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Cumulative pemetrexed dose increases the risk of nephrotoxicity

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ABSTRACT

Introduction: Pemetrexed is a pharmacotherapeutic cornerstone in the treatment of non-small cell lung cancer. As it is primarily eliminated by renal excretion, adequate renal function is essential to prevent toxic exposure. There is growing evidence for the nephrotoxic potential of pemetrexed, which even becomes a greater issue now combined immuno-chemotherapy prolongs survival. Therefore, the aim of this study was to describe the incidence of nephrotoxicity and related treatment consequences during pemetrexed-based treatment.

Methods: A retrospective cohort study was conducted in the Jeroen Bosch Hospital, Den Bosch, the Netherlands. All patients that received at least 1 cycle of pemetrexed based therapy were included in the dataset. The primary outcome was defined as a ≥25 % reduction in eGFR. Additionally, the treatment consequences of decreased renal function were assessed. Logistic regression was used to identify risk factors for nephrotoxicity during treatment with pemetrexed.

Results: Of the 359 patients included in this analysis, 21 % patients had a clinically relevant decline in renal function after treatment and 8.1 % of patients discontinued treatment due to nephrotoxicity. Cumulative dose (≥10 cycles of pemetrexed based therapy) was identified as a risk factor for the primary outcome measure (adjusted OR 5.66 (CI 1.73-18.54)).

Conclusion: This study shows that patients on pemetrexed-based treatment are at risk of developing renal impairment. Risk significantly increases with prolonged treatment. Renal impairment is expected to become an even greater issue now that pemetrexed-based immuno-chemotherapy results in longer survival and thus longer treatment duration.

1. Introduction

Pemetrexed is widely used as an anti-folate cytostatic agent for the treatment of non-small cell lung cancer (NSCLC), mesothelioma and thymoma. [1–5] Dependent on treatment indication, therapy generally exists of four cycles of induction therapy with pemetrexed and a platinum-agent, which can be combined with the recently approved programmed death-ligand 1 (PD-L1) targeting monoclonal antibody pembrolizumab [6]. Pemetrexed - and, if applicable, pembrolizumab - can be continued as maintenance treatment following the induction period [3,6].

Pemetrexed is primarily eliminated by renal excretion, with 70–90 % of the dose recovered as the unchanged drug in urine within the first 24 h after administration. [4,7] Previous studies showed that pemetrexed pharmacokinetics are linearly correlated with creatinine clearance [8,9]. Thus, to prevent high exposure, an adequate renal function is essential. Decreased creatinine clearance and higher exposure were shown to be associated with more severe haematologic toxicity. [8,10–13] Due to these safety issues and based on the study of Mita et al. (2006), pemetrexed is currently contraindicated in patients with a creatinine clearance < 45 mL/min [4,14].

Cancer patients are already at increased risk of developing renal insufficiency, possibly due to volume depletion, advanced age of patients and the use of potentially nephrotoxic anti-cancer therapy [15–17]. For treatment in non-small cell lung cancer, the most common nephrotoxic anti-cancer drugs are platinum-agents, and possibly also

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the checkpoint-inhibitors [17–21]. In addition, there is now accumulating evidence for the nephrotoxic potential of pemetrexed itself. Several case reports describe incidents of (sub)acute kidney injury during or after pemetrexed therapy [22–29]. In the PARAMOUNT study, during pemetrexed maintenance, 7.8 % of patients developed renal impairment (versus 2.3 % in the placebo group) and 4 % of patients discontinued therapy due to nephrotoxicity [30]. However, as with many registration studies, this represents only the incidence in a specific trial population. The available literature describing renal complications during pemetrexed therapy in daily practice consists mainly focusses on acute kidney injury.

The development of renal toxicity is potentially a major limitation for safe, long-term pemetrexed treatment because according to current recommendation pemetrexed dosing has to be terminated when CrCl falls below 45 mL/min. This is highly undesirable for all patients with positive clinical response to pemetrexed, but in particular to patients treated with pemetrexed-based immuno-chemotherapy who demonstrate longer survival and thus longer treatment durations. [6] Therefore, there is an urgent need for better knowledge on preventing and managing of pemetrexed-associated renal toxicity.

