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A Retrospective Study of Influence/Impact/Effect of Baseline/Pretreatment hemoglobin (Hb) level on Treatment outcomes of Cancer Cervix Patients Treated at a regional cancer center

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Abstract

Aim: The impact of anemia in outcome of treatment results in cancer patients has been recognized since long. Cancer cervix is a fairly common malignancy encountered in most of the radiotherapy out patient department in India. Anemia is very commonly seen in most of the cases of cancer of cervix. .

Methods: In the present study, we collected data of treatment results of FIGO stage II and III cancer cervix patients retrospectively treated in years of 2009-10. We have tried to assess the outcome of results in patients whom baseline haemoglobin level below 10g/dl & 10g/dl and above.

Results: Out of 200 patients of disease with baseline hemoglobin less than 10 gm/dl,120(60%) patients had no residual disease and 80 (40%) patients had residual disease after 4 weeks of completion of treatment. Out of 168 patients with baseline Hb more than 10 gm/dl, 126(75%) patients had no residual disease and 42(25 %) had residual disease.

Conclusion: Our study shows that there is a good disease control at local site in patients with higher pretreatment Hb level. Effect of pretreatment Hb on treatment outcome in terms of overall survival, disease free survival, and local relapse free survival should be studied in detail.

Keywords: Cancer, Anemia, Hb

Introduction

With advances in newer technologies in Radiotherapy, Surgery, Chemotherapy and better understanding of disease process & detection capabilities, it is often possible to give the patient, a reasonably good survival & quality of life. There are certain aspects which are either overlooked or are not being given their due importance. One of these aspects is "Anemia". Anemia is a known and recognized disorder related to cancer. The importance of anemia is ignored because patients

may experience only functional anemia i.e. Haemoglobin (Hb) less than 12.0 g/dl. Efforts to correct anemia are often not done till physiologic anemia is discovered i.e. Hb less than 8 g/dl.

Cancer of cervix is a fairly common malignancy encountered in most of the radiotherapy out patient department in India. Anemia is particularly very commonly seen in most of the cases of cancer of cervix. Cervical cancer continues to be a significant health burden in developing countries such as India, Latin America, Southern and Eastern Africa where the majority of cases are locally advanced at diagnosis; hence, radiation remains the most frequently used modality of treatment. . In our center, carcinoma of uterine cervix accounts for approximately 8-10% of all malignancies and about 20 % of all the malignancies in female patients registered in the department . Anemia has long been reported to adversely affect the efficacy of radiation treatment in cervical cancer [1].Studies have shown that hemoglobin (Hb) level is a prognostic factor for treatment outcome [2]. Most of the studies conducted on treatment outcome of carcinoma cervix in relation to hemoglobin level are in the western literature and it is not clear whether the same results can be reproduced in Indian patients. In the present study we have chosen to retrospectively see the impact of anemia in treatment of cancer cervix.

Material and methods

A total of 1104 cases of carcinoma cervix were registered in the department of radiotherapy at study center from January 2009 to December 2010. The collected data included Hb level at presentation , details of the treatment regimen, and outcomes. Cases of FIGO stage I & IV, post operative cases and patients who were non-compliant with treatment schedule were excluded from the study. Out of total 1104 cases, only 368 patients of squamous cell carcinoma cervix, stage II & III who completed their treatment were found to be fit for study purpose after above exclusion criteria. All 368 cases were investigated for routine hematological, biochemical examination, X-ray chest, and ultrasonography of abdomen and pelvis before starting treatment. All patients were examined and staged clinically according to the FIGO staging system. Details of characteristics of patient population is shown in Table no I.

