C-Reactive Protein in the Follow-up and Estimation of Infections in Acute Leukemic Patients

Vahap ASLAN, O. Meltem AKAY, Zafer GÜLBAŞ

Department of Hematology, Osmangazi University Medical School, Eski¾ehir, TURKEY

ABSTRACT

Fifty-five febrile neutropenic episodes were monitored by C-reactive protein (CRP) in 26 patients with acute leukemia. In nonfebrile period of patients, serum CRP level was 0.89 mg/dL (range 0.1-8.8 mg/dL) while it was found to be raised to 9.57 mg/dL (range 0.5-24.1 mg/dL) in the febrile group (p= 0.0001). Serum CRP level at the onset of fever was 9.25 mg/dL (range 0.1-16.2 mg/dL) in patients in whom fever was treated succesfully with antipseudomonal beta-lactam antibiotic and aminoglycoside therapy declined to normal levels (p= 0.01); 17.0 mg/dL (range 5.2-33.5 mg/dL) in patients still persisting fever with this combined therapy and so obtained vancomycin (p= 0.001); 16.6 mg/dL (range 0-38.7 mg/dL) in patients required amphotericin B in addition (p= 0.001). In the initial febrile episode; fever resolved at day 3.3 ± 1.21 in patients with serum CRP value below 5 mg/dL; at day 4.42 ± 1.88 in patients with serum CRP value between 10-15 mg/dL; at day 5.14 ± 1.68 in patients with serum CRP value above 15 mg/dL. There was no statistical difference at the time of fever resolution among the first three groups. There was a remarkable difference between groups with CRP values below 5 mg/dL and above 15 mg/dL (p= 0.04).

We conclude that determination of serum CRP level before and after infection in febrile neutropenic patients is useful for the follow-up and estimation of febrile neutropenic episode in acute leukemic patients.

Key Words: C-reactive protein, Acute leukemia, Infection.

ÖZET

Akut Lösemik Hastalarda İnfeksiyonun İzlenmesi ve Değerlendirilmesinde C-Reaktif Protein

Akut lösemi tanısı almış 26 hastada 55 febrilnötropenik atak C-reaktif protein (CRP) ile izlendi. Serum CRP düzeyi febril olmayan dönemde 0.89 mg/dL iken febril dönemde 9.57 mg/dL bulundu (p= 0.0001). Ateşin antipsödomonal beta-laktam antibiyotik ve aminoglikozid ile düştüğü hastalarda CRP düzeyleri normale indi (p= 0.01) ancak eteşi devam eden ve vankomisin ya da amfoterisin-B eklenmesi gerekenlerde yüksek kaldı. Ateşin düşmesi ile serum CRP düzeyleri 5 mg/dL altında ve 15 mg/dL üstünde olanlarda fark saptandı (p= 0.04). Febril nötropenik

hastalarda önce ve sonra serum CRP düzey tayini izleme ve değerlendirilmesi için akut lösemik hastalarda yararlıdır.

Anahtar Kelimeler: C-reaktif protein, Akut lösemi, İnfeksiyon.

Turk J Haematol 2003;20(2): 75-80

Received: *06.09.2002* ***Accepted:*** *25.11.2002*

INTRODUCTION

C-reactive protein (CRP) is an acute phase plasma protein with a characteristic pentameric annular structure. It is synthesized by hepatocytes in response to interleukin (IL)-1 and IL-6 via the gene that has been localized on chromosome 1. CRP acts as an opsonin for bacteria, parasites and immune complexes and can activate the classical pathway of complement. It can modulate the chemotactic and phagocytic function of neutrophils and macrophages; activation of natural killer cells and tumoricidal activity of macrophages[1,2].

Serum CRP concentrations are likely to increase in patients with bacterial and fungal infections, chronic inflammation, trauma, tissue infarction and surgery. For this, serum CRP level has clinical value in distinguishing between bacterial and fungal infections. Furthermore, this protein can be used as a clinical guide to differ bacterial infection-related fever from viral infection, transfusion and drug-related fever[3-6].

