European Journal of Cancer 121 (2019) 64–73

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Original Research

Pemetrexed exposure predicts toxicity in advanced non–small-cell lung cancer: A prospective cohort study

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Received 26 February 2019; received in revised form 21 July 2019; accepted 5 August 2019
Available online 24 September 2019

KEYWORDS
Non–small-cell lung cancer;
Pemetrexed;
PKPD;
Toxicity;
Alternative dosing

Abstract ***Background:*** We explored whether total exposure to pemetrexed predicts effectiveness and toxicity in advanced non–small-cell lung cancer (NSCLC). Furthermore, we investigated alternative dosing schedules.

Methods: In this prospective cohort study, patients with advanced NSCLC receiving first- or second-line pemetrexed(/platinum) were enrolled. Plasma sampling was performed weekly (cyclePK) and within 24 h (24hPK) after pemetrexed administration. With population pharmacokinetic/pharmacodynamic modelling, total exposure to pemetrexed during cycle 1 (area under the curve during chemotherapy cycle 1 [AUC_1]) was estimated and related to progression-free survival (PFS)/overall survival (OS). We compared mean AUC_1 (mg·h/L) in patients with and without severe chemotherapy-related adverse events (AEs) during total treatment. Second, different dosing schedules were simulated to minimise the estimated variability (coefficient of variation [CV]) of AUC.

Results: For 106 of 165 patients, concentrations of pemetrexed were quantified (24hPK, n = 15; cyclePK, n = 106). After adjusting for prognostic factors, sex, disease stage and World Health Organisation performance score, AUC_1 did not predict PFS/OS in treatment-naive patients (n = 95) (OS, hazard ratio [HR] = 1.05, 95% confidence interval [CI]: 1.00–1.11; PFS, HR = 1.03, 95% CI: 0.98–1.08). Patients with severe chemotherapy-related AEs (n = 55) had significantly higher AUC_1 values than patients without them (n = 51) (226 ± 53 vs 190 ± 31, $p < 0.001$). Compared with body surface area–based dosing (CV:

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https://doi.org/10.1016/j.ejca.2019.08.012

22.5%), simulation of estimated glomerular filtration rate (eGFR)–based dosing (CV 18.5%) and fixed dose of 900 mg with 25% dose reduction, if the eGFR<60 mL/min (CV: 19.1%), resulted in less interindividual variability of AUC.

Conclusions: Higher exposure to pemetrexed does not increase PFS/OS but is significantly associated with increased occurrence of severe toxicity. Our findings suggest that fixed dosing reduces interpatient pharmacokinetic variability and thereby might prevent toxicity, while preserving effectiveness.

1. Introduction

Despite the introduction of molecular targeted agents and immunotherapy, pemetrexed-based chemotherapy still has an important role in the treatment of non-squamous non–small-cell lung cancer (NSCLC) [1]. Recently, the combination of immunotherapy with platinum-based pemetrexed chemotherapy showed a superior survival benefit compared with chemotherapy alone in the first-line treatment of advanced NSCLC, regardless of programmed death-ligand 1 (PD-L1) expression. This combination treatment has now become the standard of care and is well tolerated in general [2,3]. However, in the combination arm of the registration study (KEYNOTE-189), adverse events (AEs) led to discontinuation of a treatment component (pembrolizumab or pemetrexed) twice as often compared with platinum-based pemetrexed therapy [2]. To derive optimal benefit from the combination treatment, toxicity should be minimised.

Comparable with most chemotherapeutic agents, the dosage of pemetrexed is adjusted to a patient's body surface area (BSA), which should theoretically lead to equal drug concentrations as larger patients have a larger distribution volume and a higher clearance (CL) than smaller patients [4]. Pemetrexed is eliminated primarily via the kidneys, with 70–90% of the administered drug excreted unchanged through urine within 24 h [5,6], and the occurrence of toxicities is associated with total systemic exposure [5,7]. Therefore, there might be a better rationale for adaptive dosing strategies other than those based on the BSA [8].

Using population pharmacokinetic/dynamic (popPK/PD) modelling, we explored whether total systemic exposure to pemetrexed predicts progression-free survival (PFS) and overall survival (OS) and occurrence of severe chemotherapy-related AEs in patients with NSCLC. In addition, different strategies for pemetrexed dosing were simulated and compared.