Table 1: Pretreatment characteristics for patient population

Variable	Parameter	Number of Patients (%)
Age	Less than Fifty years	151(41.03%)
	More than and equal to Fifty years	217(58.96%)
FIGO Stage	IIA	50(13.58%)
	IIB	102(27.71%)
	IIIA	94(25.54%)
	IIIB	122(33.15%)
Pretreatment Hemoglobin level	Less than 10 gm/dl	200(54.34%)
	More than or eqal to 10 gm/dl	168(45.62%)
ECOG grade	0-Fully active, able to carry on all pre-disease performance without restriction	30(8.15%)

	1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	170(46.19%)
	2-Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours	147(39.94%)
	3-Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours	22(5.97%)
Pathology	Squamous cell carcinoma-Keratinising type	221(60.05%)
	Squamous cell carcinoma-Nonkeratinising type	125(33.96%)
	Squamous cell carcinoma-Nonspecified otherwise	22(5.97%)
Treatment Schedule	Continuous	265(72.02%)
	Interrupted due to toxicity of treatment	103(27.98%)
Major presenting Symptoms	Postcoital bleed or Vaginal spotting	68(18.47%)
	Vaginal discharge	172(46.73%)
	Frank bleeding per vagina	103(27.98%)
	Other	25(6.79%)

All study cases with normal hematological, renal and hepatic function, and no prior chemotherapy, radiotherapy or surgery were subjected to concomitant chemoradiation. External beam radiotherapy (EBRT) was administered to the whole pelvis to a total dose of 50 Gray(Gy) in 25 fractions over a period of 5 weeks using a Cobalt-60 machine (780 E & 780 C) and Linear Accelerator. After completion of external radiotherapy all the cases were examined for fitness for brachytherapy. Patients were planned for brachytherapy within 10-14 days. All cases were given three fractions of HighDoseRate- IntraCavitary Radiotherapy(HDR-ICRT)(7.5Gy/fr) with a interwal of ??. The Fletcher suit applicator was used in all patients. The total equivalent dose delivered to point A was 79-85Gy. Cisplatin 40 mg/m2 weekly during radiotherapy was given as a chemotherapeutic/chemosensitiser agent after adequate hydration.

Treatment was withheld and delay of one week was also allowed in the event of radiation-related gastrointestinal or genitourinary toxicity. Patients were assessed in every 2 weeks during treatment for disease response and every week for toxicities. Weekly hemograms and complete blood biochemical examination for liver and renal functions were done in all patients. ECOG toxicity criteria were used for monitoring and documentation of hematological toxicities. When hemoglobin was below 8gm/dl, patient was considered for blood transfusion.

First follow up examination was done at four weeks after completion of treatment. A complete gynecological examination accompanied with systemic examination was performed. Patients who had persistent tumor on completion of treatment were labelled as a residual disease.Local site response rate at 4 weeks after completion of treatment was the primary end point for analysis. To check the disease response in

relation to baseline hemoglobin level, we divided patients in two groups, first group with hemoglobin less than 10 gm/dl, second group with hemoglobin more than or equal to 10 gm/dl. Local response was labeled either as no residual disease or presence of residual disease. The various prognostic factors affecting response were analyzed with the statistical software (SPSS, Version-14). The Chi-square test was used to compare proportions. A two-tailed probability (p0) value of less than 0.05 was considered as statistically significant.

Results

Overall, 122 (33.15%) patients were having residual disease at 4 weeks after completion of treatment. Details of disease status on first follow up in relation to stage is shown in Table no. II.

Table 2: Disease status on first follow up in relation to stage.

FIGO Stage of disease	No. of patients	No. of patients with no residual disease	No. of patients with residual disease
Stage II	152	113(74.34%)	39(25.65%)
IIA	50	38(76%)	12(24%)
IIB	102	75(73.53%)	27(26.47%)
Stage III	216	133(61.58%)	83(38.42%)
IIIA	94	63(67.07%)	31(32.97%)
IIIB	122	70(57.38%)	52(42.62%)

Out of 152 patients of stage II disease, 113(74.34%)patients had no residual disease and 39 (25.65%) patients had residual disease. Out of 216 patients with stage III,133 (61.58%) patients had no residual disease and 83(38.42%) patients had residual disease.

Details of disease status on first follow up with respect to pretreatment Hb level is shown in Table no. III.

