The Impact of Duration of Neutropenia in the Immunocompromised Host

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ABSTRACT:

BACK GROUND:

Patients with neutropenia can be at low-or high-risk according to the duration of neutropenia, its differential count, the ANC (absolute neutrophil count) in addition to search for any causative agents to improve the diagnostic and therapeutic outcome.

OBJECTIVE:

This study focuses on the clinical and microbiological data in relation to the duration of neutropenia in a sample of immunocompromised Iraqi patients due to leukemia and aplastic anemia.

INDIVIDUAL METHODS:

150 patients presented with pyrexia, marrow failure from oncology unit of the 7th floor of Medical City Hospital, National Center of Hematology-Iraq , Institute and Hospital of radiotherapy and nuclear medicine studied between 2008-2009 ,classified into three groups, fifty for each, with a plastic anemia, acute lymphoblastic leukemia(ALL), acute myelogenous leukemia(AML),all were investigated for WBC count, differential,ANC,Hb,Pcv,platelet count, RBC,Peripheral blood film for blast cells,ESR, specifically in those complaining from pyrexia of unknown origin. direct examination ,culture and sensitivity of the urine,stool,body fluids, sputum ,blood, tonsil and skin swab, Widal, rose Bengal tests, besides temperature recording was done for all patients with known site of infection.

RESULTS :

Neutropenia of a plastic anemia 5-70 days with a mean of 25 days is associated with a higher risk of infection particularly by the gram-negative enterobacter ,but with a mortality rate of 26%,while those suffered from ALL with a range of 11-40 day and a mean values of 16 days with a less mortality rate 22%.Unfortunatelly AML although gets a range of 7-35 day and a mean values 18 day and short lived neutropenia yet it was significantly have a higher mortality rate 52% presumably due to the combined effect of low neutropil count and chemo radiotherapy .However sever neutropenia (ANC < 500) is only found in 10 AA,6 AML,and 4 ALL patients, and moderate neutropenia (500 ≤ ANC < 1000) were explored in 7 AA,4 AML,10 ALL.

The microbiological investigation shows that gram negative microorganism especially E.coli is positive in 19 different samples followed by Klebsiella 12 positive sample, then monilia takes place12 cases, followed by the remaining microorganisms.

Lastly pyrexia of unknown origin were found to be the top problem facing immunocompromised patients with 20% AA,34%ALL,30%AML followed by chest infection 16%AA,22%ALL,15%AML, and then urinary tract infection17%AA,17%ALL,10%AML followed by other types of infections.

CONCLUSION:

Neutropenia is prolonged in a plastic anemia compared to acute leukemia with the risk of infection is directly related to it.G(-ve) enterobacter particularly E-coli is the commonest pathogen isolated.

KEY WORDS: immunocompromised host, neutropenia, leukemia, a plastic anemia.

INTRODUCTION:

Infection is a common cause of morbidity and mortality in immunocompromised patients for whom diagnosis and management require scrupulous attention and continuing awareness of the microorganisms causing infection in a particular environment in different groups of patients , most are caused by recognized pathogen, although uncommon,some times

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normal flora may be the causative agents of such infection in these patients due to their low immunity[1].

Pvrexia in Neutropenic Patients;

Fever is defined as the occurrence of three oral temperature elevations above 380c during a 24 hour period or a single oral temperature elevation of 38.50c or higher. Such fever is a very common occurrence in cancer patients, being present during 45% to 60% of hospital days [7]. In a study of 1000 cancer patients [18] , 80% of febrile episodes occurred when the ANC was less than 0.5 X 109 / l. In this study the fiure was only as low as 30%, probably due to inaccurate temperature taking or documentation on temperature charts.

LITERATURE REVIEW

Neutropenia characterized by an abnormally low number of neutrophils, the most important type of white blood cells make up 50-70% with a life span of 1-4 days[20].

Perhaps the single most important deficiency in host defense is granulocytopenia which occure most commonly in acute leukaemia and aplastic anemia. There are three general guidelines used to classify the severity of neutropenia based on the absolute neutrophil count (ANC) measured in cells per microliter of blood[17].

Mild neutropenia (1000 ≤ ANC < 1500)minimal risk infection Moderate neutropenia(500 ≤ ANC < 1000)moderate risk of infection Severe neutropenia (ANC < 500) severe risk of infection.

