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SHORT COMMUNICATION

Pharmacokinetics of panitumumab in a patient with liver dysfunction: a case report

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Abstract
Purpose Panitumumab is used for the treatment for metastatic *RAS* wild-type colorectal cancer (mCRC). It is likely that many of these patients will present with liver metastases and some with liver dysfunction. The pharmacokinetics in patients with hepatic impairment has not been investigated, and dosage adjustments are undetermined. Here, we present a case of a patient with progressive mCRC and liver dysfunction.
Methods A heavily pretreated *KRAS* wild-type mCRC patient with liver disease Child-Pugh class B was treated with 2-weekly intravenous panitumumab (6 mg/kg). The patient received 2 doses of 490 mg i.v. panitumumab after which progressive disease was documented. Toxicities were graded using CTCAEv4.0. Serum samples were collected, and panitumumab concentrations were determined using a validated immunoassay. Pharmacokinetic parameters after the first dose, including dose-normalized AUC from time zero–day 14, clearance (CL), and elimination half-life ($T_{1/2}$), were estimated via trapezoidal noncompartmental methods. Data were compared to historical data from a population with adequate liver function, as reported by Stephenson (Clin Colorectal Cancer, 8:29–37, 2009). Values within the range of the mean ±1 standard deviation (SD) were considered not deviant.
Results Calculated AUC after the first dose of 6 mg/kg panitumumab in this patient with hepatic dysfunction was 877 µg day/mL (Stephenson's cohort 1: 744 ± 195 µg day/mL). Estimated $T_{1/2}$ was 3.58 days (5.28 ± 1.90 days), and CL was 6.9 mL/day/kg (8.21 ± 3.79 mL/day/kg). Estimated PK parameters during the first cycle were inside reported mean ±1 SD of historical controls without liver dysfunction. No toxicity was reported during treatment; particularly, no diarrhea and skin toxicity were noticed.
Conclusions The pharmacokinetics of panitumumab in this patient suffering from metastatic colorectal cancer with liver dysfunction Child-Pugh class B was similar compared to patients with adequate liver function. Moreover, no substantial toxicity was detected. The here-presented data may help clinical decision making in real-life practice. Two-weekly panitumumab monotherapy seems to be safely applicable in patients with *KRAS* wild-type mCRC and hepatic dysfunction, without the need for any dose adjustments.

Keywords Panitumumab · Liver dysfunction · Pharmacokinetics · Colorectal cancer

Introduction

Panitumumab is a fully human IgG2 monoclonal antibody targeting the EGFR receptor. Panitumumab is approved for

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Table 1 Overview of the patient's laboratory tests results during the first cycle of panitumumab treatment

Marker	Ref. value	2010-08-13	2010-08-16	2010-08-25 day 1 cycle 1 panitumumab	2010-09-01	2010-09-08 day 15 cycle 2 panitumumab	2010-09-19
Sodium (mmol/)	136–144	137	130	125	130	140	140
Potassium (mmol/L)	3.6–4.8	4.4	4.2	4.2	3.3	3	4.6
Ureum (mmol/L)	2.5–7.5	9.3	10.7	14.4	10.2	3	14.4
Creatinine	62–106	112	90	96	98	63	127
eGFR (mL/min)	>60	58	>60	>60	>60	>60	50
Albumine	34–48			44	43	34	18
Bilirubine total (μmol/L)	0–17	148	136	63	40	31	165
Bilirubine conjugated (μmol/L)	0–5	109	95	43	25	19	125
Alkaline phosphatase (U/L)	40–120	232	184	133	213	293	635
Gamma GT (U/L)	5–55	230	175	164	408	498	348
ASAT (U/L)	5–35	89	91	114	69	62	207
ALAT (U/L)	5–45	110	106	165	88	61	87
INR		1.3					2.8

the treatment for patients with wild-type *RAS* metastatic colorectal cancer (mCRC). In the first line, panitumumab is indicated in combination with FOLFOX and in the second line with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan). Panitumumab as monotherapy is indicated after failure of fluoropyrimidine, oxaliplatin, and irinotecan containing regimens.

As panitumumab is used in treatment for metastatic colorectal cancer, it is likely that many of these patients will present with liver metastases and hence some even with significant liver dysfunction. In the pharmacokinetic studies of Weiner et al., Rowinsky et al., Ma et al., and Stephenson et al. [1–5], the pharmacokinetics of panitumumab have been described comprehensively. However, panitumumab has not been studied in patients with hepatic dysfunction.

