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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Better survival in impaired renal function patients with metastatic non-small cell lung cancer treated by cisplatin-pemetrexed

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Abstract

Purpose Cisplatin-pemetrexed is the first-line chemotherapy for advanced, metastatic non-squamous non-small cell lung cancer (NSCLC), but the risk of kidney toxicity limits the therapeutic schedule. We performed a retrospective study of patient survival at 1 year and glomerular filtration rate (GFR) outcomes in cisplatin-pemetrexed-treated NSCLC patients.

Methods Patients (P) treated for NSCLC between 2008 and 2014 were divided into two groups according to GFR at diagnosis: G1 (GFR ≥ 90 mL/min/1.73 m^2) and G2 (GFR between 60 and 89 mL/min/1.73 m^2). GFR were compared in the two groups at 3 and 12 months. The following statistical methods were used: multivariate generalized estimating equation model for GFR outcome, Kaplan-Meier method for patient survival rate, and Cox model for analysing survival criteria.

Results A total of 112 patients were included in the study (G1 = 87 P, G2 = 25 P). At 12 months, mean GFR significantly decreased by 28.4 mL/min/1.73 m^2 (− 22.3%, $p = 0.001$) in G1 and. 13.8 mL/min/1.73 m^2 (− 17.2%, $p = 0.001$) in G2. Median patient survival was 9.6 months (1.1–52.4) in G1 and 19.7 months (3.7–56.9) in G2. A better overall survival was significantly correlated with GFR between 60 and 89 mL/min/1.73 m^2 at diagnosis ($p = 0.04$), and higher cumulated doses of pemetrexed ($p = 0.003$) and cisplatin ($p = 0.001$).

Conclusion The better survival rate in G2 and its correlation with pemetrexed and cisplatin treatments suggest that, until other therapeutic choices become available, a cautious increase in dosage could be investigated as a way to improve poor prognoses.

Keywords Glomerular filtration rate · Non-squamous non-small cell lung cancer · Chronic renal failure · Cisplatin · Pemetrexed

Introduction

Lung cancer is an ongoing public health problem, accounting for 11.1% of new cancer cases in France and 20.2% of cancer deaths [1]. Non-squamous non-small cell lung cancer (NSCLC) accounts for more than one-third of these cases, the majority of which are diagnosed at a metastatic stage [2].

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Cisplatin-pemetrexed is one of the first-line chemotherapies for NSCLC, but the nephrotoxicity of these two compounds and their metabolites is well established [3–6]. Furthermore, more than half of patients with lung cancer have a glomerular filtration rate (GFR) below 90 mL/min/1.73 m^2 at diagnosis or during treatment [7].

However, the cisplatin-pemetrexed combination improves the overall survival of NSCLC patients regardless of their initial renal function [8]. There are few studies addressing the renal toxicity of the cisplatin-pemetrexed combination in patients with impaired renal function, but some studies have suggested that patients with renal impairment may have similar or even better overall survival [9, 10].

The aim of our retrospective study was to analyze overall patient survival and GFR at 1 year in patients with locally advanced or metastatic NSCLC after induction treatment with cisplatin plus pemetrexed. Patients were grouped according to renal function at diagnosis. Our secondary objectives were to compare progression-free survival and the reasons for the discontinuation of cisplatin-pemetrexed treatments.

Materials and methods

Patients, data collection, and study design

This retrospective observational monocentric study included all patients with locally advanced or metastatic NSCLC according to TNM classification (7th edition) first treated by cisplatin-pemetrexed chemotherapy in the Pulmonary Department of the Dijon University Hospital (France) from September 1, 2008 to July 1, 2014. Each patient must have received at least 1 cycle of chemotherapy, and serum creatinine levels were tested at least twice after cancer diagnosis.

The exclusion criteria were other treatments prior to the cisplatin-pemetrexed combination, patients lost to follow-up, glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 (MDRD) at diagnosis (according to the guidelines), altered cardiac function incompatible with overhydration (assessed on ultrasound), an identified genetic mutation for which the treatment with cisplatin-pemetrexed is replaced by a targeted therapy and an associated treatment with bevacizumab.

MDRD formula used is $186 \times (\text{creatinine } (\mu\text{mol/L}) \times 0.0113)^{-1.154} \times \text{age}^{-0.203}$ with adjustment for female sex (× 0.742) and Afro-American patients (× 1.21).

