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Febrile Episodes during Chemotherapy Induced Neutropenia in Children with Acute Lymphoblastic Leukemia at Children Hospital –Benghazi 2013-2014

Salima M. M. Alzehawi [a*], Amina Beayou [a], Najat B. Elgazal [a], Fawzia S. Khalifa [a], Salimah S. Alabeedi [a] and Mohamed M. Alferjani [a]

[a] Pediatrics Department, Faculty of Medicine, University of Benghazi, Benghazi-Libya, Libya.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Patients undergoing chemotherapy are vulnerable to infection because of immunosuppression and prolonged hospitalizations. Chemotherapy drugs affect neutrophil production through myelosuppression (1) and low inflammatory response so that fever maybe the manifestation of infection (2).

The purpose of this study was to analyze febrile neutropenic episodes associated with infections in the 1st three phases of acute lymphoblastic leukemia (ALL) treatment, document the risk factors affecting morbidity, mortality, treatment and the outcome of treatment.

The study was a cross-sectional hospital-based descriptive survey in the Hematology-Oncology Unit at Children's Hospital. It included all cases of (ALL) who were diagnosed within two years and treated with the Berlin Frankfurt Munich (BFM) protocol who developed fever during a neutropenic period. Data was recorded as gender, age, residence, nationality, number of episodes per patient, treatment phase, admission duration, length of stay (LOS) per episode, symptoms, physical examination and severity of fever. Investigations, the antibiotic used and the outcome were also recorded.

A total 27children, males accounting for 63%, 67<5 were included in the study. Febrile neutropenic episodes ranged 1–12. Their peak was in January. 40% were in phase II. LOS range 2-35 days. Fever showed a median of 38.8 °C, higher in phase II and III. Admission and therapy phases were

**Corresponding author: Email: mohanad.lawgali@uob.edu.ly;*

longer in children < 2 years old and in males. The neutrophil median was 270/mm^3. Stomatitis was seen in70% of episodes, gastroenteritis in 65%, fever of unknown origin (FUO) in 16%and pneumonias in 15%. 20/23 bacterial infections were Gram-negative. 40% of episodes required a change of antibiotics. The mortality rate was 22%.

Keywords: Acute lymphoblastic leukemia; neutropenia; fever; Children's Benghazi; Libya.

1. INTRODUCTION

Children undergoing chemotherapy for cancer are vulnerable to infection because of immunosuppression due to illness, the effects of chemo and radiotherapy, catheterization, malnutrition, hospitalizations and antibiotics [1-4].

Neutrophils are an essential part of the body's defense system. Chemotherapies affect neutrophil production through the use of immunosuppressive drugs [5]. Neutropenia (the absolute neutrophil count (ANC) is > two standard deviations below the mean) lead to an inappropriately low inflammatory response with fever as maybe the only manifestation of infection [6]. Management of this complication can vary widely, relating to different geographic patterns of infections, antimicrobial resistance, cost issues and treatment availability [7-10]. Aerobic and anaerobic Gram positive and Gram negative bacteria, fungi, viruses and parasites may cause infections in these patients [11-14]. Although empiric broad spectrum antibiotic administration at the onset of fever is the accepted standard approach for neutropenic patients, the inappropriate use of antibiotics is of special concern and is associated with colonization by hospital-acquired organisms and associated expense [15]. In spite of recent improvements in antimicrobial and supportive therapies, these infections are still associated with severe morbidity and mortality, and represent a frequent cause of treatment withdrawal [16].

Table 1. Distribution of patients according to age

Age in yrs.	No	%
0.8- 2	3	11
>2-5	15	56
6-10	7	26
>10	2	7
Total	27	100

2. OBJECTIVE

To analyze febrile neutropenic episodes associated with infections in the 1st three phases of ALL treatment, document the risk factors affecting morbidity and mortality, treatment and the outcome of treatment.

