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Original Research Article

COMPARATIVE STUDY OF RADIOTHERAPY WITH CONCURRENT WEEKLY CISPLATIN VERSUS CONCURRENT WEEKLY PACLITAXEL IN CARCINOMA CERVIX

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ABSTRACT

Background: The aim is to compare the treatment response in carcinoma cervix and toxicity Profile in study group who are receiving weekly cisplatin versus weekly paclitaxel.

Materials and Methods: A Prospective, Randomized Study was taken up in the Dept. of Radiotherapy, for a period of 20 months. A total of 60 patients who satisfied the eligibility criteria were taken for the study

Results: The age range of the study population was 18 to 65 years with the median age of 50 years. All the patients were of Stage IB-IIIB. All the patients in the study were of squamous histology only 3.3% are adeno carcinoma. The cause of treatment delay was acute toxicity in 31.3% of patients in Group A and 20% of patients in Group B. In Cisplatin arm received 5 cycles of chemotherapy but in paclitaxel arm received 4 cycles of chemotherapy due to toxicity. The most common acute toxicity seen in paclitaxel arm was peripheral neuropathy (26.7%), anaphylaxis, anemia (66.7%), diarrhea (70%) and in Cisplatin arm was vomitings (50%). weekly Paclitaxel does not provide any clinical advantage over weekly Cisplatin for concurrent chemoradiation for advanced carcinoma cervix. No grade 4 toxicity was seen in either Group. After completion of study, loco regional control was seen in 93.4% patients in Cisplatin arm and 90% patients in Paclitaxel arm. Locoregional failure was seen in 6.6% patients in Cisplatin arm and 10 %patients in Paclitaxel arm.

Conclusion: weekly Paclitaxel does not provide any clinical advantage over weekly Cisplatin for concurrent chemoradiation for advanced carcinoma cervix.

Keywords: Chemo radiotherapy (CRT), Intensity Modulated Radiotherapy (IMRT), Image guide radiotherapy (IGRT), Intracavitary brachytherapy (ICBT).

INTRODUCTION

Cervical cancer is the fourth most frequent cancer in women with an estimated 5,70,000 new cases in 2018 representing 6.6% of all female cancers. approximately 90% of deaths from cervical cancer occurred in low and middle income countries. carcinoma of the uterine cervix is a major health problem faced by the Indian women and every year approximately 120,000 women develop this disease. India accounts for 15.2 percent of the total cervical cancer deaths in the world. Although The incidence of carcinoma cervix has declined in the urban population, in the rural areas it continues to be highly prevalent. Cervical particularly squamous cell carcinoma, is one of the most common cancers among Indian women, especially in the rural areas of India. Except for the very early cases, radiation therapy is the major curative treatment option for this disease Brachytherapy is an integral component in

any radiation therapy protocol forcervical cancer. Intracavitary brachytherapy (ICBT) is the most frequently performed.

In many developing countries cervical cancer remains major public health problem with high overall incidence and higher frequency of advanced stage of diagnosis. Radiation therapy remains the main treatment modality for patients with advanced cervical cancer the result of which depends on disease stage, tumour volume, haemoglobin level, presence of involved lymphnodes, delivered radiation dose, treatment duration, the optimal use of intracavitary brachytherapy. Involvement of para-aortic group of lymph nodes was reported to be most important adverse prognostic factor, reducing survival by one-half Outcome of these patients can be improved by the use of concurrent chemo radiotherapy.[1,2]

At present the integration of Radio sensitizing cisplatin-based chemotherapy with local treatment is considered the accepted standard in the management of carcinoma cervix. Despite the use of concurrent CTRT, many patients continue to fail in the pelvis (20-25%) and at distant sites (10-20%).[2,3] Cisplatin requires adequate hydration and it is not useful in renal failure patients. So in this study an attempt was made to study other concurrent combinations with potentially more clinical effect. Paclitaxel is a taxane chemotherapy drug that was found to have significant activity in squmous cell carcinoma of Head and Neck patients.

So in this study an attempt was made to test it in squamous cell carcinoma of cervix patients. Preclinical studies have shown a Radiosensitizing effect of paclitaxel in human cervical cancer cell lines.[4] This drug exerts a preferential cytotoxic activity in human cervical cancers with low raf -1 kinase activity which makes it desirable to be used in conjunction with radiotherapy.

