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A study on concurrent chemoradiation in the treatment of locally advanced cervical cancer

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ABSTRACT

Aim –
Comparing the immediate response obtained with cisplatin based concurrent chemotherapy and external beam radiation followed by branchytherapy against the against the immediate response obtained with conventional external beam followed by branchytherapy in locally advanced cancer cervix

Materials and Method –
This is prospective study conducted in 100 patients with locally advanced cancer cervix conducted between March 2013 to March 2014 in Institute of Obstetrics and Gynecology, Egmore. Patients were selected based upon the inclusion criteria and exclusion criteria.
They were randomized into two groups - The Trail group (Concurrent Chemo radiation) and the Trail Group (radiotherapy).

Results and conclusion
The patients who received concurrent chemoradiation and higher complete response (68%) Whereas among patients who were given radiotherapy alone 42% of them had complete response which is statistically significant. This results of concurrent chemoradiation reflect rays of hope in the treatment of patients with locally advanced cancer cervix

KEYWORDS Ca Cervix, Concurrent Chemo radiation, Cisplatin, Brachytherapy.

Introduction

Worldwide, carcinoma of the cervix is the second most common cancer in women, with an incidence of approximately 500,000 new cases each year and an annual death rate approaching 200,000; may of these women present with advanced-stage disease[1]. Global burden from cervical carcinoma accounts 6% of all malignancies in women thus remaining as one of the greatest killer worldwide. Despite the declining death rates in the US and also in other developed countries. Cervical cancer remains the leading cause of cancer death rates among women in countries like Africa, Asia, Latin America and Eastern Europe[2]. The highest incidences tend to occur in populations that have low screening rates combined with a high background prevalence of Human papilloma virus infection, relatively liberal attitudes toward sexual behavior.

The ability of radiotherapy to cure locally advanced cervical cancer is limited by the size of the tumor, because the doses required to treat large tumors exceed the limit of toxicity in normal tissue.[3] Efforts to overcome this problem have included the use of large-particle radiotherapy, the use of different radiation-fractionation schedules, and the concurrent use of hyperthermia or chemotherapy.

Theoretically, chemotherapy and radiotherapy could have a synergistic effect; for example, the chemotherapy might increase the sensitivity of the tumor to radiation. Moreover, radiotherapy could be used for local disease while chemotherapy is used for systemic disease. [4] Concurrent chemotherapy inhibits the repair of sublethal damage from radiation, synchronizes cells to a particularly radiosensitive phase of the cell cycle, and is cytotoxic in vitro.[5-7] The concurrent use of single-drug and multiple-drug regimens with radiotherapy has been tested in women with cervical cancer, but combination therapy has not gained wide acceptance.[8]

Pharmacology of cisplatin

CDDP- cis chlorodiamine platinum. Cisplatin is cell cycle nonspecific although the effects on cross linking are most pronounced during the S phase. Cisplatin is a cytotoxic agent whose main mode of action is formation of adducts with both nuclear and mitochondrial DNA. This drug is mainly cell cycle non-specific and can kill cells in all stages of the cell cycle but is more active in G1 phase cisplatin given before radiation causes an increase in the slope of dose response curve cisplatin inhibits sub lethal & potentially lethal damage repair.

Aim of the study

This study aims at comparing the immediate response obtained with cisplatin based concurrent chemotherapy and external beam radiation followed by branchytherapy against the against the immediate response obtained with conventional external beam followed by branchytherapy in locally advanced cancer cervix. This study also aims at comparing the acute toxicities involved with the above two combinations of therapeutic protocols.

Materials and method.

This is prospective study conducted in 100 patients with locally advanced cancer cervix conducted between March 2013 to March 2014 in Institute of Obstetrics and Gynecology, Egmore. Patients were selected based upon the inclusion criteria and exclusion criteria.

Inclusion criteria were
1) Age between 30-60 years
2) Disease stage IIb, IIIa, IIIb
3) Sqaumos cell carcinoma
4) Hemoglobin >9gm/dl and
5) Other normal hematological and renal parameters.

