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Spectrum of Complications in Patients of Acute Leukemia- A Regional Study from Pgims, Rohtak

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Objectives: This study was conducted to determine the spectrum of complications in patients of acute leukemia.
Materials and Methods: The present study was conducted at Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak and data was collected from patients who presented with confirmed diagnosis of acute leukemia over a period of one year. Patients satisfying inclusion criteria were monitored for development of any complications. Baseline parameters were recorded on admission and then every 7 days interval till remission. Data were analyzed by statistical package for social sciences (SPSS) version16.0.
Results: The data was collected from 35 patients. Most common presenting complaint was fever in 88.6% of patients. AML was diagnosed in 16 patients (45.7%) and rest had ALL (54.2%). In our study about 25% of patients had bleeding symptoms at presentations and almost 100% of patients developed bleeding complications during induction therapy. Most common sites of bleeding in our study was cutaneous bleed (100%) followed by gum bleed (26.4%). Life threatening bleeding in form of intracranial bleed was noted in 4 patients of which 3 patients died of bleeding complications amounting to 27.2%. Among 34 patients twenty two patients (64.7%) had neutropenia. Infectious

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complications were the second most common complication noted in our study. Most common infectious complication was pneumonia seen in 25.9% of febrile patients followed by blood stream infection (18.5%). An infectious etiology was documented in 33.3% of patients with frequency of gram negative and gram positive infections was 88.9% and 11.1% respectively. *Pseudomonas sp* was the most commonly (44.4%) isolated micro-organism. Among patients with pneumonia fungal etiology was identified in 71.4% of patients making IFIs one of the most frequent infectious complications in acute leukemia patients. In our study 18.7 % of patients developed TLS, all patients had Laboratory TLS and only one patient had Clinical TLS. One patient developed L-asparaginase induced acute pancreatitis and one patient developed differentiation syndrome.

Conclusion: Acute leukemia is a devastating disease with wide spectrum of complications not only related to disease part but also because of its treatment

Keywords: Acute leukemia; acute myeloid leukemia; acute lymphoblastic leukemia; complications; febrile neutropenia; tumor lysis syndrome.

1. INTRODUCTION

Acute leukemia is a condition when a hematopoietic stem cell undergoes malignant transformation into a primitive, undifferentiated cell and developed abnormal longevity**.** These lymphoid cells (acute lymphoblastic leukemia [ALL]) or myeloid cells (acute myeloid leukemia [AML]) proliferate, replacing normal marrow tissue and hematopoietic cells and causing anemia, thrombocytopenia, and granulocytopenia. Because they are blood borne, they can infiltrate various organs and tissues, including the liver, spleen, lymph nodes, central nervous system, kidneys and gonads.

1.1 Complication of Acute Leukemia

Complications of acute leukemia are related to anemia, thrombocytopenia, leukocytosis, leukopenia and leukocyte dysfunction.

1.1.1 Risk of bleeding and thrombosis

Patients with leukemia are at increased risk of bleeding due to thrombocytopenia and platelets transfusions remains the cornerstone in treatment and prevention of bleeding. Vast majority of patients with malignant hematological disease are receiving blood products so complications secondary to transfusions are also likely.

Acute Promyelocytic leukemia also responsible for disseminated intravascular coagulation and microvascular thrombosis although it can occur in other forms of acute leukemia especially monocytic leukemia. The leukemic promyelocytes produce a procoagulant tissue factor or a plasminogen activator which ultimately contribute to hypofibrinogenemia and hemorrhage.

1.1.2 Infections

Fever during cytotoxic therapy when neutrophil counts are extremely low is nearly always a sign of infection. Febrile neutropenia defined as an oral temperature of >38.30 C (101.40 F) or two consecutive reading of >38.00 C (1010 F) for 2 hours with an Absolute Neutrophil count < 500/µL or expected to fall below 500/µL over the next 48 hours.

Intense chemotherapy with cytotoxic drugs usually results in myelosuppression and a resultant high risk of neutropenia (absolute neutrophil count 0.5×10^9/L), which has a detrimental effect on the integrity of the normal human skin and mucosa, which are at great risk of invasive infection due to the colonizing bacteria, virus and fungi as neutropenia impairs the phagocytic activity of the neutrophils [1].

Acute leukemia patients receiving intensive chemotherapy are at great risk of invasive fungal infections (IFIs).

