Original research article

WEEKLY VERSUS TRI-WEEKLY CONCURRENT CISPLATIN WITH RADIOTHERAPY IN THE TREATMENT OF CERVICAL CANCER: A STUDY COMPARING EFFICACY AND TOXICITY

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Abstract

Introduction: Concurrent chemoradiation is the standard treatment for the locally advanced cervical cancer. The optimal Cisplatin dose and dosing schedule are still undetermined. The present study aims to evaluate the efficacy and toxicity of weekly and tri-weekly cisplatin with radiotherapy in treatment of cervical cancer.

Material And Methods: Fifty patients with histologically proven Stage IA-IIIB cervical cancer were randomly assigned to weekly (Arm 1, cisplatin 35 mg/m^2, five cycles) and tri-weekly (Arm 2, cisplatin 75 mg/m^2 every 3 weeks, two cycles) chemotherapy during radiotherapy. The difference of efficacy and toxicity profiles between the two regimens was investigated, and the response rate was analyzed.

Results: All patients tolerated both treatments well. There was significantly better chemotherapy compliance in tri-weekly arm (100% vs 68%, p=0.002). Leucopenia was higher in ARM-B then ARM-A (16% vs 4%, p=0.15). Vomiting grade II/III was significantly higher in ARM-B then ARM-A (64% vs 24%, p=0.009). Grade II Genito-urinary toxicity was higher in ARM-B then ARM-A (20% vs 4%, statistically not significant).

Conclusion: Both weekly cisplatin 35 mg/m^2 and tri-weekly 75 mg/m^2 concurrent with radiotherapy are equally feasible and efficacious.

Keywords: Cervical cancer, chemoradiation, weekly cisplatin, tri-weekly cisplatin

INTRODUCTION

Current standard treatment for locally advanced cervical cancer is cisplatin-based concurrent chemoradiation. On the basis of the results of five randomized clinical trials, which consistently showed improved survival in patients treated with cisplatin-based chemoradiation, the U.S. National Cancer Institute (NCI) announced in 1992 that " Strong consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiotherapy in women who require radiotherapy for treatment of cervical cancer".[1-5]

Although recently reported meta-analyses also demonstrated improved local control rates and survival with cisplatin-based chemotherapy concurrent with radiation, the optimal cisplatin dose and dosing schedule are still undetermined.[6-8] Among the previous five randomized clinical trials, two trials performed by the Gynecologic Oncology Group (GOG) used weekly cisplatin 40 mg/m^2, whereas the other three trials used triweekly cisplatin at a dose range of 50 mg/m^2 to 75 mg/m^2 combined with 5-fluorouracil (5-FU).[1-5]

The present study aims to compare two dosing schedules of cisplatin (weekly versus tri-weekly), in terms of efficacy and toxicity, administered to the patients undergoing radiotherapy for cervical cancers.

MATERIALAND METHODS

All fifty patients of cancer cervix were, biopsy proven; age >18 years; karnofsky performance scale above 70; FIGO stage upto IIIB with no history of previous malignancy. Patients of carcinoma cervix FIGO stage IV and metastatic disease were excluded from the study.

Pre-treatment evaluation was done by complete medical and physical examination, including bimanual pelvic and rectal examination. Other investigations included were hematological tests (haemogram, renal function tests, and liver function tests); chest radiography; ultrasound abdomen or CECT abdomen and pelvis (whichever was

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feasible); cystoscopy and proctosigmoidoscopy (only if clinically indicated).

Radiotherapy for all patients was planned and delivered by conventional or 3- Dimensional Conformal Radiotherapy (3D-CRT) using four field box technique. Radiotherapy dose delivered was 50 Gy in 25 fractions at 200 cGy/ day. Concurrent cisplatin was administered to these patients.

Randomisation of patients for concurrent chemotherapy was done on the basis of two schedules of cisplatin- Group/arm I - Cisplatin weekly at the dose of 35 mg/m^2 and Group/arm II - Cisplatin tri-weekly at the dose of 75 mg/m^2.