Exclusion Criteria
1) Stage with advanced disease of >IVa and <IIa
2) Patients with extra pelvic extension
3) Patients with treatment history of same cancer
4) Patients with past history of cardiac, renal and liver diseases

The patients were categorized randomly into to two groups the Trail arm group and Control arm group,

Trail arm (Chemo RT)
50 patients were treated with radiation, in addition these patients were given concurrent chemotherapy either with cisplatin and 5-

FU every 21 days or cisplatin 40mg/m2 every week for 6 cycles, beginning along with radiation.

Control arm (RT)
The other 50 patients received external beam radiation initially upto 50Gy in 25 fraction. This was followed by brachytherapy as ICCA. Patients received LDR ICCA delivered 7-10 days after EBRT a single fraction lasting 26-28hrs.

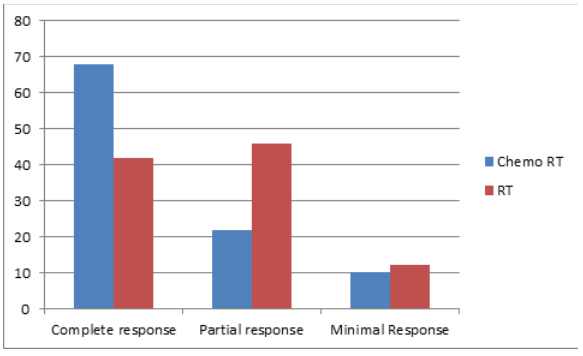
Chemotherapy protocol followed was : Weekly / 3weekly
Drug: Cisplatin and 5-FU as 3 weekly regimen
Dose: Cisplatin 75mg/m^2 and 5-FU 1000mg/m^2
Cisplatin 40mg/m^2 only as weekly regimen.
Schedule
3 weekly regimen
Some of these patients were randomized to 3 weekly protocol & they were given Cisplatin 40mg & 5-FU 500mg on day1 & 2 and Cisplatin 20mg with 5-FU 500mg on day 3 every 21 days and teletherapy was given on all the days along with chemotherapy.
Weekly regimen

Some patients were allotted to weekly protocol and given Cisplatin 40mg/m^2 every week and teletherapy was given on all the days along with chemotherapy.

Both regimes were continued as 6 cycles beginning along with radiation and completing as the end of external RT.

The response to treatment was graded as Complete response (No clinical or radiologically detectable lesion), Partial response (50% regression of measurable tumor), No response or minimal response (No change in tumor size, No growth of tumor size), Persistent disease (presence of original tumor or new tumor within 3 months of RT completion) and recurrence.

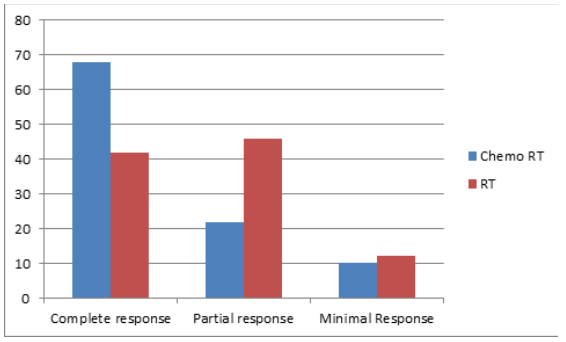
Results and Discussion
At the end of this study among patients who were grouped under the (Fig1) chemo radiation regime 68% of them had complete response and 22% of them had partial response and 10% of them had minimal response.



(Fig 1) Whereas among patients who were given radiotherapy alone 42% of them had complete response, 46% of them had partial response 12% of then had minimal response. This difference in response among the patients is statistically significant.

Patients in the trial group (chemo RT) had hematological toxicities which was in the range of 84, 54% of them had Grade I cystitis, 4% of them had Grade II cystitis, 44% of them had grade I proctitis and 12% of them had Grade II proctitis but no patient dropped out because of toxicities. They were tolerable and treatable symptomatically.

