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Original Research Article

Chemotherapy: Impact on hs-CRP Levels in Chronic Myeloid Leukemia

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Abstract: Leukemias are malignant neoplasms of hematopoietic stem cells, characterized by diffuse replacement of the marrow by neoplastic cells. It is one of the leading causes of cancer deaths. The present study was conducted in the Department of Biochemistry, in collaboration with the Department of Medicine (Clinical Haematology unit); Pt. B.D. Sharma, Post Graduate Institute of Medical Sciences, Rohtak. Thirty patients of Chronic Myeloid leukemia after confirmed diagnosis were taken up for study. CML patients were treated by imatinib therapy. Serum hs-CRP was assayed by Enzyme Linked Immunosorbent Assay (ELISA) in newly diagnosed patients and in thirty age and sex matched healthy controls. The test was repeated at first complete remission or at 3 months (whichever is earlier) in CML patients. Group I: Control group- age and sex matched healthy volunteers. Group II: CML patients at the time of diagnosis (before imatinib therapy). Group III: CML patients at first complete remission or at 3 months of imatinib therapy (whichever is earlier). Serum hsCRP levels were significantly increased (p=0.000) in group II and group III (14.75±6.51 mg/L and 9.81±4.64 mg/L respectively) as compared with group I (2.75±1.29 mg/L). In group III hsCRP levels (9.81±4.64 mg/L) were decreased significantly (p=0.001) after imatinib therapy as compared with group II. Our study revealed that hsCRP could be useful marker in determining disease progression or monitor the effectiveness of treatment in leukemic patients as increased levels are seen in CML cases both before and after chemotherapy as compared with their age matched healthy controls.
Keywords: Leukemia, CML, Imatinib, hsCRP.

INTRODUCTION:

Leukemias are malignant neoplasms of hematopoietic stem cells, characterized by diffuse replacement of the marrow by neoplastic cells. It is one of the leading causes of cancer deaths [1]. CML is the commonest adult leukemia in India and the annual incidence ranges from 0.8–2.2/100,000 population in males and 0.6–1.6/100,000 population in females [2]. CML is a pluripotent stem cell disease characterized by anemia, extreme blood granulocytosis and granulocytic immaturity, basophilia, often thrombocytosis and splenomegaly. In CML, single cell produces clone in which there is an enormous expansion of progenitors for granulocytic and often megakaryotic cells [3]. C-reactive protein (CRP) is an acute phase protein produced by liver and adipocytes [4]. CRP levels rise dramatically during inflammatory processes occurring in the body. The increment is due to rise in plasma concentration of interleukin-6 (IL-6) which is produced predominantly by macrophages [5]. Cytokines derived from macrophages and monocytes include tumour necrosis factor (TNF-λ), interleukin-1 and interleukin-6. These cytokines are primarily responsible for mediating acute phase response [6]. CRP is thought to bind to phosphocholine, thus initiating recognition and phagocytosis of damaged cells [6]. It binds Fc gamma receptors on macrophages. In vitro CRP has been found to activate a number of processes involved in inflammation. It induces expression of Vascular cell adhesion molecule 1 (VCAM 1), Intracellular cell adhesion molecule 1 (ICAM 1), E selectin and Monocyte chemo attractant protein 1 (MCP 1) in endothelial cells [7]. Expression of these markers has prognostic significance in myeloid neoplasms [8]. Most of the studies of CRP have focused on its use as a marker for early detection of bacterial infection in febrile or afebrile neutropenic leukemia patients and its use in monitoring antibiotic therapy and response to it in such patients. Some studies had reported normal levels in absence of fever and bacterial infection in leukemia patients [9]. However, few studies have documented significant increase in CRP levels in CML

patients which are not exhibiting any clinical signs of inflammation. Acute phase reactants like orosomucoid and CRP have been reported to be correlated with white blood cell count and stage of disease by Le Courte *et al.;* [10]. Sawadogo *et al.;* reported CRP levels to decrease with chemotherapy in both CML and AML [11]. CRP and hs-CRP differ from each other not in the analyte estimated but in the analytical performance. The introduction of hs-CRP has enabled identification of group of patients with minute alteration of CRP. Measurement of hs-CRP in myeloid leukemia patients enables detection of slight increase or decrease in serum CRP levels as CRP levels have been correlated with the stage of disease and response to chemotherapy [12].

