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Correlation of Haematological Toxicity with Bone Marrow Radiation Dose and Volume during Concurrent Chemoradiation in Patients with Cervical Cancer

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Abstract: Aims and objectives: *Haematological toxicity is common in patients with cervical cancer treated with concurrent chemoradiation, so our study aimed to assess this haematological toxicity and correlate the toxicity with the dose and volume of bone marrow included in the field of radiation.* ***Materials and methods:*** *Twenty five patients with histological proven cervical cancer attending the department of Radiation Oncology at Yashoda hospital, Hyderabad from June 2011 to July 2013 were the subjects of this study. Patients were treated on 15 MV linear accelerator with a radical intent, with concurrent chemotherapy using Cisplatin 40 mg/m2 weekly. The planning CT was done for all the patients before the treatment and contouring of the pelvic bone marrow apart from other organs at risk was done. Plan evaluation was done documenting the volume of bone marrow included in the field of irradiation and dose received by it. Haematological toxicity was assessed using RTOG common toxicity criteria weekly during and at 2 weeks after the completion of the treatment.* ***Conclusion****: Concurrent chemoradiation for cervical cancer is safe and is associated with minimal haematological toxicity in the form of anaemia. The toxicity is same for different volumes of bone marrow included in the field of irradiation with both 3DCRT as well as IMRT technique. The toxicity observed is probably contributed by Cisplatin.*

Keywords*: Haematological toxicity, cervical cancer, Bone marrow, Concurrent chemoradiation*.

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I. Introduction

Cervical cancer is the second most common cancer worldwide among women next to breast cancer and is the primary cause of cancer related deaths in developing countries[1]. Each year cervical cancer is diagnosed in about 5, 00,000 women globally and is responsible for 2, 60,000 deaths annually[2]. Approximately one fourth of the world cases of cervical cancer are detected each year in India, the highest incidence is seen in Chennai and the lowest in Delhi. In our department, cervical cancer formed on average of 19% of total cases of cancers and most of the patients are diagnosed in locally advanced stage, for which concurrent chemoradiation is the treatment of choice which is followed by brachytherapy[3].

Concurrent chemotherapy and radiation became the standard of care for cervical cancer since 1999-2000[1]. National Cancer Institute made a clinical announcement stating that Cisplatin based chemotherapy is the new standard of therapy for cervical cancer[1]. This NCI alert that came on 23 February, 1999 showed platinum based chemotherapy used along with radiation had twelve percent increase in local control/survival[4]. Cisplatin chemotherapy is known for its severe haematological toxicity. Pelvic radiation adds to this and is related to the extent of bone marrow that is involved in the field of radiation. The combined toxicity when severe, leads to interruption in treatment and any delay in completion of planned treatment is associated with a reduced probability of local control in patients receiving curative treatment. Several studies have suggested that there may be as much as 1% decrease in survival and local control for each extra day of treatment beyond a total treatment time of 55-60 days[5].

The haematological toxicity is assessed weekly once throughout the course of radiation and grading of toxicity is done as per RTOG toxicity criteria version 2.7. With the availability of CT scan for simulation, tumours as well as critical structures are delineated and the dose received by them can be documented. The volume and dose to the bone marrow could be correlated with the weekly blood picture values for a better understanding. The pattern of haematological toxicity would probably help us in framing new guidelines for their prevention and early intervention.

II. Materials And Methods

In this prospective observational clinical study, 25 histopathologically proven cervical cancer patients were enrolled. All patients underwent treatment at department of radiation oncology, Yashoda hospital, Hyderabad from June 2011 to July 2013. All received radical concurrent chemoradiation.

Inclusion criteria:

1. All patients diagnosed as cervical cancer histologically
2. Age: 25-65 years.
3. KPS ≥70.
4. Haemoglobin level ≥10gm%.
5. Platelets count ≥1 lakh.
6. Total leukocyte count ≥ 4000/cumm.

