criteria (Fisher et. al., 1994 and CTC Version 2.0 DCTD, NIC, NIH, DHHS March, 1998 (enclosed here with in appendix).

Patient assessment and evaluation after treatment:

During treatment and after completion of treatment patients were carefully supervised and were assessed fortnightly during treatment for chemotherapy toxicity (10-14 days after each cycle of chemotherapy) and at 2, 6 and 10 weeks after completion of 6th cycle chemotherapy to see the treatment response (symptoms improvement and tumour response) (All the patients were kept to monitor for longtime follow-up)

Limitation of the study:

The time period was not enough to conduct a quality study and all relevant investigation could not be done due to financial constraints.

Result:

Age distribution of patients:

The mean age (±SD) of the patients was 49.93 (±4.6) years ranging from 42 to 60 years. The mean age of the group A was 50.43 (±4.8) years and group B was 49.43 (±4.4) years..

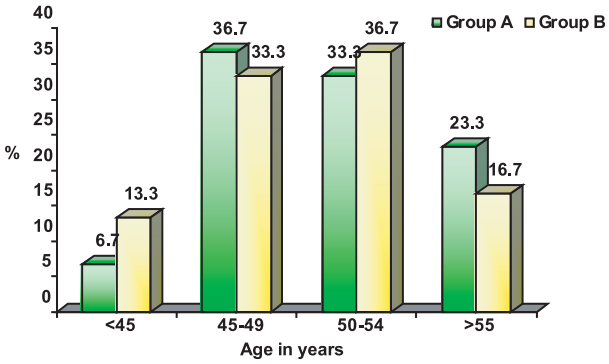

Fig.-1: *Age distribution of the patients*

Table I

Demographic characteristics of the patients

Characteristics	Subject				Total (n=60)		p value
	Group A (n=30)		Group B (n=30)				
	No.	%	No.	%	No.	%	
Religion							
Islam	17	56.7	19	63.3	36	60.0	0.598
Hinduism	10	33.3	2	6.7	12	20.0	
Christian	2	6.7	6	20.0	8	13.3	
Buddhism	1	3.3	3	10.0	4	6.7	
Marital status							
Married (living with husband)	22	73.3	14	46.7	36	60.0	0.035
Widow	7	23.3	12	40.0	19	31.7	
Separated	1	3.3	4	13.3	5	8.3	
Level of education							
Illiterate	3	10.0	4	13.3	7	11.7	1.000
Below primary	7	23.3	14	46.7	21	35.0	
Above primary upto SSC	15	50.0	6	20.0	21	35.0	
HSC	4	13.3	4	13.3	8	13.3	
Graduate	1	3.3	2	6.7	3	5.0	
Occupation							
Housewife	20	66.7	16	53.3	36	60.0	0.291
Labourer	1	3.3	0	.0	1	1.7	
Service holder	5	16.7	10	33.3	15	25.0	
Business	4	13.3	4	13.3	8	13.3	
Socio-economic status by monthly family income							
Poor	8	26.7	3	10	11	18.3	0.247
Average	19	63.3	23	40.0	42	70.0	
Good	3	10.0	4	13.3	7	11.7	

p value reached from chi square test

Table-II

Distribution of the patients by age at marriage

Variables	Subject				Total (n=60)		P value
	Group A (n=30)		Group B (n=30)				
	No.	%	No.	%	No.	%	
*Age at marriage (years)							
<18	15	50.0	13	43.3	28	46.7	
≥ 18	15	50.0	17	56.7	32	53.3	
Mean ± SD (yrs)	17.03±1.7 (13-20)		17.07±2.6 (12-20)		17.05±2.2 (12-20)		0.953

*p value reached from unpaired student's t test

Data analysis revealed that no statistically significant difference was found between group A and group B patients in terms of religion, level of education, socio-economic status by monthly family income and occupation (p>0.05) and all the patients were married (100%).

The mean age at marriage for group A patients was 17.03±1.7 and that of group B was 17.07±2.6 years. Data shows that 46.7% of the patients married at the age of less than 18 years and the rest were at the age of 18 years and above.

