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ORIGINAL RESEARCH ARTICLE

Rethinking the Application of Pemetrexed for Patients with Renal Impairment: A Pharmacokinetic Analysis

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Abstract

Background Pemetrexed is used for the treatment for non-small cell lung cancer and mesothelioma. Patients with renal impairment are withheld treatment with this drug as it is unknown what dose is well tolerated in this population.

Objective The purpose of our study was to investigate the pharmacokinetics (PK) of pemetrexed in patients with renal impairment.

Methods A population PK analysis of pemetrexed was performed using non-linear mixed-effects modelling with phase I data obtained from the manufacturer. Additionally, the impact of renal function on pemetrexed PK was assessed with a simulation study using the developed PK model and a previously developed PK model lacking the phase I data.

Results The dataset included 548 paired observations of 47 patients, with a wide range of estimated glomerular filtration rates (eGFR; 14.4–145.6 mL/min). Pemetrexed PK were best described by a three-compartment model with eGFR (calculated using the Chronic Kidney Disease–Epidemiology Collaboration [CKD-EPI] formula) as a linear covariate on renal pemetrexed clearance. Using the developed model, we found that renal clearance accounts for up to 84% (95% confidence interval 69–98%) of total pemetrexed clearance, whereas the manufacturer previously reported a 50% contribution of renal clearance.

Conclusion Renal function is more important for the clearance of pemetrexed than previously thought and this should be taken into account in patients with renal impairment. Furthermore, a third compartment may contribute to prolonged exposure to pemetrexed during drug washout.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40262-020-00972-1.

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Key Points

Understanding the pharmacokinetics of pemetrexed is essential to enable treatment in patients with impaired renal function.

This population pharmacokinetic analysis of pemetrexed included patients with renal impairment.

The contribution of renal function to systemic pemetrexed clearance is higher than previously thought.

Renal impairment can lead to prolonged and possibly toxic exposure to pemetrexed.

1 Introduction

Pemetrexed is an antifolate drug used for the chemotherapeutic treatment of non-small cell lung cancer (NSCLC), mesothelioma and thymoma [1–3]. A single intravenous dose of 500 mg/m^2 is administered every 21 days. Although pemetrexed is excreted in the urine [4], dosing recommendations do not include adjustment for renal function. Due to fatal toxicities in a study of pemetrexed in patients with renal impairment, pemetrexed is currently contraindicated when the estimated creatinine clearance (CR_{CL}) is < 45 mL/min [5].

Approximately 25% of the lung cancer population has a CR_{CL} <60 mL/min [6]. Since it is unclear what the well tolerated pemetrexed dose is for patients with impaired renal function, a large group is withheld effective treatment. Understanding the relationship between dose, renal function, pharmacokinetics (PK), toxicity and treatment outcome is essential to enable treatment in patients with impaired renal function and to prevent toxicity in patients who are already treated with pemetrexed.

Existing data on the effect of renal dysfunction on pemetrexed PK are conflicting. In phase I studies, the manufacturer showed that 70–90% of the pemetrexed dose is excreted in the urine as unchanged drug within 24 h after administration, through both tubular secretion and glomerular filtration [4, 5]. However, a large population PK study by the manufacturer, published by Latz et al. in 2006, in which the PK data of 10 phase II trials were pooled for analysis, showed that renal elimination contributed only approximately 50% to the clearance of pemetrexed [7]. Notably, this study and other more recent pemetrexed PK studies excluded patients with moderate to severe renal dysfunction (CR_{CL} <45 mL/min) [8, 9]. Thus, extrapolation of these studies to patients with impaired renal function can be questioned. Therefore, the purpose of our study was to investigate the PK of pemetrexed in patients with renal impairment.

2 Methods

2.1 Data

Rich anonymised PK data collected during the renal impairment study by the manufacturer and as described by Mita et al. [5], were obtained from the manufacturer through the Clinical Study Data Request (CSDR) platform [10]. The following patient demographics were collected for each individual: sex, age, ethnicity, weight, height and serum creatinine. Furthermore, data on pemetrexed dose, infusion rate, sampling times and pemetrexed plasma concentrations were extracted from the dataset. Patients included in the study were not allowed to use aspirin or other non-steroidal anti-inflammatory agents from 2 days before (5 days for longer-acting agents) until 2 days after pemetrexed treatment due to a possible PK interaction.

