European Journal of Molecular & Clinical Medicine (EJMCM)
ISSN: 2515-8260 Volume 09, Issue 03, 2022

Original research article

A Prospective Research to Study the Response to Standard Chemotherapy among Acute Leukaemia Patients in Central India at a Tertiary Health Care Centre.

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Abstract
Introduction: Leukemias (>95% of which are acute) constitute the most common diagnostic group of childhood cancers worldwide, and in India. Remarkable progress has been made in the treatment of acute lymphoblastic leukaemia (ALL) which constitute 75–80% of childhood acute leukemiaswith 5-year overall survival rate reaching 90% in the high-income countries. Aim: study the response to standard chemotherapy among acute leukaemia patients in central India at a tertiary health care centre. Methodology: Cases for the study collected from Sri Aurobindo Medical College and PG Institute Hospital wards attached to Department of Medical Oncology. The study comprises 106 cases of acute leukaemia. Study period was from November 2015 to November 2017. Results: At 4 months **t**he mean Hb in AML patients was 10.4gm%(7-11gm%) while WBC were mean-5547 (4000-17800/cmm), peripheral blasts were 1.73% (0%-20%),platelets mean being 168564 (80000 -202000/cmm).
Keywords: leukemia, treatment outcome, cytarabine, ALL, AML

Introduction

Leukaemia's identification as a separate malignancy happened in 1889.[1,2]Since then apart from its etiopathogenesis increasing interest has been developing in the geographic pattern of leukemia and its distribution throughout the world. Leukemias are the 10th most common cancer in men and 12th most common in women and constitute 3% of the global cancer burden.[3] Developing countries bear more than half of global cancer burden, because 75% of the world population lives in these countries.[4] The incidence of Leukemia is highest in North America and Australia/ New-zealand and lowest in sub-saharan Africa.[5] Leukemia is one of the most frequently occurring cancers in all races or ethnicities with relative proportion vary between 25-40% [3]. In 2013, males have been accounted for more than 57 percent of the new cases of leukaemia [6].

Leukemias (>95% of which are acute) constitute the most common diagnostic group of childhood cancers worldwide, and in India.[7,8,9,10] Remarkable progress has been made in the treatment of acute lymphoblastic leukaemia (ALL) which constitute 75–80% of childhood acute leukemiaswith 5-year overall survival rate reaching 90% in the high-income countries[11].Advances in acute myeloid leukemia (AML), while not so spectacular, have been steady with 5-year overall survival rates approaching 70%.[11,12] There is limited longitudinal data on leukaemia survival trends from India. Nevertheless, there is published evidence that

there has been progress in the outcomes of childhood ALL In India although the magnitude of progress has been more modest.[13,14] The data on AML are too scant to make any meaningful conclusions. Through the index research, we have tried to see the response to standard chemotherapy among acute leukemia patients in the Central India.

Methodology

This Prospective clinical study was conducted at Sri Aurobindo Medical College and PG Institute, Indore, Madhya Pradesh. Cases for the study collected from Sri Aurobindo Medical College and PG Institute Hospital wards attached to Department of Medical Oncology.

The study comprises 106 cases of acute leukaemia. Study period was from November 2015 to November 2017. A pre-tested proforma was used to collect the relevant information by interviewing, clinical examination of patients, and noting relevant investigations required for treatment. Consent form for the study purpose had been prepared. No special consent is required as clinical examination , imaging and histopathological examination are part of routine evaluation.

Inclusion criteria included All patients of Acute leukemia, equal to more than 1 years whose guardian or adults less than or equal to 70 years who are willing to give informed written consent for study.

All the diagnosed cases of ALL patients received the BFM 95 or BFM 2002 OR GMALL protocol, a standard protocol that is followed in our institution where the treatment comprised induction with four drugs using vincristine, L-asparaginase, daunomycin, and prednisolone, along with CNS prophylaxis with methotrexate,Ara-C and hydrocortisone and consolidation with high dose methotrexate and maintained with methotrexate and 6-MP.

