Standard-dose tegafur-uracil (UFT) is not a safe alternative in partial dihydropyrimidine dehydrogenase-deficient patients

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To the editor,

With interest we read the article by Dr Cubero and colleagues, in which they evaluated the safety of tegafur-uracil (UFT®) in five cases with partial dihydropyrimidine dehydrogenase (DPD) deficiency [Cubero *et al.* 2012]. Based on our previous experience [Deenen *et al.* 2010], however, we would like to express our concern about their conclusion that UFT is a safe alternative for the treatment of patients with partial DPD deficiency.

Cubero and colleagues make the erroneous and unproven statement that the presence of uracil in UFT creates an artificial DPD deficiency, and that the DPD activity in patients with normal DPD activity would then be similarly as low as in DPD-deficient patients. This assumption, however, is incorrect. As uracil is a competitive inhibitor of DPD, it competes with 5-fluorouracil (5-FU) for DPD-mediated metabolism. This does not mean that the activity of DPD is depleted, as suggested by Cubero and colleagues, in contrast, its activity is fully utilized, as well as for the metabolism of uracil, as for the metabolism of 5-FU.

We would like to caution that treating patients with partial DPD deficiency with the standard dose of UFT may unnecessarily lead to severe, potentially lethal toxicity. Unlike the cases described by Cubero and colleagues, we could previously describe four cases presenting with comparable severe toxicity profiles upon treatment with UFT as had previously occurred during treatment with capecitabine or 5-FU. In all subjects an underlying partial DPD deficiency was identified by genotype and phenotype analyses [Deenen *et al.* 2010]. Furthermore, there are several pharmacological lines of argument that support our clinical observation, i.e. that the standard dose of UFT is not safe in (partial) DPD-deficient patients.

First, pharmacokinetic studies have shown that DPD remains essential for the metabolism of UFT, with significantly longer half-lives of 5-FU after administration of UFT compared with 5-FU administered intravenously [Ho *et al.* 1998]. This is due to the presence of uracil in UFT. Since DPD-deficient patients already have longer half-lives of 5-FU than other patients [Mattison *et al.* 2006], presence of uracil increases its half-life even further. This in turn leads to prolonged and elevated circulating levels of 5-FU, with a subsequently increased risk of 5-FU-induced severe toxicity.

Another argument underscoring the importance of normal DPD function in the safe application of UFT, is the experience with S-1. S-1 is another drug combination of tegafur, consisting of tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate in a molar ratio of 1:0.4:1. CDHP inhibits DPD 200-fold more potently than does uracil [Shirasaka *et al.* 1996a, 1996b]. Even after administration of S-1, the primary 5-FU metabolite formed by DPD is observed in significant concentrations in plasma [Kim *et al.* 2007]. Thus, DPD remains an essential detoxification enzyme of 5-FU, even when its activity is strongly inhibited.

The ultimate proof of theory is the occurrence of 18 treatment-related deaths in patients with cancer and herpes zoster given UFT plus the antiviral drug sorivudine [Pharmaceutical Affairs Bureau, 1994]. Subsequent studies in rats showed that a metabolite of sorivudine, (*E*)-5-(2-bromovinyl) uracil, instantly and irreversibly inactivates DPD by covalent binding, which has been identified as the underlying mechanism of these toxic deaths [Ogura *et al.* 1998; Okuda *et al.* 1998]. It is for these arguments that the Summary of Product Characteristics of UFT notes a known DPD deficiency as a contra-indication [Merck Serono, 2011].

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The fact that the patients described by Cubero and colleagues did not develop significant toxicity might be due to patient selection, the slightly decreased dose intensity of 90%, or despite their *DPYD**2A genotype a DPD enzyme activity within the (lower) range of normal. We are not aware of this, because DPD enzyme activity was not determined in these patients.

