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Cetuximab Pharmacokinetics in End-Stage Kidney Disease Under Hemodialysis

To the Editor: Cetuximab, an anti–epidermal growth factor receptor chimeric mouse/human immunoglobulin 1 monoclonal antibody against the epidermal growth factor (Merck, Darmstadt, Germany), has been approved as a treatment for advanced head and neck cancer in combination with radiation therapy.[1,2] However, there is very little data on cetuximab in patients undergoing chronic dialysis.[3] The treatment of cancer in patients with impaired renal function is an emerging problem because the population is getting older and the rate of chronic dialysis increases by 5% yearly in Western countries. We report a pharmacokinetic study of cetuximab in a patient with renal insufficiency requiring hemodialysis. Cetuximab was instituted at a dose of 250 mg/kg weekly for a 55-year-old patient with head and neck cancer.

We characterized the pharmacokinetics and efficacy of cetuximab at conventional efficacious dose levels in combination with radiation therapy in a hemodialyzed patient with head and neck cancer. The aim of the study was to determine whether conventional doses of cetuximab in combination with radiotherapy were appropriate for hemodialyzed patients.

Cetuximab serum concentration was measured by a validated enzyme-linked immunosorbent assay. The enzyme-linked immunosorbent assay method used a recombinant human epidermal growth factor receptor (extracellular domain) adsorbed onto microtiter plates to capture cetuximab in serum. The captured cetuximab was detected using a peroxidase-conjugated goat antihuman $F(ab')_2$ specific for Fc fragment (horseradish peroxidase anti–human immunoglobin G). Lower limit of quantitation and upper limit of quantitation were 0.75 and 15 μg/mL, respectively. The limit of detection was 0.012 μg/mL. Concentrations higher than the upper limit of quantification were diluted 1:10 or 1:100, deviation and variability of this procedure being lower than 4.5%. Serum samples were used to estimate cetuximab pharmacokinetics, assuming no time-dependence, with WINNonlin (Scientific Consultant, Apex, NC; Pharsight Corporation). One- and two-compartment models with first order distribution and elimination constants were tested. The best model was selected using the usual methods, which included the analysis of plots of observed versus predicted concentrations and the Akaike information criteria. The model that best fitted the observed data was a two-compartment model with first-order elimination from the central compartment (Fig 1). Clearance from central compartment was 0.025 L/h, central compartment volume was 3.8 L, and terminal elimination half-life was 11.9 days (Table 1).

Although analyses of cetuximab pharmacokinetics were previously reported, the results obtained in our patient cannot be readily compared with these publications. Tan et al[4] did not use a formal compartment model. In the studies of Baselga et al[5] and Delbaldo et al,[6] cetuximab pharmacokinetics were described by a one-compartment model. However, a two-compartment model has previously been shown to be the best to describe the pharmacokinetics of immunoglobulin 1 monoclonal antibodies, including trastuzumab,[7] inolimomab,[8] rituximab,[9] basiliximab,[10] clenoliximab,[11] alemtuzumab,[12] and adalimumab.[13] Dirks et al[14] used a two-compartment model but with a Michaelis-Menten type of elimination. This last approach necessitates a large number of patients and the study of different dose regimens, and could not be applied to our patient.

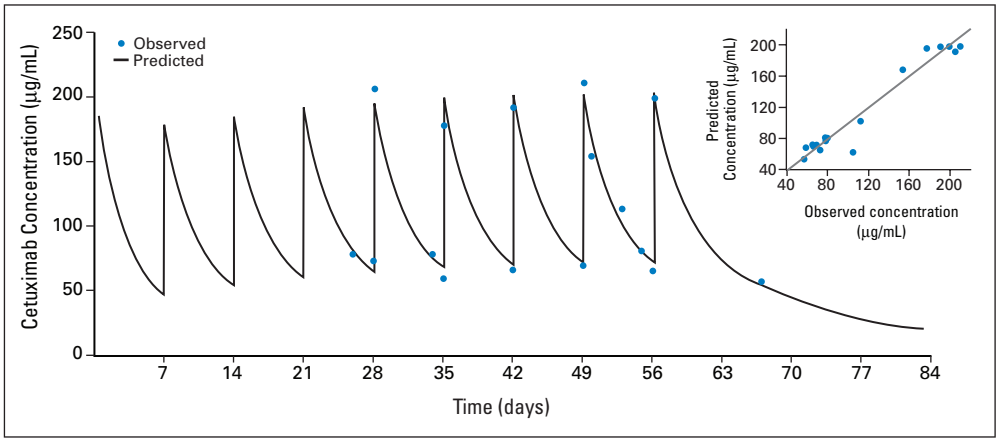

Fig 1. Observed (blue dots) and predicted (continuous lines) cetuximab concentrations over time. The correlation between predicted and observed concentrations are presented in the insert.

