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Original Article

Randomised Clinical Trial of Weekly vs. Triweekly Cisplatin Based Chemotherapy Concurrent with Radiotherapy in the Treatment of Locally Advanced Cervical Cancer

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ABSTRACT
Cervical cancer is the most common malignancy in women. The standard treatment for locally advanced surgically inoperable case is cisplatin based chemo-radiation as cisplatin is a better radio-sensitizer in comparison to 5FU. Weekly cisplatin 40mg/m2 chemotherapy is currently considered the standard regimen in locally advanced cervical cancer. Two Arms of patients (41 in each) suffering from carcinoma cervix were studied for their compliance & toxicity to the regimens of weekly cisplatin 40mg/m2 with concurrent radiation and tri-weekly cisplatin 75mg/m2 with concurrent radiation. The toxicities like haematological, gastrointestinal and dermatological and the response were compared. It is observed that the three weekly cisplatin 75mg/m2 chemotherapy concurrent with radiotherapy may be more effective and feasible and has comparable outcome with weekly cisplatin 40mg/m2 chemotherapy which is currently considered the standard regimen in locally advanced cervical cancer. The response may be due to higher peak concentration of cisplatin enhancing the synergy of chemo-radiation.

Keywords-*cancer cervix, weekly vs tri-weekly cisplatin with concurrent radiation.*

Introduction

Cervical carcinoma is one of the most common gynaecologic cancer worldwide, and remains the third most common malignancy in women with 233000 deaths every year out of 500000 sufferings per year globally[1]. The current standard treatment for locally advanced surgically inoperable case is cisplatin based chemo-radiation because of its convenience, equal effectiveness and favourable

toxicity in comparison with other 5–FU combined regimens. On the basis of five randomized trials, which consistently showed improved survival in patients treated with cisplatin based chemo-radiation, the US National Cancer Institute 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[2-5]. Sang-Young Ryu, Won-Moo Lee et al[12] are undertaking trials using a weekly cisplatin and tri-weekly cisplatin with concurrent radiation and observed tri-weekly cisplatin with concurrent radiation as more effective and feasible compared to conventional weekly cisplatin with concurrent radiation. The present study is primarily aimed at comparing the response and acute toxicity and secondarily to compare the compliance between tri-weekly cisplatin 75 mg/m2 and weekly cisplatin 40mg/m2 and with concurrent radiation in female patients with cancer cervix who presented in a Regional Cancer Centre.

Material & Methods

Eighty two (82) eligible patients of locally advanced cervical cancer who attended a Regional Cancer Centre, for treatment from December 2013 to November 2015, were included in this study after obtaining written informed consent and biopsy confirmation of the Cervical Cancer and its staging. The eligibility criteria taken were age between 20 to 70 with histologically proven invasive squamous cell carcinoma cervix from stage IIB to stage IVA as per the staging system of International Federation of Gynaecologic & Obstetric (FIGO). The patients were evaluated both by Gynaecology Oncologist and Radiation Oncologist before treatment. The ECOG performance status of 0 to 2 with adequate hematologic function of absolute neutrophil count of > 1500/ml, platelet >1,00,000/ml, calculated creatinine clearance >60ml/min and hepatic function with bilirubin < 1.5 times of normal, alkaline phosphatise and aspartate aminotransferase < 3 times normal were included in trial. The patients with previous history of other malignancies, previous chemotherapy or radiation therapy, pregnancy, serious co-morbid conditions like hypertension, diabetes, and patients with stage IVB disease with distant metastases were excluded from study. All the patients were divided to two Arms. In Arm A tri-weekly Cisplatin 75 mg/m2 for three cycles and in Arm B weekly Cisplatin 40 mg/m2 were given for five cycles. In both Arms external beam radiation of 50 Gray in 25 fractions to the whole pelvis using the mega voltage tele-cobalt machine followed by intra-cavity brachytherapy in the dose of 21Gray in 3 fractions to point A, using HDR brachytherapy. All the patients were evaluated for toxicity every week according to Radiation Therapy Oncology Group (RTOG) toxicity grading system. The response to treatment was evaluated at six, twelve and twenty four weeks interval after completion of treatment.