HsCRP is a surrogate marker of the proinflammatory cytokine release. The regulation of CRP by multiple cytokines is not completely understood and its significance as a marker of leukemic activity, immune response or status of proinflammatory cytokines in CML patients is not clear. Hence present study was planned to estimate serum hs-CRP levels in CML patients before and after chemotherapy and to compare them with age and sex matched healthy controls.

MATERIALS AND METHODS:

The present study was conducted in the Department of Biochemistry, in collaboration with the Department of Medicine (Clinical Haematology unit); Pt. B.D. Sharma, Post Graduate Institute of Medical Sciences, Rohtak. Thirty patients of Chronic Myeloid leukemia were taken up for study. The diagnosis was made by history, clinical examination, total and differential leukocyte count, bone marrow examination and cytogenetic studies. CML patients were treated by imatinib therapy.

Serum hsCRP levels were estimated along with routine biochemistry, complete hemogram, in newly diagnosed patients and in thirty age and sex matched healthy controls. The test were repeated at first complete remission or at 3 months (whichever is earlier) in CML patients. Complete history and physical examination with anthropometry were done in controls and cases (before and after treatment). Serum hs-CRP was assayed by Enzyme Linked Immunosorbent Assay (ELISA) [13].

Patients and controls were categorized into three groups

Group I: Control group- age and sex matched healthy volunteers.

Group II: CML patients at the time of diagnosis (before imatinib therapy).

Group III: CML patients at first complete remission or after 3 months of imatinib therapy (whichever is earlier).

RESULTS:

Table 1: Showing baseline characteristics of the patients

Parameters	Group I	Group II	Significance
Age (years)	39.63±11.93	39.50±11.84	P=0.965
BMI (kg/m^2)	20.13±1.63	19.15±1.75	P=0.029*
Hb (g/dL)	13.03±0.97	9.38±1.84	P=0.000**
TLC (cells/cu.mm)	7633.33±1886.31	79530.0±55203.61	P=0.000**
hsCRP (mg/L)	2.75±1.29	14.75±6.51	P=0.000**

*P= <0.05= group I significant as compared with group II

**P= < 0.001group I significant as compared with group II

Table 2: hsCRP (mg/L) levels in all groups

Group I	Group II	Group III
2.75±1.29	14.75±6.51	9.81±4.64

** Group I vs group II (p=0.000) ** group II vs group III (p=0.001)

** Group I vs group III (p=0.000)

Serum hsCRP levels were significantly increased (p=0.000) in group II and group III (14.75±6.51 mg/L and 9.81±4.64 mg/Lrespectively) as compared with group I (2.75±1.29 mg/L). In group III hsCRP levels (9.81±4.64 mg/L) were decreased significantly (p=0.001) after imatinib therapy as compared with group II.

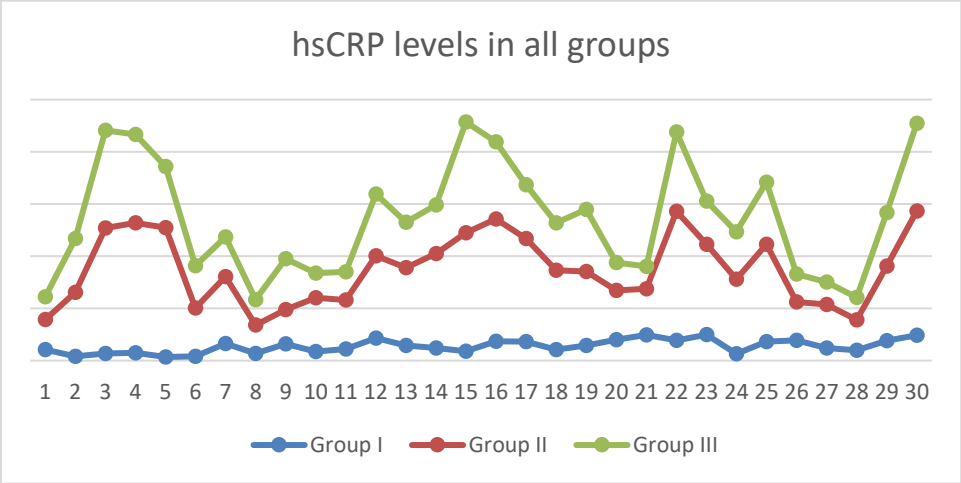

Fig 1: hsCRP levels in all groups

DISCUSSION:

