Journal of Cancer and Tumor International

10(2): 48-56, 2020; Article no.JCTI.58604
ISSN: 2454-7360

Hemoglobin Level as a Prognostic Factor for Locally Advanced Bladder Cancer Patients Treated with Radical Radiotherapy

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Authors' contributions

This work was carried out in collaboration among all authors. Author MSZ designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author WNA managed the analyses of the study. Author SHE managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JCTI/2020/v10i230126
Editor(s):
(1) Sri Lakshmi Hyndavi Yeruva, Penn State Health Milton S. Hershey Medical Center, USA.
Reviewers:
(1) Orcun Celik, Tepecik Training and Research Hospital, Turkey.
(2) Kamdev Sethy, Odisha University of Agriculture & Technology, India.
Complete Peer review History: http://www.sdiarticle4.com/review-history/58604

Original Research Article

Received 20 April 2020
Accepted 26 June 2020
Published 29 June 2020

ABSTRACT

Anemia is a common symptom in cancer patients and usually associated with poor prognosis. Urinary bladder cancer (BC) is the most common cancer in the urological tract with anemia being one the most common presenting symptom. Radical radiotherapy is the treatment of choice for advancer disease with many factors could influence the prognosis.

Aim: To identify pre-treatment hemoglobin level as prognostic factor for advanced bladder cancer treated with radiotherapy.

Materials and Methods: A retrospective study reviewed the data of 88 patients with advanced bladder cancer, treated with radical radiotherapy from 2013 to 2018.

Results: Median follow-up was 45 months. The median PFS was 26.87 months but when comparing anemic to non–anemic patient there was significant difference (17.25 and 40.02 months) respectively. Also as regards overall survival the median was 28.98 months but 20.24 and 40.47 months in anemic and non-anemic patients respectively with significant difference. Local or distant progression detected in 36 out of 50 anemic patients compared to only 4 out of 38 non-

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anemic patients. In multivariate analysis anemia was proved to be the strongest predictor of mortality.
Conclusion: Pre-treatment Hb level is an important factor affecting the prognosis of advanced bladder cancer patients treated with radical radiotherapy. Low HB level could be considered as a good biological marker for aggressive disease.

Keywords: Bladder cancer; anemia; prognostic factors.

1. INTRODUCTION

Anemia is a common presentation in cancer patients. It is reported in 31% of newly diagnosed patients with cancer, with hemoglobin (HB) level less than 12.0 g/dL [1].

Many factors are suggested to cause anemia in cancer patients, like iron deficiency, vitamin B12 deficiency and para-neoplastic syndrome [2].

Cancer patients with low HB level are more suggested to have poor prognosis as illustrated by Socinski et al who reported that in non-small lung cancer patients [3]. Even with correction of anemia during therapy, those anemic patients will not give good results as reported by Henry et al. [4].

Urinary bladder cancer (BC) is the most common cancer in the urological tract and most of cases presented with hematuria which lead to manifest anemia before starting treatment [5].

The main line of treatment for early stages bladder cancer is radical cystectomy. Young patients with good performance status (0 and 1) are the best candidates for surgery. However, a great number of patients cannot tolerate surgery because of old age, co-morbid disease or advanced disease and so the option for treatment will be radical radiotherapy [6].

Many researches identify the prognostic factors affecting patients with advanced bladder cancer undergoing radical RT. One of those factors is the pre-treatment hemoglobin (Hb) level. As ionizing radiation is affected by level of oxygen in irradiated tissues, more the degree of anemia, more the level of hypoxia inside the tissue and so resistance to radiotherapy is expected [7].

In this study, a retrospective analysis of data from advanced bladder cancer patients treated with radical RT was done to rule out the great effect of HB level on the course and outcome of the disease.

1.1 Aim of the Work

Our aim was to identify pre-treatment hemoglobin level as prognostic factor affecting local control, progression free survival and overall survival in locally advanced bladder cancer patients treated with radiotherapy.

