Prognostic Value of Hemoglobin Levels Prior to Radiotherapy for Cervical cancer – Kuwait Experience

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Abstract

Objective

To evaluate hemoglobin (Hb) levels before and during radiotherapy and its role as a prognostic factor on treatment results of patients treated for cancer cervix.

Materials and Methods

One hundred and seven patients with cervical cancer were registered and managed at KCCC during 1995 – 1999. The pre-treatment and mid treatment Hb levels were found for 47 patients only. Follow-up was done for these cases aiming at evaluation the overall and disease-free survival. Statistical analysis was done using SPSS statistical package version 10.0.

Results

The median age of patients were 45 and ranged between 26-80 years. Kuwaiti patients represented 21.3% of cases. The most common stage was Stage IIb representing 51.1% followed by IIIb representing 27.7%. Stage Ib and IIa represented 12.8%. About 89.4% were squamous cell carcinoma, while adenocarcinoma was 6.4%. Treatment outcome revealed 18 relapses (38.3%). Disease-free survival for cases with pre-treatment Hb level < 12 was 16.3%, while for those with Hb level ≥ 12 g/dL it was 62.9%. The difference was statistically significant (P=0.02).

Conclusion

Patients with pre-treatment Hb < 12 g/dL had a significantly lower disease-free survival.

Key words

Cancer cervix, Radiotherapy, Hemoglobin level, Kuwait.

Introduction

In 2003, Gynecological cancers represented about 13% of all female malignancies among Kuwaiti ladies, and about 15% among Non-Kuwait ladies. Mortality from gynecological cancer totaled 1.1/100,000 population in Kuwait in 2002. The Age Standardized Incidence Rate (ASIR) of cancer cervix was estimated at 3.5/100,000 among Kuwaiti females and 5.3/100,000 among Non-Kuwaiti females.(1)

Surgery is the preferred treatment option for patients with early stage cervical cancer. Until 1999, radiotherapy was the standard of care for patients with locally advanced cervical cancer. Recently, five prospective randomized trials reported a reduction of 24% to 51% for the risk of death for patients treated with concurrent chemo-radiation, when compared with conventional radical radiotherapy. As a consequence, chemo-radiation has replaced radiotherapy alone as the current standard of treatment for locally advanced cervical carcinoma.(2)

It is well known that locally advanced disease and adenocarcinoma poorly respond to irradiation. Also, anemia has been reported to adversely affect the efficacy of radiation treatment in cervical cancer.

It is widely acceptable that tumor hypoxia causes radiation resistance. Hypoxia may

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be one of the factors that contribute to local failure in advanced cervical carcinomas treated by radiotherapy. Low hemoglobin (Hb) concentrations before and / or during treatment could cause hypoxia, leading to an increased rate of local failures.[3] More than one third of cervical cancer patients have Hb level < 12 g/dL.[4]

The mechanism by which low hemoglobin level adversely affect survival is not known, but the existence of an increased percentage of hypoxic, relatively radio-resistant tumor cells in anemic patients has been postulated.[5]

Material and Methods

Patients

Cases with primary diagnosis of Cancer of Cervix Uteri presenting at Kuwait Cancer Control Center (KCCC) during 1995-1999, totaled 107 patients.

The medical records of these patients were retrieved. The pre-treatment and mid-treatment hemoglobin level were available for 47 patients only. The following factors were recorded: Age, FIGO stage, Hb level, pathology, mode of treatment, date of recurrence/ death or last follow up. Follow-up was done for these cases aiming at evaluation of survival and treatment failure.

Management

Patients received external beam radiotherapy to the pelvis using CT-based planning system (Helex TMS planning system). Fractions of 1.8- 2.0 Gray were delivered 5 days per week over a period of 4 – 5 weeks, for a total dose of 40-46 Gray depending on the stage of the disease. This was followed by intracavitary single insertion with a dose of 30- 40 Gray to point A using Selectron low dose rate after-loading machine with a dose rate of around 1.5 Gray per hour. This was done 7 to 10 days after the completion of pelvic external beam radiotherapy. The dose to point A was = 80 Gray.

