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Febrile neutropenia in children with acute leukemia receiving chemotherapy; Clinical, laboratory characteristics and outcome

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Abstract

Background: Fever and neutropenia among the most common and serious complications of cancer chemotherapy. The diagnosis of sepsis in children with febrile neutropenia remain difficult due to non-specific clinical and laboratory signs of infection, so hospitalization and empirical intravenous broad spectrum antibiotic should be initiated as early as possible. The aim of this prospective study is to describe clinical, laboratory characteristic and outcome of febrile neutropenic episodes.

Methods: One hundred seventy febrile neutropenic episodes observed in 100 children with acute leukemia receiving chemotherapy in the oncology department of child's central teaching hospital /Baghdad over a period of 10 months (from march through December 2007).

Results: febrile neutropenia was frequent complication, and severe neutropenia (ANC < 200 cell/mm) was encountered in 47 episodes (27%) of total episodes. Clinical signs and symptoms suggestive of infection were evident in 38% of neutropenic episodes, the respiratory system was the most frequently affected site encountered in 17%. Microbiological documented infection found in 16% (n=27) of episodes all from local sites other than blood, bacteremia couldn't be detected in any samples. G-ve bacilli were the most frequently isolated (63%) followed by G+ve microorganisms in (37%). Fatality rate was 24% of total patients.

Conclusion: This study confirmed that our laboratory is behind the global standard for isolation of causative organisms.

Keywords: Fever, fatality, episodes

Introduction

Patients with hematologic disorder are complications as a consequence of perturbation of one or more components of their host defense system [1]. Predisposed to variety of infectious Neutropenia remain the major defect for many patients and therefore continues to serve as a model system for dealing with infections in patients who are immuno compromised [2]. About 1/2 of neutropenic patients who become febrile have an established or occult infection and at least 1/5 of patients with neutrophil count < 100 cells/mm³ have bacteremia³. In mid-1980 the spectrum of bacteria causing infection began to change with steady increase in G+ve infection occurred until presently 60-70% of bacteremias [19] with Coag.-ve staph & staph. Aureus are the predominant. Although the goal of initial evaluation is to identify potential sources of infection, this will not be successful in the majority of patients [4].

Aims of study

To study febrile episodes in neutropenic pediatric patients with acute leukemia receiving chemotherapy, to stratify the risks of febrile neutropenic episodes whether it can have important implication in term of management and outcome, To determine the bacterial agents associated with infection in these episodes, To find out the correlation between outcome and degree of neutropenia.

Patients and Methods

We prospectively observed patients admitted for treatment of febrile neutropenia to the department of hematology & oncology in a Childs central teaching hospital / Baghdad, during a period of 10 months (from 1st of March through December 2007).

Patients

One hundred seventy two febrile neutropenic episodes occurred in 100 child patients with acute leukemia receiving chemotherapy treatment. The study group of patients may have one episode, two, three or even more febrile episodes are included in this study Patients enrolled in the study underwent complete physical examination, medical history was obtained and baseline laboratory and radiological investigation were performed.

Laboratory methods: As primary evaluation and before starting antibiotic therapy, (2 ml) of Blood samples were obtained by vein puncture after preparation skin with antiseptic iodine and alcohol Samples inoculated in brain-heart broth and cultured on blood MacConkey agar under aerobic condition only. Other clinical samples (throat, wound, ear) swabs in addition to urine and stool samples were collected according to patients state, and subjected for routine culture for bacteria. Aspirate for culture from any accessible sites suggesting infection were also taken. Renal and liver function testes were done for general evaluation on admission and repeated with interval according to the disease state. Complete blood count (CBC) and differential count was made every 3 days to follow the response. Other laboratory measurement and procedure were resumed if clinically indicated. Empiric antibiotic therapy was administered (third generation cephalosporin plus gentamycin in most of cases), and All antibiotics were administered intravenously.

Statistical analysis: Chi-square test was applied to determine the Relative importance of various variables.

P-value <0.05 was considered as statistically Significant.

Tables and results

Table below shows the demographic characteristics of 100 children with acute leukemia receiving chemotherapy with 172 febrile neutropenic episodes.

Table 1: Demographic characteristics of patients.

