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Early View

Original article

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Original article

Renal impairment during pemetrexed maintenance in patients with advanced non-small-cell lung cancer: a cohort study

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Take home message: There is a significant risk of renal impairment during pemetrexed maintenance, which may jeopardize further treatment

Background: Optimal survival benefit from different lines of anticancer treatment in advanced non-small-cell lung cancer (NSCLC) requires conservation of renal function. We evaluated the development of renal impairment during pemetrexed maintenance.

Patients and methods: In a prospective multi-centre cohort study, we evaluated the incidence of acute/chronic kidney disease (AKD/CKD), its related treatment discontinuation frequency and associated clinical variables with AKD in patients with stage IIIB/IV NSCLC treated with pemetrexed maintenance. We validated findings in an independent cohort.

Results: In total 190 patients received pemetrexed. In the primary cohort 149 patients started induction of whom 44 (30%) continued maintenance. In the independent cohort 41 patients received maintenance. During maintenance, 13 patients (30%) developed AKD, leading to CKD and treatment discontinuation in 8 (62%) in the primary cohort. Higher eGFR (unit 5mL/min/1.73m^2) before maintenance and induction (OR 0.70, 95%CI:0.54-0.90 and OR 0.78, 95%CI:0.62-0.98, respectively) and relative decline (per 10%) in eGFR during induction (OR 2.54, 95%CI:1.36-4.74) were associated with AKD during maintenance. In the independent cohort 20 patients (49%) developed AKD, leading to CKD in 11 (55%) and treatment discontinuation in 6 (30%).

Conclusion: Patients are at risk for renal impairment during pemetrexed maintenance, which may jeopardize further lines of anticancer treatment.

Keywords: non-small-cell lung cancer; pemetrexed; maintenance; renal impairment

Introduction

In non-squamous non-small-cell lung cancer (NSCLC) without actionable driver mutations or high PD-L1 expression, pemetrexed is widely used as first- and second-line treatment[1]. More recently, first-line platinum-based treatment with pemetrexed combined with pembrolizumab prolonged overall survival compared to chemotherapy regardless of PD-L1 expression[2]. In patients without disease progression after platinum-based induction therapy, pemetrexed is recommended as maintenance treatment[3–6]. Currently, both immunotherapy and the combination of docetaxel with antiangiogenic agents have demonstrated their superior efficacy compared to conventional chemotherapy and were approved for second line treatment[7,8]. However, to gain optimal survival benefits from all these agents, patients should be able to start as well as continue multiple lines of treatment for which it is required to maintain an adequate renal function[9,10].

Patients with (lung) cancer are at increased risk of developing acute kidney injury (AKI) [11]. Besides the exposure to nephrotoxic chemotherapeutic agents, decline in renal function in these patients is due to cancer- or chemotherapy-induced true or effective volume depletion, patient's advanced age and nephrotoxic concomitant medication[12]. The mechanism of renal injury by pemetrexed is postulated to be mainly tubulointerstitial, as pemetrexed enters the proximal tubular cells at the basolateral membrane by the reduced folate carrier and it is transported through the folate receptor- at its apical site. Once inside the tubular cells, pemetrexed undergoes polyglutamylation which results in intracellular retention and increase in affinity towards enzymes involved in folate metabolism leading to tubular injury due to impaired DNA synthesis [12,13]. Although pemetrexed administration is not recommended in patients with a creatinine clearance < 45mL/min per 1.73m^2 [14], studies have shown that even milder pre-existing renal impairment is a risk factor for drug-induced nephrotoxicity[15,16].

Irrespective of its nature, acute kidney injury is a predictor of immediate and long-term unfavourable outcomes[17–19]. Moreover, AKI is an important risk factor for the development of chronic kidney disease (CKD)[20] and may jeopardize further cancer treatment[21]. Sustained impairment of the kidney function after discontinuation of pemetrexed maintenance therapy has been described in several case reports[22,23]. The PARAMOUNT study reported renal impairment in < 10% of the patients treated with pemetrexed maintenance and < 5% of the patients discontinued treatment due to renal toxicity[24]. However, this trial population was highly selected and might underestimate the risk and consequences of renal toxicity in daily clinical practice.

Therefore, our objective was to describe the development of acute and chronic renal impairment during maintenance treatment with pemetrexed and its impact on treatment decisions in a real-world setting.

