

METHOTREXATE RELATED ACUTE HEPATOTOXICITY

METOTREKSATA BAĞLI AKUT HEPATOTOKSİSİTE

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Gazi Medical Journal 2002; 13: 69-72

ABSTRACT

Purpose: Methotrexate is one of the most effective chemotherapeutic agents used to treat non-Hodgkin lymphoma. Hepatotoxicity due to methotrexate was reported in many studies. In this study, hepatotoxicity caused by intermediate dose (1g/m²) methotrexate in 10 patients with non-Hodgkin lymphoma was investigated. **Method:** Ten patients between 3 and 13 years of age with Burkitt's Lymphoma, were investigated. Modified BFM-90 B-cell Lymphoma Protocol was used in the treatment. **Results:** No correlation was found between serum methotrexate levels and hepatic toxicity; and no other signs of hepatotoxicity were detected except temporary transaminase elevations and mild hepatomegaly. Transaminase levels returned to normal after about 2-11 days. **Conclusion:** Dose reductions in methotrexate do not seem warranted if serious liver damage has not been confirmed by histology.

Key Words: Non-Hodgkin Lymphoma, Methotrexate, Hepatotoxicity.

INTRODUCTION

Methotrexate (MTX) is a folate antagonist and a potent inhibitor of the enzyme dihydrofolatreductase, which is considered to be one of the most effective chemotherapeutic agents used in the treatment of non-Hodgkin lymphoma (1, 2). Hepatotoxicity which resulted in either fibrosis or cirrhosis due to prolonged and low dose use of MTX was reported in many studies (2, 3). Investigations have suggested that the drug is more completely distributed in the tissues of children than adults at the same infused

ÖZET

Amaç: Metotreksat, non-Hodgkin lenforma tedavisinde kullanılan en etkili ajanlardan biridir. Metotreksata bağlı hepatotoksiste daha önceki çalışmalarda bildirilmiştir. Bu çalışmada non-Nodgin Lenfomalı 10 çocuk hastada orta doz (1g/m²) metotreksata bağlı oluşabilecek hepatotoksiste incelenmiştir. **Metod:** Çalışmaya Burkitt Lenfomalı, 3-10 yaşları arasındaki 10 çocuk hasta dahil edilmiştir. Tedavide Modifiye BFM-90 B-hücre Lenfoma Protokolü kullanılmıştır. **Bulgular:** Serum metotreksat düzeyleri ile karaciğer toksisitesi arasında anlamlı korelasyon saptanmamıştır. Geçici transaminaz yüksekliği ve hafif derecede hepatomegaly dışında bulguya rastlanmamıştır. Transaminaz düzeyleri 2-11 gün sonra normale dönmüştür. **Sonuç:** Histolojik olarak karaciğer toksisitesi kanıtlanmadıkça metotreksat dozlarında indirime gidilmemelidir.

Anahtar Kelimeler: Non-Hodgkin Lenfoma, Metotreksat, Hepatotoksiste.

dosage (4). This may explain the increased tissue toxicity caused by MTX. On the other hand recurrent disease still remains as the major risk factor for children with cancer, and dose reductions or withdrawal of therapy in case of abnormal liver function tests might be more harmful than continuing treatment.

Acute hepatotoxicity due to intermediate (ID) or high dose (HD) MTX use is generally in the form of temporary and reversible hypertransaminasaemia and no chronic liver disease has been reported in children (5, 6).

The aim of our study is to evaluate the hepatotoxicity that would be caused by ID (1 gr/m²) MTX treatment and to determine the relationship between serum MTX levels and toxicity if it exists.

PATIENTS AND METHODS

Ten patients with recently diagnosed Burkitt's Lymphoma, who were between 3 and 13 years of age (median 5,5 years), were included in the study.

They had no history of liver disease before the treatment. The results of liver, kidney and hematologic function screening tests were all in the normal range. All the viral hepatitis markers were negative. Erythrocyte and thrombocyte suspensions were transfused to the patients when needed from donors screened for viral markers. The patients did not receive hepatotoxic antibiotics during the treatment courses.