The longer half-life estimated in our patient, as compared with the studies of Baselga et al[5] and Delbaldo et al,[6] may be explained by their use of a one-compartment model, which is known to underestimate the elimination half-life when a two-compartment model is needed. The concentrations measured in our patient were clinically effective, because tumor response was more than 70%. In contrast, his concentrations did not lead to a significant dose-dependent toxicity becayse only xerodermia and grade 1 acneiform rash were observed. Clinical response to cetuximab was previously reported to increase with the degree of cutaneous toxicity and a relationship was found between cetuximab trough concentrations and clinical response.[15]

Although, as indicated earlier, our results cannot be directly compared with the literature, the pharmacokinetic parameters estimated in our hemodialyzed patient are similar to those reported for other monoclonal antibodies in patients with normal kidney function. A lack of influence of hemodialysis was described for other monoclonal antibodies, such as bevacizumab.[16] Inauen et al[3] observed no effect of hemodialysis on cetuximab concentrations but the small number of blood samples did not allow them to estimate cetuximab pharmacokinetics parameters. These preliminary data indicate that treating dialyzed patients with monoclonal antibodies as a cancer therapy may be done safely. Further prospective studies are warranted to elucidate the pharmacokinetics and pharmacodynamics of monoclonal antibodies in patients with end-stage kidney disease. This report suggests that previously used pharmacokinetics models may not be appropriate.

Table 1. Estimated Pharmacokinetic Parameters

Parameter	Abbreviation	Estimated Value
Volume of central compartment, L	V1	3.8
Clearance from the central compartment, L/hour	CL	0.025
Volume of peripheral compartment, L	V2	3.77
Intercompartment clearance, L/hour	CLD2	0.022
Distribution half-life, days	$T_{1/2}\,\alpha$	1.84
Elimination half-life, days	$T_{1/2}\,\beta$	11.90
Mean residence time, days	MRT	12.62
Volume of distribution at steady state, L	Vss	7.56

Another important implication for the practicing oncologist is that hemodialyzed patients, who now have prolonged survival, should not be denied optimal treatment with monoclonal antibodies on the sole basis on their renal replacement. Translational research is needed to elucidate the pharmacokinetics and pharmacodynamics at the level of the normal and damaged kidney.

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Pharmacologic Intervention for Cancer-Related Dyspnea

To the Editor: We have read with great interest the work carried out by Ben-Aharon et al[1], who conducted a systematic review of randomized controlled trials assessing all pharmacologic and non-pharmacologic intervention for dyspnea palliation in patients with cancer. We would like to make some comments.

It is surprising that in the search terms for PubMed, chlorpromazine was not included (decreases breathlessness without affecting ventilation or producing sedation in healthy subjects).[2] In an open-labeled trial, McIver et al[3] found chlorpromzine effective for relief of dyspnea in advanced cancer.

The authors do not explain, within the study population, if those patients with cancer and other comorbidity (mainly chronic obstructive pulmonary disease) are excluded. We believe that this information is important, because if there is comorbidity, we can not discern if the cause of breathlessness was cancer or chronic obstructive pulmonary disease. In the longitudinal study conducted by our group,[4] there were two or more causes to explain the etiology of dyspnea at the end of life (both the equal importance).

As the authors note, the single trial that assessed the role of midazolam as adjunct therapy[5] to morphine, demonstrated that the beneficial effects of morphine in controlling baseline levels of dyspnea could be improved by the addition of midazolam, without increased somnolence. However, no other benzodiazepines were assessed in randomized controlled trials. Moreover, there are studies in non-oncological terminal respiratory illness, which suggest the possibility of an improvement in terminal breathlessness treated with other benzodiazepines.[6]

We think it is important to emphasize in the final discussion, one aspect that is essential for clinicians, and reflecting a common practice in our midst: our terminally ill patients with cancer who are already receiving regular doses of opioids have almost equal benefit from a supplemental equivalent of 25% to 50% of their 4-hourly oral or suncutaneous regular opioid dose, to improve their breathlessness.[7]

At present, our group is conducting a phase II randomized controlled trial to determine the efectiveness of oral transmucose fentanyl citrate for the exertion dyspnea treatment in seriously ill patients with cancer and to contribute to drug security data in that population.

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