2. Methods

Pharmacokinetic data were available from 'PEmetrexed and biomaRkerS: an observatiONAL study' (PERSONAL). This was a prospective multicentre cohort study of adult patients with locally advanced or metastatic (stage IIIB/IV) non-squamous NSCLC or unresectable mesothelioma receiving platinum-combined pemetrexed therapy as first-line treatment or pemetrexed monotherapy as second-line treatment. From October 2012 until November 2014, patients were recruited from a university hospital (Erasmus University Medical Center); two large teaching hospitals specialised in lung cancer care (Amphia Hospital; Franciscus Gasthuis & Vlietland), and a regional hospital (Bravis Hospital), located in the southwestern part of the Netherlands. For the present study, patients were eligible if blood sampling and measurement of pemetrexed concentrations were performed. Patients with unresectable mesothelioma were excluded from all analyses. For the primary outcome exploring the relation between pemetrexed pharmacokinetics and PFS/OS, only treatment-naive patients were included in the analyses. All patients provided written informed consent. This study was approved by the appropriate institutional review boards and ethics committees at each institution.

2.1. Data collection

As per the standard of care (Appendix A1), platinum-combined pemetrexed chemotherapy or pemetrexed monotherapy was administered as first-line and second-line treatment to patients as an intravenous infusion every three weeks for a maximum of 4 cycles. No patient received pembrolizumab.

We collected sociodemographic characteristics (age, sex and ethnicity), body size measures (weight and BSA), renal function and information about cancer stage and treatment. Before the initial chemotherapy, cycle baseline serum creatinine (μmol/L) was obtained. Subsequently, before and weekly after each chemotherapy administration during the induction therapy, serum creatinine was measured. Estimations of renal function were made by calculation of the estimated glomerular filtration rate (eGFR; mL/min per 1.73 m^2) using the Chronic Kidney Disease Epidemiology Collaboration equation [9].

2.2. Pharmacokinetic assessments

Before and weekly after each pemetrexed administration, sparse plasma sampling was performed (cyclePK). In a subgroup, blood samples were intensively collected on the first day of the first chemotherapy cycle at pre-infusion and 10 and 30 min and 1, 2, 4, 8 and 24 h after start of pemetrexed infusion (24hPK) additional to cyclePK sampling.

We validated an assay to quantitate the plasma pemetrexed concentrations, using a liquid chromatographic method coupled to tandem mass spectrometry. A detailed description of the validation of this assay and method can be found in Appendix A1.

2.3. Pharmacokinetic model development

Plasma concentration–time data were analysed using non-linear mixed effect modelling. A two-compartment model for pemetrexed was structure based, as schematically shown in Fig. 1. Once the base model was defined, clinical variables were tested as covariables on parameters, CL, central volume of distribution (V_c) and peripheral volume of distribution (V_p), using stepwise forward inclusion and backward elimination [10]. Detailed description of the model development and covariable analyses can be found in Appendix A1.

The final popPK model was internally validated using goodness-of-fit plots, visual predictive check plots (Figs. A1 and A2) and a bootstrap procedure. Subsequently, the final popPK model was used to estimate area under the plasma concentration versus time curves (AUCs) for all cycles of each patient. Simulations of different dosing strategies of pemetrexed were performed with the developed final popPK model: BSA-based, renal function–based and fixed dose with a dose reduction of 25% if the eGFR <60 mL/min.

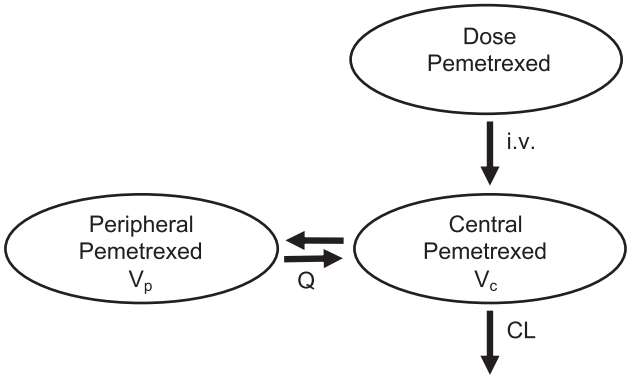

Fig. 1. Schematic representation of the population pharmacokinetic model of pemetrexed. CL, clearance; Q, intercompartmental clearance; V_c, central volume of distribution; V_p, peripheral volume of distribution.

2.4. End-points

Clinical effectiveness end-points were OS, PFS and best tumour response. Tumour response measurements were obtained according to Response Evaluation Criteria in Solid Tumours 1.1 after the 2nd and 4th cycle of chemotherapy. AEs were weekly registered during the entire treatment period and graded (severe: grade ≥III) according to the National Cancer Institute Common Terminology Criteria of Adverse Events version 4.03.