1.2 Metabolic Complication

Tumor lysis syndrome (TLS) is characterized by metabolic abnormalities including hyperuricemia, hyperphosphatemia, hyperkalemia and hypocalcaemia. These metabolic complications leads to clinical toxicities including renal insufficiency, seizures, neurological complications, cardiac arrhythmias and potentially sudden death. These metabolic complication occurs when there is release of intracellular metabolites such as nucleic acids, proteins, phosphorus and potassium from lysed

malignant cells. TLS classified as laboratory TLS (L-TLS) or clinical TLS (C-TLS).

Hyperglycemia develops in 10% percent of patient during induction therapy with prednisolone, vincristine and L-asparaginase and may require short term insulin therapy.

1.3 Gastrointestinal Complication

The etiology of most leukemic gastrointestinal complication is believed to be three fold:

1. Primary invasion by leukemic cells.
2. Altered immune state with profound neutropenia from leukemia itself and from antileukemic drugs.
3. Direct and Indirect gastrointestinal toxic effect of chemotherapy.

Profound nausea and vomiting are common problems associated with antileukemic agents and peptic ulcer disease is not rare. In addition Pancreatitis, Adynamic ileus, Hepatitis and Hemorrhagic colitis have been associated with various antileukemic drugs.

1.3.1 Hepatitis

Persistent elevation of serum transaminases occur after initiation of chemotherapy in patients of acute leukemia, is usually due to blood transfusion associated hepatitis B and C virus infection or reactivation of infection.

1.3.2 Neutropenic enterocolitis (Typhlitis)

Chemotherapy may damage the gastrointestinal tract by destroying the rapidly dividing mucosal cells which when coupled with neutropenia allows bacteria invasion of the Bowel wall. The invasive infection leads to necrosis of various layers of bowel wall. The process has a predilection for the Terminal ileum and caecum but any segment of the Bowel can be involved [2,3].

1.4 Neurological Complication

CNS involvement is present at diagnosis in less than 5% of children with ALL however, 50% to 75% will develop CNS disease in the absence of adequate CNS prophylaxis [4]. The routine use of CNS prophylaxis incorporating intrathecal (IT) chemotherapy and/or cranial irradiation has reduced this incidence to less than 10% [5]. Similar results have also been observed in the adult population.

Adverse Effects of ATRA (All Trans Retinoic acid) - Dryness of skin and lips, Skin exfoliation, Nausea, headache, Arthralgia, bone pain, Rapid increase in total blood leukocyte count to as high as 80,000/microliter in first few weeks of therapy referred as retinoic acid syndrome, is a potential cause of early death during therapy. The syndrome consist of fever, weight gain, dependent edema, pleural or pericardial effusion and bouts of hypertension. Respiratory distress is a key feature and in fatal cases pulmonary interstitial infiltration with maturing granulocyte is prominent.

2. MATERIALS AND METHODS

2.1 Study Design

This study was a longitudinal prospective observational study. This study was undertaken in the Post Graduate Department of General Medicine and in Department of Clinical Hematology of Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak.

Chart 1. Cairo–bishop definition of laboratory tumor lysis syndrome (L-TLS)

Parameters	Value	Changes from baseline
Uric acid level	>8mg/dl	25% increase
Potassium level	>6mEq/L	25% increase
Phosphate level	>4.5mg/dl	25% increase
Calcium level	<7mg/dl	25% decrease

Two or more laboratory changes within period from 3 days before to 7 days after cytotoxic therapy are required to establish the diagnosis of TLS

Chart 2. Cairo-Bishop definition of clinical tumor lysis syndrome (C-TLS)

Creatinine ≥ 1.5 times the upper limit of normal
Cardiac arrhythmia/ sudden death
Seizure
CTLS is LTLS + any one of the above

2.2 Study Population

This study was done on patients admitted at PGIMS, Rohtak with a confirmed diagnosis of acute leukemia irrespective of gender, race and social background.

2.2.1 Inclusion criteria

1. Confirmed cases of acute leukemia (by bone marrow aspiration and biopsy, Immunophenotyping) - acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), from age of 15 years or older.
2. Willingness to participate in the study after informed written consent.

2.2.2 Exclusion criteria

1. Patients less than 15 years of age.
2. Patients with comorbid conditions such as diabetes, hypertension, chronic renal failure or cardiac diseases.
3. Unwillingness to participate in the study.