Materials and methods

Prospective multi-center cohort (Primary cohort)

PEmetrexed and biomaRkerS: an observatiONAL study (PERSONAL) is a prospective multi-centre cohort study of adult patients with locally advanced or metastatic (stage IIIB/IV) non-squamous NSCLC and unresectable mesothelioma receiving platinum-combined pemetrexed as first-line and pemetrexed monotherapy as second-line treatment. Patients were recruited between October 2012 and November 2014 from a university hospital (Erasmus University Medical Centre), two large teaching hospitals specialized in lung cancer care (Amphia hospital; Franciscus Gasthuis) and a regional hospital (Bravis hospital) in the Netherlands. Patients who received pemetrexed as second-line treatment and patients with unresectable mesothelioma were excluded from analyses in the present study. The

PERSONAL cohort will be denoted as 'primary cohort' in the following parts of this paper. All patients provided written informed consent. The study was approved by the Institutional Review Board of the Erasmus University Medical Centre in Rotterdam, the Netherlands.

Per standard of care, platinum-combined pemetrexed chemotherapy was administered as an intravenous infusion every three weeks for a maximum of 4 cycle. The administered dosages of pemetrexed and cisplatin were calculated according to the body surface area, 500mg/m^2 and 75mg/m^2 respectively[14]. Carboplatin dosage was calculated based on estimated glomerular filtration rate (eGFR) and the target area under the curve of five or six following the Calvert formula[25]. If the chemotherapy schedule involved cisplatin, pre- and post-hydration treatment was given per protocol. Patients were recommended to continue with pemetrexed maintenance therapy if they had no progressive disease, no intolerable toxicities and underwent no sequential radiotherapy or surgery.

Prior to the initial chemotherapy cycle baseline serum creatinine (μmol/L) was obtained. Subsequently, prior to and weekly after each chemotherapy administration during the induction therapy, serum creatinine was measured. During maintenance treatment blood samples were only extracted prior to pemetrexed administration and at day 14 of each cycle. Estimations of renal function were made by calculation of the eGFR (mL/min/1.73m^2) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[26]. Renal adverse events were registered according to the Common Terminology Criteria of Adverse Events (CTCAE) version 3.0, for comparison to the registration trial of pemetrexed maintenance[24], and the updated version 4.03:

	All grades
CTCAE 3.0	creatinine: creatinine > upper limit of normal

	eGFR: eGFR < 75% lower limit of normal
CTCAE 4.03	Acute kidney injury: creatinine level increase of > 26.5 μmol/L (0.3mg/dL); creatinine > 1.5 × above baseline

Independent cohort

To validate findings in the primary cohort, we selected all patients with advanced NSCLC who started treatment with pemetrexed maintenance between November 2014 and December 2016 in one hospital (Amphia Hospital). We used the pharmacy database of this centre to construct a second independent cohort of patients who received pemetrexed maintenance treatment after the patient enrolment in above mentioned PERSONAL study had finished. Prior to maintenance treatment, these patients received first-line platinum-combined induction treatment with pemetrexed and hydration per standard of care (See *Prospective multi-centre cohort: Primary cohort)* creatinine level before start of induction and maintenance and during maintenance prior to each pemetrexed administration. As data in this cohort were collected retrospectively, no approval by a medical research and ethics committee was necessary according to Dutch guidelines.

Definitions of acute and chronic kidney disease

In both cohorts, patients with acute kidney disease (AKD) and chronic kidney disease (CKD) during induction and maintenance therapy were identified in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines[27,28].

AKD	eGFR < 60mL/min per 1.73m^2 for < 3 months*, OR
	Decrease in eGFR by > 35%, OR
	Increase in serum creatinine > 50% for < 3 months

CKD eGFR < 60 mL/min per 1.73m^2 for > 3 months

[*] *In patients with a baseline eGFR< 60mL/min per 1.73m^2 only change in eGFR and serum creatinine during next three months were used as criteria for AKD*

Besides the development of CKD, we registered clinical consequences related to decreased renal function in terms of discontinuation of therapy, hospitalization and dose adjustments and postponements.

Statistical analysis

Sociodemographic and clinical variables were described for all patients who were included in both cohorts. Patients from the primary cohort who underwent maintenance treatment were categorized into two groups (eGFR < 90 mL/min vs. eGFR ≥ 90 mL/min) according to their renal function at baseline (start of induction treatment) and at the start of maintenance therapy. For these groups, we reported the percentages of patients with AKD, CKD and clinical consequences with 95% confidence intervals (95% CI) calculated using the Wilson score method. The difference in incidence of AKD between these groups was examined using the χ^2-test or Fisher's exact test. With the use of logistic regression, we determined the univariable association of renal function before induction, change of renal function during induction (both per unit eGFR of 5mL/min per 1.73m^2) and other patient- and treatment-related factors with the incidence of AKD during maintenance. To verify findings from our prospective cohort study, we repeated these analyses in the second independent cohort.
All statistical analyses were performed with the use of SPSS, version 22.0 (IBM Corporation, Armonk, NY). A value of $P < 0.05$ was considered as statistically significant.

