Frequency and Etiology of Post chemotherapy Febrile Neutropenia in Patients with Hematological Malignancies;

A Single Centre Study in Nanakaly Hospital in Erbil City

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"Dedicated to my dear parents, wife sivan and my beautiful daughter waran. Those who stood by me along the way".

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Contents

Acknowledgement

List of Abbreviations

ALL: Acute Lymphoblastic Leukemia

ALP: Alkaline Phosphatase

ALT: Alanine Transaminases

AML: Acute Myeloblastic Leukemia

ANC: Absolute Neutrophil Count

APL: Acute Promyelocytic Leukemia

AST: Aspartate Transaminases

ATRA: All-Trans-Retinoic Acid

CDI: Clinically Documented Infection

CLL: Chronic Lymphocytic Leukemia

CML: Chronic Myeloid Leukemia

CNS: Central Nervous System

CSF: Colony Stimulating Factor

FN: Febrile Neutropenia

G-CSF: Granulocyte-Colony Stimulating Factor

GIT: Gastro Intestinal Tract

HBs-Ag: Hepatitis B surface Antigen

HCL: Hairy Cell Leukemia

HCV: Hepatitis C Virus

HD: Hodgkin's Disease

HIV: Human Immune deficiency Virus

LFT: Liver Function Test

MDI: Microbiologically Documented Infection

MM: Multiple Myeloma

NHL: Non-Hodgkin's Lymphoma

NL: Neutrophil

RBS: Random Blood Sugar

RFT: Renal Function Test

SPSS: Statistical Package for Social Sciences

TLC: Total Leucocytes Count

TSB: Total Serum Bilirubin

TSP: Total Serum Protein

UF: Unexplained Fever

UKALL: United Kingdom Acute Lymphoblastic Leukemia

Abstract

Background: Febrile neutropenia poses a major challenge during treatment of hematological malignancies.

Objectives: Identification of neutropenia and its severity in patients receiving chemotherapy and its relation to the frequency of febrile episodes. Elucidation of the clinical foci of infection and causative microorganisms in order to build up prophylactic and therapeutic plans to decrease the frequency and complications of febrile neutropenia. Determination of the relation between using of empirical antibiotics with the duration of febrile neutropenia and using of Granulocyte Colony Stimulating Factor with the duration of neutropenia. Identification of the frequency of comorbidity status and mortality rate in febrile neutropenic patients.

Patients and Methods: The study population consisted of 55 patients admitted to the Nanakaly Hospital between 1st September, 2009 and 15th May, 2010.The mean ages of the patients were 32 years, ranging from 14-72 years. 30 of them were males and 25 of them were females. The study outlines the main clinical and microbiological causes of febrile neutropenia with special emphasis on the clinical source of infection and types of cultures.

Results: 53 febrile episodes occurred in 90 episodes of neutropenia. Clinical foci of infection were detected in 59% of febrile neutropenic episodes. Pneumonea was the commonest clinically documented infection. Microbiologically documented infections were detected in 26% of febrile neutropenic episodes. Gram negative infections predominated (Escherichia coli, Pseudomonas aeruginosa and Klebsiella species, were the major isolates). Granulocyte Colony Stimulating Factor was used in 57 neutropenic episodes. Neutropenia duration were (< 7 days) in 28 cases, (7-14 days) in 17 cases and (>14 days) in 12 cases. Empirical antibiotics were used in 77 neutropenic episodes (48 with fever and 29 without fever). Febrile neutropenia duration were (< 7 days) in 37 cases, (7-14 days) in 9 cases and (>14 days) in 2 cases. Medical comorbidities were detected in 19 patients in the form of organ failure, diabetes mellitus and hypotension. The overall mortality rate was 29 %.

Conclusions: The frequency of febrile neutropenia is directly related to the severity of neutropenia. In febrile neutropenia, 85 percent have documented infections and 15 percent have unexplained fever. The spectrum of isolates from febrile neutropenic patients in our study shifts towards Gram-negative microorganisms. Because of the shortage of broad spectrum antibiotics, higher mortality has been associated with a documented infection, either microbiologically or clinically.

