Pharmacokinetics and safety of cetuximab in a patient with renal dysfunction.

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Short communication

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Abstract

In the literature data on the effect of renal impairment on the pharmacokinetics of anticancer drugs are scarce. Here, we report a 68 year old metastatic osteosarcoma patient with impaired renal function due to prior chemotherapy, who was treated on compassionate use basis with 400 mg/m^2 cetuximab. Pharmacokinetic parameters after the first dose, including dose normalised AUC from time zero to day 7 (AUC_{0-7}), clearance (Cl), elimination half-life ($t_{1/2}$) were estimated using trapezoidal non compartmental methods and compared to pharmacokinetic data from a study population with normal kidney function. These results showed that the pharmacokinetics of cetuximab in this patient with renal failure was similar to that with adequate renal function and suggests that cetuximab can be safely used in cancer patients with renal impairment without dose adjustment.

Introduction

Cetuximab is a monoclonal antibody, targeting epidermal growth factor receptor (EGFR) and registered for the treatment of colorectal and head and neck cancer. During its development, the drug has been investigated in patients with adequate renal and hepatic function only and a dose of 250 mg/m^2 every week, after an initial loading dose of 400 mg/m^2, is defined in the summary of product characteristics.

No specific dose recommendations are given for patients with renal impairment (http://packageinserts.bms.com/pi/pi_erbitux.pdf). The elimination of antibodies occurs via both nonspecific intracellular catabolism, following fluid-phase endocytosis, and receptor-mediated elimination after binding to their target antigen. Part of cetuximab clearance is therefore explained by binding to EGFR. Clearance of the EGFR antibody cetuximab seems independent of the liver and kidney function [Do you have references?]. In addition, there are 4 case reports [2-5] of haemodialysis patients who could safely be treated with standard doses of cetuximab. The aim of this study was to determine the pharmacokinetics of conventional dose cetuximab in patients with impaired renal function and to compare it to published data obtained in populations of cetuximab treated patients with normal renal function.

Method

Case presentation

We treated a 68 year old metastatic osteosarcoma patient with impaired renal function due to prior chemotherapy on compassionate use basis with 400 mg/m^2 cetuximab. This treatment was based on preclinical data on cetuximab activity in osteosarcoma [6] and the lack of other treatment options. The medical ethical committee approved the treatment and the pharmacokinetic analysis and the patient gave informed consent. The starting dose was 740 mg, preceded by the recommended 2 mg of the antihistamine clemastine, to avoid an allergic reaction to cetuximab.

Sample collection

Cetuximab was infused over two hours. Serum samples were collected 2, 3.5, 4.5, 44 and 168 hours after the end of the infusion in line with a previous pharmacokinetic study [7]. Cetuximab serum concentrations were measured using a validated immunoassay [8]. Limit of detection was 0.012 mg/L and lower limit of quantitation (LLOQ) was 0.75 mg/L.

Pharmacokinetic parameters

Pharmacokinetic parameters after the first dose, including dose normalised AUC from time zero to day 7 (AUC_{0-7}), clearance (Cl), elimination half-life ($t_{1/2}$) were estimated by trapezoidal non compartmental methods using MW/PHARM 3.5 (Mediware, Groningen, The Netherlands). Results were compared to historical data on cetuximab in patients with normal renal function as reported by Tan et al.[9] and Fracasso et al.[10].

Results

The maximum concentration (Cmax), measured at the end of the 2 hour infusion, in this patient was 297 µg/mL, the minimum concentration (Cmin or through level) was 34.4 µg/mL. The reported serum concentration profile, shown in figure 1, was used to calculate the AUC, Cl and t ½. In table 1,an overview of the pharmacokinetics of cetuximab in study populations with normal renal function and in this case is shown [2;9;10]. In this table the pharmacokinetics after a single dose of 400 mg/m^2 are depicted, and are used for comparison.

In this patient the calculated AUC after the first dose was 20,280 µg*day/mL. The half-life after a single dose of cetuximab was 53.2 hours with a calculated clearance of 32.6 mL/h. The Cmax was approximately 30% higher compared to the Cmax in the studies of Tan et al. and Fracasso et al. (6-7) The other parameters Cl, AUC, $T_{1/2}$ and V are comparable as reported in those 2 studies. The half-life of cetuximab in our patient is 30% shorter than that calculated in the studies.

During the first course of cetuximab, the patient experienced adverse effects: reversible grade 2 hallucinations and fatigue. After careful considerations these symptoms were deemed to be most likely caused by the 2 mg clemastine. Due to these side effects the patient refused further treatment with cetuximab. Little is known about the pharmacokinetics of clemastine, nonetheless, normally no dose reductions are advised in patient with renal impairment.

Cetuximab-related side effects such as skin toxicity and diarrhoea did not occur in this patient during the first course.

Discussion

This case report shows that the pharmacokinetics of cetuximab in a patient with renal failure is similar to that with adequate renal function. Different studies investigated the pharmacokinetics of cetuximab in population with adequate renal function. For the comparison, studies with single doses were used. Most of the studies reported cetuximab pharmacokinetic parameters at steady state after a loading dose of 400 mg/m^2 followed by weekly doses of 250 mg/m^2. Using a loading dose, steady state is usually reached within three weeks. Since this patient discontinued therapy after one single infusion, we can only compare this single dose to similar administrations available in the literature.

Our study shows some difference between the estimated parameters in our patient and patients with normal renal function. Due to inter patient variability, nonetheless, overall the kinetic profile is in line with the population with adequate renal function. Cetuximab pharmacokinetics are not studied in patients with impaired renal function, four case reports [2-5] studied the kinetics of cetuximab in patients undergoing haemodialysis. These four case studies showed that cetuximab in a patient with haemodialysis may be safely used. The estimated pharmacokinetic parameters were comparable to cetuximab patients with normal kidney function. Our study shows, for the first time, that pharmacokinetic parameters were also not altered in a patient with decreased renal function without haemodialysis.

