SKIN, OROPHARYNGEAL AND RESPIRATORY TRACT INFECTIONS IN PATIENTS WITH ACUTE LEUKAEMIA RECEIVING CHEMOTHERAPY

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ABSTRACT

BACKGROUND
Infection is a major cause of morbidity and mortality in patients receiving chemotherapy for acute leukaemias. This is an attempt to study oropharyngeal, respiratory and skin infections in patients with acute leukaemia receiving chemotherapy with reference to their aetiology, response to antimicrobial treatment and relation with neutropenia.

MATERIALS AND METHODS
All acute leukaemic patients on chemotherapy with any clinical or laboratory features of oropharyngeal, respiratory tract or skin infections admitted in the Haematology Unit of Calicut Government Medical College were included in the study. In the present study, a total of 70 febrile episodes were studied. These episodes were investigated for infectious aetiology by putting appropriate specimen(s) for culture/microscopy for bacterial, fungal and parasitic agents.

RESULTS
Maximum incidence of infections and the poorest outcome was observed when absolute neutrophil count was <500. Incidence of severe neutropenia in our study was 42.86% with high mortality in severely neutropenics (40%). Respiratory system was the commonest site of infection (54%). Pyogenic bacteria were predominating in the culture studies with 21 cultures positive. Staphylococcus aureus (47.61%) was the commonest agent in the culture samples.

CONCLUSION
Rate of neutropenia as well as mortality is high in AML patients when comparing with ALL. Most common symptom indicating infection is fever even if the patient is having defective immunity. Thrombophlebitis at intravenous cannula site is a common focus of infection. Majority of patients responded well to first line antibiotics, even though culture and sensitivity studies were negative.

KEYWORDS
Leukaemia; Absolute Neutrophil Count; Culture; Infections; Empirical Therapy.

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BACKGROUND
Infection is a major cause of morbidity and mortality in patients receiving chemotherapy for acute leukaemias. The profound pancytopenia that result from cytoreductive chemotherapy is a common and dramatic manifestation of stem cell failure.1,2 During the period of neutropenia that follow such chemotherapy, infection will develop in most patients. Bacterial infection may result in rapid clinical deterioration and if not treated appropriately death. Fungal, viral and parasitic infections may also result in potentially lethal complications during and after chemotherapy.3

Recognition and treatment of such infections in the context of different clinical situations are important. Very little data is available regarding the pattern of various infections in patients with acute leukaemia and its relation to outcome in our setup. This study is an attempt to study oropharyngeal, respiratory and skin infections in patients with acute leukaemia receiving chemotherapy with reference to their aetiology and response to antimicrobial treatment.

MATERIALS AND METHODS
The study was conducted in the Haematology Unit of Department of Medicine in Medical College, Kozhikode. If any patient on antileukaemic chemotherapy in Haematology ward developed fever or other symptoms of oropharyngeal, respiratory or skin infection, a detailed history and physical examination is done in that patient along with relevant investigations. Blood, pus and throat swab is obtained for culture and sensitivity prior to starting of antibiotics. Routine investigations including complete blood count, Absolute Neutrophil Count (ANC), urine microscopy, renal function...
test, liver function tests, chest x-ray was done in all cases. Culture and sensitivity of other specimens like cannula tip sample and swabs from skin lesions were undertaken in relevant cases. To conduct the study, a proforma was set up with special emphasis on relevant physical findings and investigations. Ethical clearance was taken from the Institutional Ethics Committee.

**Inclusion Criteria**
All acute leukaemic patients on chemotherapy with any clinical or laboratory features of oropharyngeal, respiratory tract or skin infections were included in the study.

**Exclusion Criteria**
1. Patients with evidence of clinical infections prior to chemotherapy.
2. Patients with comorbid conditions such as uncontrolled diabetes, chronic renal failure or chronic liver diseases.
3. Patients less than 13 years.