2. MATERIALS AND METHODS

Eighty-eight patients with locally advanced bladder cancer who were treated in Mansoura university hospital, clinical oncology and nuclear medicine department between Jan 2013 and June 2018. A team consists of radiation oncologists, medical oncologists, and urologists assessed all patients before starting treatment. The stage of the disease was defined using the American Joint Committee on Cancer Staging Manual, 2002 (AJCC, 6th Edition) [8] All patients were underwent either trans-uretheral resection of the bladder (TURB) or cystoscopic biopsy. Pathological assessment was done for all cases. Complete hematological assessment was done before the treatment and according to hemoglobin level, patients were categorized into 2 groups; non-anemic patients with HB equal or more than 12 g/dl (38 patients) and anemic patients with HB less than 12 g/dl (50 patients). All patients treated with radical RT (65 gy weeks with conventional fractionation) since they were not suitable for primary surgery due to advanced disease or comorbid illnesses. 54 patient received chemotherapy concurrent with radiotherapy (single agent cisplatin 35 mg/m2 weekly), 34 patients cannot tolerate chemotherapy and so received radiotherapy alone. Median follow-up period was 45 months (ranged between 21 and 69 months). Evaluations during follow up included clinical examination and radiological assessment every 3 months.

2.1 Statistical Analysis

Analyzation of results was done using the Statistical Package of Social Science (SPSS) program for Windows (Standard version 24). The

normality of data was first tested with one-sample Kolmogorov-Smirnov test.

Qualitative data were described using number and percent while continuous variables were presented as mean ± SD (standard deviation).

Kaplan- Meier test was used for survival analysis and statistical significance of differences among curves was determined by Log-Rank test. Cox regression model was used to predict the most significant determinants for mortality.

2.2 Level of Significance

For all above mentioned statistical tests the results was considered significant when $p \leq 0.05$.

2.3 Ethical Considerations

This study protocol had ethical approval from Medical Research Ethics Committee, Faculty of Medicine, Mansoura University.

3. RESULTS

Patients characteristics are listed in Table 1. 34 patients (38.6%) were presented with age less than 60 years, while 54 (61.4%) patients presented with age equal or more than 60. Majority of cases were males (69 cases 78.6%) and only 19 cases (21.6%) were females. Before receiving radiotherapy, 24 patients (27.3%) were underwent trans-uretheral resection of the bladder. and 64 patients (72.7%) were underwent just biopsy. Pathological assessment was done and according to the pathological type of the tumor, the most common was transitional cell carcinoma (TCC) presented in 66 cases (75%), squamus cell carcinoma (SQ.C.C) in 18 cases (20.5%) and adenocarcinoma in only 4 cases (4.5%). The tumor was identified as low grade in 22 cases (25%) and high grade in 66 cases (75%). All cases were assessed for staging before starting treatment and metastatic cases were excluded. 28 cases (31.8%) were presented with T3 disease and 60 cases (68.2 %) in T4 disease. 8 patients (9.1%) presented with N0 disease, 30 patients (34.1%) with N1, 40 patients (45.5%) with N2 and 10 patients (11.4%) with N3 disease. According to HB level, the median pre-treatment level for all cases were 10.93±2.58 and patients are categorized into anemic group with HB less than 12 g/dl (50 cases, 56.8%) and non-anemic group with HB level equal or more than 12 g/dl (38 cases 43.2%). All cases received radical dose of radiotherapy. 54 patients (61.4%) could have chemotherapy concurrent with radiotherapy and 34 patients (38.6%) could not tolerate chemotherapy so received radiotherapy alone. After the end of the treatment course, all cases were under follow up (median follow up period was 45 months ranged between 21 and 69 months) and at the end of the study, 51 cases were died, 20 cases (22.8%) developed local progression, 15 cases (17%) developed distant metastasis, 5 cases (5.7%) developed both local and distant progression and 48 cases (54.5%) did not develop any progression until they died or lost follow up. The median PFS was 26.87 months and the median OAS was 28.98 months.

Table 2 illustrates the predictors for progression free survival (PFS) and according to statistical analysis PFS was strongly affected by HB level. For cases with HB level less than 12 g/dl PFS was 17.25 months, while for those with level equal or more than 12, it was 40.02 months with significant P- value ≤0.001 and from Kaplan-Meier Survival Curve for PFS as shown in Fig. 1, its noticed that 30 month PFS for non-anemic patients is about 85% while its about 15% for anemic patients. It is also noticed that PFS was better in age less than 60 compared to older cases, T3 stage compared to T4, low grade tumor compared to high grade and in cases received CCRT compared to cases received radiotherapy alone with statistically significant difference. While gender, pathology, N staging and type of surgery before treatment has no significant effect on PFS.

