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Integration of Chemotherapy with Brachytherapy in the Treatment of Locally Advanced Uterine Cervical Cancer

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Abstract

Objective: Carcinoma of Uterine cervix is the second most common cancer affecting females in India. Concurrent chemoradiation has remained the sole definitive treatment available in the locally advanced stages. Our study was planned to take the advantage of radiosensitisation accruing due to chemotherapy at the time of brachytherapy when approximately forty percent of total tumour dose is applied.

Methods: Study design was prospective, randomized and comparative.100 patients with locally advanced squamous cell carcinoma of cervix (FIGO stage IIB to IVA) were included from 2017 to 2019 and divided into two arms of 50 patients each as per computer generated random number list. All were given concurrent chemoradiation followed by 3 insertions of brachytherapy as per the Manchester System, each application was 7 Gy by HDR. Patients in Arm A (Study Arm) received cisplatin 40 mg/m2 along with EBRT and brachytherapy and Arm B (Control Arm) received cisplatin 40 mg/m2 along with EBRT only.

Results: Loco regional control was superior in study arm. Clinical complete response rate was found to be 94% in study arm vs. 74% in control arm at 3 months after treatment and was statistically significant (p value=0.0230) as per SPSS version 20.0. Acute side effects were more in Arm A. Acute skin reaction, nausea, vomiting was mostly of Grade I and II. Anaemia and leukopenia were the most common haematological toxicities. No life-threatening toxicity was encountered.

Conclusion: The integration of concurrent chemotherapy with platinum compounds during brachytherapy shows good local control and acceptable toxicity in the treatment of locally advanced cervical cancer and can be considered as the standard of care in future.

Keywords: Cervical cancer; Concurrent chemo-brachytherapy; Cisplatin; High dose rate intracavitary brachytherapy

Introduction

Carcinoma of uterine cervix is the second most common cancer of females in India as per reports from National Cancer Registry Programme 2020. According to GLOCOCON 2020 statistics, the estimated number of new cases of cervix cancer is 6, 04,127 (6.5%) worldwide and 1, 23,907(18.3%) of all cancers in females in India [1].

Standard treatment regimen for locally advanced inoperable cervical cancer has remained external beam radiation with concurrent chemotherapy followed by brachytherapy [2]. However, the persistent/recurrent pelvic disease remains a significant obstacle in curative intent and prolonged survival. According to recent published literature, approximately half of locally advanced disease of cervix fails in treated pelvic area [3].

The success of treatment depends on a careful balance between external beam radiotherapy (EBRT) and brachytherapy that optimizes the dose to tumor and normal tissues and the overall duration of treatment. The addition of brachytherapy serves to boost the gross tumor, and improves disease control and survival. Cure is interlinked with radiation dose escalation however such ingredients to improve local control by increasing radiation dose is hampered by the limited tolerance of surrounding critical organs like bladder, rectum and intestines. Therefore, attempts have been made to improve the local control and survival in the advanced stages of the disease by combination of radio-sensitizers like cisplatin with external beam radiation. Several authors have claimed overall improvement of disease-free survival as compared to treatment with radiation alone [4-8]. Role of concurrent chemotherapy with EBRT is well understood but data for effect of concurrent chemotherapy with brachytherapy is limited.

Our study was designed to see the therapeutic effect of cisplatin with brachytherapy by taking the advantage of its radio sensitization property, when approximately 40% of total tumor dose is applied and also to evaluate the efficacy, feasibility and toxicity of concurrent chemotherapy and brachytherapy for Locally Advanced Cervical Carcinoma (LACC) and possibility of recurrences and distant metastasis.

Materials and Methods

Patients consisted of those with locally advanced carcinoma of cervix receiving definitive chemo radiotherapy and brachytherapy in our institute from 2017 to 2019. A total of 100 patients who were willing to give informed consent and fulfilling the specified inclusion and exclusion criteria were enrolled for the study.

