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"A Study of Febrile Neutropenia in Cases of Acute Leukemia"

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Abstract: *Infections are the most serious complications of acute leukemia. In adult lymphoblastic leukemia (ALL) and in acute myeloid leukemia (AML), profound neutropenia is expected because of intensive chemotherapy. There is an inverse correlation between granulocyte count and both the incidence and severity of infection. In this study, thirty-eight adult patients of acute leukemia (AML-25, ALL-13) were prospectively studied from January to October 2016 to evaluate the etiology and outcome of febrile episodes. There were 72 febrile episodes, related to severe neutropenia (Neutrophil <500/mm^3) in 88.8% cases. The mean duration of fever was 15 days and it correlated with the period of neutropenia. Clinical or radiological evidence of infection was seen in 50 patients (69.4%). The main sites were pneumonia (25%), abscesses (23.6%), upper respiratory tract infection (16.6%), diarrheas (12.5%) and urinary tract infection (8.7%). Microbiologically infection was documented in 27 (37.5%) episodes. Gram negative organisms were cultured in 41.4% episodes with E. coli and Klebsiella the predominant organisms. Gram positive infections were seen in 29.2%, episodes, mainly due to Staph aureus or Strep spp. Tuberculosis was seen in 3/38 cases, all in AML.*
Empirical antibiotic therapy was commenced with routinely available drugs (Ampicillin / Amoxycillin+ clavulanate / Metronidazole). Cefotaxime/ Ciprofloxacin were second line antibiotics. Antitubercular drugs and Ketoconazole were used for documented TB and oral/esophageal candidiasis respectively. Amphotericin B was not used in any patient. Fever subsided in 56 (77.7%) episodes. Cheaper antibiotics are often effective in treating infection in acute leukemia, but need to be supplemented by newer antibiotics if the response is inadequate.

Keywords: *Leukemia, Neutropenia, Infection, Pyrexia*

I. Introduction

Infections are the most serious complications of acute leukemia. In adult lymphoblastic leukemia (ALL) and in acute myeloid leukemia (AML), intensive chemotherapy is given and profound neutropenia is expected[1]. There is an inverse correlation between granulocyte count and both the incidence and severity of infection. Infections are predominantly due to gram negative bacilli, less frequently due to gram positive cocci and occasionally due to fungi, mycobacterial or viral infections[2]. The pattern of infection varies in different hospitals and geographical areas. Most of the data available is based on Western studies. There are only a few Indian studies about epidemiology of febrile neutropenia.[3] In this study 38 patients of adult acute leukemia were prospectively evaluated to determine the cause of febrile episodes over 10 months.

II. Material and Methods

Thirty-eight cases of Acute Leukemia admitted to a tertiary care hospital in Western Maharashtra from January to October 2016 were prospectively studied for the etiology and outcome of febrile episodes. There were 25 cases of Acute Myeloid Leukemia (AML) and 13 cases of Acute Lymphoblastic Leukemia (ALL), comprising of 32 males, 6 females with overall mean age 31.6 (Table I). Fever was defined as oral temperature more than 38^0C for 4 hours or a single temperature exceeding 39^0C not related to blood transfusion or intravenous fluid administration. All the patients who were neutropenic (neutrophils less than 1000/cu mm) were put on prophylactic Amoxycillin/clavulanate (or Ciprofloxacin if allergic penicillin) apart from oral antifungal suspension and antiseptic mouthwash.[4,5]

All the patients were assessed for an infectious etiology. Detailed clinical history and examination, blood counts, urinalysis, X-ray chest, blood smear for malarial parasite and cultures from blood, urine, sputum, throat and any other suspected site of infection were done.

Empirical intravenous antibiotics were commenced at onset of fever in all severely neutropenic patients (Neutrophils <500/mm^3).[6,7] In other patients, antibiotics were commenced if there was clinical or microbiological evidence of infection, or fever persisted with clinical deterioration.[8] The initial choice was Cefotaxime or Piperacillin/Tazobactum if staphylococcal or upper respiratory infection was suspected and Ciprofloxacin + Metronidazole or Imipenem/Cilastatin if gastrointestinal source was suspected. If there was no improvement in 48 hours, second line antibiotics were substituted (usually, Cefipime, or imipenam or meropenem along with an aminoglycoside usually Amikacin). If fungal infection was suspected or documented, oral Ketoconazole was added. Amphotericin B was to be used only when systemic fungal infection was definite.

Antitubercular therapy was added when indicated. X-ray chests were repeated at least once a week or earlier and cultures were repeated every 72 hours in febrile patients. HB_sAg, HCV and HIV screening was routinely done in all cases. Hepatic viral markers were repeated if jaundice developed. Clinical and radiological evidence of infection was classified as "Clinical" and as "Microbiological" if organisms were identified on culture or on special stains.

III. Results

There were total of 72 febrile episodes which occurred in 38 patients of acute leukemia. The mean duration of each febrile episode was 15 days (range 2-68 days). At onset or during induction 33/38 patients had pyrexia. The other febrile episodes were related to neutropenia developing after further chemotherapy, or due to complications of disease. There were only 8 (11.1%) episodes not related to neutropenia.