All patients were adequately hydrated with 2-2.5 liters of I.V fluids and supplemented with Inj-KCL, Inj-$MgSO_4$, Inj-MVI. Radiotherapy was delivered within 1hr of administration of cisplatin, along with proper antiemetic therapy with 5-HT_3 antagonist, dexamethasone and ranitidine.

Clinical response assessment was done during radiotherapy and every month after radiotherapy for at least 6 months. The patients were assessed for objective tumor response according to WHO criterion: Complete response (CR; total tumor regression for at least 4 weeks), Partial response (PR; 50% or more reduction in two major perpendiculars of the measurable tumor for at least 4 weeks), Stable disease (SD; Less than 50% or more reduction to less than 25% increase), Progressive disease (PD; Growth of measurable tumor by 25% or more or appearance of new lesion).

Patients were assessed weekly during chemo-radiation for acute radiation reactions. Complete blood counts, kidney function tests and liver function tests were repeated in all patients every week before each chemotherapy cycle. Radiation toxicity was assessed by RTOG acute and late morbidity scoring criteria. Hematological toxicities were graded according to common toxicity criteria 2.

Follow up in all the patients were done up to at least 6 months, from the day of completion of treatment.

Statistical analysis was done by Chi square test.

RESULTS

The mean age of the patients was 45 years (range 21-70 years). There was higher incidence of cancer cervix in post menopausal and multiparous women. Most the patients were FIGO stage IIB (46%) and IIIB (22%). On histopathology, forty eight patients had squamous cell carcinoma and only 2 patients in ARM-B were adenocarcinoma (Table-1).

Table-1: Patient characteristics in both study groups

CHARACTERISTIC	WEEKLY CISPLATIN	TRIWEEKLY CISPLATIN	*p*
Patients	25	25	-
Age (years)			
21 - 50	15 (15.5) [0.02)	16	0.770
51 - 70	10 (9.5) [0.03)	9	0.770
Menstrual status			
Post-menopausal	20	15	
Peri-menopausal	5	7	
Pre-menopausal	0	3	
No. of children			
<3	6	7	
>3	19	18	
Stage			
Stage IA - IB	2	0	
Stage IIA	5	5	
Stage IIB	10	13	
Stage IIIA	3	1	
Stage IIIB	5	6	
Histology			
SCC	25	23	
Non-SCC	0	2	

Most common symptom was yellowish/whitish discharge (80% patients) followed by bleeding P/V (58%), common in elderly women (Fig-1).

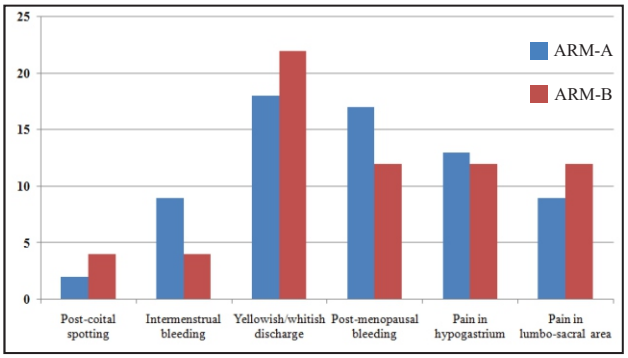

Fig.-1: Showing comparison of chief complaints in both ARMs

The compliance of chemotherapy cycles of patients in Arm-A was lower (68%) than in Arm-B (100%) which was statistically significant (p = 0.002). The scheduled treatment time or OTT (Overall Treatment Time) of 8 weeks was seen in 25 (100%) patients in Arm-A & 22 (88%) patients in Arm-B. (Table-2)

Table-2: Treatment Compliance in both study groups

TREATMENT	WEEKLY CISPLATIN	TRIWEEKLY CISPLATIN	*p*
Chemotherapy	25	25	-
Completed Cycle	17	25	0.002
Uncompleted Cycle	8	0	
Radiotherapy	25	25	
Overall Treatment Time			-
< 8 weeks	25	22	0.07
> 8 weeks	0	3	

Hemoglobin was maintained throughout the treatment by blood transfusion, oral hematinics and the dietary advice. Grade II leukopenia was higher in Arm-B then Arm-A (16% Vs 4%), but statistically not significant (p = 0.15). No grade-IV leukopenia was found in either arms. There was no thrombocytopenia seen in both the groups (Table-3).

