

Original Research Article

Incidence of neutropenic fever and sepsis in patients receiving induction chemotherapy in acute leukemia

Prasoon Sebastian, Abdul Majeed Kuruvadangal, Hitha Babu*

Department of Internal Medicine, Government Medical College Kozhikode, Kozhikode, Kerala, India

Received: 13 October 2021

Accepted: 28 October 2021

*Correspondence:

Dr. Hitha Babu,

E-mail: b.hitha@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Acute leukemias are treated with intensive chemotherapy protocols which are associated with increased risk of infections. The objective of this study was to determine the incidence of febrile neutropenia and sepsis in acute leukemia patients during induction chemotherapy.

Methods: In this prospective study we analysed the data of febrile neutropenia of forty-four patients of acute leukemia treated with intensive chemotherapy protocols. Study was conducted in hemato-oncology unit of Government Medical College, Kozhikode from January 2018 to December 2018. Events of the first month of induction were assessed, data entered in Microsoft excel and analysed with SPSS software.

Results: Febrile neutropenia developed in all patients with AML induction therapy and 21.4% patients with ALL induction therapy. Causative organism was identified in 41.6% of febrile neutropenia episodes. Major focus of infection was lower respiratory tract followed by gastrointestinal tract. Fungal infection was identified in 6.8% cases. Mortality in AML induction was 31% and that of ALL induction was 3.57%. Infection was the most common cause of mortality. No clinical or laboratory parameters were found significant to predict outcome during induction chemotherapy in acute leukemia.

Conclusions: Neutropenic fever and sepsis are the major cause of mortality in acute leukemia during induction chemotherapy. Early initiation of appropriate antibiotics will help to improve outcome in the treatment of leukemia.

Keywords: Neutropenia, Fever, Acute leukemia, Chemotherapy

INTRODUCTION

Acute leukemia is a clonal malignant disorder of hematopoietic cells resulting in uncontrolled proliferation of leukemic blast cells in the bone marrow. Acute leukemia is classified into acute myeloid leukemia and acute lymphoblastic leukemia based on the cell of origin. Both the diseases are treated with intensive chemotherapy protocols. In acute myeloid leukemia, 80-85% patients below 65 years achieve complete remission with intensive induction chemotherapy.¹

The intensive treatment is associated with prolonged episodes of febrile neutropenia resulting in significant treatment related mortality.² In pediatric ALL long-term survival has improved to nearly 90% attributed to risk

adjusted therapy. But the prolonged and intensive treatment protocols are associated with increased risk of infections which is the major cause of treatment related mortality in adult ALL.³

There are multiple factors which predispose leukemia patients on chemotherapy to develop infections which include disruption of mucosal barrier, microbial flora shifts and neutropenia. In patients with fever, 50-60% harbour an infection.⁴ Primary sites of infections are gastrointestinal tract, paranasal sinuses, lung, skin and urinary tract. Initial infections in febrile neutropenia are bacterial which is later followed by fungal, viral and multidrug resistant bacterial infections.⁵ Most deaths are caused by subsequent infections by multidrug resistant organisms. Infection risk increases as neutrophil count

decreases to $<500/\mu\text{l}$.⁶ In India there are very few published studies which discuss the outcome and infection related deaths during the treatment of acute leukemia.

The objective of this study was to identify and characterize the infections occurring during the induction treatment of acute leukemia. The study also focused on the epidemiological features, etiology and outcome of infections in acute leukemia patients on induction chemotherapy.

METHODS

This was a prospective observational study conducted in the medical oncology and hematology division, department of internal medicine, Government Medical College Hospital, Kozhikode. Total enumerative sampling of 44 consecutive patients with newly diagnosed acute leukemia receiving induction chemotherapy during January to December 2018 were included in the study. Patients with relapsed leukemia, secondary or treatment related leukemia, post stem cell transplant and patients with other immunocompromising conditions like diabetes, chronic kidney disease, liver disease were excluded from the study.

