

Thiopurine S-Methyltransferase and Methylenetetrahydrofolate Reductase Polymorphisms in Leukemia

Lösemide Tiyopürin S-Metiltransferaz ve Metilentetrahidrofolat Redüktaz Polimorfizmleri

To the Editor,

I read the paper by Belen et al. published in a recent issue of this journal with great interest [1]. They reported a 15-year-old girl with T-ALL who developed severe pancytopenia during consolidation and maintenance therapy despite dose reduction of 6-mercaptopurine (MP). They found thiopurine S-methyltransferase (TPMT) *3A/*3C polymorphisms upon TPMT genotyping. Prednisolone therapy produced a remarkable but transient bone marrow recovery in this patient.

The authors should be congratulated in that they followed the recent evidence-based clinical guidance recommendations related to safe and effective thiopurine administration. The authors began treatment with standard doses and down-titrated the MP according to the results of blood counts, and they omitted some parts of Protocol Ib and the second part of the reinduction therapy. Although in a recent systematic review 30%-50% of the normal dose for thiopurines in the case of heterozygous TPMT status was recommended [2], I agree with the authors about low-dose MP administration (2.5%-10% of normal dose) when necessary, because of the possibility of the presence of undetected deficiencies in other enzymes involved in the metabolic pathway [3]. Moreover, by omitting 6-thioguanine (6TG) treatment in reinduction therapy, the authors prevented the probable additional toxicity arising from another thiopurine drug since patients with heterozygous TPMT status have higher cytosolic 6TG nucleotide levels, the cytotoxic metabolites of both MP and 6TG [4].

On the other hand, after careful reading, some concerns and questions arose regarding the paper. First of all, it is not possible to understand that the patient had an accompanying methylenetetrahydrofolate reductase (MTHFR) polymorphism from either the title or the English abstract. Only after reading the Turkish abstract and the text I did realize that the patient had concomitant TPMT *3A/*3C and MTHFR C677T and A1298C polymorphisms, which were reported to be associated with increased myelotoxicity in children with ALL [5]. Although the authors stated that they found t(11;14) in karyotyping and that PCR tests for t(4;11) and t(9;21) were negative, they did not mention t(9;22), an important prognostic abnormality in patients with ALL. Additionally, the information about the extension of the disease at the time of diagnosis, such as involvement

of the central nervous system (CNS) or kidneys and renal impairment due to increased tumor burden, is lacking in the case presentation. The latter two, if present, might be responsible for the protracted bone marrow suppression by increasing toxic effects of methotrexate. Furthermore, it is not clear to which risk category the patient was assigned in the treatment protocol in the text or from the figure (proper reading of the figure is impossible). I would want to learn more details regarding the clinical condition of the patient, such as whether she was given CNS radiotherapy or not, her renal function test results and especially those before methotrexate administration, and whether she completed the entire chemotherapy protocol or not. Lastly, I am curious about the follow-up results of this patient, since TPMT heterozygosity was reported to be associated with better event-free survival than in TPMT wild-type patients and thiopurine-induced cytopenias did not negatively affect the treatment outcome [6].

Conflict of Interest Statement

The author of this paper has no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Key Words: Thiopurine S-methyltransferase, Methylenetetrahydrofolate reductase, Gene polymorphisms, Leukemia, Childhood

Anahtar Sözcükler: Tiyopürin S-metiltransferaz, Metilentetrahidrofolat redüktaz, Gen polimorfizmleri, Lösemi, Çocukluk çağı

Serhan Küpeli

Çukurova University Faculty of Medicine, Department of Pediatric Oncology and Pediatric Bone Marrow Transplantation Unit, Adana, Turkey

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Address for Correspondence: Serhan KÜPELİ, M.D.,
Çukurova University Faculty of Medicine, Department of Pediatric Oncology and Pediatric Bone Marrow Transplantation Unit, Adana, Turkey
Phone: +90 322 338 74 44 E-mail: serhankupeli@cu.edu.tr

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Reply:

We would like to thank for comments on our article, entitled “Severe myelotoxicity associated with thiopurine S-methyltransferase *3A/*3C polymorphisms in a patient with pediatric leukemia and the effect of steroid therapy”, published in Turkish Journal of Hematology 2014, volume 31, issue 4, pages 276-285.

Severe bone marrow suppression in our case occurred during consolidation chemotherapy which contained oral 6-mercaptopurine (6-MP), intravenous cyclophosphamide and low dose cytosine arabinoside and continued until the end of the maintenance treatment despite markedly reduced 6MP dose. It can not be attributed to renal impairment, central nervous system leukemia or methotrexate (MTX) toxicity because none of these were present during or before pancytopenia was noted. The patient is compound heterozygous for TPMT*3A and *3C polymorphisms, which is known to cause low enzyme activity and increase of intracellular thioguanine nucleotides, and lead to severe bone marrow suppression. Although Karas-Kuzelicki et al. reported that co-inheritance of MTHFR C677T with non-functional TPMT variants augments myelotoxicity during maintenance therapy with oral MTX and 6-MP in children with ALL [1], other investigators did not find significant association between these polymorphic variants

and excessive myelotoxicity [2]. In line with these data, we did not observe severe leukopenia or hepatotoxicity during the four courses of intensification therapy with high dose (5 g/m²) MTX, which was given in conjunction with adjusted dose 6-MP. This may be due to the presence of MTHFR A1298C polymorphism, which is associated with lower toxicity risk in patients with ALL. It has been suggested that linkage disequilibrium between C677T and A1298C may explain decreased toxicity during high dose MTX administration [3]. Possible effects of MTHFR C677T and A1298C polymorphisms on the stability of the TPMT enzyme were addressed in our article.

The patient was assigned to the medium risk group based on ALL-BFM-95 risk stratification criteria [4]. Renal function tests and glomerular filtration rate were within normal limits during all stages of chemotherapy. In regard to the cranial radiotherapy, 12 Gy prophylactic cranial irradiation was given before maintenance therapy without causing excessive myelosuppression. The patient is in complete remission for 3 years after completion of the maintenance chemotherapy.

Adding “MTHFR C677T and A1298C polymorphisms” to the title of our article was not possible due to the the word count restriction of Turkish Journal of Hematology.

Please kindly be informed that ‘t(9;21)’ expression in our article in Turkish Journal of Hematology 2014, volume 31, issue 4, pages 276-285 is incorrect. The correct expression should be t(9;22). We apologize for this typing error.

Burcu Belen and Türkiz Gürsel

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