Introduction

Neutrophils are ideally suited to the elimination of pathogenic bacteria because of their large stores of proteolytic enzymes and rapid production of reactive oxygen species to degrade internalized pathogens [1]. Major characteristics of these neutrophils are the potential to travel through the body to sites of injury, to phagocytose and destroy the intruders. Infections arising in the immune compromised host are directly connected with

I. Host defects induced by the underlying malignancy

II. The host defects induced by the various cytotoxic and chemotherapeutic agents including corticosteroids

III. The various invasive procedures including the long term use of indwelling catheters and

IV. Combinations of the aforementioned [2,3].

Definition of neutropenia

Neutropenia can be defined as an absolute neutrophil count (ANC) of less than 1500 cells/mm³ (normally it is ranged between 1500-8000 cells/mm³) and can be graded as mild (1000-1500 cells/mm³), moderate (500-1000 cells/mm³), severe (<500 cells/mm³) or very severe (<200 cells/mm³). Neutropenia can develop in one or more conditions including decreased bone marrow production, the sequestering of neutrophils and increased destruction of neutrophils in the peripheral blood. Decreased production in the bone marrow is seen in hereditary disorders, aplastic anemia, cancer, use of certain medications. Increased destruction of neutrophils is seen in autoimmune disorders and chemotherapy [4-6]. The infection rate and severity are inversely related to the ANC. Lower ANCs are associated with more frequent and severe infections and vice versa. The duration of neutropenia is also an important determinant of risk of infection [7-10]. A neutropenic patient who becomes febrile has a more than 60% likelihood of being infected. These are caused principally by aerobic gram-negative bacilli and gram positive cocci [11]. Infection is nearly certain when the neutrophil count is <100 cells/mm³ for more than a few days [12]. Infection in a neutropenic patient is a medical emergency: 20-30% of febrile neutropenic patients are bacteremic with the first fever. Most infecting organisms in hospitalized neutropenic patients are acquired from the hospital environment [12].

Fever

A fever can be defined as a single oral temperature ≥38.3°C or 101°F or a temperature of ≥38°C or 100.4°F for at least 1 hour [13]. Fever often is the only sign of infection in a neutropenic patient since many of the classic signs of local infection (purulent discharge, swelling, pain, infiltrate on x-ray, sputum production, etc.) result from the accumulation of neutrophils. Therefore, fever in a neutropenic patient is assumed to represent infection until proven otherwise. Fortunately, fever is rarely absent in a neutropenic patient with a true infection [12]. The current gold standard for the detection of bacterial pathogens in blood is blood culture.

However, all blood culture systems suffer from several limitations, such as lack of rapidity and low sensitivity; especially when the patient has already received antibiotics and when fastidious microorganisms are involved [14]. Colony-Stimulating Factors (CSF) are used to reduce the risk of developing neutropenic complications and to facilitate delivery of planned chemotherapy dose [15,16].

Objectives

Identification of neutropenia and its severity in patients receiving chemotherapy and its relation to the frequency of febrile episodes, elucidation of the local foci of infection and causative microorganisms behind these episodes in order to build up prophylactic and therapeutic plans to decrease the frequency and complications of febrile neutropenia. Determination of the relation between using of empirical antibiotics with the duration of febrile neutropenia and using of granulocyte colony stimulating factor with the duration of neutropenia, identification of the frequency of co-morbidity status and mortality rate in febrile neutropenic patients.

