RESEARCH ARTICLE

# Chemoradiation Related Acute Morbidity in Carcinoma Cervix and Correlation with Hematologic Toxicity: A South Indian Prospective Study

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## Abstract

**Purpose: To assess chemoradiation related acute morbidity in women with carcinoma cervix and to find and correlation between hematologic toxicity and organ system specific damage. Materials and Methods: A prospective study was carried out between August 2012 and July 2013 enrolling 79 women with cancer cervix receiving chemo-radiotherapy. Weekly assessment of acute morbidity was done using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4 and the toxicities were graded. Results: Anemia [77 (97.5%)], vomiting [75 (94.8%)] and diarrhea [72 (91.1%)], leukopenia [11 (13.9%)], cystitis [28 (35.4%], dermatitis [19 (24.1%)] and fatigue [29 (36.71%)] were the acute toxicities noted. The toxicities were most severe in 3rd and 5th week. All women could complete radiotherapy except two due to causes unrelated to radiation morbidity; seven (8.86%) had to discontinue chemotherapy due to leukopenia and intractable diarrhea. Though there was no correlation between anemia and other toxicities, it was found that all with leukopenia had diarrhea. Conclusions: Chemoradiation for cancer cervix is on the whole well tolerated. Leukopenia and severe diarrhea were the acute toxicities that compelled discontinuation of chemotherapy in two women. Though anemia had no correlation with gastrointestinal toxicity, all of those with leukopenia had diarrhea.**

**Keywords:** Cancer cervix - chemoradiation - acute toxicity - hematologic toxicity - leucopenia - anemia

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## Introduction

Chemoradiation is the current standard of care in patients with locally advanced carcinoma cervix. Although extensive literature is available on the acute morbidity due to chemoradiotherapy in women with cancer cervix, most of the studies have been done at carefully prepared academic centers in developed countries (Rose et al., 1999; Maduro et al., 2003; Ikushima et al., 2006; Mahantshetty et al., 2010; Khalid et al., 2012). Socially disadvantaged women in less developed countries of the world may be more susceptible to the combined treatment's toxic effects due to poor nutritional status, presence of co-morbid chronic conditions and of difficulties in accessing medical care during treatment. In this study we analyzed the chemoradiation induced acute morbidity in women with cancer cervix in our set up using the latest National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4 scoring system (NCI, NIH publication 2009).

The objectives of this study were to assess the chemoradiation related acute morbidity in women of South Indian ethnicity with carcinoma cervix and to see if there is any correlation between hematologic toxicity and organ system specific toxicity.

## Materials and Methods

This prospective observational study was carried out over one year between August 2012 and July 2013, in the Departments of Obstetrics and Gynecology and Radiotherapy, in a tertiary care hospital in South India. After obtaining institutional ethical committee clearance, women with carcinoma cervix on chemoradiation with performance status above 60 on Karnofsky's scale (1949) were enrolled in the study. Women requiring post operative adjuvant radiotherapy and women with cancer endometrium extending into cervix were excluded. The clinical and laboratory findings at pretreatment evaluation were collected. The treatment regimen consisted of external beam radiation therapy of 50 Grays in 25 fractions delivered 5 days a week over 5 weeks. The external beam radiotherapy (EBRT) was planned by 3D Conformal Radiotherapy using the 4-field technique. A dual energy Linear accelerator (Elekta Precise Treatment System, Elekta, UK) was used for treatment delivery for all the

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patients.

A maximum of five weekly chemosensitiser doses with either Cisplatin (40 mg/m$^2$) or Carboplatin (Calvert's formula with AUC=2) were administered as per the patient's tolerance. The chemotherapy was started after ensuring patient fitness by clinical evaluation and by assessing hemogram, renal function tests and serum electrolytes on the day before. Blood tests for hemoglobin, total count, differential count, platelet count, renal function tests and serum electrolytes were done on a weekly basis prior to the chemo sensitiser dose. Chemotherapy was interrupted if the patient had Grade 3 neutropenia, dyselectrolytemia, or more, and was restarted once the laboratory parameters improved to Grade 2 or less. If the patient had any worsening of renal parameters, further chemotherapy was either withheld, or changed over to Carboplatin. Radiotherapy was interrupted only if the patient developed Grade 4 acute toxicity. EBRT was followed by two sittings of High Dose Rate Intracavitary brachytherapy (ICR) on a Microselectron HDR brachytherapy unit (Nucleotron, Netherlands) using the Manchester technique, with 8.5 Gy prescribed to Point A on each sitting. ICR was started 2 weeks after EBRT, with 1-week gap between the two sittings.