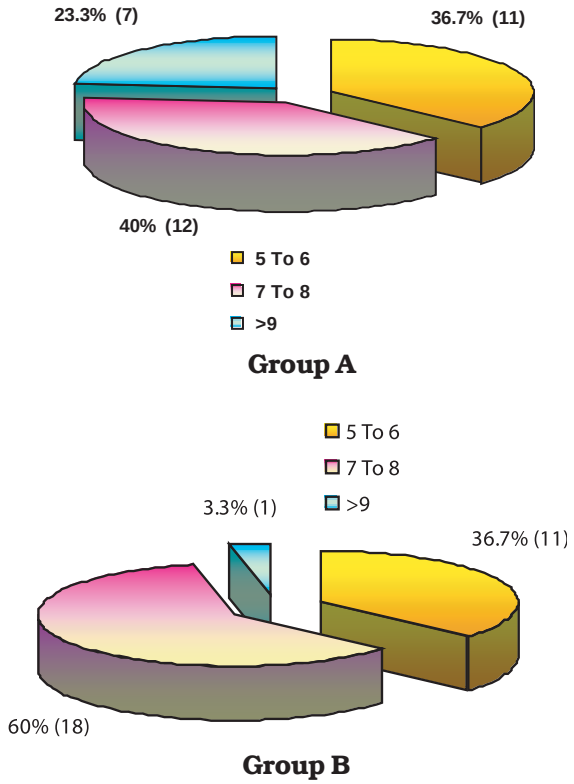

Fig.-2: *Distributions of patients by number of conception.*

Distribution of patients by number of conceptions: Data analysis reveals that, the mean number of conception was 7.20±1.5 group A patients and the for the group B patients was 6.87±1.1. Distribution of patients by number of conceptions is shown below.

Distribution of patients by histological diagnosis: Among group A patients 93.3% (28) were diagnosed as squomous cell carcinoma and 6.7% (2) were diagnosed as adenocarcinoma. Among group B atients 90% (27) were diagnosed as squomous cell carcinoma and 10% (3) were diagnosed as adenocarcinoma. Distribution of patients by histologic type are shown below.

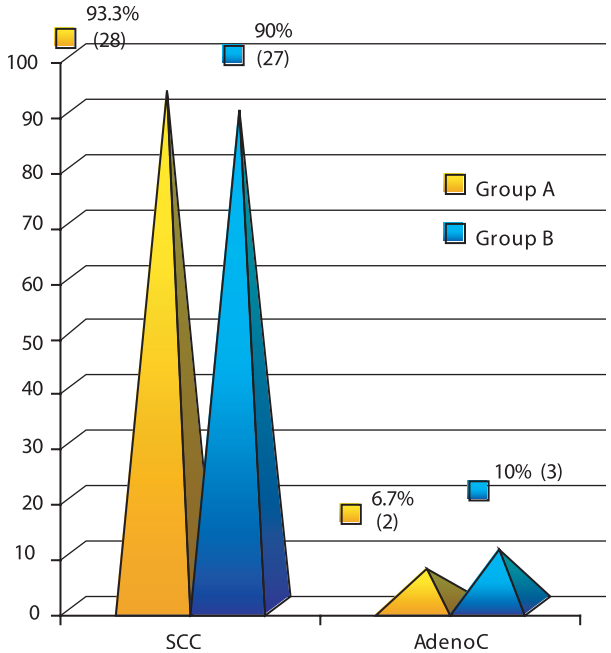

Fig.-3: *Distribution of the patients by histological diagnosis.*

Table III

Distribution of the patients by clinical presentation.