Patients with AML were treated with 7+3 induction protocol with daunorubicin and cytosine and patients with ALL were treated with BFM 95 induction protocol. Patients were closely monitored for 40 days following initiation of induction chemotherapy. Absolute neutrophil count (ANC) was monitored daily and temperature charting was done 3 times per day. Febrile neutropenia was defined as single oral temperature $>38.3^{\circ}\text{C}$ or temperature $\geq 38^{\circ}\text{C}$ for >1 hour or occurrence of three episodes of temperature of 38°C or more in a 24 hour period taken at least 4 hour apart in a patient with ANC $<500/\mu\text{l}$. Blood culture and sensitivity, urine culture and sensitivity, throat swab, swab from any skin lesion or other discharges were taken depending on the site of infection and the organism identified.

Paired blood samples from central and peripheral lines were taken in cases of suspected central line associated blood stream infection. In cases of suspected pneumonia chest X-ray and HRCT thorax were taken. Serum CRP was estimated at the initiation of induction, at the onset of fever and 4th day after onset of fever. Diagnosis of sepsis was made based on SOFA score (Sequential organ failure assessment score). SOFA score calculates severity of organ dysfunction in respiratory, coagulatory, liver, cardiovascular, renal, and neurologic systems. The parameters assessed include $\text{PaO}_2/\text{FIO}_2$; $\text{SaO}_2/\text{FIO}_2$, hypotension, Glasgow coma scale, platelet count, serum bilirubin and serum creatinine/urine output. Patients with an increase in score ≥ 2 in the clinical setting of an infection were considered to be in sepsis.

Patients with febrile neutropenia were treated with antibiotics piperacillin+tazobactam and amikacin.

Antibiotics change was made later based on culture reports.

Addition of antifungal drugs was done with appropriate indication. Events of the first month of induction were assessed, data entered in Microsoft excel and analysed with SPSS software. Qualitative variables were summarised as frequency and percentage. Mean was used as the measure of central tendency and standard deviation was used as the measure of dispersion for descriptive statistics of quantitative variables. Association of selected variables with outcome was tested with Chi square test and independent t-test depending on the type of variable. P value <0.05 was taken as statistically significant.

RESULTS

Data of 44 patients who were enrolled in the study was analysed. There were 28 patients diagnosed with ALL and 16 patients with the diagnosis of AML. The mean age of AML patients was 37.5 while that of ALL patients was 29. There were 26 male patients and 18 female patients. Mean WBC count of acute leukemia patients in our study group was $42,250/\text{mm}^3$ (Range 800-2,82,000); mean Hb was 8.7 g/dl. Platelet count varied between 50,000-1,00,000/ mm^3 .

The symptoms in acute leukemia patients were fatigue, fever, bleeding manifestations, weight loss, anorexia, bone and joint pains (Figure 1). Nearly half of the acute leukemia patients had hepatomegaly and splenomegaly. Lymphadenopathy and mediastinal mass was seen predominantly in patients with ALL (Figure 2).

In AML induction chemotherapy all patients developed febrile neutropenia (Table 1). Among 28 ALL patients, 16 patients developed neutropenia. Of these, 11 patients had fever and 5 patients remained afebrile. Out of the total 44 patients 17 (40%) developed sepsis during induction chemotherapy. The incidence of sepsis was 75% in case of AML and 20% in case of ALL. Onset and duration of fever and neutropenia was earlier and prolonged in AML as compared to ALL (Table 2). Fall in ANC was earlier and more prolonged in AML (Figure 3).

The mean CRP value on day 1 of induction chemotherapy was 8.14 mg/dl which was just above the lab cut off of 6 mg/dl. During day 1 of febrile neutropenia the value increased to 29.67 mg/dl and on day 4 mean CRP value was 42.85 mg/dl. Mean CRP value at the day of initiation of chemotherapy was lesser in those patients who did not develop neutropenic fever (7.08) than those who developed neutropenic fever (9.18); but the difference was not statistically significant (p value=0.141).

Microbiological outcome

Total febrile episodes were 42. Total neutropenic fever episodes were 36 among 27 patients. Documented site of infection was identified in 28 febrile episodes (77.7%). Majority of patients had lower respiratory tract as the

focus (32.4%) followed by gastrointestinal tract (21.4%). Diarrhoea with or without abdominal pain was the predominant gastrointestinal symptom. Third predominant site of infection was skin and soft tissue. Two patients each developed perianal abscess, urinary tract infection and septic arthritis. One patient developed central line associated blood stream infection caused by coagulase negative Staphylococcus.