Patients included were between the age of 18 to 70 years and his to pathologically proven for squamous cell carcinoma of cervix and locally advanced inoperable stage disease as per FIGO staging system (IIB-IVA). ECOG performance status was from 0 to 2. All were treatment naive except for biopsy. Patients with uncontrolled comorbidities, those who had taken prior treatment in form of chemotherapy or radiotherapy or surgery, those with hypersensitivity to cisplatin, ECOG performance status more than 2, pregnant and lactating females were excluded from the study. Presence of distant metastasis i.e. stage IVB, presence of other synchronous malignancies, recurrent disease and those not willing for giving consent were also excluded.

Complete history, general, physical and local examination with an assessment of the patient's performance was noted down. Nutritional status, hygiene, clinical examination of other organs to exclude any evidence of distant metastasis was done. Local/Pelvic examination included inspection of external genitalia, per speculum examination of vagina and uterine cervix, per rectal examination and bimanual palpation of the pelvis. Initial investigation workup included laboratory studies like complete blood count, blood sugar, kidney function test, liver function test and serum electrolytes. Imaging was done by Chest X-ray (PA view), USG abdomen and pelvis and CT/MRI abdomen and

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pelvis. After complete examination and investigative work-up all patients were staged according to FIGO staging system.

After pre-treatment evaluation and staging, patients were randomized into two arms by sequential randomization according to their first visit in our department.

Patients were planned for External Beam Radiotherapy delivered by Co^{60} teletherapy machine and followed by intracavitary brachytherapy (ICRT) using Gamma Med Plus HDR unit.

EBRT schedule was 50 Gy in 25 fractions, 5 fractions per week, 2 Gy per fraction by using parallel opposing (anterior-posterior fields)/four field box technique along with weekly cisplatin 40 mg/m^2 in both arms.

After completion of EBRT, three fractions of weekly ICRT were given starting after a gap of one week at a dose of 7 Gy for 3 fractions (total 21 Gy) as per Manchester system. Patients in Arm A were given cisplatin (40 mg/m^2) one day before brachytherapy. Total duration of completion of treatment with EBRT and ICRT was kept around 56 days (8 weeks).

Routine hydration and standard anti-emetic prophylaxis was given before and after chemotherapy as per institutional guidelines. All patients were reviewed once weekly and time to time in the OPD to assess treatment-induced toxicity. These included acute in-field toxicity (microsites and acute skin reaction), gastro intestinal toxicity (nausea, vomiting, and diarrhoea), haematological toxicity (anaemia, leukopenia and thrombocytopenia) and acute renal toxicity. Toxicity was graded according to the NCI-CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) version 4.03.

Patients in both groups were accessed weekly for local disease response. The primary tumour assessment was done at the initiation of treatment as base-line. The response of tumour was then noted at the end of treatment completion at 3rd month and monthly till 18 months. Clinical and radiological responses were evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Response was evaluated in terms of Stable Disease (SD), Partial Response (PR), Progressive Disease (PD) or Complete Response (CR).

Results

Total 100 patients were enrolled in the study and randomised into two arms. Patients in Arm A received concurrent weekly cisplatin 40 mg/m^2 with EBRT and brachytherapy while patients in Arm B received weekly cisplatin 40 mg/m^2 with EBRT alone.

The treatment arms were reasonably comparable in terms of baseline characteristics including age, performance status, stage, tumour histopathology, baseline haemoglobin, kidney function, socioeconomic and geographical distribution (Table 1).

Loco regional response

At 3rd month of completion of treatment, response was assessed using the RECIST criteria. It was found that around 47 patients out of 50 in Arm A (94%) had complete response (CR). Only 2 patients (4%) had partial response (PR) to treatment and 1 patient (1%) had progressive disease (PD). In comparison, 37 patients out of 50 (74%) had complete response, 7 patients (14%) had partial response and 6 patients (12%) had progressive disease. This difference in response was found to be statistically significant (p value=0.0230) (Tables 2 and 3).

At 6th month follow-up, 44 patients (88%) in Arm A achieved complete response and 3 patients (6%) patients had loco regional relapse whereas in Arm B 33 patients (66%) patients achieved complete response and 4 patients (8%) had loco regional relapse. Out of 50 patients of Arm A,3 patients (6%) had progressive disease as compared to 13 patients (26%) out of 50 in Arm B.

At 12th month follow-up, in Arm a 43 patients (86%) had complete response and 4 patients (8%) relapsed whereas in Arm B, 32 patients (64%) had complete response and 5 patients (10%) had loco regional relapse.