MATERIALS AND METHODS

The comparative study was conducted at MNJ institute of oncology/RCC, Hyderabad. 30 cervical cancer patients posted for external beam therapy with weekly Paclitaxel as cases and 30cervical cancer patients posted for external beam therapy with concurrent weekly Cisplatin as controls will be taken for study for 24 Months.

Complete history and physical examination including punch biopsy from the cervical lesion. Complete blood picture, renal function tests and liver function tests. Chest x-ray PA view. Ultrasound of the abdomen and pelvis. Any other investigation as and when needed. 30 cervical cancer patients posted for external beam therapy with weekly Paclitaxel as cases and 30cervical cancer patients posted for external beam therapy with concurrent weekly Cisplatin as controls will be taken for study For 24 Months. Informed consent from study group.

Inclusion Criteria

Aged 18-65 years carcinoma cervix patients stages IB to IIIB FIGO stages. 4. ECOG Criteria 1&2. 5. Adequate baseline haematological, hepatic and renal functions like Hb-10gm%; serum creatinine: less than 1.5mg/dl; serum bilirubin: less than1.5 gm/dl, histopathalogically confirmed carcinoma cervix squamous cell carcinoma.

Exclusion Criteria

ECOG Criteria more than 2, pregnant and nursing mothers, FIGO staging 1 A, stage lV, active uncontrolled tuberculosis /other comorbidities which precludes the use of Radiotherapy and chemotherapy, Uncontrolled Diabetes/Hypertension, HIV/ HBSAG positive, Metastatic disease at presentation, unfit for concurrent chemoradiation.

After patients signed the consent form, they were randomized into either Group A or Group B by Simple Randomization.

Group A – Concurrent chemo-radiation using PACLITAXEL as weekly chemotherapy. Group B – Concurrent chemo-radiation using CISPLATIN as weekly chemotherapy. Treatment plan:

Patients in both the groups were treated with a total dose of 50 Gy in 25 fractions, 2 Gy per fraction for 5 days a week along with concurrent chemotherapy, injection cisplatin i.v. 40 mg per m2 for GROUP A and injection paclitaxel 50mg/ m2 for GROUP B followed by brachytherapy, 3 fraction 7Gy per week.

Treatment Monitoring: Hydration, protein and caloric intake and hygiene were adequately maintained for all the patients during the entire treatment course. Haemogram and biochemical investigation was done and noted before giving chemotherapy. All patients were examined once weekly during the treatment. The clinical appearance of the primary tumour and at the initiation of treatment was noted. The regression of primary tumour during the treatment was assessed and noted weekly. Any delay causing treatment interruption was noted and necessary gap correction for radiotherapy was done. Patient completing the complete schedule of radiotherapy irrespective of the delay and receiving chemotherapy were evaluated for response and assessed for intracavitarybrachytherapy (ICBT) feasibility.1st fraction of High dose rate (HDR) intracavitary brachytherapy was given immediately after completing external beam radiation 7Gy per fraction in total 3 fractions with a week gap between each fraction. Patients not fit for HDR-ICBT due to central residue were boosted by lateral portals up to 66Gy and those of them with parametrial residue were boosted to 60Gy with midline block.

Technique of High Dose Rate Intracavitary brachytherapy.

Preparation of the patient: Patient is explained the entire procedure and consent taken. They are admitted the day before the procedure and kept nil per orally from 10 pm of the previous night onwards and given 2 tablets of dulcolax before going to sleep. Anxious patients are given 0.25mg alprazolam 1 hour

before sleep. On the morning of the procedure part preparation is done and a soap water enema is given before taking up the patient into the operating room.

Brachytherapy planning: DRR (Digitally reconstructed radiograph) is acquired and bladder line and rectal line are drawn for reference. Dwell points are prescribed along the central tandem and ovoids and and dose of around 700cGy to Point A (a point 2cm lateral to the centre of the uterine canal and 2cm above the mucous membrane of lateral fornix of the vagina in the plane of uterus) is prescribed. Point doses along the bladder and rectal line are seen along the dwell points and dwell point optimization is done in case of any excess point dose to the bladder or rectum. If the excess point dose is not corrected with dwell point optimization repacking is done. Pear shaped dose distribution is typically obtained and any dose below 650cGy and more than 750cGy to Point A is not accepted.

Assessment of toxicity: The acute toxicity was assessed using RTOG acute toxicity criteria weekly during treatment and at 6 weeks and 3 months after completion of the treatment Chemotherapy induced toxicity like nausea, vomiting, haematological and other toxicities were assessed as per the Common Terminology Criteria for Adverse Events (CTCAE).