The AML patients received the '3+7' dose (Dauno + Ara-C) regimen, followed by a monthly high dose of Ara-C (3 g/m^2) twice daily on alternate days for six doses. The '3+7' dose (Dauno + Ara-C) therapy was comprised of daunomycin (60 mg/m^2/day) on days one through three and cytosine arabinoside (200 mg/m^2/day) on days one through seven.Patients who were unfit for 3+7 dose were offered hypomethylating agents and best supportive care.

Supportive therapy such as blood and its components, 5-HT3 antagonists for nausea and vomiting, and chlorhexidine mouthwash after each feed for good oral hygiene were administered as and when required.

A pretested semi structured proforma was used to record the patient data and data will be entered in MS Excel sheet. Analysis was done using SPSS 23 version.

Results

In the present study, the mean age of the study sample was 27.29 years ranging from 2years to 70 years in different patients. Most of the patients belonged to the 16-35 years of age group. In patients with ALL mean age was 15.4 years(Range 2-70 Years) and for AML patients the mean age was 40 years (Range 2-70 Years).

The study sample had 67 males and 39 females among all the patients having acute leukemia.

At the time of admission **t**he mean Hb in ALL patients was 7.5 gm(1-12.7gm %) while WBC were mean-70543(300-565000/cmm),peripheral blasts were 65% (2% -98%),platelets mean being 84745 (2000 -100000/cmm). Bone marrow blasts were mean-77% (33% -100%)

FEATUREs	ALL N=55	AML N=51
HB(gm%)	7.51	7.7
WBC(/cmm)	70543	61053
PB BLAST%	65%	47%
PLATELETS(/cmm)	84745	44144
BM BLAST %	77%	69%

At the time of admission **t**he mean Hb in AML patients was 7.7 gm% (3-12.2gm%) while WBC were mean-61053(200 -565000/cmm),peripheral blasts were 47% (2% -94%),platelets mean being 44144 (7000 -202000/cmm). Bone marrow blasts were mean-69% (42% -100%)

Table : Showing LABORATORY FEATURES AT DAY 28

FEATURE	ALL N=39	AML N=26
HB(gm%)	9.6	9.8
WBC(/cmm)	4910	5125
BLAST%	2%	1%(27 PTS)
PLATELETS(/cmm)	152647	133888
BM BLASTS%	2%	2%(26 PT)

At DAY 28 **t**he mean Hb in ALL patients was 9.6gm% (6-11gm%) while WBC were mean-4910(3000-9000/cmm),peripheral blasts were 2% (0% -20%),platelets mean being 152647 (64000 -290000/cmm). Bone marrow blasts were mean-2%(0%-30%)
At DAY 28 **t**he mean Hb in AML patients was 9.8gm%(8-11gm%) while WBC were mean-5125 (2800-10000/cmm), peripheral blasts were 1% (0%-9%),platelets mean being 133888 (20000 -289000/cmm). Bone marrow blasts were mean-2% (0%-18%).
At 4 months **t**he mean Hb in ALL patients was 10.25gm% (8-11.5gm%) while WBC were mean-4227 (3500-9200/cmm),peripheral blasts were 1.21% (0% -45%),platelets mean being 193594 (52000 -320000/cmm).
At 4 months **t**he mean Hb in AML patients was 10.4gm%(7-11gm%) while WBC were mean-5547 (4000-17800/cmm), peripheral blasts were 1.73% (0%-20%),platelets mean being 168564 (80000 -202000/cmm).