Causative organism was identified in 15 out of 36 febrile neutropenia episodes (41.6%). The most commonly isolated pathogen was multidrug resistant Klebsiella. Other bacterial pathogens isolated were methicillin resistant Staphylococcus aureus, coagulase negative Staphylococcus, Enterobacter and E coli. One patient developed disseminated candidiasis; the same patient also developed varicella zoster infection during induction chemotherapy. Two patients had radiologically proven aspergillosis (Table 3).

The empirical antibiotic therapy was started with a combination of piperacillin and tazobactam and amikacin. MDR gram negative infections were treated with meropenem and colistin in appropriate situations. Vancomycin or linezolid was used to treat MRSA infection. Candida blood stream infections were mainly treated with amphotericin B deoxycholate. Caspofungin was used in selected patients for whom financial aid was available. Aspergillus pneumonia was treated with voriconazole.

Outcome of induction chemotherapy

Mortality rate in AML during induction was 31% (5/16 patients) and that of ALL was 3.57% (1/28 patients). Complete remission rate in AML was 56.2% and that among ALL patients was 78.6% (Table 4). No clinical or laboratory parameters were found significant to predict outcome during induction chemotherapy in acute leukemia.

Table 1: Incidence of neutropenia during induction chemotherapy.

Type of leukemia	Incidence of neutropenia (%)
Acute leukemia	72.3
Acute myeloblastic leukemia	100
Acute lymphoblastic leukemia	57.14
T cell acute lymphoblastic leukemia	53.34
B cell acute lymphoblastic leukemia	61.53

Table 2: Day of onset and duration of fever and neutropenia in acute leukemia.

Types	Mean±SD			
	Onset of fever	Duration	Onset neutropenia	Duration
AML	5.81±3.35	12.29±6.98	5.44±2.804	15.88±5.315
ALL	16.7±10.3	5.23±3.89	15.50±7.789	4.69±2.915
B cell	18±11.43	4.75±3.86	15.13±5.718	3.88±2.03
T cell	16.11±10.43	5.44±4.126	15.88±9.848	5.80±3.55

Table 3: Pathogen identified in neutropenic fever.

Pathogen identified	No. of cases
MDR Klebsiella	5
MRSA	2
Coagulase negative Staphylococcus	2
Enterobacter	2
E. coli	2
Aspergillus	2

Table 4: Outcome of induction chemotherapy in acute leukemia.

Diagnosis	Neutropenia		Neutropenic fever		Sepsis		Mortality		Complete remission	
	N	%	N	%	N	%	N	%	N	%
AML	16	100	16	100	12	75	5	31.25	9	56.2
ALL	16	57	6	21.42	5	17.9	1	3.5	22	78.6
B cell ALL	8	61.5	1	7.6	2	15.4	0	0	11	84.7
T cell ALL	8	53.3	5	33.33	3	20	1	6.6	11	73.7