Statistical Analysis: The information collected regarding all the selected cases was recorded in a Master Chart. Data analysis was done with the help of computer using MS-Excel, SPSS 22.0 (Trail version). Using this software, frequencies, percentage, range, mean, standard deviation. Student t 'test and p 'values were calculated. A p 'value & lt; 0.05 is shown to have significant relationship. Terms used for Statistical significance NS: not significant, S: significant

HS: highly significant.

RESULTS

Sixty patients met the eligible criteria and were enrolled. thirty patients were randomized to the cisplatin arm and thirty patients were randomized to paclitaxel arm. Age distribution given in the [Table 1]. That is distributed almost eqally in both groups, with P- value 0.45 (>0.05) not significant.

Table 1: Age distribution among cisplatin versus paclitaxel.

Age (in years)	Cisplatin		Paclitaxel	
	Frequency	Percent	Frequency	Percent
> 40	4	13.3%	9	30%
40 - 50	12	40%	10	33.4%
50 - 60	10	33.4%	7	23.3%
60 - 70	4	13.3%	4	13.3%
Total	30	100.0%	30	100.0%
chi-sqare test value = 2.634; p-value= 0.45 (>0.05) ns				

FIGO STAGE Distribution in both arms from IB to IIIB. In both arm stage distributed equally with P –value 0.996 (>0.05). various stages distribution given in [Table 2] below.

Table 2: FIGO and Histological staging distribution among cisplatin versus paclitaxel.

FIGO Stages	Cisplatin	Paclitaxel
IB	4 (13.3%)	4 (13.3%)
IIB	12 (40%)	13 (43.3%)
IIIB	4 (13.3%)	3 (10%)
IIA	7 (23.4%)	7 (23.4%)
IIIA	3 (10%)	3 (10%)
TOTAL	30 (100%)	30 (100%)
chi-sqare test value = 0.183; p-value= >0.05 NS		
Histological staging		
LCNKSCC	20 (66.8%)	20 (66.8%)
NKSCC	7 (23.3%)	7 (23.3%)
KSCC	2 (6.6%)	2 (6.6%)
ADENO CA	1 (3.3%)	1 (3.3%)
chi-sqare test value = 0.131; p-value= >0.05 NS		

In our study most of the patients are sqamous cell carcinoma. Distributed equally in both groups. only 3.3% in both arms are adeno carcinoma. Anaphylaxis only seen in paclitaxel arm because it is a plant alkaloid.

Table 3: Side effects distribution among cisplatin versus paclitaxel

Anaphylaxis	Cisplatin	Paclitaxel
Absent	30 (100%)	25 (83.3%)
Present	0	5 (16.7%)
chi-sqare test value = 0.543; p-value= >0.05 ns		
Peripheral Neuropathy		
Absent	30 (100%)	22 (73.3%)
Present	0	5 (16.7%)
Mild	0	3 (10%)

chi-sqare test value = 0.431; p-value= >0.05 ns		
Neutropenia		
Absent	29 (96.7%)	28 (93.4%)
Present	1 (3.3%)	2 (6.6%)
Total	30 (100%)	30 (100%)
chi-sqare test value = 0.351; p-value= >0.05 ns		
Anemia		
Absent	13 (43.3%)	10 (33.3%)
Grade 1	11 (36.7%)	12 (40%)
Grade 2	6 (20%)	8 (26.7%)
Total	30 (100%)	30 (100%)
chi-sqare test value = 0.720; p-value= >0.05 ns		
Diarrhea		
Absent	17 (56.8%)	9 (30%)
Present	0	1 (3.3%)
Grade 1	11 (36.6%)	11 (36.8%)
Grade 2	2 (6.6%)	8 (26.6%)
Grade 3	0	1 (3.3%)
chi-sqare test value = 0.320; p-value= >0.05 ns		
Abdominal Pain		
Absent	17 (56.7%)	14 (46.8%)
Grade 1	12 (40%)	13 (43.3%)
Grade 2	1 (3.3%)	2 (6.6%)
Grade 3	0	1 (3.3%)
chi-sqare test value = 0.543; p-value= >0.05 ns		
Cystitis/Burning Micturition		
Absent	19 (63.4%)	15 (50%)
Grade 1	7 (23.3%)	13 (43.4%)
Grade 2	4 (13.3%)	1 (3.3%)
Low Uo	0	1 (3.3%)
Fever		
Absent	15 (50%)	20 (66.7%)
Mild	15 (50%)	10 (33.3%)
Chi-Sqare Test Value = 1.714; P-Value= >0.05 Ns		
Vomiting		
Absent	15 (50%)	18(60%)
Grade 1	13 (43.4%)	12 (40%)
Grade 2	2 (6.6%)	0%
chi-sqare test value = 0.072; p-value= >0.05 ns		

No patient in either group p value when compared in both groups was statistically insignificant.

