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SHORT COMMUNICATION

Early severe toxicities after capecitabine intake: possible implication of a cytidine deaminase extensive metabolizer profile

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Abstract We report here the case of a 19-year-old female patient who suffered from extremely severe toxicities (G4 mucitis, fever, diarrhea, alteration of general state) while undergoing low-dose capecitabine treatment for her metastatic corticosurrenaloma. The severe toxicities stopped as soon as treatment was suspended. Interestingly, this patient was not deficient in DPD, a pharmacogenetic syndrome usually associated with increased risk of developing severe/lethal toxicities in patients undergoing fluoropyrimidine therapy, and she had been treated previously with 5-FU with a good tolerance. We then hypothesized that cytidine deaminase (CDA) extensive phenotype could be responsible for the severe toxicities observed with capecitabine. CDA is affected by genetic polymorphism, with subsequent acquisition of either deficient or extensive metabolizer profile. Phenotypic investigations confirmed that CDA activity in this patient was +180% higher than the ones usually recorded in the general population. This strongly suggests that the extensive activation of triple-prodrug capecitabine could have occurred in this patient, resulting in overexposure to 5-FU and its cytotoxic metabolites eventually. This case report suggest for the first time that severe toxicities with a capecitabine-containing protocol could be, at least in part, linked with an extensive-CDA syndrome. The case reported here suggests therefore that besides DPD, screening for CDA activity could be of interest to ensure a better safety in the handling of oral capecitabine at the bedside.

Keywords Capecitabine · Cytidine deaminase · Toxicity · Phenotype · Gene polymorphism

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Introduction

Capecitabine is a widely prescribed oral prodrug of 5-FU that has been designed to be bio-activated through a triple-enzymatic process, eventually generating 5-FU in tumors (Fig. 1). Capecitabine activation pattern involves cytidine deaminase (CDA), a ubiquitous enzyme found in the liver and in tumors and that is affected by several genetic polymorphisms [1, 2]. Many studies have focused on the genotype-to-phenotype relationships with CDA, with mixed, when not contradictory, results. For instance, the canonical 79A > C mutation has been associated with either increased [1], decreased [2] or no impact [3] on CDA activity. In clinical oncology, the large inter-patient variations observed in CDA activities is a rising concern with gemcitabine, the third most prescribed anticancer drug worldwide, that is detoxified in the liver by deamination. Downregulated CDA has been already associated with overexposure and subsequent severe/lethal toxicities upon gemcitabine intake [4–6]. Because CDA is a critical step in the activation pattern of capecitabine, erratic enzymatic activity should theoretically impact on drug disposition, with either loss of efficacy (low CDA levels or deficient patients) or increased toxicities (high CDA levels or extensive metabolizer).

