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Pharmacokinetically-guided dosing of pemetrexed in a patient with renal impairment and a patient requiring hemodialysis

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ABSTRACT

Objectives: Pemetrexed is indicated for non-small cell lung cancer and mesothelioma. Dosing is based on body surface are (BSA), while renal function is the only determinant for exposure and thus toxicity. BSA-based dosing introduces large variability in exposure and may lead to (hemato)toxicity in patients with impaired renal function. Therefore, pemetrexed is contraindicated in renal impairment. The presented cases provide proof-of-concept for pharmacokinetically-guided dosing of pemetrexed in a haemodialysis patient and a patient with mild renal impairment.

Methods: The pharmacokinetic target was an area under the concentration-time curve (AUC) of 123–205 mg·h/L. Using a previously developed population pharmacokinetic model, individual pharmacokinetics were estimated.

Results: Both patients had an exposure above target after the initial dose, but a proportional dose reduction resulted in a therapeutic exposure in both patients (185 and 166 mg·h/L, respectively), that was well-tolerated. Interestingly, a threefold increase in systemic clearance of pemetrexed was observed during hemodialysis (from 1.00 L/h to 3.01 L/h), which approximates the population clearance of pemetrexed.

Conclusion: Altogether, we showed that pharmacokinetically-guided dosing of pemetrexed may be a feasible strategy for patients with lung cancer and renal impairment.

1. Introduction

Pemetrexed is a pharmacotherapeutic cornerstone in the treatment of non-small cell lung cancer (NSCLC) and mesothelioma. It is mainly excreted renally, but dosing is based on body surface area (BSA) and does not take renal function into account. Impaired renal function (estimated creatinine clearance < 45 mL/min) is currently a contra-indication for treatment with pemetrexed, since renal impairment leads to (hemato)toxic exposure [1,2].

Renal impairment is highly prevalent in patients with lung cancer and the combination of pemetrexed with checkpoint inhibitors and platinum-based chemotherapy may result in even further detoriaration of renal function [3]. Approximately 24% of lung cancer patients suffer from stage 3/4 (eGFR < 60 mL/min. as measured wich Cockcroft-Gault) renal disease [3]. In routine practice, renally impaired patients are often withheld effective treatment or treated with a potentially toxic dose.This illustrates the urgent need for a safe dosing strategy of pemetrexed in renally impaired patients.

2. Cases

We here present two cases, where therapeutic drug monitoring (TDM) was used to guide pemetrexed dosing in moderate and severe renal impairment. The target exposure for pemetrexed was an area under the concentration-time curve (AUC) of 164 mg·h/L ± 25% (123–205 mg·h/L). This exposure is the population median when pemetrexed is administered according label (dose 500 mg/m^2 and adequate renal function of > 45 ml·min) and was previously shown to be a suitable surrogate endpoint for treatment efficacy and toxicity [1,2]. We measured the plasma concentrations with a validated ultra performance liquid chromatography method with ultraviolet detection (UPLC-UV). Individual pharmacokinetic (PK) parameters were obtained

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Table 1
Overview of results.

	Patient 1	Patient 2	Reference
Age (yr)	75	78	
Sex	Male	Female	
Body surface area (BSA, m^2)	1.92	1.54	
Diagnosis	Stage IVA NSCLC	Stage IIIA NSCLC	
Previous treatment	–	Surgery	
Current treatment	Pemetrexed + carboplatin	Pemetrexed + carboplatin	
Baseline estimated creatinine clearance (mL/min)[a]	10 + HD	41	
Baseline hematology			
Neutrophil count (*10^9/L)	n/d	5.7	1.4–7.7
Platelet count (*10^9/L)	227	318	130–350
Leucocyte count (*10^9/L)	7.8	8.3	3.5–11
Initial pemetrexed dose (mg)	250	755[b]	
Pemetrexed exposure (AUC mg·h/L)	*230*	*260*	123–205
Pemetrexed clearance (L/h)	1.00	2.96	
- *during hemodialysis*	3.01	–	
Pre-cycle 2 hematology[c]			
Neutrophil count (*10^9/L)	6.4	2.9	1.4–7.7
Platelet count (*10^9/L)	302	236	130–350
Leucocyte count (*10^9/L)	7.3	5.8	3.5–11
TDM-adjusted pemetrexed dose	200	500	
Pemetrexed exposure (AUC mg·h/L)	185	166	124–205
Pemetrexed clearance (L/h)	1.00	2.96	
- *during hemodialysis*	3.01	–	
Nadir hematology[d]			
Neutrophil count (*10^9/L)	*0.7*	1.7	1.4–7.7
Platelet count (*10^9/L)	*92*	*64*	130–350
Leucocyte count (*10^9/L)	*2.0*	3.7	3.5–11
Disease status after induction therapy	PR	No recurrence	