At 18th month follow-up, in Arm A, 42 patients (84%) had complete response and 5(10%) had relapsed disease whereas in Arm B, 31 patients (62%) had complete response and 6(12%) had locoregional relapse (Table 4).

Those patients with progressive or recurrent disease were managed with either adjuvant chemotherapy or palliation therapy.

Treatment related toxicity

The main treatment toxicities are summarized in Table 2. Acute skin reaction was more in Arm A as compared to in Arm B and was found to be statistically significant (p value=0.0007). Gastrointestinal toxicities like nausea and vomiting were more in Arm A majorly Grade I and II. Vomiting was found to be statistically significant (p value=0.0138). Diarrhoea was less common.

Haematological toxicities were also more common in Arm A than Arm

Table 1. Patient Characteristics.

Patient characterstics	Arm A(N=50)	Arm B (N=50)
Median age (in years)	49.2 years	51.6 years
Rural: Urban	40:10	43:7
Performance status		
ECOG 0	3(6%)	1(2%)
ECOG 1	44(88%)	46(92%)
ECOG 2	3(6%)	3(6%)
Histopathology		
WDSCC	10(20%)	13(26%)
MDSCC	37(73%)	31(62%)
PDSCC	3(6%)	6(12%)
figo stage		
IIB	9(18%)	21(42%)
IIIA	1(2%)	0(0%)
IIIB	27(54%)	18(36%)
IIIC1	8(16%)	7(14%)
IIIC2	3(6%)	1(2%)
IVA	2(4%)	3(6%)

Table 2. Common treatment related toxicities.

Most common toxicity	Arm A(N=50)	Arm B(N=50)	P-Value
Acute skin reaction (Grade I And Ii)	42	31	0.0007(SIGNIFICANT)
Nausea (Grade Ii)	14	10	0.6370
Vomiting (Grade Ii)	26	19	0.0138(SIGNIFICANT)
Diarrhoea (Grade I And Ii)	29	33	0.3710
Anaemia	37	25	0.0312(SIGNIFICANT)
Leucopenia	38	34	0.0550
Thrombocytopenia	14	5	0.0611
Acute renal toxicity (Grade I And Ii)	16	9	0.0150

Table 3. Response evaluation at 3 months.

Response after treatment (At 3 Months)	Study arm(n=50)	Control arm(n=50)	P-value
Cr (Complete response)	47(94%)	37(74%)	0.0230 (SIGNIFICANT)
Pr (Partial response)	2(4%)	7(14%)	
Pd (Progressive disease)	1(2%)	6(12%)	
Sd (Stable disease)	0(0%)	0(0%)	

B. Anaemia was the most common haematological toxicity and statistically significant (p value=0.0312). Leukopenia mostly occurred in the form of Grade I and Grade II and thrombocytopenia was a rare event.

The renal injury was found to be of acute type. Study arm had more of Grade I and Grade II toxicity. None of the patients including both arms had Grade IV toxicity.

The standard treatment time as per schedule was 56 days. In the study arm, the average time of completion of treatment was 59.24 days. Majority of the patients completed their treatment within 55-60 days (55%). Compliance of the treatment was defined in terms of completeness of chemotherapy and radiotherapy within the prescribed time limits. There was no treatment related deaths and none had metastatic disease in the follow-up period.

Statistical analysis was conducted using SPSS version 20.0. The qualitative data was compared by applying chi-square test or Fisher's exact test, as appropriate. A p-value less than 0.05 were considered significant.

Discussion

Concurrent chemo radiation (CCRT) is considered the standard treatment for patients with locally advanced cervical cancer (LACC). Based on the results of five large randomized trials that tested addition of chemotherapy to pelvic radiation, the National Cancer Centre issued an alert in 1999 that all patients with locally advanced cervical cancer should receive CCRT [4-6,8,9]. These studies demonstrated that CCRT had a significant survival advantage of 10%–15% at 5 years after treatment compared with radiotherapy alone [4-,8,9].