Patients and methods

Patients

Any patient with hematological malignancy and has developed post-chemotherapy neutropenia has been followed in this study. The frequency of fever among these patients has been registered according to the disease category and treatment protocols. Patients were included if they met all of the following inclusion criteria: [1] underling hematological malignancy, [2] neutropenia, defined according to the ANC in to mild (1000-1500 cells/mm³), moderate (500-1000 cells/mm³), severe (<500 cells/mm³) and very severe (<200 cells/mm³) [3] fever, defined as a single oral temperature of 38.3 C or an oral temperature of 38°C for at least 1 hour and [4] received chemotherapy prior to the episode of febrile neutropenia. Patients excluded from this study are those who have developed neutropenia without administration of chemotherapy but due to other causes of neutropenia. Each separate hospital admission for neutropenia was defined as one episode. Subsequent hospital admissions for neutropenia in the same patient were included as separate episodes of neutropenia.

Methods

We recruited 55 patients with 90 Neutropenic episodes. They were studied prospectively from 1st September 2009 to 15th may 2010 in the Nanakaly hospital. All patients were evaluated by full history, physical examination, complete blood count and ANC determination. The counting of the cells has been performed by an electronic coulter machine (Beckman coulter Ac Tdiff 2) and the morphological pictures of the cells together with full differential count of the white blood cells have been performed by specialist hematologists. The ANC can be figured via multiplying the total white cell count by the neutrophil percentage shown on the differential count. Biochemistry tests are LFT, RFT, RBS and TSP were done by [bt 35i Miura auto analyser], serum electrolytes by [ELITE auto analyser].

Septic work-up (e.g. blood culture, urine culture; were done for every patient. Stool culture, wound discharge culture, sputum cultures were done accordingly). These were correlated with the signs and the symptoms to classify febrile episodes as:

a) Microbiologically documented infection with or without bacteremia

b) Clinically documented infection (site of infection identified) and

c) Unexplained fever (new fever without an identifiable pathogen and site of infection).

Clinically documented infections have been recorded by performing full physical examination of each patient. Source of infection has been searched and recorded [13]. The physical examination done for each patient looking for any source of infection, sonographic study looking for any evidence of infection or collection, chest x-ray was done for all patients. Microbiologically documented infections have been recorded with bacteremia [defined as the presence of live <u>bacteria</u> in the bloodstream, a positive result of a blood culture sample] or without bacteremia [defined as a positive result of a culture sample other than blood which could explain fever of the patient]; i.e. by urine culture (mid-stream), stool microscopy and culture, analysis and culture of cerebrospinal fluid (if indicated), swab culture from throat, axilla, perineal area, apparent wounds and abrasions from any cannula, central line and any other suspicious area. Microbiological investigation of positive cultures (isolation and identification procedures), were done by classical microbiological methods.

Questionnaire form

The questionnaire form of this study was designed by the researcher and composed of the following items: Name, age, gender, underlying malignancy, malignancy status, chemotherapy protocol, ANC, post chemotherapy days to develop neutropenia, duration of neutropenia, presence of fever, duration of fever, clinically documented infection, microbiologically documented infection and the presence of comorbidity status .

Type of the study

Type of the study was review of cases.

Statistical analysis

Statistical Software was used for data entry and analysis, namely Statistical Package for Social Sciences (SPSS) version (15.0), aided by Excel. The data is presented as mean+ standard deviation (SD) for the numerical variables. The categorical variables are presented as frequency and percentages. Means of continuous variables and proportions of categorical variables were analyzed using t and Chi-Square tests. P-values < 0.05 were regarded as significant.

Results

Patients Characteristics

Between 1st September, 2009 and 15th May, 2010, a total of 55 patients were recruited with 90 neutropenic episodes. There were 30 males and 25 females. Their age ranged from 14-72 years. Figure 1 shows the age distribution.

Chemotherapy protocols used were variable and include, UKALL-12 (Cyclophosphamide, Daunorubicine, Vincristine, Prednisone, L-asparaginase, Methotrexate, Cytosine arabinoside, 6 Mercaptopurine, Adriamycin, Dexamthasone, and 6 Thioguanine) for Acute Lymphoblastic Leukemia (ALL).

