Irinotecan-based chemotherapy in a metastatic colorectal cancer patient under haemodialysis for chronic renal dysfunction: two cases considered

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The pharmacokinetics of irinotecan and its metabolites has been widely studied. No pharmacokinetic data, however, are available in haemodialysis patients. We report two clinical cases of severe toxicity, one of which was fatal, in two haemodialysis patients treated with irinotecan for a metastatic colorectal cancer. In case no. 1, M.S., aged 71 years, was treated with first-line FOLFIRI chemotherapy (irinotecan 180 mg/m^2) for local recurrence with liver metastases of a colon cancer treated with an LV5FU2 protocol as an adjuvant therapy 3 years previously. After the first cycle of irinotecan, the patient presented grade 4 diarrhoea on day 9, then a febrile grade 4 neutropenia on day 14 leading to his death on day 18. In case no. 2, M.D., aged 57 years, was treated successively by radiochemotherapy with an LV5FU2 regimen, then with four cycles of FOLFIRI (irinotecan at 125 mg/m^2) and finally with the cetuximab/irinotecan combination using the conventional dosage. Febrile neutropenia was observed on day 10 of the first irinotecan infusion with a dose of 180 mg/m^2 and on day 8 of the second infusion with a lower dose of 120 mg/m^2. The patient's general condition progressively deteriorated with the advancement of the neoplastic disease, which led ultimately to his death. In this patient, plasma concentrations of irinotecan and its metabolite, SN-38, were measured during the course of the first FOLFIRI cycle on day 2 and on day 4, before and after dialysis sessions. The observed results suggest that, although irinotecan is partially dialysable, SN-38 is not. In conclusion, dose recommendations have to be defined in haemodialysis patients with renal dysfunction owing to the potential toxicity of irinotecan in these patients. Special care should be taken in liver metastasis cases owing to the nondialysability of SN-38. *Anti-Cancer Drugs* 18:977–980

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Introduction

Irinotecan (CPT-11) is a topoisomerase I inhibitor that stabilizes complexes cleaved by DNA topoisomerase I, thereby causing cleavage of single-strand DNA. Irinotecan is metabolized to an active SN-38 derivative by carboxylesterases that are present in most tissues, especially in serum, the liver and the small intestine. As reported earlier by Sparreboom *et al.* [1], nearly 80% of the overall clearance of CPT-11 can be attributed to nonrenal processes. Less than 20% of the dose administered in 24 h is found in urine in the form of the unchanged product (19%) or active metabolites (0.25%). SN-38 is eliminated primarily by the liver [2,3]. The pharmacokinetics of irinotecan and its metabolites has been widely studied [4–6]. No pharmacokinetic information is, however, available in haemodialysis patients.

The indications of irinotecan in adults are metastatic colorectal cancers as first-line monotherapy or in combination with bevacizumab and/or 5-fluorouracil, and as second-line in combination with cetuximab. The usual dosage of irinotecan in patients with normal renal function is 350 mg/m^2, administered as an intravenous infusion every 3 weeks as monotherapy or 180 mg/m^2 every 2 weeks in combination with 5-fluorouracil and folinic acid. Diarrhoea and neutropenia are two forms of toxicity which limit the use of irinotecan.

We report two cases of severe toxicity, one of which was fatal, after the administration of an irinotecan-based chemotherapy with a conventional doseage, in two chronic renal failure patients with metastatic colorectal cancer.

Observation no. 1

M.S., aged 71 years, had been undergoing haemodialysis three times per week for the previous 4 years for chronic renal failure brought on by Wegener's disease, diagnosed in 1994. His antecedents included bronchial dilatation, sleep apnoea syndrome and well-differentiated adenocarcinoma of the left colon pT3pN1M0 diagnosed in June 2002 and treated first surgically and then by adjuvant

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LV5FU2 chemotherapy. The patient received nine of the initially planned 12 courses without any clinical or biological toxicity; the chemotherapy had been stopped at the patient's request. In June 2005 an anastomotic recurrence was documented by colonoscopy. The abdominal scan found liver metastases and [^{18}F]fluorodeoxyglucose scintigraphy found hepatic, mediastinal, and peritoneal hyperfixations.