The study started in January 2015 and completed in December 2015. It was an observational hospital-based study. Data analysis were performed using SPSS software in all cases.

**RESULTS**
The study was conducted in 70 subjects. Age of study group was from 13 yrs. to 68 yrs. The mean age of Acute Lymphocytic Leukaemia (ALL) patients were 22 yrs. and that of Acute Myeloid Leukaemia (AML) patients were 43 yrs. 13 out of 23 ALL patients and 25 out of 47 AML patients were males. 67.14% of the patients in the study group were having AML. Of the AML, majority were AML M2. ALL L2 was the commonest in ALL group. Most of the AML patients, other than AML M3 were under palliative treatment. Among the 9 AML M3 patients, 5 were receiving arsenic trioxide and 4 were receiving All-Trans-Retinoic Acid (ATRA.) All ALL patients were under MCP-841 regimen of these 10 were in induction phase, 8 were in consolidation and 5 were in maintenance, at the time of inclusion in the study. The commonest symptom indicating infection in the study group was fever, followed by respiratory symptoms and pain and swelling of intravenous cannula site.

**Neutropenia**
Neutropenia and clinical episodes of infection were found to be related in the study. Total number of episodes of severe neutropenia (ANC<500) in the study was 30 out of 70. Of these, 9 episodes were in ALL and 21 in AML (Table 1), which was not statistically significant.

<table>
<thead>
<tr>
<th>Type of Leukaemia</th>
<th>Number of Patients with ANC &lt;500</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>9</td>
<td>23</td>
</tr>
<tr>
<td>AML</td>
<td>21</td>
<td>47</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>30</strong></td>
<td><strong>70</strong></td>
</tr>
</tbody>
</table>

*Table 1. Incidence of Severe Neutropenia (ANC <500) in Leukaemia*

Renal function test were normal in the study population. The impairment in liver function tests in the group were not significant. Sputum AFB was positive in one patient who presented with fever, productive cough, weight loss and the patient was on palliative cytosine arabinoside (Ara-C) for AML.

**Focus of Infection**
Respiratory tract was the major focus of infection followed by thrombophlebitis (Table 2).

<table>
<thead>
<tr>
<th>Focus of Infection</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumoniae</td>
<td>16</td>
<td>22.86%</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>13</td>
<td>18.57%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>9</td>
<td>12.86%</td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>27</td>
<td>38.57%</td>
</tr>
<tr>
<td>Skin infection</td>
<td>14</td>
<td>20%</td>
</tr>
<tr>
<td>Oral cavity infection</td>
<td>10</td>
<td>14.29%</td>
</tr>
<tr>
<td>Oral thrush</td>
<td>22</td>
<td>31.42%</td>
</tr>
</tbody>
</table>

*Table 2. Focus of Infection*

**Culture Studies**
We had total 89 foci of infection. One case was positive for sputum AFB. Out of remaining 88 foci, 21 came as culture positive (23.86%). Blood cultures were positive in 5 cases (gram-positive 4 and gram-negative 1), sputum culture in 3 cases (gram-positive 2 and gram-negative 1), pus cultures in 5 cases (gram-positive 4 and gram-negative 1), cannula tip in 4 cases (gram-positive 4 and gram-negative 0) and throat swab in 2 cases (gram-positive 2 and gram-negative 0). We had one positive result each with pleural fluid and tracheal aspirate. Of the gram-positive group, six Methicillin-Resistant Staphylococcus Aureus (MRSA) isolates, 2 multidrug-resistant coagulase-negative Staphylococci (MDR-CoNs) and one enterococci were sensitive to vancomycin and others were sensitive to penicillins. Of the gram negative, 2 Klebsiella isolates were carbapenemase producing and were sensitive to colistin only. One isolate of Multidrug-Resistant (MDR) Acinetobacter was sensitive to colistin only. Pseudomonas was sensitive to fluoroquinolones and aminoglycosides.

