Archives of Oncology and Cancer Therapy

Volume 1, Issue 1, 2018, PP: 37-47

Outcome of Induction Therapy for Newly Diagnosed Acute Leukemia in a Calendar Year: Real World Data from a Tertiary Care Cancer Centre in South India

Smita Kayal[1], Biswajit Dubashi[1], Sunu L Cyriac[1], Debdatta Basu[2], Rakhee Kar[2], Sajini E Jacob[2] Ranjith Kumar[1], Unni Pillai[1], Ponraj Madasamy[1], Jogamaya Pattnaik[1], Naresh Jadhav[1] Kiran K Matta[1], Jagdeep Singh[1]

[1]Department of Medical oncology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry, India.

[2]Department of Pathology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry, India.

kayalsmita@gmail.com

***Corresponding Author:** Smita Kayal, Department of Medical Oncolgy, Regional Cancer Center, JIPMER, Puducherry, India.*

Abstract

Remission induction is the most intensive course of acute leukemia treatment. There is paucity of contemporary data on outcomes of induction from developing countries. In this study from a tertiary care centre in South India we report induction outcomes for all cases of acute leukemia (n = 109, ALL = 71 and AML = 38) registered in department of Medical Oncology in the calendar year 2015. 76 patients were in pediatric age group (≤ 18 years) and 33 were adults, male to female ratio was 1.6:1. All febrile neutropenia related events were more in AML, with early onset (median day to onset was day 8 in AML vs. day 17 in ALL), higher severity (94% clinically or microbiologically documented infection in AML vs. 61% in ALL), increased fungal infections (25% probable fungal pneumonia in AML vs. 6% in ALL) and consequently with more resource utilization. CR rate for ALL was 70%and 53% for AML. Fatal induction events were recorded in 17.6% ALL and 34.3% AML. Mortality during induction therapy of acute leukemia is high in resource limited settings, higher in AML than ALL, mostly because of infections (74% of induction deaths). There is a vital need for analysis of resources and improvement in supportive care during acute leukemia induction.

Keywords: *acute leukemia, induction, outcome, South India.*

Introduction

Advances in the management of acute leukemia have improved the outcome of this disease in developed world. Contemporary series from India and other developing countries report overall outcomes far removed from western figures mainly due to basic problems of infections, poor social support system, cost of treatment and inadequate treatment facilities. The long term survival reported from high income countries for pediatric acute lymphoblastic leukemia (ALL) is close to 90% [1] and for adult ALL is about 40% [2, 3]compared to 60% and 22% respectively in studies from India [4-6]. Similar survival data for acute myeloid leukemia (AML) is 35% to 40% in western series [7, 8] versus 20% to 35% from India [9, 10].Most of the outcome data from developed countries are results of clinical trials. Population based registry data describing the true incidence and treatment results of this potentially curable malignancy in the real world are lacking in India as well as in many of the developed nations [11]. Also, centre data particularly describing induction outcomes for all patients diagnosed and registered in a given time period are scant [12]. Most of the available studies describe survival results for select acute leukemia patients treated over a period of several years [4-6, 9, 10].

Remission induction is the most intensive course of treatment, both for the treating physician (in view of

the active disease burden, prolonged neutropenia and risk/occurrence of infections, other hematological and non-hematological toxicities) as well as the patient and hisfamily (considering the emotional trauma associated with the diagnosis, initial cost of treatment, guarded prognosis, and arrangement for blood donation and others). There is also a marked heterogeneity in the facilities, resources and expertise available and the treatment cost and payment structure in various centres across the country [12, 13]. In this descriptive study from a government tertiary care cancer centre with fully subsidized treatment we attempt to portray the outcome for all the patients of acute leukemia registered in a recent calendar year and focusing in particular on induction outcomes in terms of infection profile, remission rates, induction mortality and treatment drop-outs.

Patients & Methods

In this descriptive study data was collected retrospectively for demographic details, baseline disease characteristics, course and events during induction, and outcome of induction, in a predesigned proforma from available medical records maintained in the department. This study was approved by the Institute Ethics Committee. All the patients registered in the department of Medical Oncology, Regional Cancer Centre, JIPMER, Puducherry, of all age groups, with a diagnosis of acute leukemia (either ALL or AML including AML-M3) during the period from 01 January 2015 to 31 December 2015 were included in the study.