Exclusion criteria:

1. Previous radiation or chemotherapy.
2. Concomitant malignancy.

Procedure methodology

Radiotherapy

Planning CT was done for all patients using CT simulator. CT scans were obtained from second lumbar vertebra to lower edge of ischial tuberosity, using 3 mm slice thickness. Images were then transformed to Eclipse treatment planning system for contouring and planning.

Target volumes were delineated according to the International Commission on Radiation Units and Measurement Reports 62. Gross tumour volume consisted of primary tumour and lymph nodes with a diameter of greater than 10 mm or clusters of lymph nodes. The clinical target volume (CTV) consisted of the upper one half of the vagina, parametrial tissues, uterus, and regional lymph nodes including common, internal, and external iliac nodes (with abdominal aortic bifurcation as the CTV superior margin). Planning target volume was defined as a uniform 7 mm expansion to the CTV boundary as the institution protocol. The organs at risk were delineated, including the small intestine, rectum, bladder, BM, and bilateral femoral heads.

Dose prescription for the pelvic external beam radiation by 3DCRT and IMRT were set at 50Gy/5 weeks (15-MV x-ray), and all plans were normalized to cover 95% of the planning target volume with 100% of the prescribed dose. After external beam radiation, all patients received intracavitary brachytherapy using high-dose-rate brachytherapy (Ir^{192}) to point A with 7 Gy per fraction for three fractions.

Bone marrow delineation

Two methods of delineation of bone marrow are there. One on each CT section in axial cuts Anthony et al[11] have contoured the bone marrow corresponding to the inner margin of the cortex of the bone because the marrow is contained within the medullary cavity. However others have contoured the external bones on the planning CT scan slices and this was chosen to ensure easy reproducibility and to minimize dependence of the CT window and levelling and thus avoiding subjectivity while adjusting gray scale[12]. Different areas of pelvic bone marrow that were contoured 1) Ilium – Including the iliac crests extending to the superior borders of femoral heads.2) Lower pelvis – Consisting of pelvis ischium, acetabula and proximal femur extending from superior border of femoral heads to the inferior border of ischial tubersoities. 3) Lumbosacral spine – Extending from the most superior vertebral body (usually L5) contained in planning volume, interiorly to include the entire sacrum.

Chemotherapy

Patients received cisplatin chemotherapy concurrently with external radiation. Dose of cisplatin was 40 mg/m^2, given weekly based on complete blood counts which was done weekly. Cisplatin was withheld if white blood cell count was less than 2.0 × 109/L, absolute neutrophil count was less than 1.0 × 109/L, platelet count was less than 50 × 109/L, or Hb was less than 7.9 g/L.

The bone marrow volumes receiving 10 or more, 20, 30, 40, and 50Gy (V10, V20, etc) from pelvic radiation were quantified, and the dose to pelvic BM from brachytherapy was considered negligible.

Evaluation of plan included the documentation of bone marrow included in the field of irradiation and dose received to it. Haematological toxicity was assessed on weekly basis by recording the Hb, Neutrophil, Lymphocyte, ANC and Platelets using RTOG common toxicity criteria version 2.

Table 1: RTOG common toxicity criteria version 2.

Parameters	Grade 1	Grade 2	Grade 3	Grade 4
TLC (1000/ul)	3000 - < 4000	2000 - < 3000	1000 - < 2000	< 1000
ANC (1000/ul)	1500 - < 1900	1000 - < 1500	500 - < 1000	< 500
Hb (gm/dl)	9.5 – 11	7.5 - < 9.5	5 - < 7.5	< 5
PLT (1000/ul)	75000 - < 100000	50000 - < 75000	25000 - < 50000	< 25000

TLC-Total leucocyte count, ANC-Absolute neutrophil count, Hb-Haemoglobin, PLT-Platelets

At the occurrence of grade III toxicity the treatment in the form of blood transfusion, Granulocyte monocyte colony stimulating factors and giving gap in the treatment were considered. The patients were assessed throughout the entire duration of treatment and the last assessment was done two weeks after irradiation.

