Author's response to reviews

Title: Acute presentation of vasospastic angina induced by oral capecitabine: a case report.

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Author's response to reviews: see over
Dear Editor,

I hereby submit you a revised version of the article entitled " Acute presentation of vasospastic angina induced by oral capecitabine: a case report”.

(MS: 1139669541007837)

All reviewer (s)' comments were taken into account and point to point answers are included at the bottom of this letter.

Please do not hesitate to contact me if necessary,

Thank you in advance,

Sincerely yours,

Prof. K.A. Charalabopoulos MD, PhD

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POINT TO POINT CHANGES

IN GENERAL

All reviewer(s)’ suggestions were taken into account.

IN PARTICULAR

1. The manuscript was reviewed and English language was significantly improved.
2. Introduction Section: The entire first paragraph was rephrased and restructured as follows (in order to meet the reviewers criteria and answer his question regarding capecitabine pharmacokinetics). In line 2, first paragraph, the following paragraph was added: ‘Capecitabine, a thymidine phosphorylase activated fluoropyrimidine carbamate, an oral prodrug of 5-FU, is absorbed by the gastrointestinal tract and metabolized to 5-FU by a cascade of three enzymes. It is currently considered the only universally approved orally administered 5-fluorouracil (5-FU) prodrug. It belongs to a newer generation of orally administered fluoropyrimidines. It has been developed because of the clinical need for efficient, tolerable and convenient agents, which do not require continuous infusion. Capecitabine is not a cytotoxic drug in itself, but via a three-step enzymatic cascade, it is converted to 5-FU mainly within human cancer cells. Capecitabine is converted by carboxylesterase in the liver to 5'-deoxy-5-fluorocytidine (5'-DFCR), by cytidine deaminase in the liver and tumor tissue to 5'-deoxy-5-fluorouridine (5'-DFUR), and by thymidine phosphorylase to 5-FU in tumor tissue. Thymidine phosphorylase is more concentrated in tumor tissue than in normal tissue, and is upregulated by radiation in tumor tissue but not in normal tissue. Thus, oral capecitabine can result in a higher intratumoral and lower systemic 5-FU concentration than bolus 5-FU. The drug compares favorably with 5-FU in patients with colorectal cancer and breast cancer as well as it has an improved toxicity profile, mainly of gastrointestinal and dermatologic effects. Capecitabine shows antineoplastic activity and synergy with other cytotoxic agents including cyclophosphamide or docetaxel in animal models. Bioavailability after oral administration is close to 100%. Although patients can take the drug orally in the convenience of their own home, the key to successful management of capecitabine is the clinician’s awareness of its severe, but low in incidence, adverse effects, and the patients’ education, emphasizing compliance with the treatment plan, prevention and timely recognition of its toxicities. This improved therapeutic index, along with more favorable pharmacokinetics (similar to those of protracted infusion of 5-FU), and convenient oral administration without the need for central venous access and an ambulatory infusion pump, make capecitabine particularly appealing to use’.