Grade II toxicity vomiting was higher in Arm-B then Arm-A, 60% Vs 24% and it was significant (p = 0.009). No grade IV toxicity seen in both Arms. No significant episodes of diarrhea or genito-urinary symptoms were seen in either arm. (Table-3).

Table-3: Toxicities in both study arms

Toxicity	Weekly Cisplatin		Triweekly Cisplatin		
	Grade 0-1	Grade 2-3	Grade 0-1	Grade 2-3	*p*
Leucopenia	7	1	5	6	0.15
Vomiting	19	6	9	16	0.009
GIT	12	3	20	5	
GUT	24	1	20	5	
Dermatitis	21	4	22	3	

Complete tumor response at the end of the treatment was seen in 24 (96%) and 21 (84%) patients in Arm-A & -B, whereas partial response was seen in 4 (16%) in tri-weekly and 1 (4%) in weekly arm (p = 0.15). (Table-4)

Table-4: Tumor response both study arms

Tumor Response	Weekly Cisplatin	Triweekly Cisplatin	*p*
Complete Response	24	21	0.15
Partial Response	1	4	0.15

At the end of six months complete response was seen in 24 patients (96%) in Arm-A and 23 (92%) patients in Arm-B. Partial response was seen in 2 patients (8%) in Arm-B and 1 patient (4%) in Arm-A showed progressive disease.

No significant late reactions were seen in terms of haematological toxicity, urine infection, vaginal discharge or vaginal mucositis.

DISCUSSION

Chemoradiotherapy in cervical carcinoma is thought to exert its major beneficial effects by improving local control but it also has a modest systematic effect.[7]

In designing chemotherapy protocols, it is critical to note the extreme importance of avoiding delays in the delivery of radiation, a factor well established to negatively impact the ultimate outcome of patients with cervix cancer. Thus, the toxicity profile of any chemotherapy program must permit radiation administration without delay.

While a number of cisplatin-based regimens have been explored, and a definitive statement regarding an "optimal" chemo-radiation approach is not possible, many investigators currently recommend the administration of cisplatin at a dose of 30-40 mg/m^2/week beginning when external beam radiation is initiated, and continuing throughout the duration of the radiation treatment. Morris et al. study was the only one that prescribed concurrent chemotherapy with the brachytherapy portion of treatment. The importance of this is unclear, but the approach is attractive because 30-50% of the central dose of radiation is usually given during this part of the treatment.[5]

Hematological toxicities & acute reactions during treatment like leukopenia was significantly more common and more severe in the tri-weekly arm whereas there were no statistical differences in the incidence levels of vomiting, diarrhoea, dermatitis and anemia between the two arms. Our observations are similar to that of Chumworathayi B et al and Lee et al.[9,10]

Watanabe et al conducted a study as a phase I, dose-escalation trial. Concurrent CDDP was started at the dose of 30 mg/m^2 for the weekly schedule and at 50 mg/m^2 for the monthly schedule, and the doses were steadily escalated to the maximum tolerated dose (MTD).[11] A total of 45 patients with uterine-cervix carcinoma (25 receiving primary chemoradiation (CCRT) and 20 receiving adjuvant CCRT) were entered in the study. In both the primary and adjuvant CCRT patients, the MTD was observed to be 40 mg/m^2 for the weekly schedule and 80 mg/m^2 for the monthly schedule. Dose-limiting toxicity was observed in 10 patients (granulocytopenia in 9 patients and diarrhoea in 1 patient). In the present study all the patients in ARM-B was able to complete the chemotherapy cycles in comparison of ARM-A. Grade III leukopenia was noted in 2 (8%) and there was no grade IV leukopenia found in both the ARMs of our study and it was easily manageable.

