Medical complications among acute leukaemia patients receiving inward induction chemotherapy at haematology oncology section of the National Cancer Institute, Sri Lanka

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Abstract

Introduction: Acute leukaemias are complicated with numerous disease and treatment related medical complications. Infection is one of the major complications and is related to chemotherapy associated-neutropaenia. This study aims to identify medical complications in acute leukaemia patients during the induction chemotherapy period.

Results: Medical complications were observed in patients receiving induction chemotherapy N=50. Infections and electrolyte disturbances were the most frequently observed complications (74% each) followed by chemotherapy induced neutropaenia (38%), alteration of liver functions (32%), steroid induced hyperglycaemia (28%) and bleeding (16%). Thrombosis and tumour lysis were detected at lesser frequencies (4% each). Among infections, the majority showed evidence of blood stream infection (27%) followed by pulmonary infections (24.3%). Gram negative organisms were the most frequently identified pathogen. Among the electrolyte disturbances, hypokalaemia (48%), hyponatraemia (48%), and hypocalcaemia (44%) were more prevalent. Mean duration from initiation of chemotherapy to neutrophil nadir was 10.05 days.

Conclusions: Patients with acute leukaemia encounter a multitude of disease and treatment related medical complications during induction chemotherapy. Infection is the most common complication with higher rates of bacteraemia and gram-negative sepsis. This is likely to be a result of treatment related neutropaenia. However, further focused studies on neutropaenic sepsis during induction chemotherapy are recommended. Clinical vigilance, strict and improved infection control strategies are necessary to improve the outcome of these patients.

Keywords: acute leukaemia, induction chemotherapy, neutropaenia, medical complications
Introduction

Globally, malignancy poses an enormous burden on society. Cancer incidence and mortality are on the rise and contributory factors are multifactorial. Demographic transition towards an ageing population, together with increasing prevalence of non-communicable diseases and established risk factors such as smoking, overweight, physical inactivity are among the leading contributory factors. About 14.1 million new cancer cases and 8.2 million deaths occurred worldwide in 2012.(1) Over the years, the burden has shifted to less developed countries, which currently account for about 57% of cases and 65% of cancer deaths worldwide.(1)

Among the malignancies, solid organ malignancies are more prevalent than haematological malignancies. This trend is observed among the Sri Lankan population as well.(2) However, the incidence of lymphoid and myeloid leukaemia is rising with the adult population being more affected.(2) Though the trend is rising, overall survival of leukaemia is better than that of most solid organ malignancies.(3)

Among the haematological malignancies, acute leukemias which consist of acute myeloid leukaemia (AML) and acute lymphocytic leukaemia (ALL) are complicated with numerous disease and treatment related medical complications.(4-10) Infection is one of the major complications and is related to chemotherapy associated neutropaenia.(11) Metabolic disturbances are also very frequent and usually result from vomiting, diarrhoea, renal dysfunction or as a side effect of chemotherapy, antibiotics or diuretic use. Tumour lysis syndrome is a disease specific as well as treatment related complication giving rise to a myriad of metabolic disturbances which include hyperuricaemia, hyperphosphataemia, hyperkalaemia, hypocalcaemia and ultimately renal insufficiency.(9) Bleeding is another medical complication which can result from thrombocytopenia, platelet dysfunction or disorders of coagulation. Disseminated intravascular coagulation is seen with all leukaemia subtypes, especially in patients with acute promyelocytic leukaemia. Leukaemia related hyperleukocytosis and leukoerythroblastosis can present with respiratory and neurological distress and is a medical emergency.(10) Leukaemic patients are at high risk of venous thrombosis and associated complications like pulmonary embolism.(5) Lactic acidosis, acute pulmonary failure and neutropaenic enterocolitis are among other less frequent medical complications. (4,8)

These medical complications, if anticipated, detected and managed properly will have a major impact on survival of these patients. Therefore, as physicians, it is of utmost importance to be aware of the prevalence, existing deficiencies and proper management of these medical complications among the local population in order to provide the optimal care for the patients. Under such circumstances, this study aims to identify disease and treatment related medical complications among acute leukaemia patients during inward induction chemotherapy.