2.5. Statistical analysis

Using Cox proportional hazards regression analyses, the relation between AUC during cycle 1 (AUC_1) and OS/PFS in treatment-naive patients was studied, adjusted for known prognostic factors, sex, disease stage and Eastern Cooperative Oncology Group (ECOG) performance status. The association of AUC_1 with best treatment response over a total treatment of 4 cycles was tested with one-way analysis of variance. Differences in mean AUC_1 between patients with and without grade ≥III chemotherapy-related AEs during the entire course of four-cycle induction treatment were compared using the independent sample *t*-test. With regard to toxicities related to pemetrexed, we distinguished clinical and laboratory AEs.

Using the final popPK model, simulations of mentioned different dosing regimens of pemetrexed were performed and explored to minimise the estimated variability in AUC and maintain similar population median AUC values compared with the current dosing schedule. We compared the interindividual variation of AUCs of the distinct dosing regimens using coefficients of variation (CVs) and graphically visualised systemic patterns in predicted exposures plotted against corresponding BSA and renal functions of these patients. Statistical analyses were performed using SPSS version 22.0 (IBM Corporation, Armonk, NY).

3. Results

In total, 199 patients were included in the PERSONAL study. Of these patients, 165 (83%) started pemetrexed-based chemotherapy as first- or second-line treatment. The first 106 of these 165 patients (64%) were consecutively selected for the present study as in these patients weekly pemetrexed cyclePK measurements were performed (Fig. 2). In a subgroup of these patients (N = 15, 14%), we also collected repeated samples during the day of chemotherapy infusion (24hPK). Reasons for withdrawal of chemotherapeutic treatment are displayed in Supplementary Fig. A3.

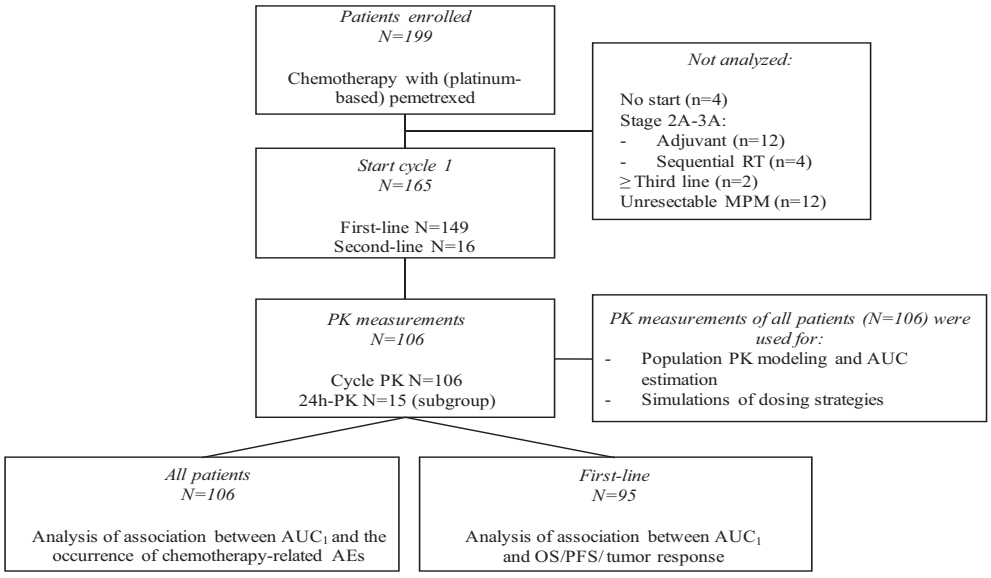

Fig. 2. Flowchart of patients in the study population. NSCLC, non–small-cell lung cancer; MPM, malignant pleural mesothelioma; RT, radiotherapy; PK, pharmacokinetic(s); AUC_1, area under the curve during cycle 1; AE, adverse event; PFS, progression-free survival; OS, overall survival.

Table 1
Characteristics of patients treated with pemetrexed (N = 106).

Characteristic	CyclePK	24hPK
	N = 106	*N* = 15
Age, mean (SD)	63.3 (9.3)	64.3 (9.7)
Sex, male	58 (54.7)	12 (80.0)
Ethnicity		
Caucasian	97 (91.5)	14 (93.3)
ECOG performance score		
0 or 1	91 (85.8)	13 (86.7)
≥ 2	14 (15.4)	2 (13.3)
Unknown	1 (0.9)	
Weight (kg), mean (SD)	72.5 (12.8)	73.9 (15.0)
BSA (m^2), mean (SD)	1.8 (0.2)	1.9 (0.2)
eGFR (ml/min/1.73m^2), median (IQR)	98 (88–105)	100 (92–109)
Type of tumour		
Adenocarcinoma	102 (96.2)	15 (100)
Large cell carcinoma	4 (3.8)	0
Stage of disease		
Locally advanced (IIIB)	16 (15.1)	5 (33.3)
Metastatic (IV)	90 (84.9)	10 (66.7)
Line of therapy		
First-line	95 (89.6)	15 (100)
Second-line	11 (10.4)	0
Treatment combination		
Cisplatin	71 (67.0)	15 (100)
Carboplatin	33 (31.1)	0
Monotherapy	2 (1.9)	0
Pemetrexed dosage (mg), mean (SD)	910.9 (87.3)	938.3 (88.1)
Number of chemotherapy cycles, median (IQR)	3.2 (2.0–4.0)	3.1 (2.0–4.0)