In the diagnosis and monitoring of febrile neutropenic patients; erythrocyte sedimentation rate, procalcitonin, tumour necrosis factor-alpha (TNF-a) , IL-1ß, IL-6 and follistatin are as valuable as CRP but CRP is the most helpful diagnostic tool for being easily obtainable[7-10]. Levels of CRP increase during the 10 hours preceeding the clinical diagnosis of a demonstrable infection. Maximum concentration of CRP is reached within 36-50 hours after the start of febrile neutropenic episode. Since the half-life of CRP is 19 hours in the adult and 21 hours in neonates, in the absence of inflammatory stimulation CRP levels will revert to normal in the space of a few days[11].

We have reported 55 febrile neutropenic episodes, monitored by serum CRP in 26 patients with acute leukemia.

PATIENTS and METHODS

Fifty-five febrile neutropenic episodes were monitored by serum CRP in 26 patients with acute leukemia (23 acute nonlymphoblastic leukemia, three acute lymphoblastic leukemia) from January 1996 through December 1998 in hematology unit of internal medicine department of Osmangazi University Medical Faculty. Thirty-three patients were given remission induction therapy (cytosine arabinoside 100 mg/m^2, seven days and daunorubucine 60 mg/m^2, three days) and 22 patients were given high-dose cytosine arabinoside (1.5 g/m^2/12 h, five days). Nine male and seventeen female patients with median age of 41.6/year (range: 19-70/year) were included.

In patients with chemotherapy-induced neutropenia, concentrations of CRP were analyzed by nephelometric assay (Beckmann Protein array-360, USA, normal reference value < 0.05 mg/dL) in nonfebrile period (baseline level); within the six-eight hours, 48 hours, 96 hours of initial febrile episode; on set, before and within the 48 hours of antibiotic modification.

All patients described here were started on antipseudomonal beta-lactam antibiotic and aminoglycoside therapy soon after the initial febrile episode. Patients, still persisted fever with this combined therapy or developed fever again after resolution; necessiated vancomycin and amphotericin B therapy, respectively.

The findings were analyzed by Wilcoxon t-test, matched in the statistical programme of SPSS.

RESULTS

In patients with acute leukemia and chemotherapy-induced neutropenia, serum CRP concentrations were 0.89 mg/dL (range 0.1-8.8 mg/dL) in nonfebrile period. High levels of CRP; 9.57 mg/dL (range 0.5-24.1 mg/dL) were found after start of fever, and there was a remarkable statistical difference between these values (p= 0.0001).

In febrile neutropenic patients who became afebrile within 48 hours of antipseudomonal beta-lactam antibiotic and aminoglycoside therapy; serum CRP value was

1.69 mg/dL (range 0.1- 4.3 mg/dL) in nonfebrile period; 9.25 mg/dL (range 0.1-16.2 mg/dL) at the onset of fever, 4.47 mg/dL (range 0.5-10.9 mg/dL) within 48 hours of antibiotherapy, 2.44 mg/dL (range 0.1-6.3 mg/dL) with in 96 hours of antibiotherapy (Figure 1). There was a remarkable statistical difference between these parameters (p= 0.005).

In patients with persistent fever despite 48 hours' antipseudomonal beta-lactam antibiotic and aminoglycoside therapy in the initial febrile episode and so obtained vancomycin; serum CRP value was 3.47 mg/dL (range 0.4-19.6 mg/dL) in nonfebrile period, 17.0 mg/dL (range 5.2-33.5 mg/dL) at the onset of fever, 11.6 mg/dL (range 2.3-24.1 mg/dL) after 48 hours' vancomycin therapy and 5.36 mg/dL (range 0.3-19.1 mg/dL) after 96 hours' vancomycin therapy (Figure 2). There was a remarkable statistical difference between these values (p= 0.01).

In patients in whom fever declined to normal values with 48 hours' antipseudomonal beta-lactam and aminoglycoside therapy, serum CRP value was 1.69 mg/dL (range 0.1-4.3 mg/dL) in nonfebrile period. However, it was found to be 3.47 mg/dL (range 0.4-19.6 mg/dL) in nonfebrile period of patients that persisted fever with this combined therapy and necessiated vancomycin.