Treatment Protocol

All patients were started on induction treatment as in-patients either in the general ward or private ward of the regional cancer centre; there was no HEPA (high efficiency particulate arresting) filter or other specific air treatment system in the wards. As department policy, MCP-841 protocol [14, 15] was used for patients' ≤ 25 years with B-ALL and BFM 95 protocol[16] was used for patients' ≤ 25 years with T-ALL. For ALL patients more than 25 years, GMALL protocol [17,18] was used irrespective of the immunophenotypic subtype. All AML patients (adult or pediatrics) received standard '3+7' regimen [19-21]with daunorubicin at 60 mg/m2 for 3 days and cytarabine at 100 mg/m2 for 7 days. For patients with a diagnosis of AML-M3 or APL (acute promyelocytic leukemia), ATRA (all trans retinoic acid) plus daunorubicin [22, 23] was used as induction therapy. For patients with poor performance status and serious baseline infection, low intensity treatment was given as decided by the treating physician – steroids alone for ALL, low dose cytarabine, hydroxyurea or metronomic therapy for AML.

Supportive Care

All AML patients were given antifungal prophylaxis, with majority receiving fluconazole. From mid-year onward, in consideration of new construction in the hospital premises, incessant rain and a rise in clinical fungal infection, all ALL patients were also given antifungal prophylaxis, mainly with fluconazole. First line empirical broad spectrum antibiotic used for febrile neutropenia (FN) was a combination of cefoperazone –sulbactum and amikacin and first line gram positive antibiotic, when indicated, was vancomycin. Meropenem was used as second line antibiotic and Amphotericin B was used as the empirical therapeutic antifungal. Blood cultures were drawn at the onset of FN, at breakthrough fever, before escalation of antibiotics and for persistent fever. Other culture samples (from urine, sputum, pus) were obtained as clinically directed. Antibiotics were changed according to the sensitivity pattern, if any culture was positive. Colistin was used for documented multi drug resistant organism (MDRO) and at the physician's discretion for sick, hemodynamically unstable patient. Patients were shifted to intensive care unit if there was hemodynamic instability requiring inotropes or respiratory compromise requiring oxygen or ventilatory support.

Definitions

Risk stratification for ALL treatment was heterogeneous as different protocols were used, however, for describing the results for this analysis; National Cancer Institute (NCI) risk stratification [24] has been applied for ALL. European Leukemia Net (ELN) recommendations for standardized reporting for cytogenetic and molecular genetic data in AML [25] was used to risk stratify patients with AML. Standard definition for FN was used and FN was classified according to Immunocompromised Host Society consensus conference and the European Society of Clinical Microbiology and Infectious Diseases guidelines into clinically documented infections (CDI), microbiologically documented infections (MDI), and fever of unknown origin (FUO) [26, 27]. All episodes of fever during the induction treatment were taken as one course of FN for a given patient. Invasive fungal infections (IFI) were categorised into possible,

probable and proven IFI, based on the definitions by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC /MSG) consensus group [28]; however, categorization was based on host factors and clinical and radiological findings, serum galactomannan and tissue biopsy were not available. Complete remission (CR) was defined morphologically [29] and patients were considered to have refractory disease after failure of one course of induction in ALL and after two courses of induction in AML [30]. Assessment for minimal residual disease (MRD) was not done. Death from any cause or leave against medical advice (LAMA) during (or, before) the course of induction were taken as induction (or, pre-induction) events.

Statistics

Descriptive statistics were used for baseline characteristics, treatment related factors and induction outcomes. Differences in proportions were assessed using the chi-square test or Fisher exact test. All statistical analyses were 2-sided and performed at the 5% significance level. Data was censored for analysis on 30 April 2016. SPSS v 16.0 was used for analysis (SPSS, Chicago, IL, USA).

Results

A total of 109 patients of acute leukemia (ALL = 70, AML = 39) of all age groups were registered in the department of Medical Oncology in the calendar year 2015 from a total of 149 cases reported from the department of Pathology. Of the total 70 registered cases of ALL, 47 (67%) were pediatric (≤ 18 years), including 3 cases of infantile leukemia, and 23 (33%) were adult patients; of the 39 registered AML cases, 10 (25.6%) were pediatric and 29 (74.4%) were adult patients. From the 109 cases of acute leukemia, 17 (15.6%) patients were from Pondicherry, 80 (73.4%) were from the neighbouring state of Tamil Nadu and 12 (11%) were from other distant states along the Eastern coast (mainly Andhra Pradesh, Odisha and West Bengal). The baseline characteristics of the ALL patients are described in Table I and for AML patients are described in Table II. Amongst the ALL patients, approximately one third were T-ALL (31.4%, n=22), two thirds had high risk features (67%, n= 47), 6% (n= 3) of the B-ALL patients were Ph positive and overall 7% (n =5) had CNS (Central nervous system) positive disease. In the AML sub-group, 15% (n=6) patients had good risk disease, 56% (n =22) had intermediate risk, 10% (n = 4) had poor risk disease and risk status could not be determined for 18% (n = 7) patients.

