

High dose methotrexate in the treatment of children with acute lymphoblastic leukemia

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Abstract

Background It has been claimed that around 70% of childhood acute lymphoblastic leukemia (ALL) can be cured. One of the important role is high dose methotrexate (HDMTX) administration during the consolidation therapy.

Objective To determine the safety and effectiveness of HDMTX in children with ALL.

Methods We reviewed patients with ALL in Pantai Indah Kapuk Hospital, Jakarta during the period August 2000 through July 2005 with observation time run through September 2006. Only patients with normal kidney function were allowed to have HDMTX. Besides good hydration and alkalinization, patients were supported with good hygiene (mouth, skin and anal area). MTX was given in loading dose of 10% from the total dose in ½ hour and the rest 23½ hours for 90%. Leucovorin rescue was started 12 hours after discontinuation of 24 hour MTX IV infusion. Leucovorin was given until the MTX concentration reached 0.1 uM/L. Patients were stratified to low, intermediate and high risk groups; 2 gram/m² was given to low risk group and 5 gram/m² to intermediate and high risk groups.

Results There were 20 patients eligible for study. All methotrexate steady-state plasma concentrations (MTX Cp_{ss}) were above 16 uM/L, and steady state concentration in CSF was always below 0.5 uM/L for 2 gram/m² and above 0.5 uM/L for 5 gram/m² doses. All 20 cases went through the procedure with only mild side effects i. e, mild mucositis, anal furuncle and diarrhea, which recovered 2 weeks later. Only 1 high risk case with initial WBC 612X10⁹/L, succumbed after he went through the HDMTX program smoothly and relapsed subsequently during reinduction phase.

Conclusion HDMTX can be given safely to ALL patients with normal kidney function with good supportive care. Five gram/m² HDMTX effectively treat the minor disease and/or prevent CNS and testicular leukemia. This study has also given an impression that HDMTX may increase event-free survival. [Paediatr Indones 2007;47:1-6].

Keywords: HDMTX, ALL, supportive care, event-free survival rate

Childhood acute lymphoblastic leukemia (ALL) is one of the most drug-responsive of human malignancy. It is claimed that around 70% of children, even higher (up to 80%) can be cured mainly by chemotherapy and good supportive care.^{1,2} One of the important roles in the increasing EFS (event free survival) rate is high doses methotrexate (HDMTX) program during the consolidation therapy.³

Clinical trials indicated that single high dose methotrexate (1000 mg/m² 24 hours infusion) will yield higher concentration of active metabolites of MTXPG (methotrexate polyglutamate) in the blast cells compared to low dose (20-30 mg/m² p.o. every 6 hours for 6 doses).⁴ Higher concentration of MTXPG in the cell blast of ALL has been proven to give greater antileukemic effect, i.e. inhibition of purine synthetase and reduction of circulating blast cells.⁵

Clinical trial in St. Jude Children Hospital indicated that the level of systemic exposure of

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HDMTX (high dose methotrexate) can have a significant influence on clinical outcome in children with ALL. A significant relation between the steady-state plasma concentration ($C_{p_{ss}}$) of MTX and event-free survival was observed in the study of children with standard-risk ALL. In Cox proportional hazard regression analysis, patients with MTX $C_{p_{ss}} < 16 \mu\text{M}$ had a significant greater risk of early treatment failure (relapse) when compared to patients with MTX $C_{p_{ss}} > 16 \mu\text{M}$.⁶ This greater risk remained statistically significant in a multivariate analysis including other prognostic factors such as white blood cell count and DNA index. In subsequent study, MTX $C_{p_{ss}}$ (methotrexate steady state plasma concentration) remained a significant prognostic factor in patient with intermediate risk (i.e. presenting white cell count $10\text{-}100 \times 10^9/\text{L}$). A similar relationship between MTX C_{p_s} and risk of ALL relapse was also reported by Pediatric Oncology Group trial.⁷ Evan *et al* found that 24-hour infusion of MTX $1000 \text{ mg}/\text{m}^2$ combined with 6-MP $50 \text{ mg}/\text{m}^2$ and MTX $25 \text{ mg}/\text{m}^2$ p.o. give MTX $C_{p_{ss}} 9.3\text{-}25.4 \text{ mM}/\text{L}$.⁸