Parametrial boost dose of 10 Gray in 5 fractions with central blocking was offered to patients with advanced stage, on completion of intracavitary treatment. In the group of patients receiving concurrent chemotherapy, Cisplatinum was given intravenously once a week at a dose of 40 mg/m2 body surface area. No chemotherapy was administered during intracavitary brachytherapy.

Statistical Analysis

Statistical analysis was performed using SPSS 10.0 for windows XP. P value was set to 0.05 for this study.

Results

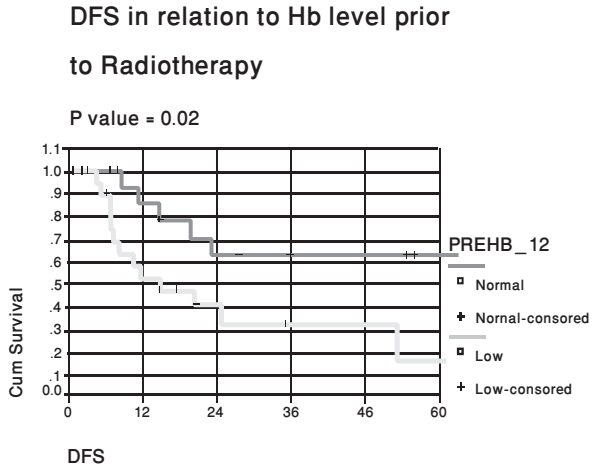
Analysis of data of 47 patients with anemia of the 107 cases of cancer cervix presented to KCCC between 1995 and 1999 showed a median age of 45 years (range 26 – 80 years). Median follow up for all patients was 15 months and ranged form 1 to 84 months. Kuwaiti patients represented 21.3% of cases. The most common stage was stage IIb representing 51.1% followed by IIIb representing 27.7%. Stage Ib and IIa represented 12.8%. About 89.4% had Squamous cell carcinoma and 6.4% had adenocarcinoma. Treatment outcome revealed 18 relapses (38.3%).

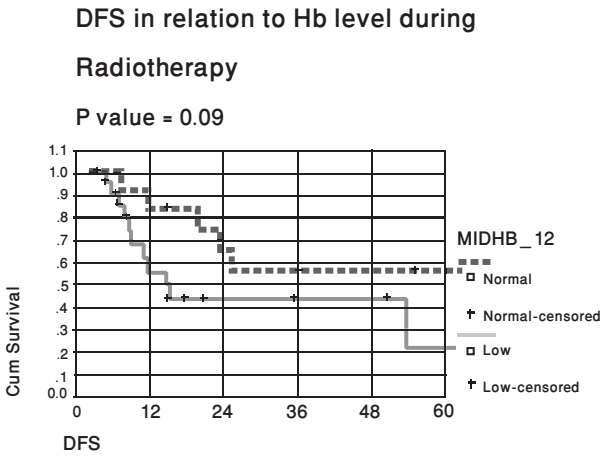
Disease-free survival for cases with pre-treatment Hb level less than 12 g/dl was 16.3% while for those with Hb level equal to or more than 12 g/dl was 62.9%. The difference was significant statistically (P= 0.02). The distribution of patients to stages Ib, IIa, IIb, III and IV was 3, 3, 24, 13 and 4 respectively. Data on the grade of differentiation were available in all patients. Fifty percent were well to moderately differentiated and 50% were poorly differentiated. Further patient's characteristics are given in Table 1.

The median age of patients was 45 and ranged from between 26-80 years. Anemia was found more frequently in patients with advanced stage. Seventy per cent of patients with stage II & IV disease had anemia. However this did not show significant statistical difference (P=0.3). Grade of differentiation showed no significant statistical difference (p=0.6).