Table I. *Baseline characteristics for Acute Lymphoblastic Leukemia (ALL) patients*

		ALL (n = 70)
Median age		13.5 years (1 month – 55 yrs)
Gender (Male:Female)		2.3:1 (49: 21)
ALL subtypes	B-ALL	48 (68.6%)
	T-ALL	22 (31.4%)
B-ALL (Ph* status) (n = 48)	Ph negative	29 (60.4%)
	Ph positive	3 (6.2%)
	Not known / not done	16 (33.3%)
Duration of symptoms (median days)		30 days (1 – 180 days)
Median Total Leucocyte Count (TLC) at presentation		22,915 (350 – 590000) / mm3
CNS (Central Nervous System) status	Positive	5 (7.1 %)
	Negative	60 (86%)
	unknown	5 (7.1%)
NCI (National Cancer Institute) Risk Stratification	Standard risk	23 (33%)
	High risk	47 (67%)
Treatment protocol	MCP-841	45 (64.3%)
	BFM-95	12 (17.1 %)
	GMALL	11 (15.7%)
	Steroids alone	2 (2.8%)
Day 8 blast (peripheral blood)	Positive	11 (15.7%)
	Negative	55 (78.5%)
	unknown	4 (5.7%)

*Ph – Philadelphia chromosome

Table II. *Baseline characteristics for Acute Myeloid Leukemia (AML) patients*

		AML (n = 39)
Median age		30 yrs (range 2 – 60)
Gender (Male:Female)		1:1.16 (18:21)
AML subtypes	M0 / M1	9
	M2	10
	M3 (APML)	2
	M4/M5	10
	M6	4
	M7	0
	Others / not known	4 (acute panmyelosis -1, BPCDN*-1)
Duration of symptoms (median days)		30 days (7 – 180 days)
Median Total Leukocyte Count (TLC) at presentation		21,840 / mm3 (670 – 762000)
Risk Stratification (ELN recommendation)	good risk	6 (15.3%)
	Intermediate† risk	22 (56.4%)
	High risk	4 (10.2%)
	Risk status not known	7 (17.9%)
Karyotype/Cytogenetic study	t(8;21) ‡	3 (7.6%)
	t (15;17)	1 (2.5%)
	Normal	20 (51.2%)
	del (3p)	1 (2.5%)
	Complex Karyotype	3 (7.6%)
	del(5q)	1 (2.5%)
	no metaphase / insufficient sample	3 (7.6%)
	Cytogenetic not available	7 (18%)
Molecular marker (s) profile	All negative (FLT-3, NPM1, CEBPA)	20 (51.2%)
	FLT – 3 positive	2 (5.1%)
	NPM 1 positive	2(5.1%)
	CEBPA positive	1(2.5%)
	FLT-3 + NPM1 positive	1 (2.5%)
	PML-RARA positive	2 (5.1%)
	Not available	11 (28.2%)

*BPCDN: blastic plasmacytoid dendritic cell neoplasm

†Intermediate 1 & 2 categories combined as number of patients were very less in Intermediate -2

‡includes one patient with three way translocation t (8; 10; 21)

Treatment Protocol

Patients with ALL, ≤ 25years, with B cell phenotype (B-ALL) were treated on MCP-841 protocol (n = 45 ,64.3% ; 3 patients with Ph positive B-ALL received Imatinib starting with induction) and patients with T-ALL were treated on BFM-95 protocol (n = 12, 17%). ALL patients > 25 years were treated on GMALL protocol (n=11, 15.7%). Two patients were started on steroids alone in view of baseline infection and poor general condition.

For patients with AML, 3+7 was the standard protocol for majority (n = 29, 74.3%); other regimens used were 2+5 for patients with borderline performance status (n = 3), ATRA+ Daunorubicin for the cases of

APL (n = 2), other low intensity treatment (low dose cytarabine, hydroxyurea) for patients with very poor performance status and severe infection (n=3). 10 patients with first induction failure received second course of induction either with the same '3+7' regimen or with high dose cytarabine.

Induction Outcomes

One hundred patients (ALL = 68, AML = 32) were included for analysis of induction outcomes in terms of febrile neutropenia and infection profile, remission rates, induction mortality and other events; Other 9 registered cases were excluded from analysis of induction outcome for either missing charts, induction done elsewhere or when planned for supportive care only. For the patients included in analysis, febrile neutropenia profile have been described for the first induction course only and remission rates & mortality have been described for both first and second induction course, when applicable. As this was a retrospectively collected dataset and since incomplete information was available in the following areas – blood product requirement and other non-hematological toxicities, they have not been separately analyzed here.