Data are expressed as numbers (%), unless otherwise stated. eGFR values according to CKD-EPI.
ECOG, Eastern Cooperative Oncology Group; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; PK, pharmacokinetics; BSA, body surface area; SD, standard deviation; IQR, interquartile range; eGFR, estimated glomerular filtration rate.

3.1. Patient characteristics

Patient characteristics are outlined in Table 1. The mean age in this population was 63.3 ± 9.3 years, and slightly more than half of the patients were males (55%). The majority of patients had metastatic NSCLC (85%) and received pemetrexed as first-line treatment (90%), mostly combined with cisplatin (67%). The mean BSA of these patients was 1.8 ± 0.2 m^2, and they had a renal function with a median eGFR of 98 mL/min (interquartile range [IQR]: 88–105).

3.2. Model development

The parameter estimates of the final popPK model are demonstrated in Table 2. A two-compartment model (population estimate [% standard error of the estimate] in terms of pemetrexed CL [4.58 L/h {3.1%}], V_c [15.9 L {3.3%}], V_p [21.6 L {5.0%}] and intercompartmental CL [Q; 0.05 L/h {4.7%}]) fitted PK data appropriately. Between-patient variability was included on CL (16.7%), and residual unexplained variability between observed and predicted measurements could be described using an additional error model.

Table A1 lists all tested covariables. A power model ($CL = 4.58 * \frac{eGFR}{91.7}^{0.461}$) described the relation between pemetrexed CL and eGFR (Fig. A4). The addition of the covariable eGFR significantly reduced between-patient variability in CL from 20.2% to 16.7% ($P < 0.005$), whereas BSA did not influence pemetrexed CL significantly.

Table 2
Estimation of pemetrexed pharmacokinetic and covariate parameters in the final population PK model.

Parameters	Units	Estimate	RSE (%)	Shrinkage (%)	Bootstrap estimate	Bootstrap 95% CI
Population parameter						
Clearance (CL)	L/h	4.58	3.0		4.60	4.08–5.27
Parameter for effect of creatinine clearance (*CrCL*) on CL[a]	L/h	0.46	12.1		0.46	0.33–0.58
Central volume of distribution (V_c)	L	15.9	3.0		16.0	14.4–17.8
Parameter for effect of the body surface area (BSA) on central volume of distribution (V_c)[b]	L	1 FIX			1 FIX	
Intercompartmental clearance (Q)	L/h	0.05	4.5		0.0464	0.0354–0.061
Peripheral volume of distribution (V_p)	L	21.6	4.9		22	16.0–29.5
Between-subject variability						
CL[c]	CV%	16.7	9	8	16.7	13.7–19.6
Residual unexplained variability						
Additional residual error	ng/mL	0.36	1.5	5	0.35	0.32–0.39

RSE, relative standard error; CV%, percentage coefficient of variation; CI, confidence interval.

[a] $CL = 4.58 * \frac{eGFR}{91.7}^{0.461}$, where 91.7 is the median eGFR during all cycles.

[b] $V_c = 15.9 * \frac{BSA}{1.84}^{1}$, where 1.85 is the median BSA at baseline.

[c] Between-subject variability was included on CL using the formula CLi = CL * exp(ηi), where CLi represents the individual parameter estimate for individual i, CL is the eGFR corrected mean value for clearance and ηi represents the between-subject variability distributed following N (0, ω^2).