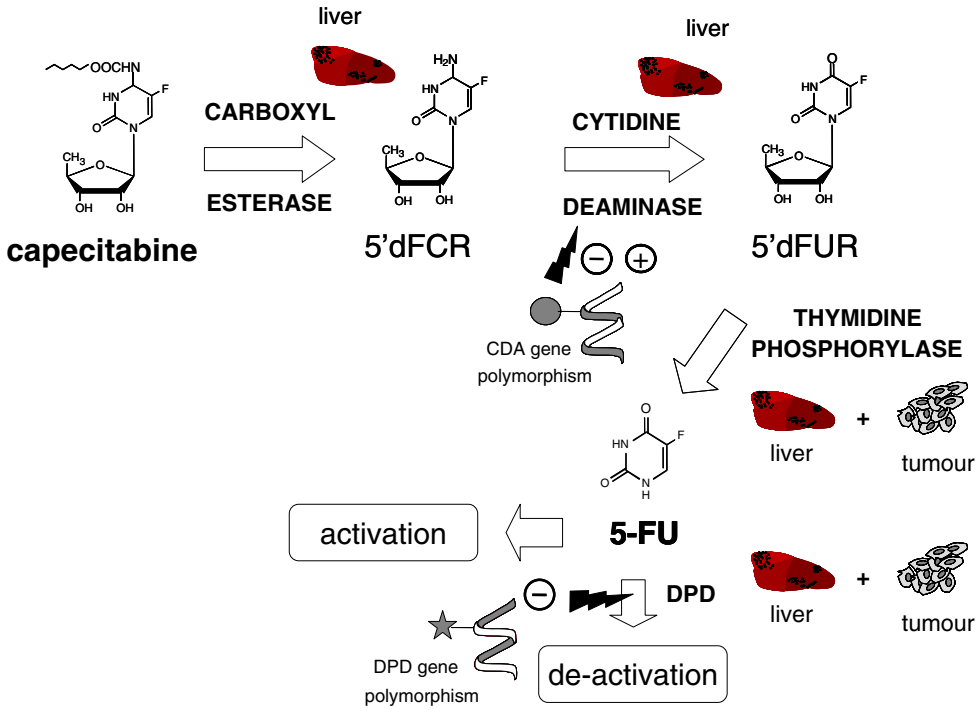

Fig. 1 Metabolic pattern of triple-prodrug capecitabine, and impact of CDA and DPD gene polymorphisms on drug disposition and activation. *5′dFCR* 5′-deoxy-5-fluorocytidine, *5′dFUR* 5′-deoxy-5-fluorouridine, *5-FU* 5-fluorouracil, *DPD* dihydropyrimidine dehydrogenase, *CDA* cytidine deaminase

However, no experimental or clinical data is available presently about the impact of CDA status on the clinical outcome with capecitabine.

Case report

We present here the case of a 19-year-old female patient, who was hospitalized at La Timone University Hospital of Marseille, France in 2007 for a metastatic corticosurrenaloma.

The patient was initially treated by surgery in 2005. Two-year later, lung metastatis were observed and the patient underwent a doxorubicin + cisplatin + VP16 combination (4 courses) followed by streptozocin (3 courses). After screening for DPD deficiency as routinely performed in our institute [7], this patient was identified as non-DPD-deficient and consequently treated with a standard 5-FU (400 mg/m² D1–D3) + dacarbazine protocol, with good tolerance but disease progression and appearance of several brain metastasis. She was then given sunitinib + radiotherapy and eventually low-dose capecitabine (1,000 mg daily with 2 weeks on and 1 week off schedule) as compassional treatment. The patient had soon to be re-hospitalized in emergency 3 days after the start of capecitabine intake due to the outbreak of extremely severe digestive toxicities while at home (G4 mucitis, CTC grading, G2 diarrhea, fever, alteration of the general state). Capecitabine intake was stopped right then. Thanks to appropriate symptomatic treatments (e.g., claventin, cifloxacin) undertaken as soon as the patient presented back in the unit, she fully recovered from her toxicities. Unfortunately, this patient died because of disease progression after she recovered from her toxicties, 3 weeks after having stopped her capecitabine intake. Because this patient had received previously 1,200 mg/m² of 5-FU with no sign of toxicities, and that her DPD status had been checked as non-deficient based upon the measurement of the U/UH2 ratio method [7], impaired detoxification of 5-FU could not be evoked here to explain the severe and early toxicities she experienced with capecitabine. We hypothesized then that CDA-mediated over-activation in the liver of prodrug capecitabine to 5-FU could be at the origin of the toxicities reported. As a triple pro-drug, capecitabine is rationally designed indeed to be preferentially activated to 5-FU by carboxylesterase, cytidine deaminase, and thymidine phosphorylase [8]. To test this hypothesis, phenotypic investigation was carried out to establish the CDA status of this patient. Evaluation of CDA residual activity in serum was performed spectrophotometrically as a surrogate for CDA status [5]. This patient's CDA activity was compared with the values previously recorded in a population of adult patients. CDA activity in our patient was 9.8 U/mg, a value markedly higher (+180%) than the mean value usually recorded at La Timone University Hospital in adult cancer patients (3.6 U/mg, $n = 130$). Regarding the general distribution in CDA activities, we identified therefore this female patient as being extensive metabolizer (Fig. 2). Unfortunately, she died because of neurologic disorders and disease progression soon after she has been sampled for CDA activity monitoring, and no material was