(Daunorubicine+ Cytosine arabinoside) or (Cytosine arabinoside+ Etoposid) for AML and all-*trans*-retinoic acid (ATRA) for Acute Promyelocytic leukemia (APL). CHOP (Rituximab+ Cyclophosphamide+ Vincristine+ Prednisone) or R-CHOP (Rituximab+ Cyclophosphamide+ Vincristine+ Prednisone) for Non-Hodgkin's Lymphoma (NHL). ABVD (Adriamycin+ Bleomycine+ Vinblastin+ Dacarbazine) for Hodgkin's Disease (HD). VAD (Vincristin+ Adriamycin+ Dexamthasone) for Multiple Myeloma (MM). FCR (Fludarabine+ Cyclophosphamide+ Rituximab) for Chronic Lymphocytic Leukemia (CLL). Cladribin for Hairy Cell Leukemia (HCL) and imatinib mesyalate for Chronic Myeloid Leukemia (CML). Clinical characteristics of these patients are given in Table 1.

In our study, 53 episodes of febrile neutropenia were documented. Granulocyte-Colony Stimulating Factor (G-CSF) was used in 57 neutropenic cases. Neutropenia duration were (<7 days) in 28 cases, (7-14 days) in 17 cases and (>14 days) in 12 cases. Empirical antibiotics (Ampiclox and Cefotaxime) were used in 77 neutropenic cases (48 with fever and 29 without fever). Febrile neutropenia duration were (<7 days) in 37 cases, (7-14 days) in 9 cases and (>14 days) in 2 cases. Medical comorbidities were detected in 19 patients in the form of organ failure, diabetes mellitus and hypotension. The overall mortality rate was 29 % (16 patients), in which the presence of febrile neutropenia and associated sepsis were the cause of death in the majority of cases (13 cases). The rest of the patients were died because of other factors like bleeding complications (in 2 patients) and ATRA SYNDROME (in 1 patient). Mortality was observed more (29.4%) in age group of <60 compared with (25%) in age group >60. Correlating mortality rate with the degree of neutropenia, our study observed that there was a higher mortality (43.7%) in those with ANC less than 200/mm^3, compared to (18.7%) in those ANC between 1000-1500/mm^3.

Underlying malignancies and febrile neutropenia

Among the underlying malignancies that were associated with neutropenia, acute leukemia's were predominated (73%). Figure 2 represents the distribution of underlying hematological malignancies in the neutropenic patients. The underlying malignancies were also analyzed according to the severity of neutropenia. Severity of neutropenia was classified according to the ANC into mild, moderate, severe and very severe neutropenia. Analyses of neutropenia severity in the underlying malignancies are given in Table 2.

Out of 90 neutropenic episodes, 15 had mild neutropenia (ANC between 1000-1500 cells/mm³), 19 had moderate neutropenia (ANC between 500-1000 cells/mm³), 19 had severe neutropenia (ANC <500 cells/mm³) and 37 had very severe neutropenia (ANC <200 cells/mm³). Regarding febrile episodes in neutropenic patients, our study revealed that there were significant relationship between neutropenia severity and the frequency of febrile episodes (P<0.05). The relationship is given in Figure 3. There were 7 febrile episodes in patients who had mild neutropenia, 9 episodes in patients with moderate neutropenia, 12 in those with severe neutropenia and 25 in patients with very severe neutropenia.
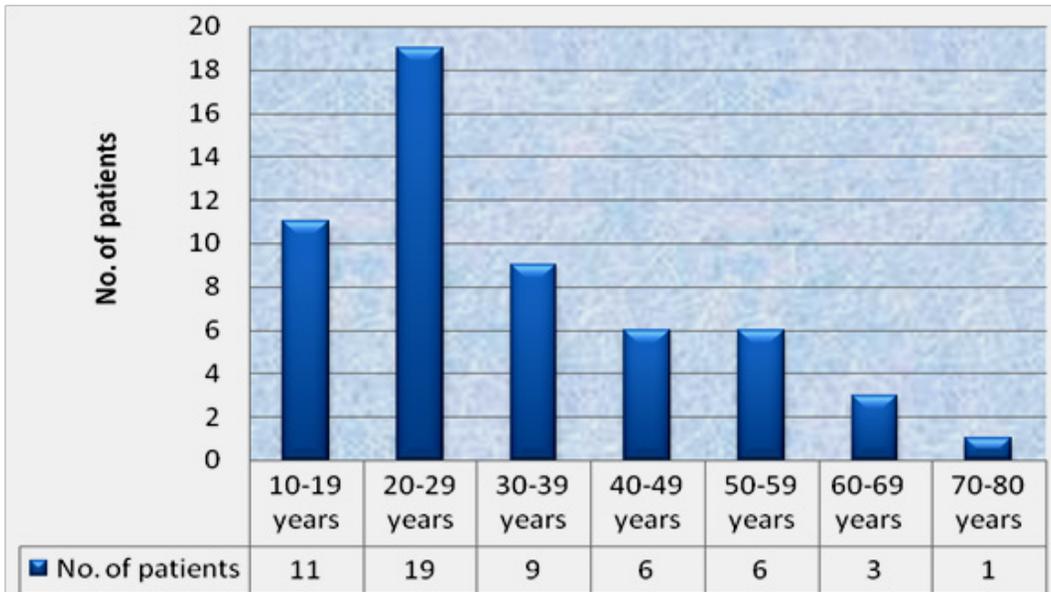