The patient was symptomatic: serous bloody diarrhoea and proctorrhagia requiring transfusional support. No local treatment could be performed. Metastatic first-line chemotherapy was started on 1 July 2005 with FOLFIRI (irinotecan of 180 mg/m^2 on day 1, 5-fluorouracil of 2400 mg/m^2 by continuous infusion over 44 h and 400 mg/m^2 as a bolus on day 1, and calcium folinate of 400 mg/m^2 on day 1). The immediate tolerance was good; but on day 9 the patient presented an increase of the symptoms. At this time, a grade III haematologic toxicity appeared with leucocytes 1.4×10^9/l, haemoglobin 0.9 g/dl, platelets 82×10^9/l. On day 14, a febrile grade 4 neutropenia appeared. The biological tests were leucocytes 0.5×10^9/l, haemoglobin 8.7 g/dl, platelets 115×10^9/l, total protein 5.6 g/dl, albumin 2.7 g/dl, C-reactive protein 24.8 mg/dl; and liver function tests normal. Treatment with broad-spectrum antibiotics was initiated. On day 16, leucocytes increased to 1.3×10^9/l with polymorphonuclear neutrophils at 1.05×10^9/l. On day 18, the patient died in a context of septic shock with refractory hypotension. Blood cultures on aerobic, anaerobic and Sabouraud's medium remained negative.

Observation no. 2

M.D., aged 57 years, had in his antecedents, hypertension, right nephrectomy in 1998 owing to a benign tumour (cystic nephroma) and a chronic renal failure owing to chronic glomerulopathy of uncertain origin. These haemodialysis sessions were performed three times per week since 22 June 2005. An anaemia refractory to erythropoietin and to iron replacement therapy permitted the diagnosis of a neoplastic rectal lesion. The lesion was a moderately differentiated adenocarcinoma classified as usT3N+ by echoendoscopy, with concomitant liver metastases. A course of radiochemotherapy was started on 26 July 2005. A dose of 45 Gy in 23 fractions was delivered to the rectum and inguinal lymph nodes with chemotherapy according to the LV5FU2 protocol (5-fluorouracil 1200 mg/m^2 by continuous infusion over 44 h with a diffuser and 400 mg/m^2 as a bolus, and calcium folinate 200 mg/m^2 on day 1 and 2). The patient received three cycles with 14-day intervals without any signs of toxicity; the treatments were administered on the day after the dialysis session. When radiotherapy was stopped the patient received intensified chemotherapy according to a modified FOLFIRI regimen, with a lower dose of irinotecan at 125 mg/m^2 at intervals of 14 days. This dose was used because of the experience with the first patient. Pharmacological assays of plasma irinotecan and SN-38 levels were performed during the first chemotherapy cycle on day 2 and 4 before and after dialysis. Technical assay used liquid chromatography coupled with mass spectrometry in tandem [7]. The results are shown in Table 1. Each haemodialysis session decreased the plasma irinotecan concentration of 50%. A noncompartmental pharmacokinetic approach suggests that irinotecan is partially dialysable under the so-called conventional haemodialysis conditions. SN-38 does not seem to be dialysable. The patient received four cycles of FOLFIRI always administered on the day after the haemodialysis session without gastric or haematological toxicity. The assessment scans after four cycles showed the progression of the liver targets. Given the patient's good overall condition (World Health Organization performance status below grade 2) second-line metastatic chemotherapy was then started, comprising cetuximab and irinotecan combination at conventional doses. On 21 November 2005, the patient received the first cetuximab infusion at a dose of 400 mg/kg on day 1 and on day 8 cetuximab 250 mg/kg and irinotecan 180 mg/m^2. A febrile grade IV neutropenia occurred at day 10 with: leucocytes 1×10^9/l with 77% polymorphonuclear neutrophils, haemoglobin 9.0 g/dl and platelets 86×10^9/l. Blood cultures remained negative and progression of the disease was favourable under broad-spectrum antibiotic therapy with recovery from aplasia on day 18. On 21 December, a second course was administered but at lower doses in the absence of any clinical or haematological contraindications. On day 8, after the administration of irinotecan at a dose of 120 mg/m^2, the patient's general condition deteriorated and he was admitted to hospital for a second episode of febrile neutropenia: leucocytes 0.9×10^9/l with 57% polymorphonuclear neutrophils, haemoglobin 8.9 g/dl, platelets 116×10^9/l, alkaline phosphatase 2668 IU/l (normal: below 270), γ-glutamyltransferase 1505 IU/l (normal: below 61), transaminases normal, total bilirubin increased to 30 μmol/l (normal: below 17), and C-reactive protein 24.8 mg/dl. Moreover, despite the fact that there was a return to a polymorphonuclear neutrophil normal count and that the infectious syndrome was under control, the patient's general condition continued to deteriorate with intrahepatic cholestasis appearance and repeated lower digestive bleeding that ultimately led to the patient's death 6 months after the beginning of the treatment.

Discussion

In these two patients irinotecan was used in combination with 5-fluorouracil. Moreover, both patients had previously undergone courses of treatment using the LV5FU2 protocol without showing any signs of clinical or haematological toxicity. In patients with renal dysfunction, regardless of its severity, it is not recommended to adjust the dosage of 5-fluorouracil [8,9].