Modified BFM-90 B-cell Lymphoma Protocol was used in the treatment as: Prephase: Cyclophosphamide 200 mg/m² intravenous (iv) (1. -5. days), prednisolone 30mg/m²/day (1. -5. days), MTX/Ara-C/Prednisolone intratechal (i.t) (1st day); and three 5-day blocks of combined intense chemotherapy as Block AA: Dexamethasone 10 mg/m²/day (1. -5. days), vincristine 1,5 mg/m² (1st day), VP-16 100 mg/m² (4. -5. days), Ara-C 150 mg/m²/dose twice a day (3. -4. days), MTX 1g/m² (1st day), Ifosphamide 800 mg/m² (1. -5. days with mesna), MTX/Ara-c/Prednisolone i.t. (1. -5. days); Block BB: Dexamethasone 10 mg/m²/day (1. -5. days),

Vincristine 1,5 mg/m² (1st day), Adriamycine 25 mg/m² (4. -5. days), MTX 1gr/m² (1st day) Cyclophosphamide 200mg/m² (1. -5. days), MTX/Ara-c/Prednisolone i.t. (1. -5. days). 10% of the total dose of MTX was given in the first 30 minutes and the rest in 23.5 hours; all with 3000cc/m² hydration and alkalisation. Leucovorine was given at a dose of 15mg/m² starting 36 hours after the beginning of MTX infusion and it was continued to be given at 6-hour intervals for 6 doses per day.

To determine the serum MTX levels, blood sampling was made in 24., 36., 48. and 72. hours after the beginning of MTX infusion and they were measured by High Performance Liquid Chromatography (HPLC) (7).

Hepatotoxicity was evaluated with the National Cancer Institute (NCI) (8) toxicity criteria at the end of MTX infusion. The relationship between the 24. and 36. hour MTX levels of patients and hepatotoxicity scores were investigated by Spearman Correlation Analysis; the difference between the level courses after the 24. hour serum MTX levels were evaluated with Wilcoxon signed-rank test.

RESULTS

The 24., 36., 48. and 72. hour mean MTX levels during a total of 46 courses of chemotherapy are shown in Table 1.

There were no other symptoms of hepatitis after the chemotherapy in the patient group except a hepatomegaly of about 2-3 centimetres in 4 patients. Posttreatment levels of serum

Table -1: The data of the 10 patients involved in the study.

No	Sex	Age	Number of MTX infusions	MTX LEVELS (MEAN±SD) (µmol/L)				Follow up period*	Outcome
				24 ^h hour	36 ^h hour	48 ^h hour	72 ^h hour		
1	M	5	7	9,31±6,12	0,45±0,62	0,0	0,0	61	ALIVE
2	M	6	4	3,66±2,26	0,77±0,62	0,0	0,0	74	ALIVE
3	M	10	2	11,33±12,83	0,20±0,11	0,0	0,0	56	ALIVE
4	F	12	5	9,69±3,89	2,52±3,74	0,0	0,0	56	ALIVE
5	M	10	3	11,27±18,25	3,68±5,14	0,8±0,06	0,0	5	DEAD
6	M	13	5	7,94±7,79	0,64±1,44	0,0	0,0	56	ALIVE
7	M	5,5	6	5,51±2,90	0,19±0,38	0,0	0,0	60	ALIVE
8	M	3	6	5,32±3,17	0,23±0,48	0,06±0,14	0,03±0,08	49	ALIVE
9	M	5	5	13,61±10,58	2,55±3,38	0,42±0,93	0,04±0,08	48	ALIVE
10	M	5,5	3	18,29±12,98	0,17±0,19	0,0	0,0	46	ALIVE

Table -1: * Months

bilirubin, albumin, gamma-glutamyltranspeptidase, alkaline phosphatase and prothrombin time were all in the normal range. The increases in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels are shown in Figure 1A and 1B. The first, second and third degree transaminase elevations of the patient group after the total treatment courses were found to be 19,6%, 21% and 13% respectively. Transaminase levels returned to normal after about 2-11 days in nine of the cases. In one case (case 7) transaminase levels continued to be elevated after the sixth course of chemotherapy. In this case's follow-up, anti-HCV antibody was found to be positive. No significant correlation was found between 24. and 36. hour serum MTX levels and hepatotoxicity score ($p>0.05$). Also there was no significant difference in terms of toxicity between the courses in the 36th hour and further serum MTX levels ($p>0.05$).

