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"Safety And Efficacy Of Cisplatin Combined With Chemoradiotherapy In Locally Advanced Cervical Cancer Patients in Tertiary Care Hospital"

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ABSTRACT

Background: The number of cases of cervical cancer has increased in India during the previous year. Cervical cancer is a disease that causes morbidity and mortality worldwide. Cervical cancer patients progressed daily as a result of inadequate knowledge about the illness. Therefore, patient education is essential for both cervical cancer treatment and prevention. This research was done to find out if patients knew about the benefits and safety of combination chemotherapy and radiation therapy, or if they had any excuses for not getting their cervical cancer screened.

Objective:

I. To evaluate the safety and efficacy of cisplatin in conjunction with radiation and chemotherapy for females suffering from locally advanced cervical cancer.
II. To investigate the early outcome of cisplatin combined with chemotherapy and radiotherapy for cervical cancer patients.

Method: The study ran from October 2023 to April 2024 over the course of 7 month. There are a total number of 100 samples based on inclusion and exclusion criteria, patient data were collected. The quality of the data was evaluated by doing a database search for the safety and efficacy of cisplatin with chemotherapy in patients with locally advanced cervical cancer in Bihar using a questionnaire methodology.

Statistical analysis: All the data were recorded and analyzed. Statistics were carried out using SPSS software.

Results: This study involved 100 individuals in total. There are now 45 cases of people with cervical cancer. Twenty cases were eliminated from the study, leaving the remaining 25 cases eligible for inclusion based on the inclusion and exclusion criteria. The results of the trial showed that cisplatin and chemoradiotherapy are a safe and efficient combination for treating locally advanced cervical cancer.

Conclusion: Our study's results indicate that cisplatin in combination with radiation and chemotherapy is a tolerated and potentially better choice for treating patients with locally advanced cervical cancer. For the treatment of locally advanced cervical cancer, cisplatin and chemoradiotherapy may be given at the same time.

KEYWORDS: - Cervical cancer, Cisplatin & Squamous cell carcinoma, Chemoradiotherapy.

INTRODUCTION: - A set of disorders known as "cancer" involve aberrant cell proliferation and have the potential to spread to other body areas in the form of benign tumours. [1,2]. Both the incidence and mortality rates of cancer are rising. By 2023, In the world, cervical cancer ranks fourth in terms of frequency among women; in 2022, there will be about 660 000 new cases and 350 000 fatal cases. Low- and middle-income nations have the greatest incidence and fatality rates from cervical cancer. This reflects significant disparities caused by social and economic factors, as well as limited access to national HPV vaccination, cervical screening, and treatment facilities. Human papillomavirus (HPV) infection is the main cause of cervical cancer. Cervical cancer is six times more common in women living with HIV than in those without the virus.

Cervical cancer can be prevented effectively and affordably with the use of screening, therapy, and HPV vaccination as a preventative measure. Early detection of cervical cancer can result in a cure. [11]. Cervical cancer is a cancer that forms in the tissues of the cervix & grow slowly. Cancer that may not have symptoms but can be detected through screening tests. Cervical cancer is one of the leading malignant diseases that cause fourth most common cancer affecting women worldwide [7]. Also caused by HPV infection, with HPV detected in 99% of cervical tumor [5]. Worldwide, there is a serious public health issue with cervical cancer [6]. Patients with diseases classified by the International Federation of Gynecology and Obstetrics (FIGO) as stages IB2 to IVA are thought to have locally advanced malignancy. In India, 122,844 women who are at risk for getting cancer are diagnosed with cervical cancer, and 67,477 of them pass away from the illness. [13,14]. Most of the cases of cervical cancer lead to morbidity and mortality in all over the world.. Very few studies have explored to provide awareness to women about cervical cancer in India. Cervical cancer patients develop due to poor awareness about the disease. So Patient education is the required for care and prevention of cervical cancer. Chemotherapy, whether administered alone or in conjunction with surgery, radiotherapy, or other treatments, is crucial in the fight against cancer. The main mode of treatment is radiotherapy, however patients with stage IB2 or IIA illness may also have definitive surgery [8].This study was conducted to know the patients are aware of safety and efficacy of

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combined chemoradiotherapy or reasons for not undergoing screening of cervical in this Bihar region because Bihar is the least literate state in India.

The safety issues associated with chemoradiation for cervical cancer treatment are difficult to take task. This study was carried out to examine the early outcomes of cisplatin combined with chemotherapy and radiation for cervical cancer patients as well as to assess the safety and efficacy of cisplatin combined with chemotherapy and radiotherapy in women with locally advanced cervical cancer.