Results

In total, 190 patients who received treatment with pemetrexed were included in the current study. In the primary cohort, 149 patients with advanced NSCLC who started first-line induction treatment with pemetrexed were enrolled. Of these patients, 44 (29.5%) ultimately received one or more cycles of pemetrexed maintenance treatment (Figure 1). The second independent cohort consisted of 41 patients with advanced NSCLC who had received ≥ 1 cycle of pemetrexed maintenance therapy after first-line induction treatment.

All patient- and treatment characteristics of patients in both cohorts are outlined in Table 1. In the primary cohort, a higher percentage of patients with maintenance pemetrexed had metastatic disease ($P = 0.003$) and they had a higher serum albumin ($P = 0.001$) than patients who only received induction treatment ($N = 105$). Between patients who underwent maintenance in both cohorts, there were no significant differences and platinum-combination treatments were similar. Slightly more female patients underwent pemetrexed maintenance in the independent cohort than in the primary cohort (65.9% vs 50.0%, $P = 0.188$). Median follow-up time was 3.2 months (Interquartile range [IQR]: 1.9-6.1) in the second cohort and 3.5 months (IQR: 1.4-8.3) in the primary cohort.

Renal impairment in the primary cohort

Induction treatment

Calculated eGFR values at baseline were significantly different between the patients treated with CISPEM and with CARPEM (98.1 ± 16.0 vs 88.7 ± 15.9, $P = 0.001$). Over the total induction treatment of 4 cycles, the mean eGFR decreased in patients treated with CISPEM ($N = 53$) in contrast to the mean eGFR in patients treated with CARPEM ($N = 29$) (-9.1 ± 9.5 vs. -2.0 ± 11.0, $P = 0.003$). Weekly median eGFR values of patients receiving platinum-

combined induction treatment are described in Supplementary Appendix S1 and Figure S1, available at *European Respiratory Journal* online).

Maintenance

The median number of maintenance pemetrexed cycles was five (IQR: 2-12) and the median eGFR before administration of the first maintenance cycle was 86.3 (IQR: 71.6-97.2). During maintenance treatment with pemetrexed 13 of the 44 patients (29.5%) developed AKD according to KDIGO definitions. From these 13 patients, 10 patients (77%) had all grades renal adverse events according to CTCAE 4.03 compared to only 7 patients (54%) using CTCAE 3.0. Hence, using CTCAE 3.0 we found only 16% of patients experienced renal adverse events.

Individual courses of patients' renal function are shown in Figure 2. Compared to patients with an eGFR ≥ 90mL/min at the start of maintenance, patients with a mildly decreased renal function (eGFR < 90mL/min) more frequently developed AKD (11/23 vs. 2/21, $P = 0.005$) and their renal function more often decreased below the recommendation threshold of pemetrexed administration (eGFR < 45mL/min, 6/21 vs. 1/21, $P = 0.017$). Two patients with an eGFR < 45 mL/min already before maintenance were excluded from this analysis.

Per unit 5mL/min/1.73m^2, higher eGFR both before start of maintenance and induction treatment were associated with a lower risk of AKD as is shown in table 2 (OR 0.70, 95% CI: 0.54-0.90 and OR 0.78, 95% CI: 0.62-0.98 respectively). In contrast, 10% decline in eGFR during induction relative to baseline was associated with an increased probability of AKD (OR 2.54, 95% CI: 1.36-4.74). In patients with AKD the mean decrease of eGFR during induction was -12.2 ± 8.9 mL/min compared to -2.1 ± 8.4mL/min in patients without AKD.

Clinical implications

The development of CKD and clinical consequences of renal impairment during maintenance therapy are outlined in Figure 3. Of the 13 patients (30%) who obtained AKD during maintenance therapy, 8 patients ultimately developed CKD (62%). Eight of the 13 patients with AKD (62%) were forced to discontinue maintenance treatment due to renal impairment. Importantly, all of these patients who developed CKD and stopped treatment already had a mildly impaired renal function (< 90 mL/min) before start of maintenance. Moreover, in patients whose renal function was already mildly impaired before induction (< 90mL/min) the proportion of patients who had to discontinue treatment was higher than in patients with a normal eGFR (6/11 vs. 2/33, $P = 0.001$). Accordingly, patients more often developed AKD (6/11 vs. 7/33, $P = 0.057$) and CKD (5/11 vs. 3/33, $P = 0.016$) if renal function was mildly impaired before induction.

