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Clinical Value of C-reactive Protein and Erythrocyte Sedimentation Rate in Advanced Bladder Cancer

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Background: The identification of biomarkers would improve the management of advanced urinary bladder carcinoma.
Aim: The current study assessed the potential prognostic role of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in advanced stage bladder cancer.
Methods: Forty-six patients with advanced urinary bladder carcinoma were included in the study. After consent, CRP and ESR were measured before treatment, after 2 cycles of chemotherapy and at the end of treatment. The relation between CRP and ESR serum measurements and patients' characteristics and treatment response were assessed.
Results: Both CRP and ESR were elevated in all included patients with mean values ± standard deviation: 35.43 ± 12.65 and 57.17 ± 18.15, respectively. The baseline CRP level was higher in patients with metastatic disease. ESR was significantly elevated in association with squamous cell carcinoma pathology and hydronephrosis and in patients who died within one year of diagnosis (p = 0.003, 0.001 and 0.03; respectively). Patients who experienced disease progression after 2 cycles of platinum-based chemotherapy had higher levels of CRP and ESR. Serial measurements during the course of treatment revealed that both CRP and ESR levels declined significantly during treatment mainly among responding patients (p = 0.001).
Conclusion: CRP and ESR might be useful noninvasive biomarkers in advanced urinary bladder carcinoma.

Keywords: Bladder cancer, C-reactive protein, Erythrocyte sedimentation rate, Prognosis, Response to chemotherapy.
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INTRODUCTION

Urinary bladder carcinoma represents the most common cancer of the urinary tract [1].

Inflammatory microenvironment may have an important role in the development of bladder cancer and its progression. It is known that there is an association between chronic infection of the urinary tact and invasive bladder carcinoma, specially the squamous cell variant [2].

The rise of erythrocyte sedimentation rate (ESR) and the release of C-reactive protein (CRP) are among the acute phase reactions that occur in response to inflammatory stimulation [3]. It was found that higher CRP level is associated poor prognosis in many cancers including non- Hodgkin's lymphoma, and lung and esophageal cancers [4]. Similarly, elevated ESR levels are associated with un-favourable outcome in malignant tumors like colorectal, renal, head and neck, breast and prostate cancers, soft tissue sarcoma, and glioma [5].

This study aimed at assessing prospectively the prognostic value of CRP and ESR in a cohort of patients with advanced stage bladder cancer.

METHODS

This prospective study was conducted at the Clinical Oncology Department - Menoufia University Hospital in the period from May 2015 to May 2017.

The study included patients who were diagnosed with advanced stage IV urinary bladder carcinoma (T4b N1, T4b N2, any T any N and M1) with good Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1), and adequate renal function (creatinine clearance ≥ 60 ml/min).

All patients known to have chronic inflammatory disease (e.g. liver cirrhosis, bronchial asthma, rheumatic fever…etc), personal history of other malignant tumors or co-morbid major physical illness (e.g. renal, hepatic or heart failure) were excluded from the study.

After consent, patients were subjected to thorough history and clinical examination and complete investigations in the form of: complete blood count (CBC), complete liver functions, complete kidney functions and creatinine clearance, computed tomography (CT) of the chest, abdomen and pelvis and bone scan for staging.

The baseline collected data included personal and tumor characteristics (size, regional lymph node status, histopathology, grade and sites and number of metastases). Staging was based on clinical TNM classification. Cystoscopic biopsy and histopathological examination were used to determine muscle invasiveness

and grades. Metastatic sites were divided into 3 groups, bone, visceral and both visceral and bone metastases. Information on the location of metastatic disease and the number of metastatic sites, number and size of metastases per site were also recorded.

Blood samples were taken from patients to measure CRP and EST at base line, after 2 cycles of chemotherapy and end of treatment. Serum CRP level was estimated using HEALES Full automatic CRP analyzer (Shenzhen Huisong Technology Development Co., Ltd, Shenzhen, China). Reference interval for CRP with the use of this method is from 0 to 5 mg/L. The manual Westergren method was used to measure ESR level. C-reactive protein level >5mg and ESR value >10 were considered elevated (according to the reference of Clinical Pathology Department lab).

