USEFULNESS OF CRP DETERMINATION IN THE INITIAL EVALUATION AND FOLLOW-UP OF FEBRILE CANCER PATIENTS

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ABSTRACT

The ability of CRP determination to detect presence of infection in febrile cancer patients was evaluated. Twenty-four children with hematopoietic malignancies were included in the study. They were divided upon admission into two groups: Group A – febrile group; and Group B – non-febrile group. Fifteen children had 18 febrile episodes (group A). The remaining nine children had no fever (Group B) upon admission. CRP levels were obtained upon admission in both groups. Follow-up determination was done in Group A patients on days two to four of antibiotic treatment and prior to discharge while follow-up determination was done only in Group B patients who subsequently developed fever in the course of their hospital stay. Two of the nine afebrile children developed fever and were reclassified under the febrile group. The 20 febrile episodes were then classified into 3 different subgroups: Group I, positive microbial cultures in the blood or if cultures from a clinically relevant focus (urine or skin) were positive and toxic appearance at presentation with or without vascular instability (5 episodes); Group II, negative cultures but with clinically and or radiologically documented focal infection (7 episodes); Group III, negative cultures and absent signs of focal infection and if the clinical course was unremarkable (8 episodes). The mean CRP level of the febrile group is significantly higher than those children in the non-febrile group (64mg/l vs. 10.3mg/l, p= <.005). There was a significant correlation between the magnitude of the admission temperature and serum CRP levels (p = .001). Children in Group I had significantly higher mean CRP levels than those children in Group III (105.6mg/l vs. 39mg/l, p= .01). Mean CRP levels of children in Group I did not differ significantly from the mean CRP levels of children in Group II (105.6mg/l vs. 65.14, p= .05). The two children who died had persistently high levels of serum CRP (>192mg/l). Those children who recovered showed a steady decline in CRP. The determination of CRP value of >40mg/l is a highly sensitive test with a high negative predictive value in distinguishing between those children with bacteriologically or clinically documented infection from those children without documented infection. CRP determination is a useful tool in monitoring the patient's response to antibiotic therapy.

Key words: C. reactive protein
fever
malignancy

INTRODUCTION

Infection in a child with cancer especially those who are neutropenic is a major cause of morbidity and mortality. Signs and symptoms of infection in the neutropenic patient may be masked; therefore these children are generally hospitalized and treated with broad spectrum antibiotics when fever occurs [1]. Such approach leads into an overuse of antibiotics and an emergence of multiresistant nosocomial strains, drug induced toxicity, and a significantly increased medical expenses [2]. The white blood cell count is often affected by the malignant process or by cytotoxic chemotherapy so that the WBC may not be reliable in indicating the presence of infection. Microbiologic confirmation of infection may take 24 hours or more. Therefore, a sensitive method for rapid, early detection of infection would be useful. Such method, is the C-reactive protein (CRP) an acute phase-reactant of inflammation, that can be quantified in the serum [3]. Serum levels of CRP have been determined in healthy individuals and these values have proven to be uniformly low (<10mg/l) in the absence of infection. Serum CRP levels of >40mg/l have been shown to be sensitive markers of bacterial infections in both adult and pediatric immunocompetent individuals with fever. Previous literature have shown that malignant disease, chemotherapy administration and transfusion of erythrocytes, platelets or granulocytes do not lead to an increase in CRP [1]. Studies have been done which found out that serial measurements of CRP in neutropenic patients is valuable in detecting infection and monitoring the response to antibiotic therapy. However, only very few studies have been done regarding the value of CRP as part of the initial diagnostic evaluation of the febrile child with cancer.

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OBJECTIVES

1. To determine if serum CRP levels in the initial evaluation of cancer patients with fever can predict presence and severity of infection.

2. To evaluate the usefulness of CRP in its ability to monitor response to antimicrobials and its ability to determine prognosis.

PATIENTS AND METHODS

Study Group

From August 9, 1995 to November 15, 1995, all infants and children with malignant disease admitted to the Hematology-Oncology Section of the Philippine Children's Medical Center were included in this study. All patients were taking prophylactic oral trimethoprim-sulfamethoxazole (8mg/kg/day divided twice daily) on alternate days 3 times a week. Patients receiving additional antibiotics were excluded from the study.