Febrile Neutropenia Profile and Related Events

Presence of fever at baseline, occurrence/recurrence of fever during the course of induction chemotherapy, type of febrile neutropenia & focus of infection, and the utilization of resources for the management of FN episodes as number of blood cultures drawn, number of antibiotics utilized are described in Table III separately for ALL and AML. Of note and as expected given the nature of the disease and its treatment, all FN related events were more in AML patients, with early onset (median day to onset was day 8 in AML vs. day 17 in ALL), higher severity (94% CDI & MDI in AML vs. 61% in ALL), increased fungal infections (25% patients having a probable fungal pneumonia in AML vs. 12% in ALL) and more resource utilization, median number of intravenous antibiotic used was 6 in AML vs. 3 in ALL, including colistin use in approximately two thirds of patients (74% in AML vs. 12.5% in ALL) and empirical antifungal use in 81% patients in AML vs. 19% in ALL.

Table III. *Febrile neutropenia profile for all analyzable (ALL & AML) patients*

		ALL (analyzed, n = 68)	AML (analyzed, n= 32)
Baseline infection and on IV(intravenous) Antibiotics before start of induction		34 (50%)	22 (69%)
1st line Antibiotics		25	19
2nd line Antibiotics		6	2
Antibiotics + Antifungal		3	0
No of pts developing at least one episode of FN* during induction		56 (82.3%)	31 (97%)
Median days to onset of FN*		Day 17 (day 0 – day 28)	Day 8 (1 -14)
Type of FN	FUO	22 (39%)	2 (6 %)
	CDI	14 (25%)	14 (44%)
	MDI	20 (36%)	16 (50%)
Focus of infection (for CDI & MDI)† (one patient can have more than one site)	Chest	15	22
	GIT (NEC)‡	4	3
	Oro-nasal	2	6
	Soft tissue	5	7
	UTI§	0	0
	Central line	5	2
	Others	6	2

Median number of blood samplesdrawn for Culture & sensitivity		2 (1 – 6)	5 (1 -9)
Culture positivity (for MDI episodes)	Gram positive (GP)	1 (5%)	2 (12.5%)
	Gram negative (GN)	15 (75%)	10 (62.5%)
	Polymicrobial (GN/GP)	4 (20%)	4 (25%)
Median Number of IV antibiotics		3(range 0 -8)	6 (range 3-9)
Gram negative Antibiotic		2 (0 – 5)	4 (1 – 6)
Gram positive Antibiotic		1 (0 – 2)	2 (0 – 3)
Colistin (Used)		7 (12.5%)	23 (74.2%)
Median day to start of 2nd line IV Antibiotic		Day 18 (day 0 – day 28)	Day 10 (0 -15)
Fungal infection (pneumo-nia/ oro-nasal)	None	56 (82.3%)	8 (25%)
	Possible	8 (12%)	16 (50%)
	Probable	4 (5.8%)	8 (25%)
	Proven	0	0
Median day to start of antifungal		Day 19 (1-28)	Day 10 (3 -18)
Therapeutic antifungal (empirical/ pre-emptive)	None	55 (81%)	6 (19%)
	Amphotericin B	12 (17.6%)	25 (78%)
	Voriconazole	1(1.4%)	1 (3%)

*FN: Febrile Neutropenia

† CDI & MDI: Clinically documented infection; Microbiologically documented infection

‡GIT(NEC) : Gastro-Intestinal Tract (Neutropenic Enterocolitis)

§UTI: Urinary Tract Infection

Disease Status & Remission Rate

At the end of induction therapy, 47 (69%) of the 68 analyzed cases of ALL attained Complete remission (CR), 3(4.4%) patients had an inconclusive report on the marrow and were continued on protocol and 6(8.8%) patients had refractory disease. For the 32 analyzed cases of AML, 11 patients (34.3%) attained CR after first induction and 11 patients (34.3%) were not in remission; the cumulative CR rate after two courses of induction was 53% (n =17) and refractory disease was seen in 4 patients (12.5%). Disease outcome for the analyzable cases are summarized in Table IV.

Table IV. *Outcome of Induction treatment for analyzable cases*

Induction outcome & event		**ALL (n = 68)**	**AML (n = 32)**
Disease / Patient outcome†	CR	47 (69%)	17 (53.1%)
	Induction failure / Refractory disease	6 (8.8%)	4 (12.5%)
	Inconclusive marrow, continued on protocol	3 (4.4%)	NA
	Died (Induction mortality)	7 (10.3%)	8 (25%)
	LAMA*	5 (7.3%)	3 (9.4%)
Disease status during Induction mortality / LAMA*	In aplasia (unknown)	9	8
	With refractory disease	3	3
	In CR	0	0
Cause of Induction Mortality /LAMA*	Infection /sepsis	8 (66.6%)	9 (81.8%)
	Bleeding	1 (8.3%)	1 (9.1%)
	Others	3 (25%)	1(9.1%)