Fig 2



(Fig 2) Among patients who were randomized to weekly chemotherapy protocol with radiation 64.5% of them had complete response, 25.8% of them had partial response , 9.6% of them had minimal response.

(Fig 2) Among patients who were randomized to 3 weekly chemotherapy along with radiation 73.6% of them had complete response, 15.7% of them had partial response and 10.52% of them had minimal response and this difference did not give statistically significant results.

While assessing the other parameters, Most of the patients in both in the trial and control groups had Hemoglobin levels between 9-10gms%, and the response was also on the higher side in patients with Hemoglobin >11gms%.

Patients who had well differentiated squamous cell carcinoma in the chemo RT group had 80% complete response and in the RT group only 62.5% of them complete response.

Table 1

	Chemo RT	Complete Remission	RT	Complete Remission
Grading of Tumors (HPE)				
Well Differentiated	10	8 (80%)	8	5(62.5%)
Moderately Differentiated	23	18 (78.26%)	14	6(42.85%)
Poorly Differentiated	17	11 (64.70%)	28	10 (35.17%)
Parametrial Involvement				
Unilateral Involvement	13	9 (69.2)	18	8 (44.4%)
Bilateral Involvement	37	25 (67.56%)	32	13(40.6%)

(Table 1) Among patients who had moderately differentiated squamous cell carcinoma in chemo RT group 78.2% of them had complete response and 42.85% patients in RT group had complete response. In patients with poorly differentiated squamous cell carcinoma with chemo RT 64.7% had complete response and 35.17% of patients with RT gave complete response.

As far as the parametrial involvement was assessed patients who had an unilateral parametrial involvement in the chemo RT group were 69.25% of them had complete response, in the RT group 44.4% had complete response. Among patients with bilateral parametrical involvement in the chemo RT group 67.56% of them had complete response. Among the patients in the RT group with bilateral involvement 40.6% of them had complete response.

Conclusions
The results of concurrent chemoradiation reflect rays of hope in the treatment of patients with locally advanced cancer cervix. The

rising incidence of this tumour in relatively young patients and the high malignancy of many of these tumours give a further stimulus to an increased effort to improve treatment and achieve cure with an absence of morbidity. In the future clinicians will be challenged to determine favourable results in patients with severe medical problems or social problems.

We also need to ensure that once the disease is diagnosed there is no delay in starting the appropriate treatment. Physicians need to to educated about the results and morbidity following simple surgery for these patients as the number of patients referred after such surgery is increasing. There is no role for neo-adjuvant chemotherapy and it should not be used as a stop gap arrangement while patient is waiting to start radiotherapy. Each center needs to address its palliative treatment schedules either to a single fraction or the shortest treatment possible so that patients requiring curative radical treatment need not wait.

References

1. American cancer society cancer facts & fingures 2005. American cancer society 2005
2. Jemal A Murray T Samuel A et al statistics 2003, CA cancer J clinics 2003; 5.35
3. Fletcher GH. Clinical dose-response curves of human malignant epithelial tumours. Br J Radiol 1973;46:1-12
4. Steel GG, Peckham MJ. Exploitable mechanisms in combined radiotherapy-chemotherapy: the concept of additivity. Int J Radiat Oncol Biol Phys 1979;5:85-91
5. Sinclair WK. The combined effect of hydroxyurea and x-rays on Chinese hamster cells in vitro. Cancer Res 1968;28:198-206
6. Phillips RA, Tolmach LJ. Repair of potentially lethal damage in x-irradiated HeLa cells. Radiat Res 1966;29:413-432
7. Fu KK. Biological basis for the interaction of chemotherapeutic agents and radiation therapy. Cancer 1985;55:Suppl:2123-2130
8. Rose PG. Locally advanced cervical carcinoma: the role of chemoradiation. Semin Oncol 1994;21:47-53
9. Wingo PA Tong T Bolden S Cancer Statistics 1995, CA cancer J clinics 1995; 15.8