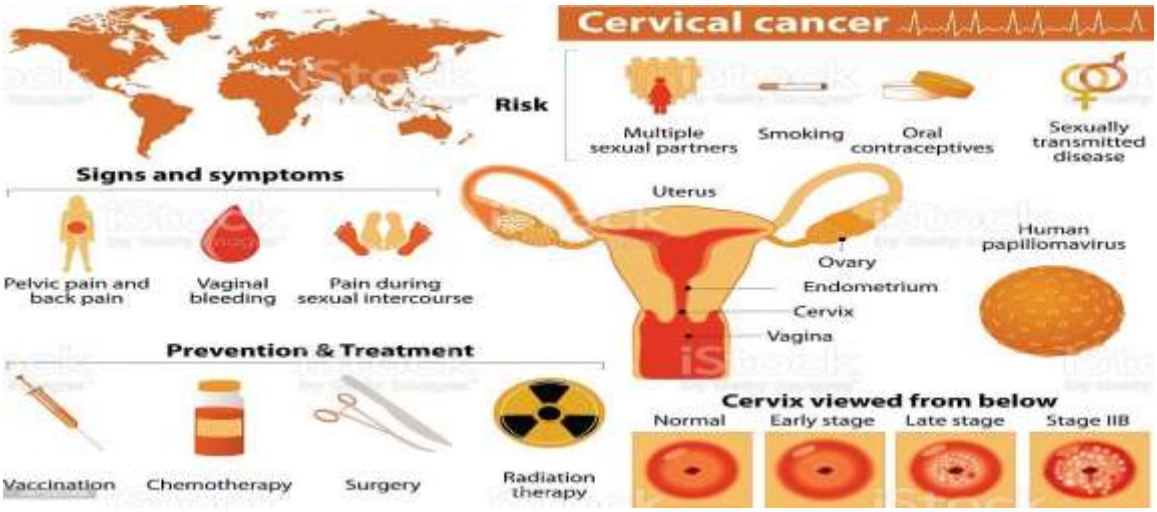

Fig. 1:Cervical cancer

MATERIALS AND METHODS:

1. **Study Design:-** This was an expected, observational study.The study was conducted in following seven months duration i.e. from October 2023 to April 2024. At the SAIMS, Indore, the study was carried out. There are 100 study subjects in total. Before the study, began, the ethics committee accepted the current study protocol. Before collection of patient's information, their voluntary informed consent form was obtained. The patients' whole personal information was kept private. Copyrights were taken from the specific researcher to make use of the above mentioned questionnaire in the study.

2. Patients:-

a) Inclusion Criteria:

1. Chemotherapeutic agent is extensively used to treat cancer of different stages.
2. Patients who wish to give informed consent form.
3. Patients aged 18 years females and above.

b) Exclusion Criteria:

1. Patients with other co-morbid conditions.
2. Patients who withdraw during the study.
3. Patients who lost the follow-up.
4. Patient diagnosed having carcinoma that required surgical intervention,
5. radiotherapy and other modality treatment
6. Patients whose age is less than 18 years.

3. **Study Method and data management:** Using Naranjo algorithm questionnaire, the questions were asked to cervical cancer patients. No study subject's names were recorded on the data collection form, to ensure patient's confidentiality and also respondents were assured that their responses will not be divulged to anyone under any circumstances. Total patients entered the OPD whose blood pressure, blood cell count levels are more than the normal during this study are 45. Among them, 20 subjects were excluded, of which 7 are excluded due to lots of follow up, 8 are excluded as they are unwilling to give informed consent form, 5 are excluded as they are having other disease conditions. Remaining 25 patients are included in the study. Finally, all these subjects were asked with the questions to check the Adverse Drug reaction of drug.

