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High Dose Methotrexate and Leucovorin Rescue Therapy in Childhood Malignancies: Experience in Resource-Limited Country

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Abstract

Background*: Administration of high dose methotrexate (HDMTX) needs meticulous monitoring. Limitations in the availability of trained staff and adequate infrastructure often are great problems in the developing country like Bangladesh.*

Objective*: The aim of this study was to evaluate the HDMTX toxicities by monitoring biochemical and serological markers where facility for serum MTX level in a tertiary care centre (Combined Military Hospital, Dhaka) of Bangladesh is available.*

Methods: *An explorative study was done among twelve cases with a confirmed diagnosis of Pre-B & T cell ALL, Burkitt's lymphoma, T cell lymphoma and osteosarcoma. All of them received four cycles of HDMTX as part of their treatment. Demographic profile, details of HDMTX infusion and Leucovorin rescue and toxicities were collected and analyzed.*

Results: *We evaluated and compared toxicity of repeated courses of high dose methotrexate (HDMTX) in five groups of pediatric patients. Neutropenia was observed in 83.3% case and vomiting in 70% during chemotherapy. Diarrhoea 12.5%, oral mucositis in 56.20% patients were noted. Low hemoglobin level, was observed in 14.58%, thrombocytopenia in 20.80% patients. Vomiting and diarrhea was most frequent in cycle 2>1>3>4, whereas mucositis, fever was most frequent in Cycle 1>2>3>4 and raised serum transaminase in cycle 3>2>1>4. Two patients had <100 creatinine clearance. There was significant relationship between neutropenia with toxicities like vomiting and mucositis ($p<0.05$).*

Conclusion: *The administration of HDMTX therapy was found to be safe without any life threatening adverse effect in a developing country like Bangladesh where there is lacking of lab support and adequate supportive management.*

Keywords: *Acute Lymphoblastic Leukemia; children, HDMTX, Leucovorin, Rescue therapy.*

Introduction

Fortunately cancer in children and adolescents is rare, but it has been noticed that the overall incidence of childhood cancer has been slowly increasing since 1975.[1] Over the last two decades dramatic improvements have been achieved in pediatric malignancies,[1] survival rate has been raised to 80-90% depending on advancement of disease. Many of the improvements are due to use of treatment with multidispilnary approach.[2]

Methotrexate (MTx) first demonstrated efficacy as a chemotherapeutic agent in acute lymphoblastic leukemia (ALL) in 1947.[3] Since that time, it became one of the most widely studied anticancer agents. Methotrexate is unique; in that it can be administered safely in a multitude of dosing strategies, including high-dose methotrexate (HD-MTX) which is defined as doses $\geq$1 g/m2.[4] It is a classical antifolate that inhibits dihydrofolic acid reductase and thymidylate synthase, enzymes that are crucial components of

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purine nucleotide and thymidylate synthesis pathways, and their inhibition ultimately interferes with DNA synthesis, repair, and cellular replication.[5,6] It is historically and currently indicated for use in pediatric neoplastic disorders, such as ALL, meningeal leukemia, osteosarcoma, some brain tumors, and non-Hodgkin's lymphoma.[7-9] These neoplastic indications are well established and researched, almost always required combination therapy.[10]

In the late 1960s, Djerassi et al. showed that increasing the dosage of MTX would secure new remissions in patients who had relapsed while receiving the drug at a lower dosage. Wang et al. demonstrated that an intravenous (IV) MTX infusion at 500 mg/m^2 over 24 hours would produce sufficiently high levels of the drug in cerebrospinal fluid to eradicate central nervous system (CNS) leukemia.[11] High-dose Methotrexate (HDMTX, i.e., higher than 1 g D m^2), is a common component of many chemotherapeutic protocols for children with ALL.[12] The combination of intrathecal chemotherapy with systemic high-dose MTX and Leucovorin rescue is an effective CNS-directed therapy. Cranial irradiation plays a crucial part in acute leukemia treatment but can also result in adverse effects on the developing brain. The elimination of cranial irradiation from current treatment protocols has improved the neurocognitive outcome without compromising survival rates.[13] The regular MTX dose of later years has been in the range of 5-8 g/m^2. The intravenous MTX dose has actually varied from 2 to 33.6 g/m^2. The highest dose, 33.6 g/m^2, has been without intrathecal instillation.[14] In various disease doses of MTX varies, for pediatric osteosarcoma doses of 12 gm/m2/ of MTX followed by leucovorin[15,16] then surgery follows with doxorubicin and cisplatin. ALL has dose ranges from 1-8 g per m^2.[17] The dose depends on the combination and whether it is CNS involved at diagnosis.[17] Meningeal leukemia, doses of intrathecal MTX are 2g/m^2/week, followed by systemic infusion of MTX within the range of 1-5 g/m2 with leucovorin rescue.[18] The recommended doses for intrathecal MTX are 6 mg for a child under 1 year of age, 8 mg for a 1 year old, 10 mg for a 2 year old, and 12 mg for any child over the age of 3.[19]