According to the World Health Organization an ANC<2000=neutropenia. Neutropenia can be acute or chronic(chronic neutropenia if the condition lasts for longer than three months), can roughly be due to problems in the production of the cells by the bone marrow or destruction of the cells elsewhere in the body.

Neutropenia generally discovered when a patient has developed severe infections which is specially a major problem in acute leukaemia[20] . If the granulocytopenia was prolonged for more than 5 weeks, then the incidence of infection was 100% .

Neutrophil counts less than 500 cells/mm3 for longer than 10 days is now viewed as a general threshold for more frequent and severe infections. In the past, aerobic gram-negative bacilli involved approximately 60-80% of the time, with *Pseudomonas aeruginosa* being a leading isolate. Of the gram-positive organisms isolated,*Staphylococcus aureus* was the most important,but from the mid 1980s, the spectrum of bacteria causing infection began to change with a steady increase in gram-positive infections occurred until presently 60-70% of bacteremias with a single organism identified will be caused by gram-positive cocci. Coagulase-negative staphylococci and *S aureus* are the predominant organisms.One of the most important gram-positive organisms infecting the neutropenic is viridians streptococci. *Streptococcus mitis*, *S. oralis*, *S. salivarius* and *S. millerei* have been the organisms most commonly involved. The enterococcus is becoming a more common agent colonizing and infecting neutropenic patients, mirroring its emerging role as a nosocomial pathogen in general. Of these organisms, *E. faecium* is overtaking *E. faecealis* as the predominant organism[21,22].

MATERIALS AND METHODS:

A total of 150 patients presented with pyrexia and suffering from marrow failure were selectively chosen and studied between 2008-2009from the oncology unit of the 7th floor of Medical City Hospital, National Center of Haematology-Iraq, and from the institute and hospital of radiotherapy and nuclear medicine, EDTA tube blood samples were collected from immunocompromised patients during their routine visits to the hospital for investigation's follow up and treatment such as chemotherapy or radiation therapy, some of the patients was selected from the word of the hospital directly. All of the cases were already diagnosed as having AA,ALL,AML, and follow up. they are divided into three groups ,fifty cases in each according to their disorder at time of presentation as acute lymphoblastic leukaemia, acute myelogenous leukaemia and aplastic anaemia .

Haematological and microbiological data were comprehensively compare between these groups. Complete blood picture , ESR, and differential with absolute neutrophil count was estimated in all of them.

Swabs for culture and sensitivity ,and for direct examination were taken from different parts of the body (urine, sputum ,blood ,throat ,skin,..etc).

Patient's temperature was also recorded.

RESULTS:

Infection was determined in the majority of the groups , 80 % of aplastic patients have a known site of infection , while it is 70 % in acute myelogenous leukaemia and only 66 % in acute lymphoblastic leukaemia

Pyrexia of undetermined cause is found in 20% ,30% ,34%, of the above respectively and the most commonest sits of infection in those febrile neutropenic patients was shown in table (1) ,where it was found that urinary tract infection is the commonest among infection in AA ,while chest and skin infection are the dominant sites for ALL and AML patients .

Table 1: Common site of infection in febrile neutropenic patients.

Sit of infection	AA		ALL		AML	
	No.	%	No.	%	No.	%
Urinary Tract	8	17	8	17	5	10
Chest	8	16	11	22	8	15
Mouth mucous membrane	7	14	-	-	4	9
Skin	4	8	2	5	6	12
Tonsils	2	4	7	13	2	3
Liver	4	8	2	4	2	5
Meningies	1	2	-	-	-	-
Periodental	2	3	-	-	2	4
Perianal skin	1	2	-	-	2	5
Multiple sites	2	5	2	3	3	6
Bone	1	1	1	2	1	1
Pyrexia of undetermined origin	10	20	17	34	15	30

The mean of duration of neutropenia is found to be more prolonged in AA compared to patients suffering from acute leukaemia Table (2) .

Table 2: Length of duration of neutropenia.