Renal impairment in the independent cohort

In the independent cohort, the median number of maintenance pemetrexed cycles was four (IQR: 3-8) and the median eGFR before administration of the first maintenance cycle was 80.6 (IQR: 63.4-93.3). Twenty patients (49%) obtained AKD, of whom 11 patients eventually developed CKD (55%) and six discontinued pemetrexed maintenance (30%). Similarly to the primary cohort, all patients who developed CKD and stopped maintenance treatment had an eGFR < 90 mL/min before start of maintenance.

We tested the same patient- and treatment related variables for their relation with development of AKD during maintenance as in the primary cohort (Table 2). Again, per unit 5mL/min/1.73m^2 higher eGFR before maintenance and before induction were univariably associated with a lower probability of AKD during maintenance (OR 0.64, 95% CI 0.48-0.84 and OR 0.78, 95% CI 0.62-0.98 respectively). Also, a 10% decline in eGFR during induction

compared to baseline was related with an increased risk of AKD (OR 1.56, 95% CI 1.03-2.36).

Discussion

In an era of accelerated development and adaptation of new agents with survival benefits for patients with advanced NSCLC, it becomes increasingly important to ascertain patients are able to start and continue multiple lines of treatment. Our study shows serious concerns with regard to the preservation of an adequate renal function during pemetrexed maintenance therapy, which might expose patients to a suboptimal oncological treatment. In a real-world setting, one-third of patients with metastatic NSCLC developed acute kidney disease during pemetrexed maintenance therapy and half of these patients were forced to discontinue maintenance treatment. Moreover, in the majority of patients with AKD renal function did not -or only partially- recover and these patients developed CKD. Importantly, these results were verified in an independent cohort of patients with advanced NSCLC treated with pemetrexed maintenance.

A ~20% lower risk of occurrence of AKD during pemetrexed maintenance therapy was observed in patients per 5mL/min higher eGFR before the start of induction therapy. The proportions of patients who developed AKD, CKD and who discontinued maintenance treatment were significantly higher in patients with an impaired renal function (eGFR < 90mL/min) at the start of maintenance and before induction. It has already been recognized that decreased renal function, even mildly, can predispose to chemotherapy-induced nephrotoxicity[15,29]. Sassier et al. also reported a linkage between renal impairment before maintenance treatment and the higher probability of discontinuing double maintenance therapy with pemetrexed and bevacizumab[30]. In contrast to our study, they did not find an association between renal function before induction and treatment discontinuation. Besides

almost 20% missing data of renal function before induction and a lack of patients with an eGFR < 60 mL/min at baseline in that study, the different pathophysiology leading to renal damage due to bevacizumab might explain this difference.

During pemetrexed maintenance, patients were at ~2-fold higher risk of developing AKD per 10% decline of eGFR during induction therapy relative to baseline. Patients treated with CISPEM showed a decline in eGFR of approximately 10mL/min, which is comparable to recent findings in patients who received cisplatin for treatment across multiple tumour types[13]. As treatment with CISPEM during induction therapy was not associated with AKD throughout the maintenance period, it is unlikely that nephrotoxicity during maintenance is solely a delayed cisplatin effect. This is supported by findings of follow-up studies in patients with various cancer types including lung cancer, which demonstrated that declines in eGFR did not deteriorate after discontinuation of cisplatin[13,31]. Although not statistically significant ($P = 0.06$), AKD occurred more often in patients who received a higher number of pemetrexed maintenance cycles. In these patients a cumulative systemic dose of pemetrexed might play a role in the development of nephrotoxicity, also recently suggested by Langer et al [32].

