ORIGINAL ARTICLE

A Prospective and Observational Study to Assess the Hematological Toxicities of Concurrent Chemoradiation Therapy Inpatients with Locally Advanced Cancersin a Tertiary Care Teaching Hospital

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Abstract

Aim: Cancer ranks as the second most prevalent non-communicable disease worldwide, urging exploration into acute and late chemoradiation-induced hematological toxicities in patients with head-and-neck cancer (HNC) and uterine cervix cancer (UCC). **Material and Methods:** Our prospective observational study, conducted in a tertiary care teaching hospital, enrolled 60 cancer patients aged over 18 years. Utilizing the National Cancer Institute Common Terminology Criteria for Adverse Events, we assessed toxicity levels. **Results and Discussion:** Results revealed a gender disparity, with females exhibiting higher frequency (73.3%), and the highest frequency occurring among individuals aged 41–50 years (36.7%). Comparing tumor types, HNC exhibited lower carcinoma incidence than UCC (68.3%). Hematological profiles during chemoradiation therapy revealed Grade 1 anemia (24%) in the 1st week and Grade 3 toxicities in subsequent weeks. Notably, Grade 5 toxicity and Grade 1 thrombocytopenia (23%) were observed. Grade 1 neutropenia was predominant in the 2nd–4th weeks (21%), while additional cases of Grade 1 lymphocytopenia surfaced in the 2nd week. Grade 4 toxicities peaked in the 1st and 3rd weeks (29%), with leucopenia prevalent in the 3rd week (13.3%). **Conclusion:** While these toxicities are generally manageable and self-limiting, vigilance is warranted to avert severe complications like febrile neutropenia and anemia, emphasizing the need for prompt intervention to prevent life-threatening outcomes.

Key words: Global cancer incidents mortality and prevalence, head and neck cancer, national cancer institute common terminology criteria for adverse events, uterine cervix cancer

INTRODUCTION

Cancer ranked second on the list of non-communicable diseases worldwide. The worldwide cancer burden is expected to reach 19.29 million new cases and 9.95 million deaths in 2020, according to GLOBOCAN 2020.[1]

Head-and-neck cancer (HNC) among men and uterine cervical cancer among females are the most common gynecological cancers in India. The HNCs consist of the lip, oral cavity,

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nasopharynx, hypopharynx, oropharynx, and larynx. HNCs account for 14.6% of all cancer fatalities and 17.3% of new cases, making them the most often diagnosed cancer overall.[2] Estimated new cases and fatalities from cervical cancer in India are 1, 23, 907, making it the second most common malignancy among women to receive a cancer diagnosis and the second leading cause of cancer-related deaths in women.

Nearly 60–70% of patients having head and neck and uterine cervical care in cancers present as a locally advanced disease. Treatment for HNC that has spread locally demands a multimodality approach which broadly includes surgery, radiotherapy (RT) and chemotherapy, chemoradiation therapy, and targeted therapy. In cervical cancer treatment, patients require multimodality treatment, which includes radiation therapy, chemotherapy, chemo-radiation therapy, and intracavitary brachytherapy.[3]

The majority of patients with HNCs and carcinoma cervix present at locally advanced stages and advanced stages such as Stage III and Stage IV. Chemoradiation therapy has been accepted as a standard therapeutic approach to locally advanced cancer in the head-and-neck area, and uterine cervical carcinoma causing improvement in better loco-regional control and overall survival.[4]

Patients receiving chemoradiation therapy usually present with acute and late radiation-induced toxicities such as mucositis, dermatitis, dysphagia, odynophagia, xerostomia, and hematological toxicities. Hematological toxicities such as anemia, neutropenia, lymphopenia, leukopenia, and thrombocytopenia are most frequently encountered in the clinical practice in patients with carcinoma of the head and neck, and carcinoma of the uterine cervix.[5] Carcinoma of cervix/cervical cancer patients having locally advanced cancer usually receive radiation therapy with concurrent 3-weekly or weekly cisplatin-based chemotherapy.[6] Various studies conducted in the past evaluated the incidence of hematological toxicities related to RT, with or without chemotherapy while treating solid tumors and their potential impact on local tumor management and survival.[7] Considering this context and a more in-depth look at the literature, we are planning to conduct a study to assess the incidences of various hematological toxicities associated with concurrent chemotherapy therapy in patients with cervical and locally advanced HNC in the RT department.[8]

The study aims to assess the incidence of various hematological toxicities of concurrent chemoradiation therapy in patients with carcinoma of the head-and-neck region, and carcinoma of the uterine cervix. The main objective of the current study is to document the incidence of hematological toxicities of all types of anemia, neutropenia, thrombocytopenia, lymphopenia, and leucopenia.

