Comparison of Response to the Concurrent Low Dose Daily Cisplatin Vs Weekly Cisplatin Vs Three Weekly Cisplatin with External Beam Radiotherapy in Carcinoma Cervix Patients of Stage IIB, IIIA & IIIB: A Prospective Study from Single Institution

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Abstract:

Introduction: Cervical cancer continues to be a major public health problem affecting middle-aged women, particularly in less-resourced countries. External beam radiation therapy along with intra cavitory insertion has long been the treatment of choice for locally advanced (IIB-IVA) cervical cancer, but long-term successes are limited in terms of pelvic recurrence or distant metastasis. Outcome of low dose daily versus weekly versus three weekly Cisplatin concurrent with External beam radiotherapy in locally advanced cervical carcinoma was compared in this study.

Methods: A prospective cross sectional study was carried out in J K cancer institute, Kanpur. Total 60 patients of cervical cancer were randomized into 3 arms. Arm I, Arm II and Arm III received External beam radiotherapy concurrent with either daily (8mg/m²), weekly (40 mg/m²) or three weekly (100 mg/m²) Cisplatin respectively. External beam radiotherapy was given with a dose of 50 Gy / 25 # / 5 week / 2 field or 4 field. Patients were evaluated weekly during treatment and afterwards up to 1year.

Results: Most of the patients were from fourth and fifth decade, low socioeconomic strata and illiterate. Majority of the cases belong to squamous cell carcinoma (96.6%) and stage III B (55%). Objective response in arm I was 80.0%, in arm II was 75.0% and in arm III was 60.0% respectively. Statistically significant difference was noted between arm III and Arm I (80%Vs60% p<0.05). Results were better in arm I as compare to arm II but not statistically significant. (80%Vs75% P>0.05)

Conclusions: This study showed that response was better in ARM I as compared to ARM III and best results was seen with Cisplatin concurrent daily with radiation.

Keywords: Cisplatin, concurrent chemotherapy, daily, weekly, three weekly, carcinoma cervix

Introduction:

Cancer ranks as a leading cause of death and an important barrier to increasing life expectancy in every country of the world.¹ According to estimates from the World Health Organization (WHO) in 2019,² cancers is the first or second leading cause of death before the age of 70 years in 112 of 183 countries. There were an estimated 19.3 million new cases and 10 million cancer deaths worldwide in 2020. The most commonly diagnosed cancer in women is dominated by two cancer sites: breast cancer (159 countries) and cervical cancer (23 of 26 remaining countries).¹ 10 years ago, cervical cancer ranked as the third most common cancer among women worldwide. However, in 42 low-resource countries, it was the most common cancer in women.³

According to a recent report, approximately 570 000 cases of cervical cancer and 311 000 deaths from the disease occurred in 2018. Cervical cancer was the fourth most common cancer in women, ranking after breast cancer (2.1 million cases), colorectal cancer (0.8 million) and lung cancer (0.7 million). Globally, the average age at diagnosis of cervical cancer was 53 years. The global average age at death from cervical cancer was 59 years. Cervical cancer ranked in the top three cancers affecting women younger than 45 years in 146 (79%) of 185 countries assessed.⁴

Most cervical cancer arises at the junction between the primary columnar epithelium of the endocervix and the squamous epithelium of the ectocervix. Cervical cancer is preceded by a precancerous condition called CIN which may or may not develop into cancer. Various studies have predicted that, if left untreated, 15% to 70% of CIN cases will eventually develop into invasive cervical cancer. The mean age of woman with CIN is approximately 15 years younger than that of women with invasive cancer, suggesting a slow progression of CIN to invasive carcinoma. Sq. cell cancer represents 90% or more of all cervical cancer. Adenocarcinoma arises from the endocervical columnar cells and account for 10 - 15% of the neoplasm.⁵ Went and Reagan (1959) categorized squamous cell carcinoma as either

large cell keratinizing, large cell non-keratinizing or small cell carcinoma.⁶

Surgery and radiotherapy are the two main modalities of treatment of cervical cancer. Controversy continues between advocates of radical surgery and radiation therapy. A number of factors influence the choice of local treatment, including tumor size, stage, histologic features, lymph node involvement, risk factor for complication of surgery and radiotherapy and patient preference.⁷ However, as a rule intraepithelial lesions are treated with superficial ablative technique, microinvasive cancers (IAI) are managed with conservative surgery, (excessional conization or extra facial hysterectomy) early invasive cancer (stage IA₂ and IB₁ and small IIA tumor) are managed with radical surgery or radiotherapy.⁸