3.3. Clinical outcomes

3.3.1. Effectiveness

The median estimated AUCs during 4 cycles of chemotherapy were 201 mg h/L (IQR: 179–224), 203 mg h/L (IQR: 176–223), 208 mg h/L (IQR: 179–233) and 208 mg h/L (IQR: 178–234) for cycle 1 (N = 106), cycle 2 (N = 90), cycle 3 (N = 73) and cycle 4 (N = 56), respectively. In the 56 patients who underwent 4 cycles of pemetrexed treatment, the AUC of pemetrexed was significantly higher during cycle 4 compared with cycle 1 (210 mg h/L vs 196 mg h/L, $P < 0.001$). The median OS and PFS in treatment-naive patients (N = 95, 89.6%) was 9.0 months (IQR: 3.9–25.7) and 4.9 months (IQR: 2.4–10.4), respectively. AUC_1 did neither univariably predict OS/PFS nor when adjusted for prognostic factors, sex, disease stage and ECOG performance score (OS, hazard ratio [HR] = 1.05, 95% confidence interval [CI] = 1.00–1.11; PFS, HR = 1.03, 95% CI = 0.98–1.08) (Table 3). Mean AUC_1 was also not significantly different between patients with a partial response, stable disease or progressive disease as best response during 4 treatment cycles (Table A2). For patients who experienced grade III/IV toxicities (N = 55) compared with patients without severe toxicities (N = 51), the mean number of cycles was not significantly different (3.2 ± 1.1 vs 3.1 ± 1.1, respectively, p = 0.69) during induction treatment.

3.3.2. Toxicity

For the analyses of associations between total systemic exposure to pemetrexed and treatment toxicities, all patients with cyclePK measurements were included (N = 106). Detailed information about treatment-related clinical and laboratory AEs is provided in Table 4. Compared with patients without severe chemotherapy-related AEs (N = 51), patients with these AEs (N = 55) had significantly higher AUC_1 values (190 mg h/L ± 31 vs 226 mg h/L ± 53, respectively, $P < 0.001$). When separated into clinical and laboratory AEs, identical results were found (Fig. 3). Patients with severe chemotherapy-related AEs during chemotherapy had a significantly higher BSA than patients without these AEs (1.88 ± 0.18 m^2 vs. 1.81 ± 0.18 m^2, respectively, P = 0.042). Furthermore, the eGFR before the start of chemotherapy was lower in patients who would

Table 3
Multivariable analyses of total systemic exposure to pemetrexed and prognostic factors associated with overall and progression-free survival.

Factor	Overall survival		Progression-free survival	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Sex				
Male vs female	1.63 (1.02, 2.59)	0.04	1.37 (0.88, 2.12)	0.16
Disease stage				
Stage IV vs IIIB	2.96 (1.37, 6.40)	0.006	2.88 (1.46, 5.68)	0.002
ECOG PS				
1 vs 0	3.0 (1.68, 5.37)	<0.001	1.80 (1.08, 2.99)	0.024
≥2 vs 0	9.91 (4.45, 22.07)	<0.001	7.34 (3.43, 15.72)	<0.001
AUC_1[a]	1.05 (1.00, 1.11)	0.058	1.03 (0.98, 1.08)	0.31

HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance score; AUC_1, area under the curve of pemetrexed during chemotherapy cycle 1.

[a] Per unit 10 mg h/L.

Table 4
Adverse events in all patients with cyclePK measurements (n = 106).

Adverse event	Frequency (%)	
	All grades	Grade ≥ III
Treatment-related[a]		
Any	105 (99)	55 (52)
Clinical		
Fatigue	86 (81)	11 (10)
Anaemia	85 (80)	9 (8)
Nausea	66 (62)	2 (2)
Decreased appetite	62 (58)	7 (7)
Oral mucositis	45 (42)	3 (3)
Constipation	41 (39)	1 (1)
Taste alteration	38 (36)	0
Dry skin	35 (33)	0
Dry eyes/watering eyes	34 (32)	0
Neuropathy sensory	28 (26)	0
Dysphagia	25 (24)	1 (1)
Diarrhoea	20 (19)	2 (2)
Vomiting	20 (19)	0
Dizziness	17 (16)	0
Alopecia	16 (15)	0
Rash	16 (15)	0
Weight loss	15 (14)	0
Dyspepsia	12 (11)	0
Laboratory		
Decreased white cell count	75 (71)	17 (16)
Decreased neutrophil count	67 (63)	28 (26)
Decreased thrombocyte count	53 (50)	12 (11)
Alanine aminotransferase elevation	43 (41)	0
Aspartate aminotransferase elevation	30 (28)	0
Blood creatinine level elevation	26 (25)	1 (1)
Alkaline phosphatase elevation	19 (18)	0

Listed are adverse events that are reported in at least 10% of the patients.
[a] Adverse events were scored as treatment related if the investigator defined relatedness as probably or definitely.

experience severe AEs throughout treatment than in those who would not (91.2 ± 14.9 mL/min vs 98.1 ± 21.0 mL/min, respectively, $P = 0.053$). For severe laboratory AEs, the difference in the eGFR was significant between patients who did not and did experience them (86.2 ± 20.7 mL/min vs 98.4 ± 16.2 mL/min, respectively, $P = 0.004$).