Age distribution was similar in group II and group I (p= 0.965). Hb levels were significantly decreased (p=0.000) in group II as compared to group I (9.38±1.84 mg/dL and 13.03±0.97 mg/dL respectively). TLC levels were significantly increased (p=0.000) in group II (79530.0±55203.61 cells/cu.mm and 7633.33±1886.31cells/cu.mm) as compared to group I.

The present study showed significantly higher (p=0.000) serum hsCRP levels in group II and group III (14.75±6.51 mg/L and 9.81±4.64 mg/L respectively) as compared with group I (2.75±1.29 mg/L). This is due to rise in plasma hsCRP concentration of IL-6 which is produced predominantly by macrophages. Above results agree with the studies on CRP which also suggest it for rapid diagnosis of infection in leukemia.

Similar to our results other studies have also reported significant elevated CRP levels in CML patients as compared to healthy controls. In a study conducted by Singer et al on cytokine profiling as prognostic markers in CML patients they observed raised CRP concentration in all CML patients (p<0.001) which is attributed to chronic inflammation [14].

At the high acute state levels seen in bacterial infections that are associated with IL-10 induction, it suppresses inflammation. At the moderately increased levels as seen in the high proportion of the CML patients, it may have an opposite effect by activating complement and inducing proinflammatory cytokines. Different receptors with varying affinity for CRP may be involved in this disparity in its biological roles at different levels [1].

Despite a wide variety of inflammatory markers now available hsCRP serve as a marker of subclinical systemic inflammation, as it has well established epidemiological and clinical determinants, little diurnal variation, and moderate within person variability, allowing long term prediction of disease [15].

In the present study group III hsCRP levels (9.81±4.64mg/L) were decreased significantly (p=0.001) after imatinib therapy as compared with group II. After chemotherapy administration elevated CRP levels in CML patients had declined signicantly from the initial CRP levels which agrees with Fang *et al.;* Takamura *et al.;* Le courte and Takayama *et al.;* [10, 16-18].

Studies have also reported statistically highly significant increase in CRP levels in CML patients not exhibiting any clinical signs of inflammation [8]. CRP has been reported to be correlated with white blood cell count and stage of disease by Le Courte *et al.;* [10]. CRP and thrombocytopenia were described as being significantly poor prognostic factors in therapy- related leukemia by Takeyama *et al.;* [18].

Most studies suggested that CRP levels were higher in cancer cases than healthy subjects and CRP levels for prediction of treatment efficacy and patients mortality with various types of cancers have been extensively reported. Serum hs-CRP was positively associated with the risk of cancer. The results also support the hypothesis that chronic inflammation plays a role in cancer [19]. Inflammation triggers development and progression of tumor, while tumor also induces inflammatory microenvironment [20]. Chronic inflammation is also an essential player in recurrence of the disease by the promotion of dissemination and growth of metastatic seeds [21].

hsCRP is a measure of low-grade chronic inflammation and potential predictor of cancer risk and/or survival [22]. A pathogenic link has been identified between inflammatory mediators,

inflammation related gene polymorphisms and carcinogenesis [23]. The persistence of chronic inflammation plays a critical role in all stages of tumorigenesis from initiation of the tumor, infiltration, local and systemic invasion [24] and thus modulating the immune response may still be an alluring goal for therapeutic intervention [25].

CONCLUSION:

Our study revealed that hsCRP could be useful marker in determining disease progression or monitor the effectiveness of treatment in leukemic patients as increased levels are seen in CML cases both before and after chemotherapy as compared with their age matched healthy controls.

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