Knowledge on the dosing in liver impaired patient is highly relevant; particularly, since in the panitumumab product, information guidelines and advices for dosing in hepatic failure are lacking [6]. The clearance of panitumumab occurs via two pathways. Panitumumab can be cleared via an EGFR sink, which results in saturation of the receptor with panitumumab and consequent clearance. Secondly, the clearance via the reticuloendothelial system is also present in the liver. The capacity of this system is extensive, due to large numbers of receptors in the body. So dose adjustments may not be necessary in case of liver dysfunction.

Here, we report on the pharmacokinetics of panitumumab in a single patient with hepatic dysfunction treated with single agent g mg/kg panitumumab intravenously administered. The objective of this case study is to describe and discuss the effects of hepatic impairment on the pharmacokinetics of panitumumab and to compare the pharmacokinetic data with data from patients without impaired hepatic function.

Subject and methods

Case presentation

In December 2005, a 60-year-old Caucasian male was diagnosed with a T3N + M0 colon carcinoma. The tumor was completely resected, and the patient was treated adjuvantly with eight cycles of capecitabine combined with oxaliplatin (CAPOX). In March 2009, the patient presented with metastatic disease and received a UFT/leucovorin plus bevacizumab regimen, followed by three-weekly irinotecan from January until April 2010.

In August 2010, the patient presented with progressive disease and liver dysfunction, Child-Pugh class B, with bilirubine, gamma GT, ALAT, and ASAT all elevated (Table 1). Treatment with two-weekly 6 mg/kg panitumumab was suggested despite the present hepatic dysfunction. Panitumumab is not contra-indicated in patients with hepatic dysfunction; however, it has not been studied in patients with hepatic impairment [6]. Since there is no clinical data supporting dose adjustments in patients with hepatic impairment, it was decided to start at the regular dose and to measure the panitumumab serum levels in this patient. In total, the patient received two cycles of panitumumab, after which disease progression was documented.

Methods

To study the effects of panitumumab in this patient with hepatic dysfunction, serum samples were collected to determine the serum drug concentrations. The patient, with a body weight of 81 kilograms, received two cycles, 14 days separated (day 1 and day 15), of 490 mg panitumumab, according to the approved dosing instructions of 2-weekly 6 mg/kg body weight. Further dosing was stopped due to early disease progression.

In both instances, panitumumab was administered intravenously in 1 h. Serum samples were collected at 0.5, 1, 2, 4, 8, 24 h, 4 days, and 7 days after the first panitumumab infusion. In addition, just before the second infusion (day 15) and 30 min and 1 h after the second infusion, blood samples were drawn [3].

The samples were allowed to clot for 30 min, followed by centrifuging at 3,000 rounds per minutes. The serum was transferred to a tube and stored at −80 °C until analysis. Panitumumab serum drug concentrations were performed by PPD (Richmond, VA, USA) using a validated immunoassay with electrochemiluminescence detection as follows. Microplate wells were coated with mouse panitumumab antibody to capture the panitumumab. Standards, quality controls, study samples, and blank were loaded into the wells after pretreating 1:100 with 1 × PBS containing 1 % BSA, 1 M NaCl, and 0.5 % Tween-20. The panitumumab in the standards, controls, and samples was captured in the wells, and unbound materials were removed by washing the cells. Horseradish peroxidase labeled rabbit panitumumab antibody was added to the wells for detection. After washing, tetramethylbenzidine peroxidase substrate was added to the wells. The produced colorimetric signal produced after the reaction was proportional to the amount of panitumumab. The color development was stopped by addition of 2 N sulfuric acid, and the optical density was measured at 450–650 nm.

For an analytical run to be acceptable, a minimum of six acceptable calibration standard levels was required to generate an acceptable calibration curve, and a minimum of four out of six controls with at least one control at each level must meet the method acceptance criteria (difference ±20 % and coefficient of variation ≤15 %). The nominal assay range was 400–20,000 ng/mL. If the sample was outside the upper limit, the sample was repeated at an increased dilution. If the sample was below the lower limit and the dilution factor was one, the sample was reported as below the quantification limit (<400 ng/mL).

Pharmacokinetic parameters

Pharmacokinetic parameters were estimated by trapezoidal noncompartmental methods using MW/PHARM 3.5 of Mediware (Groningen, The Netherlands) [7]. Pharmacokinetic parameters for panitumumab—i.e., area under the serum concentration–time curve from time zero to 14 days (AUC_{0-14}), maximum observed plasma concentration (C_{max}), and minimum observed plasma concentration (C_{min})—were determined. Plasma half-life (T½) and clearance (CL) were calculated.