* LAMA: Leave against medical advice

†outcome after 1st or 2nd induction (when applicable) for AML

Induction Mortality & Other Events

During the course of induction, death or LAMA in a sick, near terminal state was recorded in 12 (17.6%) patients with ALL, 9 patients had induction event in aplasia (with unknown disease status) and 3 patients had refractory disease. Cause of induction event was infection/sepsis in 8 patients, intracranial bleed in 1 and other causes (metabolic & refractory disease) in 3 patients. For patients with AML, 11 (34.3%) had an induction event (death or LAMA); 3 with refractory disease and 8 with aplasia. Cause of induction event was infection/sepsis in 9 patients, bleeding in 1 and refractory disease in 1 as shown in Table IV. In both the subgroups combined 17 out of 23 patients died of infective cause; 53% (n=9) patients had a MDI and 89% (8 out of 9 isolates) had gram negative sepsis; 62.5% (n=5) of gram negative isolates were carbapenem resistant. Also, 4 out of 12 patients (33.3%) with induction event in ALL had a probable/possible fungal pneumonia; similarly 8 out of 11 patients (72.7%) with induction event in AML had a probable/possible fungal pneumonia.

Association of Baseline Characteristics with Induction Outcome

An analysis for the association of age (≤ 18 years or > 18 years), total leucocyte count (≤ 50,000 or > 50,000) at presentation, baseline risk stratification and treatment protocol used with the induction outcome (CR or no CR) was done for ALL and AML patient subgroups as shown in Table V. There was no significant association between the factors analyzed and the induction outcome.

Table V. *Association of baseline factors with CR (Complete remission) rate*

For ALL				
Factors		CR (n = 50)	No CR* (n = 18)	p value
Age	≤ 18 yrs (n=46)	33 (66%)	13 (72.2%)	0.62
	> 18 yrs (n =22)	17 (34%)	5 (27.8%)	
TLC at presentation	≤ 50,000 (n=45)	31 (62%)	14 (77.8%)	0.26
	> 50,000 (n=23)	19 (38%)	4 (22.2%)	
Risk group	Standard risk (n=22)	17 (34%)	5 (27.8%)	0.62
	High risk (n=46)	33 (66%)	13 (72.2%)	
Protocol	MCP-841 (n=44)	32 (64%)	12 (75%)	0.35
	BFM-95 (n =12)	11 (22%)	1 (6.2%)	
	GMALL (n =10)	7 (14%)	3 (18.8%)	
For AML				
Factors		CR (n = 17)	No CR* (n = 15)	p value
Age	≤ 18 yrs (n=9)	4 (23.5%)	5 (33.3%)	0.69
	> 18 yrs (n =23)	13 (76.5%)	10 (66.7%)	
TLC at presentation	≤ 50,000 (n= 18)	10 (58.8%)	8 (53.3%)	0.75
	> 50,000 (n=14)	7 (41.2%)	7 (46.7%)	
Risk group	Good risk (n=6)	4 (25%)	2(15.4%)	0.16
	Intermediate (n=20)	9 (56.2%)	11 (84.6%)	
	Poor risk (n= 3)	3 (18.8%)	0	

*includes refractory disease / death /LAMA (after 1 or 2 courses of induction, as applicable)

Overall Outcome

The final outcome for all the registered cases of acute leukemia in the calendar year 2015 (ALL = 70 and AML = 39) as analyzed on 30th April 2016 is summarized in Table VI. In view of the short follow up a formal survival analysis was not done. Fifty (71.4%) patients with ALL and 12 (30.7%) patients with AML were alive on the date of last follow up. Events for other cases were death during induction or before start of induction, death during consolidation, death after relapse or being lost to follow up; for 20 (28.5%) cases of ALL and for 27 (69.2%) cases of AML.

Table VI. *Overall outcome of all registered cases (ALL & AML)*

Patient status	ALL (n = 70)	AML (n = 39)
Alive (on or off treatment)	50 (71.4%)	12 (30.7%)
Induction / pre-induction death	7 (10.3%)	11 (28.2%)
Death during consolidation (in remission)	3 (4.3%)	2 (6.2%)
Death after relapse / refractory disease	3 (4.3%)	7 (17.9%)
Unknown / LAMA* / LTFU †	7 (10.3%)	7 (17.9%)