Table 4: Local control distribution among cisplatin versus paclitaxel

Local Control	Cisplatin	Paclitaxel
No	2 (6.6%)	3 (10%)
Yes	28 (93.4%)	27 (90%)
Total	30 (100%)	30 (100%)
chi-sqare test value = 0.218; p-value= 0.64 (>0.05) ns		

Loco regional Control was seen in 28 patients (93.4%) in CISPLATIN arm and 27 patients (90%) in PACLITAXEL arm. 2 patients (6.6%) in cisplatin arm and 3 patients (10%) in paclitaxel arm developed local failure, with P value 0.64 that is statistically not significant.

DISCUSSION

In present study age range of patients in both arms was 18-65 years. with a median age of 50 years and in Group B it was 32-63 years with a median age of 50 years. This is in accordance with data from cancer registries in developing countries which suggest that about 80 to 90 percent of confirmed cervical cancers cases occur among women age 35 year or older because cervical cancer progresses slowly from precancerous condition to advanced cancer, the incidence of cancer is very low in women under the age of 25. Incidence increases at about ages 35to 40 and reaches a maximum in women in their 50s and 60 All the 60 cases of cervical cancer taken up for the study were of squamouscell carcinoma histology. Except for one patient is adeno carcinoma. The most common tumour morphology that was seen was exophytic type. All the patients in both the groups received concurrent chemoradiation. This is in compliance with NCI alert in 1999. The alert was issued following the five landmark trials: Keys et al,[5] Morris et al,[6] Rose et al,[7] 1999; Whitney et al,[8] 1999; Peters et al,[9] 2000.

All patients received chemotherapy in the form of Inj. Cisplatin at a dose of 40 mg/m2 prior to EBRT every week. Rose et al,[7] reported the results of GOG-120 trial in which a course of standard pelvic radiotherapy was combined with one of the three concurrent chemotherapy regimens – (i) cisplatin alone (40 mg / m2 weekly), (ii) cisplatin (50 mg/m2 on days 1 and

29) plus 5-FU (4 g /m2 as 96 hours infusion on days 1 and 29) plus hydroxyurea (2 g/m2 orally twice weekly), or (iii) hydroxyurea alone (3 g/m2 orally twice weekly) in patients with FIGO II B to IVA cervical carcinoma. At a median follow up of 35 months, survival curves for the two cisplatin groups were almost identical and both were statistically superior to the survival curve of the hydroxyurea alone group. However toxicities were much more in the combined drug arms than in the cisplatin alone arm.

In 1999 Keys et al,[5] reported the results of the GOG-123 study in which 369patients with bulky stage IB disease and without any evidence of para aortic lymph node metastasis was randomized between weekly cisplatin (40 mg/m2) and radiation versus radiation only. Patients underwent hysterectomy 3 – 6 weeks after completion of radiation. At a median follow up of 36 months, local recurrence and distal metastasis rates were 9% and 21% and 12% and 16% respectively, both in favour of concomitant arm. At a median follow up of 36 months, local recurrence and distal metastasis rates were 9% and 21% and 12% and 16% respectively both in favour of concomitant arm. These trials proved that single agent Cisplatin is as efficacious as a triple drug combination therapy with reduced toxicity. There have been controversies about the optimum timing of Cisplatin administration in relation to radiation treatment. Pre- clinical data suggests enhanced tumour response by a factor of 1.7 when Cisplatin was administered at least thirty minutes prior to radiation treatment. Pearcey and Maclean,[10] have extrapolated that in terms of tumour cell kill, Cisplatin appropriately synchronized with radiation would be equivalent to a ten percent increase in radiation dose, which would theoretically improve local control Cisplatin is one of the most active cytotoxic agents in squamous cell carcinoma of the uterine cervix. When cisplatin and irradiation are used concomitantly, substantial enhancement of cell killing is observed. Green et al,[11] did a Cochrane review including twenty four trials (21 published, 3 unpublished) and 4921 patients.