3. MATERIALS AND METHODS

A cross-sectional hospital-based descriptive survey the in Hematology-Oncology Unit at Children Hospital was completed, including all cases of ALL patients who were diagnosed from January, 2013 to December, 2014, and treated with BFM protocol, who developed fever during a neutropenic period. Data was recorded, including gender, age, residence, nationality, number of episodes per patient, treatment phase, (LOS) per episode, symptoms, and physical examination and severity of fever. Investigations such as radiographic, ANC, blood, urine and other culture, antibiotic usage and outcome of treatment were noted.

4. RESULTS

During the 2 years, 2013-2014, a total of 27 patients in the 1st three phases of chemotherapy (consolidation, intensification and maintenance phases), were admitted with 188 episodes of fever and neutropenia. Out of 27 patients, 98% were Libyan, 17(63%) were male and 17 (53%) were from outside Benghazi. Their age at diagnosis ranged from 0.8 to 13 years with a median of 5 years.

4.1 Analysis of Febrile Neutropenic Episodes (Admission)

4.1.1 According to number of episodes

The occurrence of episodes during treatment was from 1 to 12 per patient, with a median of 7. The majority of patients (74%) had between 5-8 episodes with their peak in January (25 episodes). In advanced phases of chemotherapy, the frequency of episodes increased. Out of 188 episodes, 76 (40%) occurred in phase II.

4.1.2 According to length of stay in the hospital (LOS)

The LOS range was from 1-35 days, with a median of 7 days. The majority of episodes, 103 (55%) lasted from 6 to10 days. Children<2 years

of age and males were admitted for a longer duration. Statistical analysis of LOS was significantly different across age and gender (P < 0.001.P = 0.527).

Table 2. Distribution of patients according to Freq. of episodes

Frequency of episodes	No. of pts.	%
1-4	3	11
4-8	20	74
> 8	4	15

Table 3. Distribution of episodes according to LOS in hospital

L O S	Episodes No.	%
Up-to 5	39	21
>5-10	103	55
>10-15	31	17
>15	15	8
total	188	100

Table 4. Frequency of episodes according to phases of therapy

Therapy phase	No. of episodes %	Median (mini- maxim)
I	46 24	2 (0-3)
II	76 40	3 (0-5)
III	66 36	2 (0-6)
Total	188 100	7 (1-12)

4.1.3 According to fever

Fever preceded admission by 1-2 days or developed during hospital admission. Length of fever ranged from 1- 27 days, with a median of 6.5.2/3 of episodes, 132(70.5%) were up to 5 days. Temperature was reported during the episodes at a median of 38.8 C˚. The initial temperature was 38.5 C˚ in 85 (45%) of episodes. Only 67 episodes (36%) reported> 39.5 C˚. The duration of fever was longer in children < 2 yrs. and in males, P = 0.004, P = 0.022. The degree of temperature was not different in all ages, genders or according to duration of LOS. In contrast, there was a correlation between the therapy phase and degree of fever, p = 0.042, but not with its duration, p= 0.278.

4.1.4 According to neutropenia

Median initial ANC was 270/mm^3 with a range of 0– 500. Ninety-eight episodes had ANC < 300/mm^3 with a duration having a median of 5 days. Of 188 episodes, 103 (55%) had 5 day duration. No relationship was seen between neutropenia severity and age, gender, LOS or phases of chemotherapy with p value s of 0.526, 0.494, 0.28and 0.566 respectively.

Table 5. Distribution of episodes according to fever duration

Duration of fever	No. of episodes	%
Up-to 5days	132	70
6- 10 days	41	22
11- 15days	13	7
>15- 27 days	2	1
Total	100	100

Younger children and males had a longer duration of neutropenia. A strong association was seen between age, gender and the duration of neutropenia (p <0.001.p= 0.017). There was no difference in chemotherapy phases p= 0.53.