2.3 Study Methodology

1. During twelve months study period all patients with acute leukemia were included in the study. After obtaining the informed consent, clinical history was taken and physical examination was performed. All Routine Laboratory investigations were done including Complete hemogram and peripheral smear, Biochemical tests -Renal function test, Liver function test, Electrolytes, Coagulation studies, Viral serologies (HIV HBsAg Anti HCV).
2. Specific investigations according to complications

2.4 Treatment Protocol

2.4.1 Acute lymphoblastic leukemia

Adult ALL Protocol – for Patients > 25 years Pre-induction: 1st week

1. Dexamethasone 5mg/m2 on day 1 & 2 , IV/PO
2. Prednisolone 60mg/m2 PO on day 3-7.

Induction

1. Daunorubicine 40mg/m2 IV weekly × 4
2. Vincristine 1.4 mg/m2 , max 2mg IV weekly x 4
3. L- Asparaginase 60000unit/ m2, total doses divided over 10 days IV/ SC on day 22-31.
4. Prednisolone 60mg/m2 daily PO for 4 weeks and then taper over 10 days.

BFM Augmented protocol - for Patients aged ≤ 25years

Induction

1. Daunorubicine 25mg/m2 IV weekly × 4
2. Vincristine 1.4 mg/m2, max 2mg IV weekly x 4
3. L- Asparaginase 6000unit/ m2 per day , IV/SC on day 3,5,7,10,12,14,17,19,21
4. Prednisolone 60mg/m2 daily PO for 4 weeks and then taper over 10 days.

Bone marrow to assess the remission status on day 32±3

2.4.2 Acute myeloid leukemia

1. Patients aged < 60 years and candidate for Intensive remission induction- Received '3+7' (Dauno + Ara-C) regimen. The '3+7' Dauno + Ara-C therapy comprised of Daunorubicin (60 mg/m2/day) on days one through three and Cytarabine (200 mg/m2/day) on days one through seven.
   - Daunorubicin 60mg/m2 in 100 ml NS over 30min on day 1, 2 ,3
   - Cytarabine 100mg/m2 in 500 ml NS over 3hrs twice a day on day 1 – 7.
2. For Acute Promyelocytic leukemia /AML M3 --ATRA based chemotherapy was given
3. Patients aged > 60 years and not a candidate for Intensive remission induction – Received low intensity therapy (Azacitidine or Decitabine)

2.5 Statistical Analysis

At the end of study data was collected, compiled and analyzed using appropriate statistical tests and prevalence of Tumor Lysis Syndrome was calculated. Data were analyzed by statistical package for social sciences (SPSS) version 16.0.

3. RESULTS

The present study was conducted in Pandit Bhagwat Dayal Post Graduate Institute of

Medical sciences, Rohtak and data was collected from thirty five patients out of which one patient lost to follow up. The age range of the study population was 15-65 years with Mean age of 34 ± 15.5 years, about one third of the study populations was in range of 15-25 years and only 14.2% of population was above 50 years of age. Almost equal proportion of male and female was noted with male patients 48.6% and female patients 51.4%.

As illustrated in Table 1, most common presenting complaints of patients with acute leukemia in our study is fever amounting to 88.6%. Nearly 68.6% of patients had easy fatigability, 28.6% of patients had cough, 25.7% of patients had bleeding symptoms and only one patients had headache at presentation. Mean duration of fever before presentation was 26.7 ± 40.3 days.

Among total 35 patients acute myeloid leukemia was diagnosed in 16 patients (45.7%) and rest had acute lymphoblastic leukemia (54.2%). Out of total nineteen ALL patients, B-ALL was diagnosed in 15 patients (42.9%) and 4 patients (11.4%) had T-ALL as diagnosis. Among B-ALL patients only two patients were BCR-ABL1 positive.

Chart 3. Complications during study period

Parameters	At the time of admission/ Induction	At every 7 days follow up till remission
❖ Metabolic complication		
➢ Tumor lysis syndrome		
• Sr. Uric acid		
• Sr. Potassium		
• Sr. Calcium		
• Sr. Phosphate		
➢ Hyperglycemia (steroid Induced)		
❖ Fever if Present		
➢ Site of infection		
• Blood culture and sensitivity		
• Chest X-ray PA		
• USG Whole abdomen		
• CT chest / abdomen (As per requirement)		
❖ Bleeding		
➢ Anatomical site of bleeding		
• Complete blood count/ platelet count		
• PT/PTTK/INR		
• Sr. Fibrinogen		
• D-dimer/FDP		
❖ CNS complication		
➢ Cranial nerve palsy		
➢ Others		
❖ Miscellaneous		
➢ Skin infections		
• Fungal infection- Tenia		
• Chancre		
• Scabies		
• Herpes zoster		
• Others		