Presentation	Subject				Total (n=60)		p value
	Group A (n=30)		Group B (n=30)				
	No.	%	No.	%	No.	%	
P/V bleeding	28	93.3	29	96.7	57	95.0	0.554
P/V Discharge	29	96.7	20	66.7	49	81.7	0.006
Backache	19	63.3	20	66.7	39	65.0	0.787
Dysurea	20	66.7	19	63.3	39	65.0	0.787
Foul smelling discharge	20	66.7	19	63.3	39	65.0	0.787
Leg edema	17	56.7	20	66.7	37	61.7	0.426
Lower abdominal pain	16	53.3	16	53.3	32	53.3	1.00
Post coital bleeding	13	43.3	10	33.3	23	38.3	0.426
Pain in defecation	3	10.0	14	46.7	17	28.3	0.002
Pain in coitus	10	33.3	5	16.7	15	25.0	0.136

Response was multiple

Overall clinical presentation indicated that highest percentage of patients had complaints of P/V bleeding (95%), backache (65%), dysurea (65%), foul smelling discharge 65%), leg edema (61.7%), lower abdominal pain (53.3%), post coital bleeding (38.3%), pain in coitus (25%) etc.

Table IV

Distribution of the patients by clinical examination findings (before chemotherapy).

Examination findings	Subject				Total (n=60)		P value
	Group A (n=30)		Group B (n=30)				
	No.	%	No.	%	No.	%	
*Per vaginal examination							
P/V bleeding	27	90.0	30	100.0	57	95.0	
Growth present	29	96.7	15	50.0	44	73.3	0.313
P/V discharge	25	83.3	18	60.0	43	71.7	
Per speculum examination							
Growth present	28	93.3	30	100.0	58	96.7	0.251
P/V discharge	24	80.0	13	43.3	37	61.7	
P/V bleeding	28	93.3	30	100.0	58	96.7	
Bi manual examination							
Growth present	15	50.0	5	16.7	20	33.3	0.001
Growth absent	15	50.0	25	83.3	40	66.7	
Per rectal examination							
Growth present	8	26.7	3	10.0	11	18.3	0.070
No growth no bleeding	20	66.7	27	90.0	47	78.3	
Bleeding present	2	6.7	0	.0	2	3.3	

*Multiple responses

On their per -speculum examination 97% of the patients examination revealed growth in the uterine cervix and also P/V bleeding was 95%.

About chemotherapy toxicities, the symptoms of nausea and vomiting was high among the Group-B patients, than Group-A patients & the difference was statistically significant ($p< 0.05$). The proportion of diarrhea episodes was higher in Group-A patients than Group-B patients and the difference was statistically significant ($p<0.05$). Fever and alopecia toxicity was high among Group B patient than Group A patient very highly significant ($p< 0.001$) (from detail toxicity data in thesis).

Table-V

Summary data about chemotherapy toxicity among total numbers of patients suffered during 6-cycle chemotherapy

Name of toxicity with grade of toxicity	Group A No.	Group A %	Group B No	Group B %.
Nausea				
Intake insignificantly decreased $=G_2$	45	26.6	40	23.7
No sufficient intake=G_3	6	3.6	0	0
Vomiting				
2-6 episodes in 24 hour $=G_2$	19	11.2	20	11.8
Diarrhoea				
2-3 stool per day over pretreatment $=G_1$	47	27.9	32	18.9
4-6 stool per day over pretreatment $=G_2$	14	8.3	2	1.2
Alopecia				
Mild hair loss $=G_1$	58	34.3	53	31.4
Pronounced hair loss $=G_2$	0	0	64	37.9
Fever				
38.1-40^0 C (100.5-104.0 ^{0} F) $=G_2$	1	0.6	42	24.9

Table VI

Distribution of the patients by PV bleeding, discharge and foul smelling discharge (symptom improvement after chemotherapy).