External beam radiation therapy along with intracavitary insertion has long been the treatment of choice for locally advanced (IIB-IVA) cervical cancer, but long-term successes are limited in terms of pelvic recurrence or distant metastasis.⁹

Several attempts have been made to improve the results of radiation and to decrease complication rates. Concurrent chemotherapy is the term which signifies the use of chemotherapy during radiation therapy. Several chemotherapeutic agents act as radiosensitizer and potentiate the sterilizing effect of ionizing radiation. Various drugs has been used in concurrent chemotherapy for cervical cancer are hydroxyurea, 5 FU, mitomycin c, irinotecan and topotecan.¹⁰

The drug which is evolved as the most effective agent is CISPLATIN, a platinum analogue, cis-diamine dichloro platinum (cis -DDP) has antitumor activity which was first demonstrated by **Rosenberg and his colleagues in 1969**. It is most active cytotoxic agent in advanced squamous cell cancer cervix.¹¹

Concurrent cisplatin-based chemoradiotherapy (CRT) is the treatment of choice in locally

advanced cervical cancer based on five randomised trials.^{12,13,14,15,16}

In this prospective study we want to assess whether the low dose daily cisplatin is superior in comparison to weekly concurrent cisplatin or three weekly concurrent cisplatin with radiotherapy.

Material and Method

The clinical material for this study was selected from the cross section of patients registered at outpatient department of J.K. Cancer Institute and other associated hospitals of GSVM Medical College, Kanpur for a period of one year. Written informed consent was taken from all patients. The study was initiated after approval from institutional ethics committee.

Inclusion Criteria:

- Previously untreated patients of carcinoma cervix IIB, IIIA and IIIB.
- Karnofsky performance scale: KPS $\geq$ 70.(Annexure A)¹⁷
- Granulocyte count $\geq$ 2000/mm³
- Platelet count $\geq$ 1,00,000/mm³
- Serum Creatinine $\leq$ 1.4 mg/dl
- No other limiting Medical conditions

Exclusion Criteria:

- Prior Radiotherapy or chemotherapy treatment
- Postoperative cases
- KPS < 70
- Any other limiting medical condition.

The patients were randomized according to age group general condition, number of pregnancy, histopathology and stage and were divided into three arms:

ARM I: EBRT + Concurrent Cisplatin 8mg/m² daily was given within 30 minutes of starting radiotherapy fraction daily with 100ml NS iv drip 5 days a week with injectable IV antiemetics(inj. Ondansetron 8mg + inj. Dexamethasone 8mg IV) before it. These patients were admitted in ward for full period of

radiotherapy and given daily 500ml fluid (DNS 5% Dextrose or NS) after receiving RT fraction of that day.

ARM II: EBRT + Concurrent Cisplatin 40mg/m² weekly was given with hydration. These patients were hospitalized for 24 hrs once a week mostly on Monday and Cisplatin is given on the same day before starting radiotherapy fraction of that week.

Proper hydration was done before chemotherapy and was delivered under cover of antiemetics (inj. Ondansetron 16mg + inj. Dexamethasone 8mg IV)

ARM III: EBRT + Concurrent Cisplatin 100mg/m² three weekly was given with proper hydration on day1, day 22 and day 35.

These patients were hospitalized for 48 hrs on due date and Cisplatin was given on the same day before starting radiotherapy fraction of that week. Proper hydration was done before chemotherapy and was delivered under cover of antiemetics (inj. Ondansetron 16mg + inj. Dexamethasone 8mg IV) and same supportive treatment repeated on next day.

RT Schedule in all the three arms will be as follows:

50 Gy / 25 # / 5 week / 2 field or 4 field depending on the field separation of the patient. If Anteroposterior separation is > 18cm 4 field RT was used.

After completion of 50Gy RT, complete evaluation of the patients was done for the response and toxicities in all the three arms. Depending on these factors, favorable patients were considered for Intracavitary Radiotherapy treatment and remaining for extended EBRT up to total 70Gy.

Concurrent Cisplatin was delivered only up to 50 Gy in all the three arms.

1 week later three applications of intracavitary Radiotherapy each of 6 Gy will be given by HDR Brachytherapy to point A. The patients were informed about the treatments arms and were told about the consequences of chemotherapy

and radiotherapy. The total dose of RT was 70 Gy to point A with optimum close profile using standard technique in all patients.