All patients received the same hydration protocol according to interregional recommendations. Pemetrexed was first administered at a dose of 500 mg/m^2 in 250 mL of saline infusion for 10 min. Cisplatin was given 30 min after the end of the pemetrexed infusion at a dose of 75 mg/m^2 in 250 mL of saline infusion for 1 h.

Patients underwent a chemotherapy cycle every 3 weeks and received at least 1 and at most 6 cycles of cisplatin-pemetrexed. Depending on the response to the treatment and tolerance, the patient then had either maintenance chemotherapy with pemetrexed, a second line of treatment, or monitoring alone (Fig. 1).

The medical file of each patient including drug doses was accessible via a hospital software database for clinical and paraclinical criteria for diagnosis and throughout follow-up. The date of the anatomopathological analysis confirming the histological diagnosis of cancer was fixed as the date of diagnosis. Serum creatinine levels were collected at diagnosis, and at 3, 6, and 12 months. The cumulative doses of cisplatin were calculated relative to the body surface of each patient to obtain comparable cumulative dose data per square meter of body surface area. The following reasons were recorded for discontinuing chemotherapy: nephrotoxicity, neurotoxicity, hematotoxicity, disease progression, other toxicities, and patient or physician's decision.

Overall survival was the time between the diagnosis of cancer and the death or the end of the study for living patients. Progression-free survival refers to the time between the first chemotherapy treatment and radiological or clinical progression.

Patients were divided into two groups of renal function at diagnosis: group 1 (G1) included patients with a GFR ≥

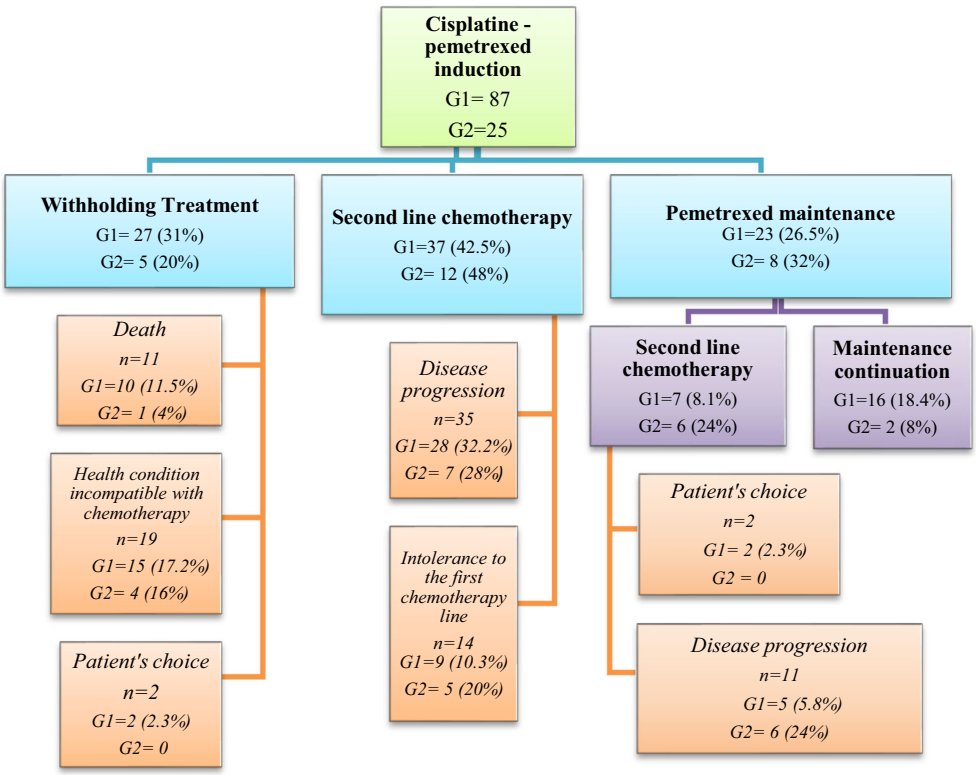

Fig. 1 Distribution of treatments received after first-line chemotherapy in G1 or G2 and the reasons for this choice (orange box). The number of patients per group and, in brackets, their proportion of the total number of patients in each group

90 mL/min/1.73 m^2. Group 2 (G2) included patients with 59 mL/min/1.73 m^2 < GFR < 90 mL/min/1.73 m^2 for at least 3 months.