Patients who persisted fever despite antipseudomonal beta-lactam antibiotic + aminoglycoside + vancomycin therapy or developed a new febrile episode obtained amphotericin B respectively. Serum CRP value was 16.6 mg/dL (range 0-38.7 mg/dL) before treatment, however declined to 10.89 mg/dL (range 1.3-16.2 mg/dL) soon after treatment (Figure 3). There was a remarkable statistical difference between these parameters (p= 0.0001).

In the initial febrile period; fever was discontinued at day 3.3 ± 1.21 in patients with serum CRP value below 5 mg/dL, at day 4.42 ± 1.88 in patients with serum CRP value between 5-10 mg/dL, at day 4.64 ± 1.95 in patients with serum CRP value between 10-15 mg/dL, at day 5.14 ± 1.68 with serum CRP value above 15 mg/dL (p= 0.04). There was no statistical difference at the time of fever resolution among the first three groups. There was a remarkable difference between groups with CRP values below 5 mg/dL and above 15 mg/dL (p= 0.04).

In our study, serum CRP value of 14 acute leukemic patients who developed nonhemolytic febrile transfusion reaction was 1.2 mg/dL (range 0.1-3.4) and 1.3 mg/dL (range 0.1-4.2) before and after the onset of fever, respectively.

DISCUSSION

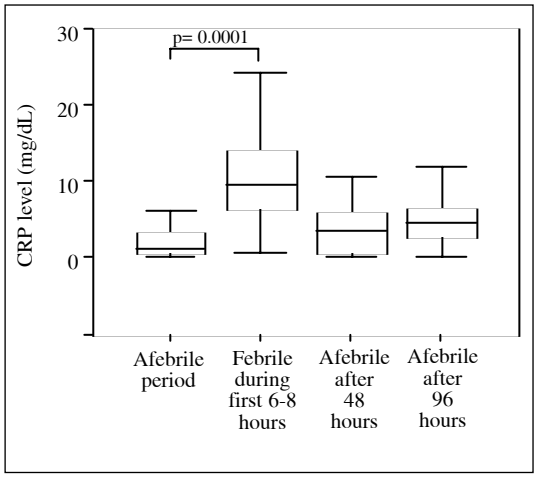

Figure 1. Values of serum CRP in patients with fever resolution under antipseudomonal beta-lactam antibiotic and aminoglycoside therapy (n= 35).

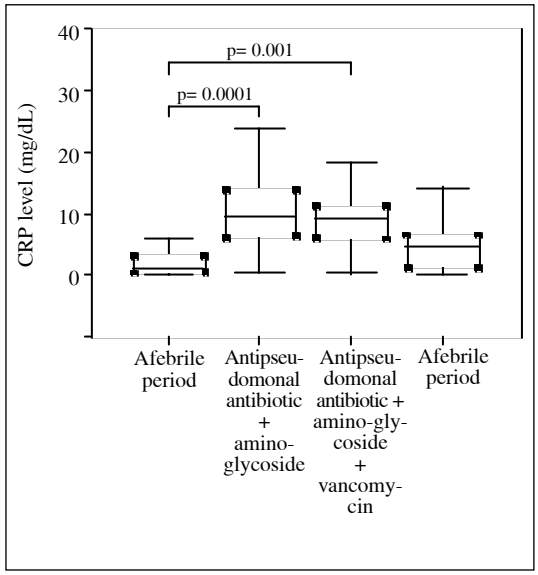

Figure 2. Values of serum CRP in patients with fever resolution under antipseudomonal beta-lactam antibiotic + aminoglycoside + vancomycin therapy (n= 11).

In patients we described here; serum CRP level was 0.89 mg/dL (range 0.1-8.8 mg/dL) before fever onset. Serum CRP level in healthy individuals is less than or equal to 1 mg/dL[12]. A minimal rise of CRP in febrile patients here may be associated with a primer pathology or acceptedeas nonspecific. Santolaya et al reported values of CRP between 0.9 ± 3.5 mg/dL in a series of afebrile neutropenic patients with malignant disorders[13].