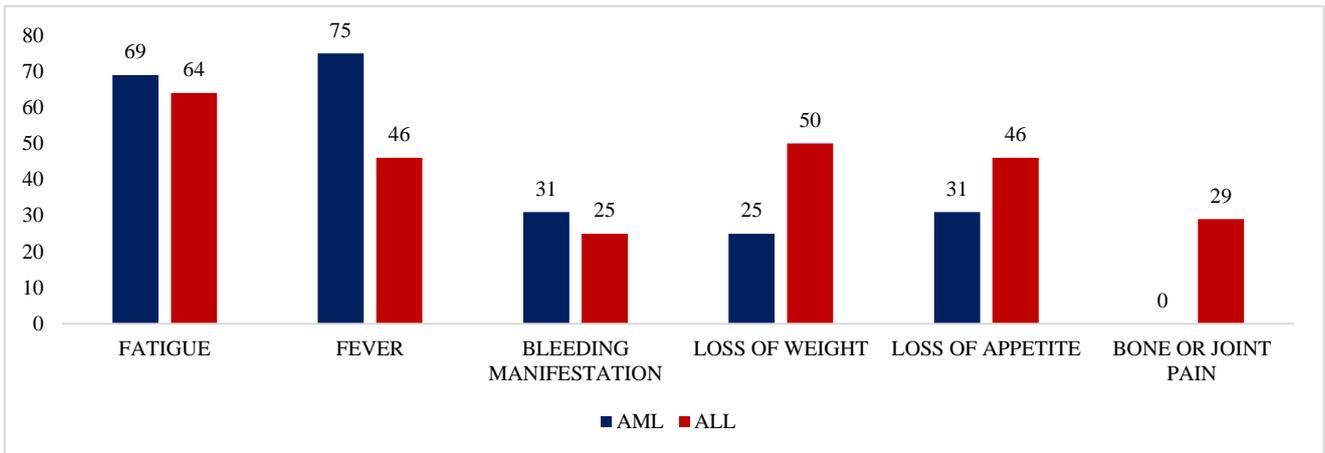


Figure 1: Presenting symptoms in acute leukemia (%).

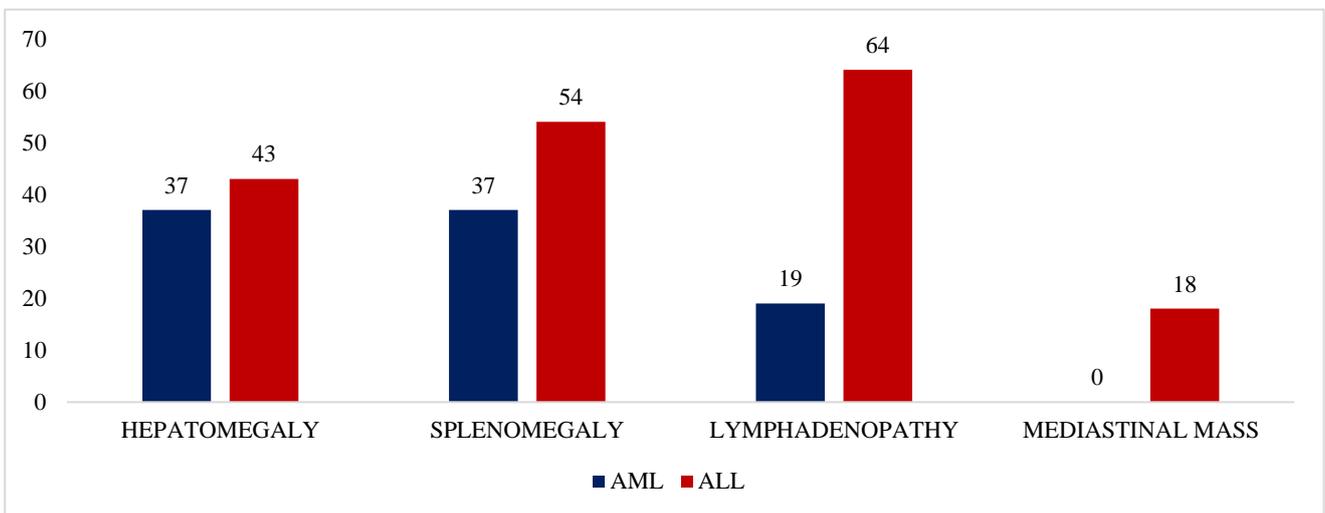


Figure 2: Examination findings in acute leukemia.