Evaluation of Response:

Weekly evaluation of CBC, LFT and RFT was done in all three arms. Response and side effects evaluation was done weekly during treatment and then at the end of radiotherapy and then monthly following completion of treatment. Grading of response was done using WHO criteria (Appendix B) ¹⁸

Follow up:

It will be done for the appearance of any acute or chronic reactions in patients of all the three arms. We shall follow the patients on daily and weekly

basis during the treatment course. Then follow up will be done monthly in 1st year and then at every 2 months in 2nd year.

Statistical Analysis:

The Chi Square test of significance will be used to determine whether the observed results are statistically significant or not. p value less than 0.05 as significant. p value less than 0.00 as highly significant.

Results

The present study was conducted on a total number of 60 patients of carcinoma cervix stage IIB-IIIB. These patients were randomized into 3 study arms (20 patients in each arm).

TABLE: 1 DISTRIBUTION OF CASES AT J.K. CANCER INSTITUTE

Total patients presented at J.K. Cancer Institute during study period	6813
Total female presented with gynecological malignancy	550
Patients of carcinoma cervix diagnosed among them	441/550=80.18%

Cervical carcinoma is the commonest gynecological malignancy among the females.

TABLE – 2 DISTRIBUTIONS OF CASES ACCORDING TO RELIGION

Religion	No. of pts.	Percentage
Hindu	59	59/60=98.33%
Muslim	01	01/60=1.66%
Christian	00	00

Total 60 cases were taken into study. Out of these 60, 59 (98.33%) belonged to Hindu and 01 (1.66%) belonged to Muslims. There were no case which belonged to Christian.

TABLE-3 DISTRIBUTION OF CASES ACCORDING TO SOCIO - ECONOMIC STATUS

F Socioeconomic status	No. of patient	Percentage
Low	48	48/60=80%
Middle / High	12	12/60=20%

Women from lower socio-economic group have a higher incidence of cervical cancer because of early age at marriage and first intercourse. In this study most of the patient (80.0%) were belonged to low socioeconomic status.

TABLE – 4 DISTRIBUTIONS OF CASES ACCORDING TO LITERACY

Literacy status	No. of patient	Percentage
Illiterate	45	45/60=75%
Literacy	15	15/60=25%

In our study most of the patients were illiterate (75.00%)

TABLE 5: DISTRIBUTIONS OF CASES ACCORDING TO AGE

Age in yr	Arm I (RT+ Daily cisplatin)	Arm II (RT+ Weekly cisplatin)	Arm III (RT+ Three weekly cisplatin)	Total
31-40	3	7	1	11 (18.33%)
41-50	10	6	5	21(35.00%)
51-60	6	5	6	17(28.33%)
61-70	1	1	5	7(11.66%)
71-80	0	1	3	4(6.66%)

Maximum patients were in the fourth and fifth decade of life in all the three arms.

GRAPH-1 DISTRIBUTION OF CASES ACCORDING TO PARITY

Multiparity was found to be a common feature in this study. Most of the patients were having more than 3 issues in all the three arms.

GRAPH-2 DISTRIBUTION OF CASES ACCORDING TO GROSS PATHOLOGY

On clinical examination, 42 (70%) patients were seen to be having exophytic cervical growth while 14 (23.33%) and 4 (6.66%) patients were having ulcerative and infiltrative growth respectively.

TABLE 6: DISTRIBUTIONS OF CASES ACCORDING TO HISTOPATHOLOGY

<i>Hotspot</i>	<i>Arm I</i> (RT+ Daily cisplatin)	<i>Arm II</i> (RT+ Weekly cisplatin)	<i>Arm III</i> (RT+ THREE WEEKLY CISPLATIN)	<i>Total</i>
<i>Squamous</i>	20	19	19	58(96.66%)
a. LCNK	15	14	8	37(61.66%)
b. LCK	5	5	11	21(35.0%)
<i>Adeno</i>	0	1	0	1(1.66%)
<i>Small cell</i>	0	0	1	1(1.66%)

In our study majority of the cases belonged to squamous cell carcinoma = 58(96.66%). Among squamous cell carcinoma maximum cases belonged to large cell nonkeratinizing type= 37(61.66%) followed by large cell keratinizing = 21(35.00%), Adenocarcinoma = 1(1.66%) and small cell = 1(1.66%).