The nephrotoxic potential of pemetrexed has been previously described in clinical studies. In the pivotal PARAMOUNT trial[3], Pujol et al. reported all grades renal toxicities according to CTCAE 3.0 in 7.8% of patients and treatment discontinuation in 4.5% of patients due to renal impairment during pemetrexed maintenance [24]. Acknowledging small patient numbers, our study notes probable underestimation of renal toxicity by using the CTCAE 3.0 compared to AKD (KDIGO). By taking into account absolute increases of creatinine and its relative increase from baseline, the results of the updated version CTCAE 4.03 corresponded better with the AKD results. Additionally, the patient population in the PARAMOUNT trial was highly selected with regard to ECOG performance score, renal function at baseline and

concomitant medication as opposed to our real-life population. Therefore, that trial probably underestimates the risk of renal insufficiency in daily practice. Although pemetrexed maintenance was combined with bevacizumab and therefore results cannot solely be attributed to pemetrexed, Sassier et al. reported renal adverse events resulting in treatment discontinuation in 17% of the patients [30].

Due to a low number of event-rate per subgroup in the primary and independent cohort, we could not perform a multivariable analysis to identify patient- and treatment-related variables associated with the development of AKD during maintenance therapy. As both cohorts differed with regard to frequency and timing of data collection of renal function by design, we did not consider it suitable to perform a combined analysis of these cohorts. We cannot exclude effect modification by the platinum compound, as all patients received CISPEM or CARPEM during induction treatment without a pemetrexed monotherapy comparator arm.

In conclusion, the results of this study in a real-life setting demonstrate that patients with advanced NSCLC are at risk to develop renal impairment during pemetrexed maintenance therapy. This has important clinical consequences, as the majority of these patients develop CKD, ~15-20% are forced to stop maintenance treatment and further anticancer treatment may be jeopardized. Increased awareness and further exploration of renal protective strategies for patients at increased risk might be beneficial, such as continuation of hydration during pemetrexed maintenance.

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Disclosures

Dr. Joachim Aerts has a consultant/advisory role with Eli Lilly and Company, Roche, Bristol-Myers Squibb, MSD and Boehringer Ingelheim. All remaining authors have declared no conflicts of interest.

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Table 1. Characteristics of all patients with advanced NSCLC who received treatment with pemetrexed (N = 190)

	COHORT 1		COHORT 2
	No maintenance pemetrexed N = 105	Maintenance pemetrexed N = 44	Maintenance pemetrexed N = 41
Age, mean (SD)	63.7 (9.4)	62.9 (7.5)	62.8 (6.7)
Sex, male	52 (49.5)	22 (50.0)	14 (34.1)
Ethnicity			
Caucasian	100 (95.2)	42 (95.5)	38 (92.7)
Negroid	1 (1.0)	0	0
Asian	2 (1.9)	0	0
Other	2 (1.9)	2 (4.5)	3 (7.3)
BMI, mean (SD)	24.3 (3.9)	25.3 (3.7)	24.8 (5.3)
Packyears (SD)	38.3 (36.4)	34.7 (23.3)	34.0 (21.0)
Type of tumor			
Adenocarcinoma	102 (97.1)	44 (100)	41 (100)
Large cell carcinoma	3 (2.9)	0	0
Cancer stage[†]			
Locally advanced (IIIB)	20 (19.0)	0	2 (4.8)
Metastatic (IV)	85 (81.0)	44 (100)	39 (95.1)
Line of induction treatment			
First-line	105 (100)	44 (100)	41 (100)
Platinum combination			
Cisplatin	65 (61.9)	32 (72.7)	31 (75.6)
Carboplatin	40 (38.1)	12 (27.3)	13 (24.4)
Laboratory values			
Creatinine (mL/min), median (IQR)	61.0 (49.0-72.5)	57.5 (52.0-70.0)	64.0 (51.5-79.0)
eGFR (mL/min per 1.73m^2), median (IQR)	96.9 (85.4-104.7)	97.6 (88.6-106.1)	95.4 (79.4-101.0)
eGFR < 60 mL/min per 1.73m^2	6 (5.7)	2 (4.5)	1 (2.4)
Albumine (g/L), mean (SD)	38.6 (5.3)	41.3 (3.8)	unknown
Comorbidity			
Cardiovascular disease	47 (44.8)	16 (36.4)	18 (43.9)
Diabetes mellitus	17 (16.2)	4 (9.1)	5 (12.2)

Data are expressed as numbers (%) unless stated otherwise. eGFR was calculated using the CKDEPI formula. [*]Patient received only palliative chemotherapy (lymfangitis carcinomatosa). Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; SD, standard deviation; IQR, interquartile range.