Statistical analysis

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean $\pm$ SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance. Analysis of covariance of toxic levels for adjusting the maximum dose, between two groups of treatment was measured. Analysis of variance has been used to find the significant changes in toxic levels at different levels of volume of dose for different time periods. Significant figures are Suggestive significant (P value: $0.05 < P < 0.10$), Moderately significant (P value: $0.01 < P \leq 0.05$), Strongly significant (P value: $P \leq 0.01$). The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 and Systat 12.0 were used for the analysis of the data and Microsoft Word and Excel have been used to generate graphs, tables etc.

III. Results

The age group of patients ranged from 38-81 yrs with a mean of 54 yrs. Most of the patients were in the early stage with stage IIB accounting for 48%(12) of 25 patients. One patient had Stage IB, four had Stage IIIB, six were treated with Post Operative intent and two had Vault recurrence. All patients received radiation dose of 5000 cGy over 25 fractions with concurrent weekly chemotherapy of cisplatin 40mg/m^2. Fourteen patients underwent 3DCRT technique and 11 with IMRT technique. All patients received radiation without any gap.

Haematological toxicity in the form of Anaemia i.e. Grade I was seen in 19 patients, Grade II in 12 patients and Grade III in 2 patients. Eight patients had Grade I at 1st, 2nd and 3rd weeks, 11 patients in 4th week and 13 patients in the 5th week. However at 2 weeks after treatment only 7 patients continued to have Grade I.

Grade II anaemia was observed from 2nd week onwards and persisted in 3 patients at 2 weeks after treatment. Grade III was observed in 1 patient at 5th week and in another patient at 2 weeks after treatment. Seven patients received blood transfusion. Among them one patient had Grade III; one had Grade II anaemia during 3rd, 4th and 5th week of treatment. The remaining three received blood transfusion before the commencement of RT. Twelve patients had gap in chemotherapy for 2-4 days. The reasons for the gap were grade III anaemia in one and gastrointestinal toxicity in the form of vomiting, loose stools etc in others. Thirteen patients received 5 cycles of chemotherapy, 10 patients received 4 and 2 patients received only 3 cycles. The reason for only 3 cycles was acute enteritis. None of the patients encountered WBC or Platelets toxicity.

Table 2: Summary of patient and treatment characteristics.

Characteristics		**No. of patients**
Age (yrs)	31-40	3
	41-50	8
	51-60	7
	> 60	7
Stage	Stage 1B	1
	Stage 11B	12
	Stage 111B	4
	Cervix post op	6
	Vault	2
Treatment modality	3DCRT	14
	IMRT	11
No. of chemotherapy cycles received	3	2
	4	10
	5	13
Blood transfusion	No	19
	Yes	6

3DCRT-three dimensional conformal radiotherapy, IMRT-intensity modulated radiotherapy

Table 3: Percentage of bone marrow receiving various doses.

Percentage of bone marrow receiving RT dose	**Range in percentage (%)**	**Mean in percentage (%)**
4 Gy	82.31-100	91.2
10 Gy	78.54-100	89.3
20 Gy	66.76-100	83.4
30 Gy	20.54-88.87	54.8
40 Gy	6.89-73.35	40.1

Table 4: Estimates of toxicity based on haemoglobin, platelet count, total count, ANC and lymphocyte.