It is true that the clinical response of T-cell leukemia may differ. However, in a randomized study it was found that HDMTX was superior with 7 year event-free survival for B or T-cell ALL.⁵ Research data showed that it takes at least 8 hours after I.V. MTX to reach the "steady state concentration" in the cerebrospinal fluid.⁸ Without IT MTX, at least $3 \text{ gram}/\text{m}^2$ is needed to reach the therapeutic level $0.5 \mu\text{M}/\text{L}$ for treatment of subclonic invasion of malignant lymphoid cells.^{9,10}

The objective of this study was to prove that high dose of MTX can be given safely to ALL patients with normal kidney function with good supportive care. We also wanted to see whether this drug can effectively treat the minor disease, prevent the CNS and testicular leukemia and to increase the EFS with possible cure. Time duration between discontinuation of methotrexate administration and leucovorin rescue discontinuation will also be sought for.

Methods

The dose determination of MTX was based on the minimal steady state concentration to reach in plasma $16 \mu\text{M}/\text{L}$ and CSF $0.5 \mu\text{M}/\text{L}$ after HDMTX dose.

MTX dose for low risk ALL

As previously observed, administration of MTX $1 \text{ gram}/\text{m}^2$ will yield MTX $C_{p_{ss}} 9.3\text{-}25.4 \mu\text{M}/\text{L}$. We used 24 hour infusion of $2 \text{ gram}/\text{m}^2$ MTX for patients with low risk ALL that will yield $C_{p_{ss}} > 16 \mu\text{M}/\text{L}$ and MTX steady state cerebrospinal fluid concentration $< 0.5 \mu\text{M}/\text{L}$ in general. Since most ALL patients from low risk group have no CNS involvement at initial diagnosis, triple IT cytostatics may adequately prevent CNS leukemia.

MTX dose for intermediate and high risk ALL

In patients with intermediate and high risk cases, we frequently encounter subclonic CNS leukemia. Without IT MTX, at least $3 \text{ gram}/\text{m}^2$ is needed to reach therapeutic level $0.5 \mu\text{M}/\text{L}$ for treatment of subclonic invasion of malignant lymphoid cells.⁹ For those reasons, to guarantee that the level of $> 0.5 \mu\text{M}/\text{L}$ can reach cerebrospinal fluid with minimal toxicity, we used with $5 \text{ gram}/\text{m}^2$ I.V. MTX for intermediate and high risk groups. In addition, we also added triple IT.

Procedure of HMTX administration

Hydration and alkalinization

Hydration and alkalinization was started 12 hours prior to MTX administration. We used $1/5$ solution (0.2% NaCl) with infusion rate of $120 \text{ ml}/\text{m}^2/\text{hour}$ and 8.4% NaHCO_3 $6 \text{ ml}/\text{m}^2/\text{hour}$. Urine output and pH were measured between 7.0-8.0 by measuring urine volume and pH every 4 hours.

Furosemide $0.5\text{-}1.0 \text{ mg}/\text{kgBW}$ was administered if input more than output for $15 \text{ ml}/\text{kgBW}/4$ hours, and NaHCO_3 $1 \text{ ml}/\text{hour}$ was given if urine pH < 7.0 and reduced $1 \text{ ml}/\text{hour}$ if the urine pH > 8.0 . Methotrexate was given 12 hours after hydration and alkalinization with 10% loading dose from the total dose for the first $1/2$ hour followed by 90% of the total dose for the rest $23 1/2$ hours.

Intrathecal administration

We gave triple methotrexate, ara-C and hydrocortison simultaneously after loading dose, to reach steady state of MTX concentration in CSF. It usually takes 2 hours after starting of MTX infusion or 2 hours prior to the discontinuation of MTX administration.

The patient was maintained in Trendelenberg position for at least 4 hours.

Leucovorin rescue

Leucovorin 15 mg/m² was administered 36 hours after starting hydration or 12 hours after discontinuation of methotrexate administration. Interval administration is 3 hours for 5 doses and then 6 hours until plasma concentration reaches less than 0.1 μM/L.¹¹

HDMTX was administered to all patients who had gone through the initial induction (induction Ia and Ib) and at phase of consolidation (consolidation M or Block 1 and 2 for high risk group). Patients of low and intermediate groups had 4 doses while those of high risk group got 2 doses (or 4, modified as needed) with time interval 2 of weeks. Triple IT MTX, Ara-C and hydrocortison were administered at the period of presumed MTX steady state of cerebrospinal fluid concentration.

