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Case Report

High methotrexate exposure and toxicity in children with t(9;22) positive acute lymphoblastic leukaemia treated with imatinib

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SUMMARY

What is known and objective: **Although there is one report on the possible reduced clearance of methotrexate in an adult patient when given concomitantly with imatinib, there is little information on the possible pharmacokinetic interaction. We report on three cases of delayed elimination of methotrexate in children with chromosome Philadelphia-positive acute lymphoblastic leukaemia treated concomitantly with imatinib.**

Case summary: **Three patients, aged 9–17 years, presented with high methotrexate blood levels following co-administration of imatinib and high-dose methotrexate. Two patients presented with clinical symptoms (nausea, epigastric pain and mucositis, acute renal failure, liver cytolysis). One patient required extra supplementary folinic acid doses than used in the standard protocol and one child required the use of carboxypeptidase-G2.**

What is new and conclusion: **There is an apparent pharmacokinetic interaction between imatinib and methotrexate in children. Several mechanisms could explain this interaction, including competition for BCRP or ABCB transporters. Temporary withdrawal of imatinib may be necessary for preventing severe methotrexate-related adverse events.**

WHAT IS KNOWN AND OBJECTIVES

There has been a report of reduced methotrexate elimination in an adult patient also on imatinib.[1] To our knowledge, there is no report of a pharmacokinetic interaction between imatinib and methotrexate, which may increase methotrexate exposure in children. We report on three such cases.

DETAILS OF THE CASES

Three paediatric patients with Ph^+ [i.e. t(9; 22) positive] precursor-B (n = 2) or T (n = 1) acute lymphoblastic leukaemia (ALL) were treated with a combination of methotrexate and imatinib according to the ESPHALL protocol (EudraCT 2004-001647-30, NCT00287105). The trial is an open-label study to evaluate the safety and efficacy of imatinib with chemotherapy in paediatric patients with Ph^+/BCR-ABL^+ ALL. Imatinib was administered at 300 mg/m^2 orally once daily. During consolidation blocks – HR1 and HR2 – high-dose intravenous methotrexate (HD-MTX) 5 g/m^2 was administered with folinic acid rescue of 7·5 mg/m^2 (levo form) at hours 42, 48 and 54 from start of HD-MTX infusion. Starting from hour 60, folinic acid is needed only if serum levels at hour 48 exceed 0·5 μM. Common medications that could potentially reduce methotrexate clearance (pantoprazole, cotrimoxazole, penicillin or fluoroquinolone antibiotics) were withheld from these patients: pantoprazole and cotrimoxazole for the three patients and antibiotics for patient 2.

The three patients, aged 9–17 years (Table 1), presented with high methotrexate levels (more than 0·5 μM at hour 48) following co-administration of imatinib and HD-MTX. Two patients presented with clinical symptoms. The first patient showed high MTX plasma levels (2·96 and 1·46 μM after HR1 and HR2 blocks, respectively) but did not present with any clinical signs of toxicity. The second patient (MTX plasma levels = 0·76 and 3·08 μM after HR1 and HR2 blocks, respectively) developed nausea, epigastric pain and mucositis and required extra supplementary folinic acid doses than used in the standard protocol. The third child developed serious adverse events (acute renal failure, liver cytolysis) who required the use of carboxypeptidase-G2. Measurements of serum MTX levels showed that MTX elimination was achieved after 10 days. Afterwards, patients treated for Ph^+ ALL stopped receiving imatinib and HD-MTX concomitantly, and no further toxicity was observed. These observations suggest that imatinib may substantially increase methotrexate plasma concentrations.

Several mechanisms may explain the pharmacokinetic interaction between imatinib and methotrexate. Firstly, imatinib is known to inhibit the human breast cancer resistance protein (BCRP)-mediated transport of MTX in a concentration-dependent manner.[2] Furthermore, *in vitro*, imatinib, a BCRP inhibitor, is known to reduce MTX renal secretion[3] in a manner similar to the competition for BCRP between MTX and benzimidazoles. Interaction between imatinib and methotrexate at other shared transporters such as ABCB1 may also contribute to the interaction.[4,5]

Moreover, as imatinib is highly plasma protein-bound (95%), increased toxicity may result from reduced plasma protein binding. Oedemas, possibly induced by imatinib may also enhance the distribution and aqueous retention of HD-MTX in the body.[1]

No study has been published about potential metabolic interactions between imatinib and HD-MTX. Otherwise, imatinib and

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Table 1. Patients and treatment characteristics

	Patient 1		Patient 2		Patient 3	
Block	HR1	HR2	HR1	HR2	HR1	HR2
Demographics						
Age (year)	17	17	13	13	9	9
Gender	Female		Male		Female	
BSA (m^2)	1·53	1·48	1·45	1·44	1·17	1·11
Weight (kg)	54·0	49·8	47·9	47·1	34·0	31·0
Drug administration						
HD-MTX	20/07/2011	17/08/2011	08/06/2012	30/06/2012	27/06/2014	18/07/2014
Imatinib	Co-administration	Stopped	Co-administration	Co-administration	Co-administration	Stopped
Carboxypeptidase					Yes	
Drug dosage (mg)						
MTX	7675	7340	7320	7320	5780	5780
Imatinib	450	450	450	450	400/300[a]	400/300[a]
Number of doses of folinic acid	3	3	3	15	3	3
Biology						
Creatinine (μM)						
Before MTX			48	56	36	27
After MTX (day 2)			40	64	98	29
MTX concentrations (μM)						
Day 1 (H24)					29·85	
Day 2 (H48)	2·96	1·46	0·76	3·08	13·35	0·40
Day 3 (H72)			0·38	0·66	3·57	0·08
Day 4 (H96)			0·06	0·26	2·89	
Day 5 (H120)	0·21			0·19	3·28	
Toxicity symptom(s)	NA	NA	Nausea, epigastric pain	Mucosa toxicity	Acute renal failure, hepatic cytolysis	NA

BSA, body surface area; HD-MTX, high-dose methotrexate; NA, not applicable.
[a]Every other day.

its N-desmethyl metabolite are modulators of P-glycoprotein (P-gp) and cytochrome P450 (CYP3A4, CYP2D6, CYP2C9) and may be involved in a number of drug–drug interactions.[6] The duration and intensity of MTX exposure is the principal contributing factor for toxicity.[7] Therefore, stopping imatinib temporarily should be considered for preventing severe MTX-related adverse events like acute renal failure.

WHAT IS NEW AND CONCLUSION

There is an apparent pharmacokinetic interaction between imatinib and methotrexate in children. Several mechanisms could explain this interaction, including competition for BCRP or ABCB transporters. Temporary withdrawal of imatinib may be necessary for preventing severe MTX-related adverse events.

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