	Haemoglobin	Platelet count	Total count	ANC	Lymphocyte count
Before RT	11.62+1.22	3.58+1.28	8812+2795.85	5926.32+2162.54	1957.84+721.14
Week 1	11.70+1.43	3.45+1.09	6397.72+1958.35	4520.2+1742.41	1273.76+592.81
Week 11	11.06+1.49	2.7+0.91	5952.8+2210.53	4415.08+1994.87	883.72+404.18
Week 111	10.98+1.44	2.47+0.72	5016.8+1990.76	3696.04+1729.49	754.76+479.48
Week 1V	10.61+1.04	2.29+0.69	4662.8+2311.7	3403.72+1787.57	682.80+265.00
Week V	10.18+1.2	2.22+0.61	4647.2+2104.56	3406.84+1902.66	711.76+423.86
After RT	10.72+1.11	2.75+0.98	5122.8+2220.9	3442.32+1721.77	1168.44+690.64
P value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

IV. Discussion

Age group of patients ranged from 38-81 yrs with a mean of 54 yrs. According to various other authors[11, 13] the mean age were ranging from 37-52 yrs. Most of the patients in our study were in the early stage with stage IIB accounting for 48 %(12) of 25 patients and a similar occurrence of 45% is noted as per different authors[9, 13].

All patients received radiation dose of 50Gy over 25 fractions with concurrent weekly chemotherapy of cisplatin 40mg/m^2. Similar studies done by authors used RT dose varying from 4300-5000 cGy over 25-28 fractions**.** Haematological toxicity in the form of anaemia was noted in 80% of our patients. Grade I was noted in 19(95%) patients, Grade II in 12(60%) patients and Grade III in 2(10%) patients at various points of time during treatment. Among the patients who developed Grade III toxicity, one patient was in the 5th week of CTRT and hence the 5th cycle of cisplatin was withheld while the second patient developed at 2 weeks following CTRT. Others authors like Bhavaraju et al[9] noted anaemia in 62.9% overall, Grade I in 51.1% and Grade II in 11.4% of patients, Grade III, IV were not present. Singh et al noted the similar Grade I, II in 75% and 55% respectively. In a study by Shibita et al Grade III, IV in 50% and 14% higher toxicity is because of 70 mg/m2 of cisplatin dose along with 5-FU. Aich et al[13] noted Grade 0 in none and Grade I, II, III in 54%, 18% and 6% respectively. Rose et al[1] noted Grade I, II, III, IV in 7%, 15%, 5%, 2% patients with concurrent chemoradiation with cisplatin dose of 40mg/m2. In GOG study, Keys et al[10] noted Grade 0, I, II, III, IV in 80%, 0.9%, 0.8%, 0.16% and 0% respectively. In study by Peters et al[8] in SWOG trial, CT with cisplatin 70 mg/m2 with 5FU Grades I, II, III and IV anaemia in RT+CT were 23%, 22%, 0.2% and 0%. None of the patients in our study had thrombocytopenia. However Bhavaraju et al [28] did observe Grade 0, I, II and III toxicity in 82.9%, 14.3%, 2.8% and 0 patients respectively. Aich et al[74] observed Grade 0 in 36% and Grade I, II, III in 55%, 9% and 0% respectively. Rose et al[1] noted Grade 0, I, II, III, IV in 44%, 0.8%, 0.2%, 0.1% and 0% of patients respectively. Peters et al[24] noted Grades I, II, III, IV thrombocytopenia in 22%, 0.18, 0.08% and 0% respectively. None of the patients in our study had TLC toxicity. In a study by Bhavaraju et al[9] leucopoenia was noted with Grade I in 20% and Grade II 31.4%. Aich et al[13] observed Grade 0 in 44% and Grade I, II, III in 33%, 16% and 7% respectively. Rose et al[1] noted Grade 0, I, II, III, IV in 19%, 0.9%, 14%, 11%, 0.16% patients. Peters et al[8] noted Grades I, II, III, IV leucopoenia in 13%, 38%, 32% and 0.02% respectively. None of the patients in our study had ANC toxicity. However in the study by Bhavaraju et al[9] an overall of 51.4% had fall in ANC counts with Grade 0, I, II and III were found to be in 48.6%, 20%, 31.4% and 0% patients respectively. Twelve patients had a gap in chemotherapy for 2-4 days.11 patients had HT and one patient had severe vomiting and burning micturition. In a study by Abu-Rustum[6] 29.2% of patients had incomplete chemotherapy, 13% due to Haematological toxicity. In study by Bhavaraju et al[9] interruptions in chemoradiotherapy for a period of 1-4 days was observed in 57% patients for the reason of lack of transportation and the patient being unwell and sick. Aich et al[13] in their study observed treatment in general was delayed by a week due to HT during CTRT. In our study, thirteen (52%) patients received 5 cycles of chemotherapy, 10(40%) patients received 4 cycles of chemotherapy and 2(0.08%) patients received 3 cycles. Among the patients who received only 3 cycles, one patient developed jaundice the cause of which was not known and the other patient had severe vomiting and so the remaining chemotherapy was not contemplated. In the study by Abu-Rustum et al 10.8% of patients received six cycles of cisplatin but majority (60%) received planned five courses of cisplatin. Serkies et al[4] noted 55% did not receive the planned five cycles of cisplatin due to treatment related haematological toxicity (31%) and non compliance due to delayed first cycle administration or omission of a cycle for reason other than toxicity. In a study by Myrna et al[7] only 67% of patients received the six planned courses of weekly cisplatin. Keys et al noted that one (0.55%) patient received 2 cycles and all other (99.45%) received 4-6 cycles of chemotherapy. In a study by Rose et al 0.6%,1.1%,1.1%,4%,10.2%,33.5%,49.4% patients received 1,2,3,4,5 and >6 cycles of cisplatin chemotherapy respectively. Fourteen patients underwent 3DCRT technique and 11 with IMRT technique and there was no significant difference in the toxicities as far as these techniques were considered.

