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Pulmonary Infiltrates during Chemotherapy-induced Febrile Neutropenia: Incidence, Patterns and Outcomes

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Abstract

Objective: To analyze the incidence, etiologies, radiographic patterns, and clinical outcomes of adult leukemics with prolonged febrile neutropenia and pneumonia.

Methods: A retrospective study was conducted at a tertiary care hospital. The medical records of adult patients with acute myeloid leukemia diagnosed between January 1989 and June 2000 and undergoing induction chemotherapy were included. Only the patients who presented with a pulmonary infiltrate, secondary leukemia (e.g., transformed chronic myeloid leukemia underlying myelodysplastic syndrome, or disease following alkylating agent therapy) were included and those developing infiltrates following consolidation chemotherapy were excluded.

Results: A total of 124 patients were admitted to the hospital with a diagnosis of AML during the study period. Thirty-one patients were excluded; 93 patients received induction chemotherapy and were included in the study analysis. The median age was 36 years (15 - 70 years); 58 males and 35 females. Sixty two percent patients received Cytosine Arabinoside (Ara-C), 17% received Etoposide, 11% received Ara-C and Mitoxantrone, and 6% received All-trans-retinoic Acid. The mean onset and duration of neutropenia were 5 and 15 days, respectively. Pulmonary infiltrates were identified during 45% of neutropenic episodes. A presumptive causative organism was isolated from 50% of patients with an infiltrate: Gram- positive bacteria were most common (47%) followed by Gram-negative bacilli (33%) and fungi (20%). Survival data were available for 88 patients; median disease free survival for the entire cohort was 7 months. Male sex ($p=0.015$), onset of neutropenia ($p=0.02$) and bilateral distribution of an infiltrate ($p=0.03$) were statistically significant predictors of early mortality. For patients with and without pneumonia, the median disease-free interval and overall survival were 2.5 and 4.6 months and 9 and 13 months ($p=0.038$ and $p=0.095$) respectively.

Conclusion: Neutropenia occurred at a mean of 5.0 after initiation of induction chemotherapy. The majority of patients had bilateral pulmonary infiltrates. Male sex, onset of neutropenia and bilateral distribution of an infiltrate were found to be statistically significant predictors of early mortality (JPMA 54:285;2004).

Introduction

The risk of morbidity and mortality from infection in patients with acute leukemia undergoing cancer chemotherapy depends upon the degree and duration of neutropenia.[1,2] Pneumonia is a life-threatening complication in patients who develop neutropenia following cancer chemotherapy.[3,4] Approximately 30%-40% of persons with prolonged neutropenia (>7 days) may develop pulmonary infiltrates.[5] We sought to determine the incidence, etiologies, radiographic patterns and outcomes of pneumonia in patients with acute myeloid leukemia and neutropenia in Pakistan.

Patients and Methods

We retrospectively reviewed the medical charts of 93 patients (aged >14 years) with acute myeloid leukemia and undergoing induction chemotherapy between January 1989 and June 2000 at our hospital. Excluded patients were those who presented to the hospital with a pulmonary infiltrate, or with a secondary leukemia (e.g., transformed chronic myeloid leukemia underlying myelodysplastic syndrome, or disease following alkylating agent therapy), and those developing infiltrates following consolidation chemotherapy. Extracted data included: morphologic type of acute myeloid leukemia, type of induction regimen, onset and duration of neutropenia, choice of initial empiric antibiotic therapy and subsequent modifications, use of colony stimulating factors, use of prophylactic and therapeutic antifungal agents, clinical sites of infection, presence and type of pulmonary radiographic abnormalities, relevant culture and sensitivity data and clinical outcomes.

The chest radiographs of all patients taken during the neutropenic period were independently reviewed by a radiologist and the data were logged after classifying the infiltrates into various patterns. Microbiological data were retrieved from the medical charts and microbiology laboratory log books. Microorganism obtained from blood culture, bone marrow culture, sputum culture, bronchoalveolar lavage (BAL), bronchoscopic biopsy, tracheal aspirates and skin biopsies were considered as

presumptive causes of pulmonary infiltrates. Organisms isolated from stool, urine and abscess sites were generally not considered clinically relevant.