Figure 1: The distribution of patients with respect of age.
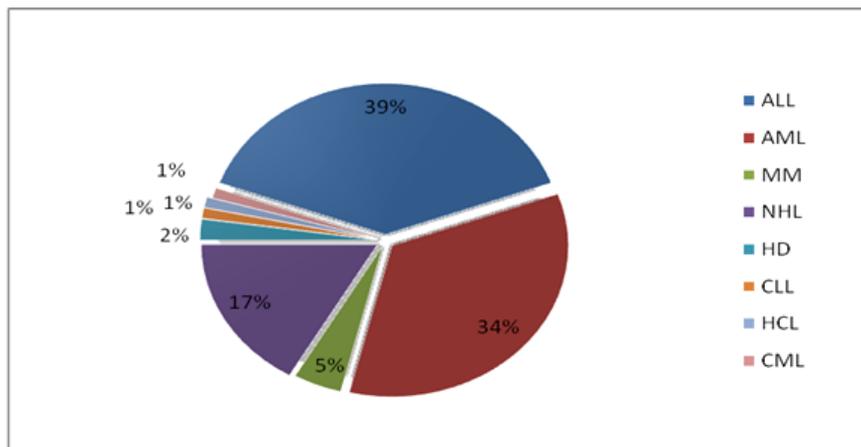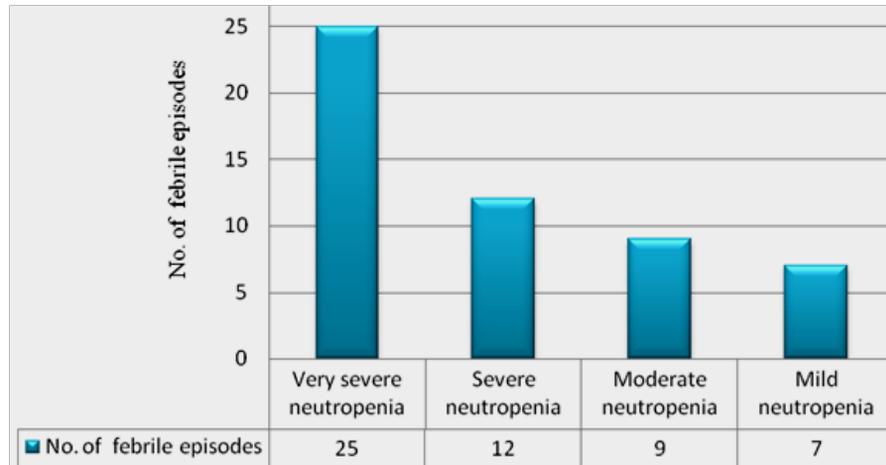

Figure 2: Distribution of underlying hematological malignancies.