Tangsiriwatthana et al noted that grade III and IV hematological toxicities were found in 6% of the patients, who were treated with pelvic radiotherapy.[12] In our study no grade IV hematological toxicities were noted and 1 (4%) patient in ARM-A and 2 (8%) had leukopenia in ARM-B and this data is similar to this study.

Chen et al. reported that the 4-year actuarial survival was 74% for the CCRT group and 68% for the Radiotherapy (RT) group (p = 0.60).[13] The cumulative incidence of gastrointestinal and genitourinary injuries of grade III or above was 14.3% for the CCRT group and 7.9% for the RT group (p = 0.19). No grade III or IV gastrointestinal and genitourinary toxicity was found in our present study.

Ryu et al. evaluated 104 patients with histologically proven stage IIB-IVA cervical cancer, who were randomly

assigned by a computer-generated procedure to weekly (cisplatin 40 mg/m^2, six cycles) and tri-weekly (cisplatin 75 mg/m^2 every 3 weeks, three cycles) chemotherapy arms during concurrent radiotherapy.[14] There was no statistically significant difference in compliance between the two arms. Grade III-IV neutropenia was more frequent in the weekly arm (39.2%) than in the tri-weekly arm (22.6%) (p = 0.03). This study results slightly varies from our study, as there was no grade III-IV hematological toxicity was noted. But chemotherapy compliance wise is similar to this study.

Kim et al. evaluated a total of 158 patients (stages IIB through IVA) with para-aortic lymph nodes were randomized to receive 3 monthly cycles of 5-FU (1000 mg/m2/day I/V) plus cisplatin (20 mg/m^2/day I/V) for 5 days (Group I, n=79) or 6 cycles of weekly cisplatin (30 mg/m^2 I/V) (Group II, n=79), concurrent with definitive radiotherapy.[15] Radiotherapy consisted of external irradiation to the whole pelvis of 41.5 - 50.4 Gy in 23-28 fractions plus high-dose rate (HDR) intracavitary brachytherapy (30-35 Gy in 6-7 fractions) to point A, together with a parametrial boost. The incidence of acute grade III or IV hematologic toxicity was 43% and 26% (p = 0.037). They concluded that the regimen of chemoradiation using weekly cisplatin significantly improves compliance with treatment and reduces hematologic toxicity, while not affecting response and survival rates. In our study 8 (32%) patients were not able to complete the scheduled chemotherapy cycle in weekly arm i.e. 5, due to grade I and II hematological toxicities and acute reactions.

Stehman et al reported that an increased rate of early hematologic and gastrointestinal toxicity was seen with CT plus RT.[16] They concluded that concurrent weekly cisplatin with RT significantly improves long-term PFS and OS when compared with RT alone. This study shows the similar result as that of our study, that grade I and II, i.e. early toxicities are seen in both ARMs in comparison of grade III and IV hematological toxicities.

Tadahiro et al. took 20 patients with locally advanced squamous cell carcinoma of the uterine cervix at clinical stage IB2-IIIB were studied.[17] Two 21-day cycles consisting of intravenous administration of cisplatin at 70 mg/m^2 (Day 1) and irinotecan at 70 mg/m^2 (Days 1 and 8) were performed. Grade III or IV neutropenia was noted in 12 patients, and 4 patients had grade III or IV anaemia. Their data indicated that the tri-weekly cisplatin and irinotecan combination neo-adjuvant chemotherapy involves only controllable toxicity and yields a high response rate, suggesting that this combination is a useful therapy regimen. Our study was done on the basis of single chemotherapy agent, i.e cisplatin 75 mg/m^2 (which is ARM-B). There was no grade III or IV anemia found in any of the patient and no grade grade IV leukopenia. Only 2(8%) patients had grade III leukopenia.