Post-HDMTX toxicity is common, and associated with increased risk of infections and interruption of maintenance treatment, which has been linked to a reduced cure rate. The enzyme methylene tetrahydrofolatereductase (MTHFR) catalyses the irreversible conversion of 5,10-methylene tetrahydrofolate to 5-methyl tetrahydrofolate.[20] The side effects profile of MTX varies markedly according to dose and duration.

The HD MTX usually deliver in lethal dose over 4 to 36 hours infusion and require 2-3 days period of multiple leucovorin doses to terminate the toxic effects of MTX which termed as Rescue. Successful rescue by leucovorin depends on rapid elimination of MTX by kidneys, which requires aggressive pretreatment as well as post treatment hydration and urinary alkalization.[10] Low dose (<30 mg/m^2) and intermediate dose (< 1 gm/m^2) MTX usually not provide therapeutic concentration in CSF.[10] Known side effect and toxic manifestations include bone marrow depression, mucositis, diarrhea, liver and kidney dysfunction, dermatitis, and neurologic disturbances. However, severe and fatal reactions have also been reported following this method of administration.[21] Alkalinization, vigorous hydration and rescue with leucovorin are needed to minimize the toxicity of this drug.[22]

There is great concern about the quality of life among the directed therapy is an integral part of the treatment of pediatric malignancies especially ALL.[23] Despite more than 50 years of evaluation and treatment refinements, important questions remain to be addressed about how best to use methotrexate for children with ALL.

The aim of this study was to evaluate the HDMTX toxicities by monitoring biochemical and serological markers where facility for serum MTX level is not available.

Materials and Methods

This explorative study was conducted in the paediatric haematology and oncology unit of Department of Paediatric in Combined Military hospital (CMH), Dhaka, Bangladesh. Twelve (12) childhood cancer patients with ages ranged from 2 to 16 years who received high dose Methotrexate from July 2014 to December 2015 in the same institute were selected for this study. They were newly diagnosed confirmed cases of childhood cancer like ALL (T Cell & Pre B Cell High risk group), NHL (T cell, Burkitt lymphoma stage IV), osteosarcoma were treated with disease specific intensive treatment protocol. Exclusion criteria were 1. Patients who received low or intermediate

doses of MTx, 2. Patients with Standard risk of malignant disease. 3. Patient with impaired renal function 4. Cytogenetics was excluded to categorize high risk.

For each child a semi-structured questionnaire was prepared. Informed written consents were obtained from parents of patients. For every child proper counseling had been done with their parents providing adequate information about diet, living habits, oral and anal care and most importantly maintaining hygiene with hand washing method.

The confirmation of diagnosis of ALL was done by cytomorphological and immunophenotyping of Peripheral blood and Bone marrow smears, risk stratification was done by cytogenetics. In case of NHL & Osteosarcoma diagnosis was done by histopathology (by FNAC, excision tissue biopsy) of lymph node or palpable tumor mass and immunohistochemistry. Opinion were taken from surgeon, pathologists. Assessment of the staging of the disease was made on physical examination, radiology and laboratory studies. Intensified systemic combination chemotherapy was administered to all patients, for T Cell ALL variety TMC T Cell, Pre B ALL Cell variety TMC Pre B protocol, lymphoblastic lymphoma (LL) BFM protocol, for Osteosarcoma EUROMOS chemotherapy protocol were provided. During proving High Dose Methotrexate, dose and schedule were chosen according to the disease specific protocol. In case of Pre B ALL 3 gm/m^2, T-cell ALL 5 gm/m^2, NHL-T cell 5 gm/m^2, NHL-Burkitt 8 gm/m2, Osteosarcoma 12 gm/m^2. First dose of leucovorin rescue was given at 42 hours from the start of HD-MTX infusion in ALL (T cell, Pre B High risk) & NHL- T cell and 24 hours in case of osteosarcoma and NHL (Burkitt) at dose of 15 mg/m^2 6 hourly 10-12 doses. All patients received appropriate supportive care with Antimicrobials, blood and platelet transfusions and nutritional diet.