A total of 24 children with leukemia were included in the study. They were divided into 2 groups on admission. One group (Group A), included those children who were admitted because of fever with or without the presence of neutropenia; the other group (Group B) were those patients who had no fever on admission but was admitted either for blood transfusion and/or chemotherapy. Fever was defined as a single T = >38.5°C or serial oral temperatures of 38.0°C for >6 hrs. Neutropenia was defined as an absolute neutrophil count of <500/cumm.

CRP levels were obtained upon admission in both groups. Other laboratory parameters were requested among febrile patients before the start of antibiotics: Chest X-ray, CBC, blood cultures, urinalysis, and urine cultures. Antibiotic treatment with a third generation cephalosporin was generally started. Antibiotic coverage was modified as indicated according to the clinical status and the culture results. The physician in charge of the patients was not aware of the results of the CRP determination.

Follow-up determination was done in Group A patients on days 2 to 4 of antibiotic treatment and prior to discharge. Follow-up CRP determination and other laboratory parameters (e.g. Chest x-ray, blood CS, urinalysis, urine culture) were done on patients belonging to the non-febrile group who subsequently developed fever during the course of their hospital stay.

All children who had fever were then classified into 3 subgroups [1,3]:

Group I – patients with positive microbial cultures in the blood or if cultures from a clinically relevant focus (urine or skin) were positive and toxic appearance at presentation with or without cardiovascular instability.

Group II – patients with negative cultures but with clinically and or radiologically documented focal infection.

Group III – patients with negative cultures and absent signs of focal infection and if the clinical course was unremarkable.

Determination of CRP

Serum CRP determination was determined using the latex agglutination test.

Latex particles allow visual observation of the antigen-antibody reaction. If the reaction takes place, due to the presence of C-reactive protein in the serum, the latex suspension changes its uniform appearance and a clear agglutination becomes evident.

The presence of agglutination indicates a content of C-reactive protein in the serum equal to or greater than 6mg/l. The absence of agglutination indicates a content of C-reactive protein in the serum of less than 6mg/l which was regarded as normal.

The CRP value of >40mg/l was assigned as the cutoff point for bacterial infection in our pediatric population.

Statistical Analysis

The t-test was used to study the differences in mean CRP values among the 3 patient subgroups. With the use of the correlation coefficient a correlation analysis was done for all patients to determine whether the magnitude of admission temperature correlated with the elevation of CRP. Sensitivity, specificity, positive predictive value, negative predictive value were determined for each group of patients using >40mg/l as the cutoff levels for all patients. Numerical values were expressed as mean ± standard deviations and as percentages.

RESULTS

Twenty-four patients with malignant disease were included in the study. All the 24 patients had hematopoeitic malignancies. Fifteen (62.5%) had ALL, 5 (20.8%) had AML and 4 (16.7%) had CML. The mean patient age was 7.6 years (range, 1.2 to 17 years). Male to female ratio was 1.4 : 1.

Fifteen children had 18 febrile episodes 13 (72.2%) of whom had neutropenia while 5 (27.8%) had normal absolute neutrophil count. The remaining nine children were neither febrile nor neutropenic on admission but were admitted for chemotherapy and/or blood transfusion.

The mean CRP level of children in the febrile group was significantly higher than those children in the non-febrile group (64 ± 50.52mg/l vs. 10.3 ± 8.0mg/l, p value = <.05) (Table I). There was also a significant correlation between the magnitude of the admission temperature and serum CRP levels with p value of .001.

Table 1 *Admission CRP Levels of the Febrile vs. Afebrile Group with Corresponding Temperature*

Diagnosis	Age/sex	CRP(mg/L)	Adm Temp(C)
FEBRILE GROUP			
Group I			
ALL	8yo/M	192	40.0
AML	9yo/F	96	39.0
ALL	7yo/M	48	38.3
ALL	5yo/F	96	40.0
ALL	4yo/M	96	40.3
Group II			
ALL	9yo/M	48	39.0
CML	1.2/M	48	38.6
ALL	9yo/M	48	39.0
ALL	8yo/F	24	38.2
ALL	8yo/F	48	38.8
ALL	12yo/M	192	41.0
Group III			
AML	5yo/F	24	38.0
ALL	7yo/M	24	38.2
ALL	5yo/M	24	38.1
AML	9yo/M	48	38.9
ALL	1yo/F	48	38.7
ALL	8yo/M	96	40.0
ALL	8yo/F	24	38.0
AFEBRILE GOUP			
AML	8yo/F	6	37.0
ALL	17yo/M	24	37.5
ALL	8yo/M	6	36.5
AML	9yo/F	6	36.8
ALL	4yo/F	24	37.6
AML	8yo/F	6	36.9
CML	1.4yo/M	12	37.7
CML	4yo/M	6	37.0
ALL	7yo/M	6	36.6

