Chapter 5

5FU and oxaliplatin containing chemotherapy in two dihydropyrimidine dehydrogenase deficient patients

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Abstract
Patients with a germline mutation leading to a deficiency for the dihydropyrimidine dehydrogenase (DPD) enzyme are at risk from developing severe toxicity due to the administration of 5FU containing chemotherapy. We report on the implications of this inborn genetic error in 2 patients who received 5FU and oxaliplatin. A possible co-medication effect of oxaliplatin is discussed and the consequences of screening for DPD deficiency.

Introduction
Mutations in the gene that encodes for the 5FU metabolizing enzyme DPD lead to severe toxicity in individuals exposed to 5FU or its analogs. From all patients with severe 5FU induced toxicity 30-57 % was found to be due to this deficiency (1;2). The genetic basis of DPD deficiency has been analyzed intensively in recent years resulting in a greatly increased understanding of the pathology and epidemiology of the syndrome. Basically these mutations lead to a decreased metabolism of 5FU, resulting in accumulation of toxic compounds. Accordingly the end results in an afflicted patient exposed to 5FU or analogs are the symptoms of an overdose of FU both in normal tissues and in the tumor. In two patients who developed severe toxicity after 5FU and oxaliplatin containing chemotherapy, we found DPD deficiency. The short and long term sequelae of this exposition are described. We further discuss a possible relation with the oxaliplatin medication given in both of these patients.

Case histories
The first patient, a 68 year old woman was diagnosed with an irresectable obstructing rectal carcinoma. Treatment was started with the construction of a deviating colostoma. One month later chemo-radiation was started, radiotherapy was given in a total dose of 50.4 Gy in 28 fractions of 1.8 Gy, chemotherapy consisted of 5FU 350 mg/m², leucovorin 20 mg/m² and oxaliplatin 130 mg/m². On day 21 of this treatment (after 1 cycle of chemotherapy and 15 fractions of 1.8 Gy) she was hospitalized due to diarrhea, mucositis, leucopenic fever and dehydration. She was hospitalized for 142 days of which 10 on the intensive care unit (ICU). Leucopenia resolved rapidly, within one week, however the diarrhea took a prolonged course over four months during this period biopsies were taken during colono- and gastroduodenoscopy. Biopsies showed non specific inflammation and villous atrophy. Clinically there were no signs of toxicity due to oxaliplatin (e.g. sensory neuropathy). One month after discharge patient underwent an abdomino-perineal resection en block with the
posterior vaginal wall, without further preoperative chemo-or radiotherapy. Pathological TN-stage of the specimen was pT3N0 with a microscopic tumor free radical resection margin. One year after surgery patient was doing well, she had normal blood chemistry and adequate bowel function with a colostomy.

The second patient, a woman of 58 years of age had a curative resection of a Dukes B sigmoid colon carcinoma at the age of 52. Four years later, she presented with liver metastases for which she underwent a right hemihepatectomy. After a period of 18 months lung metastases developed and palliative chemotherapy was started with biweekly 5FU (2600 mg/m2, 24h infusion), leucovorin (200 mg/m2 1h bolus) and oxaliplatin (85 mg/m2, 2h bolus). Fifteen days after the first treatment patient developed oral mucositis, diarrhea grade II and leucopenia grade III (WBC 1.0 x 10^9/l). After recovery the second course was given after a 10 day delay. Sixteen days later she was hospitalized for 5 days because of the development of fever, leucopenia grade III (WBC 1.1 x 10^9/l), anemia grade II (Hb 5.6 mmol/l) and mild cerebellar ataxia. After a period of 2 weeks blood counts normalized and cerebellar ataxia improved gradually until full recovery after 5 months. Assessment of tumor response after the first chemotherapy cycle showed stable disease and 2 weeks after the second cycle there was progression of disease. After DPD deficiency was established, no 5FU based treatment was given, she received oxaliplatin monotherapy with minor toxicity, without response. Finally irinotecan was given, but also without response. Seventeen months after the first treatment with 5FU, the patient was alive with slowly progressive disease without signs of bowel or cerebellar dysfunction.