The aim of this study was to describe the incidence of nephrotoxicity and related treatment consequences during pemetrexed-based therapy. The secondary objective was to identify risk factors for the decrease in renal function.

2. Methods

2.1. Study design and population

This retrospective cohort study was performed in the Jeroen Bosch Hospital, Den Bosch, the Netherlands and approved by the local medical research ethics committee. The medical ethics committee waived the necessity of acquiring informed consent. Through a system search in the hospital information systems (HiX, Chipsoft, version 6.1 and Centrasys, CSC, version 6.30.0.50 − 4.1) all consecutive patients who received at least 1 cycle of pemetrexed between January 1st 2014 and February 1st 2019 were identified.

2.2. Data collection

All data used in this study were collected as part of routine care. For each patient the following patient demographics were obtained: Sex, ethnicity, age, weight and length at baseline, diagnosis, pre-treatment, number of neutropenic events and comorbidities and comedication affecting renal function (see appendix for details). Length and weight were used to calculate Body Surface Area (BSA, according to Du Bois and Du Bois' formula [31]) and Body Mass Index (BMI).

Regarding pemetrexed-based therapy, dates of the initial cycle (defined as baseline) and the last cycle of pemetrexed-based therapy were collected. In addition, pemetrexed dose and concomitant chemo- and/or immunotherapy at baseline, total number of cycles pemetrexed, and the date and reason of discontinuation of treatment were obtained. For patients still on treatment during data analysis, their last cycle before May 13th 2019 was considered as last cycle of therapy for analysis.

For the assessment of renal function, serum creatinine was used. Measurements of serum creatinine (μmol/L) at baseline and at the end of therapy were collected. The cut-off date for the measurements at baseline was a maximum of 28 days prior to the initial chemotherapy cycle, or – only if not available – a maximum of 7 days after the initial chemotherapy cycle. The cut-off dates for the measurements at the end of therapy were a maximum of 28 days after the last cycle, or – only if not available – a maximum of 7 days prior to the last cycle. The estimated glomerular filtration rate (eGFR) (mL/min/1.73 m^2) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI). [32] Additionally, the occurrence of acute kidney injury (AKI) during therapy (as a reported diagnosis in the patient file by the physician) was investigated.

2.3. Outcome

The primary outcome was defined as a ≥ 25 % reduction in eGFR (in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines [33]). The relative change in eGFR from baseline (bs) to end of therapy (eot) was calculated for each patient as: $\frac{(eGFRbs - eGFReot)}{eGFRbs} * 100\%$. To assess the treatment consequences of decreased renal function in patients with pemetrexed-based treatment, the incidence of treatment discontinuation due to nephrotoxicity and combined nephrotoxicity and hematologic toxicity was investigated. The secondary outcome was the identification of potential risk factors for nephrotoxicity during pemetrexed-based treatment.

2.4. Statistical analysis

Descriptive statistics were used to calculate the primary outcome measures. To identify risk factors for the development of renal impairment during pemetrexed-based therapy, the sample set was divided in cases (patients with ≥ 25 % reduction in renal function) and non-cases. For both cases and controls, the prevalence of each variable was determined. All variables were expressed as categorical data. Within a variable, categories were divided based on equal group sizes. Multivariate logistic regression was used to calculate odds ratios for the various risk factors. The tested variables included: sex, age, body mass index (BMI), number of comorbidities and comedications affecting renal function, smoking status, pre-treatment, concomitant induction therapy and total number of cycles. Based on the first analysis, age and gender were included as potential confounding factors, resulting in adjusted odds ratios for all tested variables. A Bonferroni correction was applied to correct for multiple testing, resulting in an adjusted p-value for significance of $p = 0.005$. Accordingly, odds ratios were calculated with 99.5 % confidence intervals (CI). All statistical analyses were performed using SPSS version 22.0 (IBM, Armonk, NY, USA). As an exploratory objective, the incidence of neutropenic events in both the cases and non-cases was calculated. A Fisher's exact test was applied to assess for significant difference.