We administered HDMTX during consolidation period even though some of them were not in complete remission, but showed much improvement from the initial induction (Induction Ia and Ib). Among them, there were 2 patients with mixed lineage and 1 patient with high risk adolescence, which have showed marked improvement from the initial induction (Blast cell in the marrow above 5%, but less than 20%).

Adjuvant therapy

To reduce or eliminate side effects or complications which may develop during or after HDMTX administration, we administered additional therapies e.g., by maintaining the skin pH at 3-4 with lactoserum and lactic acid, anal pH at

2-3 with 2% acetic acid in Burrow Solution, and mouth gargle with Hexetidine.

Results

There were 20 patients enrolled during the study period, consisted of 10 patients with low risk, 6 with intermediate risk, and 4 with high risk ALL. Te total dose of HDMTX given to low risk groups were 40, to intermediate risk 24, and to high risk groups were 14.

Means of plasma steady state concentration during 24 hour administration are depicted in **Figure 1**. Level of plasma concentration ≤ 0.1 uM/L was reached in 36 to 48 hours for all risk groups, which is safe to stop the Leucovorine Rescue Program.

Table 1 depicts means and SD MTX Cp_{ss} according to low, intermediate, and high risk groups, while **Table 2** describes MTX steady state concentration in CNS 2 hours after the start according to risk groups. Means and SD of plasma MTX concentration for low, intermediate and high risk group after discontinuation of MTX administration are shown in **Figure 2**.

All patients were discharged if the level of MTX Cp_{ss} ≤ 0.1 uM/L, i.e., between 36–48 hours after

Table 1. Mean and SD MTX Cp_{ss} according to risk group

Risk group	N	Mean	SD	95% CI	
				Low	High
Low risk	10	22.68	4.83	19.69	25.67
Intermediate risk	6	60.49	18.09	46.01	74.97
High risk	4	68.14	15.06	53.38	82.90

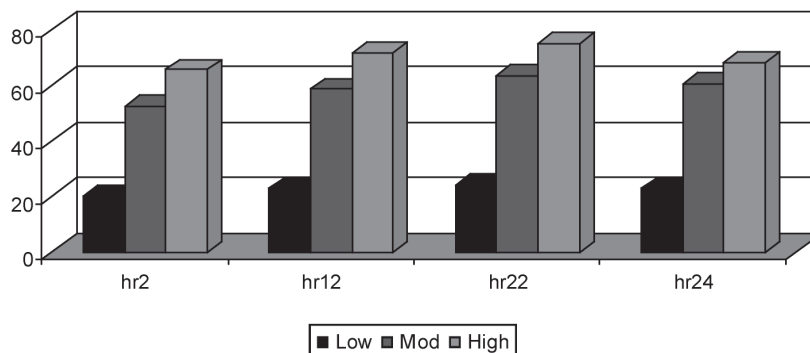


Figure 1. Means of plasma steady state concentration during 24 hour administration

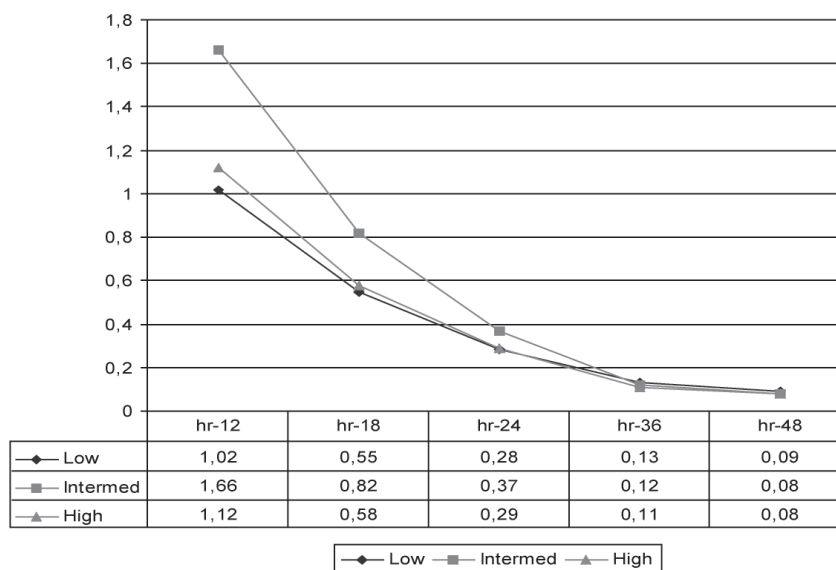


Figure 2. Means and SD of plasma MTX concentration for low, intermediate and high risk group after discontinuation of MTX administration