Table 1. Baseline characteristics of the study population

Parameters	N(%)
Age ,years, mean±SD	34 ± 15.5
Sex, n ,M/F	17/18
Presenting Complaints	
• Easy fatigability	24 (68.6%)
• Duration of Fatigability, days, mean±SD	53.8 ± 69.7
• Bleeding symptoms	9(25.7%)
• Duration of bleeding symptoms, days, mean±SD	6.8 ± 7.8
• Fever	31(88.6%)
• Duration of fever, days, mean±SD	26.7 ± 40.3
• Cough	10(28.6%)
• Headache	1(2.9%)
Physical examinations	
• Pallor	34(100%)
• Petechial spots , ecchymosis	11(31.4%)
• Bony tenderness	16(45.7%)
• Raised temperature	27(77.1%)
• Gum hypertrophy	2(5.7%
• Skin infiltration	2(5.7%)
• Poor dentition	0
• Hepatomegaly	12(34.3%)
• Splenomegaly	11(31.4%)
• Lymphadenopathy	12(34.3%)

Physical examination findings suggestive of pallor in almost all patients. Sternal tenderness was present in 45.7% of patients. Hepatomegaly was noted in 34.3% of patients, of which 83.3 % of patients had ALL as diagnosis. Splenomegaly was noted in 31.4% of patients, of which 81.8 % of patients had ALL as diagnosis. Lymphadenopathy was seen in 34.3% of patients, of which almost 90% had ALL as diagnosis. Above data indicates that organomegaly at presentation is more common in ALL as compared to AML as only 16-18% of AML patients had Hepatosplenomegaly at presentation. Almost 50% of ALL patients had hepatosplenomegaly at presentation.

As depicted in Table 3 , about 60% of patients received Hypomethylating agent (Decitabine, Azacitidine) as chemotherapy whereas 33.3% of AML patients received standard high intensive '3+7' chemotherapy. One patients had acute promyelocytic leukemia who received ATRA based chemotherapy in form of ATRA+ Daunorubicin.

Among ALL patients (Table-4) nine patients were given chemotherapy according to Adult ALL Protocol amounting to 52.9% whereas eight patients (47.1%) received chemotherapy according to Augmented BFM protocol. Two patients with B cell-ALL diagnosis was BCR-ABL1 positive was given Imatinib along with standard chemotherapy.

3.1 Complications

3.1.1 Bleeding complications

In our study, 25.7% of patients presented with bleeding complications with mean duration of bleeding symptoms was 6.89 ± 7.52 days. On induction chemotherapy bleeding complications developed in almost all patients. Most common bleeding symptoms were petechial spots and purpura which was noted in almost all patients. Other bleeding complications observed were Gum bleeding in 26.4%, Epistaxis in 8.8%, Per vaginal bleed in 11.7%, Per rectal bleed and Hematuria noted in 2.9% of patients.

Life threatening bleeding such as Intracranial bleed noted in 4 patients amounting to 11.7% and one patient developed Retinal hemorrhages with blurring of vision. In our study, all patients received multiples Packed cell volume (PCV) and Platelet rich plasma (PRP) transfusion.

Table 2. Baseline parameters in Study population

Parameters	AML (n=16)	ALL (n=19)	Total (n=35)
Hemoglobin level, mean±SD	7.0 ± 1.39	8.0 ± 2.11	7.5 ± 1.87
Hemoglobin			
• ≥8gm/dl	4(25%)	8(42%)	12(34%)
• <8gm/dl	12(75%)	11(58%)	23(66%)
Total Leukocyte count			
• ≥50,000/µl	3(19%)	7(37%)	10(28.5%)
• <50,000/µl	13(81%)	12(63%)	25(71.5%)
Platelet count			
• >20,000/µl	8(50%)	12(63%)	20(57%)
• ≤20,000/ µl	8(50%)	7(37%)	15(43%)
Organomegaly			
• Hepatomegaly	2(12.5%)	10(52.6%)	12(34.3%)
• Splenomegaly	2(12.5%)	9(47.3%)	11(31.4%)
• Lymphadenopathy	1(6.2)	11(57.8%)	12(34.3%)

Table 3. Chemotherapy given in AML patients

Chemotherapy	AML patients N=16
'3+7' Regimen	5(33.3%)
ATRA+ Daunorubicin	1(6.7%)
Decitabine	8(53.3%)
Azacitidine	1(6.7%)

One patients died before start of chemotherapy due to complications

Table 4. Chemotherapy given in ALL patients

Chemotherapy	ALL patients N=19
Adult ALL Protocol	9(52.9%)
Augmented BFM Protocol	8(47.1%)

One patients died before start of chemotherapy due to complications and One patient lost to Follow up