3. Results

3.1. Patient demographics

The system search identified 386 patients who received at least one cycle of pemetrexed between January 1st 2014 and February 1st 2019. Due to missing data regarding pemetrexed therapy and/or serum creatinine measurements, 27 patients were excluded. The final analysis dataset consisted of 359 patients.

In Table 1 the baseline characteristics are presented. Gender was well balanced within the study population (54 % male). The median age was 65 years. Approximately half of patients had a baseline eGFR of > 90 mL/min/1.73m^2 (53 %). The majority of patients was diagnosed with stage IV NSCLC (69 %) and was treatment-naïve (73 %). The number of received pemetrexed-based cycles had a wide range of 1 − 103, with a median of 4 cycles and median follow-up time of 3 months.

3.2. Decrease in renal function and treatment consequences

The mean eGFR (CKD-EPI) at baseline was 87.8 ± 15.4 mL/min/1.73m^2. In total, 21 % of the patients (74 out of 359) had a clinically relevant decrease in eGFR of ≥ 25 % from baseline to end of treatment. The mean absolute change of eGFR over treatment time was a decrease of 8.6 mL/min/1.73m^2 (mean eGFR at the end of therapy was

Table 1
patient demographics and results of risk factor analysis for development of renal impairment during pemetrexed-based treatment. OR = odds ratio, CI = confidence interval, eGFR = estimated glomerular filtration rate, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration equation, BMI = body mass index, NSCLC = non-small cell lung cancer, n/a = not applicable.

Parameter	Total N (%) 359 (100)	Cases N (%) 74 (21)	Controls N (%) 285 (79)	OR adjusted (99.5 % CI)	P-value (< 0.005 = significant)
Sex					
Male	195 (54)	33 (45)	162 (57)	Reference	
Female	164 (46)	41 (55)	123 (43)	1.68 (0.79 – 3.59)	0.056
Age (mean: 64.9 years; range 32 – 86)					
0 – 60 years	104 (29)	17 (23)	87 (31)	Reference	
61 – 69 years	135 (38)	39 (53)	96 (34)	2.15 (0.86 – 5.41)	0.020
≥ 70 years	120 (33)	18 (24)	102 (36)	1.02 (0.35 – 2.92)	0.967
Baseline eGFR (CKD-EPI)					
≥ 90 mL/min/1.73m^2	189 (53)	35 (47)	154 (54)	Reference	
< 90 mL/min/1.73m^2	170 (47)	39 (53)	131 (46)	1.35 (0.59 – 3.09)	0.305
BMI					
< 25 kg/m^2	185 (52)	32 (43)	153 (54)	Reference	
25 – 30 kg/m^2	130 (36)	29 (39)	101 (35)	1.43 (0.63 – 3.24)	0.224
> 30 kg/m^2	44 (12)	13 (18)	31 (11)	1.86 (0.63 – 5.52)	0.109
Diagnosis					
Mesothelioma	27 (7.5)	3 (11)	24 (8.4)	Reference	
NSCLC stage I-III	84 (23)	13 (18)	71 (25)	1.35 (0.19 – 9.55)	0.666
NSCLC stage IV	246 (69)	57 (77)	189 (66)	2.35 (0.38 – 14.59)	0.188
Other	2 (0.6)	1 (1.4)	1 (0.4)	n/a	n/a
Pre-treatment					
No pretreatment	261 (73)	56 (76)	205 (72)	Reference	
Pretreatment	98 (27)	18 (24)	80 (28)	0.81 (0.35 – 1.90)	0.483
Smoking status					
Never	20 (5.6)	2 (2.7)	18 (6.3)	Reference	
Past	129 (36)	31 (42)	98 (34)	3.00 (0.34 – 26.60)	0.157
Current (< 20 cigarettes/day)	120 (33)	22 (30)	98 (34)	2.14 (0.24 – 19.38)	0.335
Current (≥ 20 cigarettes/day)	68 (19)	16 (22)	52 (18)	2.97 (0.31 – 28.41)	0.177
Not known	22 (6.1)	3 (4.1)	19 (6.7)	1.61 (0.10 – 24.83)	n/a
Number of comorbidities					
None	80 (22)	12 (16)	68 (24)	Reference	
One	116 (32)	23 (31)	93 (33)	1.53 (0.50 – 4.62)	0.284
Two	107 (30)	24 (32)	83 (29)	1.81 (0.60 – 5.52)	0.134
Three or more	56 (16)	15 (20)	41 (14)	2.32 (0.67 – 8.08)	0.058
Number of comedications					
None	152 (42)	27 (37)	125 (44)	Reference	
One	128 (36)	25 (34)	103 (36)	1.15 (0.48 – 2.73)	0.658
Two or more	79 (22)	22 (30)	57 (20)	1.77 (0.70 – 4.51)	0.085
Concomitant induction therapy					
No induction therapy	22 (6.1)	5 (6.8)	17 (6.0)	Reference	
Cisplatin	123 (34)	25 (34)	98 (34)	0.90 (0.19 – 4.32)	0.847
Carboplatin	179 (50)	35 (47)	144 (51)	0.85 (0.18 – 4.00)	0.775
Other	35 (9.7)	9 (12)	26 (9.1)	n/a	n/a
Total number of cycles (median 4; range 1 – 103)					
1 – 2	79 (22)	10 (14)	69 (24)	Reference	
3 – 4	144 (40)	18 (24)	126 (44)	0.96 (0.29 – 3.15)	0.921
5 – 9	68 (19)	15 (20)	53 (19)	1.98 (0.56 – 6.96)	0.130
≥ 10	68 (19)	31 (42)	37 (13)	5.66 (1.73 – 18.54)	< ***0.001***