Table 5: The various volumes of bone marrow were compared with those of other authors and are as shown in the table below:

Dose received by bone marrow volume	Present study	AP/PA (loren)[11]	Four field (loren)[11]	IMRT	IMRT-BMS (loren)[11]
V 4	91.2	72.4	99.6	100	90.4
V10	89.3	66.9	97.3	100	76.5
V20	83.4	62.9	92.7	96	57.5
V30	54.8	59.1	59.9	76	46.1
V40	40.1	54.1	48.9	49	33.7

Our observations are: 1) V4,V10,V20 Gy is least in AP/PA plan because of only two fields with majority of the bone marrow being outside the field of radiation. 2) All the volume is lesser in the four-field than IMRT because in IMRT multiple fields are used, so in low dose region especially, more of bone marrow volume is receiving greater radiation dose than in four-field box technique. 3) In IMRT-BMS bone marrow can be set as a constraint and then reduction in volume can be accomplished.

Regarding the toxicities that we observed in our study, Grade II Anaemia was seen in 12 and Grade III in 2 patients that is probably attributed to Cisplatin chemotherapy as it did not correlate with the bone marrow volume in the field of irradiation. Using statistical methods, an effort was made to analyse the haematological toxicity adjusting for that week's maximum dose, the same was analysed without adjusting the maximum dose. This was done because not only the volume was different for different patients but also the dose received on the day of assessing the toxicity was different. However we did not observe any difference between the two groups. We did have certain limitations in our study. The sample size is very small and hence further studies enrolling a large number of patients are required to see if the same results can be duplicated. Our last assessment of toxicity was at two weeks after completion of treatment and hence it is difficult to comment on the delayed haematological toxicity that is observed with cisplatin. Bone marrow contouring was done entirely from lumbosacral junction (L5) to ischial tubersoities. Contouring different regions like ileum, ischium, and pubis separately will probably help us to understand the toxicity profile better.

V. Conclusion

Concurrent chemoradiation for cervical cancer is safe, can be completed as scheduled and is associated with minimal haematological toxicity in the form of anaemia and no leucopoenia or thrombocytopenia. Chemoradiation induced anaemia requiring blood transfusion is uncommon. The volume of bone marrow in the field of irradiation does not correlate with the clinical occurrence of acute haematological toxicity as far as 3DCRT/IMRT techniques are considered. Minimal toxicity associated, is probably contributed by concurrent cisplatin administration.

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