In summary, we would like to state that standard-dose UFT is not a safe treatment in (partial) DPD-deficient patients. Instead, dose reductions of on average 50% of either capecitabine, 5-FU or UFT with careful monitoring of safety and further dose titration are proposed as the standard of care [Deenen *et al.* 2011].

Conflict of interest statement

The authors declare that there are no conflicts of interest.

References

Cubero, D., Cruz, F., Santi, P., Silva, I. and Del, G. (2012) Tegafur-uracil is a safe alternative for the treatment of colorectal cancer in patients with partial dihydropyrimidine dehydrogenase deficiency: a proof of principle. *Ther Adv Med Oncol* 4: 167–172.

Deenen, M., Cats, A., Sechterberger, M., Severens, J., Smits, P., Bakker, R. *et al.* (2011) Safety, pharmacokinetics (PK), and cost-effectiveness of upfront genotyping of *DPYD* in fluoropyrimidine therapy. *J Clin Oncol* 29(Suppl. 15): 3606.

Deenen, M., Terpstra, W., Cats, A., Boot, H. and Schellens, J. (2010) Standard-dose tegafur combined with uracil is not safe treatment after severe toxicity from 5-fluorouracil or capecitabine. *Ann Intern Med* 153: 767–768.

Ho, D., Pazdur, R., Covington, W., Brown, N., Huo, Y., Lassere, Y. *et al.* (1998) Comparison of 5-fluorouracil pharmacokinetics in patients receiving continuous 5-fluorouracil infusion and oral uracil plus N1-(2'-tetrahydrofuryl)-5-fluorouracil. *Clin Cancer Res* 4: 2085–2088.

Kim, W., Nakata, B. and Hirakawa, K. (2007) Alternative pharmacokinetics of S-1 components, 5-fluorouracil, dihydrofluorouracil and alpha-fluoro-beta-alanine after oral administration of S-1 following total gastrectomy. *Cancer Sci* 98: 1604–1608.

Mattison, L., Fourie, J., Hirao, Y., Koga, T., Desmond, R., King, J. *et al.* (2006) The uracil breath test in the assessment of dihydropyrimidine dehydrogenase activity: pharmacokinetic relationship between expired $^{13}\text{CO}_2$ and plasma [$2-^{13}\text{C}$] dihydrouracil. *Clin Cancer Res* 12: 549–555.

Serono, Merck (2011) Summary of product characteristics of UFT oral. <http://www.medicines.org.uk/emc/medicine/4399>

Ogura, K., Nishiyama, T., Takubo, H., Kato, A., Okuda, H., Arakawa, K. *et al.* (1998) Suicidal inactivation of human dihydropyrimidine dehydrogenase by (E)-5-(2-bromovinyl)uracil derived from the antiviral, sorivudine. *Cancer Lett* 122: 107–113.

Okuda, H., Ogura, K., Kato, A., Takubo, H. and Watabe, T. (1998) A possible mechanism of eighteen patient deaths caused by interactions of sorivudine, a new antiviral drug, with oral 5-fluorouracil prodrugs. *J Pharmacol Exp Ther* 287: 791–799.

Pharmaceutical Affairs Bureau (1994) *A Report on Investigation of Side Effects of Sorivudine: Deaths Caused by Interactions between Sorivudine and 5-FU Prodrugs*. Japanese Ministry of Health and Welfare (in Japanese).

Shirasaka, T., Nakano, K., Takechi, T., Satake, H., Uchida, J., Fujioka, A. *et al.* (1996a) Antitumor activity of 1 M tegafur-0.4 M 5-chloro-2,4-dihydroxypyridine-1 M potassium oxonate (S-1) against human colon carcinoma orthotopically implanted into nude rats. *Cancer Res* 56: 2602–2606.

Shirasaka, T., Shimamoto, Y., Ohshimo, H., Yamaguchi, M., Kato, T., Yonekura, K. *et al.* (1996b) Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. *Anticancer Drugs* 7: 548–557.