Methods

This is a descriptive cross-sectional study carried out from December 2018 to May 2019 in the Hemato-Oncology sections at the National Cancer Institute Sri Lanka. Out of 212 acute leukaemia patients receiving inward treatment during the study period, the patients receiving induction chemotherapy regimen were only 50 and all of them were recruited to the study.

Data was collected via interviews and bedhead tickets. Informed consent was obtained from the patients. SPSS version 21 software was used to analyse data. Patients were followed up throughout the period of inward chemotherapy, which varied from 7-21 days depending on the chemotherapy regimen.

Results

Majority of the patients (66%) receiving induction chemotherapy were without prior medical comorbidities. Diabetes was observed in 6% and hypertension in 2% and the remaining 26% had other comorbidities like asthma, heart disease etc. None of them had chronic kidney disease.

Figure 1 summarises the main medical complications among the patients (N=50) receiving inward induction chemotherapy. Infections and electrolyte disturbances were the most frequently observed complications (74% each) followed by chemotherapy induced neutropaenia (38%).

Evidence of infections was defined as the presence of one or more of fever, elevated c-reactive protein (CRP), positive cultures or a clinically identifiable infective focus. Out of the 50 patients, 37 (74%) had evidence of infection at some point during induction chemotherapy. Among the 37 patients with evidence of infection, 23 (62.1%) had fever and 36 (97.3%) had elevated CRP levels.
Table 1 demonstrates the focus of infection among the 37 patients who had evidence of infection. Majority showed evidence of blood stream infection 10 (27%) followed by pulmonary 9 (24.3%) infections. In another significant proportion, 8 (21.6%), the focus was not identified.

In the 37 patients with evidence of infection, 10 (27%) had positive blood cultures. The majority 5 (50%) were gram negative pathogens. None of the fungal cultures were noted to be positive during the study period. This is shown in table 2. Urine culture alone was positive for gram negative organisms in 2 patients.

Table 3 shows the patterns of antibiotics used in patients with evidence of infection. The majority [30 out of 37 (81.1%)] were treated with the combination of beta-lactam or cephalosporin with antipseudomonal cover and an aminoglycoside. Addition of gram-positive cover in 13 (35.1%) and antifungal cover in 6 (16.2%) was utilised less frequently.

Detailed analysis of neutropenia during induction chemotherapy revealed that 40% had disease related neutropenia prior to initiation of chemotherapy. Chemotherapy induced neutropenia was present in 38 %. According to the absolute neutrophil count (ANC) they were categorised as mild (ANC 1-1.5, in 6%), moderate (ANC 1- 0.5, in 20%) and severe (ANC <0.5, in 12%). Mean duration from initiation of chemotherapy to lowest neutrophil count (i.e neutrophil nadir) was 10.05 days (95% CI 7.71-12.4).

Among the electrolyte disturbances, hypokalaemia (48%), hyponatraemia (48%), hypocalcaemia (44%) were the most prevalent (figure 2).

Alteration of liver transaminases and serum bilirubin levels were seen in 16 (32%) out of the 50 patients in induction chemotherapy. Among these 16 patients, 14 (87.5%) were ALL patients and only 2 (12.5%) were AML patients. No cases of acute liver failure were documented.

Bleeding was exclusively seen among AML patients.