ALL, acute lymphoblastic leukemia
AML, acute myelogenous leukemia
CML, chronic myelogenous leukemia

Of the nine initially afebrile children, two developed fever during the course of their hospital stay. One had neutropenia who developed fever on the 2nd hospital day while the other one developed fever on the third hospital day but had no neutropenia. CRP monitoring showed a corresponding increase of CRP to 48mg/l and 24mg/l respectively. These two children were reclassified under the febrile group.

There were a total of 20 febrile episodes that were classified into 3 different subgroups as described above. Patients with microbiologically documented infections (Groups I) had significantly higher mean serum CRP concentrations than those children without documented infections (Groups III) (105.6 ± 52.58 vs. 39.0 ± 25.45 mg/l, p = .01). The mean CRP levels of children in Group I did not differ significantly from the mean CRP levels of children in Group II (105.6 ± 52.58 vs. 65.14 ± 56.64, p = >.05). The final diagnosis for all the 20 febrile episodes as well as the criteria used for the diagnosis is shown in Table 2.

Table 2 *Final Diagnosis and Diagnostic Criteria for 20 febrile episodes in 17 children with cancer*

Diagnosis	No. of episodes criteria	Diagnostic
Group I	5	
Klebsiella infection 1		blood culture
Pseudomonas infection 1		blood culture
Staphylococcus coagulase negative	1	blood culture
E. coli infection	2	2 urine cultures
Group II	7	
Pneumonia	5	chest x-ray
Oral cavity infection 2		clinical
Group III		
no focus	3	

In these cancer children who had fever, a serum CRP value of >40mg/l, used as a diagnostic tool to differentiate between patients with bacteriologically documented infection versus patients without documented infection (group I vs. group III) showed a sensitivity of 100%, a specificity of 62.5%, an accuracy of 77%, a positive predictive value of 62.5% and a negative predictive value of 100%. If children in Groups I and II were combined vs. Group III, this test showed a sensitivity of 91.7%, a specificity of 62.5%, an accuracy of 75%, a positive predictive value of 78.5% and a negative predictive value of 83. 3% (Table 3).

Table 3 *Ability of serum CRP concentration in differentiating septicemic/nonsepticemic and infected/non-infected in febrile children with malignancy*

	A. septicemic vs. non-septicemic	B. bacteriologically or clinically documented infection vs. undocumented infection
Sensitivity	100	91.7
Specificity	62.5	62.5
PPV	62.5	78.5
NPV	100	83.3

Of the total 17 children with 20 febrile episodes, 2 died and 15 recovered. One of the mortalities, an 8-year old male with ALL on the induction phase of therapy who died on the 7th hospital day and grew Klebsiella in the blood. The other death, an 8-year old male with ALL on the induction phase of therapy died on the 12th hos-

pital day because of pneumonia. On admission, CRP levels of these two children were both elevated at 192mg/l, and subsequent monitoring of their CRP showed persistently high levels of >192mg/l. All those 15 children who recovered showed a steady decline in CRP levels and upon discharge they either had levels of 6mg/l or <6mg/l (Fig I).

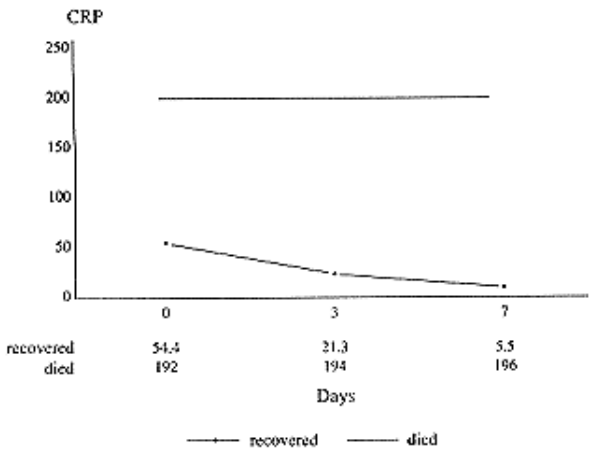

Fig 1. Follow - up serum CRP levels

DISCUSSION

Patients with cancer are more prone to infection secondary to aplasia of the bone marrow and more frequently this is a common cause of death especially with delayed antibiotic treatment owing to lack of a rapid, sensitive and specific diagnostic tool to detect infection. Initial evaluation of the febrile child with cancer especially if neutropenic is difficult because clinical signs of infection are often subtle [1]. Thus, many have advocated antimicrobial treatment of febrile cancer patients in the presence of neutropenia. This practice though have led to overtreatment. Several studies have established the CRP value as a reliable indicator of sepsis in febrile patients with malignancies.