No clinical or microbiological features suggestive of infection were detected during 22 (30.5%) episodes of fever. There was some clinical or radiological evidence of infection in 50/72 (69.4%) episodes (Table II). Forty-one infections were documented microbiologically in 27 instances (Table III). Septicemia was suspected during 21 febrile episodes due to associated features like hypotension, DIC and multiorgan dysfunction. A focus of infection was present in 18 episodes i.e. pneumonia, urinary tract infection, boils or abscesses, thrombophlebitis, or diarrhea. However, blood cultures were positive in only 3 cases. In 56 (77.7%) episodes of fever including 9 septicemias, the pyrexia subsided with prolonged antibiotic therapy with available drugs and recovery of neutrophil counts. Vancomycin was used once in a case of multiple staphylococcal abscesses and septicemia, with dramatic improvement in 5 days. Cefotaxime and ciprofloxacin (if not already on prophylactic Ciprofloxacin) were used in less than 20% cases, while Amphotericin was not used in any case.

IV. Discussion

This study shows that all the patients developed episodes of pyrexia and in 88.9% cases, it was related to neutropenia. Thirty-three patients were febrile at onset or on induction therapy when neutropenia was severe. The mean duration of fever (15 days) also correlated with the period of neutropenia and patients showed recovery with rising neutrophil counts, in contrast to patients who remained neutropenic and often with adverse outcome. A clinical or radiological localisation of infection was made in 69.4% of febrile episodes. This is higher than reported in other centres from India.[9] possibly as this was a prospective study. Pneumonia (25%), abscess or boils (23.6%), upper respiratory infection (16.6%), diarrhea (12.5%) and urinary tract infection (8.7%) were the main sites involved. Microbiological evidence of infection was seen in 27/72 (37.5%) episodes. Gram negative organisms were cultured in 41.4% and E. coli and Klebsiella were more common than Pseudomonas or Proteus. This is in contrast to the other Indian studies where E. coli was uncommon.[10] Gram positive infection were seen in 29.2% and mainly comprised of Staph aureus and streptococci. Septicemia was clinically diagnosed in 21 (29.6%) episodes, but blood cultures were positive in only 3 cases. Overall 18/21 had a clinical source of infection.

The clinical diagnosis of septicemia is difficult in acute leukemia as features of hypotension and multiorgan dysfunction can also occur due to bleeding and leukemia per se. Thus, if blood cultures are taken as a criterion for bacteremia, there will be an under estimation of septicemia. The reason for a low positivity on blood culture may be due to the prophylactic antibacterial agents which are routinely administered to all patients. Fungal infections are an important cause of fever and most centers routinely administer Amphotericin B in pyrexias unresponsive to antibiotics.[11] In this study ketoconazole was given for esophageal or pharyngeal candidiasis, but Amphotericin was not administered in any patient as definite evidence of systemic fungal infection was lacking. Tuberculosis has not been a major cause of pyrexia in Western literature. Even in India, TB was seen in 9 out of 130 cases of AML.[12] We found 3/38 cases of tuberculosis, all in AML.

Most Western countries advocates antibiotic therapy in neutropenic patients with aminoglycosides, beta-lactams and carbapenems and other drugs such as vancomycin, teicoplanin, linezolid, colistin and tigecycline etc. These newer drugs are undoubtedly more effective, but are also more toxic and often unaffordable in hospitals where resources are a constraint. This study shows that with cheaper medicine (amikacin + ampicillin, amoxycillin/clavulanate, ciprofloxacin and metronidazole) used as first line drugs, 56 (77.7%) of febrile episodes subsided. However, these drugs were not successful in eradicating fever in 16 patients.

V. CONCLUSION

This study demonstrates that infections are the major cause of pyrexia in patients of acute leukemia. Apart from gram negative organisms, gram positive organisms especially staphylococci, are an important cause of infections. Empirical antibiotic therapy for fever in the neutropenic patients appears justified even in the absence of positive blood cultures. Routinely available antibiotics may be effective in therapy of infection in a

significant number of patients and, where resources are limited, may be used as first line drugs. Newer antibiotics are nevertheless required in patients with unresponsive pyrexia.

Table I- PATIENT CHARACTERISTICS; DIAGNOSIS, AGE, SEX

DIAGNOSIS	**AML (25)**	**ALL (13)**
MALE	22	10
FEMALE	3	3
AGE		
11-20 Yrs	2	2
21-30 Yrs	6	7
31-40 Yrs	11	2
41-50 Yrs	5	1
51-60 Yrs	1	1
MEAN AGE (YEARS)	33.4	28.4
TOTAL	**25**	**13**

Table II- CLINICAL & RADIOLOGICAL EVIDENCE OF INFECTION IN 50 FEBRILE EPISODES*

SITE OF INFECTION	NUMBER
Septicemia (Clinical)	21
Pneumonia	18
Pleuritis / Effusion	3
URTI	12
Perianal Abscess	9
Boils / Furuncles	8
UTI	7
Diarrhea	9
Oral Ulcer	5
Thrombophlebitis	6
Tuberculosis	3
Otitis Media	2
Malaria	1
Hepatitis	3

URTI = Upper Respiratory Tract Infection,
UTI = Urinary Tract Infection
* More than one site affected in some episodes.

Table III- MICROBIOLOGICAL EVIDENCE OF INFECTION IN 27 FEBRILE EPISODES*

SITE / SOURCE	POSITIVE CULTURE	ORGANISM
Blood (Culture)	3	E coli-1, Pseudomonas-1, Acinetobacter - 1
Boils	7	S aureus-3, Strept-1, E coli-1, Proteus-1
Perianal Abscess	2	E coli-1, S aureus-1
UTI	9	E coli-5, Klebsiella-4
URTI	11	S aureus-4, S albus-1, Strep-1, Candida-4, Aspergillus-1
Lung (Sputum)	3	Strept-1, Klebasiella-1, AFB-1
Blood (Viral)	5	HBsAg Positive (Conversion)
Blood (Malarial Parasite)	1	Plasmodium Vivax

* More than one organism from different sites isolated in some episodes.

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