Figure 3: Frequency of febrile episodes in associasion with neutropenia severity.

Table 1: Patients characteristics

Patients number: (55)
No. of Neutropenic episodes: (90)
No. of febrile Neutropenic episodes: 53 (33 in males & 20 in females)
Age: Mean: (32)   SD: (16)   Median: (26)
Sex: Males: (30) 54.6%   Females: (25) 45.4%
Chemotherapy protocols
ALL : UKALL-12
AML : (D+C),(C+E)
NHL : CHOP , R-CHOP
HD : ABVD
MM : VAD
CLL : FC,FCR
HCL : Cladribine
CML : Imatinib mesylate
Duration of Neutropenia
< 7 days : (40) 44.5%
7-14 days : (30) 33.3%
>14 days : (20) 22.2%
Duration of febrile Neutropenia
< 7 days: (42) 79.2%
7-14 days: (9) 17%
>14 days: (2) 3.8%
Use of G-CSF: Yes: (57) 63.3%   **No:** (33) 36.7%
Use of Emprical antibiotics: Yes : (77) 85.6%   **No**: (13)14.4%
Medical co-morbidity: Yes : (19) 34.55%   **No**: (36)55.45%
Malignancy status: **Relapse:** (27) 30%   **No relapse:** (63) 70%
Outcome: **Alive:** (39) 71%   **Dead:** (16) 29%

Table 2: Analyses of neutropenia severity in the underlying malignancies

Underlying Malignancy	Very severe neutropenia		Severe neutropenia		Moderate neutropenia		Mild neutropenia	
	No.	%	No.	%	No.	%	No.	%
ALL	15	42.90%	7	20.00%	7	20.00%	6	17.10%
AML	13	41.90%	7	22.60%	6	19.40%	5	16.10%
MM	1	25.00%	1	25.00%	1	25.00%	1	25.00%
NHL	8	53.30%	3	20.00%	3	20.00%	1	6.70%
HD	0	0.00%	1	50.00%	1	50.00%	0	0.00%
CLL	0	0.00%	0	0.00%	0	0.00%	1	100%
HCL	0	0.00%	0	0.00%	0	0.00%	1	100%
CML	0	0.00%	0	0.00%	1	100%	0	0.00%
Total	37		19		19		15	

Regarding the frequency of febrile neutropenia in each type of hematological malignancy, the results are given in Table 3. In ALL group 13 out of 35 patients with neutropenia had fever, so the frequency of FN was 48.6% in this type of malignancy, while In AML group 21 out of 31 patients with neutropenia had fever, so the frequency of FN was 67.8%. In NHL group 12 out of 15 patients with neutropenia had fever, so the frequency of FN was 80.0%. In Myeloma group 2 out of 4 patients with neutropenia had fever, so the frequency of FN was 50.0%. Only one patient had CML with neutropenia and fever was detected, so the frequency of FN was 100%. Finally In 2 patients with HD, 1 patient with CLL, 1 patient with HCL; no febrile episodes were detected, so the frequency of FN in these hematological malignancies was 0.0%.

Infective Etiology

In 90 neutropenic patients, 53 episodes of fever were observed. The cause of fever were due to CDI in 31 episodes (59%), MDI in 14 episodes (26%) and in 8 episodes (15%) no clinical site of infection or causative organism were detected, therefore marked as UF. Figure 4 represents the distribution of Infective aetiology in febrile neutropenic patients. Our study observed that the number of documented infections were directly proportional to the degree of neutropenia ($p < 0.05$). 39.2 % of total infections were observed at an ANC less than 200/mm^3 and only 17.6% of total infections occurred at an ANC between 1000-1500/mm^3.