The review strongly suggested that chemo radiation improves overall survival and progression free survival, with absolute benefits of 10% and 13% respectively. There was some evidence that the effect was greater in trials including a high proportion of stage I and II patients. Chemo radiation also showed significant benefit for local recurrence and a suggestion of a benefit for distant recurrence. Acute haematological and gastrointestinal toxicity was significantly greater in the concomitant chemo radiation group. Late effects of treatment were not well reported and so the impact of chemo radiation on these effects could not be determined adequately.

In our study, cisplatin arm received 5 cycles weekly chemotherapy compared to in paclitaxel arm received 4 cycles chemotherapy due to toxicity. The 5th cycle was omitted due to toxicity in paclitaxel arm. Almost all patients in both the groups completed treatment (EBRT and ICRT) in eight weeks (≤56 days). The gap between EBRT & ICRT was seven days or less in all the patients who completed the treatment. ICRT was given at a dose of 7 Gy per fraction for 3 fractions, once every week, specified at point A, dose varying depending upon the bladder and rectum doses. The American Brachytherapy Society recommendation for HDR brachytherapy is a schedule of 5-6 Gy for five fractions, specified at point A. In comparison to developed countries, developing countries have a higher incidence of cervical cancer. So using more fractions for treatment increases the burden on health care system. It increases the duration of treatment and adversely affects the local control of tumor while adding to cost.

A trial done by Bahena et al,[12] concluded that the use of three fractions, once per week, allowed inclusion of greater number of patients during the life span of Iridium-192 source, there by decreasing the cost of treatment. In addition the three fractions were safe and effective in the management of patients with locally advanced cervical cancer. Treatment related toxicity we observed are anaphylaxis, anaemia, peripheral neuropathy, vomiting, fever, abdominal pain, cystitis, nuetropenia, diarrhea. in above toxicity profile anaphylaxis and peripheral neuropathy is specific to paclitaxel.

To prevent anaphylaxis we added inj Hydrocortisone 100mg i/v start and inj. AVIL 1 ampule i/v start before paclitaxel injections .in case after injection of premedication also patient develops anaphylactic reaction stop the drug temporarly, one more Hydrocortisone 100mg given again started the infusion .most of the time anaphylaxis appeared in first cycle of paclitaxel injection.

Peripheral neuropathy is seen in only Paclitaxel arm to prevent that we give prophylactic vit B12 tablets and vit E. If patient is symptomatic during radiotherapy Tablet pregabalin given. anemia most common in paclitaxel arm compared to cisplatin arm but that is not statistically significant. If hemoglobin less than 8 gm/dl we transfuse blood. Every week before chemotherapy asses the general condition with CBP,RFT,LFT. Neutropenia seen in both cisplatin and paclitaxel arm (3.3% vs 6.6%) but this is not statistically significant (p>0.05). In our patient wont develop severe neutropenia. If patient develops neutropenia graded and treated with G-CSF.

Vomiting seen both the groups, seen more in cisplatin arm but this also not significant (p>0.05). Anti emetics added in chemotherapy schedule to prevent vomiting and nausea. In our study we used 5HT-3 receptor antagonist. fever is more common in cisplatin arm compare to paclitaxel arm (50% vs 33.3%) but this is not significant(p>0.05). Fever is treated by symptomatic management. If patient develops infections added antibiotics.

Abdominal pain more common in cisplatin arm but more severe in paclitaxel arm if it is present. Diarrhea most common in paclitaxel arm compared to cisplatin arm. Diarrhea mostly seen paclitaxel arm and greater severity in paclitaxel arm. Treated sympamatically if

required we added antibiotics especially to cover anaerobes. cystitis more common in cisplatin arm compared to paclitaxel arm. Every patient we advised drink plenty of water and maintain good personal hygiene. Treated symptomatically. There was no significant difference between both the groups but overall the number of patients having acute upper gastrointestinal toxicity in the form of nausea and vomiting was very high. Also, grade 2 toxicity was seen from the first week of treatment in some patients in both the groups. Though all the patients were counselled about chemotherapy, the anti-emetic medication compliance was not good. Few patients were not taking anti-emetics properly. Either they missed their dose or took only half of what was prescribed. This led to decrease in oral intake which decreased the overall performance status of the patient.