MATERIALS AND METHODS

To assess the hematological toxicities in patients receiving chemoradiation therapy for HNCs and cervical cancer, these investigations employ a prospective observational study design and are being conducted in the radiation oncology division of the Sree Venkateswara Institute of Medical Sciences (IEC No.1440) in Tirupati, Andhra Pradesh, India. To ensure statistical power and feasibility, a minimum sample size of 60 participants is targeted. Data will be sourced from multiple sources to ensure a comprehensive representation, including patient case records for hematological parameters related to concurrent chemoradiation therapy during treatment using National Cancer Institute Common Terminology Criteria for Adverse Events and patient medical records for demographic details. The trial is scheduled to run for 6 months, from October 2022 to March 2023, to allow for a thorough evaluation of hematological toxicities.

Statistical analysis

Patient's treatment and study parameters will be entered first in predesigned proforma and later transferred to Microsoft Office Excel and data. Continuous variables will be presented as mean ± standard deviation, and category table variables will be presented as count and percentage. Data will be checked for normality before statistical analysis. The data are calculated in frequency and percentages represented in histograms and pie diagrams. Statistical analysis will be done by a Statistical Package for the Social Sciences 26.0 V version.

RESULTS

The participants' average age was 51.9333% of a lifetime. Based on the 60 study participants, the majority of subjects were between the ages of 41 and 50 (n = 22), which included 36.70% of patients, followed by patients between the ages of 51 and 60 (n = 13), which included 21.70% of patients, and patients between the ages of 31 and 40 (n = 11), which included 18.30% of patients, patients between the ages of 61 and 70 (n = 8), which included 13.30% of patients, and patients aged 71 and above (n = 6), which included 10% of patients, as indicated in [Table 1].

Table 1: Age-wise distribution of subjects

S. No.	Age groups (years)	(n=60)	Percent
1.	31–40	11	18.30
2.	41–50	22	36.70
3.	51–60	13	21.70
4.	61–70	8	13.30
5.	71 and above years	6	10.00

Table 2: Distribution of subjects based on gender

S. No	Gender	Frequency	Percent
1.	Male	16	26.70
2.	Female	44	73.30
	Total	60	100.00

Table 3: Distribution of subjects based on type of cancer

S. No	Type of cancer	Frequency	Percent
1.	Ca. Cervix	41	68.30
2.	Ca. Hypophyrynx	2	3.30
3.	Ca. Larynx	4	6.70
4.	Ca. Left nasal cavity	1	1.70
5.	Ca. Nasopharynx	1	1.70
6.	Ca. Oral cavity	2	3.30
7.	Ca. Tongue	6	10.00
8.	Ca. Left lower alveolus	1	1.70
9.	Ca. Oropharhnx	1	1.70
10.	Ca. Vocal cord	1	1.70
	Total	60	100.00

Table 3a: Distribution of subjects based on type of cancer

S. No.	Type	Frequency	Percent
1.	Ca. Cervix	41	68.3
2.	Ca. Head and neck region	19	31.66

In our study, 73.30% of participants were female, and 26.70% were male. The subjects have been divided according to gender, as demonstrated in [Table 2].

Tumor characteristics

In this study, we include carcinoma of the uterine cervix consisting of 68.3% of patients and carcinoma of the head-and-neck region consisting of 31.66% of patients as shown in [Table 3a].

Type of cancer

In this study, we include carcinoma uterine cervix consisting of 68.3% of patients and head-and neck carcinoma. It includes cancer of the tongue consisting 10% of patients followed by cancer of the larynx in 6.7% of patients followed by cancer of the oral cavity consisting 3.30% of patients followed by cancer of the hypopharynx consisting 3.30% of patients followed by cancer of nasal cavity consisting 1.70% of patients followed with cancer of the nasopharynx consisting 1.70% of patients followed with cancer of lower alveolus consisting 1.70% of patients followed with cancer of the oropharynx consisting 1.70% of patients followed with cancer of vocal cord consisting 1.70% of patients as shown in [Table 3b].

