Delayed Elimination of Methotrexate Associated with Co-Administration of Proton Pump Inhibitors

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Abstract. *Aim: We conducted a retrospective non-interventional cohort study to analyze the impact of proton pump inhibitors co-administration on methotrexate elimination in cancer patients receiving treatment protocol with the antifolate at high dose (>1 g/m^2 intravenously). Patients and Methods: Between 2005 and 2008, 79 patients (mean age: 48.8 years; range: 16-76 years) were treated by high dose methotrexate for 197 cycles. Results: Delayed methotrexate elimination (i.e., plasma concentration >15 μmol/l at 24 h, >1.5 μmol/l at 48 h and/or >0.15 μmol/l at 72 h) occurred in 16% (32/197) of the cycles. The co-prescription of a proton pump inhibitor (pantoprazole, lansoprazole, omeprazole, esomeprazole) was found in 53% (17/32) of the courses with delayed elimination and in 15% (24/165) of the cycles without delayed elimination. We identified co-administration of proton pump inhibitors as a major risk factor for delayed elimination (odds ratio 6.66, 95% confidence interval 3.13, 14.17). Conclusion: Proton pump inhibitors should not be administered during methotrexate treatment.*

Methotrexate is an antifolate agent used in the treament of numerous types of cancer and is primarily eliminated by the kidneys (1). Increased plasma concentrations of methotrexate elimination associated with serious side-effects may be observed following the co-administration of drugs such as probenecid, antiinflammatory drugs or antibacterial agents (2-9). These pharmacokinetic drug–drug interactions are possibly due to a reduction of the renal secretion of the antifolate in relation with the blockade of basal proximal drug transporters (10, 11). Delayed elimination of methotrexate associated with serious side-effects has also been attributed to the co-administration of benzimidazole proton pump inhibitors (omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole) (12-18). The possible mechanism of interaction is the inhibition of tubular secretion *via* the luminal transporter breast cancer resistance protein (BCRP also referred to as ABCG2) (19, 20). With the exception of two studies that include 76 and 74 patients, respectively (15, 17), most of the observations refer to case reports or small series.

Recently, we showed that 5 out of 6 cancer patients with severe intoxication to methotrexate (those who had specifically received the rescue agent glucarpidase) were co-treated with proton pump inhibitors (18). The purpose of this study was to analyze the impact of proton pump inhibitors co-administration on methotrexate elimination in a general population of cancer patients receiving treatment protocol with the antifolate at high dose (*i.e.*, >1 g/m^2 intravenously).

Patients and Methods

We conducted a retrospective non-interventional study on all patients treated by high-dose methotrexate, between 2005 and 2008 at the University Hospital of Strasbourg, France. Plasma methotrexate concentrations were determined 24, 48 and 72 hours after the start of treatment as a routine practice. Methotrexate was analyzed in plasma by an immuno-enzyme assay in homogeneous phase (Emit®). Delayed elimination of methotrexate was defined by plasma concentration over 15 μmol/l at 24 hours, 1.5 μmol/l at 48 hours and/or 0.15 μmol/l at 72 hours. In patients whose duration of infusion exceeded 24 hours we did not use the plasma concentration at 24 hours in the assessment of delayed elimination. The cycles of high-dose methotrexate therapy were categorized into delayed and normal elimination group. Different risk factors of delayed elimination were searched: pre-existing renal impairment, insufficient hydration or alkalinization, co-administration of benzimidazole proton pump inhibitors (*i.e.*, those used in our hospital: omeprazole, esomeprazole, pantoprazole, lansoprazole) and recognized drug–drug interactions according to the French Drug Agency. The analysis excluded cycles associated preventable errors (insufficient hydration or alkalinization, recognized drug–drug interactions). Differences in patient

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Key Words: Methotrexate, proton pump inhibitor, BCRP, ABCG2, drug–drug interaction.

Table I. *Patient characteristics with delayed and normal methotrexate elimination.*

	Delayed elimination	Normal elimination	*P*-value
Number of cycles	32	165	
Gender, male/female (n)	16/16	78/87	NS
Age, years (range)	54 (17-74)	50 (16-76)	NS
Methotrexate dose (mg)	5700 (1000-12350)	5000 (1000-12300)	NS
Infusion time (h)	0.5 (0.5-24)	0.5 (0.5-24)	NS
Plasma methotrexate concentrations μmol/l			
24 h	3.57 (0.63-43.6)	0.88 (0.1-9.8)	<0.01
48 h	0.695 (0.11-13.2)	0.12 (0.03-1.4)	<0.01
72 h	0.325 (0.15-8.2)	0.04 (0.02-0.14)	<0.01
Co-administration of proton pump inhibitors (%)	17 (53.1)	24 (15.0)	<0.001

Data are presented as number (%) or median (range). n, number of cycles; NS, not significant.

characteristics and methotrexate dosing regimen were compared between the delayed and normal elimination groups by the χ^2 test, Fisher's exact probability test. The odd ratio (OR) and its 95% confidence interval (CI) were calculated by Sigma Stat 3.5 (Systat Software Inc, Chicago, IL, USA).

Results

Between 2005 and 2008, 82 patients were treated by high-dose methotrexate for 230 cycles. Delayed methotrexate elimination was observed in 39 (17%) cycles. For 33 (14%) of all cycles, recognized drug–drug interactions (n=41) and/or defects in hydration or urine alkalinization (n=2) were identified. The potential drug–drug interactions included co-administration of piperacillin/tazobactam (n=11), penicillin (n=8), cotrimoxazole (n=8), vancomycin (n=6), aspirin (n=6) and ciprofloxacin (n=2). Among the 39 cycles with delayed elimination, 7 were possibly attributable to a recognized drug–drug interaction and 17 to proton pump inhibitors (see below). No cause was found for 15 cycles.