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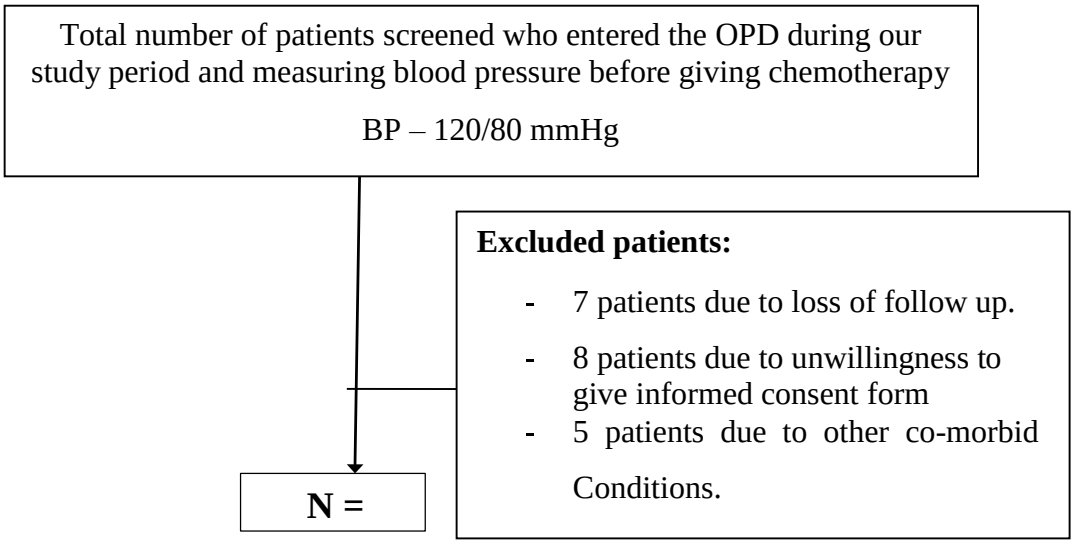

Fig.2: Data management and study procedure

4. **Study Tools:** The Naranjo algorithm scale was developed and it was prepared in two languages: Hindi and English. It consisted of 10 questions. These question for the adverse drug reaction in the drug in the basis of mild moderate and severity of disease.
5. **Questionnaire design:** A questionnaire created by Naranjo et al. is known as the Naranjo algorithm, Naranjo Scale, or Naranjo Nomogram. and it is approved for figuring out how likely it is that an adverse drug response (ADR) is brought on by a medicine rather than another source. A score system known as "definite, probable, possible, or uncertain" is used to assign probability. Scores were given based on the numbers of correct answers. Each question in the practice part attains ≥ 9 = definite ADR, 5-8 = probable ADR, 1-4 = possible ADR, 0 = doubtful ADR. By this way, scores were determined. In peer reviews, scoring values derived from this technique are frequently used to confirm the accuracy of authors' judgements about adverse drug reactions. The WHO-UMC system for systematic causality evaluation for suspected adverse medication reactions is frequently used as a comparison (ADRs). The strength of association between Naranjo algorithm questionnaire and demographic information of the patient was checked using chi- square test.

Questions	**Do not know**	**Yes**	**No**	**Score**
1. Was the reaction more severe with a higher dose or less severe with a lower dose?	0	+1	0	
2. Did the reaction reappear when a placebo was given?	0	-1	+1	
3. Did stopping the medication or using a particular antagonist make the adverse response better?	0	+1	0	
4. Had the patient previously been exposed to the same or a comparable medicine and experienced a similar reaction?	0	+1	0	
5. Did the unpleasant event return when the medication was delivered again?	0	+2	-1	
6. Did any unbiased evidence support the bad event?				
7. Were medication amounts known to be harmful found in blood (or other fluids)?	0	+1	0	
8. Have there been any conclusive reports on this response in the past?	0	+1	0	
9. Did the side effect manifest after the suspected medicine was taken?	0	+2	-1	
10. Are there any additional factors (not related to the medication) that might independently have contributed to the reaction?	0	-1	+2	
Total score				

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ADR type	Scoring
Definite ADR	>9
Probable ADR	5- 8
Possible ADR	1 – 4
Doubtful ADR	0

Table.1=Naranjo Scoring

6. **Statistical Plan:** All the data were recorded and analyzed. Statistics were carried out using SPSS software. Patient's demographic details like gender, age, level of education, socio-economic status were reported using descriptive statistics.

RESULTS:-

1. **Demographic details:** About 45 cases of cervical cancer patients have collected. Twenty cases were eliminated from the study's inclusion and exclusion criteria, leaving 25 cases. The age range of study population is from 18 years to above 60 years. Gender is categorized as female. The other demographic details of the patient are religion, education level, marriage, residence. Due to concomitant conditions such renal failure and cardiovascular disease, CCRT was preferred in 65 individuals. 88 percent of cases were squamous cell carcinoma.