Table 3: Details of disease status on first follow up with respect to pretreatment Hemoglobin(Hb) level

Pretreatment Hemoglobin level(Hb)	Disease status	Stage IIA	Stage IIB	Stage IIIA	Stage IIIB
Hb less than 10 gm/dl	No residual disease	12/16(75%)	23/34(67.65%)	40/64(62.5%)	45(52.33%)
	Residual disease	4/16(25%)	11/34(32.35%)	24/64(37.5%)	41/86(47.67%)
Hb more than or eqal to 10 gm/dl	No residual disease	26/34(76.48%)	52/68(76.48%)	23/30(76.67%)	25/36(69.45%)
	Residual disease	8/34(23.52%)	16/68(23.52%)	7/30(23.33%)	11/36(30.55%)

Out of 16 patients for stage IIA with Hb less than 10 gm/dl,12(75%) patients had no residual disease and 4(25%) patients had residual disease. Out of 34 patients with IIA with baseline Hb more than 10 gm/dl, 26(76.48%) patients had no residual disease and 8(23.52%) had residual disease.

Out of 34 patients for stage IIB with Hb less than 10 gm/dl ,23(67.65%) patients had no residual disease and

11(32.35%) patients had residual disease. Out of 68 patients with IIB with baseline Hb more than 10 gm/dl,52(76.48%) patients had no residual disease and 16(23.52%) had residual disease.

Out of 64 patients of stage IIIA disease with baseline hemoglobin less than 10 gm/dl,40(62.5%) patients had no residual disease and 24 (37.5%) patients had residual disease. Out of 30 patients with IIIA with baseline Hb more than 10 gm/dl, 23(76.67%) patients had no residual disease and 7(23.33%) had residual disease.

Out of 86 patients of stage IIIB disease with baseline hemoglobin less than 10 gm/dl,45(52.33%) patients had no residual disease and 41 (47.67%) patients had residual disease. Out of 36 patients with IIIB with baseline Hb more than 10 gm/dl, 25(69.45%) patients had no residual disease and 11(30.55%) had residual disease.

Discussion

The causes of anemia related to cancer may be many. The common ones being disease process involving marrow, bleeding from tumor site, tumor affecting the kidneys thus decreasing the production of erythropoietin etc. Anemia can also be profoundly seen in nutritionally deprived and cachexic patients. Anemia can also be the result of treatment i.e. chemotherapy or large field of radiotherapy involving the important sites of blood formation. Although stage, tumor volume, histologic type of the lesion, and vascular or lymphatic invasion are known to affect the prognosis of patients with cervical carcinoma.[3]. Hemoglobin levels have also been the subject of extensive investigation in this regard.

The oxygenation level of solid tumors is affected by Hb level [4,5,6] & current concepts favour anemia as a cause of tumor hypoxia leading to loco-regional failure. Aggressive management of anemia when carefully incorporated in management of cancer significantly improve the clinical outcome [7,8] Blomer et al [9] suggested that anemia may be a significant independent prognostic factor for treatment response and survival in patients on chemotherapy or radiotherapy. Girinski et al, [10] in his retrospective analyses, has reported that a hemoglobin less than 10 gm% during or before radiation treatment was associated with reduced cause-specific survival and locoregional control.Results of different studies showing relationship between treatment outcome of Carcinoma Cervix and Anemia shown in table IV.

Table 4: Other studies showing relationship between treatment outcome of Carcinoma Cervix and Anemia.

Author	Total number of patients	Cut-off Hemoglobin(Hb) level	Parameter	Results
Haensgen et Al. [15]	70	Hb<11	3 year Survival rate	27%
		Hb>=11	3 year Sourvival rate	62%
Bush RS.[5]	1055	Hb<9(29)	Local Relapse Rate Distant Relapse Rate	0.46 0.18
		Hb-10-11.9(319)	Local Relapse Rate & Distant Relapse Rate	0.29 & 0.24