3.4. Dosing strategies

Compared with BSA-based dosing (CV: 22.5%, AUC: 206 mg h/L [IQR: 178–240]), both simulation of eGFR-based dosing (CV: 18.5%, AUC: 206 mg h/L [IQR: 183–232]) and a fixed dose of 900 mg with a 25% dose reduction if the eGFR<60 (CV: 19.1%, AUC: 197 mg h/L [IQR: 174–224]) showed less interindividual variability of AUC, whereas the median AUC was comparable with the estimated AUC in our population (Fig. 4A).

The BSA-based dosing strategy leads to an over-correction as large patients have a higher total exposure to pemetrexed than smaller patients. Because this dosing strategy does not adjust the dose to renal function, a main predictor of CL and therefore AUC, patients with a decreased renal function are also exposed to a higher AUC (Fig. 4B, panel 1). A fixed dose with a 25% dose reduction if the eGFR <60 ml/min or renal function–based dosing results in a more stable exposure independent of body size and renal function (Fig. 4B, panels 2 and 3).

4. Discussion

In a real-world setting, we developed and internally validated a popPK model for patients with advanced

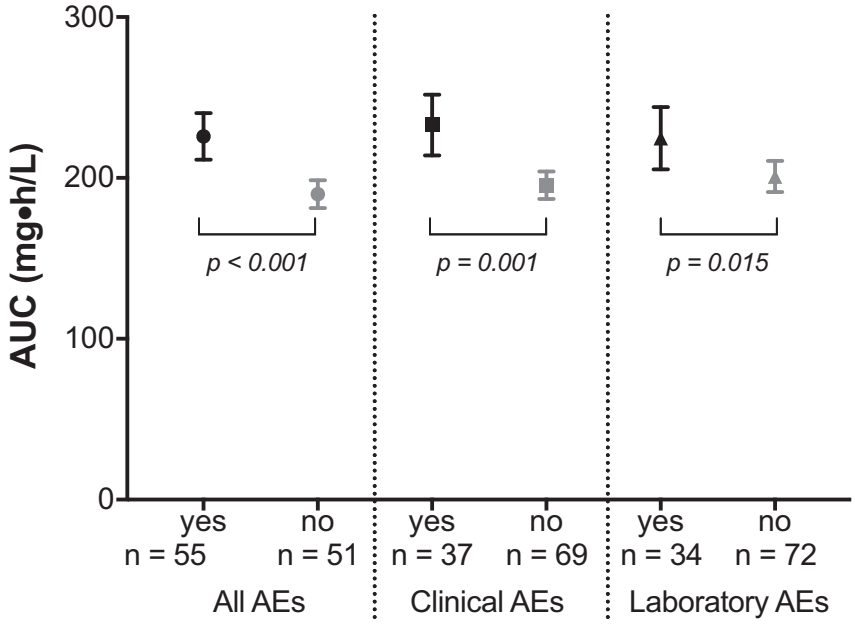

Fig. 3. Differences in AUC_1 between patients with and without chemotherapy-related adverse events of ≥ grade III during 4 cycles of chemotherapy. Means and error bars representing 95% confidence intervals. AUC, area under the curve; AE, adverse event.