Table.2 - Demographic data and clinical characteristics of LACC

Variables	Frequency	Percentage	p-value
Age group			
18 - 30	8	3.60	
31 – 50	10	4.50	<0.001
51 – 60	15	6.75	
>60	12	5.40	
Past History			
Yes	8	3.60	<0.001
No	37	16.65	
Family History			
Yes	4	1.80	<0.001
No	41	18.45	
Marital status			
Married	37	16.65	<0.001
Unmarried	3	1.35	
Widow	5	2.25	
Area			
Urban	34	15.30	<0.001
Rural	11	4.95	
Education status			
Yes	10	4.50	<0.001
No	35	15.75	
Dietary Habit			
Veg	5	2.25	<0.001
Non-veg	40	18	
Hypertension History			
Yes	6	2.70	<0.001
No	39	17.55	
Performance status			
0	10	4.50	
1	15	6.75	<0.001
2	20	9.00	
Treatment approaches			
Radiotherapy	5	2.25	
Chemotherapy	10	4.50	<0.001
Chemoradiotherapy	30	13.50	
Pathological diagnosis			
Squamous cell carcinoma	36	16.20	<0.001
Adenocarcinoma	9	4.05	

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Table.3 – Mean and standard deviation of variables

Variables	Mean ± SD
Age	**44.92± 10.01**
Height	**150.15 ± 6.10**
Weight	**52.98 ± 9.41**
BMI	**17.62 ± 2.92**
Performance score	**2.53 ± 1.24**

2. **Safety assessment measurement:-** Table 7 displays the types and rates of adverse treatment-related events that women with locally advanced cervical cancer encountered following cisplatin combination with chemoradiotherapy. Nephrotoxicity and gastrointestinal disruption were the most frequent side effects following cisplatin and chemoradiotherapy, however no grade 4 occurrences were reported. The grade 3 toxicity events observed were,anemia (4%),leukocytopenia (4%),radiodermatitis (1%), thrombocytopenia (5%),and gastrointestinal disturbance (3%). The most frequent adverse events of all grades reported (occurs in 20% of patients) after cisplatin combined with chemoradiotherapy were gastrointestinal disturbance (15 subject), leukocytopenia (13 subject), anemia (25 subject), thrombocytopenia (13 subject). Other less frequent adverse effects of all grades were nausea/vomiting (19%), anorexia (16%), radiodermatitis (19%), fatigue (15%) ,rash (16%), and weight loss (16%)after cisplatin was combined with chemotherapy and radiation therapy.No patients died as a result of the treatment. Due to negative outcomes, no patient was removed from the trial or the study medication. Overall, the safety information points to an acceptable safety profile for cisplatin in women with locally advanced cervical cancer in the Tertiary Care Hospital when paired with radiation and chemotherapy.

Table.4 – Assessment of ADR scoring among age groups of study subjects:

Variables	**Age group**				**P – value**
	<= 39.00	**40.00 – 49.00**	**50.00 – 59.00**	**> = 60**	
Anemia					
Yes	3	2	3	4	0.113
No	2	13	3	14	
Total	5	15	6	18	
Thrombocytopenia					
Yes	2	4	1	5	0.861
No	3	11	5	13	
Total	5	15	6	18	
Nausea vomiting					
Yes	1	4	1	5	0.943
No	4	11	5	13	
Total	5	16	6	18	
Abdominal pain					
Yes	3	4	1	4	0.351
No	2	11	5	14	
Total	5	15	6	18	
Constipation					
Yes	3	6	1	1	
No	2	9	5	17	
Total	5	15	6	18	0.030
Acidity					
Yes	1	2	2	3	
No	4	13	4	15	0.753
Total	5	15	6	18	
Diarrhea					
Yes	2	5	3	3	
No	3	10	3	15	
Total	5	15	6	18	0.391

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Weight loss Yes No Total	 2 3 5	 2 13 15	 2 4 6	 5 13 18	 0.575

Table .5 –According to BMI :

Variable	**According to BMI**			**P – value**
	<= 18.50	**18.51 – 22.99**	**25.00**	
Anemia Yes No Total	 9 23 32	 3 8 11	 0 1 1	 0.824
Thrombocytopenia Yes No Total	 8 24 32	 3 8 11	 1 0 1	 0.253
Nausea vomiting Yes No Total	 7 25 32	 3 8 11	 1 0 1	 0.202
Constipation Yes No Total	 8 24 32	 3 8 11	 0 1 0	 0.834
Acidity Yes No Total	 6 26 32	 2 9 11	 0 1 0	 0.892
Diarrhea Yes No Total	 8 24 32	 4 7 11	 1 0 1	 0.299

3. **EFFICACY ASSESSMENT:-**After CCRT was finished, the regional reaction was assessed by radiologic and pathologic investigation. The same modality used for baseline evaluation was employed to assess treatment response in accordance with RECIST criteria (1.1). A total of 45 cervical cancer patients with a locally advanced stage were treated, and of those, none had a complete response (CR), 21 had partial responses (PR), and 14 had progressing disease (20%), for total reaction rate of 15%. (Table 9). The illness control rate was 88% (70/80), with a total of 23 patients having SD (74%).