TREATMENT & OUTCOME

OUTCOME AT 28 DAYS	TOTAL	CR	IF	EXPIRY	LOST TO FOLLOW UP
BFM 95	23	22(95.65%)	0	1(4.35%)	0
BFM 2002	20	15(75%)	0	5(25%)	0
GMALL	3	1(33.33%)	0	2(66.66%)	0
BSC	1	0	0	1(100%)	0
ABANDONED	7	NA			

Table : Showing OUTCOME OF ALL CASES AS PER TREATMENT PROTOCOL AT 28 DAYS

Table: Showing OUTCOME OF AML CASES AS PER TREATMENT PROTOCOL AT 28 DAYS

OUTCOME AT DAY 28	TOTAL	CR	IF	EXPIRY	LFU
3+7 dose	11	2(18.18%)	3(27.27%)	6(54.54%)	0
3+7 dose,3HIDAC	10	10(100%)	0	0	0
3+7 dose,4HIDAC	6	6(100%)	0	0	0
3+7+VP16	1	0	0	1(100%)	0
ATRA+DAUNO	2	NA	NA	NA	NA
HYPOM	10	3(30%)	2(20%)	2(20%)	3(30%)
BSC	4	0	0	3(75%)	0
ABANDONED	7	NA			

3+7 dose was the most common protocol used in AML patientsat our centre followed by Hypomethylating agents.

Discussion:

Acute Leukemias were mainly classified into AML and ALL, on the basis of laboratory data and morphological features of leukemic cells.

Of total 106 cases of acute leukemia, 55 cases (51.9%) were ALL and 51 cases (48.1%) were AML.[14-17]

ALL [Young]

Over the last two decades, the world's leading leukemia groups have achieved 5-year survival rates of approximately 90%, with 2% to 3% deaths as a result of toxicity in childhood ALL. A major concern with BFM-type chemotherapy in the hands of less experienced groups with limited resources was the potential risk of excessive treatment related mortality. Indeed, we observed a 13.9% rate of death in induction in patients on BFM 95 or BFM 2002 protocol.

Most of our ALL patients fell in intermediate risk category (76.4%),followed by standard risk(20%).(SR,IR and HR stratification was done as per BFM 2002 protocol's criteria as-SR-age 1-5 years,WBS<20000; IR-Age<1, or>=6,WBC>20000; HR-t(4;11) or t(9;22).Prednisolone response was not monitored in cases who were on BFM 95 protocol hence wasn't applicable for all cases).[15-18]

ADULT ALL

The remission induction rates with conventional four-drug induction in our series was 33.33% which is lower than to published data from the West.[16,17] . There is very little published data on the outcome of adult ALL in India. A small series of 42 patients treated with an aggressive regime has reported an OS of 41.9% at the end of 5 years.[18]. Older age has consistently been shown to be an adverse prognostic feature in adult ALL as was seen in our study.[15]

AML(Young adults)

The combination of "standard dose"cytarabine plus daunorubicin has been the historical standard for remission induction in AML. In this regimen, cytarabine is given by continuous

intravenous (IV) infusion for 7 to 10 days plus daunorubicin by intravenous push or short infusion daily for the first three days. Standard dosing for patients less than 60 years old include:Cytarabine100-200 mg/m2 Cytarabine for 7-10 days plus daunorubicin 60-90 mg/m2 Daunorubicin for 3 days

Depending upon age and patient selection, 70 to 80 percent of youngeradults achieve a CR with these regimens [10,17]. Most remissions come after a single course.

AML(older adults)

DNA hypomethylating agents (eg, azacitidine, decitabine) target the aberrant DNA methylation seen in AML[16]. Both azacitidine and decitabine are pyrimidine nucleoside analogs of cytidine that strongly inhibit DNA methylation and are commonly used for the treatment of myelodysplastic syndromes (MDS). These agents can induce remissions and potentially prolong survival in a fraction of older patients with newly diagnosed AML (although typically those with lower blast cell counts and less proliferative disease) or advanced MDS [17-21]

Azacitidine is commonly used for the treatment of MDS and has demonstrated activity in patients with AML. Studies in AML suggest that, when compared with supportive care alone, azacitidine improves symptoms and quality of life[15-22]

Conclusion: Azacitidine is commonly used for the treatment of MDS and has demonstrated activity in patients with AML. When compared with supportive care alone, azacitidine improves symptoms and quality of life.

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