Patients who became afebrile after 48 hours' antipseudomonal beta-lactam antibiotic and aminoglycoside therapy, serum CRP level was 1.69 mg/dL (range 0.1-4.3 mg/dL) in nonfebrile period; however it was found to be 9.25 mg/dL (range 0.1-16.2 mg/dL) after start of fever. Serum CRP level declined to 4.47 mg/dL (range 0.5-10.9 mg/dL) over the 48 hours and 2.44 mg/dL (range 0.1-6.3 mg/dL) over the 96 hours of fever resolution.

These findings suggest that; CRP level is elevated significantly with fever onset and under effective antibiotic therapy, serum CRP level is found to be decreased by 50% within the 48 hours and declined to baseline value within the 96 hours of therapy.

In patients persisting fever despite antipseudomonal beta-lactam antibiotic and aminoglycoside therapy and necessiating vancomycin; serum CRP value was 3.47 mg/dL (range 0.4-19.6 mg/dL) in the initial febrile episode, 17.0 mg/dL (range 5.2-33.5 mg/dL) during the febrile the period, 11.6 mg/dL (range 2.3-24.1 mg/dL) within 48 hours of vancomycine therapy, 5.36 mg/dL (range 0.3-19.1 mg/dL) after fever resolution. We observed that the marked decrease in serum CRP level under effective therapy had also occured in patients described herein. In this group; the finding of high levels of serum CRP at initial febrile episode, only a slightly decrease (25%) within the 48 hours of first-line therapy but a sizeable decrease to normal values with vancomycin therapy may indicate that; the initial febrile response is related both to gram-negative and gram-positive microorganism. Regarding to literature; CRP rise did not differ during gram-negative and nongram-negative episodes[14].

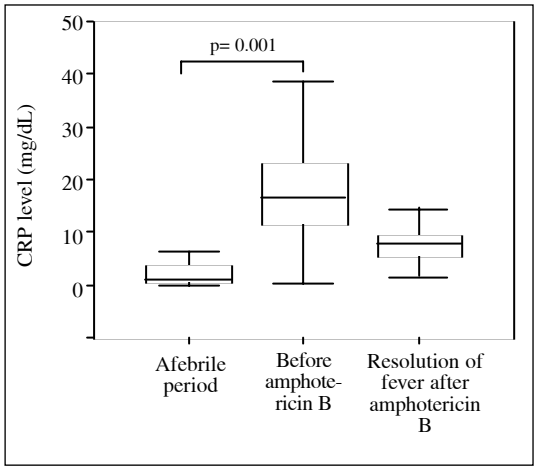

Figure 3. Values of serum CRP in patients with fever under amphotericin B therapy (n= 23).

We performed serial determinations of CRP in nonfebrile period in order to determine its use, as an indication for the diagnosis of the severity of an infection in febrile period. In nonfebrile period of patients with fever resolution under antipseudomonal beta-lactam antibiotic and aminoglycoside therapy, serum CRP value was 1.69 mg/dL (range 0.1-4.3 mg/dL). Nevertheless, it was found to be 3.47 mg/dL (range 0.4-19.6 mg/dL) in nonfebrile period of patients, with persistant fever despite first-line therapy and received vancomycin.

In this regard, we conclude that serial measurements of serum CRP levels in non-febrile period may be helpful in determining the severity of a subsequent infection. An exhaustive review of a literature yielded no similar data.

Patients who became afebrile with amphotericin B therapy; serum CRP level was 16.6 mg/dL (range 0-38.7 mg/dL) before the onset of fever, but 10.89 mg/dL (range 1.3-16.2 mg/dL) after the resolution of fever. These findings indicate that, fungal infections result in increased CRP production which normalizes with amphotericin B therapy. There is similar data in the literature that describes an increase of CRP in fungal septicaemia followed by a decrease soon after antifungal therapy[12].

In the initial febrile episode; fever was discontinued at day 3.3 ± 1.21 in patients with serum CRP value below 5 mg/dL, at day 4.42 ± 1.88 in patients with serum CRP value between 5-10 mg/dL, at day 4.64 ± 1.33 in patients with serum CRP value between 10-15 mg/dL, at day 5.14 ± 1.68 in patients with serum CRP value above 15 mg/dL. The literature yielded no association between serum CRP level and the time of fever

resolution. However, our results suggest that resolution of fever was found to be later at initial febrile episode with higher levels of serum CRP. This finding indicates that; serum CRP level is helpful in determining the extent of fever resolution and high serum CRP levels indicate delayed fever resolution.

