Letter to the Editor

Gender, Cytidine Deaminase, and 5-Aza/Decitabine—Letter

Joseph Ciccolini1, Godefridus J. Peters2, and Elisa Giovannetti2

We have read with interest the observational study by Mahfouz and colleagues (1), who examined the role of cytidine deaminase (CDA) on outcomes of patients treated with 5-azacytidine or decitabine. Surprisingly, gender emerged as the main determinant of CDA levels, and consequently, male patients displayed worse outcome as compared with females.

These data do not match the results of all previous clinical studies on the role of CDA on outcome and toxicity of several nucleoside analogs. In particular, when monitoring CDA activities as part of routine pretreatment screening over the last 2 years at Marseille University Hospital (Marseille, France), CDA activities recorded in 252 adults were 4.3 ± 3.4 U/mg proteins for women and 3.9 ± 3.5 U/mg proteins for men, with no significant difference between genders ($P = 0.278$). Similarly, in our recent study conducted at VU University Medical Center (Amsterdam, the Netherlands) on 126 patients (2), no significant correlations were detected between CDA activity and gender ($P = 0.382$).

Moreover, in our opinion, some key points should be discussed in more detail. As stated by the authors, CDA activity and polymorphisms have been studied for years in patients treated with gemcitabine, another nucleoside analog widely prescribed in a variety of settings (3). In addition, erratic CDA activities are a rising issue with cytarabine and capecitabine, because atypical metabolizers are at risk of life-threatening toxicities (4). However, Mahfouz and colleagues did not find a relationship between gender, and therefore CDA status, and outcome in cytarabine-treated patients.

Besides, it is unclear why patients undergoing azacytidine and decitabine were grouped before analysis. The analysis of each group separately would have been useful to verify whether the role of CDA and gender holds true for azacytidine, decitabine, or both, whereas a cohort of patients who are not treated with these drugs is needed to distinguish their prognostic versus predictive values. Because CDA is supposed to play a role only with nucleoside analogs, its correlation with progression-free rather than overall survival would have been more relevant because no data are provided about subsequent treatments.

The impact of 79A > C CDA polymorphism remains debated (2), and the small sample size and low number of patients carrying the polymorphic variant are another caveat of this study.

Finally, Mahfouz and colleagues claim that due to the pharmacodynamics of azacytidine and decitabine, low circulating concentrations make ultra rapid metabolizers at risk of treatment failure the actual concern. However, no information is provided about poor metabolizers at risk of being overexposed. On the basis of our clinical expertise, poor metabolizers treated with 75 mg/m2 azacytidine are at risk of life-threatening pancytopenia (5).

Overall, though a gender-based adaptive dosing is interesting, we believe that extensive analyses of CDA, using both genotyping and phenotyping approaches, remain the most relevant strategy to improve the outcome in patients treated with nucleoside analogs, including azacytidine and decitabine.

Disclosure of Potential Conflicts of Interest

J. Ciccolini has ownership interest (including patents) in patent method for assessing the ability of a patient to respond to or be safely treated by a nucleoside analog-based chemotherapy, US 20130011392 A1 (January 2013). No potential conflicts of interest were disclosed by the other authors.

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