In a met analysis by Green, it is mentioned that for women who develop locally advanced cervical cancer, the standard of care has evolved from external beam radiation therapy (EBRT) alone, to EBRT plus brachytherapy, to combined EBRT plus brachytherapy with concurrent chemotherapy [10]. Since approximately half of locally advanced disease fails in treated pelvic area attributing to presence of bulk of the primary lesion with its attendant increase in hypoxic cells, poor geometry, impaired blood supply and increase in growth fraction thereby resulting in poor radiation response, the standard treatment regimen for such cases has remained external beam radiation with concurrent chemotherapy followed by brachytherapy [2,3,11].

Cure is interlinked with radiation dose escalation however; such a step to improve local control by increasing radiation dose is hampered by the limited tolerance of surrounding critical organs like bladder, rectum and intestines. Therefore, several attempts have been made to improve the local control and survival in the advanced stages of the disease by combination of radio-sensitizers like cisplatin with external beam radiation. Many authors have claimed overall improvement of disease-free survival as compared to treatment with radiation alone [4-6, 9,12].

The success of treatment depends on a careful balance between External Beam Radiotherapy (EBRT) and brachytherapy that optimizes the dose to tumour and normal tissues and the overall duration of treatment. The addition of brachytherapy serves to boost the gross tumour, and improves disease control and survival [13-17].

About 40% of total tumour dose is delivered in brachytherapy in uterine cervix and parametric and the minimum dose to the rectum and bladder can be achieved by accurate treatment planning. Therefore, it is logical concept to expect that the best time to apply chemotherapy during the course of radiotherapy will be during the brachytherapy insertions assuming that the dose of radiation applied during one brachytherapy insertion is much higher than external radiation; due to this difference we can expect that the effects of the combination of brachytherapy and chemotherapy are substantially greater than either of both [18]. The second reason can be that the dose rate of brachytherapy is decreasing by inverse-square law and thus potentially results in less toxicity to surrounding normal tissues.

Adding a chemotherapeutic agent to cause radio sensitisation of the tumour cells, gives rise to an alteration in the shape of the cell-survival curve after irradiation which may be due to direct tumour cell cytotoxicity or inhibition of sub-lethal or potentially lethal radiation-induced damage repair.

Our study was aimed to compare concurrent 40 mg/m^2 cisplatin along with brachytherapy against conventional brachytherapy for locally advanced cervical cancer at our institute. Trials by Steel, Dewit show that cisplatin has been considered the most effective single agent as systemic therapy in eradicating micro-metastasis and moreover as a radio sensitizer in uterine cervical carcinoma [19,20].

Mean age in Arm A was 49.2 years while in Arm B was 51.6 years. As far as age distribution is concerned there was no statistically significant difference (p value=0.283). Similar distribution of age of the patients was found in the study by Aghili where the mean age was 53.2 years and Giridhar where the mean age was 51.25 years [20,21].

As per the FIGO staging system maximum number of the patients in both arms belonged to stage II and stage III. Majority (45%) belonged to stage IIIB. Study group had 27 patients (54%) and control arm had 18 patients (26%) with stage IIIB disease. Most of the patients including both arms resided in the rural areas. 83% of the total patients belonged to rural area and 17% to the urban area. It was seen in the study that about 76% of the patients comprised the category of lower socio-economic class.

Baseline hemoglobin was evaluated in both the arms and since most the patients presented to us with the initial complaint of bleeding per vagina, they were found to be mostly anemic. 56% of all patients had hemoglobin level ranging between 8-10 gm/dl whereas only 11% had >12 gm/dl. Incidentally, majority of the anemic patients belonged to the study arm.

Baseline renal parameters were also evaluated, since patient had to be given cisplatin along with radiation and it is known to be a nephrotoxic drug. Only 2 patients in the study arm and 3 patients in the control arm had raised blood urea levels (>40 mg/dl). Serum creatinine levels were also noted at baseline level. Those patients with raised levels were admitted and further investigated and adequately hydrated to normalize the renal parameters.

Acute skin reactions was a statistically significant finding which was managed adequately by conservative management (p value=0.0007). No patient had Grade IV skin toxicity.