Chumworathayi B et al. reported that the toxicity-related incomplete treatments rate and G-CSF doses used were significantly higher in tri-weekly arm than in the weekly arm.[9] And the same was noted in our study that 4 (16%) and 2 (8%) patients had grade II and III leukopenia and had to receive G-CSF, to continue the further treatment.

Mancebo et al. retrospectively reviewed 69 patients with locally advanced cervical cancer who received chemoradiation.[18] Cisplatin was administered for six weeks during external beam radiation. Fifty two patients presented some degree of acute adverse toxicity (gastrointestinal 65%, haematological 48%, and genitourinary 10%. Overall survival according to stages IB2-IIB and III-IVA was 74.8% and 34.9%, respectively (p = 0.0376). They concluded that in patients with locally advanced cervical cancer, adding a weekly regimen of cisplatin to standard pelvic radiation in an out-of-protocol basis is feasible, effective, and showed no unexpected toxicity. In our weekly arm (cisplatin 35 mg/m^2) 6 had grade II vomiting, 3 had grade II GIT, 1 had grade II GUT and the rest 4 had grade II dermatitis. Whereas, in tri-weekly arm 1(4%) had grade III vomiting, 5 (20%) had grade II diarrhoea, 5 (20%) had grade II GIT and 1 (4%) had grade III dermatitis. So compared to above study it is also feasible and effective, and showed no unexpected toxicity.

Acute-phase vomiting after cisplatin treatment is thought to be primarily mediated via the serotonin receptors, and is nearly universal. In the present study majority of the patients in both the arms (11 in weekly arm and 22 in tri-weekly arm) had grade I or II vomiting, while only 1 patient in tri-weekly arm had grade 3 vomiting; these changes were not statistically significant.

Tan et al. conducted an audit of acute treatment-related toxicity during chemo-radiotherapy for cervical cancer to assess its tolerance outside research settings.[19] The most common adverse effects were diarrhoea (80.6%), malaise (66.7%) and nausea (62.5%). The most common haematological toxicity was anaemia, with 41.7% patients developing grade I or II toxicity. Only 3 (4.2%) patients had grade III or IV toxicity. These results are similar to present study where anemia is the most common toxicity of grade I or II.

Overall treatment time : The American Brachytherapy Society recommends keeping the total treatment duration

to less than 8 weeks, because prolongation of total treatment duration can adversely affect local control and survival.[20-24] In this present study, the duration of treatment is almost same (58 days vs 57 days) and did not influence significantly on local control. In ARM-A 25 (100%) patients & 22 (88%) patients in ARM-B completed the treatment within 8 weeks. Only 3(12%) patients in tri-weekly ARM were extended more than 8 weeks.

The delay in treatment and inability to complete all the chemotherapy cycles was mostly due to adverse effects such as vomiting, diarrhoea, leukopenia and dermatitis or in some cases due to patient compliance related factor.

The follow up time is too short to assess definitively the local control as only response was assessed up to 6 months.

Ryu et al. reported that the two cisplatin-based chemoradiation regimens were tolerated very well, with 86.3% and 92.5% completion rates of scheduled chemotherapy cycles for the weekly and tri-weekly arms, respectively. There was no statistically significant difference of compliance between the two arms ($p>0.05$).[14] In our study the completion rate of scheduled chemotherapy in both the groups is statistically significant ($p = 0.002$).

Chumworathayi B et al while comparing weekly versus three-weekly cisplatin as an adjunct to radiation therapy in high-risk stage I-IIA cervical cancer after surgery reported a higher rate of incomplete and delayed treatments in the tri-weekly cisplatin group ($p<0.001$ and $p=0.0236$ respectively).[9] In our present study there was delay in treatment in 3 (12%) patients in tri-weekly arm, and it is statistically not significant ($p = 0.07$).