Table 2. MTX steady state concentration in CNS 2 hours after the start according to risk group

Risk group	N	Mean	SD	95% CI	
				Low	High
Low risk	10	0.32	0.17	0.22	0.43
Intermediate risk	6	1.35	0.66	0.83	1.88
High risk	4	1.37	0.64	0.75	2.00

discontinuation of 24-hour MTX group infusion. In term of toxicity, for low risk group there were 3 patients developed mild diarrhea after 24-hour infusion of MTX finished, but this improved in 48 hours before the patients being discharged. There were two patients in the intermediate risk group who had mild mucositis in the mouth, and one of the high risk group had furuncle at the anal area (this patient was treated with oral antibiotic) and showed much improvement. They were sent home 60 hours after the termination of MTX.

One of the 20 patients who was diagnosed with T-cell ALL with initial WBC count of $612 \times 10^9 /L$, died 5 months after being diagnosed. The patient went through severe tumor lysis syndrome; he had relapse with dominant CD33 in very depressed marrow and sepsis. The observation ranged between 5 months to 72 months with a survival rate of 95%.

Discussion

MTX $C_{p_{ss}}$ above 16 mMol/L, as it was in our class, was reported to be significantly increased in EFS. Since most ALL with low risk groups have no CNS involvement at the initial diagnosis, we believed that triple IT cytostatics should be adequate to prevent CNS leukemia.

After discontinuation of MTX, the MTX plasma concentration decreased most steeply at the first 6 hours with half-life between 30 to 60 minutes. These are due to hydration, alkalization and maintaining good urine output (always above 3ml/KgBW/hour). The decrement in the MTX concentration is much faster than that reported previously.¹¹

This study has given an impression that this procedure can reduce an unnecessary exposure of MTX to the normal tissue. This probably explained the very low/insignificant side effects and effectively improved the remission in our cases.

All MTX concentration in plasma will be at/less than 0.1 mMol/L between 36-48 hours after the discontinuation of MTX administration, which is considered safe to discontinue Leucovorine administration. There were mild side effect observed during methotrexate administration about 2 weeks,

after the termination of administration and prior to the next course of HDMTX administration. With hydration, alkalinization, maintaining the urine output at least 3 ml/kgBW/hour and good supportive cares, HDMTX administration is considered very safe to be given to low risk ALL.

All our low risk patients during observation of 1 year 8 months to 5 years 4 months are still in remission. This study has shown that HDMTX may increase long term EFS for low risk patients, but the number of patients are too small and the time of observation is too short to draw the definite conclusion.

HDMTX is also safe to be given to intermediate and high risk ALL. The dose of 5 gram/m² and the C_{p_{ss}} of MTX of >16 mMol/L, were proven to be significantly related to long term EFS. The dose of 5 gram/m² and the MTX concentrations in CSF above 0.5 mMol/L are considered effective to treat subclenic CNS and testicular involvement. All intermediate risk patients during the observation of 1 year 8 months to 5 years 4 months are still in remission, and one of 4 high risk patients are died during the reinduction phase with any signs of sepsis and relapse. Other 3 high risk patients are still in remission.

The following conclusions can be made:

1. With normal kidney function and good supportive care, it is safe to give HDMTX as part of the consolidation therapy.
2. Leucovorin rescue programs can be discontinued 36 to 48 hours after termination of methotrexate administration for low (MTX dose 2 gram/m²), intermediate and high risk groups (with MTX doses 5 gram/m²).
3. MTX plasma concentration shows the fastest decrement at the first 6 hours after termination of the MTX administration. 24 hour infusion which yielded high MTX C_{p_{ss}} had given good exposure to the tumor cells; after 24 hour infusion, MTX concentration decreased steeply, which gave much less exposure to the normal tissue. This probably explains the low or insignificant side effect on our cases.
4. Our preliminary study with small number of cases revealed that half life of MTX is less than 1 hour (between 30 – 60 minutes).
5. High dose methotrexate may effectively treat the minor diseases and/or prevent CNS and testicular leukemia. However, further study

with larger number of patients and a longer duration of observation is needed to prove this statement.

6. High dose methotrexate program at the consolidation part of ALL protocol may increase EFS. Larger number of patients and longer duration to emphasize this statement.

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