*LAMA: Leave against medical advice

†LTFU: Lost to follow up

Discussion

This study describes the contemporary short term outcomes of annual registered cases of acute leukemia from a growing department in an old central government hospital in South India with necessary resources and where the treatment is nearly fully subsidized. Standard of care treatment was given to 97% of the registered ALL cases and 82% of the AML cases. Though almost all of the reported cases of ALL from the department of Pathology were registered for treatment in our department, only 50% of the reported cases of AML were registered. Status of the remaining 50% of AML cases is not known in detail, they were either advised supportive care, or family was not willing for further treatment or they have gone elsewhere for treatment. Their outcomes also are not known. These numbers are disconcerting despite treatment being highly subsidized.Approximately 10% of patients registered were from far off states and this may have added to the family's burden of arranging resources for treatment and overall cost and thus also contributing to treatment refusal and drop-out. A recent report from another tertiary care hospital in South India revealed that only 29% of the diagnosed cases of AML opted for treatment at the given centre [12]. There is a wide variability in all aspects of management of acute leukemia across the country and sporadic isolated reports of equally diverse outcomes [9,10,12], underscoring the vital need for prospective multi-centric approach, possibly population based, in identifying the baseline data and available resources for the treatment of this disease, and in analyzing the key problems.

The CR ratefor ALL was 70% and for AML was 53% in our study which are rather lower than that reported in other Indian series [5,6,9,10] possibly because our study included all the registered cases in the denominator and also because of relatively high induction events with inclusion of LAMA as an induction event in addition to induction mortality in the hospital.Some common features between the current study and other recently reported acute leukemia series from India are a younger median age at presentation especially for AML, 30 years in our study and 28 – 40 years in other series [12,31];higher proportion of patients with T-ALL (31%) and high risk features in ALL (67%)comparable to the results of a recently reported series of ALL, 39% and 66% respectively [4];high rates of induction events or mortality mainly from gram negative sepsis and fungal pneumonia, 34.4% for AML in our study and 18.4% to 25% in other studies on AML [9,12]; emerging MDR infections [12,32,33], and consequently poor outcomes.Whereas similar data from developed countries report a median age for AML of 50 years [11], percentage of NCI high risk ALL patients to be 30% to 34% [34], induction mortality of 3% to 4% for AML [35] lower rates for MDI [36-38], and improved outcomes.

For the AML subgroup, relatively lower percentage of patients (10%) in the ELN high risk category may be due to younger age distribution in our cohort, it is well known that adverse cytogenetic features increases with increasing age [39], small sample size and missing cytogenetic details for a sizable number. A comparatively high incidence of fungal infections (both pulmonary and oro-nasal) in AML with 25% probable and 50% possible IFI in our series, compared to 14% to 22% in western literature [40,41] and about 30% in other Indian study [12,31],needs further evaluation with better diagnostic facilities, more accurate assessment of individual cases and consideration for up gradation of antifungal prophylaxis. Several factors

could have contributed to this high incidence of IFI rate including new construction work at the hospital premises, lower threshold for radiological diagnosis of probable and possible fungal pneumonia on CT scan and the use of fluconazole as antifungal prophylaxis in our centre. Another area of pressing concern is the high incidence of clinically and/or microbiologically documented infections (61% for ALL and 94% for AML) with consequently excessive use of antibiotics including higher antibiotics as colistin.Other aspects of infection prevention (environment, health worker and patient/care giver related) and management has to be prospectively and comprehensively studied for improving infection related events so that focus can be shifted to improving disease related outcomes.

The primary goal of this small cases series was to underline the challenges faced in the treatment of acute leukemia mainly during the induction course and recognize induction outcomes for all recorded cases. Several limitations were the retrospectively collected data with inherent bias and missing information on some parameters, relatively small number of cases precluding any meaningful results of association between baseline factors and induction outcomes and heterogeneity of cases and treatment used. A prospective multi-centre study is warranted to have a more complete picture of the other factors involved in the management and outcome of acute leukemia.

Acknowledgements

We thank all the medical and para-medical staff of the department of Medical Oncology for their committed patient care in the face of limited resources. We acknowledge the help from Cankids, non-governmental organization, in supporting the treatment of pediatric patients with acute leukemia.

References

[1] Hunger SP, Lu X, Devidas M, Camitta BM, Gaynon PS, Winick NJ, et al.. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. J. Clin. Oncol. 2012;30(14):1663–1669.

[2] Goldstone AH, Richards SM, Lazarus HM, Tallman MS, Buck G, Fielding AK, et al. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). Blood. 2008;111(4):1827–1833.

[3] Marks DI. Treating the "older" adult with acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program. 2010;2010:13–20.

[4] Radhakrishnan V, Gupta S, Ganesan P, Rajendranath R, Ganesan TS, Rajalekshmy KR, et al.Acute lymphoblastic leukemia: A single center experience with Berlin, Frankfurt, and Munster-95 protocol. Indian J Med Paediatr Oncol. 2015;36(4):261–264.

[5] Bajel A, George B, Mathews V, Viswabandya A, Kavitha ML, Srivastava A, et al. Treatment of children with acute lymphoblastic leukemia in India using a BFM protocol. Pediatr Blood Cancer. 2008;51(5):621–625.