2.2 Population Pharmacokinetic Modelling

A population PK analysis was performed using the nonlinear mixed-effect modelling software package NONMEM V7.4 (Icon plc, Dublin, Ireland). The following proxies for renal function were tested as continuous covariates for pemetrexed clearance: estimated CR_{CL} (calculated using the Cockcroft–Gault formula [11]) and estimated glomerular filtration rates (eGFR; calculated using the Modification of Diet in Renal Disease [MDRD] [12] and Chronic Kidney Disease–Epidemiology Collaboration [CKD-EPI] [13] formulae). MDRD and CKD-EPI were used as absolute values, and thus uncorrected for body surface area (BSA). When including renal function as a covariate for clearance, we estimated both the non-renal contribution to clearance (CL_{NR}) and the renal clearance (CL_R). The renal function estimate (CR_{CL} or eGFR) that resulted in the best model fit (decrease in objective function value [OFV]) and largest decrease in interindividual variability (IIV) was retained in the final model. Model selection and diagnostics were performed in line with best practice [14]. A detailed description of the PK analysis can be found in the electronic supplementary material.

2.3 Assessment of the Impact of Renal Function on Pemetrexed Pharmacokinetics

After model development, we compared the manufacturer's model (published by Latz et al. [7]) and the model developed herein, on several aspects. First, we assessed the difference in exposure, using the target area under the concentration-time curve from the start of infusion until infinity (AUC). In a virtual study, a cohort of 1000 patients was simulated with NONMEM V7.4 using Monte Carlo simulations. Age, sex, height and weight were extracted from the National Health and Nutrition Examination Survey (NHANES) database [15], and serum creatinine was randomly drawn from a normal distribution based on a median (male 110 µmol/L, female 95 µmol/L) with 25% variability (based on clinical data). These variables were used to calculate CR_{CL}. Dosing was based on BSA according to the drug label (500 mg/m^2). Subsequently, pemetrexed exposure (AUC) was simulated for these individuals using the manufacturer's PK model and the model developed herein. This was performed for a population with a CR_{CL} ≥45 mL/min and a population with a CR_{CL} < 45 mL/min. To compare exposure between these

groups, the geometric means of the AUCs with the coefficient of variation were calculated.

Second, the disposition of pemetrexed was investigated visually. We simulated one PK curve up to 96 h after administration, with both models using a systemic pemetrexed clearance of 3 L/h for a typical individual with impaired renal function (age 40 years, height 180 cm, weight 70 kg, BSA 1.85 m^2). A 3 L/h clearance was chosen as it represents a typical individual with decreased pemetrexed clearance, for example due to renal impairment.

3 Results

3.1 Dataset Characteristics

The final dataset consisted of 47 patients with a total of 548 paired observations of time and plasma concentrations over a time window of 0–72 h after administration. Table 1 shows the baseline characteristics of the population. Approximately three-quarters of the population were male and the median age was 62 years (range 25–79), with a wide range in eGFR (14.4–145.6 mL/min, calculated using the CKD-EPI).

3.2 Population Pharmacokinetic Model

The PK data were best described by a three-compartment model. Inclusion of renal function as a covariate for clearance of pemetrexed resulted in significant improvement of the model ($p < 0.0001$). Inclusion of the eGFR calculated using the CKD-EPI formula [13] explained approximately 45% of the IIV in clearance (reduction from 38.7 to 21.0% IIV in clearance). Of the three tested renal function formulae, CKD-EPI best explained the observed IIV in clearance. Typical population values for CL_R and CL_{NR} (with 95% confidence intervals) were 3.42 L/h (2.80–3.99) and 0.66 L/h (0.24–1.13). For central volume of distribution (V_1) and peripheral volume of distribution (V_2 and V_3), typical values were 6.70 L (5.93–7.53), 8.01 L (7.20–8.95) and 1.23 L (1.02–1.55), respectively. The detailed results of the base model and covariate models are described in the electronic supplementary material.

Table 1 Baseline characteristics of the population

Total	$N = 47$
Sex, male [*n* (%)]	36 (77)
Age, years	62 (25–79)
Weight, kg	79.3 (48.1–124.3)
BSA, m^2	1.95 (1.44–2.47)
CR_{CL}, mL/min	69.4 (16.8–202.4)
CKD-EPI, mL/min	73.4 (14.4–145.6)
CKD-EPI ≥45 mL/min	$n = 42$
CKD-EPI < 45 mL/min	$n = 5$
Pemetrexed dose, mg/m^2	500 (150–600)

Data are expressed as median (range) unless otherwise specified

BSA body surface area, *CR_{CL}* creatinine clearance, *CKD-EPI* Chronic Kidney Disease–Epidemiology Collaboration formula

