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 of the dihydropyrimidine dehydrogenase (DPD) enzyme are at risk from developing severe toxicity on the administration of 5FU-containing chemotherapy. We report on the implications of this inborn genetic error in two patients who received 5FU and oxaliplatin. A possible co-medication effect of oxaliplatin is considered, as are the consequences of screening for DPD deficiency.

Mutations in the gene that encodes for the 5FU metabolising enzyme dihydropyrimidine dehydrogenase (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 analysed intensively in recent years, resulting in a greatly increased understanding of the pathology and epidemiology of the syndrome. Basically this mutation leads to a decreased metabolism of 5FU, resulting in accumulation of toxic compounds. Accordingly the end result in an afflicted patient exposed to 5FU or analogs are the symptoms of an overdose of FU both in normal tissues and in the tumour.

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 exposure are described. We further discuss a possible relationship with the oxaliplatin medication given to 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 to 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 hospitalised due to diarrhea, mucositis, leukopenic fever and dehydration. She was hospitalised for 142 days of which 10 were in the intensive care unit (ICU). Leucopenia resolved rapidly, within one week, however the diarrhea took a prolonged course over four months during which period biopsies were taken during colono- and gastroduodenoscopy. The 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 the patient underwent an abdomino-perineal resection en bloc with the posterior vaginal wall, without further preoperative chemo- or radiotherapy. The pathological TN-stage of the specimen was pT3N0 with a microscopic tumour-free radical resection margin. One year after surgery the patient was doing well with normal blood chemistry and adequate bowel function with a colostomy.

The second patient, a woman of 58 years of age, had 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 the patient developed oral mucositis, diarrhea grade II and leucopenia grade III (WBC 1.0 x 10⁹/l) and oxaliplatin (85 mg/m², 2h bolus). Fifteen days after the first treatment the patient developed oral mucositis, diarrhea grade II and leucopenia grade III (WBC 1.0 x 10⁹/l). After recovery the second course was given following a 10-day delay. Sixteen days later she was hospitalised for 5 days because of the development of fever, leucopenia grade III (WBC 1.1 x 10⁹/l), anemia grade II (Hb 5.6 mmol/l) and mild cerebellar ataxia. After a period of 2 weeks, blood counts normalised and cerebellar ataxia improved gradually until full recovery after 5 months. Assessment of tumour response after the first chemotherapy cycle showed stable disease but, 2 weeks after
the second cycle, there was progression of disease. After DPD deficiency was established, no 5FU-based treatment was given, and she received oxaliplatin monotherapy with minor toxicity, but 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 activities in the patients was obtained during their 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), becoming 0.5 nmol/mg/h or 5%) after recovery. The 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 additionally described especially an increased incidence of severe neurotoxicity in 7 out of 19 DPD deficient patients (confusion, cerebellar syndrome or coma) (1). Other toxicities such as mucositis, gastro-intestinal toxicity and especially diarrhea and cardiotoxicity are also in line with the spectrum of 5FU side-effects in patients with a normal DPD activity. Considering the findings in our patients, the intensity of toxicity was excessive, but the spectrum of symptoms was recognisable. Thus, 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 haematological 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 administration could be caused by this genetic defect.

Also the overall mortality after 5FU, estimated to be 0.5% (3), could be explained by 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, which in both cases consisted of the new platinum analogue oxaliplatin. Kim investigated the mechanism of anti-tumour 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 the metabolism of 5FU may be altered by platinum analogs. Fischel analysed 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 exposing 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 the 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% were Dukes’ C stage (n=2580) (12). Probably at least half of them will receive chemotherapy. With the given incidence of DPD deficiency, approximately 30 hospitalisations 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 a result of screening.

Furthermore, there are a growing number of studies being performed with oral 5FU prodrugs (e.g. capecitabine, doxifuridine and tegafur) for indications other 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).
References


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