DISCUSSION

Methotrexate is an antimetabolite which is a potent inhibitor of the enzyme dihydrofolate reductase. It has been used for the last 45 years in the treatment of a number of malignancies including leukemias as well as a variety of solid tumors, and has been used in both conventional and high-dose schedules. Although transaminase elevations are often seen after HD-MTX treatment, this finding is temporary and levels generally return to normal after one or two weeks. The incidence and degree of acute hypertransaminasaemia are said to be directly

related to the number of MTX courses (4). Individual variations in the pharmacokinetics of MTX seem not to play an important role in hepatotoxicity, as demonstrated in the studies made to measure erythrocyte MTX levels (9). On the other hand fatal fulminant hepatic failure due to initial HD-MTX therapy was reported (10).

In our study, only in one case (case 7), did posttreatment transaminase levels not return to normal. Besides this case, who was later diagnosed to have hepatitis C, all others had only temporary transaminase elevations. Also there was no significant correlation between serum MTX levels and hepatotoxicity score in our study. This observation suggests that MTX treatment may modify an underlying hepatic disease of the patients rather than causing fulminant hepatic failure. For this reason patients should be closely followed up clinically; and biochemical and viral markers should be evaluated both during and after the therapy (11).

Previous studies have shown a significant correlation between the rise in serum transaminase levels and reduced relapse risk (12). For that reason reduced hepatotoxicity could parallel an increased risk for relapse, and until prospective studies demonstrate that hepatotoxicity is a greater threat to patients than the risk of relapse, dose reductions do not seem warranted if serious liver damage has not been confirmed by histology. Although we did not reduce the MTX doses, all but one (case 5) are in remission; as shown in Table 1.

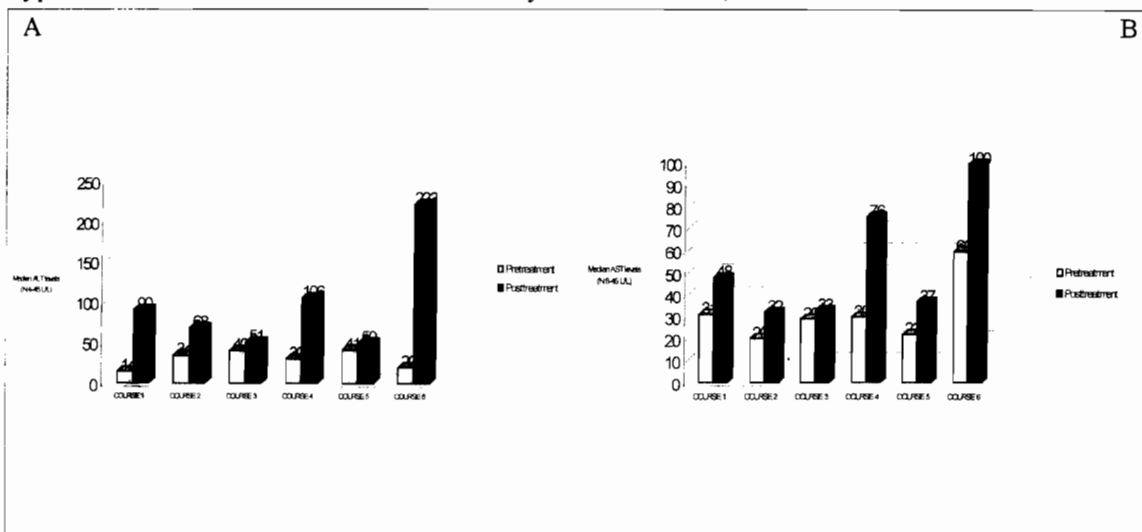


Fig. 1: Pretreatment and posttreatment median ALT levels of the patients (A). Pretreatment and posttreatment median AST levels of the patients (B).

It should be always kept in mind that hepatotoxicity in children receiving MTX therapy appears to be more common in patients who have some degree of underlying chronic liver disease and that the likelihood of this toxicity can be significantly reduced or even eliminated by using intermittent forms of therapy rather than long term treatment.

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