[6] Malhotra P, Varma S, Varma N, Kumari S, Das R, Jain S, et al. Outcome of adult acute lymphoblastic leukemia with BFM protocol in a resource-constrained setting. Leuk. Lymphoma. 2007;48(6):1173–1178.

[7] Büchner T, Berdel WE, Haferlach C, Haferlach T, Schnittger S, Müller-Tidow C, et al. Age-related risk profile and chemotherapy dose response in acute myeloid leukemia: a study by the German Acute Myeloid Leukemia Cooperative Group. J. Clin. Oncol. 2009;27(1):61–69.

[8] Rowe JM, Tallman MS. How I treat acute myeloid leukemia. Blood. 2010;116(17):3147–3156.

[9] Bahl A, Sharma A, Raina V, Kumar L, Bakhshi S, Gupta R, et al. Long-term outcomes for patients with acute myeloid leukemia: a single-center experience from AIIMS, India. Asia Pac J Clin Oncol. 2015;11(3):242–252.

[10] Saikia TK, Bakshi A, Bhagwat R, Tawde S, Nair R, Nair CN, et al. Outcome of acute myeloid leukaemia in adults: a retrospective analysis. Natl Med J India. 2005;18(1):12–15.

[11] Juliusson G, Lazarevic V, Hörstedt A-S, Hagberg O, Höglund M, Swedish Acute Leukemia Registry Group. Acute myeloid leukemia in the real world: why population-based registries are needed. Blood. 2012;119(17):3890–3899.

[12] Philip C, George B, Ganapule A, Korula A, Jain P, Alex AA, et al. Acute myeloid leukaemia: challenges and real world data from India. Br. J. Haematol. 2015;170(1):110–117.

[13] Horton R, Das P. Indian health: the path from crisis to progress. Lancet. 2011;377(9761):181–183.

[14] Raje NS, Vaidya SJ, Kapoor G, Pai SK, Nair CN, Kurkure PA, et al. Low incidence of CNS relapse with cranial radiotherapy and intrathecal methotrexate in acute lymphoblastic leukemia. Indian Pediatr. 1996;33(7):556–560.

[15] Magrath I, Shanta V, Advani S, Adde M, Arya LS, Banavali S, et al. Treatment of acute lymphoblastic leukaemia in countries with limited resources; lessons from use of a single protocol in India over a twenty year period [corrected]. Eur. J. Cancer. 2005;41(11):1570–1583.

[16] 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):4477–4489.

[17] Gökbuget N, Hoelzer D, Arnold R, Böhme A, Bartram CR, Freund M, et al. Treatment of Adult ALL according to protocols of the German Multicenter Study Group for Adult ALL (GMALL). Hematol. Oncol. Clin. North Am. 2000;14(6):1307–1325, ix.

[18] Bajel A, George B, Mathews V, Viswabandya A, Kavitha ML, Srivastava A, et al. Adult ALL: treatment outcome and prognostic factors in an Indian population using a modified German ALL (GMALL) protocol. Leukemia. 2007;21(10):2230–2233.

[19] Schiller G, Gajewski J, Territo M, Nimer S, Lee M, Belin T, et al. Long-term outcome of high-dose cytarabine-based consolidation chemotherapy for adults with acute myelogenous leukemia. Blood. 1992;80(12):2977–2982.

[20] Khattry N, Kumar L, Kumar R, Patel C, Raina V, Sharma A, et al. Comparison of 2 doses of daunorubicin(45mg/m2 vs 60mg/m2) in induction therapy of patients of de novo acute myeloid leukemia [abstract]. ASCO Meeting Abstracts. 2006;24(18_suppl):6581.

[21] Padron E, Fernandez H. Anthracycline dose intensification in young adults with acute myeloid leukemia. Ther Adv Hematol. 2012;3(1):17–27.

[22] Sanz MA, Martín G, Rayón C, Esteve J, González M, Díaz-Mediavilla J, et al. A modified AIDA protocol with anthracycline-based consolidation results in high antileukemic efficacy and reduced toxicity in newly diagnosed PML/RARalpha-positive acute promyelocytic leukemia. PETHEMA group. Blood. 1999;94(9):3015–3021.

[23] Adès L, Chevret S, Raffoux E, de Botton S, Guerci A, Pigneux A, et al. Is cytarabine useful in the treatment of acute promyelocytic leukemia? Results of a randomized trial from the European Acute Promyelocytic Leukemia Group. J. Clin. Oncol. 2006;24(36):5703–5710.

[24] Smith M, Arthur D, Camitta B, Carroll AJ, Crist W, Gaynon P, et al. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. J. Clin. Oncol. 1996;14(1):18–24.