NSCLC = non-small cell lung cancer.
HD = hemodialysis.
AUC = area under the concentration-time curve.
TDM = therapeutic drug monitoring.
n/d = not determined.
PR = partial response.
[a] As calculated with Cockcroft-Gault.
[b] Dosing based on BSA.
[c] 0–7 days prior to next cycle of chemotherapy.
[d] Nadir count of any hematology parameter during 4 cycles.

with a MAP Bayesian technique using the posthoc option in the software package NONMEM 7.4.1 (Icon, Ireland), based on the sampled pharmacokinetic data and the previously developed model. In a patient with hemodialysis, we fixed all parameters of the model, yet we allowed the model to estimate a temporary change in clearance during hemodialysis. The AUC was obtained from integrating cumulative drug exposure from one dose from time of infusion to infinity. Pharmacokinetic sampling was performed based on a validated limited sampling strategy, with addition of samples before and after hemodialysis [4].

The first patient was a 75-year-old male, BSA 1.54 m^2, with stage 4A NSCLC and end-stage renal disease, dependent on hemodialysis. Treatment was started with carboplatin AUC = 5 (corresponding with a dose of 180 mg) and pemetrexed 250 mg.

The patient underwent conventional hemodialysis (without hemodiafiltration) three times a week. Pemetrexed was administered on the day before hemodialysis. As a safety measure, the dose in the first cycle was 250 mg. This corresponds with approximately half the dose required to achieve the desired AUC in a typical individual without renal function [1,2]. After administration of pemetrexed, blood was sampled at 0.5, 3 and 6 h (during the 1st and 2nd cycle) and just before and immediately after hemodialysis (during 1st and 3rd cycle). Routine clinical chemistry and hematology evaluation was performed prior to each cycle.

Pemetrexed clearance without and with hemodialysis was estimated to be 1.00 L/h and 3.01 L/h, respectively. The AUC after the first 250 mg dose was estimated to be 230 mg·h/L. Therefore, the dose was decreased to 200 mg and maintained during subsequent cycles. The estimated AUC during these cycles was 185 mg·h/L, which was within the desired therapeutic window. At the evaluation after three cycles, therapy was well-tolerated. There was a course of fever in between cycles, which appeared to be due to an upper respiratory tract infection (without signs of neutropenia). Nadir counts of neutrophils, platelets and leukocytes were reached at day 7–16 after the first administration. Recovery was sufficient to resume therapy according schedule (Table 1). Furthermore, the patient experienced a slight reduction in taste and some fatigue. After the fourth cycle, a partial response was observed. Due to the development of neuropathy in both hands (which can be an adverse effect of both carboplatin and pemetrexed) and dialysis dependency, no pemetrexed maintenance therapy was initiated.

The second patient was a 78-year-old female, with stage 3A NSCLC. The patient had an estimated creatinine clearance of 41 mL/min (calculated with Cockcroft-Gault) before the first cycle. Renal function remained stable thereafter. She received adjuvant treatment with carboplatin (AUC = 5) and pemetrexed. The initial pemetrexed dose was 755 mg (500 mg/m^2, conventional dosing). Pharmacokinetic sampling was performed at at 0.5, 3 and 6 h after administration (during the 1st and 3rd cycle). The AUC after the initial dose was estimated to be 260 mg·h/L. As expected, this was considerably higher than the target exposure. To reach the target AUC, the dose was reduced to 500 mg. At the subsequent pharmacokinetic evaluation, the estimated AUC was within target: 166 mg·h/L. The dose was maintained at 500 mg at the

following cycles. At the evaluation after three cycles, the patient indicated she experienced vertigo, shortness of breath and some hearing loss. An audiologic test did not confirm deterioration of hearing. After the fourth cycle, there were no signs of tumor recurrence. Vertigo remained, and a temporary decrease of haemoglobin (Hb) and platelets was observed (see also Table 1). Further hematology parameters remained stable during cycles. There was no indication for maintenance therapy.

3. Discussion

With these two cases we showed that pharmacokinetically-guided dosing of pemetrexed may be a feasible strategy to allow safe treatment with pemetrexed in renal impairment, where pemetrexed is usually contraindicated. Therapeutic exposure was reached after dose adjustment and pemetrexed was well-tolerated in both cases.

Furthermore, this is the first report on pemetrexed pharmacokinetics during hemodialysis. We found that during hemodialysis pemetrexed clearance was increased three-fold (from 1.00 L/h to 3.01 L/h). The typical pemetrexed clearance in the population with adequate renal function is 5.4 L/h (± 19.3% CV) [1]. The pemetrexed clearance during hemodialysis, therefore, almost approximated normal clearance.

We demonstrated the feasibility of pharmacokinetically-guided dosing to allow safe treatment with a proven effective systemic exposure to pemetrexed in patients with renal impairment and lung cancer. Our results encourage further evaluation of individualized dosing of pemetrexed in a prospective clinical study in patients with renal impaiment who are currently often withheld pemetrexed treatment.

Conflict of interest

The authors have no relevant conflict of interest regarding this manuscript.

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