Condition	Rang in days	Means in days
AA	5-70	25
All	11-40	16
AML	7-35	18

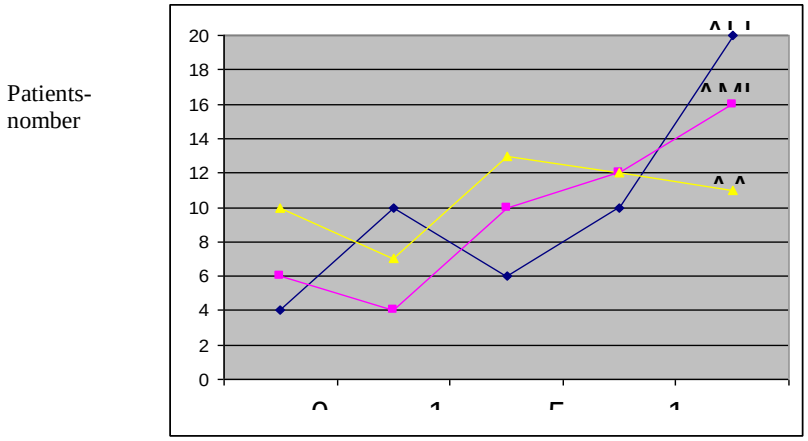
The mean value of all haematological parameters of the 150 patients are analysed from which the degree of neutropenia is concluded in Table (3).

Table 3: Haematological parameters- (Mean Value of 50 patients in each group).

Blood count	Means		
	AA	ALL	AML
RBC	2.3 X 10^{12} /l	2.2 X 10^{12} / l	2.4 X 10^{12} /l
Hb. g/dl	6.2	7.9	7.7
Platelet count	43.6 X 10^{9} /l	10.3 X 10^{9} /l	55 X 10^{9} /l
PCV	20.3	24.9	22.5
WBC	2.8 X 10^{9} / l	10.8 X 10^{9} /l	16.3 X 10^{9} /l
Differential - % Neutrophil Lymphocyte Monocyte Eosinophil Basophil	 14 31.7 2.7 1.3 0.3	 14 35 1.2 0.5 0.1	 12 16.8 3 0.5 0.17
Peripheral blood blast cell count	0	4.92	6.473

Sever neutropenia in which the ANC is lower than 0.5 x 10^{9} /L is only present in about 22% of all patients (10 in AA ,6 in AML ,and 4 in

ALL) . However ANC between 0.5 $X10^9$ /L to 1$X10^9$ /L accounts 14% in all groups (7 in AA,4 in AML ,and 10 in ALL) Figure 1 .



Absolute neutrophil count (ANC)
Figure number.1,Severty of Neutropen

There is a strong relationship between the type of haematological disorder concerned in this study and ANC , duration of neutropenia and monocyte count (ALL) .

Out of 150 patients with neutropenia and pyrexia,only 115 one shows positive microbiological results (Tab.4), Gram negative enrerobacter specialy E-coli and klbsiella are among the commonest microorganism isolated(Tab.5) .

Table 4: Microbioligical documented infection.

Microbiological investigation	AA	ALL	AML
Urine culture	13	10	18
Stool culture	8	10	6
Blood culture	4	5	4
Throat swab	3	5	7
Skin swab	4	1	3
Sputum	4	2	2
Positive Serum for Hepatitis-B-surface Antigen.	1	1	0
Widal test	1	1	0
Rose Bengal test	1	0	1
Total number	39	35	41

Table 5: Types of microorganisms in febrile neutropenic patients.

microorg.	%	number
E.coli	16.5	19
Klebsiella	10.4	12
staphylococcus	8.7	10
streptoccus	7.8	9
salmonella	4.3	5
monilia	10.4	12
dilicoccus pneumonia	6	7
heamaphilus influenza	2.6	3
pseudomonous	6	7
alcaligines feacalis	0.8	1
mixed infection	5.2	6
ascariasis	2.6	3
giardiasis	2.6	3
entamoebiasis	1.7	2
hepatitisB	3.4	4
brucellosis	1.7	2
mycobacterum T.B	2.6	3
proteus	2.6	3
Klebsiella	3.4	4
Total	%	115

Mortality rate during the short hospital stay of all patients were observed to be maximum in patients with AML (52 %) and 22 % , 26 % in ALL and AA patients respectively (Fig.2) .
The direct cause of death was not determined in the majority of our patients.

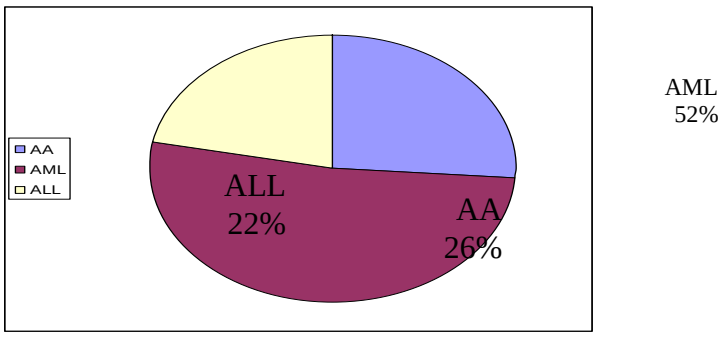


Figure 2: Mortality rate in febrile neutropenic patients.

