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Original Article

Role of acute phase reactant as predictive of response in cancer bladder patients receive platinum based chemotherapy

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ABSTRACT

Background: Until today, there is no reliable prognostic or predictive parameter for the prognosis of patients with urothelial cancer of the bladder prior to chemo therapy. Recently, serum C-reactive protein (CRP) level has been shown to be associated with prognosis with various malignancies including localized and metastatic renal cell carcinoma, upper urinary tract as well as penile cancer.

Aim: The aim of this study was to assess relation between studied acute phase reactants (CRP and ESR) and response in locally advanced and metastatic bladder cancer receiving platinum based chemotherapy.

Method: This Study include forty six patients, 9 patients locally advanced cancer bladder receive neo adjuvant chemotherapy and 37 patients metastatic bladder cancer receive palliative chemotherapy all patients receive platinum based Chemotherapy.

Results: In our study show significant reduction in the percentage of patients with CRP and ESR after 3&6 cycles of treatment (p value<0.001). We take cut off point of different levels of ESR and CRP .There is no significant difference among different response to treatment and level of ESR and CRP.

Conclusion: acute phase reactants were considered as non -invasive biomarkers of inflammatory response and had significant impact on patients' outcomes in cancer bladder.

Keywords
Biomarker,
C-reactive protein,
Cystectomy,
Inflammation,
Urinary bladder neoplasms

INTRODUCTION

Bladder cancer ranks the ninth in worldwide cancer incidence and the second most common among genitourinary malignancies, and urothelial (transitional cell) carcinoma makes up for nearly 90 % of all primary bladder tumors. Treatment strategies include radiation, chemotherapy and surgical approaches. For high-grade and/or muscle-invasive tumors, radical cystectomy has become a standard approach, but about 50 % of patients treated with cystectomy eventually develop disease progression. [1]There have been numerous reports about the relationship between chronic inflammation and cancer. The inflammatory cells and cytokines found in tumour highly likely to contribute to tumour growth, progression, and immunosuppression compared to cope with an effective host antitumor response.[2] In fact, about 15% of cancers are initiated by chronic inflammation or infection such as helicobacter pylori, hepatitis virus, Epstein-Barr virus, and other bacteria. Persistent infection of the host induces chronic inflammation, and inflammatory cells induce DNA damage in proliferating cell, by generating reactive oxygen and nitrogen species.[3] Furthermore, it is well demonstrated by laboratory research that pro-inflammatory cytokines could promote tumour growth and metastasis by altering tumour cell biology and activating stromal cells in the tumour microenvironment.[4]

C-reactive protein (CRP) is a nonspecific serum marker of acute-phase inflammatory response, and it is produced by hepatocytes which are regulated by interleukin (IL)-6.[5] Several possible mechanisms have been postulated for the relationship

between CRP and cancers; first, tumour growth can cause tissue inflammation, hence increasing CRP level. Second, CRP could be an indicator of an immune response to tumour antigens. Third, cancer cells could increase the production of inflammatory cytokines, which could induce high CRP concentration in cancer patients.[6] Many studies showed the elevation of pretreatment CRP to be a significant prognostic parameter in patients with esophageal cancer, hepatocellular carcinoma, colorectal cancer, renal cell cancer, ovarian cancer, and cancer bladder. Furthermore, we recently reported an association between preoperative serum CRP levels and pathologic parameter such as tumour size and lymph vascular invasion in patients with cancer bladder [7]

MATERIALS AND METHODS

Search Strategy: This case control study was carried out on patients with histopathological proof cancer bladder patients who attended to new cases clinic in clinical Oncology Department, Faculty of Medicine, Menoufiya University. In the study period, from May 2015 to march 2017. All patients were subjected to full history taking (including age, surgical interference), thorough clinical examination (including performance status, local and general examination), full investigations (body computed tomography, cystoscopy, CBC, full kidney and liver functions). Ethical approval was obtained from the Research Ethics Committee, Faculty of Medicine, Menoufiya University and informed consent was obtained from every participant. All patients were subjected to the analysis of CRP&ESR in peripheral blood specimen

Study Selection: All the studies were independently assessed for inclusion. They were included if they fulfilled the following criteria:

Inclusion criteria of the published studies:

- Published in English language.
- Patient normal renal function.
- Focused on patient performance state 0-1.
- Discussed the relation between CRP &ESR in cancer bladder patients receive platinum based chemotherapy.
- If a study had several publications on certain aspects we used the latest publication giving the most relevant data.

Data Extraction: If the studies did not fulfill the above criteria, they were excluded such as, patient creatinin clearance <30mg/l, brain insult and performance state >1.

