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## Letter to the editor: pharmacokinetics of gemcitabine in non-small-cell lung cancer patients: impact of the 79A>C cytidine deaminase polymorphism

Cédric Mercier, Laetitia Dahan, L'Houcine Ouafik, Nicolas André, Joseph Ciccolini

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**Letter to the Editor : Pharmacokinetics of gemcitabine in non-small-cell lung cancer patients: impact of the 79A>C cytidine deaminase polymorphism**

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3 **Letter to the Editor : Pharmacokinetics of gemcitabine in non-small-cell lung**  
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5 **cancer patients: impact of the 79A>C cytidine deaminase polymorphism**  
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12 **Cédric Mercier, Laetitia Dahan, L'Houcine Ouafik, Nicolas André, Joseph**  
13 **Ciccolini**  
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19  
20 C. Mercier : Medical Oncology Unit, La Timone University Hospital of Marseille,  
21 France.  
22

23  
24 L. Dahan: Digestive Oncology, La Timone University Hospital of Marseille, France.  
25

26  
27 L. Ouafik: Transfer Oncology Laboratory, North University Hospital of Marseille,  
28 France.  
29

30  
31 N. André, Paediatric Oncology Unit, La Timone University Hospital of Marseille,  
32 France.  
33

34  
35  
36 J. Ciccolini (✉): Transfer Oncology Laboratory, North University Hospital of  
37  
38 Marseille, 13015 Marseille France. Email: joseph.ciccolini@univmed.fr  
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3 Dear Sir,  
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8 We have read with great interest the article entitled "Pharmacokinetics of gemcitabine  
9 in non-small-cell lung cancer patients: impact of the 79A>C cytidine deaminase  
10 polymorphism" by Maring J et al. which has been recently published in the European  
11 Journal of Clinical Pharmacology [1]. We would like to comment on the article by  
12 referring to our own non-clinical and clinical studies on evaluating the relationships  
13 between CDA status (either determined from a phenotypic or a genotypic basis) and  
14 pharmacokinetics or clinical outcome in individuals treated with gemcitabine [2].  
15 Maring et al. studied the impact of the canonical 79A>C polymorphism in the cytidine  
16 deaminase (CDA) gene on the pharmacokinetics of gemcitabine and its main inactive  
17 metabolite 2',2'-difluorodeoxyuridine (dFdU) in non-small-cell lung cancer (NSCLC)  
18 patients. They conclude, from this genotypic-based study, that this polymorphism has  
19 little impact on gemcitabine pharmacokinetics eventually. Of note, in this study, CDA  
20 status was never evaluated using a functional test, and no clinical data (e.g.,  
21 relationships between allelic variants and the incidence of severe toxicities) were  
22 made available to further confirm the little relevance 79A>C polymorphism had on  
23 clinical outcome with gemcitabine. However, as fairly underlined by the authors,  
24 several experimental or clinical reports have previously evidenced the importance of  
25 the 79A>C mutation, both in term of impact on CDA activity, or as a biomarker  
26 predictive of toxicity/response with gemcitabine at the bedside [3-5]. In their paper,  
27 Maring et al. list a variety of possible confounding factors explaining this discrepancy,  
28 such as epigenetic deregulations, dose levels, sample size or lack of treatment  
29 uniformity in the patients they enrolled. In the light of our own expertise on genetic  
30 polymorphism affecting CDA and subsequently patients undergoing gemcitabine-  
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3 based therapies, we do believe that the absence of impact of the 79A>C Maring et al.  
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5 have evidenced is not artifactual. Actually, we reached the same conclusion in a pilot  
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7 study performed in animals as well as in 150 patients (130 adults, 20 children)  
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9 designed to evaluate whether CDA genetic polymorphism was a culprit for early  
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11 severe toxicities upon gemcitabine intake [2]. In our study, we proved that CDA  
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13 deficiency led to marked alterations of the gemcitabine pharmacokinetics profile in  
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15 animals, with subsequent unrecoverable haematological toxicities. In patients, the  
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17 79A>C mutation was screened along with the 208G>A and 435T>C polymorphisms,  
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19 and failed to be correlated with either CDA activity or clinical outcome. Conversely,  
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21 sorting the same patients next on a CDA phenotypic status, rather than on a  
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23 genotypic one, was fully predictive of those undergoing drug-induced severe  
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25 toxicities, regardless of the dose administered, or the associated treatments. In this  
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27 respect, the recent study by Maring et al. is of interest, because it fully supports the  
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29 hypothesis that the gemcitabine pharmacogenetics issue should be better addressed  
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31 using functional tools, rather than with a candidate gene approach. Finally, we would  
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33 like to emphasize that the apparently negative conclusions of this paper should not  
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35 deter physicians from moving toward a more personalized medicine with  
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37 gemcitabine, since it all depends on the tools you use to custom treatment.  
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