Figure 1 - Most common medical complications among the acute leukaemia patients receiving induction chemotherapy regimen. N=50
Table 1 - Focus of infection among the patients who had evidence of infection

<table>
<thead>
<tr>
<th>Focus of Infection</th>
<th>n</th>
<th>percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteremia</td>
<td>10</td>
<td>27</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>9</td>
<td>24.3</td>
</tr>
<tr>
<td>Unidentified</td>
<td>8</td>
<td>21.6</td>
</tr>
<tr>
<td>Soft Tissue</td>
<td>5</td>
<td>13.5</td>
</tr>
<tr>
<td>GI</td>
<td>2</td>
<td>5.4</td>
</tr>
<tr>
<td>GU</td>
<td>2</td>
<td>5.4</td>
</tr>
<tr>
<td>Multiple</td>
<td>1</td>
<td>2.7</td>
</tr>
</tbody>
</table>

n=37, GI - Gastrointestinal, GU - Genitourinary

Table 2 - Microorganisms identified from blood cultures

<table>
<thead>
<tr>
<th>Organism Isolated</th>
<th>n</th>
<th>percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram Positive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coagulase Negative Staphylococcus</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Methicillin Resistant Staphylococcus aureus (MRSA)</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Enterococci</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td><strong>Gram Negative</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Not Specified</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td><strong>Mixed Gram positive and Gram Negative</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coagulase Negative Staphylococcus and Gram - Bacilli</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td><strong>Fungal</strong></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

n=10

Table 3 - Antibiotics used in patients with evidence of infection

<table>
<thead>
<tr>
<th>Antibiotic Regimen</th>
<th>n</th>
<th>percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Antibiotic</td>
<td>4</td>
<td>10.8</td>
</tr>
<tr>
<td>Beta-lactam or Cephalosporin with antipseudomonal cover + Aminoglycoside</td>
<td>30</td>
<td>81.1</td>
</tr>
<tr>
<td>Other Combinations</td>
<td>3</td>
<td>8.1</td>
</tr>
<tr>
<td>Addition of Gram + cover</td>
<td>13</td>
<td>35.1</td>
</tr>
<tr>
<td>Addition of antifungal cover</td>
<td>6</td>
<td>16.2</td>
</tr>
</tbody>
</table>

n=37
and all the reported thrombosis episodes were among ALL patients. There were no reported cases of pulmonary embolism. Bleeding events mainly comprised melaena, epistaxis or skin bruising. The two thrombotic episodes consisted of thrombosis of subclavian vein and inferior vena cava.

Discussion

This study findings highlight important medical complications of acute leukaemia patients during induction chemotherapy. Neutropaenia, neutropaenia induced sepsis and disturbances in electrolyte composition are the main complications detected. These complications are mainly related to the induction chemotherapy regimen received by the patient.

There are different types of chemotherapy regimens for the patient with acute leukaemia receiving inward treatment. The first chemotherapy regimen following diagnosis is the induction chemotherapy followed by consolidation/intensification and a separate regimen for patients with relapse. The maintenance course of chemotherapy is given on an outpatient basis at clinic level. Majority of the patients receiving induction chemotherapy developed medical complications in comparison to patients receiving other regimens. Creutzig et al has also noted the complications, in particular the infections to be more common during the induction period and that neutropaenic sepsis leading to fatal infection as the main cause of death in AML patients rather than the progression of the leukaemic process.(12)

Around 74% of patients developed infections following induction chemotherapy. Other studies carried out in the same context reported similar high rates of infections.(12,13) A study by Yang et al revealed a rate of infection of 82.2% during induction therapy in acute leukaemia.(13) Lungs were the main focus of infection in several studies.(11,13) In contrast, our study showed a higher rate of bacteremia (27%) overtaking pulmonary infections (24.3%). Inadequate facilities to properly isolate patients with neutropaenia, and poor infection control methods are the likely reasons for this observation which needs to be further evaluated. In another significant proportion, the site of infection was unclear (21.6%). This can be explained by the phenomenon of “febrile neutropaenia” defined as occurrence of fever during a period of significant neutropaenia often without an identifiable source of infection.(14) The predominance of gram-negative organisms identified from blood cultures are in keeping with the results from Yang et al(13) however the fact that none of the fungal cultures were positive must be highlighted. All the patients who received
antibiotics did so either due to presence of infections or febrile neutropaenic episodes. Antibiotic prophylaxis is not used during induction chemotherapy. The decision to add gram positive cover is based on positive cultures, or clinical suspicion. Antifungal treatment is added for persistent or recurrent fevers with neutropaenia. This practice is in keeping with the 2016 National Guideline on empirical and prophylactic use of antibiotics.(15)