Table 2. Univariable analysis of clinical and treatment-related factors associated with acute kidney disease during pemetrexed maintenance

	Primary cohort (N = 44)		Independent cohort (N = 41)	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age	1.07 (0.98 - 1.18)	0.14	0.98 (0.89 - 1.07)	0.62
Sex male vs. female	0.52 (0.14 - 1.93)	0.34	0.28 (0.068 - 1.11)	0.069
History of cardiovascular disease yes vs. no	0.70 (0.18 - 2.80)	0.62	0.73 (0.21 - 2.53)	0.62
Combination CISPEM during induction yes vs. no	2.62 (0.49 - 14.11)	0.26	0.94 (0.23 - 3.90)	0.93
No. of cycles pemetrexed maintenance	1.08 (1.0 - 1.17)	0.059	1.09 (0.96 - 1.23)	0.2
eGFR decrease during induction*	2.54 (1.36 - 4.74)	0.004	1.56 (1.03 - 2.36)	0.038
eGFR before induction†	0.78 (0.62 - 0.98)	0.032	0.78 (0.62 - 0.98)	0.035
eGFR before maintenance†	0.70 (0.54 - 0.90)	0.005	0.64 (0.48 - 0.84)	0.001

*eGFR change relative to baseline per 10%. †eGFR per unit 5ml min^{-1} per 1.73m^2. Abbreviations: CISPEM, cisplatin and pemetrexed; eGFR, estimated glomerular filtration rate; CI, confidence interval

