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Leucovorin Rescue Doses in Acute Lymphoblastic Leukemia Patients Receiving High Dose Methotrexate

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ABSTRACT

Our aim is to determine the average Leucovorin (LV) doses given to Acute Lymphoblastic Leukemia (ALL) patients receiving High Dose Methotrexate in their consolidation phase of the treatment. An observational retrospective study was conducted in the inpatient department of Aware Gleneagles Global Hospital, Hyderabad, India. In a total of 73 pediatric and adult patients with Acute Lymphoblastic Leukemia (ALL) from various age groups who are in their Consolidation stage, comprising of 4 cycles each, containing a course high dose methotrexate from 2016-2021 were included in the investigation. All the data important was gathered from the patient case sheets and electronic clinical records in the planned patient's Performa or information assortment structure i.e., data collection which incorporates patient's demographic subtleties, laboratory values, and so forth. Among the 73 subjects of ALL, the most average number of Leucovorin doses given in HDMTX is 6 among all the three subtypes of ALL diagnosis. It was also evident that there is an association between the HDMTX toxicity symptoms and age group, gender, diagnosis and HDMTX doses respectively. Consequently, we have concluded that number of leucovorin doses is correlated with the toxicity of methotrexate. The toxicity caused due to leucovorin can be cured with extraordinary degree by satisfactory and adequate hydration/Alkalinization, precise dose of anti-emetics and regular monitoring of Urine pH, Serum Creatinine, Serum Methotrexate levels, Complete Blood Count as to identify any toxicity and intense management of the toxicity.

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INTRODUCTION

Acute Lymphoblastic Leukaemia (ALL) is a type of cancer in blood that starts in the white blood cells of the bone marrow (the soft inner part of the bones). It develops from immature lymphocytes, a white blood cell type essential for your immune system. It can also develop in the lymph nodes, spleen, liver, central nervous system, and other organs. Acute Lymphoblastic Leukaemia usually progresses quickly if no treatment given [1]. According to World Health Organization (WHO) system, ALL is classified based on the white blood cell type that has led to the cancer, and the characteristics the cell has [2–4]. The distinctive subtypes are:

1. Pre-B cell ALL [5]
2. B- cell ALL
3. T cell ALL

Epidemiologic investigations of acute leukaemia in children have analysed various conceivable hazard

factors (e.g., natural, hereditary, or infectious) [6]. It occurs with the extended re-occurrence in patients among neurofibromatosis type I, down disorder, bloom condition, and ataxia- telangiectasia [6, 7]. The most widely recognized research related laboratory abnormalities in ALL are fever (caused by auxiliary contamination optional to neutropenia), anxiety and lethargy (due to anaemia), bone torments, joint pains, bleeding diathesis (identified with thrombocytopenia) [7], pallor (paleness), and leukopenia is also known as leucocytosis, with hyperleukocytosis (>100 1́09/L) identified in the paediatric patients [8]. In many focuses, the therapy of ALL includes transitory escalated chemotherapies [7, 9] which include: Induction, Consolidation, Maintenance, and Re-induction.

Methotrexate is a significant part of the treatment in acute lymphoblastic leukemia [10]. It is given in the consolidation phase of the treatment. High-dose intravenous methotrexate is a significant chemotherapeutic agent for childhood ALL [11, 12]. Doses $\geq$ 500 mg/m^2 or above given intravenously are known as high-dose methotrexate (HDMTX) which is used to treat the adult and pediatric cancers. HDMTX can cause toxicities like Myelosuppression, Oral mucositis, Acute Renal Failure, Hepatotoxicity, Neurologic toxicity [13, 14] etc. Thus may lead to morbidity, occasional mortality, and interrupting the cancer therapy consequently [14–16]. Supportive care is given, for example, Continuous Hydration, Alkalinization and Leucovorin rescue and so forth. Aggressive monitoring of Methotrexate can be done as there might be any delayed excretion of the drug [17], increased serum concentration thus causing toxicity [18–20].