This comparative study provides a direct comparison between cisplatin and paclitaxel used as weekly concurrent chemotherapy with definitive radiation for advanced carcinoma of the cervix. Our data indicate that the local response rates with the use of paclitaxel, which is the experimental arm, are not superior to those with cisplatin. In fact, there were non-significant trends higher gastrointestinal toxicity, and more allergic reactions in the concurrent paclitaxel group. Taken together, these results indicate that paclitaxel does not provide any clinical advantage over the current standard of concurrent cisplatin in CTRT for patients with advanced cervical carcinoma. Although many prospective studies had shown that CTRT with cisplatin-based chemotherapy clearly improve the outcome of patients with carcinoma of the cervix, many patients treated on these protocols continue to fail in the pelvis and at distant sites.[6,16,22,23] In addition, one intergroup study using weekly concurrent cisplatin with radiotherapy for patients with carcinoma of the cervix could not demonstrate a beneficial effect of CTRT over standard RT alone.[13] This non-superiority finding was attributed to many factors like possible enrollment of patients with para aortic lymph nodes, and an imbalance among randomization groups for known prognostic factors such as anemia.[14] These facts have lead many groups to investigate other drugs for CTRT like paclitaxel in an attempt to improve on what can be achieved by concurrent cisplatin.[15] In all these studies paclitaxel was used in conjunction with either cisplatin (4/7 studies) or carboplatin (3/7 studies) but was never used alone for CTRT. The majority of these studies was phase I (4/7 studies), with one study being a combined phase I/II study conducted by the GOG. The number of patients enrolled in these studies varied between 8 and 35 patients and the rates of progression free survival ranged between 39 and 88%.

The dose limiting toxicity was primarily neutropenia in 4 studies,[17] or diarrhea. In our comparative study reported here, we enrolled 60 patients and local control was 93.4% for the cisplatin arm and 90% for the paclitaxel arm with severe grade III diarrhea being the most common toxicity in paclitaxel arm. These data are in agreement with what other groups have reported and do not suggest that paclitaxel provides any advantage in out-come or toxicity over the current standard using cisplatin. This finding is in line with what was found in a larger study by the GOG which also compared concurrent single agent CTRT consisting of either weekly cisplatin or protracted 5-fluorouracil (5-Fu) infusion. The results of that study showed no superiority of the experimental 5-Fu arm and the study was prematurely closed.

There are many studies that investigated other experimental protocols for concurrent CTRT in advanced carcinoma of the cervix using various chemotherapy regimens such as 5-Fu, epirubicin, 5-Fu with mitomycin C, hydroxyurea, gemcitabine, carboplatin, tirapazamine, topotecan, or vinorelbine.[18] Few of these drugs were tested in randomized trials like 5-Fu, epirubicin, hydroxyurea, mitomycin and gemcitabine, as single agents or in combination.[19] Others have only been tested in phase I/II studies and some of them have shown promising results. Perhaps the most promising and most studied drugs of this group are gemcitabine, tirapazamine, and topotecan. In a phase II randomized study by Dueñas-Gonzalez et al,[20] patients with stage IB2-IIB disease were randomized to cisplatin or cisplatin plus gemcitabine and concurrent radiation therapy, followed by radical hysterectomy 4 weeks later. The complete pathologic response rate was higher in the cisplatin plus gemcitabine arm compared to the cisplatin alone arm (75% vs. 55%, respectively; p = 0.02), but gastrointestinal and hematologic toxicities were significantly lower in the cisplatin-alone arm.

A phase III randomized trial testing this combination for definitive CTRT in stages IIB to IVA disease, has completed accrual but results are not yet available. Similarly, encouraging results have been obtained in phase I studies using cisplatin- combination CTRT with either topotecan or tirapazamine.[21] Several phase I/II studies are currently investigating the combination cisplatin- topotecan and GOG trial 0219 is testing the added value of tirapazamine to cisplatin for CTRT in carcinoma of the cervix.