The following clinical data were collected: details of HDMTX infusion, urine pH, fluid intake, and urine output. Details of leucovorin rescue including starting time, doses & duration of rescue was recorded. Toxicities were observed and recorded like Nausea, vomiting, diarrhea, mucositis, myelosuppression, fever. Effects like hematological parameter, liver function, kidney function were recorded .Additional hospitalization delay for the next cycle of chemotherapy was not assessed in this study. Stage and measurement of toxicities severity were done by World Health Organization's (WHO's) "Toxicity Grading Scale for Determining the Severity of Adverse Events."

Hematological Toxicity Grade-1: Hemoglobin 10-10.9 gm/dL, Absolute Neutrophil Count (ANC) 750-1200/mm^3, Platelets 75,000-99,999/mm^3, Grade-2: Hemoglobin 7.0-9.9 gm/dL, ANC 400-749/mm^3, Platelets 50,000-75,000/mm^3, Grade-3: Hemoglobin <7 gm/dL, ANC 250-399/mm^3 Platelets 25,000-49,999/mm^3, Grade-4: Hemoglobin- cardiac failure secondary to anemia, ANC <500/mm^3, Platelets <25,000/mm^3.

Hepatotoxicity by ALT (SGPT) Grade-1 is 1.1 - 4.9xULN Grade-2 is 5-9.9xULN, Grade-3 is 10-15xULN, Grade is >15xULN.

Gastrointestinal toxicity like Nausea Grade-1: mild or transient, Grade-2: Moderate-decreased oral intake, Grade-3: Severe-little oral intake, Grade-4 Unable to ingest food or fluid for more than 24 hours. Vomiting grade-1 is 1 episode/day, grade-2 is 2-3 episodes/day, grade-3 is 4-6 episodes/day, grade-4 is greater than 6 episodes per day or intractable vomiting. For diarrhea grade-1: slight change in consistency and/or frequency of stools, grade-2: liquid stools, grade-3: liquid stools greater that 4x the amount or number normal for this child grade 4 Liquid stools greater than 8x the amount or number normal for this child. Stomatitis grade 1: Mild discomfort, grade-2: Painful, difficulty swallowing, but able to eat and drink. Grade-3: Painful: unable to swallow solids, grade 4 Painful: unable to swallow liquids; requires IV fluids.

Nephrotoxicity were graded by creatinine measurement according to age group. For children of 2 to 12 years of age grade 1: 0.7-1.0 mg/dL, grade-2: 1.1-1.6 mg/dL, grade 3: 1.7-2.0 mg/dL, grade 4: >2.0 mg/dL. For children greater than 12 Years of age grade-1: 1.0-1.7 mg/dL, grade-2: 1.8-2.4 mg/dL, grade-3: 2.5-3.5 mg/dL, grade-4: >3.5 mg/dL.

All this information had enrolled to a questionnaire. Data analysis was done by using statistical package for social science (SPSS 20). The findings were considered statistically significant at P value of <0.05.

There had not been any ethical compromise in preparation of this report nor there any possibility of any harm for anybody from the dissemination of this report. This study did not give any extra financial burden to the family. Reassurance was given to parents

regarding safety during study and benefit for clinicians for future patients.

Results

We observed total twelve patients were in this study. Among them nine were male and three were female child. Body Surface Area (BSA) ranges from 0.62 m^2-1.2 m^2, average 0.8 m^2. Age ranges from 23 months to 12 years. Patient's characteristics were shown in Table I.

Table I

Patient's characteristics (n=12)

Characteristics	Variables	Number	Percentage
Gender	Male	9	75.0
	Female	3	25.0
Age at diagnosis	1-10 years	8	66.7
	>10 years	4	33.3
Diseases	ALL- 09	9	75.0
	Pre B All	7	58.3
	T cell All	2	16.7
	NHL Burkitt's	1	8.3
	NHL T- Cell	1	8.3
	Osteosarcoma	1	8.3
BSA Range		0.62-1.2	
Median		0.91	

We evaluated and compared toxicity of high dose methotrexate (HDMTX) repeated courses in five groups of pediatric patients seven patients had Pre-B ALL and were treated with four courses of HD-MTX (total of 28 courses); two patients had ALL- T cell and were treated with four courses of HD-MTX (total 08 courses), one patient with NHL T-cell received 04 cycles of HD-MTX, one patient of NHL (Burkitt) treated with four courses of HD-MTX, one patient diagnosed as non-metastatic osteosarcoma of extremities, treated with four courses of HD-MTX in his preoperative phase of treatment. All the cycles met the prerequisite criteria of prehydration, urine alkalanization. During methotrexate infusion duration of methotrexate infusion, rate of flow, duration of post hydration along with appropriate leucovorin rescue also considered strictly.