Leucovorin rescue is used for HDMTX treatment for more than 30 years. Leucovorin has its importance in the prevention of Myelosuppression and neurotoxicity during treatment with HDMTX [21]. Chemotherapy protocols of HDMTX also include timing, dose, and duration of leucovorin administration to protect normal cells from injury. Since leucovorin effectively balances the impact of methotrexate, it should not began too soon because it would then diminish not only toxicity but also anticancer efficacy [22, 23]. The prevention of toxicity was highly scheduled dependent and that the delayed administration of leucovorin might be therapeutically advantageous; i.e., the toxicity of the folate antagonists was hugely avoided [24, 25]. An evaluation of leucovorin in methotrexate rescue is a determination of the efficacy of leucovorin in preventing the severe toxicity that would otherwise accompany the administration of high-dose methotrexate [26].

Leucovorin Rescue Regimens

Leucovorin rescue was commenced 36 hours after the start of HDMTX treatment. The first dose is generally 15 mg/m^2 for low-severity children and 30 mg/m^2 for moderate and high-severity children. Then, for children without elimination delay, LV (15 mg/m^2) was given once every 6 hours until the plasma HDMTX concentration was <0.1 μmol/l. A total of 5–8 LV doses were given. For children with elimination delay, the LV rescue regimen was prescribed as previously detailed until the plasma HDMTX concentration was <0.1 μmol/l [22, 26, 27].

METHODOLOGY

Study Design

A retrospective study was conducted on 73 in patients with Acute Lymphoblastic Leukemia patients from the age of 1-60 years in their consolidation phase, consisting of 4 cycles containing a course of HDMTX and leucovorin from 2016-2021.

Study Period

The study was conducted for a period of six months (December 2020 – May 2021).

Study Site

Inpatient department of Aware Gleneagles Global Hospital, Hyderabad. The study was conducted in the Department of Oncology, Aware Gleneagles Global Hospital. It is a 300 bedded specialized hospital located in the Karmanghat area of Hyderabad in the Indian state of Telangana.

Study Approval

The study was approved by Ethical Committee of Sree Dattha Institute of Pharmacy. Permission for access to patient case sheets and electronic medical records for the collection of data was taken from the Head of the Medical Record Room Department before starting the study.

Sample Size

A total of 73 patients with Acute Lymphoblastic Leukemia who received leucovorin in their HDMTX cycles in their consolidation phase of their treatment protocol of BFM 90 modified BFM 95, GMALL.

Inclusion Criteria

All the inpatients with Acute Lymphoblastic Leukemia receiving high dose methotrexate in their consolidation phase of treatment protocol which incorporate a wide range of hereditary changes and chromosomal translocations and a wide range of karyotyping and cytogenetics by a specialist clinical oncologist in oncology department included in

the study. The patients who were under BFM 90, modified BFM95, GMALL were included.

Exclusion Criteria

1. All outpatients in OPD's.
2. Mentally ill patients.
3. Pregnant and lactating women.
4. Geriatric population.
5. Patients less than 1 year.
6. Patients receiving combinational chemotherapy along with high dose methotrexate.
7. Patients of relapsed ALL.

Plan of Work

1. Study was carried out to evaluate the number of leucovorin doses given to a patient with Acute Lymphoblastic Leukemia receiving High dose Methotrexate.
2. The information was collected from the Biochemistry department, medical record room and pediatric wards.
3. Then the data was collected from the Patient case sheets and Electronic medical records.
4. A standard data entry format for collecting patient's details was designed and the data collected included Patient Demographic details; Chief Complaints; Diagnosis; Medical History; Laboratory data related to Hematology, Renal etc. and supportive medications such as Leucovorin (no. of doses, route of administration, duration, and frequency, hydration, Alkalization agents etc.).
5. Literatures which support the study was collected and were reviewed for study on clinical use of High dose Methotrexate in Acute Lymphoblastic Leukemia patients.

Statistical Analysis

The average number of Leucovorin doses in HDMTX in ALL patients with respect to gender, age group, differential diagnosis and toxic side effects was determined by using SPSS statistics software version 26.0.

RESULTS

A study was performed with a total of 73 patients with acute lymphoblastic admitted in the hospital. The Mean Age was 15.9 years and the standard deviation was 11.7 years represented in Figure 1. Among the 73 subjects, 26% (19) were found to be diagnosed with B-ALL, 63% (46) with PRE-B-ALL and 11% (8) with T-ALL respectively represented in Figure 2.