Figure legends

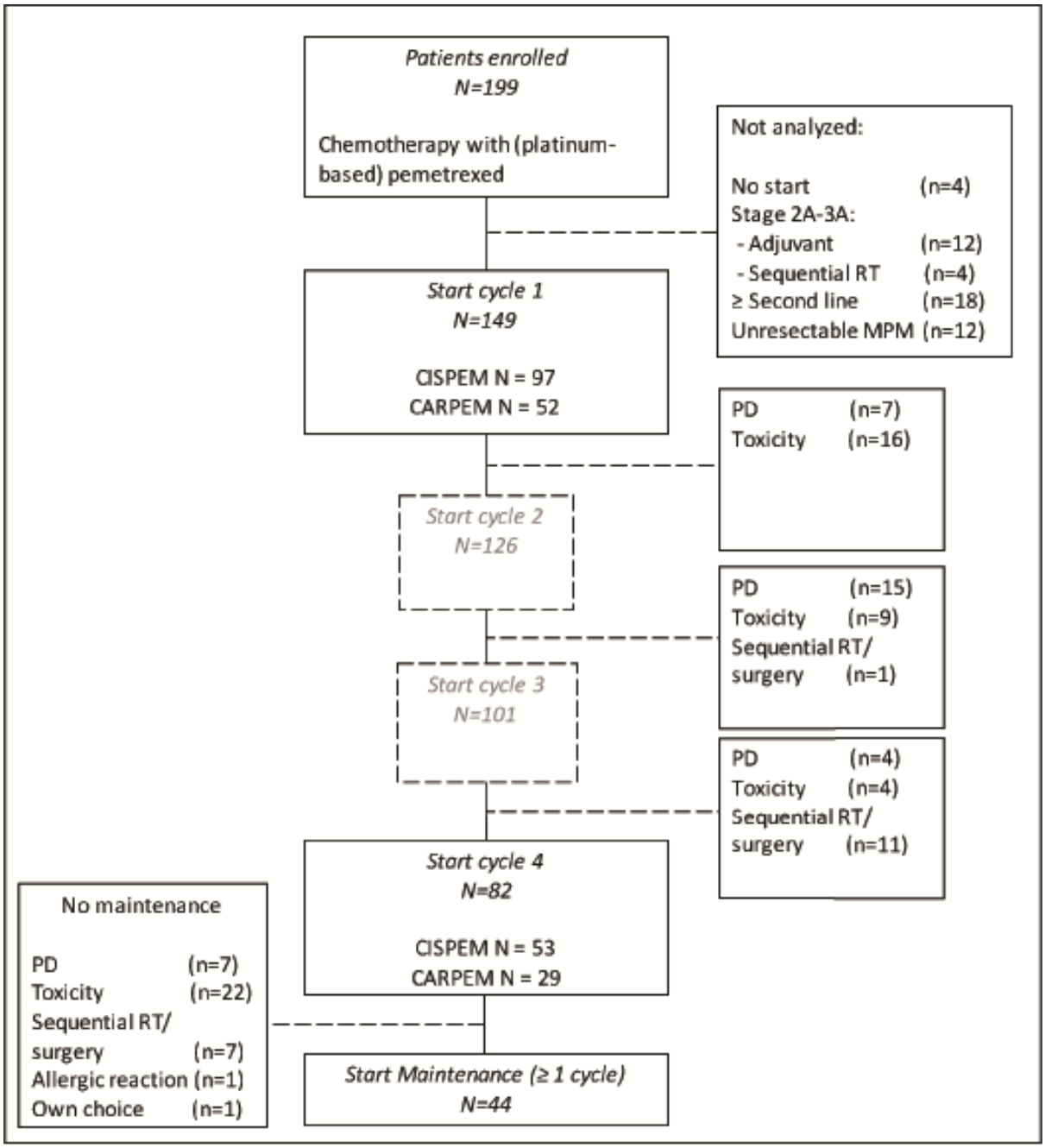

Figure 1. Flowchart of patients in the primary cohort.

Abbreviations: NSCLC, non-small cell lung cancer; MPM, malignant pleural mesothelioma; PD, progressive disease; RT, radiotherapy.

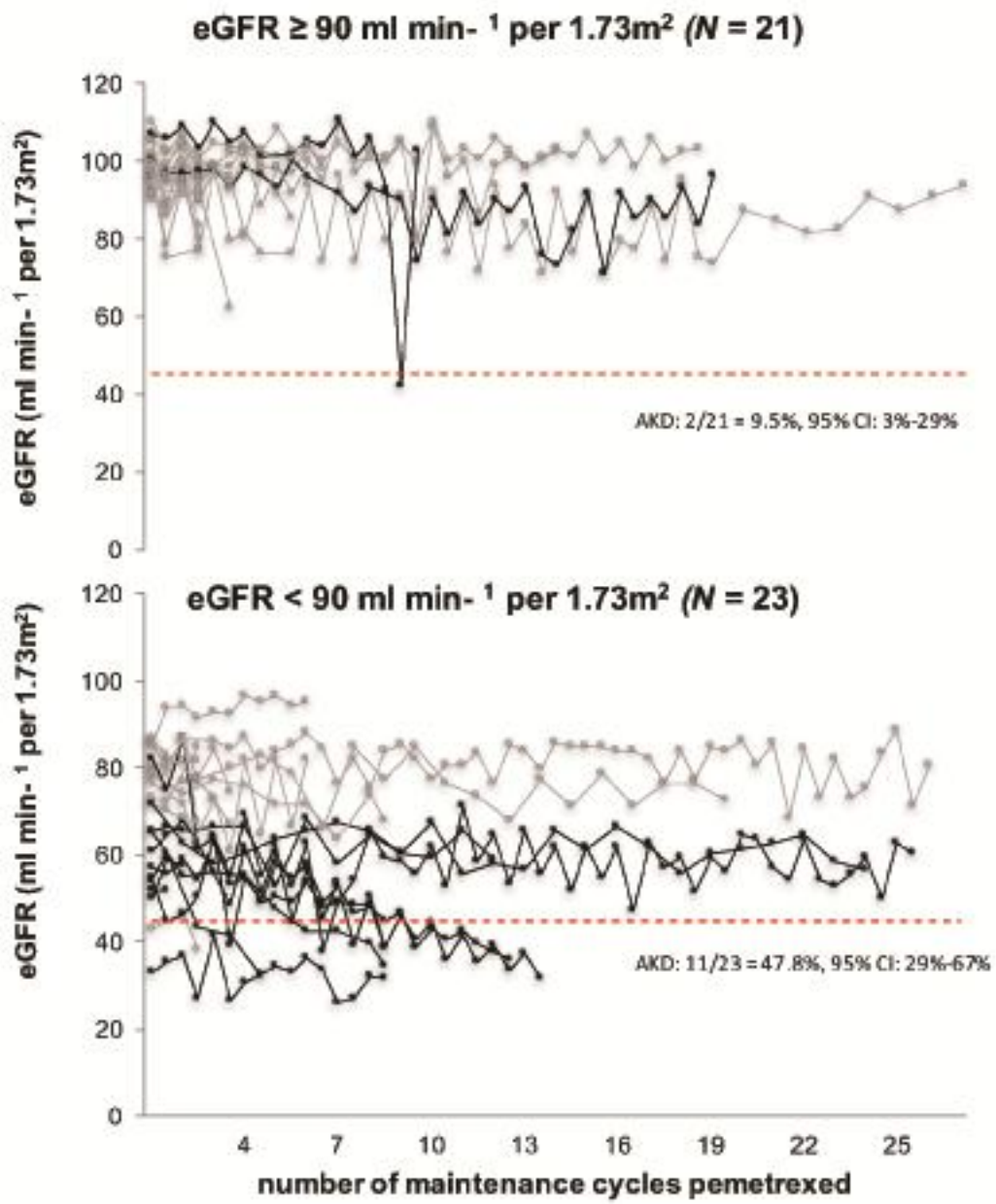

Figure 2. Renal function and development of AKD during pemetrexed maintenance therapy in the primary cohort (N = 44).