PV bleeding, discharge and foul smelling discharge	Group A No.	Group A %	Group B No.	Group B %	Group A Mean score	Group B Mean scor	P value
After 1st chemotherapy	n=30		n=30				
Completely relieved	2	6.7	0	.0	3.03	3.30	.108
Partially relieved	1	3.3	1	3.3			
Static	21	70.0	19	63.4			
Worsen	6	20.0	10	33.3			
After 2nd chemotherapy	n=30		n=30				
Completely relieved	2	6.7	0	.0	2.70	2.47	.108
Partially relieved	5	16.7	16	53.3			
Static	23	76.6	14	46.7			
After 3rd chemotherapy	n=28		n=29				
Completely relieved	3	10.7	1	3.4	2.03	2.03	1.000
Partially relieved	21	75.0	26	89.7			
Static	4	14.3	2	6.9			
After 4th chemotherapy	n=27		n=29				
Completely relieved	7	25.9	14	48.3	1.77	1.53	.060
Partially relieved	20	74.1	15	51.7			
After 5th chemotherapy	n=27		n=29				
Completely relieved	15	55.6	27	93.1	1.43	1.03	.000
Partially relieved	12	44.4	2	6.9			
After 6th chemotherapy	n=27		n=29				
Completely relieved	15	55.6	27	93.1	1.43	1.03	.000
Partially relieved	12	44.4	2	6.9			

p value reached from unpaired student's t test.

Data analysis shows that the no statistically significant difference was found between two groups of patients in terms of PV bleeding (p>0.05), but during subsequent chemotherapy, a statistically significant difference was found between two groups. Data also showed that proportion of completely bleeding relieved was found to be higher in group B patients compared to group A patients and was statistically very highly significant (p<0.001).

No statistically significant difference was found between two groups of patients in P/S examination in 1st and 2nd follow-up (p>0.05). However, a statistically significant difference was found between two groups during 3rd follow-up (p<0.05) with proportion of completely relieved (complete disappearance of tumour) was found to be higher among the group B patients (82.1%) than the group A patients (50).

Table-VII

Distribution the tumour response of the patients by P/S examination finding.

P/S examination	Group A		Group B		Group A	Group B	P
	No.	%	No.	%	Mean score	Mean score	value
P/S examination (1st F/U)	n=29		n=29				
Partially relieved	5	17.2	7	24.1	2.80	2.77	.759
Static	24	82.8	22	75.9			
P/S examination (2nd F/U)	n=28		n=28				
Completely relieved	1	3.6	5	17.9	2.03	1.93	.374
Partially relieved	25	89.3	21	75.0			
Static	2	7.1	2	7.1			
P/S examination (3rd F/U)	n=28		n=28				
Completely relieved	14	50.00	23	82.1	1.50	1.20	.014
Partially relieved	14	50.00	5	17.9			

p value reached from unpaired student's t test

Table VIII

Distribution of the tumour response of the patients by Pap test.

Pap test	Group A		Group B		Group A	Group B	P
	No.	%	No.	%	Mean score	Mean score	value
Pap's Test (1st F/U)	n=29		n=29				
Completely relieved	10	34.5	27	93.1	2.3±0.9	1.2±0.6	0.001
Static	19	65.5	2	6.9			
Pap's Test (2nd F/U)	n=28		n=28				
Completely relieved	24	85.7	26	92.9	1.3±0.7	1.1±0.5	0.398
Static	4	14.3	2	7.1			
Pap's Test (3rd F/U)	n=28		n=28				
Completely relieved	26	92.9	27	96.4	1.1±0.5	1.1±0.4	0.561
Static	2	7.1	1	3.6			

p value reached from unpaired student's t test

In 1st follow up Pap smear test indicated that tumour was completely relieved (Pap test -ve) in group B was higher (93.1%) than the group A patients (34.5%) and the mean difference was statistically significant ($p<0.05$). Similar pattern was also found in 2nd follow-up where 92.9% were completely relieved in group B patients and 85.7% in group A patients, but the difference was not statistically significant ($p>0.05$). This trend was also seen in 3rd follow-up But the difference was not statistically significant ($p>0.05$) between two groups of patients.