Determination of the DPD activity in peripheral blood mononuclear (PBM) cells was performed according to methods previously described (2). The DPD activity in the patients was obtained during the toxicity crisis and repeated after full recovery. A DPD activity of 2.1 nmol/mg/h was detected in the PBM cells of the first patient, 21% when compared with that observed in controls (10.0 ± 3.4 nmol/mg/h; n = 22) and 0.5 nmol/mg/h (5 %) after recovery. DPD activity in the second patient was 3.7 nmol/mg/h (37 %) during cytopenia and 4.2 nmol/mg/h (42 %) after 5 months.

**Discussion**

The toxicity most often encountered in patients with a low DPD activity receiving 5FU is a grade III-IV neutropenia (2), Milano described in addition especially an increased incidence of severe neurotoxicity in 7 of the 19 DPD deficient patients (confusion, cerebellar syndrome or coma) (1). Other toxicities such as mucositis, gastro-intestinal toxicity, especially diarrhea and
cardiotoxicity are also in line with the spectrum of 5FU side effects in patients with a normal DPD activity. Consistent with the findings in our patients the intensity of toxicity is excessive, but the spectrum of symptoms is recognizable. In consequence a fraction of the severe toxicities occurring during regular treatment with 5FU can be ascribed to the prevalence of DPD deficiency in the population.

The incidence of grade IV hematological toxicity, mucositis and diarrhea was 2.5 % (3) in a meta-analysis of patients treated with 5FU for colorectal cancer. This is close to the estimated 3 % incidence of relevant DPD deficiency with activity below 70 % (1), suggesting that the majority of toxic events on 5FU could be caused by this genetic defect.

Also the overall mortality after 5FU, estimated to be 0.5 % (3), could be explained with the approximate mortality of 10 % among patients with DPD deficiency related 5FU toxicity (1). Some observations suggest that the risk of 5FU induced toxicity might be somewhat higher than expected in women (4). This could be due to a gender effect, as suggested by Milano (1), but this could not be confirmed by Kuilenburg (2). Alternatively co-medication might play a role, as breast cancer patients often receive agents in addition to 5FU. In this respect the co-medication in our patients might be of interest, in both this consisted of the new platinum analogue oxaliplatin. Kim investigated the mechanism of antitumor activity in combination treatment of 5FU and cisplatinum in human gastric cell lines (5). They found that the DPD activity and 5FU concentration were not changed by treatment with cisplatinum.

Other data however suggest that metabolism of 5FU may be altered by platinum analogs. Fischel analyzed the intracellular determinants of the combination of 5FU and oxaliplatin in a human colon cancer cell line (6). They found a reduction of the 5FU catabolism due to the addition of oxaliplatin. A pharmacokinetic study by Boisdron-Celle showed a decreased plasma clearance of 5FU after the addition of oxaliplatin in a group of 29 patients with colorectal cancer (7). These findings were not linked to a DPD inhibition.

The high financial costs of treatment for the complications encountered in our patients underscores the potential importance of screening for DPD deficiency. A requirement for a screening test would in addition to specificity and sensitivity be its rapid availability preferably without exposition of the patient to 5FU.

Determination of the DPD activity in PBM cells is possible by an analysis using reverse phase high performance liquid chromatography as used in our patients (8). Alternatives are mutation analysis in the DPD gene after PCR amplification of the coding exons (9).
Maring et al. described measurement of 5FU clearance after an initial supposedly non-toxic chemotherapy dose to identify patients with a low DPD activity (10).

Some estimates concerning cost benefit relation of screening for DPD deficiency can be made; assuming that for some time to come the most common indication for 5FU or analog will be Dukes C colon cancer.

In 1997, 8600 new colorectal cancer patients were registered in the Netherlands (11), of whom 30 % with a Dukes C stage (n=2580) (12). Probably at least half of them will receive chemotherapy. With the given incidence of DPD deficiency approximately 30 hospitalizations and 3 deaths might be prevented, the cost benefit ratio could be improved if fewer controls for the non-risk patients could be scheduled as result of screening.

Furthermore there are a growing number of studies being performed with oral 5FU prodrugs (e.g. capecitabine, doxifluridine and tegafur) also for other indications than colon cancer. With an increase of the use of these drugs the incidence of severe 5FU related toxicity will also increase. DPD deficient patients might be selected for alternative treatment modalities containing novel non-fluoropyrimidine compounds or raltitrexed. Irinotecan and oxaliplatin have been shown to possess anti-neoplastic activity in colorectal cancer and these agents have been safely applied in the treatment of a patient suffering from a partial DPD deficiency (13).
DPD deficiency

Reference List