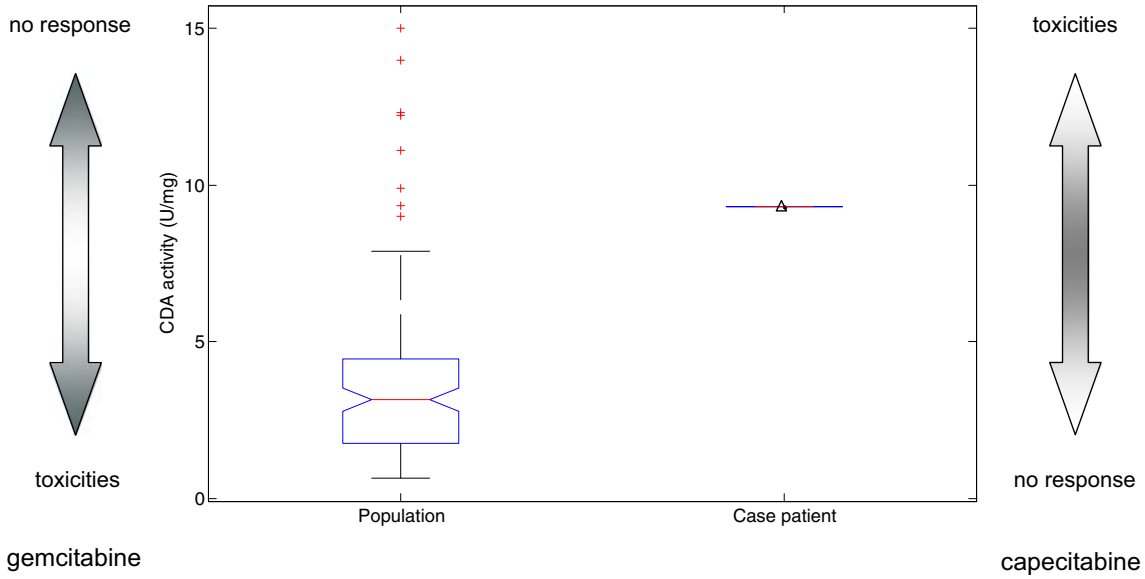

Fig. 2 Distribution of CDA activities in adult cancer patients ($n = 130$) and comparison with the CDA value measured in the patient with severe toxicities upon capecitabine intake. Little CDA values are associated with increased risk of developing toxicities with gemcitabine, whereas patients with elevated CDA activity are theoretically at a risk of non-response. The opposite is expected with capecitabine (the higher the activity, the higher the toxic-risk)

left to perform genetic studies next to check whether this elevated activity was related to a particular genetic mutation on the CDA gene.

Discussion

Identifying markers associated with response/toxicities of anticancer drugs is a rising concern in clinical oncology [9]. Our group has previously reported the very first toxic death case upon gemcitabine administration in relation with CDA gene polymorphism [5], and the very first toxic death case upon capecitabine intake in relation with DPD downregulation [10]. Despite the growing number of clinical evidences indicating that DPD screening should be done prior to giving capecitabine [11], little is done in most institutes to secure the use of this widely prescribed oral therapy [12].

Here, our data strongly suggest that the early severe toxicities observed in a patient undergoing capecitabine-containing protocol was not caused by DPD deficiency, but could be, at least in part, linked instead with an extensive-CDA syndrome. Our group has previously investigated the distribution of CDA activity in Caucasian adult cancer patients [5]. CDA status could be used as a marker to detect either individuals likely to develop severe toxicities upon gemcitabine intake (CDA-deficient patients) and, potentially, non-responding patients (CDA-extensive patients) [5, 13, 14]. We previously observed a wide inter-patient variability range in CDA activities (mean 3.6 ± 2.6 U/mg; min: 0.65 U/mg, max: 15 U/mg, $n = 130$) and about 7% of our population exhibited particularly elevated levels (e.g., > 7 U/mg) and could be thus described as extensive metabolizers. The activity found in our new patient (9.8 U/mg) strongly suggests that she had as well an extensive CDA metabolic profile. Of note, in the toxic case reported here, drug dosage was already reduced by 25% (1,000 mg a day), a dose level markedly lower than standard capecitabine-based protocols. To the best of our knowledge, this is the first time that treatment-related toxicities involving capecitabine can be linked with CDA dysregulation, a syndrome usually associated to clinical outcome with gemcitabine so far. In a recent report, Saif et al. [15] reported the cases of two gemcitabine-refractory pancreatic cancer patients exhibiting spectacular long-term survival after capecitabine intake. The authors had then investigated the DPD/TP issue as a possible pharmacogenetic explanation for the unusually long response duration they observed in these patients. In the light of our present data, one can hypothesize that elevated CDA activity could explain poor responses with gemcitabine due to hyper-deactivation in the liver, whereas conversely capecitabine could have been next over-activated towards its anti-TS metabolites, thus ensuring an optimal efficacy. Because near 10% of the Caucasian population seem to exhibit an extensive phenotype, our data raise therefore the question of the utility of determining CDA status prior to administration of widely prescribed capecitabine. Although it is know fully acknowledged now that DPD can be an issue in the management of toxic risk with capecitabine, and regarding the growing number of patients being treated with this drug, CDA status could

therefore be a new critical parameter to be considered at the bedside. Further clinical studies will have to be conducted to fully confirm the impact of extensive CDA metabolic status in the incidence of early severe toxicities with capecitabine.

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