The frequencies of various toxicities observed with HDMTX are shown in Table II.

Hematological toxicity (83.3%) and vomiting (70%) were the most frequent toxicity

Among all GIT Toxicity, vomiting (70%) was the most frequent; but only 14.6% cycles had grade 3 [6-10 episodes of vomiting]. Diarrhea occurred in 12.5% cases, however grade 3 [7 to 9 episodes of diarrhea] and 4 [more than 9 episodes of diarrhea] were not observed in any of the cycles. Oral mucositis occurred

Table II

Observed Toxicities with HD-MTX infusion by cycle number

Toxicities	Cycle -1 No (%)	Cycle-2 No (%)	Cycle -3 No (%)	Cycle -4 No (%)	Cycle -5 No (%)
Vomiting					
Total	09 (75)	10 (83.3)	08 (66.7)	07 (58.3)	34 (70.9)
Grade 1 & 2	06 (50)	07 (58.3)	07 (58.3)	07 (58.3)	27 (56.3)
Grade 3 & 4	03 (25)	03 (25)	01 (08.3)	0 (0)	07 (14.6)
Diarrhea					
Total	02 (16.7)	03 (25)	01 (1.3)	0 (0)	06 (12.5)
Grade 1 & 2	02 (16.2)	03 (25)	01 (1.3)	0 (0)	06 (12.5)
Grade 3 & 4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Mucositis					
Total	09 (75.0)	08 (66.7)	07 (58.3)	03 (25)	27 (56.2)
Grade 1 & 2	07 (58.3)	06 (50.0)	07 (58.3)	03 (25)	23 (47.9)
Grade 3 & 4	02 (16.7)	02 (16.7)	0 (0)	0 (0)	04 (8.3)
Fever	05 (41.7)	04 (33.3)	03 (25)	02(16.7)	14 (29.2)
Raised ALT	02 (16.7)	01 (8.3)	03 (25)	0 (0)	06 (12.5)
Creatinine clearance(<100)	01 (8.3)	0 (0)	0 (0)	01(8.3)	02 (4.12)
Impaired GFR	01(8.3)	0 (0)	0 (0)	01(8.3)	02 (4.12)
Neutropenia	12(100)	10 (83.3)	10 (83.3)	08 (66.7)	40 (83.3)
Thrombocytopenia	05 (41.7)	03 (25)	01 (8.3)	01 (8.3)	10 (20.8)

in 56.2% patients and grade 3, as defined by presence of painful ulcer erythema/edema and cannot tolerate diet & can swallow liquid, occurred in 08.3%. None needed parenteral nutrition.

Hematological toxicity in the form neutropenia (ANC <1 x10^9/L) was observed in 83.30% patients. This changes starts to occur from day 5 of starting HD-MTX cycle onwards and hematological recovery usually occurred by day 12 as evident by median ANC. These patients were managed by G-CSF except ALL patients for whom we waited for spontaneous recovery. Thrombocytopenia (platelet count <50x10^9/L) was observed in 20.8% patients (Table II). They were managed by transfusion of platelet concentrate.

Transient elevation of serum alanine transaminases (ALT) levels occurred in 12.5% cases, ranging from 5 to 30 times upper than normal limit. It was occurred in patient with Pre-B ALL & osteosarcoma. They returned to normal level in subsequent follow-up. Nephrotoxicity (raised serum urea, creatinine, potassium and low GFR) was not observed but creatinine clearance (CCr) <100 found in two patients. Neurotoxicity (convulsion) did not occur in any patient.

Fever was observed in 29.2% cases, mostly seen in patients with Pre B ALL, T cell ALL and Osteosarcoma.

Vomiting and diarrhoea was most frequent in cycle 2>1>3>4, whereas mucositis, fever was most frequent in Cycle 1>2>3>4 and raised serum transaminase (ALT) in cycle 3>2>1>4.

There was significant relationship between neutropenia with toxicities like vomiting and mucositis were found ($p<0.05$) (Table III) whereas others had no significant association.