	Number (%)	Anemia (%)	P Value
Nationality			
Kuwaiti	10 (21.3)	7 (70.0)	0 .3
Non Kuwaiti	37 (78.7)	20 (54.1)	
Stage			
IB, IIA	6 (12.8)	3 (50.0)	0 .4
IIB	24 (51.1)	12 (50.0)	
III, IV	17 (36.2)	12 (70.6)	
Histology			
Squamous	42 (89.4)	24 (57.1)	0 .33
Adenocarcinoma	3 (6.4)	1 (33.3)	
Others	2 (4.2)	2 (100.0)	
Differentiation			
Well / Moderate	19 (50.0)	12 (63.2)	0 .6
Poor	19 (50.0)	9 (47.4)	

Table 1: Patient's characteristics in relation to anemia prior to radiotherapy.





Recurrence was more prevalent among cases with anemia (48.1%) compared to cases without anemia (25.0%). This finding was not statistically significant. (P=0.14).

Disease-free survival for cases with pre-treatment Hb level less than 12 g/dL was 16.3% while for those with Hb level equal to or more than 12 g/dl was 62.9%. The difference was statistically significant (P= 0.02), (Fig. 1). Neither OS nor DFS showed statistical significance difference in relation to Hb level during treatment. (Fig. 2)

Discussion

Hypoxia is a characteristic feature of solid tumors, which is thought to occur, when tumor growth exceeds the ability of the local microvasculature to supply oxygen. It is thought that about 60% of locally advanced cervical carcinomas contain hypoxic areas of tissue.[6]

The association between anemia and poorer outcomes may reflect more aggressive or extensive tumor burden rather than a direct effect of the anemia itself, but there is evidence that tumor cell hypoxia, potentially exacerbated by anemia, may affect radiosensitivity adversely.[7, 8, 9, 10] Early studies by Bush et al[8] found that although a cure rate of 62% was obtained with radiotherapy for cervical carcinoma, a Hb level of < 12 g/dL during treatment was associated with a significantly higher recurrence rate. The correction of anemia decreased the recurrence rate and increased the cure rate. These results are consistent with the belief that tumor hypoxia is greater in anemic patients and that this

hypoxia influences the radiation local control rate. Disease-free survival also has been found to be associated significantly with Hb level and tumor oxygenation in patients with cervical carcinoma.[11]

A large Canadian study[4] showed that the hemoglobin levels at baseline correlated with patient survival. Those with pretreatment Hb level ≥ 12 g/dL had 12% greater 5-years survival rate. Also the survival data from this study generate the hypothesis that maintaining Hb levels above 12 g/dL can improve the response to radiotherapy.

Although prognostic importance of anemia in cervical cancers is well established, the patho-physiologic mechanisms are controversially discussed even in the recent literature.

Some retrospective investigations have found an independent factor of anemia on prognosis in multivariate analysis.[12]

Other researchers assume that the prognostic significance of anemia results from an association between anemia and tumor volume and that anemia does not exert an independent impact.[13]

Three possible explanations exist to explain why anemia appears to be associated with a worse outcome:

1. The presence of anemia might indicate tumors, which are biologically more aggressive.
2. Anemia might be surrogate marker of tumor hypoxia.
3. A mechanism different from anemia might not only mediate resistance to therapy, but also induce anemia as a consequence.[14]

Disease progression was significantly more likely in patients, who became anemic during chemo-radiation compared to patients, who maintained normal Hb level. This was not the case in our study.

There are several potentially reversible causes of anemia (e.g. nutritional deficiencies and chronic blood loss), which should be sought and, if possible, corrected in patients presenting with anemia. Transfusion of red blood cells is one readily available management option. Recombinant human erythropoietin is an alternative option.[15]

In our univariate analysis, Hb concentration before treatment was prognostic (Fig.1), which is in agreement with many other studies. [3,8,12,16] On the other hand, it did not show statistical significance for those with mid treatment anemia as found in other studies.[14]

Our results are in accordance with the majority of studies, which have demonstrated a significant impact of Hb levels on survival.

Conclusion

This retrospective analysis of cases of cervical carcinoma treated in Kuwait showed that patients with pretreatment Hb value below 12 g/dL had a significantly lower disease free survival.

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