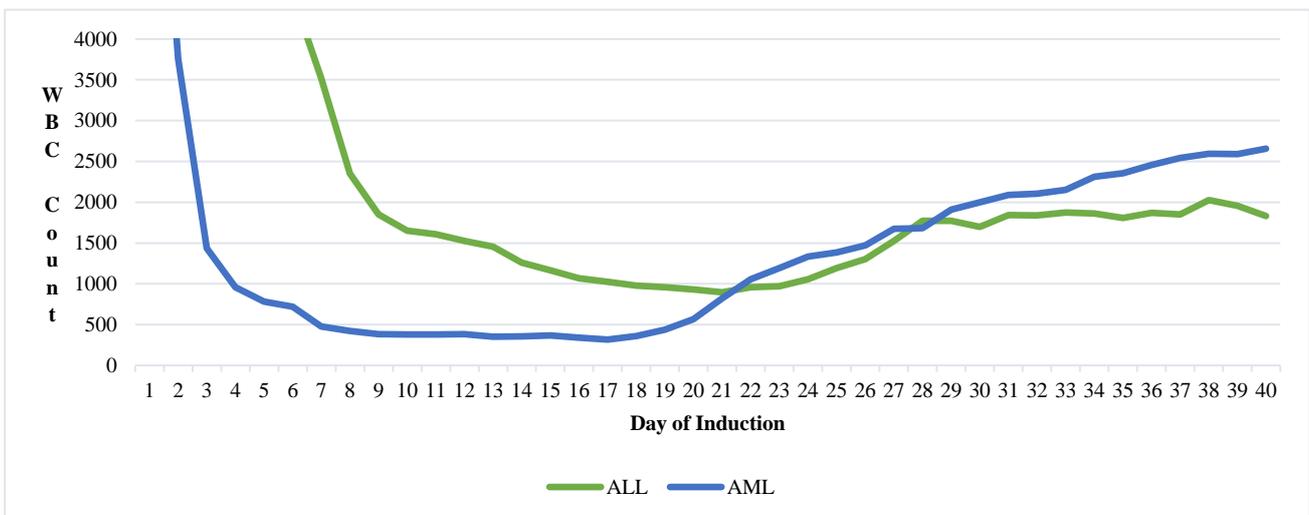


Figure 3: Average ANC in AML and ALL during induction chemotherapy.

DISCUSSION

Our study analysed the incidence of febrile neutropenia in acute leukemia induction chemotherapy. In this study 63.4% patients had ALL and 36.6% had AML as diagnosis. This is in contrast to most studies which include higher proportion of AML than ALL patients. In a study of acute leukemia by Dores et al 65.7% had AML.⁷ This difference in our study is due to the fact that many AML patients were unfit to receive induction chemotherapy due to age and comorbidities. Incidence of neutropenia in acute leukemia in our study is 72.3%.

In the AML group who received 7+3 induction, 100% developed neutropenia. The results are comparable to the study conducted by Biswas et al in AML patients where the incidence of neutropenia was 90%.⁸ In our ALL group who received BFM 95 protocol 57.14% developed neutropenia. In a study by Malkan et al 45% of ALL patients on BFM 95 induction developed neutropenia.⁹ Average time during which patient remained in neutropenia in the AML group was 15.88 days and that in ALL group was 4.69 days. In a study by Iqbal et al the incidence of neutropenic fever in ALL patients was 21.4%.¹⁰ This is in contrast to a study by Malkan et al where the incidence of neutropenia was found to be 55%. This may be due to the higher percentage of B cell ALL in the group where the incidence of neutropenic fever was lower.

In our study we used SOFA score to define organ dysfunction. Increase in score of two or more is considered as sepsis which is associated with 10% mortality.¹¹ In our study, 40% developed sepsis. 75% patients in the AML group and 20% in the ALL group developed sepsis. Mortality rate among patients who developed sepsis was 35.30%. Early sepsis was the major cause of mortality among patients who received induction chemotherapy.

We have observed that AML patients have 30% risk of death due to sepsis compared to ALL patients, who had only 2.5% risk of death during induction chemotherapy. In a study by Hamaleinin et al mortality in AML induction was 11% and that in ALL induction was 3.5%.¹² In a study by Chang et al mortality in induction chemotherapy was 6%.¹³ Moricke et al reported 0.7% mortality in ALL induction patients.¹⁴

Clinically documented site of infection was seen in 77% febrile episodes. The major site of infection in our group was respiratory tract and abdomen. This is comparable with observation in the study conducted by Biswal et al. In our study gram negative organisms were isolated in 69% cases of febrile neutropenia. This is in contrast to the study by Biswal et al where gram positive organisms constituted 38.3% cases and gram-negative organisms constituted 27.6% cases.

Our study provided the real time data from resource constraint government sector where many poor patients

with leukemia receive chemotherapy. Limitation of our study was that it constituted a small group. The study provided information regarding the pattern of infection, drug therapy and mortality during induction chemotherapy and this data can be used to plan larger studies and to improve infection related mortality and morbidity in leukemia patients.