Results

In both the Arms of study maximum number of patients were in 41 to 50 years. The Eastern Cooperative Oncology Group (ECOG) status, distribution of stages of patients, the overall treatment time, completion of chemotherapy cycles are shown in Table 1.

Table. No 1 Profile of patients

Sl No	Parameters	Arm A Tri weekly	Arm B Weekly
1	Age distribution		
	<20years	0	0
	20 years to 30 years	3 (7.32%)	2(4.88%)
	31 years to 40 years	6 (14.63%)	6 (14.63%)
	41 years to 50 years	21 (51.22%)	22 (51.22%)
	51 years to 60 years	11 (26.83%)	11 (26.83%)
	61 years to 70 years	0	0
2	Performance status		
	ECOG 1	41 (100%)	29 (70.73%)
	ECOG 2	0	12 (29.27%)
3	Stages		
	Stage IIB	21 (51.22 %)	12 (29.27%)
	Stage IIIA	2 (4.88%)	3 (7.32 %)
	Stage IIIB	18 (43.90 %)	26 (63.41 %)
	Stage IVA	0	0

The response of the patient to the drugs was observed at 6, 12 and 24 weeks interval after completion of treatment are shown in table No.2

Table. No 2 Response of the patient

Sl No	Parameters	Arm A Tri weekly	Arm B Weekly
1	Response at 6 weeks		
	Complete response	39 (95.12%)	36(87.8%)
	Partial response	2 (4.87%)	5(12.20%)
	Stable disease	0	0
	Progressive disease	0	0
2	Response at 12 weeks		
	Complete response	39 (95.12%)	36(87.8%)
	Partial response	2 (4.87%)	5(12.20%)
	Stable disease	0	0
	Progressive disease	0	0
3	Response at 24 weeks		
	Complete response	39 (95.12%)	36(87.8%)
	Partial response	2 (4.87%)	5(12.20%)
	Stable disease	0	0
	Progressive disease	0	0

In both the Arms of studies the different toxicity found were mostly haematological like anaemia, leucopenia, neutropenia and gastrointestinal like nausea, vomiting, diarrhoea. The percentage of this toxicity is shown in Table No.3.

Table. No 3 Toxicity

Grade	Type of toxicity	Arm A Tri weekly	Arm B Weekly
	Haematological Toxicities		
	Anaemia		
0	> 11 gm%	12 (29.27%)	03 (7.32%)
1	9.5 to 11 gm%	18 (43.90%)	18 (43.9%)
2	7.5 to 9.5 gm%	11 (26.83%)	18 (43.9%)
3	5 to 7.5 gm%	0	03 (7.32%)
	Neutropenia		
0	>1900/cmm	41 (100%)	39 (95.12%)
1	1500 to 1900/cmm	0	0
2	1000 to 1500 /cmm	0	2(4.88%)
3	500 to 1000/cmm	0	0
4	< 500/cmm	0	0
	Gastrointestinal toxicity		
	Nausea		
0	None	0	0
1	Reasonable intake	12 (29.27%)	09 (21.95%)
2	Decreased intake	26 (63.41%)	23 (56.09%)
3	No significant intake	03 (7.32%)	09 (21.95 %)
	Vomiting		
0	None	0	0
1	1 episode in 24 hr	18 (43.9%)	17 (41.46%)
2	2 to 5 in 24 hr	18 (43.9%)	18 (43.9%)
3	6 to 10 in 24 hr	05 (12.19%)	06 (14.63%)
4	> 10in 24 hr	0	0
	Diarrhoea		
0	No diarrhoea	35 (85.37%)	30 (73.17%)
1	2 to 3 stool /day	3 (7.32 %)	0
2	4 to 6 stools/day with cramp	3 (7.32 %)	9 (21.95%)
3	7 to 9 stools / day with incontinence	0	02(4.88%)
4	> 10 stools /day with cramp and blood	0	0
	Dermatological Toxicity		
0	No change	0	0
1	Dull erythema, Dry desquamation	21(51.22%)	21(51.22%)
2	Tender erythema, patchy moist desquamation	15(36.59%)	15(36.59%)
3	Confluent moist desquamation	05 (12.20%)	05 (12.20%)
4	Ulceration with huge necrosis	0	0

The compliance of patients in terms of overall treatment duration and completion of chemotherapy cycles is shown in Table 4.