Treatment characteristics

Hematological profiles

Distribution of subjects based on hemoglobin: In this study, we include hemoglobin to determine the anemia. The study

Table 4: Distribution of subjects based on haemoglobin

S. No.	Haemoglobin	*n*/%	Haemoglobin				Total
			Normal	Grade 1	Grade 2	Grade 3	
1.	Baseline	*n*	36	11	9	4	60
		%	25.90	15.70	23.10	66.70	23.60
2.	1st Week	*n*	34	17	9	0	60
		%	24.50	24.30	23.10	0.00	23.60
3.	2nd week	*n*	35	13	8	1	57
		%	25.20	18.60	20.50	16.70	22.40
4.	3rd week	*n*	18	15	8	0	41
		%	12.90	21.40	20.50	0.00	16.10
5.	4th week	*n*	12	9	4	1	26
		%	8.60	12.90	10.30	16.70	10.20
6.	5th week	*n*	4	4	1	0	9
		%	2.90	5.70	2.60	0.00	3.50
7.	6th week	*n*	0	1	0	0	1
		%	0.00	1.40	0.00	0.00	0.40
Total		*n*	139	70	39	6	254
		%	100.00	100.00	100.00	100.00	100.00

P=0.755

Table 5: Distribution based on hematological parameters

S. No.	Parameters	Value (*n*)	Mean	SD	*P*-value
1.	Haemoglobin (g/dL)				
	Baseline	60	11.65	2.29	0.755
	1st week	60	11.77	1.77	
	2nd week	57	11.95	1.88	
	3rd week	41	11.47	1.75	
	4th week	26	11.33	1.76	
	5th week	9	12.07	1.95	
	6th week	1	10.40	0.00	
	Total	254	11.69	1.92	
2.	Platelet count (lakhs/cumm)				
	Baseline	60	3.12	0.90	0.009
	1st week	60	2.97	0.98	
	2nd week	57	2.74	0.86	
	3rd week	41	2.53	0.73	
	4th week	26	2.52	0.84	
	5th week	9	2.95	0.61	
	6th week	1	3.35	0.00	
	Total	254	2.84	0.89	
3.	Neutrophils (%)				
	Baseline	60	65.43	12.97	0.001
	1st week	60	73.42	11.71	
	2nd week	57	76.93	9.83	
	3rd week	41	79.90	8.67	
	4th week	26	75.00	11.89	
	5th week	9	72.22	11.25	
	6th week	1	83.00	0.00	
	Total	254	73.52	12.16	
4.	ALC				
	Baseline	60	1536.30	847.51	0.001
	1st week	60	996.18	682.42	
	2nd week	57	712.23	534.38	
	3rd week	41	585.80	500.39	
	4th week	26	619.50	511.07	
	5th week	9	633.44	440.29	
	6th week	1	250.00	0.00	
	Total	254	939.46	737.37	
5.	WBC				
	Leukopenia	23	4.6	2.059	0.001

WBC: White blood cell, SD: Standard deviation, ALC: Absolute lymphocyte count

includes baseline therapy week-wise RT therapies and grade-wise hemoglobin values (Grade – I, II, III and IV). In this therapy, we observed a small increase in hemoglobin in the 1st week at Grade 1, followed by the 3rd week (n = 15), 2nd week (n = 13), 4th week (n = 9), 5th week (n = 4), and 6th week (n = 1). In Grade 2, we found a modest increase in hemoglobin in the 1st week (n = 9), followed by the 2nd week (n = 8). Third week (n = 8), 4th week (n = 4), 5th week (n = 1), and 6th week (n = 0). In Grade 3, we observed a small increase in hemoglobin in the 2nd week (n = 1), followed by the 4th week (n = 1), 1st week (n = 0), 5th week (n = 0), and 6th week (n = 0) 9 [Tables 4 and 5].