Table 3 indicate predictors for overall survival (OAS). HB level was found to strongly affect OAS. For HB level less than 12 g/dl, OAS was 20. 24 months while in cases with level equal or more than 12 g/dl, it was 40.47 months with significant P-value≤0.001 and from Kaplan-Meier Survival Curve as shown in Fig. 2, the 2 year survival for anemic patients is about 40% while it is near 98% in non-anemic patients. Also, its noticed that young age patients compared to older, cases received CCRT compared to cases received radiotherapy alone and TURB rather than just biopsy were found to significantly affect OAS while gender, pathology, T and N staging was not found to have significant effect.

On multivariate analysis of independent predictors for mortality, only HB level and absence of chemotherapy were found to have significant effect with P-value <0.0001 and 0.016 respectively. All other factors including age,

gender, pathology, staging and type of surgery were found to have non-significant effect. This data confirms the strong effect of HB level as prognostic factor for this disease as shown in Table 4.

Table 5 illustrate the relation between cases who developed failure either local or distant and level of HB. Out of 38 non-anemic patients, only 4 case (10.5%) developed progression. While in anemic patients 36 out of 50 cases (72%) showed local or distant failure. This difference was found to be statistically significant with P-value ≤0.001. Between other parameter examined in this study, also giving chemotherapy concurrent with radiotherapy appear to have some effect on rate or progression as out of 54 patients received CCRT, only 22 cases (40.7%) developed progression local or distant while out of 34 patients did not receive chemotherapy, 18 cases (52.9%) had treatment failure.

Table 1. Patients characteristics among the studied group

Patients characteristics	Study group (n=88)
Age/years	
Mean ± SD	**60.16±6.92**
<60 y	34 (38.6%)
≥60 y	54 (61.4%)
Gender	69 (78.4%)
Male	19 (21.6%)
Female	
Pathology	66 (75%)
TCC	18 (20.5%)
SQ.CC	4 (4.5%)
Adenocarcinoma	
Hemoglobin level	**10.93±2.58**
<12	50 (56.8%)
≥ 12	38 (43.2%)
T staging	28 (31.8%)
T3	60 (68.2%)
T4	
N staging	
0	8 (9.1%)
1	30 (34.1%)
2	40 (45.5%)
3	10 (11.4%)
Grade	22 (25%)
Low	66 (75%)
High	
Pre RT ttt	24 (27.3%)
TURB	64 (72.7%)
Biopsy	
CTH with RT	54 (61.4%)
Received	34 (38.6%)
Not	
Progression	
local	20 (22.8%)
distant	15 (17.0%)
Local+distant	5 (5.7%)
No	48 (54.5%)
PFS	**26.87±12.47**
Overall survival in months	**28.98±11.18**

Table 2. Predictors for progression free survival

Patients characteristics	Progression free survival/ month				
	Mean survival time	Std. error	95% CI	Log rank test	P – value
Age/years	29.79	2.20	25.5-34.1	3.85	0.05*
≤60 y	25.04	1.63	21.8-28.2		
>60 y					
Gender	27.00	1.47	24.1-29.9	0.169	0.681
Male	26.42	3.13	20.3-32.5		
Female					
Pathology	26.00	1.51	23.03-28.9	3.12	0.211
TCC	27.72	3.12	21.6-33.8		
SQ.CC	37.50	4.29	29.1-45.9		
adenocarcinoma					
Hemoglobin level	17.25	0.76	15.8-19.7	67.25	≤0.001*
< 12	40.02	0.93	38.5-48.8		
≥12					
T staging	29.39	2.41	23.7-36.1	4.40	0.036*
T3	26.16	1.59	23.03-29.3		
T4					
N staging	27.78	2.18	23.5-32.07	1.82	0.176
0 &1	26.18	1.66	22.9-29.4		
2 & 3					
Grade	30.7	2.79	22.6-39.6	4.31	0.038*
Low	24.3	1.52	23.5-29.3		
High					
Pre RT ttt	30.29	2.61	25.2-35.4	1.43	0.231
TURB	25.59	1.52	22.6-28.6		
biopsy					
CTH with RT	29.75	1.64	26.5-32.9	5.82	0.016*
Received	22.29	2.03	18.3-26.3		
Not					