For comparison, historical data from the Summary of Product Characteristics (SPC) [6] and cohort 1 of Stephenson et al. [4] were used. From this study, the dose-normalized (for the first dose of 6 milligram per kilogram) AUC, clearance, elimination half-life, minimum and maximum concentrations were used. In case the value was within the reported serum level ±1 standard deviation, the found value was considered not to be clinically relevant or clinically different.

Toxicity

Information on toxicities was scheduled to be collected at baseline, just before each course, at the day of infusion and 7 days after infusion. Information on toxicities was also scheduled to be collected during each unplanned hospital visit or contact. Toxicities were graded using CTCAEv4.0.

Results

The C_{max} measured in this patient was 176 µg/mL after the first infusion and 164 µg/mL after the second infusion. The C_{min} (10.5 µg/mL) was determined just before the second administration of panitumumab. The reported serum concentrations of panitumumab have been used to calculate the AUC_{0-14} (µg day/mL), half-life (days), and clearance (mL/day/kg) (Table 2).

In Table 2, the pharmacokinetic parameters of panitumumab in this patient with Child-Pugh class B liver dysfunction are reported. In this table, the historical pharmacokinetic data of panitumumab in patients with normal liver function are shown as well [4, 6]. In Fig. 1, the plasma concentration versus time curves are shown. In summary, in our patient, the calculated AUC was 877 µg day/mL. In Stephenson's cohort 1 [4], after the first dose of 6 mg/kg, a mean AUC of 744 ± 195 µg day/mL was calculated. The half-life calculated in our single patient was 3.58 days with a calculated clearance of 6.9 mL/day/kg. The study of Stephenson reported a half-life of 5.28 ± 1.90 days and a clearance of 8.21 ± 3.79 mL/day/kg. All these parameters following the first administration of panitumumab reported in our patient with severe liver dysfunction are within the range of one standard deviation around the mean of the data reported for cohort 1 in the study of Stephenson [4]. Likewise, the maximum and minimum concentration,

Table 2 Historical comparison of pharmacokinetic parameters of panitumumab of the single patient with severe liver dysfunction with patients with adequate liver function

Descriptive statistic	Cmax (μg/mL)	Cmin (μg/mL)	$AUC_{0\text{-tau}}$ (μg day/mL)	$T_{1/2}$ (days)	CL (mL/day/kg)
Cohort 1 first dose 6 mg/kg (2-weekly) Stephenson	152 (29.2)	18.1 (8.6)	744 (195)	5.28 (1.90)	8.21 (3.79)
Cohort 1 third dose 6 mg/kg (2-weekly) Stephenson	232 (71.2)	46.6 (16.9)	1,310 (375)	9.08 (3.61)	4.96 (1.49)
SPC 6 mg/kg (2-weekly)	213 (59)	39 (14)	1,306 (374)	7.5	4.9
Case first dose	179	10.5	877	3.58	6.9
Case second dose	164	n/a	n/a	n/a	n/a

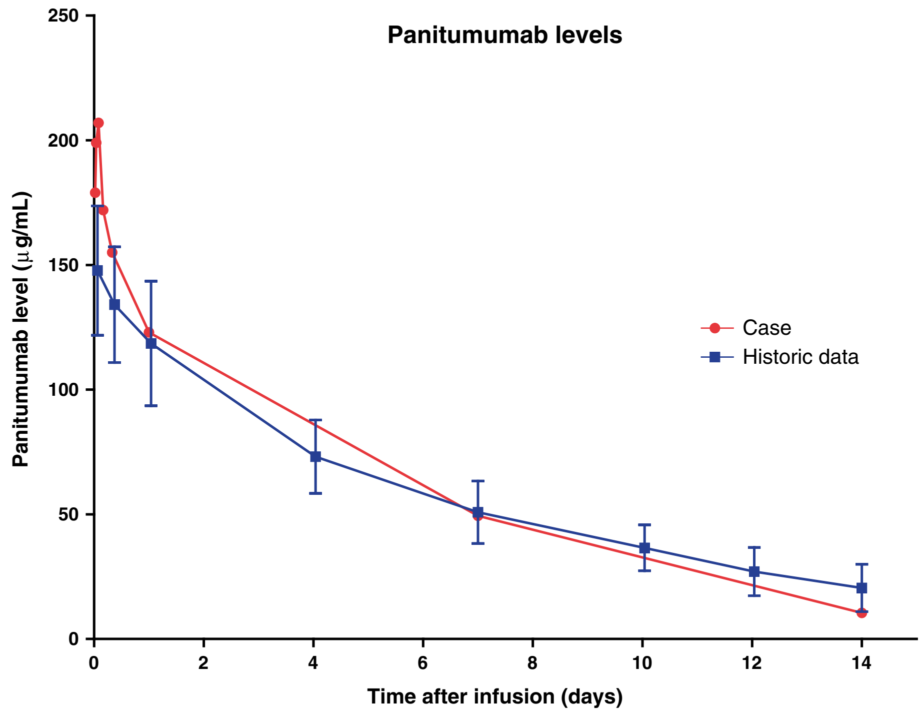

Fig. 1 Time curve of serum panitumumab concentrations following 1 h infusion of 690 mg (6 mg/kg) panitumumab in a metastasized colon cancer patient with Child-Pugh B liver dysfunction