DISCUSSION:

Some reversible depression of the bone marrow is an inevitable consequence of many chemotherapy regimens used in oncology [3].
Such periods of neutropenia are usually short, if prolonged they would probably lead to a reduction in the dosage of cytotoxic drugs for latter courses.
In the management of acute leukaemia, however,

and more recently in lymphoma and some solid tumors long period of marrow hypoplasia and neutropenial are the consequence of deliberate attempts to maximize the kill of tumor cells. These periods of neutropenia, lasting up to four weeks, are also seen after autologous and allogeniec bone marrow transplantation and carry the risk of severe bacterial , fungal and viral infection [5]. This has not yet been comparable to our patients because such procedures like marrow transplantation are not in practice yet. The mean duration of neutropenia in this study of aplastic anemia is longer than that of acute leukaemics as had been the case ten or fifteen years ago.

The incidence of the above mentioned infections are greater than those seen in aplastic anaemia since chemotherapy and radiotherapy damage the membrane of the oropharynx. gut and lung and thereby permit predominantly gram negative organisms to enter the systemic circulation or the lung parenchyma more readily [6]. Patients with neutropenia due to severe aplastic anemia rarely suffer from serious infections with Gram negative organisms, their frequency being related to the monocyte count [17]. In our series the number of documented infection is 80% , 70% , and 60% in AA, AML , ALL respectively, similar to the majority of studies not undergoing marrow transplantation or very intensive chemoradiotherapeutic regimens for leukaemic patients. However, Gram negative enterobacters remain as the outstanding pathogen in these groups.

Having said that , very low neutrophil count is not always easy to calculate by current auto analyzers. The later being out dated, poorly maintained, lack of parts and reagents for calibration [8].

Generally speaking 11% of febrile episodes have bacteraemia (pathogen is known by blood culture) while the detection rate of bactaeremiain in similar studies is as high as 20%[12]. Approximately 65% show microbiologically documented infection but with negative blood culture. In 23% microbiological documentation was not possible because culture was not or could not be obtained, hence one third of pyrexial patients of all groups were labeled as being of undetermined origin (PUO).

DIAGNOSTIC EVALUATION AND FUTURE PROSPECTS .

For the last two to three decades great improvement has been achieved in prolonging the survival of patients with marrow failure which is obtained by the use of more effective chemotherapy and supportive care for such patients [9,10].

Because infections are common and can be serious or even fatal, an infectious etiology must be sought to explain each new febrile episode. However , detection of infection is made more difficult by the associated neutropenia witch alters the host`s inflammatory response .

The lung, soft tissue, and mucosal surfaces are the most frequent sites of serious infection,so history taking with full investigation should be perfomed in such patients [10,11].

Base line infection screen is worth attempting on first admission to be continued by intense follow up program [12].

Blood culture, Fungal isolates, viral diagnosis,c-reactive protein testing and other measures as radiographic examination should be comprehensively practiced in those patients [13].

Most infections in immunocompromised patients are endogenous or transmitted on the hand of the hospital staff. Hand washing therefore is the most important factor during their nursing [14].

Complete or selective gut decontamination with proper uses of antibiotic should be controlled 9150.

Fever may persist or recur during antibiotic treatment for the following causes[16].

1- Resistant bacterium.
2- Virus infection.
3- Fungus infection.
4- Thrombophleditis (drip site or leg vein).
5- Drug fever.
6- Abscess formation.
7- Endocarditis.
8- Underlying disease activity.

Many Iraqi searches were studied in the same field showing that there were a significant relationship between neutropenia and leukemia[23,24].

CONCLUSION:

This simple study has demonstrated that the duration of neutropenia is longer in aplastic anaemia patients compared to acute leukaemias and the risk of infection is directly related to the severity (ANC) as well as to the duration of the neutropenia.

In two third of patients there is a documented positive microbiological result with the presence of localized signs and symptoms of infection.

Gram negative enterobacter particularly E. coli is the commonest pathogen isolated from the submitted material.

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