The baseline characteristics of the patients are expressed as mean ± standard deviation, median (range) and number (percentage). The univariate analysis was performed by means of Independent-samples t-test, Pearson Chi-square test, Fisher Exact tests whenever appropriate. The Overall Survival and disease free survival curves were generated by the Kaplan-Meier and compared by means of the Long rank test. A $p<0.05$ was considered statistically significant. These analyses were carried out using the statistical software SPSS 10.0.

Results

Over the study period of June 1989 to August 2000, a total of 124 patients were admitted to the hospital with AML. Thirty-one patients were excluded; fourteen had transformed from an underlying CML, six had antecedent myelodysplastic features and nine were never treated at the hospital, they were either referred to another hospital (n = 6) or died before the commencement of chemotherapy (n = 3). Two patients above the age of 70 were treated with supportive care only. A total of 93 patients received induction chemotherapy and were included in the study analysis. The median age was 36 years (15-70 years); with 58 males and 35 females.

The morphological subtypes of leukemia, based upon the French-American-British (FAB) Board criteria, were as follows: M0 (2 patients), M1 (2 patients), M2 (13 patients), M3 (11 patients), M4 (44 patients), M5 (9 patients), unspecified (12 patients). Baseline hematological and biochemical profiles are shown in Table 1. Neutropenia (ANC <500/ul) occurred at a mean of 5.0 ± 3.4 days after initiation of induction chemotherapy. The mean duration of neutropenia was 15 ± 6.1 days.

Fifty-eight (62%) patients received Cytosine Arabinoside (Ara-C) 100 mg/m² as continuous intravenous infusion (C.I.V.) for 7 days and Daunorubicin 50 mg/m² as a slow push for 1st three days. Sixteen (17%) patients received Etoposide 100 mg/m² as a 2-hour infusion for 4 consecutive days in addition to Ara-C and Daunorubicin. Ten (11%) patients received Ara-C 100 mg/m² C.I.V. and Mitoxantrone 12 mg/m² as slow push for 3 consecutive days. Six (6%) patients received All-trans-retinoic Acid (ATRA) orally at 45 mg/m² in 2 divided doses either in combination with chemotherapy (n=2) or alone (n=4).

During the study period empiric antibiotic regimens were formulated after periodic review of in vitro susceptibility patterns and trends among hospital isolates of clinically relevant bacteria. Of the 93 patients; 35 received Amikacin 15mg/kg/day and Piperacillin 4gm every 6 hours,

Table 1. Hematological and biochemical profiles of 93 patients with acute myeloid leukemia.

Laboratory test	Mean Value
Hemoglobin (gm/dL)	8.4 ± 2.4
Total Leukocyte count (cells/mm2)	48 ± 56
% Neutrophils	19 ± 21
% Lymphocyte	20 ± 18
% Blasts	60 ± 28
Platelets (cells/mm2)	69 ± 81
BUN (mg/dL)	13 ± 6
Creatinine (mg/dL)	1.0 ± 0.7
Total Bilirubin (mg/dL)	1.8 ± 5.8
Alkaline Transferase (IU)	32 ± 30
Alkaline Phosphate (IU)	32 ± 30
Albumin (gm/dL)	3.2 ± 0.6
LDH (IU)	1,945 ± 1,792
Uric acid (mg/dL)	7.0 ± 12

39 received Amikacin 15 mg/kg/day and Ceftazidime 1 gm every 8 hours and 19 patients received Amikacin and Tazocin.

Cloxacillin 2 gm 6 hourly was added to the empiric regimen whenever an apparent focus of infection thought to be related to gram positive organisms was present at the onset of neutropenia and fever. Metronidazole 500 mgq 8 hours was added whenever patients had moderate to severe oral mucositis or diarrhea at the onset of fever and neutropenia. Patients who were persistently febrile on the 5th day of empiric antibiotic therapy also received Amphotericin 1 mg/kg/day. Eighteen patients received prophylactic Itraconazole 200 mg b.i.d. from the day of onset of febrile neutropenia, 5 of these patients later required Amphotericin.