As chemotherapy receiving leukemic patients frequently requires blood transfusions, difficulties may occur in mediating antibiotherapy due to transfusion-related fever. In our study, serum CRP value of 14 acute leukemic patients who developed fever during transfusion was 1.2 mg/dL (range 0.1-3.4) and 1.3 mg/dL (range 0.1-4.2) before and after the onset of fever, respectively. This finding suggests that nonhemolytic febrile transfusion reaction do not cause any rise in serum CRP levels and so, CRP can be an useful marker in differentiating between nonhemolytic febrile transfusion reaction from infections.

Our findings suggest that; determination of serum CRP level in febrile neutropenic patients with acute leukemia is useful for both the severity and the duration of infection. In this respect; CRP can be a valuable marker in the follow up and estimation of infections in acute leukemic patients.

REFERENCES

1. Steel DM, Whitehead AS. The major acute phase reactants: C-reactive protein, serum amyloid P component and serum amyloid A protein. Immunol Today 1994;15:81-6.
2. Baumann H, Gauldie J. The acute phase response. Immunol Today 1994;15:74-80.
3. Grützmeier S, Sandström E. C-reactive protein levels in HIV complicated by oppurtunistic infections and infections with common bacterial pathogens. Scand J Infect Dis 1999;31:229-34.
4. Manian FA. A prospective study of daily measurement of C-reactive protein in serum of adults with neutropenia. Clin Infect Dis 1995;21:114-21.
5. Heiskanen-Kosma T, Korpii M. Serum C-reactive protein cannot differentiate bacterial and viral aetiology of community-acquired pneumonia in children in primary healthcare setting. Scand J Infect Dis 2000;32:399-402.
6. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 1999;340:448-54.
7. Kallio R, Bloigu A, Surcel HM, Syrjala H. C-reactive protein and erythrocyte sedimentation rate in differential diagnosis between infections and neoplastic fever in patients with solid tumours and lymphomas. Support Care Cancer 2001;9:124-8.
8. Lacour AG, Gervaix A, Zamora SM, Vadas L, Lombard PR, Dayer JM, Suter S. Procalcitonin, IL-6, IL-8, IL-1 receptor antagonist and C-reactive protein as identificators of serious bacterial infections in children with fever without localising signs. Eur J Pediatr 2001;160:95-100.
9. Povoa P, Almeida E, Moreira P, Fernandes A, Mealha R, Aragao A, Sabino H. C-reactive protein as an indicator of sepsis. Intensive Care Med 1998;24: 1052-6.
10. Michel U, Shintani Y, Nau R. Serum follistatin concentrations are increased in patients with septicaemia. Clin Endocrinol (Oxf) 1998;48:413-7.
11. Pizzini C, Mussap M, Plebani M, Fanos V. C-reactive protein and serum amyloid A protein in neonatal infection. Scand J Infect Dis 2000;32:229-35.
12. Fleischhack G, Kambeck I, Cipic D, Hasan C, Bode U. Procalcitonin in paediatric cancer patients: Its diagnostic relevance is superior to that of C-reactive protein, interleukin 6, interleukin 8, soluble interleukin 2 receptor soluble tumour necrosis factor receptor II. Br J Haematol 2000;111:1093-102.
13. Santolaya ME, Cofre J, Beresi V. C-reactive protein: A valuable aid for the management of febrile children with cancer and neutropenia. Clin Infect Dis 1994;18:589-95.
14. Engervall P, Granstrom M, Andersson B, Bjorkholm M. Monitoring of endotoxin, interleukin-6 and C-reactive protein serum concentrations in neutropenic patients with fever. Eur J Haematol 1995;54:226-34.

Address for Correspondence:

Zafer GÜLBAŞ, MD

Department of Hematology
Osmangazi University Medical School
26480, Eskişehir, TURKEY

e-mail: *zgulbas@mail.ogu.edu.tr*