79.2 ± 22.5 mL/min/1.73m^2). This corresponds with a mean relative change of eGFR during therapy of −9.6 %. As reported in the patient files by the physician, only 1.9 % of patients had AKI.

Decrease in renal function can eventually lead to cessation of effective therapy. In our cohort 8.1 % of patients discontinued treatment due to nephrotoxicity. In approximately one-third of these patients, nephrotoxicity was accompanied with hematotoxicity. From the patients with a clinically relevant decline in renal function (cases), 35.1 % experienced ≥ 1 neutropenic event, compared to 13.7 % in the controls ($p < 0.001$).

3.3. Risk factors for the development of renal impairment

Table 1 summarizes the results of the analysed risk factors. The cumulative dose of pemetrexed (≥ 10 cycles) was a significant risk factor (adjusted OR 5.66 (1.73 – 18.54), p-value < 0.001). Fig. 1 visualizes the number of cycles versus the relative change in eGFR. The graph shows a relation between the treatment duration and decrease in

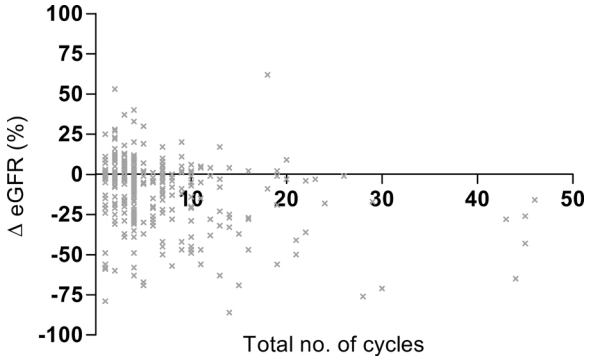

Fig. 1. Total number of cycles versus relative change in eGFR n.b.: for clarity, the datapoint of 103 cycles is not visualized in the graph.

renal function.

No significant effect was observed for the other tested variables.

4. Discussion

To our knowledge this is the first study to investigate both the incidence and a broad panel of associated risk factors for renal impairment during pemetrexed-based therapy in a relatively large population in every day clinical practice. It confirms the nephrotoxic potential of pemetrexed. We demonstrated that, in clinical practice, approximately one-fifth of patients on pemetrexed-based therapy have a clinically relevant decline in eGFR. Additionally, around 8% of patients had to cease treatment due to nephrotoxicity. The risk of renal impairment increases with longer treatment duration (≥ 10 cycles of pemetrexed-based treatment: adjusted OR 5.66 (1.73 − 18.54)) and is associated with an increased risk on hematotoxicity.