Granulocytes - macrophage colony stimulating factor (GM-CSF) and Granulocyte Colony stimulating factor (G-CSF) were administered to 14 and 6 patients respectively from the 11th day of induction of chemotherapy (after a bone marrow confirmation of hypoplasia on the 10th day).

Of the 93 patients, 42 (46%) developed pulmonary infiltrates during the course of neutropenia with 66% in the right lung and 33% in the left lung.. At the time of detection of the abnormality, the infiltrates were unilateral in 61% of cases and bilateral in 39% cases. The distribution in upper, middle and lower lobes of lungs was 43%, 11% and 25% respectively. The difference radiographic patterns are shown in Table 2.

The bacteria and fungi isolated from either blood,

Table 2. Incidence, anatomical distribution and radiographic patterns of pulmonary infiltrates in 93 patients with acute myeloid leukemia

Radiographic Pattern	%age of patients
Segmental consolidation	50
Pleural effusion	24
Lobar consolidation	18
Atelectasis	12
Diffuse macronodular	10
Cavitation	3
Large solitary nodule	3
Pleural thickening	3

Figure 2. Kaplan-Meier curve showing overall survival in 93 patients with acute leukemics with and without pulmonary infiltrates.

bone marrow, sputum, BAL, bronchoscopic biopsy, deep tracheal aspirate or skin biopsies were considered to be presumptive causative agents. Organisms must have been isolated from clinical specimens obtained during the course of febrile neutropenia. One-half of the cohort group with radiographic abnormalities (21 of 42 patients) had a microbiologic isolate recovered from one of the aforementioned sites. In 13 cases a single causative organism was presumed, whereas the infection was polymicrobial in 8 cases. A total of 30 organisms were isolated; 14 (47%) were gram- positive bacteria, 10 (33%) were gram-negative bacteria, and 6 (20%) were fungi.

Survival data were available for 88 patients (five subjects were lost to follow-up). Of these patients, 41 developed an infiltrate, out of whom 14 died. The median disease free survival and the overall survival for the entire cohort was 7 months. For patients with and without pneumonia, the median disease-free survival and overall survival were 2.5 and 4.6 months and 9 and 13 months (p=0.038 and p= 0.095) respectively (Figures 1 and 2).
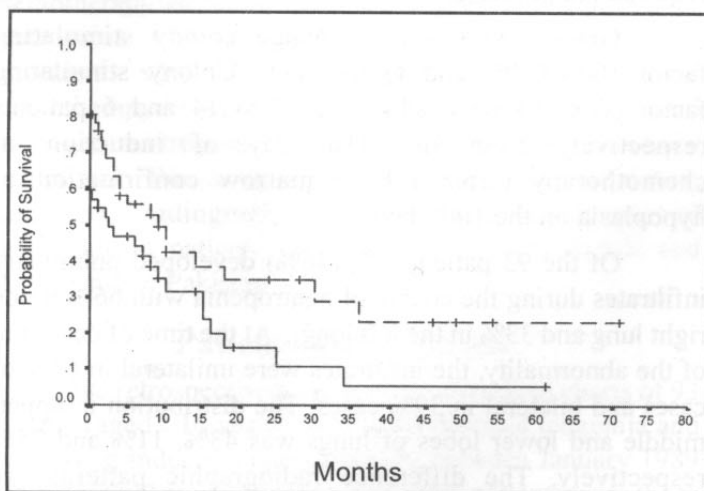