Table 6: Distribution of subjects according to platelet count

S. No.	Platelet count	Platelet count		Total
		Normal	Grade 1	
1.	Baseline			
	n	8	52	60
	%	47.10	21.90	23.60
2.	1st week			
	n	4	56	60
	%	23.50	23.60	23.60
3	2nd week			
	n	3	54	57
	%	17.60	22.80	22.40
4.	3rd week			
	n	0	41	41
	%	0.00	17.30	16.10
5.	4th week			
	n	2	24	26
	%	11.80	10.10	10.20
6.	5th week			
	n	0	9	9
	%	0.00	3.80	3.50
7.	6th week			
	n	0	1	1
	%	0.00	0.40	0.40
	Total			
	n	17	237	254
	%	100.00	100.00	100.00

P=0.009

In the study, we include platelet count to determine the thrombocytopenia. The study includes baseline therapy week-wise RT therapies and Grade wise platelet count values (Grades – I, II, III, IV). However, we included only Grade 1 because all the patients are in Grade 1. We have seen a minor increase in the 1st week (n = 56) of this therapy, which is followed by the 2nd week (n = 54), the 3rd week (n = 41), the 4th week (n = 24), the 5th week (n = 9), and the 6th week (n = 1) [Tables 5 and 6].

In this study, we include a neutrophil count to determine the neutropenia. This study includes baseline therapy week-wise

Table 7: Neutrophils grading

S. No.	Neutrophils	Neutrophils				Total
		Normal	Grade 1	Grade 2	Grade 4	
1.	Baseline					
	n	55	4	0	1	60
	%	23.60	26.70	0.00	100.00	23.60
2.	1st week					
	n	58	2	0	0	60
	%	24.90	13.30	0.00	0.00	23.60
3.	2nd week					
	n	52	3	2	0	57
	%	22.30	20.00	40.00	0.00	22.40
4.	3rd week					
	n	37	3	1	0	41
	%	15.90	20.00	20.00	0.00	16.10
5.	4th week					
	n	22	3	1	0	26
	%	9.40	20.00	20.00	0.00	10.20
6.	5th week					
	n	8	0	1	0	9
	%	3.40	0.00	20.00	0.00	3.50
7.	6th week					
	n	1	0	0	0	1
	%	0.40	0.00	0.00	0.00	0.40
	Total					
	n	233	15	5	1	254
	%	100.00	100.00	100.00	100.00	100.00

RT therapies and Grade neutrophil values (Grade – I, II, III, IV). In Grade 1, we have found a minor increase in the 2nd week ($n = 3$), 3rd week ($n = 3$), and 4th week ($n = 3$), followed by the 1st week ($n = 2$). Weeks 5 and 6 ($n = 0$). In grade 2, we saw a minor increase in the 2nd week ($n = 2$) followed by the 3rd week ($n = 1$). 4th week ($n = 1$) and 5th week ($n = 0$). In Grades 3 and 4, no patients have been reported [Tables 5 and 7].

In the study, we include lymphocyte count to determine the lymphopenia this study includes baseline therapy, week-wise RT therapies, and grade-wise lymphocyte values (Grade – I, II, III, IV). In Grade 1, we saw a minor increase in week 1 ($n = 29$), followed by the 2nd week ($n = 15$), 3rd week ($n = 9$), 4th week ($n = 6$), 5th week ($n = 1$), and 6th week ($n = 0$). In Grade 2, we have noticed a minor increase in the 2nd week ($n = 15$), followed by the 1st week ($n = 14$) and the 3rd week ($n = 7$) 4th week ($n = 6$), the 5th week ($n = 3$), and the 6th week ($n = 0$). In Grade 3, there was a minor increase in the 2nd week ($n = 23$), followed by the 3rd week ($n = 20$), 1st week ($n = 12$), and 4th week ($n = 11$). Week 5 ($n = 5$) 6th week ($n = 1$). In Grade 4, we saw a minor increase in the 1st week ($n = 5$), and the 3rd week ($n = 5$). Followed by 2nd week ($n = 3$) 4th week ($n = 3$) and 5th week ($n = 0$) [Tables 5 and 8].

In this study, we include white blood cell count to determine the leucopenia. In this study, we include week-wise therapies. We observed a minor rise in the 3rd week ($n = 8$), followed by the 2nd week ($n = 5$), 4th week ($n = 5$), 1st week ($n = 3$), and 5th week ($n = 2$) [Tables 5 and 9].