Acute phase plasma reactants constitute a heterogenous group of proteins synthesized in the liver in response to cytokine stimulation. One of the widely used acute phase proteins is the C-reactive protein (CRP). Originally named for its capacity to bind the C-polysaccharide of pneumococcus, the CRP was shown to function in vitro as an opsonin for bacteria, parasites and immune complexes. It can likewise, initiate complement cascade and enhance macrophage tumouricidal activity. Due to its exquisite responsiveness to an inflammatory stimulus, its wide concentration range and its ease of measurement, it is widely used to monitor accurately the severity of inflammation and the efficacy of disease management [4].

CRP value usually rise within 6-8 hours of injury with large incremental increases of 10 to 1000 fold, peak concentration in 2-3 days, a short half-life and a behavior consistent in different forms of inflammation [5].

A significantly higher admission CRP level in the febrile group vs. the non-febrile group shown in this study is due to an acute phase response to inflammation initiated by the cytokines which stimulates the liver to produce acute phase proteins (e.g. CRP) and also affects the CNS resulting to fever. The inflammation may be secondary to a pathogen, or tissue injury in malignancy.

The magnitude of the admission temperature correlated significantly with the serum CRP level. This was not well appreciated by Katz.

The 2 initially afebrile patients who developed fever showed increasing increment of CRP as expected.

The presence of bacteriologically documented infection whether isolated from the blood or other specimens (Groups I) had significantly higher admission CRP levels compared with those without documented infection (Groups III). The admission serum CRP value was able to differentiate between bacteremic and non-septic febrile patients at hospital admission. Although the sensitivity and the negative predictive value test were both 100% at CRP concentration of >40mg/l, the specificity was only 62.5% and the positive predictive value was also low at 62.5%. This result was remarkably comparable with that of Santolaya. The specificity and the positive predictive value in this study was however higher than that obtained by Katz. When Groups I and II were combined (bacteriologically and clinically documented infection) vs Group III (non-documented infection) the sensitivity, specificity, and negative predictive value were lower as also observed by Katz and Santolaya (Table 4).

Table 4 *Sensitivity, specificity, predictive value of CRP concentration to differentiate septicemic/non-septicemic infected/non-infected febrile children with malignancy in various studies.*

A. septicemic vs. non-septicemic

	Botin	Katz	Santolaya
sensitivity	100	71	100
specificity	62.5	67	76.6
PPV	62.5	12	77.4
NPV 100	97	100	

B. Bacteriologic or Clinically Documented Infection vs. Undocumented Infection

	Botin	Katz	Santolaya
sensitivity	91.7	46	94.5
specificity	62.5	75	76.7
PPV	78.5	63	88
NPV	83.3	60	88.5

PPV – positive predictive value
NPV – negative predictive value

Noteworthy, the CRP values of the majority 16 (80%) of the febrile children were followed and rapidly normalized after the initiation of antimicrobial therapy (third day of antimicrobial use). Two (10%) children had normal CRP only on the 6th day of therapy. The remaining two (10%) died with persistently high CRP value of >192mg/l.

CONCLUSIONS/RECOMMENDATIONS

The determination of the C-reactive protein (CRP value >40mg/l) is a highly sensitive test with high negative predictive value in identifying bacteriologic or clinical infection among febrile cancer patients.

Patients with malignancy who develop fever and obtain CRP values >40mg/l should be immediately given antimicrobial therapy while awaiting culture results. In case of negative bacteriologic findings, antibiotics should be continued as long as focus of infection such as pneumonia is recognized.

Febrile cancer patients with CRP values <40mg/l may not be given antibiotic therapy but should be observed for any clinical sign/focus of infection.

Aside from rapid diagnosis of infection, CRP is a useful tool in monitoring the patient's response to antibiotic therapy.

Future studies are recommended to determine the usefulness of CRP as a guide to duration of antibiotic use and as a predictor of mortality.

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"Ang iyong ifinanim, siya mo ring aanihin"