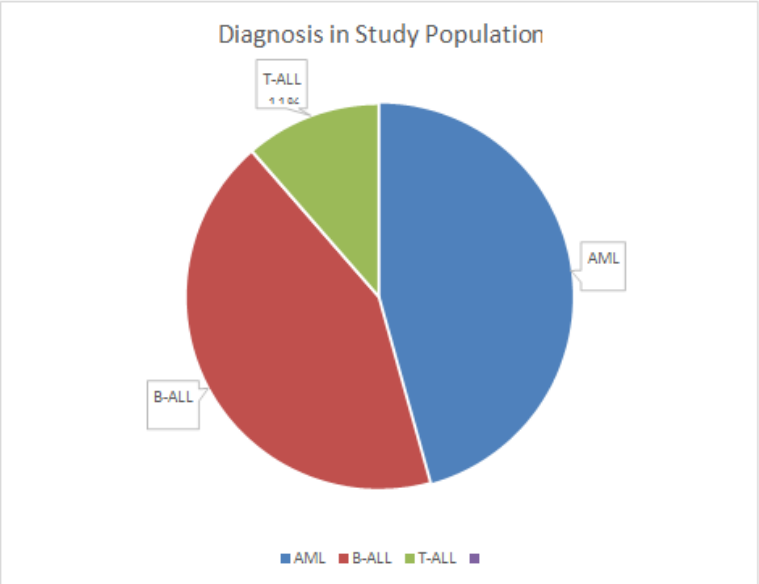

Fig. 1. Diagnosis in study population

3.1.2 Metabolic complications

In this study six patients developed Tumor lysis syndrome which approximate to 18.7% and all patients had laboratory TLS, only one patient developed Clinical TLS. Among AML patients only one patient developed TLS (6.6%) and in ALL patients five patients developed TLS amounting to 26.3%.

Only one patient of ALL developed steroid induced hyperglycemia which was well controlled on Insulin therapy.

3.1.3 Infectious complications

Among 34 patients twenty two patients (64.7%) had neutropenia, while twelve patients did not developed neutropenia. Twenty patients with neutropenia had evidences of infection and seven non-neutropenic patients also had evidences of infections.

Among 27 patients an infectious etiology was documented in 13 patients (48.1%). Blood stream infection was documented in 5 patients (18.5%) with blood culture positive. 7 patients was diagnosed as pneumonia on clinical basis and on chest X-ray finding subsequently sputum culture was positive in 3 patient and fungal etiology was identified in 5 patients on chest CT. One patient had Neutropenic enterocolitis on clinical basis and USG abdomen findings. One had UTI with urine culture positive.

Most common micro-organism encountered in febrile patients was fungal followed by Pseudomonas sp. In this study incidence of gram negative bacterial infection was more common than gram positive infections.

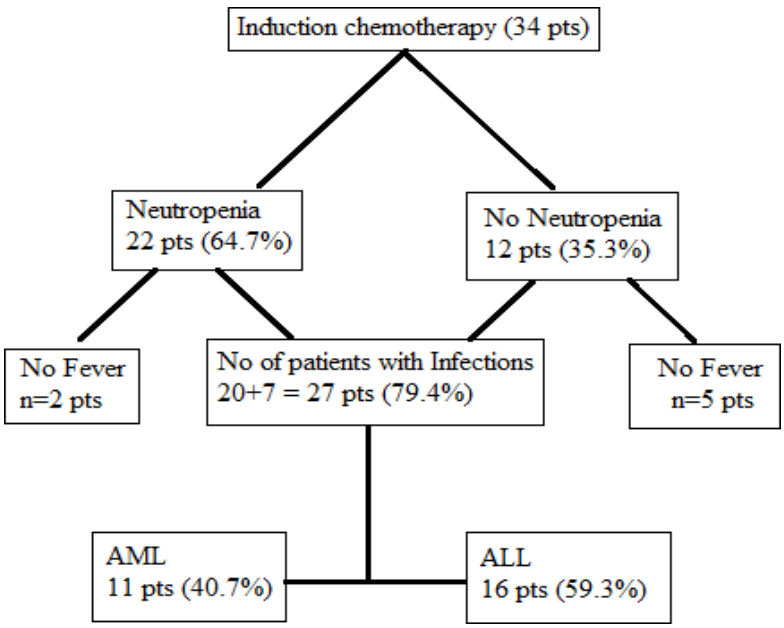

Fig. 2. Flowchart of Infectious complications

Table 5. Sites of infection in febrile patients

Sites of Infections	N (%) Total febrile patient=27
Pneumonia	7 (25.9)
Blood stream Infection	5(18.5)
UTI	1(3.7)
Necrotizing Enterocolitis	1(3.7)
Cellulitis	4(14.8)
Perianal infection	5(18.5)
Not known	4(14.8%)
Other minor Skin infections Herpes zoster	1
Intertrigo	1
Tenia corporis	3