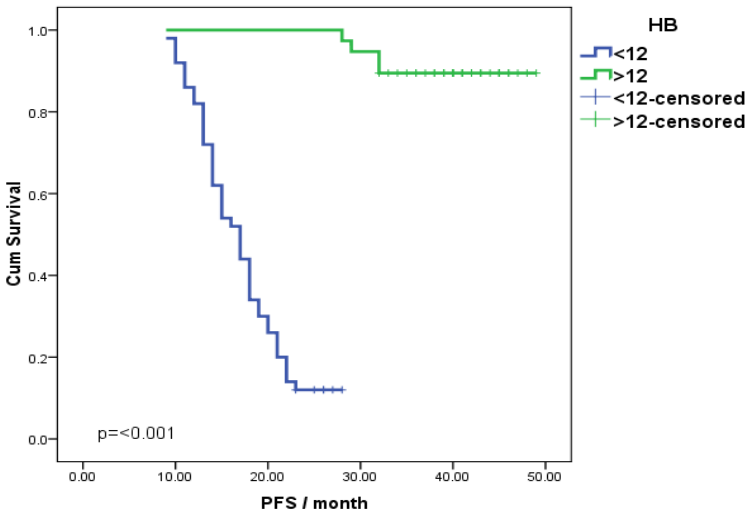

Fig. 1. Kaplan-meier survival curves showing the difference in PFS between anemic and nonanemic patients

Table 3. Predictors for overall survival

Patients characteristics	Overall survival/ month				
	Mean Survival time	Std. Error	95% CI	Log rank test	P – value
Age/years	31.85	1.89	28.2-35.5	4.01	0.045*
≤60 y	27.16	1.49	24.2-30.1		
>60 y					
Gender	29.17	1.31	26.6-31.7	0.108	0.743
Male	28.26	2.86	22.6-33.9		
Female					
Pathology	28.48	1.34	25.8-31.1	2.51	0.285
TCC	28.89	2.94	23.1-34.7		
SQ.CC	37.50	4.29	29.1-45.9		
adenocarcinoma					
Hemoglobin level	20.24	0.72	18.8-21.7	92.7	≤0.001*
<12	40.47	0.73	39.0-41.9		
≥ 12					
T staging	28.86	2.35	24.2-33.5	0.052	0.820
T3	29.03	1.37	26.3-31.7		
T4					
N staging	30.10	1.88	26.4-33.8	2.07	0.15
0 &1	28.12	1.53	25.1-31.1		
2 & 3					
Grade	29.13	2.63	23.97-34.3	0.237	0.626
Low	28.92	1.34	26.30-31.5		
High					
Pre RT ttt	30.58	2.54	25.6-35.6	0.786	0.375
TURB	28.37	1.34	25.7-30.9		
Biopsy					
CTH with RT	31.83	1.43	29.03-34.6	6.39	0.011*
Received	24.44	1.85	20.8-28.1		
Not					
Progression	22.15	1.03	20.1-24.2	40.24	≤0.001*
Yes	34.67	1.60	31.5-37.8		
No					

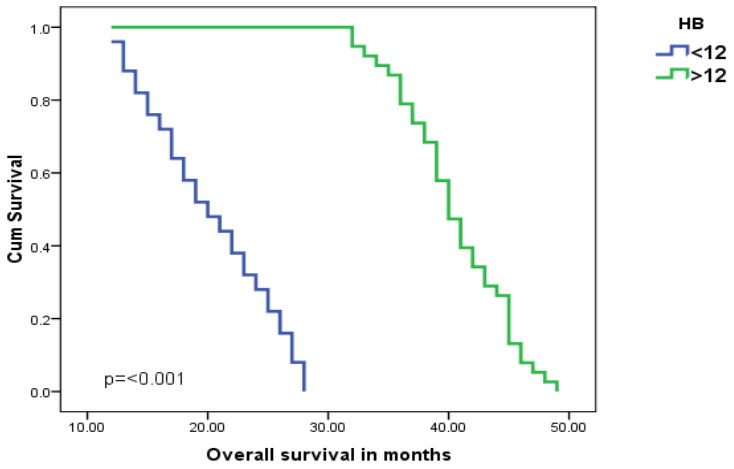

Fig. 2. Kaplan-meier survival curves showing the difference in OAS between anemic and nonanemic patients

4. DISCUSSION

Radical surgery is the main line of treatment for bladder cancer. Radical radiotherapy is indicated in patients with advanced disease or co-morbid condition. The aim of this research was to study the prognostic factors affecting local control and survival in locally advanced bladder cancer patients treated with radical RT.

Milosevic et al concluded that definitive external-beam RT leads to local control of advanced bladder cancer in approximately 30% to 50% of patients but distant metastases then developed in >50% of patients [7]. In our study, local control is achieved in 48 out of 88 cases (54.5%), distant metastasis developed in only 20 cases (22.7%).