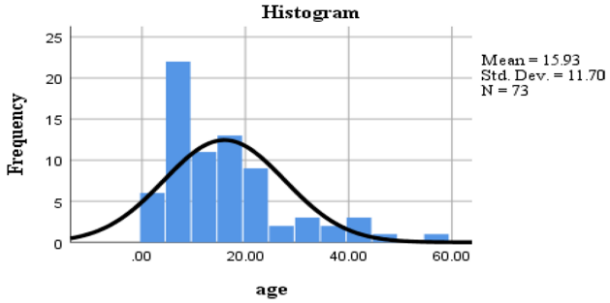

Figure 1: Histogram of Age Groups

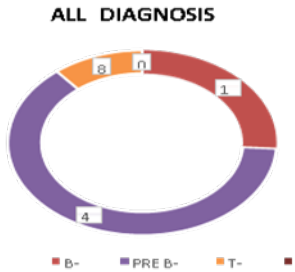

Figure 2: Pie chart Distribution of subjects based on diagnosis

In the male patients who received HDMTX dose of 1-5g/m^2 the average LV dose was 5, 5-7g/m^2 the average LV dose was 8 and 7g/m^2 and above the average LV dose was 9 respectively. Whereas, in the female patients who received HDMTX dose of 1-5g/m^2 the average LV dose was 6, 5-7g/m^2 the average LV dose was 7 and 7g/m^2 and above the average LV dose was 6 respectively and shown in Table 1.

Among age group of children who received HDMTX dose of 1-5g/m^2 the average LV dose was 5, 5-7g/m^2 the average LV dose was 5 and 7g/m^2 and above the average LV dose was 0 respectively. Among the age group of adolescents who received HDMTX dose of 1-5g/m^2 the average LV dose was 6, 5-7g/m^2 the average LV dose was 8 and 7g/m^2 and above the average LV dose was 7 respectively. Among age group of adults who received HDMTX dose of 1-5g/m^2 the average LV dose was 6, 5-7g/m^2 the average LV dose was 8 and 7g/m^2 and above the average LV dose was 9 respectively. These details were shown in Table 2.

Table 1: Calculation of Average Leucovorin Doses for Hdmtx Categories with Respect to Gender

Gender	HDMTX Doses	Average Leucovorin Doses
Male	1-5g/m^2	5
	5-7g/m^2	8
	7g/m^2	9
Female	1-5g/m^2	6
	5-7g/m^2	7
	7g/m^2	6

Table 2: Calculation of Average Leucovorin Doses for Hdmtx Categories with Respect to Age Group

Age Group	HDMTX Dose	Average Leucovorin Dose
Children	1-5g/m^2	5
	5-7g/m^2	5
	7g/m^2	-
Adolescents	1-5g/m^2	6
	5-7g/m^2	8
	7g/m^2	7
Adults	1-5g/m^2	6
	5-7g/m^2	8
	7g/m^2	9

Table 3: Calculation of Average Leucovorin Doses for Hdmtx Categories with Respect to Diagnosis

Diagnosis	HDMTX Doses	Average Leucovorin Doses
B-ALL	1-5g/m^2	6
	5-7g/m^2	8
	7g/m^2	9
PRE-B-ALL	1-5g/m^2	5
	5-7g/m^2	8
	7g/m^2	7
T-ALL	1-5g/m^2	7
	5-7g/m^2	8
	7g/m^2	0

Among B-ALL patients who received HDMTX dose of 1-5g/m^2 the average LV dose were 6, 5- 7g/m^2 the average LV dose were 8 and 7g/m^2 and above the average LV dose were 9 respectively. Among PRE-B-ALL patients who received HDMTX dose of 1-5g/m^2 the average LV dose was 5, 5-7g/m^2 the average LV dose was 8 and 7g/m^2 and above the average LV dose was 7 respectively. Among T-ALL patients who received HDMTX dose of 1-5g/m^2 the average LV dose was 7, 5-7g/m^2 the average LV dose was 8 and 7g/m^2 and above the average LV dose was 0 respectively. These details were shown in Table 3.