Table 6. Causative agent associated with infections N (%) N=9

Blood culture	**Gram Negative microorganism**	
	• *Pseudomonas sp*	2
	• *Acinetobacter baumannii*	1
	• *Klebsiella sp*	2
Urine culture	• *Escherichia coli*	1
Sputum culture	Gram Positive microorganism	
	• *Staphylococcus sp*	1
	Gram negative microorganism	
	• *Pseudomonas sp*	2

3.1.4 Miscellaneous complications

As depicted in Table-7, rare complication was rare in our study also. Only three patients had leukemic pulmonary infiltrates diagnosed on Chest CT findings. One patient developed malignant pleural effusion. Two patients developed life threatening rare complications, one patient developed L-Asparaginase induced acute pancreatitis with raised amylase and lipase levels and second one developed ATRA syndrome.

Table 7. Showing Miscellaneous/Rare complication

Miscellaneous Complications	**N**
Leukemic pulmonary infiltrates	3
Malignant Pleural Effusion	1
Chloromas	1
L-Asparaginase Induced Acute pancreatitis	1
ATRA Syndrome	1

4. DISCUSSION

In this study total 35 patients were included with almost equal proportion of Males and Females. Among total 35 patients acute myeloid leukemia was diagnosed in 16 patients (45.7%) and rest had acute lymphoblastic leukemia (54.2%). The complete Remission rate in AML patients was 50% while in ALL it was 72.7%.

4.1 Bleeding Complications

This study demonstrated that bleeding is most common complication encountered in acute leukemia patients requiring multiple transfusion of PCV and PRP. Thrombocytopenia is an important factor in bleeding complications which occurs due to bone marrow invasions by leukemic cells and/or due to myelosuppressive effects of chemotherapy but there are numbers of other reasons for bleeding in acute leukemia such as acquired abnormalities in platelet function, circulating anticoagulants, endothelial injury and hepatic dysfunctions. About 40-70 % of patients with acute leukemia presents with minor bleeding such as petechial spots, purpura, ecchymosis and other less common sites of bleedings.[6] In our study about 25% of patients had bleeding symptoms at presentations and almost 100% of patients developed bleeding complications during induction therapy. Most common sites of bleeding in our study was cutaneous bleed (100%) followed by gum bleed (26.4%). Life threatening bleeding in form of intracranial bleed was noted in 4 patients of which 3 patients died of bleeding complications amounting to 27.2%. This data is consistent with the previous reported mortality in acute leukemia where the hemorrhage alone or in combination was responsible for death in 24% of patients. [7] In our study prophylactic platelet transfusion was done in patients having absolute platelet count less than 10,000/µl and transfusion with higher platelet level was done in patients with signs of bleedings, high grade of fever and rapid fall of platelet count. In our study almost all patients received prophylactic platelet transfusion.

4.2 Metabolic Complications

In our study 18.7% of patients developed TLS, all patients had Laboratory TLS and only one patient had Clinical TLS who died due to sudden cardiac death. In our study the reported incidence of TLS was 6.7% and 29.4% in AML and ALL patients respectively. Our study showing a lower incidence of TLS as compared to previous studies. In a previous multicenter cohort study of 153 high risk patients with Hematological malignancies the reported incidence of TLS in acute leukemia was 33.7% and the reported incidence of TLS in ALL and AML patients was 50% and 31.2% respectively.[8]. Ahsan Ejaz et al. also reported

32% incidence of TLS in acute myeloid leukemia (AML) patients using retrospective analysis of 183 patients.[9].

In our study incidence of TLS was higher in ALL as compared to AML patients (29.4% vs 6.7%). Mato et al studied 194 patients receiving induction therapy for AML and found a TLS incidence of 9.8% [10] whereas in our study the incidence of TLS in patients with AML was 6.7%. TLS prophylaxis is recommended to all patients with hematological malignancies as prevention is the best treatment for TLS. In our study all patients received adequate hydration with tablet Allopurinol before start of induction chemotherapy.