Table No. 4 Compliance of patients

Sl No.	Compliance	Arm A Tri weekly	Arm B Weekly
1	Overall treatment duration		
	9 weeks	33 (80.91 %)	18 (43.90 %)
	10 weeks	8 (19.51 %)	9 (21.95 %)
	11 weeks	0	14 (34.15 %)
	12 weeks	0	0
2	Completion of chemotherapy cycles		
	2 cycles	2 (4.88%)	6 (14.63 %)
	3 cycles	39 (95.12 %)	9 (21.95 %)
	4 cycles	0	12 (29.27 %)
	5 cycles	0	14 (34.15 %)

Discussion

The study was designed to compare the response, toxicity and compliance between two cisplatin based regimens of weekly cisplatin 40mg/m2 and tri-weekly cisplatin 75mg/m2 in a single institution trial. The role of 5 FU as radio-sensitiser was debatable and despite the diversity and heterogeneity in cisplatin dose, cisplatin 40mg/m2 is widely accepted[2-8]. In the present study 82 number of patients were analysed who attended a Regional Cancer Centre, during the period of December 2013 to November 2015.

It is observed that the three weekly cisplatin 75mg/m2 chemotherapy concurrent with radiotherapy is more effective, feasible and has comparable outcome with weekly cisplatin 40mg/m2 chemotherapy which is currently considered the standard regimen in locally advanced cervical cancer. It may be due to higher peak concentration of cisplatin enhancing the synergy of chemo-radiation because in the tri weekly regimen the third cycle of cisplatin is administered close to the

brachytherapy as compared to the weekly cisplatin exposure[9]. The third cycle of cisplatin was delivered on an average 3 to 4 days before brachytherapy and considering the fact that 25% of radiation dose is delivered during brachytherapy, it is deduced that the administration of cisplatin during or close to brachytherapy may be a reasonable way to increase the synergy of chemo-radiation where the cisplatin acts as a radio-sensitiser during brachytherapy.

Bonomi P, Blessing JA, Stehman FB, et al.[10] studied to reduce the cisplatin peak concentration and Mitsuhasi A, Uno T, Tanaka N et al [11] studied daily cisplatin along with radiation but did not show any enhanced survival.

In the tri-weekly group the complete response was 95.12 % and partial response was seen in 4.8 % compared to complete response of 87.8 % and partial response of 12.2 % in weekly cisplatin regimen. The tri-weekly group of patients had a better compliance in terms of completion of schedule with in time.

Major toxicities included anaemia, neutropenia, nausea, vomiting, diarrhoea and skin toxicity which were slightly less severe in tri-weekly regimen of cisplatin. No patient developed nephrotoxicity, neurotoxicity and ototoxicity. All the toxicities were well managed and there were no drop out or death.

The Grade 2, 3 and 4 toxicities were more frequently found in the weekly cisplatin group and there was little treatment delay in both the Arms which is also found by other study groups[12] High incidence of neutropenia in the weekly regimen was reported because of the shorter recovery time as compared to the tri-weekly regimen. However the adverse effect was well tolerated and manageable in both the Arms.

Conclusion

From our study it may be concluded that the tri weekly cisplatin 75mg/m2 concurrent with radiotherapy can be rather a better dose and dosing schedule to induce the synergy of chemo-radiation consistently with comparable toxicity as in weekly cisplatin 40mg/m2 concurrent with radiotherapy.

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