The rate of gastrointestinal (GI) toxicity in our study manifesting as severe diarrhea, was high in both arms although slightly higher in the paclitaxel arm. In addition there were more severe allergic reactions in the paclitaxel arm and in 2 patients, chemotherapy had to be discontinued due to the severity of these allergic reactions, and in general, more chemotherapy delays were encountered in this group. It is difficult to compare this toxicity pattern with other studies from the literature, because none of these studies used either paclitaxel or cisplatin alone for CTRT, instead they used both drugs in combination with various dose-administration schedules. However, one could note that in at least 3 of the phase I studies that included paclitaxel, severe diarrhea was the limiting toxicity which agrees with our findings.[22] It is of

concern that this difference in toxicity between our treatment groups with the disruption and delays in chemotherapy delivery in paclitaxel arm. In our study we follow up the patient up to 16 to 18 months, in this period we didn't find any systemic metastasis. However, because of the small size of the study it was not possible to fully evaluate the influence of these factors either separately or all combined. Taken as individual studies, data from the various CTRT trials have not consistently shown a reduction in distant metastases (DM) in patients receiving systemic chemotherapy when it was primarily given as a radiosensitizer.[13] However, when these data were analyzed together, two metaanalyses found a positive effect of concurrent CTRT on distant recurrence.[11]

Among the studies that used platinum-based chemotherapy, only the radiation therapy and oncology group (RTOG) 90-01 study showed a significant effect of CT on the reduction of DM at both 5 and 8 years of follow-up.[23] It is of interest to note, that in that study, chemotherapy was given as full cycles of cisplatin and 5-Fu during the course of RT, and the dose of cisplatin was highest compared to what was used in the other studies (75mg/m2 vs. 60, 50, or 40 mg/m2).Among the studies with non cisplatin-based chemotherapy, only the study reported by Wong et al,[24] showed a significant impact on DM. In that trial, CT consisted of epirubicin as a single agent for concurrent CTRT followed by adjuvant therapy with the same drug for 5 cycles. It remains unclear what are the key factors that made the experimental arm in these two particular studies effective against DM. One could speculate that the delivery of full cycle and higher doses of chemotherapy, and/or the use of planned adjuvant chemotherapy could, in theory, better address the risk of systemic recurrence. However, this remains speculative until it is demonstrated in controlled randomized studies, and unfortunately, to our knowledge, there are no such studies currently in progress.

The only available information comes from retrospective studies and there are some which critically examined this question and reported similar findings. In a single institution study, Kim et al,[25] reported a comparison between 2 well balanced groups of patients with stage IB-II carcinoma of the cervix who were treated by concurrent CTRT with or without 3 additional cycles of adjuvant platinum (cisplatin or carboplatin)-5Fu chemotherapy. The authors found no effect of adjuvant chemotherapy on the incidence of distant metastases or distant nodal relapses. They also found that adjuvant chemotherapy was relatively difficult to complete, with only 63% of the patients receiving all 3 cycles, and those in the adjuvant group experienced a higher rate of late grade III-IV rectal complications. Similar results were published by Lee et al,[15] on patients receiving adjuvant CTRT after radical hysterectomy and treated either by 3 additional cycles of cisplatin-5Fu or no additional therapy. Although these two studies are not prospective or randomized trials, they still indicate that the routine use of adjuvant cisplatin-based chemotherapy may not be the best approach to address the risk of distant relapse in this patient population.

In summary, these data show that concurrent chemo radiation for advanced cervical cancer using weekly paclitaxel was not superior to concurrent cisplatin and was possibly associated with more severe gastrointestinal toxicity and more allergic reactions. Local tumour control was equivalent with both drugs with little increased Toxicity on paclitaxel arm.

CONCLUSION

Concurrent weekly cisplatin routinely used in carcinoma cervix along with radiation. Concurrent weekly Paclitaxel used when Cisplatin is contraindicated. we randomized the patients to two groups to compare the local control and toxicity profile in both arms .From our study, we conclude that weekly Paclitaxel does not provide any clinical advantage over weekly Cisplatin for concurrent chemoradiation for advanced carcinoma cervix. But we consider Paclitaxel as concurrent weekly chemotherapy when Cisplatin is contraindicated.

