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LETTER TO THE EDITOR

MTHFR 677TT genotype and toxicity of methotrexate: controversial results

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Dear Editor,

We have read with interest the contribution by D'Angelo et al. [1] regarding the study entitled "Methotrexate toxicity and efficacy during the consolidation in paediatric acute lymphoblastic leukaemia and MTHFR polymorphisms as pharmacogenetic determinants".

In this study, the authors described that when global toxicity and MTHFR C677T genotypes in the two MTX treatment groups (2 g/m^2 vs. 5 g/m^2) were analysed, the toxicity risk was significantly more common among homozygotes for 677TT. In more detail, they stated that among the patients treated with MTX 2 g, the 677TT genotype had a 12-fold higher risk of developing toxicity than patients with other genotypes (OR = 12.2; 95% CI; 2.54–58.9; $p = 0.001$). However, when we reanalysed the data provided by the authors in Tables 2 and 3 of their article, our conclusions differ from those of the authors.

Our reanalysis with the odds ratios (OR) of the associations from univariate logistic regressions is presented in Table 1. Contrary to what was stated by the authors, we did not find a significant association ($p < 0.05$) of the MTHFR 677TT genotype with increase in toxicity. In fact, we observed that the 677TT genotype was significantly associated with a decreased risk of global toxicity within the group of patients treated with MTX 5 g (OR = 0.17; 95% CI: 0.04–0.67).

Therefore, we conclude that in the study by D'Angelo et al., there is no correlation between the 677TT genotype and increased toxicity and that the small effect of the polymorphism would be protective.

These results are in concordance with the reports by other authors that do not find a correlation between the MTHFR 677T variant and toxicity [2–12] or that even found a small protective effect for this polymorphism [13–15].

The implication of MTHFR C677T polymorphism in paediatric ALL patients treated with MTX is a subject which has generated a great controversy in the past. Lately, the evidences provided by most studies support the idea that MTHFR C677T is not a good predictor of MTX toxicity for children with ALL [2–15].

Conflict of interest None.

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Table 1 Methotrexate toxicity and MTHFR C677T polymorphism

	MTHFR C677T	*r*/*N*	OR (95% CI)	*p* value
MTX 2 g				
Global toxicity	CC	14/21	Reference	
	CT	22/38	0.69 (0.23 to 2.09)	0.509
	TT	14/19	1.40 (0.36 to 5.49)	0.629
Haematological toxicity	CC	8/21	Reference	
	CT	10/38	0.58 (0.19 to 1.81)	0.349
	TT	3/19	0.30 (0.07 to 1.39)	0.124
Non-haematological toxicity	CC	6/21	Reference	
	CT	12/38	1.15 (0.36 to 3.71)	0.810
	TT	11/19	3.44 (0.92 to 12.79)	0.065
MTX 5 g				
Global toxicity	CC	20/27	Reference	
	CT	29/33	2.54 (0.65 to 9.83)	0.178
	TT	4/13	0.16 (0.04 to 0.67)	0.012*
Haematological toxicity	CC	9/27	Reference	
	CT	13/33	1.30 (0.45 to 3.76)	0.628
	TT	1/13	0.17 (0.02 to 1.49)	0.109
Non-haematological toxicity	CC	11/27	Reference	
	CT	16/33	1.37 (0.49 to 3.82)	0.549
	TT	3/13	0.44 (0.10 to 1.96)	0.279

* $p < 0.05$

r number of subjects presenting toxicity, *N* total number of subjects

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