

## LETTER to the EDITOR

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# Vincristine and CYP3A5 Genetic Polymorphism in Rhabdomyosarcoma: Comment

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### Dear Editor

we would like to share ideas on “Efficacy and Toxicity of Vincristine and CYP3A5 Genetic Polymorphism in Rhabdomyosarcoma Pediatric Egyptian Patients [1].” In this study, the association between pediatric RMS patients’ vincristine-induced neuropathy and CYP3A5 genotypes was examined. Researchers discovered that CYP3A5\*3/\*3 genotype patients had the highest prevalence of neuropathy, whereas CYP3A5\*1/\*6 genotype patients had the lowest frequency. They did not discover any association between RMS survival and CYP3A5 genotypes, though. Other variables that significantly impacted overall survival were also found in the study, including starting risk, metastasis, response, convulsions, unsteady gait, and hepatotoxicity grade.

This study’s disregard for potential confounders, especially the impact of other genetic variants, is one of its weaknesses. Given the significant variation in genetic makeup among individuals, it is crucial to take into consideration additional genetic variables that might interact with CYP3A5 genotypes to affect the metabolism and toxicity of vincristine (such as CYP3A4 and ABCB1 [2]). Furthermore, the limited generalizability of the results could be attributed to the small sample size of 150 pediatric patients. To increase the validity of the findings, more extensive and varied patient populations should be the focus of future research.

Further research in this field may entail a more thorough examination of genetic polymorphisms, such as those in other drug-metabolizing enzymes or transporters, that may have an impact on vincristine metabolism and toxicity. Researchers can gain a better understanding of the intricate relationship between genetic variation and treatment response in young RMS patients by taking a broader variety of genetic factors into account. Furthermore, investigating how environmental factors, such food and exposure to pollutants, affect drug metabolism and toxicity may offer important new insights into individualized treatment plans for RMS patients.

Examining the function of epigenetic changes in vincristine metabolism and toxicity is another possible avenue for future study. Drug metabolism pathways may be impacted by epigenetic factors that affect gene expression and protein function, such as DNA methylation and histone modification. Future research endeavors may find new pathways that underlie individual diversity in medication responsiveness and toxicity, provided that

epigenetic analyses are integrated. Treatment plans for pediatric RMS patients may become more individualized and effective as a result of this comprehensive approach to personalized medicine.

In conclusion, there are a number of topics that need more research even if this study offers insightful information on the connection between CYP3A5 genotypes and vincristine-induced neuropathy in pediatric RMS patients. We could improve our understanding of individualized treatment methods for RMS by taking into account the impact of other genetic variants and potential confounders, increasing the sample size, investigating new genetic and environmental factors, and investigating epigenetic pathways. Future investigations may enhance precision medicine in pediatric oncology by tackling these constraints and exploring novel research directions.

*HP 50 % ideas, writing, analyzing, approval*

*VW 50 % ideas, supervision, approval* Conflict of interest : Authors declare no conflict of interest Acknowledgement: none data availability statement: there is no new data

### References

1. Shalaby N, Zaki HF, Badary OA, Kamal S, Nagy M, Makhoulouf D, et al. Efficacy and toxicity of vincristine and cyp3a5 genetic polymorphism in rhabdomyosarcoma pediatric egyptian patients. *Asian Pac J Cancer Prev*. 2024;25(4):1391-409. <https://doi.org/10.31557/apjcp.2024.25.4.1391>.
2. Guilhaumou R, Solas C, Bourgarel-Rey V, Quaranta S, Rome A, Simon N, et al. Impact of plasma and intracellular exposure and cyp3a4, cyp3a5, and abcb1 genetic polymorphisms on vincristine-induced neurotoxicity. *Cancer Chemother Pharmacol*. 2011;68(6):1633-8. <https://doi.org/10.1007/s00280-011-1745-2>.

### Reply to the letter to the editor: Vincristine and CYP3A5 Genetic Polymorphism in Rhabdomyosarcoma

#### Dear Editor

We thank Hinpetch Daungsupawong and Viroj Wiwanitkit for their comments and appreciate their interest in our work regarding “Efficacy and Toxicity of Vincristine and CYP3A5 Genetic Polymorphism in Rhabdomyosarcoma Pediatric Egyptian Patients” [1].

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They raised queries including association between RMS survival and CYP3A5 genotypes, and also disregarding for potential confounders, especially the impact of other genetic variants. We agree with these thoughtful responses as our main objective was to report a clinical experience from the largest children cancer hospital in Egypt and how would the variation of some genetic alleles of CYP3A5 genotypes affect the clinical outcome of vincristine in Rhabdomyosarcoma Pediatric patients. CYP3A5\*3/\*3 genotype patients had the highest prevalence of neuropathy, whereas CYP3A5\*1/\*6 genotype patients had the lowest frequency. We already acknowledged the limitations of our study in the discussion section including the low prevalence of the variant alleles and relatively small sample size as well as the limited study duration to follow the overall survival of the patents. The inclusion of the available parameters such as starting risk, metastasis, response, convulsions, unsteady gait, and hepatotoxicity grade allowed us to better understand and discuss the clinical findings without waiting for the long-term overall survival. On the other hand, it would be of great interest to study the effects of other genetic and epigenetic factors on the clinical efficacy and toxicity of vincristine in treated cancer patients, as suggested by the authors in the letter to the editors, and should be taken in consideration when we design future research in this field. Although beyond the scope of our research work, investigating how environmental factors, such food and exposure to pollutants, affect vincristine metabolism and toxicity may offer important new insights into precision management for RMS patients. In conclusion, Our study and the comments of Hinpetch Daungsupawong and Viroj Wiwanitkit point to the real need for a large prospective clinical trial investigating the impact of many genetic and epigenetic factors on the clinical phenotypes of vincristine and similar anticancer drugs in cancer patients to improve our understanding of individualized treatment methods for RMS.

## References

1. Shalaby N, Zaki HF, Badary OA, Kamal S, Nagy M, Makhlof D, et al. Efficacy and toxicity of vincristine and cyp3a5 genetic polymorphism in rhabdomyosarcoma pediatric egyptian patients. *Asian Pac J Cancer Prev.* 2024;25(4):1391-409. <https://doi.org/10.31557/apjcp.2024.25.4.1391>.

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