Table 1 Pharmacokinetic assays of irinotecan and its metabolite SN-38

	Before dialysis day 2	After dialysis day 2	Before dialysis day 4	After dialysis day 4
Irinotecan (μg/l)	402	221	23	12.2
SN-38 (μg/l)	5.41	6.83	1.38	1

The plasma levels of irinotecan and its metabolite SN-38 were determined on day 2 and day 4 after administration of the first FOLFIRI cycle before and after the dialysis session by a method using liquid chromatography coupled with tandem mass spectrometry.

Theoretically there is no risk of saturation of irinotecan's metabolism and therefore little risk of toxic accumulation, as this drug is metabolized by carboxylases which are present in large quantities in the body. As the active metabolite, SN-38, is eliminated largely by the liver, renal failure should have little effect on the pharmacokinetics of this compound. In the two cases presented herein, both patients had liver metastases but a normal bilirubin level. So, according to previously published data [10], there was theoretically no indication for a dose reduction of irinotecan in these patients. Only three cases of irinotecan administered to haemodialysis patients have been reported in the literature. Stemmler *et al.* [11] and Budakoglu *et al.* [12] have reported the feasibility of a weekly irinotecan regimen with a dose of 50–80 mg/m^2, and also described a grade 4 digestive toxicity when using doses of 100 mg/m^2 [11]. Shinozaki *et al.* [13] published in a Japanese journal a case of grade 4 neutropenia after the infusion of a 'dose-reduced CPT-11' (exact dose not reported) in a haemodialysis patient.

In this study, we report the first measurements of plasma irinotecan and SN-38 concentrations in a patient, with chronic renal failure. These assays were performed both before and after two dialysis sessions. The measured concentrations suggest that irinotecan (the blood's stock of SN-38) can be partially dialysed. On the contrary, SN-38 that is strongly bound to plasma proteins and to erythrocytes does not seem to be dialysable in standard conditions. The metabolism of irinotecan is extremely complex as it involves multiple enzyme systems: esterases that induce the formation of SN-38, UGT-1A1 that is involved in the glucuronidation of SN-38 and CYP3A4 that leads to the formation of various inactive oxide compounds [14]. The elimination of irinotecan relies on several transport proteins, including P-glycoprotein, and anion transporters present in bile capillaries. Individual variations in the expression of these phase I or II enzymes and of these transporters explain, at least partially, the pharmacokinetic variations in irinotecan and SN-38, that make it difficult to interpret the values observed in our patient [15,16].

Cetuximab is a chimaeric IgG1 monoclonal antibody that recognizes the epidermal growth factor. The drug is metabolized principally by biodegradation in the liver and in the skin into small peptides or amino acids. Very few data are available on the routes of elimination of monoclonal antibodies. By analogy with endogenous G immunoglobulins (IgGs), monoclonal antibodies seem to be catabolized in endothelial cells. Renal excretion of monoclonal antibodies currently on the market, however, is only rarely documented [17,18]. Nevertheless, pharmacokinetic, tolerability, and efficacy data suggest that renal dysfunction has no impact on the elimination of monoclonal antibodies in man. Therefore, adjusting the dosage of cetuximab in haemodialysis patients is probably not necessary. In our observation, M.D. presented a haematological toxicity when he received the second cycle combining irinotecan and cetuximab despite of the reduction in the dose of irinotecan. No pharmacokinetic interaction between irinotecan and cetuximab has been described up to now [19]. So, this toxicity can probably be attributed to the deterioration in the patient's general and nutritional condition and hepatic progression but not to the use of cetuximab.

Oxaliplatin could have been a reasonable substitute for irinotecan in the treatment of metastatic colorectal cancer. In a patient with normal renal function, 40–50% of the drug is renally excreted. Nevertheless, some pharmacokinetic studies performed in patients with different stages of renal failure demonstrate that there is not any correlation between an increased platinum exposure and toxicity [20,21]. These data suggest that dose reductions of the single-agent oxaliplatin are not necessary in patients with a creatinine clearance of more than 20 ml/min. No pharmacokinetic studies of oxaliplatin in renal failure patients with creatinine clearance less than 15 ml/min or in haemodialysis, however, have been published yet.

Conclusion

Toxic death in a patient with advanced colorectal cancer undergoing haemodialysis is difficult to admit. As for the numerous other anticancer drugs, no recommended dose is proposed for CPT-11 and its use in these patients is open to research. Thus, the optimal dose of irinotecan has to be determined by performing dose-escalation studies. The preliminary results presented herein indicated a probable nondialysability of SN-38 in standard conditions. The monitoring of haemodialysis patients with colorectal cancer and in particular those with liver metastases (and/or impaired liver function) should be improved using irinotecan and SN-38 blood concentrations obtained before and just after a dialysis session. These results need to be confirmed by further studies.

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