CONCLUSION

Neutropenic fever and sepsis are the major cause of mortality in acute leukemia induction chemotherapy. Incidence of neutropenic fever and sepsis are higher among patients with acute myeloid leukemia than acute lymphoblastic leukemia. In our study we could identify the site of infection in 70% cases of neutropenic fever and isolate the organism in 41.6% cases. Early initiation of appropriate antibiotics will help to improve outcome in the treatment of leukemia.

ACKNOWLEDGEMENTS

Authors would like to thank Dr. N. K. Thulaseedharan, faculty in microbiology department and resident doctors in medicine for their help and support for the conduct of this work.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Hämäläinen S, Kuittinen T, Matinlahti I, Nousiainen T, Koivula I, Jantunen E. Neutropenic fever and severe sepsis in adult acute myeloid leukemia (AML) patients receiving intensive chemotherapy: Causes and consequences. *Leuk Lymphoma*. 2008;49(3):495-501.
2. Koistinen P, Rätty R, Itälä M, Jantunen E, Koivunen E, Nousiainen T, et al. Long-term outcome of intensive chemotherapy for adults with de novo acute myeloid leukaemia (AML): the nationwide AML-92 study by the Finnish Leukaemia Group. *Eur J Haematol*. 2007;78(6):477-86.
3. Koistinen P, Rätty R, Itälä M, Jantunen E, Koivunen E, Nousiainen T, et al. Long-term outcome of intensive chemotherapy for adults with de novo acute myeloid leukaemia (AML): the nationwide AML-92 study by the Finnish Leukaemia Group. *Eur J Haematol*. 2007;78(6):477-86.
4. DiNubile MJ. Fever and neutropenia: still a challenge. *Contemp Intern Med*. 1995;7(1):35-7.
5. Rolston KV. The Infectious Diseases Society of America 2002 guidelines for the use of antimicrobial agents in patients with cancer and neutropenia: salient features and comments. *Clin Infect Dis*. 2004;39.

6. Bodey GP, Buckley M, Sathe YS, Freireich EJ. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Ann Intern Med.* 1966;64(2):328-40.
7. Shah A, Andersson TM, Racht B, Björkholm M, Lambert PC. Survival and cure of acute myeloid leukaemia in England, 1971-2006: a population-based study. *Br J Haematol.* 2013;162(4):509-16.
8. Biswal S, Godnaik C. Incidence and management of infections in patients with acute leukemia following chemotherapy in general wards. *Ecancermedalscience.* 2013;7:310.
9. Malkan UY. Pediatric Chemotherapeutic Regimen (BFM-95) is Superior for Overall Survival in Adult Acute Lymphoblastic Leukemia. *Int J Hematol. Oncol.* 2018;28(4):254-60.
10. Iqbal M, Phan M, Machiorlatti M, Vesely SK, Morton JM, Holter J, et al. Impact of Duration of Neutropenia and Lymphopenia on AML Patients Undergoing Induction Chemotherapy. *Blood.* 2016;128(22):5178-82.
11. Singer M, Deutschman CS, Seymour CW, Shankar HM, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA.* 2016;315(8):801-10.
12. Hämäläinen S, Kuittinen T, Matinlauri I, Nousiainen T, Koivula I, Jantunen E. Neutropenic fever and severe sepsis in adult acute myeloid leukemia (AML) patients receiving intensive chemotherapy: Causes and consequences. *Leuk Lymphoma.* 2008;49(3):495-501.
13. Chang JE, Medlin SC, Kahl BS, Longo WL, Williams EC, Lionberger J, et al. Augmented and standard Berlin-Frankfurt-Munster chemotherapy for treatment of adult acute lymphoblastic leukemia. *Leuk Lymphoma.* 2008;49(12):2298-307.
14. Möricke A, Reiter A, Zimmermann M, Gadner H, Stanulla M, Dördelmann M, et al. Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: treatment results of 2169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95. *Blood.* 2008;111(9):4477-89.

Cite this article as: Sebastian P, Kuruvadangal AM, Babu H. Incidence of neutropenic fever and sepsis in patients receiving induction chemotherapy in acute leukemia. *Int J Res Med Sci* 2021;9:3335-40.