Neutropaenia following induction chemotherapy is a well-documented complication. In this study the reported mean duration of induction to neutrophil nadir level of 10.05 days (95% CI 7.71-12.4) is in keeping with the study by Han et al(16) where the duration was less than or equal to ten days. However, this study did not assess the correlation between timing of neutropaenia and occurrence of infection.

The literature shows numerous electrolyte and acid-base disturbances in acute leukaemia patients.(14,15) Filippatos et al found an array of electrolyte abnormalities in the clinical setting of acute leukaemia, attributable to the disease process itself and/or to the treatment strategies.(17) Multitude of electrolyte disturbances were the focus of research by Sean O'Regan et al where pathogenesis of which was again based on the leukemic process and chemotherapy protocols.(18) The disturbances were particularly seen in relation to potassium, sodium, calcium, phosphorus and magnesium homeostasis as well as in the acid base status. In this study, hypokalaemia was most frequently observed along with hyponatraemia, hypophosphataemia, hypocalcaemia, hypomagnesaemia and acid base disturbances at lesser frequencies. Leukaemia and lysozyme induced tubular damage, cytotoxic drugs and antibiotics, syndrome of inappropriate antidiuretic hormone secretion (SIADH), hypoalbuminaemia and malnutrition are among the numerous underlying pathogenic mechanisms. This study population exhibited a high frequency of hypokalaemia in keeping with other studies. There was also a higher incidence of hyponatraemia and hypocalcaemia. Acid base status was not routinely measured unless a disturbance was clinically suspected, hence the study failed to characterise such details.

Liver dysfunction in acute leukaemia is multifactorial. Leukaemic infiltration, drug induced liver failure (antifungals and chemotherapy) and bacterial and fungal infections are among the leading causes. The finding of altered liver functions at a high rate in ALL patients in our study is supported by Thiele et al(19) where liver infiltration was seen in >95% of ALL patients compared to only 75% in AML. The use of methotrexate in the treatment regimen of ALL is another contributory factor which was observed during the study which can explain the higher incidence in ALL patients.

Glucocorticoids are routinely used as a part of acute leukaemia treatment regimens and the finding of a significant proportion (28%) of glucocorticoid induced hyperglycaemia is well documented. According to Harris et al the reported frequency is much higher (77.8%).(20)

The thrombotic events were much less (4%) compared with other studies(21) where the rate has been around 43% in adult ALL patients. Similarly, tumour lysis syndrome (TLS) was observed less frequently. Wasim et al(22) documented a 14% incidence with a similar sample size. Further evaluation is needed in this regard to identify the contributory factors for the above observations.

Conclusion

Patients with acute leukaemia encounter a multitude of disease and treatment related medical complications during induction chemotherapy. Infection is the most common complication with higher rates of bacteraemia and gram-negative sepsis observed in this study. Higher infection rate is likely to be a result of treatment related neutropaenia. However, further focused studies on neutropaenic sepsis during induction chemotherapy are recommended to evaluate this further. Assessment of demographic characteristics and comparison of age-related mortality outcomes in the induction chemotherapy group is also recommended for future studies. Clinical vigilance, strict and improved infection control strategies are necessary to improve the outcome of these patients.

Declarations

Author contributions

UMW conceived the original study idea and contributed to research designing. UMW contributed to literature review and collected information. UMW reviewed the collected data for analysis, contributed to the data analysis and drafted the manuscript. PM guided as senior author in data analysis, preparing the manuscript and corrected the manuscript. All the authors revised and approved the final manuscript.

Conflicts of Interests

There are no conflicts of interest. All the authors declare that they have no competing interests.
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