All patients received platinum-based chemotherapy. Response was assessed by CTs and cystoscopy and graded according to RECIST criteria.

The relations between the baseline CRP and ESR levels and patients features were estimated. The optimum CRP and ESR cutoff values to predict prognosis was calculated using receiver operating characteristics (ROC) analysis referring response to treatment.

Data were analyzed using SPSS v. 20 (SPSS Inc. Realesed 2011. IBM SPSS statistics for windows, version 20.0, Armnok, NY: IBM Corp.) Student's t-test was used for comparison of normally-distributed quantitative variables between two groups, while Mann Whitney's test was used for comparison of abnormally-distributed quantitative variables between two groups. Wilcoxon test was used to compare 2 consecutive readings of abnormally-distributed data in the same group while Friedman test was used for more than two consecutive measures in the same group of abnormally distributed data. Mcnemar test was used to evaluate multiple testing for paired categorical data measured only 2 times with only 2 outcomes while Cochran's test was used to evaluate multiple testing for paired categorical data measured more than 2 times 2 outcomes. Two sided p value of < 0.05 was considered statistically significant.

RESULTS

Personal characteristics, disease characteristics and treatment received are illustrated in table 1. Thirty-seven patients had metastatic disease and 9 patients had locally advanced disease (T4b N1, T4b N2). All patients had elevated both CRP and ESR at presentation (pretreatment) with mean ± standard deviation (SD) values of 35.43 mg/L ± 12.65 and 57.17 mm ± 18.15, respectively.

Combination chemotherapy (gemcitabine plus cisplatin) was received as palliative treatment in 37 (80.4 %) metastatic patients or as neo-adjuvant treatment in 9 (19.6 %) patients with locally advanced disease. After 2 cycles of chemotherapy, > 2/3 of patients experienced partial response. After 12 months from the date of diagnosis 9(19.6%) patients died due to cancer related causes.

Table 1: Demographic and clinical features of the patients

	No.	%
Age		
Mean (±SD)	57.3 (±9.93)	
Gender		
Male	39	84.8
Female	7	15.2
Smoking		
No	25	54.3
Yes	11	45.7
Schistosomiasis		
No	41	89.1
Yes	5	10.9
Presenting symptoms		
Dysuria	15	32.6
Hematuria	15	32.6
Frequent urination	11	23.9
Urgency	5	10.9
Pathological subtype		
Transitional cell carcinoma	34	73.9
Squamous cell carcinoma	10	21.7
Adenocarcinoma	2	4.3
Grade		
Low grade	20	43.5
High grade	26	56.5
Urine cytology		
Negative	43	93.5
Positive	3	6.5
Hydronephrosis		
Absent	30	65.2
Present	16	34.8
Comorbidities		
None	37	80.4
Diabetes mellitus & hypertension	2	4.3
Hypertension	4	8.7
Diabetes mellitus	3	6.5
Site of distant metastases (37 pts.)		
Bone & visceral	17	47.2
Bone only	12	32.4
Visceral only	8	21.6
Locally advanced vs. metastatic		
Locally advanced	9	19.6
Metastatic	37	80.4
Initial treatment		
Palliative chemotherapy	37	80.4
Neoadjuvant chemotherapy	9	19.6
Response to initial treatment		
Disease progression	9	19.6
Partial response	32	69.6
Stationary disease	5	10.9
Further treatment		
Concomitant chemo-radiotherapy	7	34.8
Surgery	2	8.7
2nd line chemotherapy	7	15.2
Completed 6 cycles of chemotherapy	30	41.3
Status after 1 year follow up		
Alive	37	80.4
Died	9	19.6
ECOG performance status		
0	19	41.3
1	27	58.7
Hemoglobin		
≤10	42	91.3
>10	4	8.7