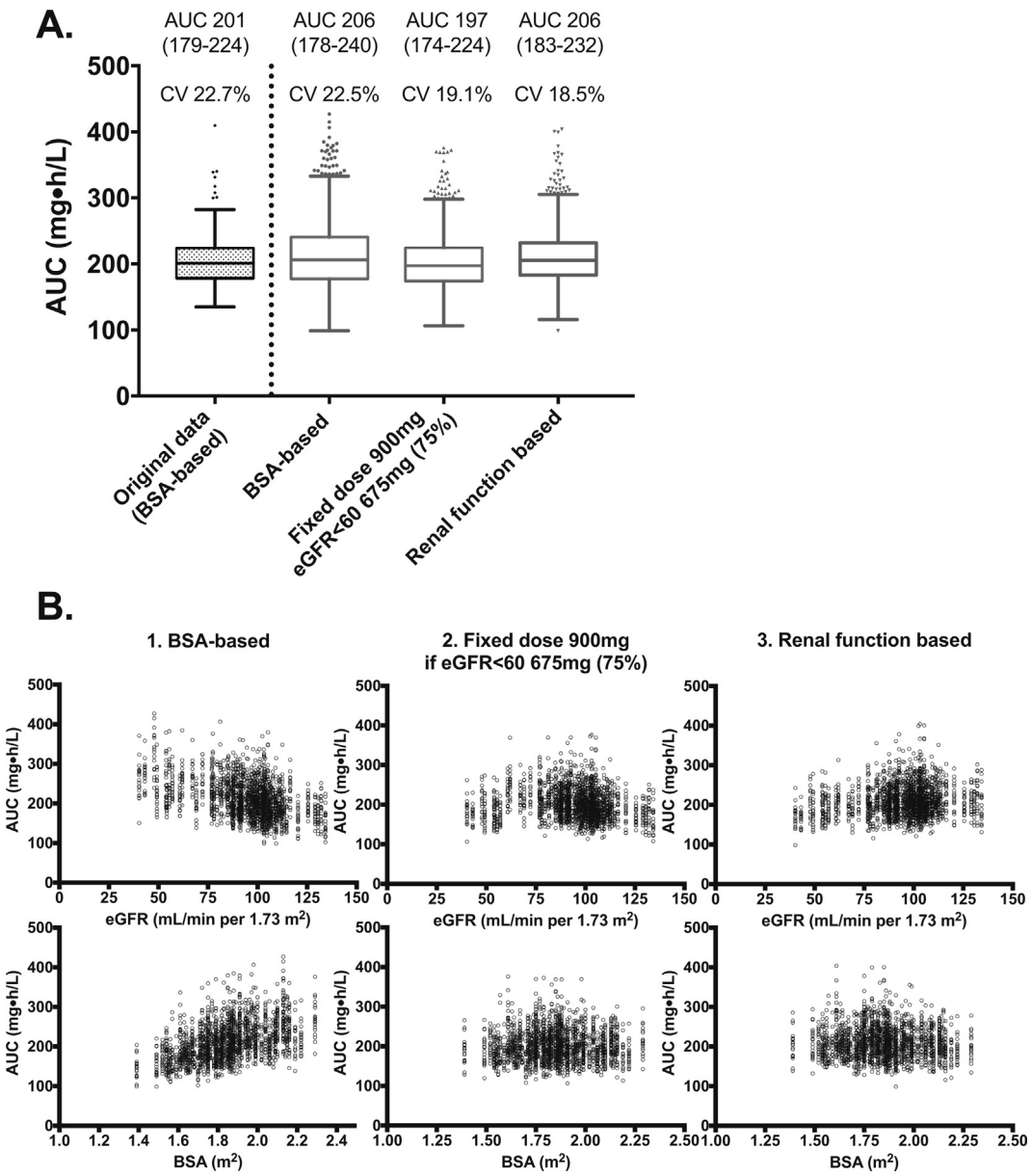

Fig. 4. Pemetrexed exposure (AUC) and interindividual variability for each of three dosing strategies. (A) Boxplots representing medians and interquartile ranges of total exposure in BSA-based dosing in original (unsimulated) data and three different dosing regimens after simulations. Whiskers represent minimum and maximum 1.5 interquartile range (Tukey). (B) Simulations of total exposure to pemetrexed (AUC) by body surface area or renal function for dosing strategies. Panel 1: BSA-based; panel 2: fixed dose 900 mg, if eGFR <60 than 675 mg (75%); panel 3: renal function−based. As illustrated, BSA-based dosing results in increased variability in total exposure; larger patients and those with a decreased renal function have higher pemetrexed exposure (1). AUC, area under the curve; CV, coefficient of variation; BSA, body surface area; eGFR, estimated glomerular filtration rate.

NSCLC treated with pemetrexed, using sparse data sampling during their total treatment period in addition to 24hPK data. Total exposure to pemetrexed did not predict clinical effectiveness, whereas the occurrence of severe chemotherapy-related toxicity was significantly associated with higher exposure.

Previous PK analyses demonstrated that the AUC of pemetrexed increases linearly with the dose [5,11]. However, Cullen *et al.* [12] and Ohe *et al.* [13] showed that higher doses (900 mg/m^2)—and thus higher AUCs—were not associated with an additional survival benefit in patients receiving pemetrexed as second-line or third-line treatment. There might be a threshold dose at which the dose−response curve levels off. The absence of an exposure−response relation might also be explained by limitations in transport capacity, variable intracellular formation of more effective polyglutamate metabolites or dose-dependent gene expression of target enzymes beyond a certain dose [14–16].