Gastrointestinal side effects like nausea and vomiting were more in Arm A, majorly Grade I and II. Vomiting was found to be statistically significant (p value=0.0138). Diarrhoea was less common and was mostly of Grade I. No patient in control arm had grade III or grade IV toxicity. Similar toxicity profile for nausea, vomiting and diarrhoea was also found in the study carried out by Chandel and Jain [22,23].

Haematological side effects were very common and significantly more in Arm A. Anaemia was the most common among them, grade I and II toxicity being higher in Arm A than Arm B in (84% vs. 62%). This association was statistically significant (p value=.0312). Anaemia that occurred in patients was similar to the results found in study by Aghili in Iran [22]. Leukopenia mostly occurred of Grade I and Grade II toxicity in both arms. The study arm patients had more of Grade II (30%) and Grade III (18%) toxicity whereas the control arm had more of Grade I toxicity. None of the patients had Grade IV toxicity. Eduard also reported similar kind of incidence of leucopenia [23]. Thrombocytopenia was a rare event.

The renal injury that was found in the patients was of acute type. 75% of patients had Grade 0 toxicity and rest 25% patients had individuals divided among Grade I and Grade II with Grade I toxicity being more than Grade II. Study arm had more of Grade I and Grade II toxicity. None of the patients including both arms had Grade IV toxicity. Similar renal dysfunction was also found in the study carried out by Koumantaki**s** [24]. Mallick also had similar differences in acute toxicities like our study and control arm [11].

The standard treatment time as per schedule was 56 days. In Arm A, the average time of completion of treatment was 59.24 days and in Arm B was 59.54 days. In Arm A,27 patients (54%) completed their treatment within 55-60 days (8 weeks), 20 patients (40%) completed within 60-65 days and only 3 patients (6%) took 65 days or more to complete the same treatment. In the Arm

B, 28 patients (56%) completed their treatment within 55-60 days (8 weeks) from start of treatment,18 patients (36%) within 60-65 days (9 weeks) and only 4 patients (8%) took 65 days or more to complete the same treatment. Compliance of the treatment can be defined in terms of completeness of chemotherapy and radiotherapy within the prescribed time limits [25-27].

Patient local control response evaluation was done after the treatment completion and at follow up. It was found that around 47 patients out of 50 in study arm (94%) had Complete Response (CR). Only 2 patients (4%) had partial response (PR) to treatment and 1 patient had progressive disease (PD). None of the patient had a stable disease. Kuske and Stumpf also reported similar kind of results in the response [28,29]. In comparison, in control arm 37 patients out of 50 (74%) had complete response, 7 patients (14%) had partial response and 6 patients (12%) had progressive disease. None of the patients had stable disease. This difference in response between both the arms was found to be statistically significant (p value=0.0230). Strauss achieved a complete response of 88% including all patient vs. 84% in our study [30]. There were no treatment related deaths and during the follow-up period, none of the patient had metastatic disease. Similar overall response results were also found in the study carried out by Chandel and Jain [23].

Conclusion

Standard treatment for locally advanced inoperable carcinoma of cervix is concurrent chemo radiotherapy followed by brachytherapy. Role of concurrent chemotherapy with EBRT is well understood but data for effect of concurrent chemotherapy with brachytherapy is limited. Since about 40% of total tumour dose of radiation is delivered in brachytherapy in uterine cervix and parametric and the minimum dose to the rectum and bladder can be achieved by accurate treatment planning, it is a logical concept to expect that the best time to apply chemotherapy during the course of radiotherapy will be during the brachytherapy insertions. This prospective randomized comparative study provides a direct comparison of concurrent chemo-brachytherapy with definitive chemo radiotherapy in locally advanced cases of carcinoma cervix.

The loco regional control was better in the study group and was found to be statistically significant. The treatment related toxicities were manageable. No patient suffered treatment related death or presented to us with metastatic disease.

Based on the results, the present study concludes that the integration of concurrent chemotherapy with platinum compounds during brachytherapy shows good local control and acceptable toxicity in the treatment of locally advanced cervical cancer and can be considered as the standard of care in future.

However, the results are encouraging but further study with large number of patients and long-term follow-up on overall survival, disease-free survival, long term squeal or complications would clearly define the role of concurrent chemotherapy with brachytherapy in the management of locally advanced carcinoma cervix.

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