CASE REPORT

Safe administration of S-1 after 5-fluorouracil-induced cardiotoxicity in a patient with colorectal cancer

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SUMMARY

Cardiotoxicity is a rare but challenging complication of 5-fluorouracil (5-FU) therapy. Compared with 5-FU, after application of S-1 lower plasma levels of the cardiotoxic metabolite alpha-fluoro-beta-alanine have been reported. Evidence for safe administration of S-1 following 5-FU cardiotoxicity is limited to a case report in an Asian patient. Herein we report the first case of S-1 application after 5-FU cardiotoxicity in a Caucasian patient.

A 67-year-old man with right-sided metastatic colorectal cancer and history of 5-FU cardiotoxicity had a progressive disease after 8-month therapy with irinotecan and bevacizumab. In consideration of known 5-FU cardiotoxicity, he was referred to our department for therapy counselling. We started a combination therapy with S-1, oxaliplatin and bevacizumab. The treatment was well tolerated without any cardiac problems.

Our report confirms the safety of S-1 in cases of 5-FU cardiotoxicity also in a Caucasian patient.

S-1 in combination with oxaliplatin (SOX) in older patients with CRC was evaluated. Overall, 41% and 45% had partial response and stable disease, respectively (disease control rate 86%). Median progression-free survival was 8.5 months, and median overall survival was 18.5 months.⁴

We report the first clinical case in Europe of a patient with CRC and history of 5-FU-related cardiotoxicity in which a therapy with S-1 was safely performed.

CASE PRESENTATION

A 67-year-old Caucasian man in good general condition was referred to our GI-oncology centre from an oncological practice. One year before, a RAS-mutant right-sided CRC with extensive hepatic metastases was diagnosed. Because of large-bowel obstruction, surgical resection of the primary cancer was performed first. According to the current guidelines, subsequently a palliative treatment with bevacizumab in combination with irinotecan bolus, followed by infusional 5-FU and leucovorin (FOLFIRI), was begun. 5-FU was given at the standard dose of 400 mg/m² bolus followed by continuous pump infusion of 2400 mg/m². However, the very first pump infusion had to be discontinued since oppressive chest pain with ECG changes (hyperacute T wave) occurred (see figure 1). Apart from mild hypertension, the patient was not known to have any cardiac pathologies. The only concomitant medication was pantoprazole. The symptoms disappeared spontaneously after the discontinuation of 5-FU with the ECG also returning to normal. No vasodilating drugs were required. The serum markers for myocardial damage (CK-MB, troponin T) were not elevated. No coronary angiogram was performed. Because of this event, the administration of 5-FU was not continued and chemotherapy was performed with irinotecan and bevacizumab only. A disease control was achieved for a period of 8 months; after that a CT scan documented a progress with an increase in size and number of liver metastases. At this point, the patient was referred to our university radiology department for local ablation of the liver metastases. Selective internal radiation therapy of the right liver lobe and three sessions of CT-guided high-dose-rate brachytherapy of further liver lesions were performed. Despite this aggressive local therapy, the disease was not controlled and

BACKGROUND

In the past decades, the antimetabolite 5-fluorouracil (5-FU) has been established as a backbone of cytostatic treatment for colorectal cancer (CRC) and other malignancies. 5-FU is used as monotherapy or in combination with other cytostatics and newer targeted agents as standard of care for adjuvant and palliative treatment of CRC. Common adverse effects of 5-FU are myelosuppression, mucositis and diarrhoea, whereas cardiotoxicity has rarely been reported. Angina-like chest pain is apparent during or within a short period after the first application of the drug. Severe, life-threatening cardiac side effects as congestive heart failure, myocardial infarction, major arrhythmia and sudden cardiac death are exceptional.¹ The potentially lethal complications of 5-FU cardiotoxicity compel to discontinue this highly effective drug. The nature of cardiac damage is not completely understood. The serum level of the 5-FU degradation metabolite alpha-fluoro-beta-alanine (FBAL) is reported to play a major role.² The newly developed fluoropyrimidines (FPs) S-1 and TAS-102 inhibit the dihydropyridine dehydrogenase (DPD)-dependent degradation pathway with consequently reduced formation of FBAL. Thus less cardiotoxic effects may be expected.³ In a recent Scandinavian study, the safety and efficacy of

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Figure 1 ECG changes: hyperacute T wave posterolateral during the episode of oppressive chest pain.

thus a new systemic treatment approach was mandatory. Therefore, the patient was referred to our oncological department. In consideration of the history of 5-FU-related cardiotoxicity, but the potentially high efficacy of FP in the treatment of CRC, we started a combination therapy with S-1, oxaliplatin and bevacizumab (SOX/bevacizumab). S-1 was given at the standard dose of 25 mg/m² twice a day for 2 weeks in three-week cycles. The health insurance approved in this case the reimbursement of the off-label therapy with S-1. The first chemotherapy cycle was performed as a precaution in an inpatient setting and was well tolerated without any cardiac complications. Subsequently, the treatment was continued in our outpatient department.