Demographic character	No. of patients	Percentage
Gender		
Male	68	68
Female	32	32
Age (years)		
Range	4 mo. – 14 years	
Average	5.9 + 1.2	
Mean	5.9	
Number Episodes		
1 episode	40	40
2 episodes	49	49
3 episodes	10	10
> 3 episodes	1	1

Acute lymphoblastic leukemia (ALL) was the most common type of leukemia and therefore the high percentage of episodes.

Table 2: Relation between the type of leukemia and number of febrile episodes.

Type of malignancy	No. of patients (%)	No. of episodes (%)
ALL	74 (74)	135 (78)
AML	26 (26)	37 (22)
Total	100 (100)	172 (100)

Table below divided the neutropenia in to (Mild, moderate and severe) according to Absolute neutrophil count (ANC).

Table 3: distribution of episodes according to the degree of severity of neutropenia

Degree of neutropenia	No. of episodes	%
Mild (> 500)	69	40
Moderate (200-500)	56	33
Severe (<200)	47	27
Total	172	100

Table below shows that the clinical signs and symptoms suggestive of infection were evident in 38% of febrile neutropenic episodes. The respiratory system was the most affected site. The microbiological documented infection were detected in 16% (n= 27) of the episodes. In majority of episodes there were no focus of infection whether clinical or microbiological.

Table 4: Incidence of clinically and microbiologically documented infections.

	No. of episodes	%
Clinically documented infections	65	38
Respiratory system	30	17
Soft tissue	17	10
GIT	15	9
Urinary system	3	2
Absent signs and symptoms of infection	107	62
Microbiologically documented infections	27	16
No Microbiological document of infection	145	84

Out of 237 cultures (172 from blood and 56 from sites other than blood). Positive isolates were detected in 27 cultures only (11%) of total cultures G-ve bacilli were the most frequently isolated organisms 63% (n=17) of positive isolates. Pseudomonas aeruginosa was the most commonly

encountered bacterium in positive cultures 37% (n=10), and wounds were the most common sites for isolation 26% (n=7). G +ve bacteria represented 37% of positive isolates. Other organisms isolate and their percentage are shown in table (5) below.

Table 5: Distribution and frequency of isolated bacteria according to the site of culture

Isolated Organism	Wound swab (%)	Throat swab (%)	Ear swab (%)	Urine (%)	Stool (%)	Blood (%)	Total
<i>Pseudomonas aerugo.</i>	7 (26)	2 (7.4)	1 (3.7)	0	0	0	10 (37.1)
<i>Staph. epidermidis</i>	1 (3.7)	2 (7.4)	2 (7.4)	0	0	0	5 (18.5)
<i>Klebsiella a spp.</i>	2 (7.4)	1 (3.7)	0	2 (7.4)	0	0	5 (18.5)
<i>Strept. Pneumoniae</i>	0	3 (11.1)	2 (7.4)	0	0	0	5 (18.5)
<i>E. coli</i>	0	0	0	0	2 (7.4)	0	2 (7.4)
Total	10 (37.1)	8 (29.6)	5 (18.5)	2 (7.4)	2 (7.4)	0	27 (100%)

Table below shows the percentage of prolonged fever and neutropenia (>1 week) documented at hospital, and idea about the risk of patients for morbidity and mortality.

Table 6: Duration of fever and neutropenia during episodes.

	No. episodes	%
Duration of fever		
<1 week	131	76
>1 week	41	24
Duration of neutropenia		
<1 week	117	68
>1 week	55	32

Table below shows that, the case fatality rate was 24% (n = 24) of total patients with febrile neutropenia.

With a significant mortality in severe neutropenic episodes than in moderate and mild

Table 7: Relationship between mortality rate and degree of neutropenia among neutropenic cancer patients.

Degree of neutropenia	Mild		Moderate		Severe		Total
	No.	%	No.	%	No.	%	
No. of episodes	69	40	56	33	47	27	172
No. pf death	3	4	6	11	15	32	24

Chi-square=12.99 p-value=0.0015 (highly significant)

Discussion

With cancer chemotherapy, infectious complications are life threatening and may limit the benefit of antineoplastic therapy.