In the PARAMOUNT study (a phase III study of maintenance treatment with pemetrexed versus placebo), the investigators reported an incidence of 7.8 % for renal toxicities and 4% of treatment discontinuation due to renal toxicity. [34,35] Interestingly, the researchers also suggest the potential risk for a cumulative effect of pemetrexed on renal toxicity [35]. The incidence in our patient cohort is three times greater. Our patient population representing clinical practice has, when compared to the trial population, probably more heterogeneous performance score and more comorbidities and comedication affecting renal function. It is suggested that a physiologic decline in renal function in adults > 65 years is 0.75 mL/min per year. [36]. In our cohort, the difference between mean eGFR at baseline and end of treatment was 8.6 mL/min/1.73m^2 over a median follow-up time of three months. In the PARAMOUNT study, no effect on renal function was observed in the placebo group refuting the suggestion that the occurrence of clinically relevant decline in renal function might reflect the natural course. Therefore, the observed decline in renal function in our cohort can be attributable to treatment. In addition, it is generally known that cancer patients frequently suffer from sarcopenia, which may lead to overestimation of renal function [37] and thus, the actual prevalence of renal impairment may be even higher.

Visser et al. recently investigated the occurrence of renal impairment during pemetrexed maintenance therapy in clinical practice prospectively. In their cohorts, 15–20 % of patients ceased treatment due to nephrotoxicity, versus 8.1 % in our study. Additionally, they report a very high incidence of AKI of 29.5 % in their primary cohort, compared to approximately 2% in our population [38]. An explanation for these discrepancies is the possibility of underreporting in our study, as we only collected the AKI diagnoses that were reported by the physicians in the patient files. Our main objective focussed on gradual decline of renal function rather than acute injury.

As it stands, risk factors for pemetrexed-related nephrotoxicity have not been extensively studied. Visser et al. included a set of treatment-related factors associated with AKI and found baseline eGFR to be an important determinant. This finding was not confirmed in our study. In line with the findings of Langer et al. (2018) and Middleton et al. (2018), we also found an increasing risk of renal impairment with longer exposure to pemetrexed-based treatment. [35] A significant effect was observed in the patient group that received ≥10 cycles pemetrexed. The number of patients in this group was relatively small (n = 68), which is reflected in de large confidence interval. Nevertheless, there was a clear trend with increasing number of cycles, indicating an actual effect rather that a coincidental finding.

In our cohort, use of cisplatin in induction therapy was not associated with increased risk of renal impairment, despite its nephrotoxic potential. Extensive pre- and post-hydration schedules and administration of diuretics are nowadays used to minimize cisplatin nephrotoxicity, which may explain why cisplatin coadministration does not pose an additional risk. Another risk factor for nephrotoxicity is the use of radiocontrast agents [40]. Unfortunately, data on use of contrast was not available in the dataset. Theoretically, the amount of CT scans increases proportionally with the amount of cycles and are therefore difficult to distinguish. In the general population with normal renal function at baseline, the incidence of contrast-induced nephropathy is estimated to be low (1 − 2 %) [40], much lower that the incidence of nephrotoxicity in this study. Additionally, both cisplatin and radiocontrast are mainly associated with acute nephrotoxicity rather than chronic decline of renal function [19,21,39,40].

Altogether, the significant effect of cumulative dose implies a possible causal relationship between pemetrexed and renal impairment.