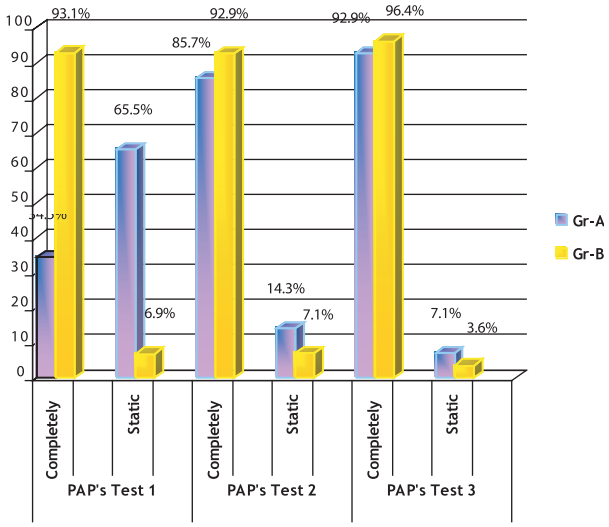

Fig.-4: *Percentage Distribution of the patients by Pap test.*

Discussion:

The present study findings were discussed and compared with previously published relevant studies. In this study the age of the patients were ranged between 42 to 60years. 35% of the patients in Group-A belong to 45-49 years of age & 33% in Group-B belonged to 50-54 years . Afroza Sultana et al study states that the mean age was 46 & highest incidence between 40-55 years [6]. Annual report 2005 based on hospital cancer registry in National Institute of Cancer Research and Hospital stated that in Bangladesh mean age of cancer cervix is 46.8 years . Range was 20 to 80 years [4]. Chowdhury Reziatul Ferdous [7] et al study it was found that 40% of the patient was in age group of 46-55 years. 38% of carcinoma cervix patients were in 40-49 years of age group . Nahar S. study shows mean age of patients of cervical cancer were 44.93 years and peak occurrence between 40 and 49 years [8].

Regarding the risk factors in this study it was found that there is a significant tendency towards early marriage, the mean age of marriage was 17 years. Data shows that 46.7% of the patients were married at age of less than 18 years and the rest were (53.3%) at the age of 18 years and above. The study reveals that the cent percent of the patients were multiparous. The mean number of conception was 7.About 76% of woman had give birth to 5-8 children in Group-A & 86% in Group-B. in either of the group, the tendency to have more children was nearly absolute. About marital status, 100% of the patients were married . In Afroza Sultana [6] et al study 70% were married & living with husband .In Reziatul Ferdous [7] et al it was found that age of marriage at all the patients below 20 years and a significant majorities were married below 15 years of age (73% to 80%) and majority of patients were multiparous and 47% of them have 5-8 children in arm A and 53% in arm B, the tendency to have more children is nearly absolute. According to Sample Vital Registration System (SVRS) of Bangladesh Bureau of Statistics (BBS) mean age at marriage 1981 to 2004 was 16 for female [9].

In this study it was observed that more than 80% of patients were from low income group. Regarding occupation about 60% were house-wife. Hossain Zebunnessa[10] et al and Afroza Sultana [6] et al, their findings were in line more or less similar. Chowdhury Reziatul Ferdous [7] et al found among cancer patient about 47% of the patient were from poor socio-economic background 53% were found lower middle class.

About chemotherapy toxicities of group A and group B, initially the symptoms of nausea & vomiting was found to be high among the Group-B patients, than Group-A patients & the mean difference was statistically significant ($p< 0.05$). The proportion of diarrhoea episodes was higher in Group-B patient. About fever, the group containing Paclitaxel (Group-B) complaints of fever was a little bit higher than Group-A patients. Complaints of fever gradually

increased in Group-B patients after 3rd chemotherapy to onward and the difference was statistically highly significant ($p < 0.001$). All the findings of toxicities have similarity with text [11, 12]. Tumour response in terms of relieve of symptoms and clinical tumor response was found to be high in Group B than Group A and was statistically significant ($p< 0.05$).The results of these combination regimen in cervical cancer reflects a common set of findings in combination chemotherapy of recurrent cervical cancer, namely an acceptable response rate, with Cisplatin Paclitaxel (group B) regimen than Cisplatin 5-FU (group A) regimen.

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