Among the category of HDMTX dose of 1-5g/m^2, the highest average number of LV doses received are 6 i.e., out of 43 subjects, 14 (32.5%) have received 1-5g/m^2. Among the 5-7g/m^2 category, the highest average number of LV doses received are 6 i.e., out of 26 subjects, 6 (23.07%) have received 5-7g/m^2. Among 7g/m^2 and above category, the highest average number of LV doses received are 6 and 9 with each average dose consisting of 2 subjects out of total 4 subjects. These details were shown in Table 4.

The Chi-Square Test was conducted for testing the statistical significance of association between HDMTX dose and average LV doses at 5% level of significance, the Asymptotic (2 sided) Significance is 0.121 which is more than the critical level of 0.05 shown in Table 5. Therefore, it can be concluded that there is a significant level of association between HDMTX dose and average LV doses.

Table 4: Cross Tabulation of Hdmtx Dose and Average Number of Leucovorin Doses

S.No	Average Leucovorin Doses	1-5g/m^2	5-7g/m^2	7g/m^2 and above	Total
1	Count	7	1	0	8
	% Within average leucovorin dose	87.5%	12.5%	0%	100.0%
2	Count	6	1	0	7
	% Within average leucovorin dose	85.7%	14.3%	0%	100.0%
3	Count	4	2	0	6
	% Within average leucovorin dose	66.7%	33.3%	0%	100.0%
4	Count	3	5	2	21
	% Within average leucovorin dose	37.5%	23.8%	9.5%	100.0%
5	Count	2	3	0	9
	% Within average leucovorin dose	28.6%	33.3%	0%	100.0%
6	Count	1	5	0	8
	% Within average leucovorin dose	50.0%	62.5%	0%	100.0%
7	Count	0	3	2	7
	% Within average leucovorin dose	0%	42.9%	28.6%	100.0%
8	Count	0	1	0	2
	% Within average leucovorin dose	0%	50.0%	0%	100.0%
9	Count	14	1	0	1
	% Within average leucovorin dose	66.7%	100.0%	0%	100.0%
10	Count	6	3	0	3
	% Within average leucovorin dose	66.7%	100.0%	0%	100.0%
11	Count	0	1	0	1
	% Within average leucovorin dose	0%	100.0%	0%	100.0%
Total	Count	43	26	4	73
	% Within average leucovorin dose	58.9%	35.6%	5.5%	100.0%

Table 5: Calculation of Association Between Hdmtx Doses and Average Number of Leucovorin Doses

	Chi-Square Tests value	df	Asymptotic significance (2-sided)
Pearson chi-square	27.526[a]	20	.121

Table 6: Calculation of Association Between Hdmtx Dose and Nausea/Vomiting

	Chi-Square Tests Value	df	Asymptomatic significance (2-sided)
Pearson Chi-Square	1.814	2	.404

Table 7: Calculation of Association Between Hdmtx Dose and Loose Stools

	Chi-Square Tests Value	df	Asymptomatic significance (2-sided)
Pearson Chi-Square	2.583	2	.240

Table 8: Calculation of Association Between Hdmtx Dose and Fever Spikes

	Chi-Square Tests Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	.826	2	.662

Table 9: Calculation of Association Between Hdmtx Dose and Oral Mucositis

	Chi-Square Tests Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	.324	2	.850

The Chi-Square Test was conducted for testing the statistical significance of association between HDMTX dose and nausea/ vomiting at 5% level of significance, the Asymptotic (2 sided) Significance is 0.404 which is more than the critical level of 0.05 shown in Table 6. Therefore, it can be concluded that there is a significant level of association between HDMTX dose and nausea/ vomiting.

The Chi-Square Test was conducted for testing the statistical significance of association between HDMTX dose and loose stools at 5% level of significance, the Asymptotic (2 sided) Significance is 0.240 which is more than the critical level of 0.05 shown in Table 7. Therefore, it can be concluded that there is a significant level of association between HDMTX dose and loose stools.