Table 6. Distribution of episodes according to neutropenia duration

Duration /days	No	%
Up 5	103	55
6-10	65	34.6
11-15	13	7
>15	7	3.5
Total	188	100

Table 7. Distribution of episodes according to neutrophil count

Neutrophil count /mm^3	Episodes No.	%
<100	12	6
100 - 299	86	46
300 - 500	90	48
Total	188	100

4.1.5 According to causes of fever and modality of diagnosis

The diagnosis was made initially by clinical examination in 70% of episodes. To confirm the diagnosis, further investigations, either laboratory 9.6%, or radiological 14.6%, or both**.** Oropharyngeal infections were seen in 70% of episodes, 57% were Gastroenteritis (GE), 33 (17%) upper respiratory tract infection (URTI) and 28 (15%) pneumonias. 30(16%) were noted as FUO, and skin infection comprised fourteen cases. There were 12 cases of UTI, another 5 cases of pyuria and bacteriuria (culture no growth) another 4 patients had symptoms of

urinary tract infection (UTI) only. One- hundred and five blood cultures were taken, with 91 (87%) showing no growth, 9 (9%) were microbiologically-confirmed infections.

Of 23 bacterial isolates, 20 (87 %) were gram-negative. The most common site was urine 12 (52%). Fungal infections were suspected in 20 episodes.

Table 8. Sites of documented infections

Site of infection	No.	%
Mouth ulcer & gingivitis	130	70
Gastroenteritis (GE)	108	57
Respiratory		
Upper respiratory tract	70	37
infection (URTI)	33	18
Pneumonia	28	15
Otitis media (OM)	9	5
FUO	30	16
Skin infection	14	8
Abscess	7	4
Perianal Pyoderma	4	2
Cellulites	3	2
Chickenpox	2	1
Urinary tract infection (UTI)	12	6
Sepsis	9	5

Table 9. Types of isolated bacteria

Type of bacteria	No	%
Gram Negative		
E. coli.	8	40
Kleb	7	35
Pseudomonas	3	15
Serritia	1	5
Acinetobacter	1	5
Total	20	100
Gram Positive		
S. aureus	1	33
S. albous.	1	33
Epidermidis	1	33
Total	3	100

4.1.6 Treatment

The mean duration of antibiotic treatment was 6.8 (+2.1) days. Empiric broad-spectrum antibiotics were started as soon as cultures were obtained in most episodes**.** Reasons for changes of antibiotics were poor clinical response (72%), resistance of organisms (3%), new infections (11.6%). A combination of 2 or more reasons were seen in (13%) episodes. In 10.6% of episodes, anti-fungal medications were added, and anti-viral treatment was used in 3.2% of episodes.

Table 10. Treatment used in an infections

Treatment	Episodes no	%
Antibiotic		
1st line	131	70
2nd line	71	37
3rd line	46	24
Antifungal	20	11
Antiviral	6	3

4.1.7 Outcome

Length of follow up ranged from 25 to 49 months for all patients. The two year disease free survival rate was 78%. The mortality rate was 6 (22%) patients during the study period. All were due to overwhelming sepsis, among them one was contributed to by leukemia relapse. The majority of deaths were in the younger age group with 5< 3 years, 4< 2years, (one child 8 months, one child 1 year of age). Five were males, but there was no correlation between age and gender or frequency of admission or phases of treatment with deaths, p value = 0. 628, 0.363, 0.555 and > 0.5, respectively. All deaths showed a high degree and long duration of fever (p= 0.026 and 0.000).

Outcome was worse with severe neutropenia, which persisted for a longer period. Statistical analysis show significant correlation between the degree and duration of neutropenia with deaths p = 0.012 and 0.000 respectively**.** All deaths were of patients on the 2nd or 3rd line of antibiotics as well as antifungal treatment.