The patients had daily clinical evaluations in terms of symptoms and weekly evaluation for Anemia (Hb <12g%), leukopenia (TC<4000/cu.mm), thrombocytopenia (Platelet count <1.5 lakhs), diarrhea, vomiting, proctitis, cystitis, dermatitis and fatigue which were graded using the latest National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4 scoring system.

Statistical Package for the Social Sciences version 16 (SPSS, Chicago, USA) was used for statistical compilation and analysis. Following statistical analysis, statistical significance was sought using chi-square tests, and was accepted at p value less than 0.05.

## Results

Seventy-nine women who underwent chemoradiation as the primary treatment modality for cancer cervix were included in the study. Patient profile and presenting symptoms are as shown in Table 1.

Most of the women belonged to poor socio-economic back ground. This was evidenced by the high prevalence of anemia [59 (74.6%)], poor nutritional status [45 (56.9%)], level of basic education that was below 10 th standard in more than three fouth of the women as well as their early ages of marriage [62 (78.4%)].

Forty two (53%) of the patients had squamous cell carcinoma of the cervix, twenty-six (33%) had large cell carcinoma and eleven (14%) had adenocarcinoma of the cervix. The patients receiving chemoradiation had cancer cervix ranging from Stage IB2 to Stage IVA (FIGO classification).

Out of 79 women who underwent chemoradiation, 69 received Cisplatin as the chemo sensitiser while 10 had Carboplatin as the chemo sensitiser.

All completed the prescribed 50 grays of radiotherapy except two, of which one expired of myocardial infarction in the third week of treatment, unrelated to radiation morbidity, and another discontinued treatment after the third week of chemoradiation in view of domestic problems. Chemotherapy could be completed only in 90.9%, as seven patients had to discontinue it due to severe acute morbidity especially leukopenia.

The radiation related morbidity was as shown in Table 2. Trend of acute morbidities over the treatment duration was as shown in Figure 1. Vomiting [75 (94.8%)] and diarrhoea [72 (91.13%)] were the most common gastrointestinal toxicities. Severe (grade 3 and more) toxicity was found mainly in gastrointestinal [14 (17.7%)] and hematologic systems [3 (3.8%)] and predominantly at 3$^{rd}$ to 5$^{th}$ week of treatment (Table 3).

Anemia was prevalent in 59 (74.7%) of women at the start of treatment. As per the protocol, when hemoglobin was more than 10g% even if they had mild anemia, chemoradiation was started. Weekly evaluation during the treatment course showed deterioration in 19 (32.2%) who were anemic to start with; Four women (20%) developed anemia of grade 2 severity in the group who had no anemia 20 (25.3%) at the start of treatment. Twenty two women received packed cell transfusions when the hemoglobin levels went down below 10g%. Highest grade of anemia noted was grade 3 in four women during the course, of which one had severe grade anemia even at the beginning of treatment which was corrected with packed cell transfusion. Most severe leukopenia was Grade 2 and was in the third week. Urinary, Skin and general toxicities were only of milder grades. No statistical significant correlation was noted between the stage of the disease and the severity of treatment morbidity.

*Correlation between hematologic and systemic toxicity*

No significant correlation was noted between gastro intestinal morbidity and anemia. Again no statistically significant correlation was noted between anemia and other systemic chemoradiation induced acute radiation morbidity (Table 4).

All the eleven women who had leukopenia had diarrhoea with 4 (36.4%) developing grade 3 diarrhoea. Six (50%) of the 11 women with leukopenia had poorly controlled diabetes.

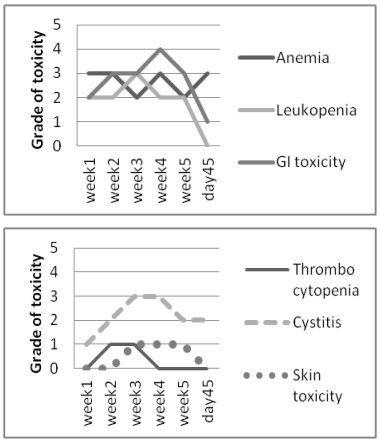


**Figure 1. The Trend of Severity of Toxicity during the Treatment Duration**

**Table 1. Demographic Details (N=79)**

| | | No. | % |
|---|---|---|---|
| Age group | ≤40 years | 12 | 15.2 |
| | 41-60 years | 55 | 69.6 |
| | ≥61 years | 12 | 15.2 |
| Menstrual status | Premenopausal | 29 | 37 |
| | Post menopausal | 50 | 63 |
| Parity | Parous | 78 | 98.8 |
| | Nulliparous | 1 | 1.2 |
| BMI | Underweight | 38 | 46.9 |
| | Average | 33 | 40.7 |
| | Overweight | 10 | 12.3 |
| Presenting complaints | Postmenopausal bleeding PV | 29 | 32.9 |
| | White discharge PV | 26 | 27.8 |
| | Irregular bleeding PV | 17 | 21.5 |
| | Pain abdomen | 11 | 8.9 |