4.3 Infectious Complications

Infectious complications were the second most common complication noted in our study. In our study 79.4% of patients developed febrile episodes of which 40.7% case were of AML and 59.3% of ALL. Febrile neutropenia was documented in 62.9% of patients. Microbiologically documented infection was noted in 33.3% while clinically documented infection was noted in 66.7% of patients. Most common infectious complication was pneumonia seen in 25.9% of febrile patients followed by blood stream infection (18.5%). No source of infection was documented in 14.8% of patients. An infectious etiology was documented in 33.3% of patients with frequency of gram negative and gram positive infections was 88.9% and 11.1% respectively. *Pseudomonas sp* was the most commonly (44.4%) isolated micro-organism. In previous documented studies there were equal predominance of gram positive and gram negative micro-organism. Study from Turkey reported gram negative micro-organisms as 58.4 % and gram positive as 36.1 % among the documented cultures in febrile neutropenia.[11]. The previous Indian data showed predominantly higher frequency of infections with gram negative micro-organisms 75.8 % (*Klebsiella pneumonae* the most frequent) while gram positive micro-organisms was 24 %.[12].

Our finding is surprising and not consistent with literature of hematological malignancies as well as solid cancers in which gram positive infections dominate over gram negative infections. This gram positive pattern can be attributed to widespread use of indwelling intravenous catheter and use of prophylactic agents targeting Gram negative organism. In our study this predominance of gram negative infections might be because of less use of indwelling intravenous catheter as only few patients was inserted with Central venous line and PICC line. However the gram negative infections are frequently reported from the developing world.[13].

European data from some centers shows the re-emergence of gram negative bacilli as dominant pathogen in the etiology of febrile neutropenia.[14][15]. In developing countries, Gram-negative organisms including *Klebsiella* species, *E. coli* and *Pseudomonas aeruginosa*, predominate with the pattern of infection in patients with acute leukemia. These findings are consistent with the findings of the present study.

In this study the incidence of probable Invasive fungal infections reported in 18.5% of febrile patients on the basis of CT Chest findings. The reported incidence of IFIs in our study is slightly higher than the previous reported 12% incidence rate in acute leukemia patients treated with intensive cytotoxic therapy.[16]. Among patients with pneumonia fungal etiology was identified in 71.4% of patients making IFIs one of the most frequent infectious complications in acute leukemia patients.

Other infectious complications noted in this study was cellulitis at cannula site in 14.8% of patients, perianal infections in 18.5%, minor skin infections such as Herpes zoster in one patient, cutaneous fungal infections including Intertrigo in one and Tenia corporis in three patients.

4.4 Miscellaneous/Rare complications

In rare complications leukemic pulmonary infiltration was seen in 8.8% of patients on CT chest findings and malignant pleural effusion noted in 2.9% of patients. As acute leukemia is a disease of circulating blood cells, it is not surprising to find leukemic cell infiltrations in various organs. The pulmonary leukemic cells infiltration may be perivascular, peribronchial, alveolar or sub pleural. The level of circulating leukemic cells in the peripheral blood correlate with the degree of pulmonary leukemic infiltrates. Leukostasis in pulmonary vessels has been observed, usually in patients with leukocyte counts of greater than 100,000/cu mm. [17]. In our study three patients (8.8%) were having leukemic Pulmonary infiltrates with minor respiratory complaints, all were having ALL as primary diagnosis and circulating blast was more than 60% (two patients having >90%) with TLC >

50,000/µL (one patients with >1.5 lac/ µL). It is important to recognize that leukemic pulmonary infiltration is rare and needs to confirm by biopsy whereas most respiratory sign and symptoms in acute leukemia patients are due to infection that needs to be rule out first.

L-asparaginase is a wonderful medication in the treatment of ALL, increases the overall survival but it is also associated with potential side effects such as Anaphylaxis, Pancreatitis, liver dysfunctions, clotting defects, hyperglycemia, hyperlipidemia and CNS dysfunctions.[18]. In some case L-asparaginase induced acute pancreatitis can be life threatening, on suspicions all chemotherapy must be discontinued. There is no relationship of dose and duration of L-asparaginase exposure for development of acute pancreatitis. The incidence of L asparaginase induced pancreatitis is estimated as 3-8% [19][20]. In our study total 17 patients of ALL received L-asparaginase chemotherapy and only one patient developed acute pancreatitis amounting to 5.9%. The symptoms of acute pancreatitis developed on day 24 of chemotherapy after receiving 3rd dose of L-asparaginase amounting to total dose of 30000IU. Patient developed typical complaints consistent with acute pancreatitis such as abdominal pain more localized to upper abdomen with nausea, vomiting and obstipation. Biliary disease was excluded as the cause of acute pancreatitis by normal level of Bilirubin, Alkaline phosphatase and normal GB and CBD on USG. All chemotherapy withheld immediately and patient was managed conservatively but on subsequent days condition of the patients deteriorated with hypotension, altered sensorium with features of ARDS and patient expired on day 27 of chemotherapy. Pancreatitis is one of the most severe complication of L-asparaginase therapy. Exact mechanism of L-asp induced pancreatitis has not been established because of use of other chemotherapeutic agents during treatment. There is no well-established prophylaxis for L-asp induced pancreatitis so patients who are receiving L-asp therapy should be kept under strong observation especially in early part of chemotherapy.