A few limitations of the present study have to be taken into consideration. First, it was a retrospective study with its flaws. Not all data might have been captured by the electronic patient file. Despite this design we were able to confirm the findings of previous studies. Secondly, whereas the combination of pembrolizumab with a pemetrexed and platinum has now become the preferred first line treatment the number of patients with this combination in the study is very limited. It is expected that the number of cycles of pemetrexed per patients will increase because of the increased disease control because of combined chemoimmunotherapy. [6] Besides, the checkpoint-inhibitors also have nephrotoxic potential [18,20], but this mainly manifests as acute kidney injury. In the KEYNOTE-189 trial, acute kidney injury occurred more frequently in the pembrolizumab-combination group than in the placebo-combination group (5.2 % vs. 0.5 %) [6]. Nevertheless, combining immunotherapy with chemotherapy may increase the risk for long term nephrotoxicity as both agents have nephrotoxic potential and because patients have longer treatment duration, but we do not have data to support this synergistic toxicity. Thirdly, for assessing renal function, we calculated eGFR according to the CKD-EPI equation, which is not validated for eGFR > 90 mL/min. This could have led to incorrect calculation of the relative change of eGFR and thus, to misclassification of cases and controls. In order to assess the impact of using the CKD-EPI, a second analysis was performed using absolute serum creatinine (results not shown). This analysis yielded similar results on both the primary outcome and the risk factor analysis, indicating that inaccuracies in the calculation of eGFR had no significant impact on our conclusions.

One may argue that pemetrexed excretion interferes with creatinine clearance, as both are partially eliminated by active tubular secretion. The organic anion transporter 3 (OAT3) is involved in pemetrexed elimination, while organic cation transporter 2 (OCT2) is responsible for the active secretion of creatinine. [41–43] However, OAT3 was also shown to be involved in creatinine excretion in mice [44]. Nevertheless, we consider the possible effects of pemetrexed on creatinine secretion not relevant for our analysis as end of treatment serum creatinine measurements were not performed within 24 h of pemetrexed administration. Pemetrexed has a relatively short half-life (3.5 h), whereas up to 90 % is excreted within the first 24 h [9].

In conclusion, this study shows that patients on pemetrexed-based treatment are at risk of developing clinically relevant renal impairment. Risk significantly increases with prolonged treatment, which suggests the cumulative dose of pemetrexed may be an important risk factor for the development of nephrotoxicity. Renal impairment is expected to become an even greater issue now that pemetrexed-based immunochemotherapy results in longer survival and thus longer treatment duration. Our data call for innovative interventions to allow safe and effective long-term treatment with pemetrexed. Also, further research is needed to investigate the incidence of renal impairment in patients using both pembrolizumab and pemetrexed, as well as the reversibility of renal impairment after discontinuing pemetrexed therapy.

5. Transparency document

The Transparency document associated with this article can be found in the online version.

CRediT authorship contribution statement

N. de Rouw: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing - original draft, Visualization, Supervision, Project administration. **R.J. Boosman:** Conceptualization, Methodology, Writing - original draft, Visualization, Supervision. **H. van de Bruinhorst:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Visualization. **B. Biesma:** Conceptualization, Writing - review & editing. **M.M. van den Heuvel:** Conceptualization, Methodology, Visualization, Writing - review & editing, Supervision. **D.M. Burger:** Conceptualization, Writing - review & editing, Supervision. **L.B. Hilbrands:** Conceptualization, Methodology, Visualization, Writing - review & editing, Supervision. **R. ter Heine:** Conceptualization, Methodology, Visualization, Writing - review & editing, Supervision. **H.J. Derijks:** Conceptualization, Methodology, Visualization, Formal analysis, Writing - review & editing, Supervision.

Declarations of Competing Interest

None.

Appendix A

Comedications affecting renal function (C.A. Naughton 2008)

- o Vancomycine
- o Aminoglycosides
- o Ciprofloxacine
- o Sulphonamides
- o Cotrimoxazol
- o NSAIDs (chronic use)
- o Herpes antivirals ((val)acyclovir, (valg)anciclovir, foscarnet)
- o Calcineurin inhibitors (tacrolimus, ciclosporin, pimecrolimus)
- o Antidiuretics (thiazides, triamterene, loop diuretics)
- o RAAS-inhibitors (ACE-inhibitors + ARB)
- o Methotrexate
- o Lithium
- o HIV antivirals (tenofovir + protease inhibitors)
- o Bisphosphonates iv
- o Amphotericin B (conventional and liposomal)
- o Allopurinol

Comorbidities

- o Hypertension,
- o Heart failture
- o Other CVD,
- o Diabetes,
- o Gout
- o COPD/asthma
- o Liver disease
- o Obesity
- o Prior renal disease

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