Treatment regimens

Patients eligible for this analysis received palliative chemotherapy due to metastatic disease. Gemcitabine in combination with cisplatin was applied in 37 patients as first-line chemotherapy. Also include locally advanced cancer bladder 9 patients receive concurrent chemo radiotherapy and two patients receive neoadjuvant chemotherapy then surgery

The SPSS16 (SPSS Inc., Chicago, IL, USA) was used in data analysis. Descriptive statistics were used to present the distribution of demographic and clinical characteristics. The Chi-square and fisher's exact tests were used for qualitative data. t, Mann-Whitney and Kruskal-Wallis tests were used to test the difference in quantitative data. The odds ratio (OR) and 95% confidence intervals (CI) were calculated. P value less than 0.05 was considered to be statistically significant. Response to treatment was assessed according to revised RECIST guide line (version 1.1) [8]

Quality Assessment: The quality of all the studies was assessed. Important factors included, study design, attainment of ethical approval, evidence of a power calculation, specified eligibility criteria, appropriate controls, and adequate information and specified assessment measures. It was expected that confounding factors would be reported and controlled for and appropriate data analysis made in addition to an explanation of missing data.

Data Synthesis: A structured systematic review was performed with the results tabulated.

RESULTS

Serial measures of serum level of CRP and ESR during treatment course reveal that. The mean readings of both CRP and ESR were significantly reduced in the whole group. In the responders both CRP and ESR levels were significantly reduced but never reached the normal limit. While In non-responders, the ESR levels were significantly decreased. However, reduction in CRP mean level decreased but did not reach the significant value and again didn't reach normal level

DISCUSSION

Bladder cancer is a disease that can have significant morbidity if not diagnosed and treated early. Prognosis is mainly determined by the stage and grade of the disease.

Serum biomarkers are not commonly used in the evaluation of bladder cancer but it may be of diagnostic or prognostic value or both. [9]

Among the 46 patients included in the study no patients had normal CRP serum level or ESR level at presentation while in the study conducted by Grimm et al the range of preoperative CRP level in patients with bladder carcinoma were (0.1–28.3) indicating that some of the patients had baseline normal CRP levels.[9]

Also Bruins and his colleagues found that only 23.4% and 28.7% out of 320 patients of bladder cancer that they studied had elevated baseline CRP and ESR level respectively.

These variations may be due to the difference in sample size and also squamous cell carcinoma included in this study associated with chronic inflammation compared with other studies include only transitional cell carcinoma , so base line (ESR and CRP) higher than other studies. [10]

Both CRP and ESR were elevated in value 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 found statistically significant relation between baseline CRP

levels and age.[11]

In the current study we found that there is significant relation between the baseline CRP level and smoking where 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.

Also it was found that patients with metastatic disease had higher pretreatment CRP levels than localized disease nevertheless, the difference in ESR level between metastatic and localized disease patients was less pronounced.

The median CRP value suggest level correlate with stage , prechemotherapy treatment within metastatic patients in the current study was 37.64 ± 12.33 mg/l versus 32.00 ± 12.72 mg/l in patients with localized disease, so CRP value increase with stage but this difference was not statistically significant.

The value of CRP levels for metastatic patients in this study was comparable to that founded by Eggers et al who found that the median CRP values within metastatic patients before surgery was 35.5 mg/l.

These results were supported by Grimm et al who found that there was a relation between baseline CRP and initial patients' stage. Also, Lepara and his colleagues found that CRP level correlated with different stages of bladder cancer. [12]

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.

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 were consistent with that of Stein et al who found that CRP was significantly related to tumor stage and presence of metastases and grade. However, Eggers et al found that CRP was not correlated to tumor grade.

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

There was no statistically significant relation between patients' initial response and baseline serum CRP level.

While, baseline ESR levels were statistically related to patients' fate as the mean baseline serum ESR was significantly higher in patients who died within one year of the study.

Mean levels of serum CRP and ESR were significantly reduced in the whole group and responders during the course of treatment (both in interval assessment after three cycles and at end of treatment). Consequently, the number of patients with very high measures was also reduced during the course of treatment.

These improvements in serum levels can be related to reduction in tumor burden as a result of treatment.

Based on response to initial induction chemotherapy ROC curve was plotted for both CRP and ESR to determine the cutoff point for each and patients then categorized into patients with high and very high serum measures.

On referral to cutoff points the very high CRP and ESR levels were significantly more prevalent among patients with SCC pathology this can be related to the pathogenesis of this specific pathological subtype where chronic inflammation is an important predisposing factor.

And very high ESR levels were also more prevalent among patients who died at the end of follow up period this indicate its possible prognostic value.

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

CONCLUSION

Acute phase reactants are noninvasive biomarker for systemic inflammatory response could be significantly prognostic factors in patients with bladder carcinoma.

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