

Additional File 2. Adverse events in grade 2 or higher of high-dose methotrexate therapy

	grade ≤ 1	grade ≥ 2	<i>p</i>
Anemia [n]	[134]	[83]	
C _{max}	956.68 $\pm$ 174.40	938.78 $\pm$ 175.88	0.465 ^a
C _{mean(1-6)}	774.07 $\pm$ 132.45	751.05 $\pm$ 110.22	0.187 ^a
AUC	6,604.78 $\pm$ 1365.68	6,411.25 $\pm$ 955.06	0.221 ^b
CL _{MTX}	5.31 $\pm$ 1.14	5.19 $\pm$ 1.01	0.427 ^a
Age	20.97 $\pm$ 12.27	22.60 $\pm$ 15.31	0.413 ^b
Leukopenia [n]	[150]	[67]	
C _{max}	964.02 $\pm$ 180.20	918.08 $\pm$ 158.71	0.074 ^a
C _{mean(1-6)}	773.88 $\pm$ 119.67	745.98 $\pm$ 134.10	0.128 ^a
AUC	6,629.76 $\pm$ 1206.04	6,309.10 $\pm$ 1250.97	0.075 ^a
CL _{MTX}	5.26 $\pm$ 1.09	5.25 $\pm$ 1.11	0.951 ^a
Age	21.86 $\pm$ 13.27	20.99 $\pm$ 14.10	0.662 ^a
Increased AST [n]	[140]	[77]	
C _{max}	952.01 $\pm$ 172.76	945.87 $\pm$ 179.46	0.805 ^a
C _{mean(1-6)}	759.32 $\pm$ 118.36	776.08 $\pm$ 135.50	0.344 ^a
AUC	6,378.16 $\pm$ 1067.58	6,808.21 $\pm$ 1438.03	0.023 ^b
CL _{MTX}	5.38 $\pm$ 1.08	5.04 $\pm$ 1.10	0.030 ^a
Age	23.61 $\pm$ 14.39	17.94 $\pm$ 10.88	0.001 ^b
Increased ALT [n]	[126]	[91]	

$C_{\max}$	939.57 $\pm$ 170.03	964.04 $\pm$ 181.14	0.310 ^a
$C_{\text{mean}(1-6)}$	752.68 $\pm$ 119.38	782.69 $\pm$ 130.27	0.080 ^a
AUC	6,274.20 $\pm$ 1056.30	6,885.99 $\pm$ 1356.15	<0.001 ^b
CL_{MTX}	5.50 $\pm$ 1.07	4.93 $\pm$ 1.05	<0.001 ^a
Age	23.42 $\pm$ 13.95	19.06 $\pm$ 12.49	0.016 ^b
grade 0		grade 1 $\leq$	
Increased SCr [n]	[215]	[2]	
$C_{\max}$	947.93 $\pm$ 173.57	1,154.65 $\pm$ 258.31	0.096 ^a
$C_{\text{mean}(1-6)}$	764.43 $\pm$ 124.68	854.75 $\pm$ 118.09	0.309 ^a
AUC	6,502.27 $\pm$ 1184.97	9,592.65 $\pm$ 2315.14	<0.001 ^a
CL_{MTX}	5.28 $\pm$ 1.08	3.45 $\pm$ 1.00	0.018 ^a
Age	21.60 $\pm$ 13.55	20.50 $\pm$ 9.19	0.909 ^a

Values are presented as mean $\pm$ standard deviation or number (%).

^aStudent's t-test

^bMann–Whitney's U test

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the concentration-time curve; $C_{\max}$, maximum concentration; $C_{\text{mean}(1-6)}$, mean concentration during the maintenance dose; CL_{MTX} , total body clearance of methotrexate; SCr, serum clearance.