The Chi-Square Test was conducted for testing the statistical significance of association between HDMTX dose and fever spikes at 5% level of significance, the Asymptotic (2 sided) Significance is 0.662 which is more than the critical level of 0.05 shown in Table 8. Therefore, it can be concluded that there is a significant level of association between HDMTX dose and fever spikes.

The Chi-Square Test was conducted for testing the statistical significance of association between HDMTX dose and oral mucositis at 5% level of significance, the Asymptotic (2 sided) Significance is 0.850 which is more than the critical level of 0.05 shown in Table 9. Therefore, it can be concluded that there is a significant level of association between HDMTX dose and oral mucositis. Association between Gender and Diagnosis of ALL was represented in Figure 3.

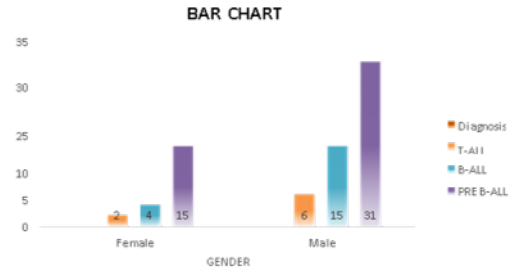

Figure 3: Bar Chart Representation of Association Between Gender and Diagnosis of ALL

DISCUSSION

It was observed that, PRE-B-ALL sub type is the most common followed by B-ALL and T-ALL sub types, also that, the three sub types of ALL are diagnosed more in male rather than in female, from which it can be concluded that, males are at higher risk of being diagnosed with ALL rather than female. PRE-B-ALL diagnosis was more in children than in adolescents, making children the highest risk group among PRE-B-ALL categories. However, B-ALL and T-ALL were mostly diagnosed in adults followed by children and adolescents.

An association between HDMTX doses and average number of LV doses in with respect to gender, age group and diagnosis was found in the study. The most average number of LV doses among the 73 subjects is 6 for all the three categories of HDMTX doses. It was found that, the average LV doses administered to female were independent of HDMTX doses as the range of LV doses was only 1, whereas, the range of average LV doses administered to male with respect to HDMTX doses was 4, making the average LV dose dependent on HDMTX doses for male. The average LV dose given to adolescents and adults depends on the HDMTX dose whereas, it did not depend in the case of children. Average LV doses were associated with HDMTX doses with respect to PRE-B-ALL, B-ALL and independent with respect to T-ALL.

In terms of toxicity, out of a total of 73 patients, 24

patients showed symptoms related to HDMTX toxicity of which, 13 patients received HDMTX dose of 1-5g/m^2, 9 patients with dose of 5-7g/m^2, and 2 patients with 7g/m^2 and above.

We have also found an association between the dose of HDMTX and toxicity symptoms. Out of 12 patients who showed nausea /vomiting, 6 patients received HDMT dose of 1-5 g/m^2, 6 patients received 5-7 g/m^2 and none received 7g/m^2 and above. Amongst 6 patients who had loose stools, 2 received HDMTX dose of 1-5 g/m^2, 4 received 5-7 g/m^2 and none received 7g/m^2 and above. The results were similar with fever spikes and oral mucositis.

Hence, nausea/vomiting is the most common side effect for HDMTX even with respect to HDMTX dose, followed by loose stools and oral mucositis whereas fever spike was found in none. Oral mucositis is found to be the less frequent and dose-dependent toxic effect of HDMTX.

CONCLUSION

From the study, we have achieved our primary objective of calculating the average number of Leucovorin rescue doses given with respect to HDMTX in the consolidation phase of the treatment plan of ALL patients. A strong association was identified between the HDMTX doses and average number of LV doses given through chi-square test with a significance level of 5%, the asymptomatic significance (2-sided) of 0.121, which is more than the critical level of 0.05. Hence, it can be concluded that there is a significant level of association between HDMTX doses and average number of LV doses given. It was evident from the results that HDMTX toxicity can be developed any time after 24 hours from the start of HDMTX infusion and it is dependent on HDMTX dose and rate of elimination. A significant level of association was also found between the HDMTX toxicity symptoms and age group, gender, diagnosis and HDMTX doses.

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Conflict of Interest

The authors declare that there is no conflict of interest for this study.

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