5. DISCUSSION

In spite of recent improvements in antimicrobial and supportive therapies, infections are a major complication associated with severe morbidity and mortality, and represent a frequent cause of treatment withdrawal [6, 17, 18]. Differences in the intensity of anti-leukemia treatment and the immune system may explain differences in the occurrence of susceptibility to infections [6, 15].

In the present study, we investigated infectious complications that occurred in 27 children with febrile neutropenia, including 17(63%) males, with median age of 5 and 67% of them <5 years. Our finding was in accordance with a Singapore study where almost two thirds of their patients

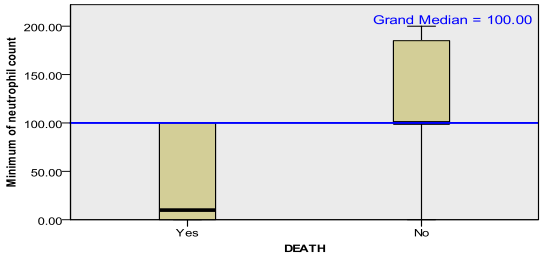

Fig. 1. Correlation between of neutrophil count and deaths

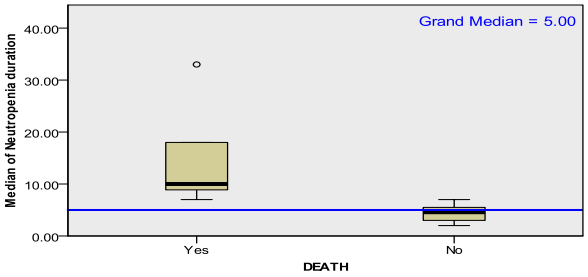

Fig. 2. Correlation between neutropenia duration and deaths

were males and 55% of them < 5 years of age [19], while in a study done by Bakhshi S, et al. [20] where 53% of the study group was aged 5 months to 11 years with males in predominance.

The ages of patients in the above studies were near to the Guatemala report, in which the ages ranged from 8 months to 15 years. However, males represented only 45% of the study group [21]. The occurrence of febrile episodes during anticancer treatment varies from 2.6 to 4.2 episodes per patient year at risk, which more is frequent during the induction as compared to the consolidation phase [22].

Of 102 episodes evaluated in 88 patients, in whom risk factors and blood cultures were tested, 74 children (84%) had 1 episode, 11 (12%) had 2 episodes, and 2 (2%) had 3 episodes [21].

In a survey conducted by Minna et al., concerning the number of 156 febrile episodes in 51 children with leukemia during patient days at risk, the mean number of febrile episodes was 3.1 (range 0-17) per patient [18].

In a study done in Singapore, Chong et al. [19] during an 8 1/2year period, there were 77 episodes in 32 children with a mean of 2.4 episodes (range 1 to 6 episodes), with 24 episodes occurring during the post-induction and 28 post-intensification phases of chemotherapy.

In comparison with earlier studies, the number episodes in our study varied from 1 to 12 with a median of 7.74% of patients had between 5-8 episodes, 11% of patients developed more than 10 episodes.

Out of 188 episodes, 76(40%) occurred in phase II, versus 46(24%) episodes in phase I.

We compared our data regarding LOS, which ranged from 1-35 days, with a median of 7 days. The majority of the episodes, 55%, were extended, from6 -10 days, 8% > 16 days and significantly longer in younger children and in males, P = 0.001 P < 0.001.

Our findings were consistent with the study carried out by Aslihand Emireet et al. [23] which reported that the median time of LOS was 10 days (range: 2-34 days) with a strong association between LOS and neutrophil count, but not with patient characteristics of gender or age.

Similarly Akova et al. [24] reported the median time of LOS as 10 days (range: 1-28 days).

During the survey by Minnaet et al., the number of hospital days was 29.3 per year, days on antibiotics therapy 17.4 per year, and fever days 5.1 per year [18].