OUTCOME AND FOLLOW-UP

Until today, altogether four SOX/bevacizumab cycles were performed and well tolerated, without any cardiac complications.

DISCUSSION

FPs are the key agents in the adjuvant and palliative cytostatic treatment of CRC. Particularly 5-FU and its oral prodrug capecitabine may both induce cardiac adverse events. Therefore, in cases of cardiac complications a switch between these drugs should be avoided. The cardiac side effects are mainly caused by the formation of the cardiotoxic degradation metabolite FBAL. The newly developed FP S-1 (tegafur/gimeracil/oteracil) and

TAS-102 (trifluridine/tipiracil) are combination preparations that contain DPD inhibitors. Consequently, less FBAL concentrations are observed in the degradation process and lower rates of cardiac complications may be expected.⁵ The individual susceptibility to cardiotoxic side effects of FP administration is rather related to different enzyme polymorphisms in the catabolising pathway than to pre-existing cardiovascular conditions.⁶ Discontinuing FP in the therapy of CRC is a reasonable but potentially less effective compromise.⁷ In our case, a disease control for a period of 8 months was achieved with the combination of irinotecan and bevacizumab. The novel FP S-1 and TAS-102 seem to offer an innovative opportunity for a safe administration of FP after occurrence of 5-FU cardiotoxicity. However, most clinical trials with these cytostatic drugs have been conducted in East Asian patients. This is relevant as pharmacokinetics, possibly due to hepatic CYP-enzyme polymorphisms, is different in Caucasian people. For example, the serum concentration of FBAL after application of similar S-1 doses is reported to be higher in Caucasians compared with East Asian subjects, whereas the serum level of the active substance 5-FU is not different.⁸ In the Asian population, the efficacy of S-1 and capecitabine seems to be equivalent in patients with CRC.⁹ For the time being, S-1 in Europe has been only approved for gastric cancer therapy. With respect to CRC, the experience with S-1 is limited to promising retrospective data in older Caucasian patients.⁴ However, prospective randomised survival data from a Dutch cohort are

expected to be published soon.¹⁰ The clinical experience for treatment with S-1 after 5-FU cardiotoxicity is limited to a case report of an Asian patient.²

The similar drug TAS-102, which also contains a DPD inhibitor, is labelled for third-line therapy in CRC in Europe. However, currently there are no available data for combination regimens with TAS-102 in humans.¹¹ Likewise, there is no reported experience for the use of TAS-102 in cases of 5-FU cardiotoxicity.³

CONCLUSION

In the patient reported here, the application of S-1 was a safe alternative after 5-FU-related cardiotoxicity. This is the first case of a Caucasian patient with CRC and the use of S-1 after 5-FU-related cardiotoxicity. The drug is not labelled for CRC in Europe yet and TAS-102 has been approved only in the third line as monotherapy. The experience with this patient calls for studies with these novel FP in patients with CRC and 5-FU

cardiotoxicity to provide more safety for physicians who use these drugs currently off-label.

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Learning points

- ▶ 5-fluorouracil (5-FU) cardiotoxicity is mostly not associated to pre-existing cardiac conditions. The individual susceptibility seems to be attributed to CYP-enzyme polymorphism.
- ▶ Compared with 5-FU and capecitabine, the novel fluoropyrimidines S-1 and TAS-102 are associated with lower plasma levels of the cardiotoxic agent alpha-fluoro-beta-alanine.
- ▶ The metabolism of fluoropyrimidines depends on individual enzyme polymorphism and therefore different effects and side effects may be expected in variable population groups because of diverse pharmacogenomics.
- ▶ The administration of S-1 may represent a safe alternative in cases of 5-FU cardiotoxicity also in Caucasian patients.
- ▶ Prospective trials are needed to define the role of S-1 in the treatment of tumour entities other than gastric cancer in Caucasians.

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