Severe haematological and clinical chemotherapy-related AEs were more common in patients with a higher AUC of pemetrexed. The toxicities observed in our study were comparable with findings in phase III trials, and the incidence was similar [12,17]. The correlation between total exposure to pemetrexed and the occurrence of haematological toxicity has been demonstrated in previous research [5,7,12,13]. Early data in phase I trials were contradicting with regard to the association between baseline renal function and the development of severe toxicity [5,18]. Supporting our findings, a recent study of our group showed that the occurrence of renal toxicity during maintenance treatment with pemetrexed was associated with decreased renal function at baseline or deterioration of renal function during induction [19]. Importantly, the significantly higher AUC in patients after 4 cycles suggests that patients are more prone to toxicity after a higher number of cycles. In a cycle-by-cycle analysis, Langer *et al.* [20] already reported an increase in treatment-related clinical and haematological toxicities during induction treatment combined with cisplatin/pemetrexed and a decrease in renal function during pemetrexed maintenance.

There is a lack of a rationale to use BSA-based dosing if the BSA is not an important predictor of the interpatient variability of total exposure [21–23]. Our findings suggest that eGFR-based dosing reduces interpatient variability, while similar population median AUC values are maintained compared with the current BSA-based dosing schedule. Therefore, this dosing strategy might prevent severe toxicity with preservation of effectiveness. These results are supported by an earlier large popPK analysis by Latz *et al.* [7], who already suggested that dose adjustments based on renal function might be considered favourable as total exposure to pemetrexed was dependent on renal function and the primary determinant of neutropenic response was AUC and not the peak concentration (C_{max}) [7,8]. However, the best substitute for the current pemetrexed dosing schedule in our view is a flat-fixed dosing of 900 mg pemetrexed every three weeks with a dose reduction of 25% if the eGFR <60 mL/min. This schedule reduced interindividual variability to the same extent as eGFR-based dosing in our simulation study and may have additional safety and economic benefits as it is less prone to errors and single-dose vials can be used [21,24].

Our findings are of even more importance in the light of current developments of systemic treatment of NSCLC, where combinations with pemetrexed and anti–programmed death (PD)-1 pembrolizumab or anti–PD-L1 atezolizumab are new standard treatments in all patients without sensitising mutations, regardless of PD-L1 status of the tumour [2,3]. Because the combination treatment led to more severe toxicities and withdrawal of treatment in these trials [2,25], focus on minimising adverse effects of pemetrexed is warranted.

A dosing schedule with a 3-weekly fixed dose of 900 mg as tested in our simulation would indicate that approximately half of the population would receive a dose reduction compared with the currently used dosing regimen. Because our data were not suitable to elaborate further on the role of C_{max}, its impact on treatment effectiveness remains unclear. In addition, it remains questionable whether the established differences between interindividual variation of dosing strategies in simulations are associated with clinical relevance. The covariable eGFR only reduced the between-patient variability of pemetrexed CL by approximately 20%, and thus, the larger part of this variability is still unexplained. Although BSA did not affect pemetrexed CL, body composition might influence drug CL and thus exposure and toxicity [26,27]. Other factors, such as genetic polymorphisms in metabolising enzymes and drug transporters, might affect CL and therefore AUC even more. At last, confounding of the association between AUC of pemetrexed and toxicity by the nephrotoxic platinum compound cannot be excluded without a pemetrexed monotherapy comparator arm. However, it is unlikely that the increased toxicity in patients with higher exposure to pemetrexed is solely a cisplatin effect as the pharmacokinetics of cisplatin and pemetrexed is not significantly influenced by each other [28,29]. In addition, creatinine CL is not a main predictor of cisplatin CL in contrast to pemetrexed CL [30,31].

In conclusion, total systemic exposure to pemetrexed does not predict clinical effectiveness but is significantly associated with more frequent occurrence of severe haematological and clinical AEs. Although we currently dose pemetrexed based on the BSA, our data show a better rationale for a 3-weekly flat-fixed dose of 900 mg (with a 25% dose reduction if the eGFR <60). However, benefit of this alternative dosing strategy should be confirmed in a randomised clinical trial with direct comparison with the current BSA-based dosing strategy.

Funding

This study was supported by ZonMw, the Netherlands (grant number: 152001017). The funding source had no involvement in decisions with regard to study design; data collection, analysis and interpretation; writing of the report and in the decision to submit the article for publication.

Conflict of interest statement

J.G.J.V.A. has a consultant/advisory role with Eli Lilly and Company, Roche, Bristol-Myers Squibb, MSD, AstraZeneca, Bayer, Takeda and Boehringer

Ingelheim. J.G.J.V.A. is stock owner of Amphera. The other authors declare no conflict of interest.

Acknowledgements

The authors thank Hans in 't Veen (Franciscus Gasthuis) and Ton van Boxem (Bravis hospital) for providing data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.08.012.

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