Our study showed that the length of fever ranged from 1-27 days with a median of 6.5, 70.5% were up to 5 days and only 2 episodes with prolonged fever of more than 2 weeks. The degree of temperature ranged from 38.5 to 41^{o}C, with a median of 38.8^{o}C. The 67 episodes (36%) reported > 39.5^{o}C.

The median of initial ANC was 270/mm^{3}. Ninety-eight episodes had< 300/mm^{3}, and 12(6%) were < 100/mm^{3}. The duration ranged from 3- 33 days with a median of 5. 55% had 5 days duration and from 6 -10 days duration and were recorded at 34.6%. Males and younger patients had a longer duration of neutropenia, p = 0.017 and <0.001respectively.

A study done of 318 children during induction and maintenance, with ANC< 500/mm^{3}, one-third of the patients had a temperature > 38.5^{o}C. The length of fever ranged from 3 -16 days with a mean of 5.9 days, but only 4.1% had positive blood cultures [18].

In another study of 21 episodes of febrile neutropenia the average initial ANC was 223/mm^{3}, 9 had initial ANC of 300-500/mm^{3}, seven were in the 100-299/mm^{3} range and five < 100/mm^{3}.The mean duration of neutropenia was 12 days (1-74 days) [5].

The relationship between fever, neutropenia, and bacteremia with patients is characteristic and has been widely known for more than 40 years [21].

As seen in studies [25, 26, 27,28] which reported a strong correlation between the duration of neutropenia of more than 7 days and super infection, the duration of neutropenia, fever resolution, and antibiotic administration was significantly longer in younger children and males [29,30,31].

Our findings showed that in 70% of episodes diagnosis was made by clinical examination, 9.6% laboratory, 14.6% radiological or a combination of both.

In 70% of episodes, patients had stomatitis, 57% GE, 17% URT, 15% pneumonias, 5% otitis media and 16% were shown as FUO. 14cases were skin infection.

Similar to our study, in the Minna et al. study overall 78% of infections documented occurred during induction/consolidation phases, in patients with oral mucositis, which were associated with a significant increase in febrile episodes (P=0.047). This condition appeared to be the major portal of entry of streptococcal bacteraemia as the patients did not have a central venous catheter [18].

In contrast to our findings, the study in Singapore reported 93 cases (52%) which were identified as FUO [19].

As seen in study done in Guatemala, on admission22 patients (23%) had clinical evidence of infection, the most common symptoms: diarrhea (27%), cellulitis (18%), and otitis (14%) [21].

Among the46 documented infections in the Makati, Philippine center study, the respiratory tract (35.4%), skin and soft tissues (20.8%), oropharyngeal mucosa (10.4%), urinary tract (8.3%), gastrointestinal tract (8.7%), and peritoneum (2.1%) were noted sites of infection [5].

In our survey, of 23 bacterial isolates, most were Gram-negative 20 (87 %). These were isolated as twelve from urine, seven from blood and one from an ear swab with acinetobacter spp. And of the Gram-positive isolates, three (13 %) two were isolated from blood and one from an ear swab.

Further, fungal infections in 20 episodes were documented clinically and radiologically.

The Bakhshi et al. [20] study demonstrated that of 69 bacterial isolates, 46 were Gram-negative (blood 50%, urine 32.6%) and 23 Gram-positive with (78.3%) from Blood.

In the study in Makati center, blood cultures were taken in 17 episodes with 13 (76.5%) showing no growth. Bacteremia was seen in 4 cases (2 Gram positive and 2 Gram negative) [5].

Some researchers in India and Sao Paulo stressed changing epidemiological patterns, with majority of fungal infections being detected during induction chemotherapy (2%) [32,33]. Furthermore, the fungal infections were documented clinically and radiologically rather than microbiologically. This may be explained by the fact that prolonged neutropenia is the most important risk factor for fungal infections [24, 34, 35].