DISCUSSION

In our country, HNCs among men and carcinoma of the uterine cervix among female gynecological cancer are the most prevalent cancers in India. Nearly 60–70% of individuals with HNC present as a locally progressed illness. Most patients with HNC and carcinoma of the cervix present at locally advanced stages and advanced stages such as Stage III and Stage IV. Concurrent chemo-radiation therapy has been considered a standard therapeutic approach for locally advanced cancers.[9] Hematological toxicity has been observed as one of the most common toxicities among patients receiving chemoradiation therapy. Our study has demonstrated chemotherapy-induced hematological toxicities Such as anemia, neutropenia, leukopenia, thrombocytopenia, and lymphocytopenia as discussed

Table 8: Distribution of subjects based on lymphocyte count

S. No.	ALC	ALC					Total
		Normal	Grade 1	Grade 2	Grade 3	Grade 4	
1.	Baseline						
	n	2	43	6	8	1	60
	%	66.70	41.70	11.80	10.00	5.90	23.60
2.	1st week						
	n	0	29	14	12	5	60
	%	0.00	28.20	27.50	15.00	29.40	23.60
3.	2nd week						
	n	1	15	15	23	3	57
	%	33.30	14.60	29.40	28.80	17.60	22.40
4.	3rd week						
	n	0	9	7	20	5	41
	%	0.00	8.70	13.70	25.00	29.40	16.10
5.	4th week						
	n	0	6	6	11	3	26
	%	0.00	5.80	11.80	13.80	17.60	10.20
6.	5th week						
	n	0	1	3	5	0	9
	%	0.00	1.00	5.90	6.20	0.00	3.50
7.	6th week						
	n	0	0	0	1	0	1
	%	0.00	0.00	0.00	1.20	0.00	0.40
	Total						
	n	3	103	51	80	17	254
	%	100.00	100.00	100.00	100.00	100.00	100.00

P=0.001. ALC: Absolute lymphocyte count

Table 9: Distribution of subjects based on WBC count

Sl. No	RT therapy weeks	No. of patients with leukopenia	Number of members (%)
1.	1stWeek	3	5
2.	2nd Week	5	8.3
3.	3rdWeek	8	13.3
4.	4thWeek	5	8.3
5.	5thWeek	2	3.3

P=0.001. WBC: White blood cell

below – The current study sample was mostly composed of women with uterine cervical cancer between the age group of 30 and 70 years. In this present study, the observed weekly hematological toxicities among patients during the treatment period were documented and described as follows: The features of anemia have been documented. Grade 1 toxicities were detected higher during the 1st week of therapy (24%), while Grade 3 toxicities were observed in the 2nd and 4th weeks (16%). The Grade 1 toxicities of thrombocytopenia have been observed more during the 1st week of treatment (23.6%) and lowest at the 6th week of treatment (0.40%).[4] No Grade 2–Grade 5 toxicities were observed. The Grade 1 neutropenia toxicities have been observed more during the 2nd, 3rd, and 4th week of the treatment (20%) and Grade 4 toxicities have been observed more during the 5th week. In Grade 1, lymphocytopenia toxicities have been observed more during the 2nd week of the treatment (29.40%), and Grade 4 toxicities have been observed more during 1st week and 3rd week. The leucopenia was observed to be higher during the 3rd week (n = 8) patients consisting (13.3%) and lower during the 5th week (n = 2) patients consisting (3.3%). The above toxicities observed in our study were found to half more or less similar trend regarding their occurrence in the previous studies by Baruah *et al*. However, these toxicities were found to be predictable, non-serious, and self-limiting, spontaneously resolving non-deleterious complications as part of chemoradiotherapy in solid malignancies such as both uterine cervical cancer and HNC.

Limitation of the study

- Relatively small sample size
- Relatively short duration follow-up
- No correlation between the hematological toxicities and local tumor control and survival was.

CONCLUSION

From the above findings as observed in our present study, it may therefore be concluded that hematological toxicity such as anemia, neutropenia, thrombocytopenia, leucopenia, and lymphocytopenia are commonly observed laboratory findings among patients receiving concurrent chemoradiation therapy in cancer of the uterine cervix and head-and-neck region. Although the above side effects are frequently observed and predictable, non-deleterious, and self-limiting in more circumstances, then adverse events such as febrile neutropenia and severe thrombocytopenia and anemia might occur during and post-treatment follow-up period, which needs a prompt and timely intervention to avoid life-threatening complications. However, the inclusion of more study subjects and longer follow-up may be done to evaluate the impact of hematological toxicity on local tumor control and survival.

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