TABLE 7: FIGO STAGEWISE DISTRIBUTION OF CASES STAGE

<i>Stage</i>	<i>Arm I</i> (RT+ Daily cisplatin)	<i>Arm II</i> (RT+ Weekly cisplatin)	<i>Arm III</i> (RT+ Three weekly cisplatin)	<i>TOTAL</i>
II B	5	6	5	16 (26.6%)
III A	3	4	4	11 (18.3%)
III B	12	10	11	33 (55.0%)

Cervical cancer usually present in advanced stage. In our study majority of the cases were of stage III B = 33(55.0%). All the 3 arms were almost similar regarding FIGO stage wise distribution of cases.

TABLE 8: OVERALL RESPONSE TO TREATMENT

Arms	Subjective	Objective
Arm I (RT+ Daily cisplatin)	18 (90%)	16 (80%)
Arm II (RT+ Weekly cisplatin)	20 (100%)	15 (75%)
Arm III (RT+ Three weekly cisplatin)	18 (90%)	12 (60%)

Response to treatment can be divided into subjective and objective response. In our study criteria of subjective response was decrease in vaginal discharge, bleeding and pain by 50% while objective response was assessed clinically and was complete clinical regression of tumor. In Arm I subjective response was 90.0%, in arm II 100.0% and in arm III 90.0%. Best subjective response was seen in arm II. Objective response in arm I was 80.0%, in arm II was 75.0% and in arm III was 60.0%. Statistically significant difference was noted between arm III and Arm I. Results were better in arm I as compare to arm II but not statistically significant. ($P > 0.05$)

TABLE 9: TUMOR REGRESSION OBSERVED 1 MONTH AFTER TREATMENT

	Arm I (RT+ DAILY CISPLATIN)	Arm II (RT+ WEEKLY CISPLATIN)	Arm III (RT+ THREE WEEKLY CISPLATIN)
Complete clinical regression (CR)	16 (80%)	15 (75%)	12 (60%)
Residual disease (PR)	4 (20%)	5 (25%)	8 (40%)

In our study response was significantly high in ARM I as compared to ARM III (80% Vs 60% $p < 0.05$), while ARM I & ARM II response was nearly equal (80% Vs 75% $p > 0.05$) and not significant.

TABLE 10: RESPONSE ACCORDING TO FIGO STAGE

FIGO Stage	Arm I (RT+ Daily Cisplatin)	Arm II (RT+ Weekly Cisplatin)	Arm III (RT+ Three weekly cisplatin)
II B	5/5 (100%)	6/6 (100%)	5/5 (100%)
III A	3/3 (100%)	3/4 (75%)	2/4 (50%)
III B	8/12 (66.66%)	6/10 (60%)	5/11 (45.45%)

In our study response was better in ARM I as compared to ARM III and best results were seen with Cisplatin concurrent daily with radiation. According to stage also best results were seen with RT+ Daily Cisplatin followed by RT+ Weekly Cisplatin.

Discussion

At our institute during the study period, total patients of cancer registered were 6813, out of which gynaecological cancers were 550. Among these gynaecological cancers, carcinoma cervix diagnosed were 441 (80.18%). This is similar to the incidence reported at the department of Radiotherapy and Oncology, Government Medical College, Aurangabad by Rao et al.¹⁹

In our study most of the patients (80%) were from low socioeconomic strata. The association of developing cervical cancer in poor socio-economic group seems to be due to early marriage and early child bearing.²⁰ Most of our patients (75%) were illiterate and multiparous i.e. having more than three children.²¹ In our study maximum patients were in the fourth and fifth decade of life in all the three arms. Similar results were obtained by Ehab abdou et al where Patient's age ranged between 25-66 years with median age of 46 years.²²

We observed that 42 (70%) patients were seen to be having exophytic cervical growth while 14 (23.33%) and 4 (6.66%) patients were having ulcerative and infiltrative growth respectively. In our study maximum cases were of squamous cell carcinoma (96.66%). Among the squamous cell carcinoma, maximum number of cases belonged to large cell non-keratinizing type (61.66%). This pattern is in accordance with the available literature. Kimio Ushijima *et al* observed **88% cases of SCC in their study**.²³ Many trials have demonstrated that squamous cell carcinoma cervix gives better results with concurrent chemo-

radiation and cisplatin is the most active agent.²⁴ In our study majority of the cases were of stage III B = 33(55.0%) followed by IIB=16(26.6%). Another study reported 73% patients were of stage IIB.²⁵

In our study we found the objective response rates were 80%, 75%, and 60%, for Arm 1, 2, and 3, respectively. Arm III containing three weekly Cisplatin 100mg/m² resulted into low response as compare to Arm I and Arm II. A study conducted by Hasan MR et al, Cisplatin 40 mg/m², weekly was given along with radiotherapy to the patients of Arm A (n=40) while the patients of Arm B (n=40) received cisplatin 75 mg/m², 3 weekly along with the radiotherapy. Complete response at 6 months of follow up was observed in 30 (75%) and 36 (90%) patients of Arm A and B respectively.²⁶

Five phase III trials have also demonstrated a 30 - 50% reduction in the relative risk of recurrence and improvement in survival with cisplatin containing chemo radiation.