**Death**
Of the 70 cases studied, 13 patients succumbed to the infection (18.57%). The death rate was more common in severe neutropenics. Out of 30 patients with ANC <500, 12 patients expired. The relation was statistically significant with a p value of 0.007.

**Response to Empirical Antibiotics**
57 out of 70 cases responded well to treatment. 36 episodes responded to first line antibiotics. 7 cases responded to second line drugs and on adding vancomycin the number rose to 16. Third and fourth line drugs were needed in 2 and 3 cases, respectively. First line agents were ciprofloxacin with gentamicin, ampicillin, cloxacillin, third generation cephalosporins and metronidazole. Second line drugs used were piperacillin/tazobactum with amikacin and/or...
vancomycin. Amphotericin and meropenem were used as third and fourth line drugs, respectively (Table 3).

<table>
<thead>
<tr>
<th>Antibiotic Regime</th>
<th>Total Number of Cases</th>
<th>Number of Cases Responded</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line</td>
<td>70</td>
<td>35</td>
</tr>
<tr>
<td>Second line</td>
<td>35</td>
<td>16</td>
</tr>
<tr>
<td>Third line</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Fourth line</td>
<td>17</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 3. Response to Antibiotics

DISCUSSION

Most of the clinical episodes of infection in ALL occurred in the induction phase. This may be due to more aggressive chemotherapy and associated immune suppression in induction phase.\(^1\)\(^2\) In AML patients, also major infections were in the curative phase involving intensive treatment when compared to palliation. Comparable results were seen in Banaras Hindu University (BHU) as well as in Shri Ramachandra Bhanj Medical College (SCB) study.

Clinical Features

A total of 70 clinical episodes of infections were studied. The commonest symptom was fever (88.57%). This is similar to the case with Banaras Hindu University study,\(^2\) AIIMS study and SCB\(^3\) study. The most common systemic symptoms were of the respiratory system that included cough with scanty sputum (38.57%), dyspnoea (30%) and sore throat (12.86%). This is also comparable with BHU and SCB studies.\(^2\)\(^3\) The sputum was scanty and nonpurulent. It may be due to neutropenia in these patients. Pain and swelling of the IV cannula site suggestive of thrombophlebitis was seen in 37.14%. The thrombophlebitis maybe partly due to failure in aseptic precautions while inserting the IV cannula.\(^4\) The process needs to be rectified to prevent infective episodes. Folliculitis, cutaneous abscess and ulcerations were seen in 22.86%. The next in the list was oral cavity infections including gingivitis and abscesses.

19.86% of total episodes of infection were associated with bleeding manifestations due to thrombocytopenia. It was more in the AML group probably because cytosine arabinoside, which is a potent myelosuppressive agent, which is used in AML patients. The mean haemoglobin in the study group was 8.1 mg/dL. ESR was elevated in only 22 patients even though they have infection, so it is not a useful marker of infection in this group.

Out of 29 patients with lower respiratory tract infection (41.3%), only 16 (55.16%) were showing chest x-ray abnormalities. It is because in patients with impaired immunity, it is difficult to get radiological abnormalities even though infections are common in the respiratory tract.

Neutropenia

The incidence of severe neutropenia was 30 out of 70 episodes of infection. Severe neutropenia was more common in the AML group than in ALL group. This may be due to the myelosuppressive effect of chemotherapy. But, it was not statistically significant. Similar finding were seen in AIIMS\(^5\) study. In SCB\(^3\) study, the incidence of severe neutropenia was 89.2%. The disparity maybe because they carried out the study in patients on curative treatment.

Culture Results

We had a total of 89 foci of infection. One was sputum positive pulmonary tuberculosis. Of the remaining 88 cases, 21 came as culture positive (23.86%). Much more cases were culture positive in the comparison studies. The culture positivity in BHU study was 68%,\(^2\) but in SCB study, it was only 33%.\(^3\) This maybe because of several factors. Patients might have received antibiotics from outside prior to taking culture or can be due to presence of infections with fungi and viruses for which the cultures are not routinely used. This can also be due to errors in sampling as well as culture techniques.