**Table 2. Incidence of Various Chemoradiation Morbidity (N=79)**

| Toxicity | Individual toxicity | No. of patients | % |
|---|---|---|---|
| Hematologic toxicity | Anemia | 77 | 97.5 |
| | Leukopenia | 11 | 13.9 |
| | Thrombocytopenia | 1 | 1.13 |
| GIT Toxicity | Diarrhoea | 72 | 91.1 |
| | Vomiting | 75 | 94.8 |
| | Proctitis | 20 | 25.3 |
| Bladder | Cystitis | 27 | 35.3 |
| Skin | Skin toxicity | 19 | 24.1 |
| General | Fatigue | 29 | 36.7 |

**Table 3. Common Toxicities: Gastrointestinal and Hematologic Morbidity with Severity (N=79)**

| Toxicities assessed | Toxicity grades | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 |
| Diarrhoea | 7 (8.9) | 43 (54.4) | 16 (20.3) | 12 (15.2) | 1 (1.2) |
| Vomiting | 4 (5.1) | 58 (73.4) | 15 (19.0) | 2 (2.5) | 0 (0) |
| Proctitis | 59 (74.6) | 15 (19.0) | 4 (5.1) | 1 (1.3) | 0 (0) |
| Anemia | 2 (2.5) | 51 (64.6) | 23 (29.1) | 3 (3.8) | 0 (0)) |
| Leukopenia | 68 (86.0) | 0 (0) | 10 (12.7) | 1 (1.3) | 0 (0) |
| Thrombocytopenia | 78 (98.7) | 1 (1.3) | 0 (0) | 0 (0) | 0 (0) |

**Table 4. Correlation between Anemia and Organ System Toxicity**

| Number of patients with anemia (N=77) | | | Grade | | | | p value |
|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 4 | |
| Gastrointestinal toxicity (N=77) | | | | | | | |
| No anemia | (Hb ≥12g/dl) | N=2 | 2 | 0 | 0 | 0 | >0.05 |
| Grade1 anemia | (Hb 10-11.9g/dl) | N=51 | 26 | 14 | 9 | 1 | |
| Grade2 anemia | (Hb 8-10g/dl) | N=22 | 12 | 6 | 3 | 0 | |
| Grade3 anemia | (Hb <8g/dl) | N=3 | 1 | 1 | 1 | 0 | |
| Urinary System Toxicity (N=27) | | | | | | | |
| Grade 1 anemia | (Hb 10-11.9g/dl) | N=19 | 14 | 4 | 1 | 0 | >0.05 |
| Grade 2/3 anemia | (Hb <10g/dl) | N=7 | 4 | 1 | 2 | 0 | |
| Skin toxicity (N=19) | | | | | | | |
| Grade 1 anemia | (Hb 10-11.9g/dl) | N=13 | 13 | 0 | 0 | 0 | >0.05 |
| Grade 2/3 anemia | (Hb <10g/dl) | N=4 | 4 | 0 | 0 | 0 | |
| Fatigue (N= 28) | | | | | | | |
| Grade 1 anemia | (Hb 10-11.9g/dl) | N=19 | 19 | 0 | 0 | 0 | >0.05 |
| Grade 2/3 anemia | (Hb <10g/dl) | N=7 | 7 | 0 | 0 | 0 | |

## Discussion

Chemoradiation with platinum compounds Cisplatin/ Carboplatin as the chemosensitiser is the current first line treatment modality for cancer cervix stage IIA and above. Published literature shows that there are differences in the incidences and severity of various morbidities depending on various demographic characteristics (Ikushima et al., 2006; Yuenyao et al., 2007; Khalid et al., 2012). Knowing about these differences is of importance in planning treatment in a country like India where demographic characteristics are very dynamic and vary depending on geography, socio economic background, cultural and religious practices in different areas.