Table 2: Relation between baseline CRP and ESR and the studied variables

	Baseline CRP, mg/L (Mean ±SD)	**P value**	**Baseline ESR, mm** (Mean ± SD)	**P value**
Gender				
Male	35.17 ± 13.06	0.66	56.41 ± 19.05	0.53
Female	36.85 ± 10.83		61.42 ± 12.14	
Smoking				
No	31.33 ± 9.98	0.03	58.8 ± 19.22	0.63
Yes	38.88 ± 13.79		55.8 ± 17.48	
Schistosomiasis				
No	35.24 ± 13.19	0.55	56.70 ± 18.86	0.68
Yes	37 ± 7.58		61 ± 11.4	
Presenting symptom				
Hematuria	37.6 ± 15	0.15	59.66 ± 15.86	0.27
Frequency	28.27 ± 7.81		47.72 ± 16.93	
Dysuria	38.80 ± 13.33		61.33 ± 17.77	
Urgency	34.60 ± 6.14		58.00 ± 25.88	
Histopathology				
Transitional cell carcinoma	34.52 ± 13.6	0.51	54.7 ± 17.53	0.003
Squamous cell carcinoma	38.80 ± 10.32		71 ± 11	
Adenocarcinoma	34 ± 0		30 ± 0	
Grade				
Low	33.15 ± 14.71	0.2	52.50 ± 16.89	0.14
High	37.19 ± 10.79		60.76 ± 18.58	
Urine cytology				
Negative	35.34 ± 12.66	0.82	56.27 ± 18.32	0.17
Positive	36.66 ± 15.27		70 ± 10	
Hydronephrosis				
No	34.73 ± 13.84	0.61	51.0 ± 16.78	0.001
Yes	36.75 ± 10.34		68.75 ± 15.0	
Comorbidities				
None	34.35 ± 11.74	0.37	57.02 ± 18.76	0.6
Diabetes mellitus + hypertension	49.5 ± 6.36		65.00 ± 7.07	
Hypertension only	40 ± 23.09		65.00 ± 5.77	
Diabetes mellitus only	40		30 ± 0	
Site of distant metastases				
None	32 ± 12.72	0.31	53.33 ± 18.78	0.3
Bone only	37 ± 10.29		60.5 ± 17.7	
Visceral only	37.87 ± 14.1		56.87 ± 17.87	
Bone + visceral	39 ± 12.72		77.5 ± 3.53	
Locally advanced vs. metastatic				
Locally advanced	32.00 ± 12.72	0.06	53.33 ± 18.78	0.33
Metastatic	37.64 ± 12.33		59.64 ± 17.63	
Initial treatment				
Palliative chemotherapy	37.81 ± 12.53	0.07	60.0 ± 17.86	0.17
Neoadjuvant chemotherapy	32.16 ± 12.71		51.66 ± 17.57	
Response to initial treatment				
Disease progression	32.11 ± 16.52	0.67	67.77 ± 16.6	0.051
Partial response	36.43 ± 11.48		55.78 ± 18.36	
Stationary disease	35.0 ± 14.14		47 ± 12.04	
Further treatment				
Concomitant chemo-radiotherapy	33.68 ± 12.68	0.65	56.25 ± 17.07	0.06
Surgery	28.75 ± 6.29		42.5 ± 15	
2nd line chemotherapy	36.28 ± 18.58		67.14 ± 18.22	
Completed 6 cycles of chemotherapy	36.43 ± 11.48		55.78 ± 18.36	
Status at 1 year				
Alive	36.13 ± 11.98	0.57	54.59 ± 18.98	0.03
Died	32.55 ± 15.58		67.77 ±8.70	
ECOG performance status				
0	34.68 ± 16.17	0.49	58.94 ± 17.36	0.42
1	35.96 ± 9.77		55.92 ± 18.19	
Hemoglobin (gm/L)				
≤10	35.23 ± 12.79	0.63	56.9 ± 18.6	0.81
>10	37.5 ± 12.58		60 ± 14.14	
Creatinine (mg/dL)				
≤ 1.5	35.78 ± 11.73	0.58	55.27 ± 17.11	0.09
> 1.5	34.0 ± 16.70		65.0 ± 21.21	
Albumin (gm/dL)				
<3	36.0 ± 12.15	0.92	54.61 ± 18.53	0.68
3	36.27 ± 12.34		55.90 ± 18.74	
>3	33.09 ± 14.67		62.72 ± 16.93	