Serkies et al. evaluated locally advanced or high-risk early-stage cervical cancer patients treated with RT and concurrent weekly cisplatin at a dose of 40 mg/m^2 I/V (maximum dose, 70 mg) for five cycles.[25] Definitive RT included whole pelvic external beam RT dose of 40 Gy plus a 10 Gy boost to the parametrium and two brachytherapy applications of 20 Gy. They concluded that their results show that pelvic RT combined with weekly cisplatin in cervical cancer patients is a accompanied by considerable acute toxicity. In the present study grade II and III anaemia was seen in 28%. No grade III and IV acute reactions were seen, but grade I and II vomiting in 54%, GIT in 32%, GUT in 4% and dermatitis in 84% was seen and it is being supported by the above study.

Tumor Response: Bonomi P et al. while three different cisplatin dose schedules (cisplatin 50 mg/m^2 every 21 days, 100 mg/m^2 every 21 days and cisplatin 20 mg/m^2 for five consecutive days repeated every 21 days) also observed that the regimen consisting of a 100 mg/m^2 single dose produced no appreciable differences in complete remission rate, response duration, progression-free interval, or survival.[26] Lee et al evaluated patients with stage IB1 to stage IIB cervical cancer who had undergone radical hysterectomy with pelvic lymph node dissection, followed by concurrent adjuvant chemoradiation therapy with either the tri-weekly combination chemotherapy group or the weekly cisplatin chemotharepy group.[10] They also concluded that the weekly cisplatin chemotherapy group experienced the same therapeutics effect as the tri-weekly combination chemotherapy group but with less toxicity. There were 5 patients in 50 with partial response, 1 in weekly arm and 4 in the tri-weekly arm. 1 patient with partial response in the weekly arm had b/l parametrium involvement (on P/R examination). Whereas, 1 patient with partial response in the tri-weekly arm had unilateral (right) parametrium involvement at the end of 6 months and 3 had ulcerative growth over the cervical lip. This was not statistically significant ($p = 0.15$).

Singh et al. conducted a prospective randomized study evaluating the role of chemoradiation of fifty patients.[27] The early treatment response as assessed after two months of treatment conclusion were 79.1%, 13.9%, 93.0% and 58.5%, 31.7%, 90.2% as complete response (CR), partial response (PR), and total response (TR) respectively for the study and control groups. In present study 96% CR and 4% PD in weekly arm, whereas 92% CR and 8% PR in triweekly arm and statistically not significant ($p = 0.55$; CR and $p = 0.14$:PR).

Punushapai et al. randomly assigned 140 patients of FIGO stage IB2-IVA (half in each group) to receive weekly cisplatin at a dose of 40 mg/m^2 compared to 20 mg/m^2, concurrent with radiotherapy for 6 cycles.[28] Complete responses were found in 69/70 (98.6%) and 68/70 (97.1%) respectively, with no significant difference. Acute toxicities in the first group was significantly higher when compared to the second group ($p < 0.05$). They concluded that their prospective trial had sufficient data to support the conclusion that concurrent chemoradiotherapy with weekly cisplatin 40 mg/m^2 in locally advanced cervical cancer gives good treatment outcomes. Similar results was found in present study, complete response in 24/25 (96%) patient in weekly arm and 21/25 (84%) in tri-weekly arm ($p =0.15$).

Ryu et al reported no statistically significant difference in

the local control/recurrence of the disease and progression free survival in the two arms, but there was a significant improvement in the 5 year survival rate.[14]

CONCLUSION

This study showed that both weekly cisplatin 35mg/m^2 and tri-weekly 75mg/m^2 concurrent with radiation are equally feasible and efficacious.

The compliance of chemotherapy cycles is statistically significant in tri-weekly arm. Overall Treatment Time (OTT) is not statistically significant. Clinical response at the end of completion of treatment and after months of follow-up had equivalent results.

With relatively easier dosage schedule, a better compliance can be expected in the tri-weekly arm, although there was no statistically significantly significant difference between the two arms.

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