The gynecologic oncology group (GOG) protocol 85 compared Cisplatin and 5FU with hydroxyurea when used concurrent with radiation in patients with stage IIB-IVA cervical cancer. The 3 year survival rates were 67% versus 57%.¹²

The GOG protocol 120 has shown 65% 3 year survival. with cisplatin / 5FU / hydroxyurea with radiation and cisplatin alone with radiation compared to 47% 3 year survival for hydroxyurea with radiation.¹³

GOG protocol 123 included bulky stage IB tumors treated with chemoradiation or radiation alone followed by extrafascial hysterectomy. The survival rate was 83% for chemoradiation as compared to 74% for radiation arm.¹⁴

Radiation therapy oncology group (RTOG) protocol 90-01 have demonstrated 75% 3 year survival for patients treated with Cisplatin / 5Fluorouracil (5FU) concurrent with radiation as compared to 63%, 3 year survival for patients treated with radiation alone in stage IIB - IVA cervical cancer.¹⁵

The Southwest oncology group protocol 8797 included stage IA2 to IIA patients. The 3 year survival for cisplatin 1 5FU + radiation arm was 87% as compared to 77% for adjuvant radiation alone arm.¹⁶

Based on these trials NCI released a clinical announcement stating that concurrent Cisplatin based chemoradiation is the new standard treatment for high risk early stage and locally advanced cervical cancer.

In our study response was better in ARM I as compared to ARM III and best results was seen with Cisplatin concurrent daily with radiation. According to stage also best results were seen with RT+ Daily Cisplatin followed by RT+ Weekly Cisplatin.

Despite decades of development, the failure rate for treatment for locally advanced disease has remained high. According to FIGO's annual report, the five year survival rates has improved for stage I and II during 2006-09 as compared to 1950 - 1954, results are still low for stage III and stage IV (Annual report on the results of treatment in gynaecological cancer, Vol. 27)²⁷ Clinicians have investigated ways of combining chemotherapy and radiation for more than 35 years to improve control rates.

Conclusion

Cancer cervix is the most common gynecological malignancy among the females in India. Cervical carcinoma usually presented in advanced stages specially stage IIB. Exophytic growth was seen in most of the patients in this series and most

common histopathological findings were large cell nonkeratinizing variety. Concurrent chemo radiation with weekly Cisplatin 40mg/m2 treatment is better as compared to daily Cisplatin 8mg/m2 and three weekly Cisplatin 100mg/m2 when used as a radiosensitizer for locally advanced cervical carcinoma both in terms of response versus toxicity. Stage II responded better to stage III in all the three arms. Stage III responded better in Arm I (66.66%) than Arm II (60%) than Arm III (45.45%) In our study it was observed that weekly cisplatin based concurrent chemoradiation is the best option for locally advanced cervical carcinoma.

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Annexure – A

Karnofsky performance scale

- 100% - Normal, no complaints, no evidence of disease
- 90% - Able to carry on normal activity, minor signs or symptoms of disease.
- 80% - Normal activity with efforts, some signs or symptoms of disease.
- 70% - Cares for self, unable to carry out normal activity or to do active work
- 60%- Requires occasional assistance, but is mostly able to care for self.
- 50% - Requires considerable assistance and frequent medical care.
- 40%- Disabled, requires special care and assistance
- 20%- Severely disabled, hospitalization indicated, death not imminent.
- 20%- Very sick, hospitalization necessary, active supportive treatment necessary.
- 10% - Moribund, fatal processes, progressing rapidly
- 0% - Dead

Annexure - B

EVALUATION OF RESPONSE:

Evaluation of response will be done according to WHO criteria 1982 as follows:

1. Complete Response (CR): The disappearance of all known disease, determined by two observations, not less than four weeks apart.
2. Partial response (PR): Decrease of 50% or more of tumor and nodal status judged by two observations not less than 4 weeks apart. In addition there can be no appearance of new lesion or progression of any old lesion.
3. No Response (NR): less than 50% response in total tumor size but not more than 25% increase in size of measurable lesion.
4. Disease Progression (DP): 25% or more increase in size of one or more measurable lesion or appearance of new lesions.