Table 3: Changes in CRP and ESR serum level measures during the treatment course

	Measurement			Significance of difference (p value)			
	At baseline	After 2 cycles	At the end of treatment	Between the three measurements *	Baseline vs. after 2 cycles **	Baseline vs. end of treatment **	After 2 cycels vs. end of treatment **
	Mean ± SD			P value			
All patients (n=46)							
CRP (mg/L)	35.43 ± 12.65	28.28 ± 12.41	29.0 ± 19.67	<0.001	<0.001	0.01	0.59
ESR (mm)	57.17 ± 18.15	45.54 ± 21.32	46.41 ± 31.422	0.001	<0.001	0.003	0.89
Responders (n=32)							
CRP (mg/L)	36.43 ± 11.48	27.15± 10.99	28.34 ± 19.04	<0.001	<0.001	0.01	0.47
ESR (mm)	55.78 ± 18.36	43.25 ± 20.06	44.21 ± 28.93	0.001	<0.001	0.009	0.79
Non-responders (n=14)							
CRP (mg/L)	33.14 ± 15.22	30.85 ± 15.32	---	---	0.21	---	---
ESR (mm)	60.35 ± 17.91	50.71 ± 23.92	---	---	0.01	---	---

* Friedman test; ** Wilcoxon test

The correlation between baseline CRP and ESR measurements and the studied variables is shown in table 2.

The only factor that was associated with significantly higher baseline CRP level was smoking.

Baseline ESR level differed significantly according to the histopathological subtype and was significantly higher among patients with hydronephrosis and those who died within 1 year. Cases with squamous pathology had significantly higher baseline ESR than both transitional and adenocarcinoma (p <0.01 and <0.001) , also transitional had significantly higher than adenocarcinoma (p <0.001)

Regarding the relation between the ESR and patients response, initial ESR levels were elevated in patients who experienced progressive disease on initial evaluation after 2 cycles compared to the patients who experienced stable and regressive disease and also this difference was not statistically significant.

Both CRP and ESR levels were significantly reduced in responding patients but never reached the normal limit. Meanwhile, the ESR levels were significantly decreased in non-responders (table 3).

ROC curve analysis showed that a baseline CRP cutoff value of 27.5 mg/L differentiates between responders and non- responders with 84.4% sensitivity, 35.7% specificity, 75% positive predictive value, 50% negative predictive value and 70% accuracy (figure 1).

ROC curve analysis showed that a baseline ESR cutoff value of 47.5 mm differentiates between responders and non- responders with 78.6% sensitivity, 31.2% specificity, 33% positive predictive value, 77% negative predictive value and 46% accuracy (figure 2).