3.3 Effect of Renal Function on Pemetrexed Pharmacokinetics

The box and whiskers plot in Fig. 1 depicts the predicted exposure according to both models (manufacturer's model and the present model), for two separate groups: CR_{CL} <45 mL/min and $CR_{CL} \geq 45$ mL/min. In their study, Latz et al. concluded that renal elimination contributed to the clearance of pemetrexed by approximately 50%. This is reflected in Fig. 1, where it can be observed that exposure seems to be in the same order of magnitude regardless of renal function, with moderate variability (white bars). With our model, developed using the data of patients with a wide range of renal function, a major impact of renal function on pemetrexed exposure can be observed from both the increased variability in AUC as well as the increased exposure in the renal impairment group. We predict that pemetrexed exposure in patients with renal impairment is approximately 1.7-fold higher than previously postulated by the manufacturer (see Table 2). Figure 2 shows two simulated PK curves, one for each model, using the same

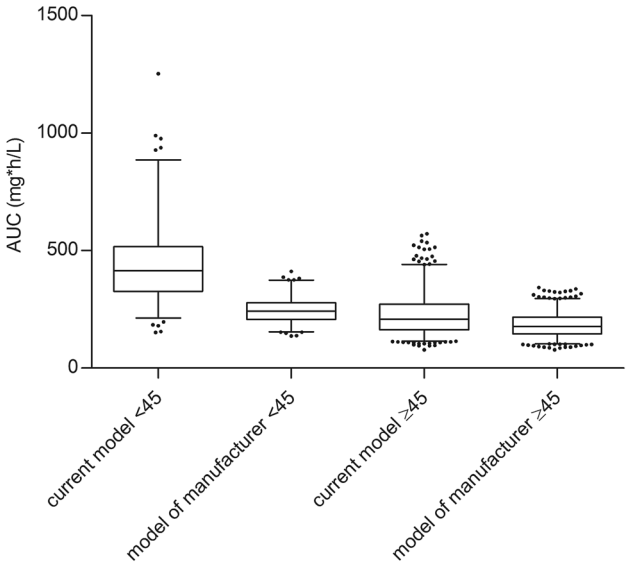

Fig. 1 Box and whiskers plot for simulation exposure using both the present model and the manufacturer's model, separated for two categories of renal function (CR_{CL} of <45 and ≥45 mL/min, respectively). The box represents the 25th–75th percentiles with geometric mean, and the whiskers indicate the 2.5th–97.5th percentile. The *dots* represent the outliers. *CR_{CL}* creatinine clearance

Table 2 Comparison of the geometric mean AUCs of the simulated population with both the current model and the manufacturer's model, divided into impaired and adequate renal function (CR_{CL} of < 45 and ≥ 45 mL/min, respectively)

Group (model/CR_{CL})	Geometric mean AUC (CV%)	Ratio
Current < 45 mL/min	415 (38.9)	1.7
Manufacturer < 45 mL/min	240 (21.9)	
Current ≥ 45 mL/min	208 (41.4)	1.2
Manufacturer ≥ 45 mL/min	172 (29.5)	

CR_{CL} creatinine clearance, *AUC* area under the concentration-time curve, *CV%* percentage coefficient of variation

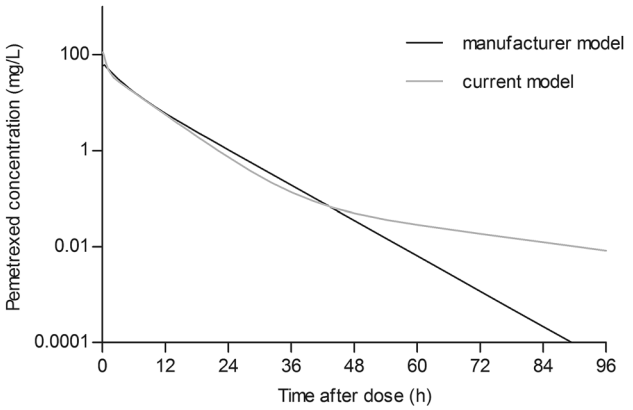

Fig. 2 Two concentration-time curves of pemetrexed using both models with the same systemic pemetrexed clearance of 3 L/h, to demonstrate the difference in distribution compartments. The black line represents the curve of the typical individual simulated using the manufacturer's model, and shows two compartments, while the light-grey line represents the present model, identifying the third compartment >24 h. *AUC* area under the concentration-time curve

systemic clearance of pemetrexed of 3 L/h. For the present model, the impact of the presence of a third compartment on the concentration-time curve can be observed, resulting in prolonged higher exposure at approximately 48 h after drug administration and onwards.