In our study, group with 21 culture positive samples, only 4 were showing gram-negative organisms, the remaining 17 yielded gram-positive organisms. Other comparison studies were also having a similar picture-AIIMS,\(^2\) SCB\(^3\) and BHU.\(^2\) But, our study is not sufficient to reach any such conclusion due to the low culture positivity rate. The gram-positive organisms in the group were Staph. aureus, Streptococci and Enterococci, while the gram-negative ones were Klebsiella, Pseudomonas and Acinetobacter. In SCB, the culture was positive for gram-positive organisms in 38.3% and gram negative in 27%.

Response to Antibiotics

57 out of 70 cases responded well to treatment. 36 episodes responded to first line antibiotics including fluconazole in candidiasis. 9 cases responded to second line drugs and on adding vancomycin the number rose to 15. Third and fourth line drugs were needed in 2 and 4 cases, respectively. Episodes that needed third and fourth line drugs were generally having severe neutropenia. According to literature, chance of fungal infections and infections with uncommon bacteria are more if the ANC is <500.\(^6\) Those patients may hence require antifungals and broad-spectrum antibiotics.

Mortality

The present study had 70 cases of infection of which 13 patients (18.57%) expired due to antibiotic nonresponsiveness. Of the total 13 deaths, 12 were associated with severe neutropenia. By Chi-square test, a statistically significant increase in mortality was found in severe neutropenics (P<0.05). A similar finding was obtained in BHU study also.\(^2\) Out of the total 13 deaths, 6 were culture positive with the specimen. 7 deaths were in the culture-negative group. But by Chi-square test, no statistically significant change in mortality was found with presence of culture positivity or negativity (p>0.05). This is also comparable with BHU study.\(^2\)
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<tbody>
<tr>
<td>Incidence of severe neutropenia</td>
<td>42.86%</td>
<td>27.36%</td>
<td>89%</td>
<td>52%</td>
</tr>
<tr>
<td>Respiratory focus of infection</td>
<td>54%</td>
<td>58.7%</td>
<td>32.6%</td>
<td></td>
</tr>
<tr>
<td>All site culture positivity</td>
<td>23.86%</td>
<td>68.4%</td>
<td>33%</td>
<td>35.8%</td>
</tr>
<tr>
<td>Mortality in severely neutropenic</td>
<td>40%</td>
<td>34.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality in ANC&gt;500</td>
<td>2.5%</td>
<td>19.2%</td>
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Table 4. Comparison Between Present Study and Other Studies

ANC - Absolute Neutrophil Count.
BHU - Study done in Banaras Hindu University, Varanasi, in 2001.
AIIMS - Study done in All India Institute of Medical Sciences in 1997-99.
SCB - Shri Ramachandra Bhanj Medical College, Orissa, 2012.

CONCLUSION
Rate of neutropenia as well as mortality is high in AML patients when comparing with ALL. Anaemia and thrombocytopenia are common associations of infection and may indicate myelosuppression. So, proper supportive care may reduce incidence of infection. Most common symptom indicating infection is fever even if the patient is having defective immunity. Thrombophlebitis at intravenous cannula site is a common focus of infection, which can be reduced by proper aseptic precautions.

Markers of inflammation like ESR may not be helpful in majority. Isolation of organism is also difficult in majority episodes. Gram-positive organisms are predominating in respiratory, skin and oral cavity infections.

Majority of patients responded well to first line antibiotics, even though culture and sensitivity studies were negative. The combination of ciprofloxacin with gentamicin is found to be an effective first line antibiotic regimen in neutropenia. The combination of piperacillin-tazobactum with amikacin is an effective second line regime. Mortality is significantly high in severely neutropenic patients when compared to the rest, but the chance of getting infection is not significantly different. There is no significant difference in mortality between culture positive and culture negative episodes.

REFERENCES