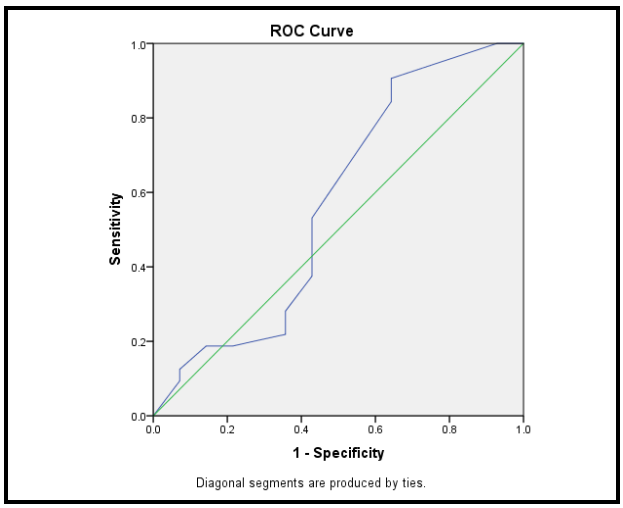

Figure 1: ROC curve of baseline CRP between responders and non-responders

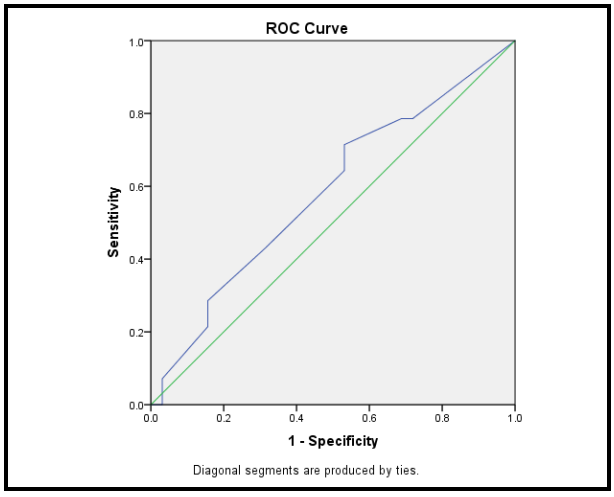

Figure 2: ROC curve of baseline ESR between responders and non-responders

DISCUSSION

The role of serum biomarkers in the management of bladder cancer is limited; however they may be of

diagnostic or prognostic value or both [6]. C-reactive protein is a systemic biomarker for diagnosing acute and chronic inflammation [7], and it may increase by many folds in case of systemic infections, trauma, and malignant tumors [8].

All patients included in the current study had elevated serum CRP and ESR level at presentation while in the study conducted by Grimm et al the range of preoperative CRP level in patients with bladder carcinoma was from 0.1 to 28.3 mg/L indicating that some of the patients had normal baseline CRP levels [9]. Also Bruins et al found that only 23.4% and 28.7% out of 320 patients with bladder had elevated baseline CRP and ESR level respectively [10]. These variations may be due to the difference in sample size and pathological subtypes between these studies and the current one.

Both CRP and ESR were elevated in males than females but this elevation was not statistically significant. In agreement with our results, Grimm et al and Eggers et al did not find statistically significant relation between baseline CRP levels and age [9, 11].

In the current study we found that there is significant relation between the baseline CRP level and smoking while the CRP level was higher among smokers this can be explained by the chronic inflammatory state created by smoking in these patients. ESR baseline levels were significantly higher in patients with hydronephrosis compared to patients with no hydronephrosis .

The median value of CRP level among metastatic patients in our study was comparable to that founded by Eggers et al who found that the median CRP value among metastatic bladder cancer patients before surgery is 35.5 mg/L [11].

Also it was found that patients with metastatic disease had higher pretreatment CRP levels than localized disease. CRP levels and ESR levels were higher in patients with grade III tumors indicating that it may be correlated with the tumor aggressiveness. These findings are consistent with that of Stein et al who found that CRP was significantly related to tumor stage, grade and the presence of metastases. However, Eggers et al found no correlation between CRP and tumor grade [11, 12]. These results were supported by Grimm et al who found that there was a relation between baseline CRP and initial patients' stage and confirmed by Lepara et al who reported a correlation between CRP level and different stages of bladder cancer [9, 13].

We also found that patients with both visceral and bone involvement had higher levels of serum CRP. These findings can be explained by continues tumor growth (in case of metastatic disease) that caused the persistent stimulation of CRP production especially in case of visceral involvement.

All these previous studies were carried out on patients with transitional cell carcinoma pathology only while in our study we considered other pathological subtypes and CRP was higher in patients with squamous cell carcinoma pathology. Baseline ESR level was significantly higher in patients with SCC pathology which can be explained by the chronic inflammatory state that usually contribute to carcinogenesis in this pathological subtype.

While, baseline ESR levels were statistically related to patients' fate as the mean baseline serum ESR was significantly higher in patients who died due to disease related causes within one year of the study. Mean levels of serum CRP and ESR levels were significantly reduced in the whole group and responders during the course of treatment (both at interval assessment after two cycles and at the end of treatment). These improvements in serum levels may be related to the reduction in tumor burden in response to treatment.

These results suggest that baseline and serial measurements of both CRP and ESR may be used as indicators for treatment response in patients with advanced stage bladder cancer.

Conclusion

Baseline and serial measurements of both CRP and ESR might be useful noninvasive serological markers for follow up in patients with advanced urinary bladder carcinoma. However these results need to be further investigated through larger size of patients and further analysis of data.

Conflict of interest

None to declare

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