We had one patient of Acute promyelocytic leukemia, who was treated with ATRA based chemotherapy including daunorubicine. Patient developed ATRA syndrome (Differentiation syndrome) on day 7 of chemotherapy. Patient started complaining of high grade fever with Shortness of breath, CT chest was showing extensive interstitial and intraalveolar pulmonary infiltrates. Subsequently ATRA was withheld and patient was started on Injection Dexamethasone 10mg twice daily. Patient improved on dexamethasone therapy. ATRA was reintroduced with close observation and patient completed induction with ATRA with no further side effects.

Differentiation syndrome is a life threatening complication in patients with APL undergoing induction therapy with ATRA or ATO. It is characterized by Fever not attributable to infections, weight gain, dyspnea, hypotension, and ARF.

ATRA triggers the APL cells to differentiate into mature granulocytes and promotes tissue infiltration. There is also other factors that contribute to DS including systemic inflammatory response associated with increase cytokine expression, endothelial damage with capillary leak syndrome and occlusion of microcirculation. Inflammatory vasoactive cytokines that have been implicated in DS includes IL-1, IL-6, IL-8, TNF-α, and CCL2. [21][22]. Regarding incidence of DS most studies reported that approximately 25% of patients with APL receiving ATRA as induction develop DS. [23]. As we had only one patient of APL who developed DS comment on incidence is not possible. As far as treatment is concerned it consist of high suspicion with prompt recognition of symptoms and treatment with systemic corticosteroids by Intravenous route for few days till clinical resolution.

5. CONCLUSIONS

Acute leukemia is a devastating disease with wide spectrum of complications not only related to disease part but also because of its treatment. The most common complication in acute leukemia is hemorrhage which can be mild such as Petechial spots, ecchymosis and purpura or may be life threatening bleed such as ICH. In this study hemorrhage was the most common complication. Almost all patients developed bleeding complication, most common site of bleeding was cutaneous bleed followed by gum bleed. Life threatening bleed with ICH was noted in four patient leading to death in three patients.

Second most common complication encountered was infections. Patients with acute leukemia are highly vulnerable to infectious diseases due to factors associated with the disease itself, factors attributed to treatment and specific individual risk factors in each patient. The etiology is usually

unknown in infectious complications, although adequate patient evaluation and sampling have diagnostic, prognostic and treatment-related consequences. Although infections was the second most common complication in this study but was responsible for most mortality (54.5%). Pneumonia was the most common infectious complication noted in this study. Fungal etiology was documented in around 70% of pneumonia cases on Chest CT finding. Blood stream infection was documented in 18.5% of febrile patients. In this study incidence of gram negative bacterial infection was more common than gram positive infections. *Pseudomonas sp* was the most commonly (44.4%) isolated micro-organism. Other infectious complication seen were cellulitis, Perianal infections, cutaneous skin infections such as Intertrigo and Tenia. Neutropenic enterocolitis was noted in one patients who recovered on conservative treatment.

Tumor lysis syndrome (TLS) is important complications associated with hematological malignancies leading to increased morbidity and mortality. In our study 18.7 % of patients developed TLS, all patients had Laboratory TLS and only one patient had Clinical TLS who died due to sudden cardiac death. In our study incidence of TLS was higher in ALL as compared to AML patients (29.4% vs 6.7%). Our study showing a lower incidence of TLS as compared to previous studies. In our study all patients received adequate hydration with tablet Allopurinol before start of induction chemotherapy.

In rare complications leukemic pulmonary infiltration was seen in 8.8% of patients on CT chest findings and malignant pleural effusion noted in 2.9% of patients. L-asp induced pancreatitis was seen in only one patient who died due to its complications. Differentiation syndrome is a life threatening complication in patients with APL undergoing induction therapy with ATRA or ATO. We had one patient of Acute promyelocytic leukemia, who was treated with ATRA based chemotherapy including daunorubicine and developed ATRA syndrome who recovered on IV dexamethasone therapy.

CONSENT

The authors certify that they have obtained all appropriate patient consent forms. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity.

ETHICS APPROVAL

Ethical clearance was taken for this study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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