Many drugs that enter the market are studied in a patient population with normal renal function and no dose recommendations are made for patients with impaired organ function and formal organ impairment studies are lacking. This is also the case for cetuximab. Other than from common sense and four case reports in haemodialysis patients there was no information available to guide our decision on how to use cetuximab in this patient. As renal impairment is a common problem in head and neck cancer patients due to prior cisplatin chemotherapy and in colorectal cancer patients due to the high incidence of the disease our finding of no clinically relevant alteration of cetuximab

pharmacokinetics in our patient with impaired renal function has clinical importance for dose guidance in future patients.

Acknowledgements

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Study	**model**	**Dose**	**Cmax µg/mL**	**Cmin µg/mL**	**AUC_{0-7} h*mg/L**	**CL mL/h**	**$T_{½}$ Hours**	**V Litre**
Case	Non compartmental model	740 mg (400 mg/m2)	297.0	34.4	20.280	32.6	53.2	2.48
Tan et al. 2006	Non compartmental model	400 mg/m^2 single dose	205.0 (65.7) (µg/mL)	n/a	19,000 (7,802)	21.5 (7.68)	75.10 (15.9)	2.44 (0.43)
Fracasso et al. 2007	Non compartmental model	400 mg/m2 single dose	228.9 (6,5) µg/mL	n/a	24,620 (9,555)	43.6 (15.8) mL/h	97.5 (20.7) h	4.8 (2.2)

Table 1: Pharmacokinetic parameters of the case and historical data from two studies

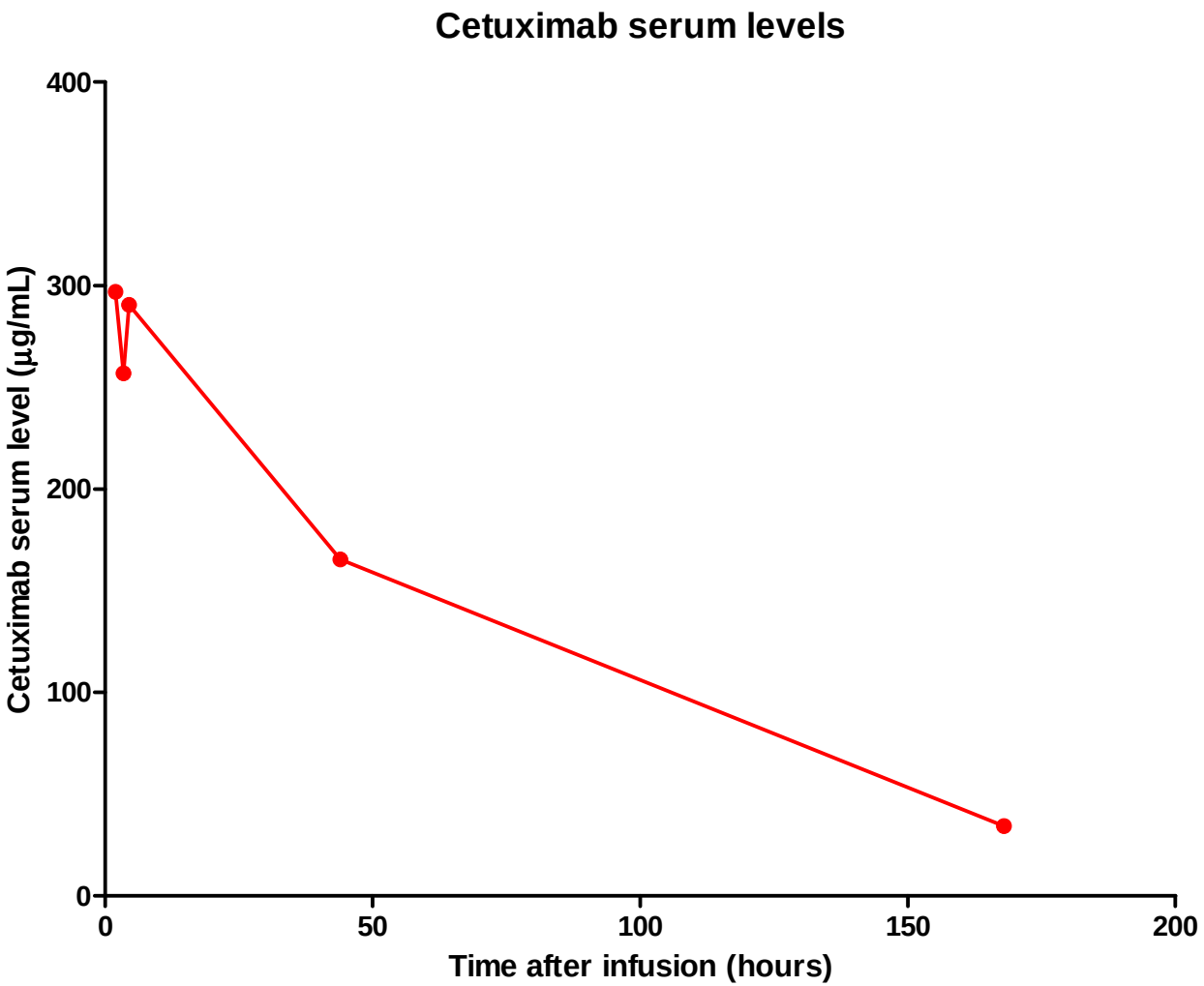

Figure 1: Time curve of serum cetuximab concentration following two hour infusion of 740 mg cetuximab in a patient with a glomerular filtration rate of approximately 30 mL per minute.