		Hb-12-13.9(578)	Local Relapse Rate & Distant Relapse Rate	0.20 & 0.16
		Hb>=14(129)	Local Relapse Rate & Distant Relapse Rate	0.20 & 0.18
Girinski et Al[10].	386	Hb <10	Significant Higher Risk of Local Relapse Rate than Hb>=10	
Thomas G.[2]	605	Average Weekly Nadir Hb >=12	Local control Rate & Disease free Survival Rate high compared to Hb<12 gm/dl	
Grigiene R.[14]	162	Hb>=12 gm/dl	In both Univariate and Multivariate Analysis, Hb >12 had a significant influence on Overall Survival ,Disease Free Survival ,Local Relapse Free Survival	

Among studies that have demonstrated a relationship between Hemoglobin level and prognosis in patients with locally advanced carcinoma cervix[5,10,11],strongest evidence that anemia plays a causative role in pelvic recurrence comes from a small 1978 randomised study conducted at Princess Margaret hospital by Bush RS [5]. Subsequently, Thomas [2] reviewed the Canadian experience and found that in 605 eligible patients with cervical cancer, 25% received blood transfusions, most frequently when Hb was below 10 gm/dl. On multivariate analysis baseline Hb was not a significant prognostic factor, but average weekly nadir during radiation therapy was significant.Those patients with values higher than 12 gm/dl had lower incidence of local relapses and distant metastasis and better 5-year survival than patients with lower Hb levels.

In another study done by S K Azad,V Choudhary, at Dr. B.R.A.M. Hospital, R.C.C, Raipur, India in a group with pretreatment Hb less than 10 gm/dl did not show any impact on treatment outcome(p=0.194).[13] In our study pretreatment Hb shows impact on treatment outcome in terms of residual disease(p--). ?This might be explained by use of chemotherapeutic agent along with radiotherapy.

A retrospective study was carried out by Girinski at Department of Radiotherapy, Gustave-Roussy institute, Villejuif, France on 386 patients with advanced cervical carcinomas treated with radiation therapy between 1973 and 1983.[10] The influence of hemoglobin concentrations and blood transfusions before and/or during treatment on the occurrence of distant and/or local regional failures were examined in a univariate and multivariate analyses. In the multivariate analysis hemoglobin concentrations were prognostic only during treatment and patients with at least one value below the threshold of 10 gm% had a significantly higher risk of local regional failure than the patients with all their values above the threshold. Moreover 70% of these high risk patients had less than half of their values below the threshold. It is possible that blood transfusions might be beneficial when given before treatment. However, although it was not significant, blood transfusions given during treatment tended to be an adverse prognostic factor suggesting that blood transfusions might not have completely offset acute anemia prior to transfusion. This study suggests that

anemia during treatment, even of short duration might be detrimental to patients. Similarly our study results show high risk of local failure but at the same time distant failure was not considered.

Grigiene et al. conducted study at Institute of Oncology, Vilnius University, Lithuania to evaluate the prognostic value of anemia in uterine cervical carcinoma patients treated with irradiation [14]. This study indicates hemoglobin level before treatment is a significant prognostic factor for patients with uterine cervical carcinoma treated with irradiation .In our study, cut off value for Hb was taken as 10 gm/dl, and results were described in terms of local disease response at completion of treatment and after 4 weeks thereafter.

Haensgen et al. [15], studied in vivo oxygenation and patient hemoglobin level in 70 patients with stage IIB to IVA cervical cancer treated with EBRT and brachytherapy. Patients with hemoglobin <11 g/dL had a 3-year survival rate of 27%, compared with 62% in those with hemoglobin >11 g/dL (p = 0.006).Advanced stage and pretreatment hemoglobin are independent prognostic factors in cervical carcinoma.

Conclusion

Thus our study shows that there is a good disease control at local site in patients with higher pretreatment Hb level. Effect of pretreatment Hb on treatment outcome in terms of overall survival, disease free survival, and local relapse free survival should be studied in detail.

Authors of this study advise large scale prospective randomized univariate and multivariate trials to further analyse the effect of anemia on treatment outcomes. Other factors such as role of erythropoietin with simultaneous administration of iron to correct anemia and thereby treatment outcome should be evaluated.

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