REFERENCES

1. Einhorn N, Trope C, Ridderheim M, et al: A systematic overview of radiation therapy effects in cervical cancer (cervix uteri). Acta Oncol 2003, 42(5-6):546-56.
2. Kumar JV, Doval DC, Rao R, Rawal S: A retrospective study of patients with locally advanced cancer of the cervix treated with neoadjuvantchemotherapy followed by radical surgery. Int J Gynecol Cancer 2009,19(3):417-22.
3. Park DC, Suh MJ, Yeo SG: Neoadjuvant paclitaxel and cisplatin in uterine cervical cancer: long-term results. Int J Gynecol Cancer 2009, 19(5):943-7.
4. Strauss GM, Herndon J, Maddaus MA, et al: Randomized clinical trial of adjuvant chemotherapy with paclitaxel and carboplatin following resection in Stage IB non-small cell lung cancer (NSCLC): Report of Cancer and Leukemia Group B (CALGB) Protocol 9633. Proc Am Soc Clin Oncol 2004, 23:619, abstract no. 7019.
5. Keys HM, Bundy BN, Stehman FB, et al: Cisplatin, radiation and adjuvanthysterectomy compared with radiation and adjuvant hysterectomy for Bulky stage IB cervical carcinoma. N Engl J Med 1999, 340:1154-61.
6. Morris M, Eifel PJ, Lu J, et al: Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high- risk cervical cancer. N Engl J Med 1999, 340:1137-43.
7. Rose PG, Bundy BN, Watkins EB, et al: Concurrent Cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 1999, 340:1144-53.
8. Whitney CW, Sause W, Bundy BN, et al: Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. J Clin Oncol 1999, 17(5):1339-48.
9. Peters WA, Liu PY, Barrett RJ, et al: Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol 2000, 18(8):1606 13.
10. Pearcey R, Brundage M, Drouin P, et al: Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. J Clin Oncol 2002,20(4):966-72.

11. Green J, Kirwan J, Tierney J, et al: Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix. Cochrane Database Syst Rev 2005, 20(3).
12. Bahena JH et al. Spatial reproducibility of the ring and tendem high dose rate cervix applicatior. Int J Radiat Oncol Biol Phys. 1998:41 , 13-9.
13. Pearcey R, Brundage M, Drouin P, et al: Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. J Clin Oncol 2002,20(4):966-72
14. Rose PG, Bundy BN: Chemoradiation for Locally Advanced Cervical Cancer: Does It Help? J Clin Oncol 2002, 20(4):891-893.
15. Lee MY, Wu HG, Kim K, et al: Concurrent radiotherapy with paclitaxel/carboplatin chemotherapy as a definitive treatment for squamous cell carcinoma of the uterine cervix. Gynecol Oncol 2007, 104(1):95-9.
16. Rao GG, Rogers P, Drake RD, et al: Phase I clinical trial of weekly paclitaxel, weekly carboplatin, and concurrent radiotherapy for primary cervical cancer. Gynecol Oncol 2005, 96(1):168-72.
17. Miglietta L, Franzone P, Centurioni MG, et al: A phase II trial with cisplatin- paclitaxel cytotoxic treatment and concurrent external and endocavitary radiation therapy in locally advanced or recurrent cervical cancer.Oncology 2006, 70(1):19-24.
18. Mundt AJ, Rotmensch J, Waggoner SE, et al: Phase I trial of concomitant vinorelbine, cisplatin, and pelvic irradiation in cervical carcinoma and other advanced pelvic malignancies. Gynecol Oncol 2004, 92:801-805.
19. Lanciano R, Calkins A, Bundy BN, et al: Randomized comparison of weekly cisplatin or protracted venous infusion of fluorouracil in combination with pelvic radiation in advanced cervix cancer: a gynecologic oncology group study. J Clin Oncol 2005, 23(33):8289-95.
20. Duenas-Gonzalez A, Cetina-Perez L, Lopez-Graniel C, et al: Pathologic response and toxicity assessment of chemoradiotherapy with cisplatin versus cisplatin plus gemcitabine in cervical cancer: a randomized phase II study. Int J Radiation Oncology Biol Phys 2005, 61:817-823.
21. Dunton CJ, King SA, Neufeld J, et al: Phase I study of topotecan and radiation therapy in advanced cervical cancer. Gynecol Oncol 2002, 85:185-188.
22. De Vos FY, Bos AM, Gietema JA, et al: Paclitaxel and carboplatin concurrent with radiotherapy for primary cervical cancer. Anticancer Res 2004, 24(1):345-8.
23. Eifel PJ, Winter K, Morris M, et al: Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01. J Clin Oncol 2004, 22(5):872- 80.
24. Wong LC, Ngan HYS, Cheung ANY, et al: Chemoradiation and adjuvant chemotherapy in cervical cancer. J Clin Oncol 1999, 17:2055-2060.
25. Kim YB, Cho JH, Keum KC, et al: Concurrent chemoradiotherapy followed by adjuvant chemotherapy in uterine cervical cancer patients with high-risk factors. Gynecol Oncol 2007, 104(1):58-63.