Empiric antimicrobial therapy is the mainstay of therapy for febrile neutropenic episodes pending the culture results [19, 36]. Length of antibiotic treatment was hard to determine because signs and symptoms tended to overlap and there were instances where there were more than one infection at one time [37, 38, 39]. A change in antibiotics was equally necessary no matter what combination of empiric antibiotics was used. These changes included additions or modifications of the initial regime or the addition of antiviral therapy. Amphotericin B should be started by day 5 if no clinical improvement is seen [19, 40, 41-43].

In this, serial antibiotic is given for 6.8 (±2.1 SD) days ranging from 2 – 25days. Empiric broad-spectrum antibiotics had been started initially with 1st line in 131 (70%). There were 52\131 (40%) episodes requiring a change of antibiotics to other lines, for the following reasons: poor clinical response (72%), resistance of organisms (3%), new infections (11.6%) and combination of 2 or more reasons in (13%) episodes. In 10.6% of episodes, antifungal treatment was added. In addition, about 3.2% experienced anti-viral treatment.

The study done in India [20] showed that 95/222 (42.8%) febrile neutropenic episodes improved with broad-spectrum first-line antibiotic therapy that had efficacy against pseudomonas spp. while modification was required in 127 episodes (57.2%). Antifungal treatment was used in 86 episodes (38.7%).

Mortality due to overwhelming infection occurred in 6 (22%) patients. Among them, relapse contributed to one death. The majority of deaths were in younger aged children and males, but no correlation between them and deaths, p value = 628, and 0.363 respectively.

Outcome was worse with severe neutropenia, which persisted for a longer period [44-46]. Statistical analysis showed a significant correlation between degree, duration and deaths p = 0.012 and 0.000 respectively.

All deaths had a high degree and longer duration of fever, with strong correlation to deaths p= 0.026 and 0.000.

All deaths were on the 2nd or 3rd line antibiotic as well as antifungal treatment.

Our mortality rate was near to the study carried out in Singapore. There were 7 deaths (22%) {3 (9%) due to overwhelming sepsis and 4 with relapse}. Mortality was increased by prolonged neutropenia, relapse and invasive fungal infection.

The median duration of neutropenia was 7 days (P= 0.047) compared to a median of 21 days in those who died (P = 0.0096). The outcome did not depend on the duration of fever, the median of which was 3 days in those who recovered versus 7 days in those who died (P = 0.07). Nor did the severity of neutropenia affect the mortality (P = 0.366) [19].

Only a few studies [47-53] were conducted in children with cancer for evaluation of risk prediction criteria and treatment policies, stressing the importance of frequent reviewing of type, frequency, severity, and outcome of infection.

6. CONCLUSIONS

- The febrile episodes ranged from 1-12 episodes with a median of 7. The peak was in January (25 episodes), and increased with advanced therapy phases (40% in phases II).
- Younger patients and males had longer duration of admissions, neutropenia and duration of fever.
- In 85 (45%) episodes, the initial temperature was 38.5 C˚. Phases II and III had a higher degree of fever.
- From our findings, in 70% of episodes, the diagnosis was initially clinical. In 70% of episodes, gingivostomatitis was likely to be the site of infection, gastroenteritis 57%and 16% as FUO.
- Of 23 bacterial isolates, Gram-negative bacteria were 20 (87 %) and Gram-positive bacteria were 3(13%). Fungal infections were documented clinically in 20 episodes.
- Fifty-two (40%) of episodes required a change of antibiotics from 1st line to other combinations. 10.6% of episodes received antifungal. And in 3.2% antiviral treatment were added.
- The 2-year disease free survival rate was 78%, and the mortality rate was 6 (22%) patients, due to sepsis. The majority were younger aged children and males. There was no correlation between death with age group p = 0.628, gender p= 0 .363 or phases of chemotherapy p > 0.5, but correlation was seen with degree and

duration of fever (p= 0.026 and 0.000) and severe persistent neutropenia (p=0.012 and 0.000). All mortalities were on the 2nd or 3rd line antibiotic as well as antifungal treatment.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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