elimination half-life, and clearance were comparable (Fig. 1 and Table 2). A difference between the data from the SPC and parameters after the third dose was noted; however, it should be noted that these parameters were not determined following single dose but after multiple dosing, in the steady state phase.

In our patient with Child-Pugh class B liver dysfunction, no toxicity was recorded after the first two doses of panitumumab; specifically, no diarrhea and no skin toxicity were seen.

Discussion

No advice on the necessity of adjusting the dose of panitumumab, a fully human antibody targeting the EGFR that is dosed two-weekly, in special populations, such as patients with hepatic dysfunction, is available. Also, the safety and pharmacokinetics have not been studied specifically in patients with liver impairment. Like other EGFR targeting agents, panitumumab only has been tested in clinical trials in metastatic colorectal cancer in selected populations with adequate laboratory tests and good performance characteristics. In real-life practice, however, many patients do not match these criteria and may present for example with severe liver dysfunction. There is a clear need for studies in different populations to guide the clinician in real-life practice [8].

The here-reported results of our pharmacokinetic study in a single, heavily pretreated patient suffering from metastasized colorectal cancer treated with 6 mg/kg 2-weekly monotherapy panitumumab do not indicate the necessity of any dose adjustments in patients with liver dysfunction and appear to be tolerable and safe. Pharmacokinetic parameters reported are within the range of one single standard deviation of previously reported data in patients with adequate liver functions. In addition, no substantial toxicity was noticed. However, larger studies of panitumumab in liver impaired patients are needed before firm conclusions can be drawn, and a more solid advice on the necessity of dose adjustments in patients with various degrees of hepatic dysfunction can be given.

The side-effect profile of cetuximab in a liver impaired patient has been presented recently by Moosman et al. [9]. In that particular case report, Moosman and colleagues report on a 57-year-old metastasized colorectal cancer patient with severe liver dysfunction that was successfully treated with cetuximab, a weekly administered chimeric monoclonal antibody targeting the EGFR as well. Based on their observation, it was concluded by the authors that cetuximab is an effective treatment in patients who cannot be treated with cytotoxic agents due to hepatic dysfunction. However, no pharmacokinetic data are presented. The here-reported data on panitumumab add to their conclusion. However, it should be noted that there are important differences between the EGFR antibodies cetuximab and panitumumab. For example, cetuximab is a chimeric antibody, whereas panitumumab is a fully human antibody. Next, cetuximab is an IgG2 antibody, whereas panitumumab is an IgG1 antibody. As a consequence, the serum clearance, Fc domain interactions, and potential initiation of ADCC differ between both antibodies. Therefore, it is not possible to directly extrapolate the pharmacokinetic profiles of one of these antibodies to the other [10].

Successful treatment for solid tumors relies on the ability of EGFR inhibitors to penetrate into the tumor tissue. Clearance of both panitumumab and cetuximab occurs by the EGFR sink and the reticuloendothelial system. Their clearance may also partly depend on the EGFR-positive tumor burden and antigen density in the tumor, i.e., a high tumor burden and/or a high density of EGFR may lead to subsequent higher clearance of panitumumab. In our patient, unfortunately, the tumor burden and the antigen density in the tumor were not known. The impact of EGFR binding sites in the liver on serum clearance of EGFR antibodies remains to be fully clarified. A study of Schechter et al. with 99MTC-cetuximab, however, indicated that the liver may not have any EGFR binding sites, but simply extracts EGFR antibodies, which are not cleared elsewhere in the body [11]. This aforementioned extraction by the liver and the impact of liver dysfunction on total EGFR-antibody clearance needs further clarification.

In conclusion, the pharmacokinetics of panitumumab in our single patient suffering from metastatic colorectal cancer with liver dysfunction Child-Pugh class B do not seem to be altered compared with patients with adequate liver function. Moreover, no substantial toxicity was noticed. Based on these data, panitumumab can be considered safe for treatment in patients with hepatic dysfunction without any dose adjustment. However, more studies seem warranted before firm conclusions can be drawn to guide clinical decision in daily practice.

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