Table-III

Toxicities in relation with neutropenia

Neutropenia vs. other toxicities	Neutropenia present	Neutropenia absent	P-value*
No. of cycles=48	40/48 (83.30)	8/48 (16.7)	
Vomiting	30 (75)	02 (25)	0.002
Diarrhea	06 (15)	08 (100)	0.313
Mucositis	23 (57.5)	07 (87.5)	0.049
Fever	12 (30)	08 (100)	0.572
Raised ALT	05 (12.5)	07 (87.5)	0.687
Thrombocytopenia	09 (22.5)	07 (87.5)	0.464

Discussion

Leukemia is a clonal disease resulting from genetic mutations and transformation of a single early progenitor myeloid or lymphoid cell. Despite much research the causes of acute leukemia remain largely unknown.[24] It is the most common childhood malignancies, comprises 25-30% of all childhood cancers. Acute leukemias constitute 97% and Chronic myeloid leukemias constitute 3% of all childhood leukemias. peak incidence is between 2 and 5 years of age. [25]

NHL, third most common childhood malignancy after leukemia and CNS tumor; represents approximately 6-8% of all malignancies in patients under 20 years of age. Median age of presentation is 10 years. Pediatric NHL is mostly (more than 95%) high-grade and includes the following four major subtypes: (1) B- and T-lymphoblastic lymphoma (LL) (2) Burkitt lymphoma (BL) (3) Diffuse large B-cell lymphoma (DLBCL) (4) ALCL.[25] At present, 80–90% of children with NHL are cured with intensive risk-adapted chemotherapy in the developed countries. [26]

Malignant bone tumors constitute approximately 6% of all childhood malignancies, osteosarcoma (54%) is the most common among them in children under 20 years of age. [25] Osteosarcoma (OS) is a pleomorphic malignant tumor of bone in which the proliferating spindle cells produce osteoid or immature bone. [27] Advances in adjuvant and neo-adjuvant chemotherapy have improved the 5 year disease-free survival to more than 60%.[28]

Methotrexate is one of the folate antagonists used in different childhood malignancies like ALL and has been a mainstay of treatment ever since. A biological explanation for its efficacy may lie in the ability of lymphoblasts, particularly those of common ALL, to accumulate methotrexate, and the correlation of this ability with a better chance of long term survival.[29] MTX exerts its cytotoxic effects by competitively inhibiting dihydrofolate reductase (DHFR), the enzyme responsible for converting folates to tetrahydrofolate, the reduced folate carriers which function in the transfer of carbon units. These carbon units are responsible for *de novo* purine synthesis and the methylation of purine to thymine in DNA synthesis. To avoid excessive destruction of host cells, leucovorin (a folate analogue) is used to rescue cells from MTX inhibition. [30] In cancer chemotherapy, routine monitoring of drug concentrations has been practical only for

methotrexate (MTX). The primary setting for pharmacokinetic monitoring of MTX done only if uses in high doses as adjuvant therapy for osteosarcoma, for single-agent treatment of intracranial lymphomas, and in combination therapy of childhood leukemia as well as adult and pediatric non- Hodgkin lymphomas. [31]

Serum concentrations and pharmacokinetic parameters of MTX are not related with outcome of ALL. Prognoses based on single-drug pharmacokinetic estimates within a complex multiple-agent protocol appear to be unreliable. However, therapeutic drug monitoring of HD-MTx remains a useful tool for early detection of impaired elimination and thus avoiding systemic toxicity.[12] But it was not done in this study as this serological test is not available in our country. Here, we strictly maintained the hyper hydration, urine alkalinity, leucovorin rescue. We also routinely assessed serological and biochemical investigations for early detection and prevention of toxic effects of HDMTX.

MTX is poorly soluble at acidic pH, and its metabolites, 7-OH-MTX and DAMPA, are six- to tenfold less soluble than MTX, respectively. An increase in the urine pH from 6.0 to 7.0 results in a 5 to 8 fold greater solubility of MTX and its metabolites. This finding encourages the recommendation of Intravenous hyper hydration and urine alkalinization. Hydration started from 12 hours before MTX infusion and continuing up to 24-48 hours, at the rate of 2.5–3.5 liters of fluid/m^2/24 hours. Urine alkalinization done with sodium bicarbonate at the dose of 40–50 mEq per liter of I/V fluid; prior to, during, and after the administration of HDMTX along with hydration. Urinary alkalinization also reduces the risk of intratubular renal crystal formation. [32]