**Table 3:** Frequency of febrile neutropenia between hematological malignancies

U M	No. of patients	No. of patients with FN	Frequency of FN
ALL	35	17	48.60%
AML	31	21	67.80%
MM	4	2	50.00%
NHL	15	12	80.00%
HD	2	0	0.00%
CLL	1	0	0.00%
HCL	1	0	0.00%
CML	1	1	100%

The most common clinically documented infection was Pneumonia (35.4%), followed by urinary tract infection (UTI) and cannula site infection, (Each account for 16.1%). Table 4 summarized the clinically identified sites of infection. 14 Out of 53 episodes of febrile neutropenia had MDI. Bacterial isolates were obtained from different samples i.e. cultures from wound swab, sputum, urine, stool or blood. The yield of blood culture was 14 % i.e. 2/14, for urine was 36% i.e. 5/14, for stool was 14% i.e. 2/14, for sputum was 22% i.e. 3/14 while for wound swab showed 14 % i.e. 2/14 yield. Gram negative organisms accounted for 66% of overall MDI, among them, Klebsiella species, Escherichia coli

and Pseudomonas aeruginosa, were the most commonly encountered organisms from specimens, while Gram positive organisms accounted for 44% of overall MDI, and among them, Staphylococcus aureus & Streptococcus species, were the most commonly isolated organisms. The patterns of microbiological isolates obtained in patients with febrile neutropenia were summarized in Table 5. UF was defined as both the absence of any clinical or radiological sign of infection and no isolation of causative organism. The overall percentage of UF was 15%, noted in 8 episodes of fever.
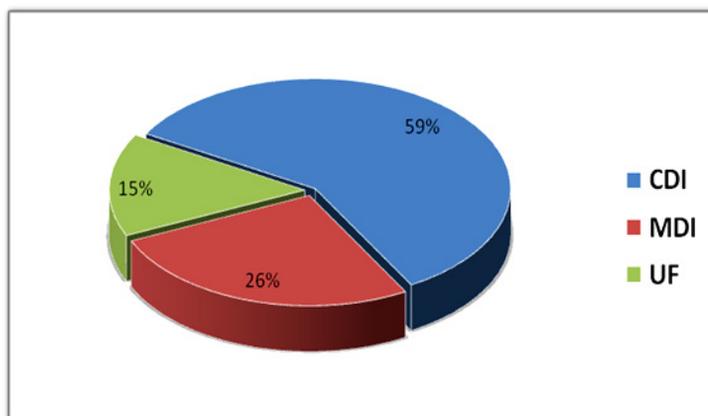
Figure 4: Etiology of Infection in febrile neutropenic patients.

Table 4: The Clinically Documented Infections.

Percentage	No.	Clinically Documented infection
35.40%	11	Pneumonia
16.10%	5	UTI
16.10%	5	Cannula site infection
6.40%	2	Tonsillitis
6.40%	2	Perianal infection
6.40%	2	Pulmonary Tuberculosis
3.30%	1	Herpes virus infection
3.30%	1	Genital infection
3.30%	1	Mucositis
3.30%	1	Typhoid fever
100%	31	Total

Table 5: The Microbiologically Documented Infections.

Percentage	No.	Type of bacteria	Cultures
14	2	*gram negative*	Wound swab culture
22	3	*gram positive*	Urine culture
-14	2	*gram negative*	Urine culture
-22	3	*gram positive*	Sputum culture
-14	2	*gram negative*	Stool culture
-14	2	*gram negative*	Blood culture
-100	14		Total

Discussion

Febrile neutropenia remains a frequent complication after chemotherapy among patients with malignant hematological diseases. In daily practice, febrile neutropenia represents a significant challenge for hematologists. In our study, prevalent age group was of young age group between 20-29 years old and minority was of elderly age group. This is similar to a study done by another researcher [17]. Mortality was observed more (29.4%) in age group of <60 years compared with (25%) in age group >60 years. But other studies found higher age to be a risk factor for the development of severe neutropenia [4,18]. The reason behind this discrepancy is that most of elderly grouped patients were treated with less aggressive chemotherapy in our circumstances.