TablT.6 -Efficacy assessment measurement by using RECIST criteria

Variable	**RECIST CRITEIA**			**P – value**
	PR	**SD**	**Total**	
Age < = 39 40.00 – 49.00 50 .00 – 59.00 >= 60	 2 8 1 10	 3 7 5 8	 5 15 6 18	 0. 381
BMI < = 18	 16	 16	 32	

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18.51 -22. 99 > 25	5 0	6 1	11 1	0.606
Staging Stage II Stage IIB Stage III	 3 15 1	 3 20 3	 6 35 4	 < 0.001
Children's 2 3 4 5 6 7 8 9	 3 3 7 3 0 1 4 0	 3 4 5 4 2 0 4 1	 6 7 12 7 2 1 8 1	 0. 716

4. **NARANJO SCALE:-** The Naranjo criteria categorise the likelihood that an adverse event is related to drug therapy based on a list of weighted questions that look at things like the temporal relationship between the administration of the drug and the event's occurrence, dose-response relationships, potential causes of the event, drug levels, and prior patient experiences with the medication. Drug-drug interactions are not taken into account by the Naranjo criteria. When assessing the causality of a drug, points are subtracted if it is possible that another cause may have contributed to the adverse event, weakening the causal link.

Table 5: Naranjo ADR Assessment scale

Variables	**Causality assessment**				**P – value**
	Possible	**Probable**	**Definite**	**Total**	
Age < = 30 40.00 – 49.00 50.00 – 59.00 > = 60	 2 7 3 5	 2 7 3 11	 1 1 0 2	 5 15 6 18	 0.823
BMI < = 18 18. 51 – 22.99 25	 15 2 0	 14 8 1	 3 1 0	 32 11 1	 0.407
Staging Stage II Stage IIB Stage III	 2 15 0	 4 17 2	 1 2 1	 7 35 3	 0.849
Children's 2 3 4 5 6 7 8 9	 1 3 7 2 0 1 2	 4 3 5 5 2 0 4	 1 1 0 0 0 0 2	 6 7 12 7 2 1 8	 0.510

DISCUSSION: - Nowadays, cervical cancer is the leading cause of illness and death for women worldwide and is also a very frequent problem. Due to a lack of knowledge about cervical cancer, the majority of individuals with the disease experience associated difficulties. The purpose of this study was to investigate the safety and effectiveness of cisplatin in combination with chemotherapy and radiation therapy in a group of patients with cervical cancer who had previously visited the outpatient department. Based on inclusion and exclusion criteria, 45 female patients with cervical cancer underwent a retrospective, prospective, and observational study to determine the stage of the disease, the drug's adverse drug reaction, and the anticancer drug prescribing patterns. The medication selection was found to be generally in accordance with accepted recommendations, such as the NCCN guidelines. The prescribed medicine usage pattern

following educational interventions, which involves coordinating the administration of antiemetic and anticancer treatments between patients, physicians, and other healthcare workers. The results of the study show that in cases with locally advanced cervical cancer, cisplatin in combination with radiation therapy and chemotherapy is well tolerated. According to studies, the most common acute toxic effects in patients receiving cisplatin treatment for locally advanced cervical cancer combined with chemotherapy include hematological, vulvo-vaginal, gastrointestinal, and urinary tract infection disorders; the most common late toxic effects are rectal bleeding, stenosis or recto vaginal fistula.

CONCLUSION:- There is a significant morbidity and mortality rate linked to cervical cancer. Cervical cancer prevention and control are greatly aided by health education and individual counselling. For the treatment of locally advanced cervical cancer, cisplatin and chemoradiotherapy may be given at the same time. Our research yields results that are consistent with those reported in the literature, which suggests that individuals with lower educational profiles are more likely to get cancer and, as a result, have lower cognitive abilities than those with higher educational profiles. Ultimately, menopause has a detrimental syngestic effect in patients receiving weekly cisplatin combined with chemoradiotherapy for cervical cancer, and increasing age and weight also results in a decline in cognitive function.
These studies are necessary to develop efficient awareness campaigns and illness prevention techniques. These studies are necessary. Our study's conclusions indicate that cisplatin in combination with radiation and chemotherapy is a manageable and maybe better treatment choice for patients with locally advanced cervical cancer.

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