In the study we aimed to identify the chemoradiation associated morbidity, the trend of grades of morbidity during the course and to find correlation between hematologic parameters and other organ system toxicity.

Gastrointestinal and hematological toxicities were the most common acute morbidity related to chemoradiation for cancer cervix. Anemia, vomiting and diarrhoea were more frequent; occurred in almost all patients in our study group although the grades of severity were mild and well tolerated. Leukopenia was the main chemotherapy restricting morbidity noted in our study group and was seen in women with poorly controlled medical co morbidities especially diabetes.

The severe grades of toxicity were less, their incidence comparable to those in developed countries. These systemic toxicities did not significantly interfere with the treatment course, except in seven women (8%) in whom chemosensitisation had to be discontinued owing mainly to leukopenia (85.7%) and intractable diarrhoea (14.3%).

The chemosensitiser drop rate in our group is less compared to that in other groups (25%-29%) (Abu Rustum et al., 2001; Tan et al., 2004; Gunawan et al., 2012). The fact that our patients had in-patient management throughout the course of chemoradiation might have minimized the rate of noncompliance; besides it might have contributed to the low discontinuation rate too as we were confident of managing the toxicities as and when they appeared.

There was a higher prevalence of anemia (97.5%) in the present study compared to that in other studies (ranging from 27-62%) (Tan et al., 2004; Yuenyao et al., 2007; (Khalid et al., 2012). However, chemoradiation related anemia was found in 32.9% of our group. We also noted that anemia alone did not result in any treatment delay or discontinuation.

Our study showed chemoradiation induced leukopenia in 13.5% patients which was considerably less than the observations made in previous studies, (Green, 2001; Bhavaraju, 2004; Khalid et al., 2012) and comparable to the latest study where the incidence of leucopenia was only 10% (Mahantshetty, 2010). Considering that the patients were of a poor nutritional status to start with, the low incidence of leucopenia could be due to a superior bone marrow reserve among our patients. In addition, most patients in our study would have had a relatively lower body surface area, and thus would have received lower absolute doses of sensitiser chemotherapy. However, we noted that leukopenia was responsible for discontinuation of chemotherapy in six of seven patients who had to discontinue chemotherapy. Another interesting observation was that 50% of women who developed leukopenia had diabetes mellitus.

Thrombocytopenia was uncommon in our study. Only one patient who developed pancytopenia had mild

thrombocytopenia.

Severe cystitis had been cited to occur after 5 weeks of chemoradiation. However, in our study cystitis was seen in patients from third week of treatment and persisted until Intra cavitary radiotherapy was over.

We found no correlation between anemia and gastrointestinal toxicity. It was noteworthy that all of those with leukopenia had diarrhea. However among those with diarrhea only 14% had leukopenia.

It is an interesting observation that hematologic toxicity and other toxicities were not going parallel to each other. This probably indicates that the causative factors for hematologic toxicities are different from that for other toxicities. To be more precise, it appears that it is the chemotherapy that predominantly contributes to hematologic changes and radiotherapy that results in gastrointestinal and other toxicities. This argument is indirectly supported by the observations in the studies by Hu et al. (2012) where it was found that the hematologic toxicity was less with weekly cisplatin (40mg/m$^2$) compared to triweekly cisplatin (75 mg/m$^2$) and that the other toxicities did not show any difference with the two regimens.

Amouzegar-Hashemi et al. (2013) observed only 10% of anemia and leukopenia among the group where both gemcitabine and cisplatin were used as chemosensitisers.

As new regimens of chemoradiation are being tested and are emerging out it is important to observe their effect on specific populations. This will guide oncologists to modify the chemotherapy regimen to minimise the hematologic and systemic adverse effects.

Merits of the study are that it is a prospective study with fairly good number of subjects. The observations were made on day-to-day basis as the women received treatment as in-patient management. We looked for correlation between hematologic and other organ system toxicity which was not tested till now in the previous studies. Demerits of the study is that unlike other studies on acute toxicity which tested the toxicity till 3 months after brachytherapy, our study tested the toxicity only unto the end of teletherapy.

In conclusion, chemoradiation for cancer cervix is on the whole, well tolerated. Most complications were readily ameliorated with prompt detection and treatment. Leukopenia and severe diarrhoea were the toxicities that compelled the discontinuation of chemotherapy in few women. These complications were noted in women with poorly controlled medical co morbidity. Though anemia had no correlation with gastrointestinal toxicity, all of those with leukopenia had diarrhoea.

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