4 Discussion

This thorough PK analysis of pemetrexed in a population that included patients with impaired renal function, led to two major findings. First, we found that renal function is more important for pemetrexed clearance than the 50% contribution previously described by the manufacturer [16]. The manufacturer's analysis did not include patients with impaired renal function (CR_{CL} < 45 mL/min). We showed, in a representative population, that CL_R accounts for up to 84% of total pemetrexed clearance, which is in line with the manufacturer's early mass balance studies showing that 70–90% of the administered dose could be recovered in urine [4]. Thus, impaired renal function has a more pronounced impact on pemetrexed exposure than previously thought. Our second important finding relates to the disposition of pemetrexed. To date, it has been found that pemetrexed distributes over two compartments [7–9]. The data used in this analysis included sampling up to 72 h after administration and this revealed the presence of a third compartment. A third compartment can suggest the presence of extravascular fluid or a difference in redistributing tissues. It is unknown what holds true for pemetrexed, but as this is a hydrophilic drug, extravascular distribution is plausible. However, Dickgreber et al. showed no effect of third space fluid on the PK and toxicity of pemetrexed [17]. This implicates that during drug washout, there can be prolonged exposure to higher concentrations of pemetrexed than previously thought. The driving mechanism for pemetrexed toxicity is the subject of discussion. Mita et al. showed no correlation between renal function (and thus exposure) and non-haematological toxicities [5]. With regard to haematotoxicity, it is hypothesized that neutropenia is associated with the total exposure (AUC) [18, 19]. Based on this, it has been suggested that the dose should be adjusted to reach a target based on renal function, instead of BSA [7, 19, 20]. AUC-based dosing in a 21-day cycle is also routinely applied for carboplatin, where CR_{CL} and the desired AUC are used to calculate the patient's individual dose [21]. It is unknown whether this hypothesis holds true for pemetrexed, as it is known that for other antifolate drugs, such as methotrexate, haematological toxicity is threshold-driven [22]. For example, in an early phase I trial, it was shown that prolonged exposure to low concentrations of pemetrexed from daily administration resulted in severe neutropenia as a dose-limiting toxicity, with a maximum tolerated dose of only 4 mg/m^2 for 5 consecutive days without supplementation of vitamin B12 or folic acid [23]. The predominant role of time above the threshold concentration in determining toxicity is supported by the observation that the maximum tolerated dose of pemetrexed administered in a 21-day cycle, also without vitamin supplementation, was markedly higher (600 mg/m^2) [4]. Threshold-driven toxicity will be an issue, particularly in renal impairment, as clearance becomes so low that the pemetrexed plasma concentration exceeds the toxicity threshold for a prolonged period. This would explain why previous studies with pemetrexed in patients with renal impairment [5] were not successful. Currently, the PK determinant for the efficacy of pemetrexed is a topic of discussion. Dose adjustment to reach an AUC target will probably entail toxicity concerns when there is low systemic clearance, for example due to renal dysfunction. To allow safe and effective treatment in renal impairment, innovative interventions are needed to overcome toxicity. For example, rescue therapy with folinic acid, as widely

applied with pemetrexed's structural analogue methotrexate [24], may be a feasible option.

A limitation of this study is that the number of patients with severe renal impairment (eGFR <30 mL/min) was limited due to the toxicity concerns that arose during the conduction of the phase I study. Nonetheless, as it stands, these data are the only currently available data to elucidate the clinical PK of pemetrexed in patients with impaired renal function.

5 Conclusion

Overall, we found that the contribution of renal function was greater than previously thought and that a third compartment may contribute to prolonged exposure during drug washout. Since both factors may contribute to pemetrexed toxicity, they should be accounted for when developing dosing strategies for pemetrexed in patients with renal impairment.

The present PK model can be used to further unravel the PK–toxicity relationship of pemetrexed. In parallel, we must think of innovative strategies to overcome the haematological toxicity of pemetrexed in patients with impaired renal function, such as rescue therapy with folinic acid.

Declarations

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Conflicts of interests Nikki de Rouw, Rene J. Boosman, Alwin D.R. Huitema, Luuk B. Hilbrands, Elin M. Svensson, Hieronymus J. Derijks, Michel M. van den Heuvel, David M. Burger, and Rob ter Heine have no conflicts of interest to declare.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Manufacturer's consent for publication.

Availability of data and material Not applicable.

Code availability Supplementary file.

Authors' contributions Study concepts: NR, RJB, ADRH, LBH, EMS, HJD, MMH, DMB, RH. Study design: NR, RJB, ADRH, RH. Data acquisition and control: NR, RJB, RH. Data analysis and interpretation and statistical analysis: NR, RH. Manuscript preparations: NR, RH. Manuscript editing and revisions: NR, RJB, ADRH, LBH, EMS, HJD, MMH, DMB, RH.

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