Dots: individual measurements of renal function. Solid lines: course of renal function during maintenance therapy of individuals who develop AKD (black) and do not develop AKD (grey). Dashed line (red): eGFR = 45 mL/min, value below which pemetrexed administration is not recommended. Abbreviations: AKD, acute kidney disease; eGFR, estimated glomerular filtration rate; CI, confidence interval.

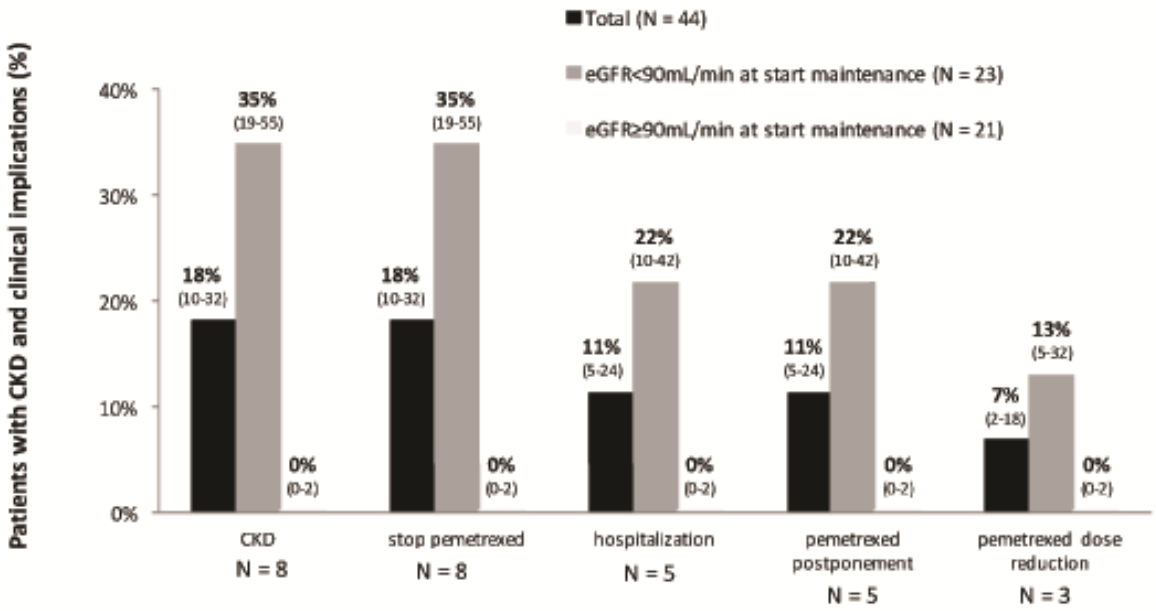

Figure 3. Chronic kidney disease and clinical implications due to renal impairment during pemetrexed maintenance therapy in the primary cohort (N = 44).

Data are expressed as percentages with 95% confidence interval. Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Supplementary data (Appendix S1)

Primary cohort: Renal impairment during induction treatment

During the total induction period, 48 patients (49.5%) treated with CISPEM developed AKD at any time during the induction period compared to 20 patients (31%) treated with CARPEM. The proportion of patients with AKD during CARPEM treatment remained constant around 15% per cycle. In contrast, the occurrence of AKD accumulated with the number of cycles of treatment with CISPEM (20% during cycle 1, 50% during cycle 4) (Figure S1).

Figure S1. Renal function and development of AKD during induction treatment (N = 149) in the primary cohort.

(A) Squares: median eGFR with interquartile range at weekly measurements in patients at risk. Lines: course of renal function during induction pemetrexed combined with cisplatin (solid) and carboplatin (dashed). (B) Columns: weekly percentage of patients at risk who develop acute kidney disease during induction pemetrexed combined with cisplatin (filled) and carboplatin (pattern). Abbreviations: AKD, acute kidney disease; eGFR, estimated glomerular filtration rate; CISPEM, cisplatin combined with pemetrexed; CARPEM, carboplatin combined with pemetrexed; PD, progressive disease; RT, radiotherapy.