With the appropriate application of colony-stimulating factor, we can decrease the duration of neutropenia, which in turn favorably alters the course of infections. In our study, G-CSF was used in 57 neutropenic episodes. Neutropenia duration were (< 7 days) in 28 cases, (7-14 days) in 17 cases and (>14 days) in 12 cases. This is consistent with other studies [13,19,20]. Regarding febrile episodes in neutropenic patients, our study revealed significant relationship between neutropenia severity and the frequency of febrile episodes. There were 7 febrile episodes in patients who had mild neutropenia, 9 episodes in patients with moderate neutropenia, 12 in those with severe neutropenia and 25 in patients with very severe neutropenia. This is similar to a study done by another researcher [21]. Empirical antibiotics were used in 77 neutropenic episodes (48 with fever and 29 without fever). Febrile neutropenia duration were (<7 days) in 37 cases, (7-14 days) in 9 cases and (>14 days) in 2 cases. Therefore, the initiation of empirical antibiotics in febrile neutropenia is absolutely essential. This is consistent with other studies [22,23].

Medical comorbidities were detected in 19 patients in the form of organ failure, diabetes mellitus and hypotension, 16 out of the 19 were died. The presence of co-morbid conditions with cancer has been shown to increase the risk for neutropenia and its complications. This is similar to studies done by other researchers [24,25]. The overall mortality rate in our study was 29 % (16 patients), in which the presence of febrile neutropenia and associated sepsis were the cause of death in the majority of cases (13 cases). The rest of the patients were died because of other factors like bleeding complications (in 2 patients) and Atra Syndrome (in 1 patient). Correlating mortality rate with the degree of neutropenia, our study observed that there was a higher mortality (43.7%) in those with ANC less than 200/mm³, compared to (18.7%) in those ANC between 1000-1500/mm³ [26]. In our study, the underlying disease associated with neutropenia was predominantly due to acute leukemia and the types of chemotherapy agents that used in acute leukemia were more myelo-suppressive than in other type of hematological malignancies, therefore, severe neutropenia and risk of infections encountered frequently in acute leukemia's. This is consistent with other studies [8,27]. In which the type of chemotherapy agents, the dosage and number of drugs are clearly related to the risk of neutropenia and infections.

In our study, the frequency of documented infections was directly related to the degree of neutropenia. 39.2% of total infections were observed at an ANC less than 200/mm³ and only 17.6% occurred at an ANC between 1000-1500/mm³. This result is similar to other studies [2,11]. Among the clinically documented infections, pneumonia used to be the most frequent infection, followed by UTI and cannula site infections. This is similar to another study done by a researcher [28]. In our study, a predominance of Gram-negative isolates from neutropenic patients had been observed. Among the Gram-negative bacteria, *Escherichia coli, Pseudomonas aeruginosa* and *Klebsiella* species were the common pathogens. Among Gram-positive organisms, *Staphylococcus aureus* and *Streptococcus species* were the commonest isolates. This is consistent with other studies [29-33].

Conclusion

The frequency of febrile neutropenia is directly related to the severity of neutropenia. In febrile neutropenia, 85 percent have documented infections and 15 percent have unexplained fever. Higher mortality is associated with a documented infection, either microbiologically or clinically due to shortage of broad spectrum antibiotics. The spectrum of isolates from febrile neutropenic patients in our study shifts towards Gram-negative microorganisms.

Recommendations

Special care and strict close follow up for patients with severe and very severe neutropenia. Urgent interference once febrile neutropenia documented. Use of G-CSF is important prophylactic factor shortening period of severe neutropenia. A quality infection control policy with a close and strict clinical and microbiological surveillance system aiming at early detection of infections remains the standard of care in neutropenic patients. Our work is, therefore, only a step to looking at the association between type of chemotherapy, hematological malignancy and neutropenia duration, and further studies are certainly required to obtain a tool that might be of true practical importance.

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