Figure 1. Kaplan-Meier curves showing disease-free survival for acute leukemics with and without pulmonary infiltrates.
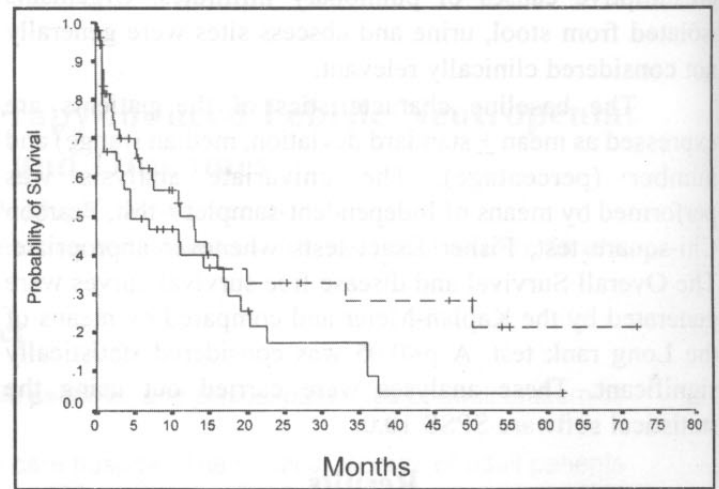
Using univariate analysis, the following variables were tested for prediction of mortality and development of pneumonia: age, sex, morphological subtype, type of chemotherapy, onset and duration of neutropenia, type of initial empiric antibiotic therapy, use of prophylactic Itraconazole, use of either GM-CSF or G-CSF, presence or absence of a pulmonary infiltrate, pattern of pulmonary infiltrate, the presence or absence of a microbiological isolate and type of isolate (gram positive versus gram negative versus fungus). Male sex (p=0.015) onset of neutropenia (p=0.02) and bilateral distribution of an infiltrate (p=0.03) were statistically significant predictors of early mortality. None of these factors predicted the development of a pulmonary infiltrate.

Discussion

The lung is one of the commonest sites for life-threatening infections in adults with acute leukemia receiving chemotherapy.[6,7] While a number of radiographic abnormalities may develop, segmental and lobar consolidation are most frequently encountered and reflect the predominance of bacterial and, to a lesser extent, fungal causes of pneumonia in these patients. Diffuse interstitial infiltrates are less frequently seen and are generally caused by opportunistic and non-opportunistic viral, mycoplasmal, fungal and parasitic pathogens including cytomegalovirus, influenza virus, adenovirus, respiratory syncitial virus, Mycoplasma pneumoniae, and Pneumocystis carinii. In our setting, sophisticated viral diagnostics are not available and thus viral pathogens were not included in the microbiologic causes of pneumonia in our study cohort.

Cavitary pulmonary lesions in the context of febrile neutropenia generally suggest a non-viral etiology, with bacteria (such as Staphylococcus aureus, Klebsiella species, Pseudomonas aeruginosa, and anaerobes), mycobacteria,

fungi and parasites as potential pathogens. In contrast, nodules or nodular infiltrates, are generally caused by organisms other than bacteria (e.g., fungi, Nocardia, mycobacteria, and parasites). The more frequent occurrence of right-sided pneumonia in our patients may be explained by a simple anatomic predilection via aspiration.

The microbiology of infection in patients with acute leukemia and febrile neutropenia depends upon a number of factors including local hospital flora, use of prophylactic antimicrobial agents, and type of intravascular catheterization. We observed a predominance of Gram-positive organisms in our study cohort with pneumonia, a finding commonly reported in recent years.[8] In general, over the past decade factors influencing a shift from Gram-negative to Gram-positive infections in febrile neutropenia include the use of more permanent central venous catheters, and the use of prophylactic antibacterial and antifungal antibiotics such as Trimethoprim-Sulfamethoxazole, Fluoroquinolones, and Imidazoles.[4,8] However, during our study period no Hickman or Broviac catheters, and few subcutaneous implantable catheters were used in our patient cohort, and prophylactic antibiotics were uncommonly prescribed.

Radiographic abnormalities in patients with febrile neutropenia have many potential infectious and non-infectious etiologies including pneumonia, hemorrhage, drug toxicity, pulmonary edema, tumor infiltration, leukagglutinin reaction, and thromboembolism.[9] For several reasons, it is logical to study pneumonia in persons undergoing therapy for acute leukemia. First, these patients have a predictable occurrence of prolonged neutropenia (usually 12-16 days), which predisposes to lung infection. Secondly, cytotoxic agents used in the treatment of adult leukemia generally do not cause pulmonary or cardiac toxicity, thereby reducing the incidence of non-infectious causes of pulmonary infiltrates.

Adult patients with acute leukemia who undergo chemotherapy and develop neutropenia are at significant risk for pneumonia and death.[10,11] Bacterial and fungal infections of the lung are most identifiable and treatable in our local setting. Improved methods of preventing and accurately diagnosing early infection in these patients are urgently needed.[12]

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