For more than 30 years, leucovorin rescue has been a cornerstone of HDMTX treatment. Early HDMTX protocols were built on the observation that MTX toxicities could be prevented or ameliorated in patients with high plasma MTX concentrations who received pharmacokinetically guided doses of leucovorin. Leucovorin is particularly effective in the prevention of myelosuppression, GI toxicity, and neurotoxicity during treatment with HDMTX. Standard chemotherapy protocols now include leucovorin administration within 24 to 36 hours of HDMTX to prevent normal cells from suffering injury.[33]

Assessment of renal function may be a useful means of monitoring plasma MTX concentrations during HDMTX for ALL and NHL[34] We had assessed estimated Creatinine Clearance (CCr) and GFR (Schwartz method) as a method of renal function in our patients by considering all above mentioned criteria as MTX level cannot be done in our country and follow up also done for six months after chemotherapy. Only two patients developed CCr <100 during chemotherapy which subsequently became normal in next follow-up. There was no significant deterioration of renal functions which was also observed by Maryna KR et al. and Ridolfi L et al. [35,36] The vast majority of MTX is cleared by the kidneys (more than 90%). Using hyper hydration of fluids to induce high urinary flow rates protects the kidney from injury during treatment with HDMTX. Intavenous fluids can also be used to correct hypovolemia and reduce the risk of HDMTX associated nephrotoxicity.

Proper monitoring and supportive care along with tailoring treatment is vital in improving cure rates and minimizing toxicities in childhood ALL.[37] In our study, clinical monitoring, hydration, urine alkalization, GFR monitoring, and leucovorin rescue remain essential to HDMTX administration. Among these, ensuring a urine pH of >7.0 and prehydration at least 06 hours before start of HDMTX infusion, bedside pH monitoring per void, intravenous hydration, and exact timing of first dose of leucovorin are not to be compromised. Though monitoring methotrexate level is necessary for every cycle to detect early complication of HDMTX we could not do that due to unavailability of this test in our country rather we monitored drug toxicities by above mentioned parameters.

In different studies the common toxicities were encountered like vomiting, diarrhea, mucositis, fever, myelosuppression, and elevated transaminase levels. [11,12,20-22,38-40] In this study, gastrointestinal toxicity in the form of vomiting (70%) was commonly found.

Hematological toxicity in the form of v3.0 (CTCAE) grade-3 & 4 neutropenia was observed in 83% cycles and were higher than what the other studies have reported 25% [23] and 8-9%.[41,42]

GIT toxicities in the form of vomiting, mucositis and diarrhea occurred in 70%, 66% and 12.5% respectively which was much higher than other studies [23,41-43] may be as because we evaluated different type of diseases with different doses of HDMTX.

Fever was present in 31.25% cycles in our study which was similar to the incidence (30%) reported by Rask et al. [41] and 28% by Kapoor et al.[23]

Abnormal liver function observed in 8.40% of cycles were not comparable to those reported in other studies 35% [23] and 50–64%.[44,45] These abnormalities were transient and reversible as also observed by others and, in children, have not been reported to result in chronic liver disease.[46]

Creatinine clearance has been generally accepted as a clinically useful measure of GFR despite some limitations. The accuracy of creatinine clearance is influenced by the completeness of timed urine collections, the amount of meat in the diet and the method of cooking, the within-subject and analytical variability, strenuous exercise, and stress trauma, severe infection, and the menstrual cycle. Creatinine clearance is proportional to body size, resulting in gender differences. Correction for lean body mass or body surface area may eliminate or reduce the gender variation.[47]

Cytogenetics is not available in our country and also for many patients unable to afford from abroad. Only few patients were able to do this test. So this has been observed only and not included in the study.

We followed up all patients by observing CBC, serum electrolyte, urea, creatinine, ALT every fortnightly for at least 06 months after HDMTX and none of them developed renal or other complications in long run.

Conclusion

It has been seen that HDMTX is safe and effective with minimum toxicities. With appropriate supportive care, toxicities are reversible even in the settings of resource limited countries like Bangladesh.

Recommendation

HDMTX can be given in a tertiary care center in developing countries, without any significant life threatening complications. Even with unavailability of serum MTX level monitoring, observing routine biochemical and serological profiles were sufficient to avoid toxicities. Trained nurses and medical staffs including meticulous monitoring of treating oncologist is the mainstay of early detection and prompt management of complications if arise. This topics study has been studied for first time, so it need further studies required to established this alternate pathway.

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