Definition of anemia was important before going through the study and according to the WHO, HB level between 12 – 14 g/dl represents an optimal oxygen pressure [9]. Therefore, we defined anemia as HB less than 12 g/dl in our study.

The presence of anemia can be used to predict reduced local control after RT as well as higher rates of distant metastases and death from bladder cancer. Many studies reported that a pre-treatment Hb level less than 12 g/dl is a poor prognostic indicator for tumor response, local control and OAS in patients with bladder cancer. This may be explained by anemia-induced tumor hypoxia, which leads to genetic instability and the emergence of more aggressive metastatic phenotypes. Furthermore, patients who are anemic at diagnosis may be more likely to have advanced disease [10].

Even in cases treated with radical cystectomy, low HB level was found to be a bad prognostic factor. Lei Lei et al. evaluate the impact of preoperative anemia status on the outcome of bladder cancer patients treated with radical cystectomy. And they concluded that Preoperative anemia and low hemoglobin level are associated with earlier recurrence and shorter survival of those patients [11].

In our study, the multivariate analyses showed that the pre-treatment Hb level was the strongest independent prognostic factor for local control, PSF and overall survival comparing anemic to non-anemic patients. Taking into consideration that all anemic patients received blood

Table 4. Cox regression analysis for independent predictors of mortality

Independent predictors	β	SE	P value	HR (95%CI)
Age/years >60 y	0.43	0.22	0.056	1.5 (0.9-2.4)
Gender Male	0.08	0.26	0.75	1.08 (0.6-1.8)
Pathology TCC (r) SQ.CC adenocarcinoma	- 0.68 0.405	- 0.53 0.56	- 0.201 0.470	1 1.9 (0.7-5.6) 1.5 (0.49-4.5)
Hemoglobin <12	2.17	1.2	≤0.001*	17.7 (5.6-201)
T staging T4	0.05	0.23	0.827	1.1 (0.7-1.6)
N staging 2 & 3	0.31	0.22	0.166	1.4 (0.88-2.1
High grade	0.12	0.25	0.641	1.1 (0.7-1.8)
Pre RT ttt Biopsy	0.206	0.24	0.395	1.2 (0.76-1.9)
Not receiving CTH	0.536	0.22	0.016*	1.7 (1.1-2.6)
Recurrence	1.62	0.28	≤0.001*	5.1 (2.9-8.8)

HR: Hazard ratio, CI: Confidence interval, (r); reference group

Table 5. The table showing progression and p-values

	Progression	No progression	P value
HB <12	36 (90%)	14 (29.2%)	≤0.001*
HB ≥ 12	4 (10.5%)	34 (70.8%)	

transfusions during treatment, and the Hb levels were within the normal range during RT, so anemia related hypoxia and radio-resistance are not enough explanation to the question why the local control rate is better in non-anemic compared to anemic patients. Many investigators try to search for other factors that lead to this result and according to one hypothesis they speculated that low Hb levels is not only negatively affect oxygen level inside irradiated tissues leading to radiation resistance, but also low Hb level is an indicator of a more aggressive tumor which is intrinsically radioresistant. Therefore, correction of anemia by blood transfusion during treatment will not alter the end results [7].

A retrospective study was done by Cheng et al on 317 patients diagnosed with BC. 109 patients (34.4%) were anemic and after a median follow up of 6 years, the median recurrence-free survival (RFS), progression-free survival (PFS), and overall survival (OS) were significantly lower in anemic compared to non-anemic patients (p-value 0.001). Multivariate Cox analysis also indicated that anemia remained an independent predictor of PFS and OS (p=0.010, 0.007) [12]. This result is so matched with the results of our study which showed the marked better PFS and OAS in non-anemic patients compared to anemic cases.

Vuslat et al study the effect of using chemotherapy concurrent with radiotherapy in advanced bladder cancer patients and found that it improves local control significantly but without significant effect on OAS [8]. Univariate analysis of our study showed that concurrent chemoradiotherapy significantly increased OAS. This result matches with the study done by A.M. Block et al which revealed a statistically significant improvement in OS with CRT versus RT in muscle invasive bladder cancer. This survival benefit persists irrespective of radiotherapy dose [13].

5. CONCLUSION

Pre-treatment Hb level in advanced bladder cancer patients treated with radical radiotherapy is one of the most important prognostic factors for local control and survival. Anemia may act as a good biological marker for aggressive disease even if corrected during course of treatment.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/58604