The analysis of the impact of proton pump inhibitors on methotrexate elimination concerned 197 cycles (the 33 cycles associated with insufficient alkalinization/hydration and/or recognized drug–drug interactions were excluded). The included patients (N=79, n=197 cycles, mean age: 48.8 years, range: 16-76 years) were treated for adenocarcinoma (n=2), germ cell tumor (n=1), osteosarcoma (n=1), breast cancer (n=3), carcinoma (n=1), leukaemia (n=19), lymphoma (n=51) and neuroblastoma (n=1). The dose of intravenous methotrexate varied between 1 and 12.35g per cycle.

Excluding preventable errors such as the non interception of recognized drug–drug interactions, the overall risk of delayed methotrexate elimination was 16% (32/197) for patients receiving high-dose methotrexate therapy. Plasma methotrexate concentrations in the delayed elimination group were significantly higher than in the normal elimination group (Table I). Gender, age, methotrexate dose, infusion time did not differ between the two groups (Table I). The clinical and biological consequences of delayed methotrexate elimination (n=32 cycles) were acute renal failure (n=6), aplastic anemia (n=5), lysis syndrome (n=5), diarrhea (n=4), bacterial infection (n=9), fungal infection (n=1), cholestasis (n=4), arrhythmia (n=2), cardiac arrhythmias (n=1). Two patients were transferred to an intensive care unit where they were hospitalized for 8 and 16 days. The management of side-effects led to an additional duration of hospitalization (mean 4 days; range: 1-16 days). All the patients with delayed methotrexate elimination recovered from side-effects.

The co-prescription of a proton pump inhibitor (pantoprazole, lansoprazole, omeprazole, esomeprazole) was found in 53% (17/32) of the courses with delayed elimination and in 15% (24/165) of the cycles without delayed elimination. Co-administration of a proton pump inhibitor was a major risk factor for delayed elimination of the antifolate (odds ratio 6.66, 95% confidence interval 3.13, 14.17). In addition, patients receiving concomitant proton pump inhibitor displayed significant higher plasma concentrations of methotrexate than those without (Figure 1).

Discussion

Delayed methotrexate elimination may lead to serious side-effects necessitating in severe cases the use of the costly rescue agent glucarpidase that hydrolyzes the antifolate in the plasma. Elevated concentrations may be attributable to nephrotoxicity in relation to a direct toxic effect of methotrexate and a defect in hydration or urine alkalinization that prevents the intra-tubular precipitation of the parent drug and the metabolite (7-hydroxy-methotrexate) (21). It is also related to drug–drug interactions due to agents that block the renal secretion of methotrexate (2-9, 12-18). Fortunately, most of these interactions are known (*i.e.*, are included in drug compendia) and thus are

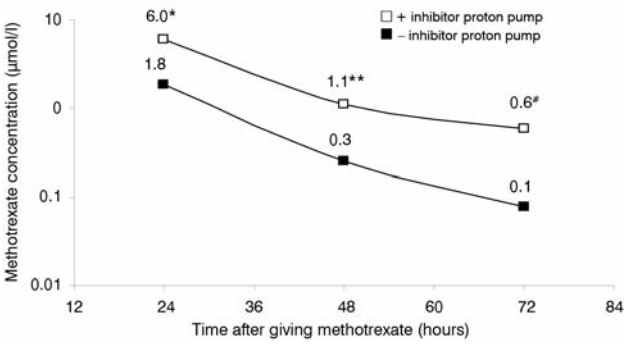

Figure 1. *Plasma concentration of methotrexate with or without inhibitor proton pump. *p-value <0.01, **p-value <0.02, #p-value <0.05. Group methotrexate n=156 (median MTX dose: 5200 mg), group methotrexate+inhibitor proton pump n=41 (median methotrexate dose:5300 mg).*

preventable. Drug–drug interactions with proton pump inhibitors (omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole) have been described since 1993 but are not mentioned (at least in France) in the official labelling (12-18). In patients with severe intoxication to methotrexate who are treated by the rescue agent glucarpidase, we found that 5 out of 6 patients were co-treated with proton pump inhibitors (18). The possible mechanism of delayed elimination of methotrexate by proton pump inhibitors is the reduction of renal secretion of the antifolate *via* the blockade of the drug transporter BCRP expressed at the luminal side of proximal cells (19, 20).

In this study, we have evaluated the risk of delayed methotrexate elimination in a general population of 79 patients treated by the antifolate at high dose. Overall, delayed methotrexate elimination was observed in 39 (17%) cycles for which 24 were possibly attributable to drug–drug interactions. Interactions were known for 7 cycles and should have been intercepted before the administration of methotexate. Interactions with proton pump inhibitors were observed for 17 cycles associated with delayed elimination. Thus excluding preventable errors, the co-administration of high-dose methotrexate and proton pump inhibitor increased the risk of delayed elimination of the antifolate by 6.66 times. This result supports previous findings in a population of 76 cancer patients showing that proton pump inhibitors decrease by 27% methotrexate systemic clearance (15). Increased risk of delayed methotrexate elimination has also been seen in 74 Japanese patients but to a lower extent (2.65 times) (17). In conclusion, proton pump inhibitor administration should be discontinuated during methotrexate treatment. We have contacted the French Drug Agency for an eventual updating of the drug–drug interactions compendium. This study has also highlighted a deficit in the interception of known drug–drug interactions.

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