[25] Döhner H, Estey EH, Amadori S, Appelbaum FR, Büchner T, Burnett AK, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood. 2010;115(3):453–474.

[26] From the Immunocompromised Host Society. The design, analysis, and reporting of clinical trials on the empirical antibiotic management of the neutropenic patient. Report of a consensus panel. J. Infect. Dis. 1990;161(3):397–401.

[27] Hughes WT, Pizzo PA, Wade JC, Armstrong D, Webb CD, Young LS. Evaluation of new anti-infective drugs for the treatment of febrile episodes in neutropenic patients. Infectious Diseases Society of America and the Food and Drug Administration. Clin. Infect. Dis. 1992;15 Suppl 1:S206-215.

[28] De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin. Infect. Dis. 2008;46(12):1813–1821.

[29] Cheson BD, Bennett JM, Kopecky KJ, Büchner T, Willman CL, Estey EH, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J. Clin. Oncol. 2003;21(24):4642–4649.

[30] Rowe JM, Kim HT, Cassileth PA, Lazarus HM, Litzow MR, Wiernik PH, et al. Adult patients with acute myeloid leukemia who achieve complete remission after 1 or 2 cycles of induction have a similar prognosis: a report on 1980 patients registered to 6 studies conducted by the Eastern Cooperative Oncology Group. Cancer. 2010;116(21):5012–5021.

[31] Gupta A, Singh M, Singh H, Kumar L, Sharma A, Bakhshi S, et al. Infections in acute myeloid leukemia: an analysis of 382 febrile episodes. Med. Oncol. 2010;27(4):1037–1045.

[32] Ghosh I, Raina V, Kumar L, Sharma A, Bakhshi S, Thulkar S, et al. Profile of infections and outcome in high-risk febrile neutropenia: experience from a tertiary care cancer center in India. Med. Oncol. 2012;29(2):1354–1360.

[33] Bakhshi S, Padmanjali KS, Arya LS. Infections in childhood acute lymphoblastic leukemia: an analysis of 222 febrile neutropenic episodes. Pediatr Hematol Oncol. 2008;25(5):385–392.

[34] Schultz KR, Pullen DJ, Sather HN, Shuster JJ, Devidas M, Borowitz MJ, et al. Risk- and response-based classification of childhood B-precursor acute lymphoblastic leukemia: a combined analysis of prognostic markers from the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG). Blood. 2007;109(3):926–935.

[35] Othus M, Kantarjian H, Petersdorf S, Ravandi F, Godwin J, Cortes J, et al. Declining rates of treatment-related mortality in patients with newly diagnosed AML given "intense" induction regimens: a report from SWOG and MD Anderson. Leukemia. 2014;28(2):289–292.

[36] Buckley SA, Othus M, Estey EH, Walter RB. The treatment-related mortality score is associated with non-fatal adverse events following intensive AML induction chemotherapy. Blood Cancer J. 2015;5:e276.

[37] Afzal S, Ethier M-C, Dupuis LL, Tang L, Punnett AS, Richardson SE, et al.Risk factors for infection-related outcomes during induction therapy for childhood acute lymphoblastic leukemia. Pediatr. Infect. Dis. J. 2009;28(12):1064–1068.

[38] Lehrnbecher T, Varwig D, Kaiser J, Reinhardt D, Klingebiel T, Creutzig U. Infectious complications in pediatric acute myeloid leukemia: analysis of the prospective multi-institutional clinical trial AML-BFM 93. Leukemia. 2004;18(1):72–77.

[39] Bacher U, Kern W, Schnittger S, Hiddemann W, Haferlach T, Schoch C. Population-based age-specific incidences of cytogenetic subgroups of acute myeloid leukemia. Haematologica. 2005;90(11):1502–1510.

[40] Gomes MZR, Mulanovich VE, Jiang Y, Lewis RE, Kontoyiannis DP. Incidence density of invasive fungal infections during primary antifungal prophylaxis in newly diagnosed acute myeloid leukemia patients in a tertiary cancer center, 2009 to 2011. Antimicrob. Agents Chemother. 2014;58(2):865–873.

[41] Barreto JN, Beach CL, Wolf RC, Merten JA, Tosh PK, Wilson JW, et al. The incidence of invasive fungal infections in neutropenic patients with acute leukemia and myelodysplastic syndromes receiving primary antifungal prophylaxis with voriconazole. Am. J. Hematol. 2013;88(4):283–288.

Citation: **Smita Kayal, et al.**. *Outcome of Induction Therapy for Newly Diagnosed Acute Leukemia in a Calendar Year: Real World Data from a Tertiary Care Cancer Centre in South India. Archives of Oncology and Cancer Therapy. 2018; 1(1): 37-47.*