In this study the frequency of occurrence of fever and neutropenia in leukemic patients was similar to that reported by Stabell N *et al.*,^[6] Paganini HR. *et al.*^[7] and Majd Z *et al.*^[8] That the most common underlying malignant disease was Acute lymphoblastic leukemia (ALL) and so the frequency of febrile neutropenic episodes. Clinical signs or symptoms of infection, except for fever in febrile neutropenic patients with malignancies were documented by EL- Maghraby SM. *et al.*^[9] in 45.9% of their study. Haider M. *et al.*^[5] reported clinically documented infection in 39% of their study. In study carried out by Paganini HR. *et al.*^[7], clinically documented infection was 47%.

In this study clinical signs or symptoms of infection were documented in 38% of febrile neutropenic episodes and the respiratory system was the most common site of infection encountered in 17% of episodes, similar to Haider M. *et al.*^[5] found 17% on his study.

In this study microbiological documented infection was 16% of episodes, G-ve organisms were the most frequently isolated in 63%, followed by G +ve organisms in 37% of positive isolates, and this probably due to lack of Central access device in our center.

Hammerstrom J. *et al.*^[10], found that G-ve bacteria represent 54% of bacteremia in acute leukemia patients with severe neutropenia. Haider M. *et al.*^[5], reported a microbiological documented infection in 59% of episodes G

+ve were the most frequently isolates in 54% and G-ve In 39% of isolates AL-Maghraby SM. *et al.*^[9], found microbiological documented infection in febrile neutropenic children with hematological malignancies was 69% local sites of infection in 45% and bacteremia in 24%), the G +ve were the predominant organisms.

In this study bacteremia couldn't be detected in any sample. in contrary to all other studs where bacteremia detected in a percentage ranging from 10 -30% Kocak U. *et al.*^[11], found that 18% of febrile neutropenic children with leukemia had bacteremia, and the G+ve was the predominant organisms. Mahmood S *et al.*^[12], found a total of 18.8% of neutropenic episodes associated with cancer were accompanied by positive blood cultures and G +ve was predominant. The high percentage of episodes with no clinical microbiological evidence of infection agrees with what found by Castagnola E. *et al.*^[11], who found that the most frequent clinical diagnosis in febrile episodes during chemotherapy induced neutropenia in children was fever of unknown origin in 79% followed by bacteremia in 10%. Kocak U. *et al.*^[11], found that fever of unexplained origin was seen in 73% of febrile neutropenic episodes, bacteremia found in 18%. However the use of more sophisticated techniques for isolation of causative microorganisms may lower this percentage.

In this study the case Fatality Rate of 24% in comparison with other studies was high, and highly significant death rate in severe neutropenic episodes was an alarming outcome.

Haider M. *et al.*^[5], reported (FR) of 3% of their study, Stabell N. *et al.*^[6], found a mortality rate of 1%. Basu K. *et al.*^[15], reported a mortality rate of 3% Hamalainen S. *et al.*^[14], reported 11% died due to severe sepsis. Majid Z. *et al.*^[8], found that the mortality rate in severe neutropenia was 44% Kocak U. *et al.*^[11] found the fatality rate was zero in febrile neutropenic patients with malignancy.

The prompt initiation of effective empirical antimicrobial therapy, availability of supportive care and better knowledge of microbiology of infection of these patients, the institution and probably in update changing empirical treatment made the overall mortality among cancer patients in developed countries significantly lower than observed in this study. In our oncology department the choice of antibiotics depend on availabilities of drugs but does not depend on the ideal combination for Coverage of most common pathogen associated with infection in these groups of patients which are (ceftazidime plus vancomycin or carbencillin plus gentamycin), The availabilities and the cost of these drugs make the combination of (ceftriaxone plus garamycin) is the our choice in spite of it is weak action against *P.aeruginosa* or *Staph. Epidermidis*, and for this reason 49% of episodes in this study required modification of empirical antibiotic treatment, in contrary to

Kocak U *et al.* [11] and Hammerstrom J *et al.* [10], both founds that only 25% needs modification of their empirical antibiotic treatment. The difficulty of getting blood and its products, Unavailability of systemic broad spectrum antifungal treatment, Unavailability of supportive medication like hemopoietic growth Factor although it debatable, Late presentation of our patients may be due to poor socio-economic status, bad security conditions or due to difficult transportation. All can be added as additional factors for high mortality.

Conclusions

Gram-negative bacteria was the most common encountered in positive cultures from local sites other than blood, and wounds swab was the most common site of isolation, Negative blood culture does not exclude presence of bacteremia, There is obvious increase in mortality rate among severely neutropenic patients.

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