Statistical analysis

Data were presented as means and standard deviations (SD) for continuous variables and as numbers and proportions (%) for qualitative variables. The *t* test or Kruskal-Wallis tests were used to compare averages. Percentages were compared using the Chi^2 test or Fisher's exact method. Multiple logistic regression was used to identify factors associated with GFR at diagnosis.

A multivariate generalized estimating equations (GEE) model was used for the correlated data in order to assess the time trend analysis of GFR. Survival (overall and progression-free survival) was estimated using the Kaplan-Meier method. The log rank test (or equivalently univariate Cox's proportional hazard model) was used to compare the overall and progression-free survival between the groups. A Cox model (with a robust variance estimator) was used to analyze overall and progression-free survival. Variables with a degree of significance $p < 0.20$ in univariate analysis were entered in the multivariate model. Harell's C index was used as an alternative measure of discrimination.

Scaled Schoenfeld residuals (graphical inspection and formal testing for a non-zero slope in a regression of the residuals on functions of time) were used to check the Cox model.

We found that cumulated doses of pemetrexed and cisplatin violated the proportional hazard assumption. Based on this result, we fit a Royston Parmar model [11].

The functional form of continuous variables was checked with Martingale residuals and by means of fractional polynomials.

All statistical tests were two-tailed, and $p < 0.05$ was considered to indicate statistical significance. Statistical analyses were performed with Stata (version 14). Goodness of fit was assessed with Cox-Snell residuals.

Results

Patient characteristics by group (Table 1)

Over a 6-year period, we recruited 112 patients with locally advanced or metastatic NSCLC received induction treatment with cisplatin plus pemetrexed. Eighty-seven patients (77.7%) were included in G1 (GFR ≥ 90 mL/min/1.73 m^2 at diagnosis) and 25 patients (22.3%) in G2 (GFR between 60 and 89 mL/min/1.73 m^2 at diagnosis). The two groups were not different for comorbidities, cancer stage, or histology, but G2 patients were significantly older at inclusion ($p = 0.005$), as seen in Table 1. All patients had adenocarcinoma except two patients in G1 and one patient in G2.

After induction treatment, patients received either pemetrexed maintenance (26.5% in G1 and 32.0% in G2) or a second-line treatment (42.5% in G1 and 48.0% in G2). As a result of death, altered health incompatible with chemotherapy, or patient choice, 31% of G1 and 20% of G2 did not receive other treatments (Fig. 1). The number and the cumulative doses of cisplatin ($p = 0.38$) and pemetrexed ($p = 0.5$) were not different in the two groups (Table 1).

Overall survival

The median survival was 9.6 months (range 1.1–52.4) for G1 and 19.7 months (range 3.7–56.9) for G2 and the number of survivors was significantly higher in G2 (28% vs 10.3%, $p = 0.01$) (Fig. 2). Better overall survival is significantly correlated with lower GFR at diagnosis (G2 group) ($p = 0.04$), and a higher cumulated dose of pemetrexed ($p = 0.003$) and cisplatin ($p = 0.001$) in univariate and multivariate analysis. Malnutrition is significantly associated with higher mortality (Table 2).

Progression-free survival

The median progression-free survival (PFS) was 3.8 months (0.2–49.7) for G1 and 8.3 months (0.7–25.4) for G2 ($p = 0.09$). In univariate and multivariate analysis, a higher PFS was positively correlated with the number of pemetrexed treatments ($p < 0.001$) and the cumulative dose of cisplatin ($p = 0.03$).

Impact of chemotherapy on renal function

Time trends analysis (Fig. 3)

At 3 months in both groups, GFR was not different from the initial values. At 12 months, mean GFR had significantly decreased by 28.4 mL/min/1.73 m^2 (− 22.3%, $p = 0.001$) for G1 and 13.8 mL/min/1.73 m^2 (− 17.2%, $p = 0.001$) for G2.

However, the slope of the decrease in GFR was not significantly different in the two groups during follow-up (Fig. 3): a mean GFR difference of 40 mL/min/1.73 m^2 is observed at day 1 and 1 year in the two groups. During follow up, mean GFR decreased by 1.7 mL/min/1.73 m^2 (CI 95% [− 2.5; − 0.9] $p < 0.001$) every month regardless of the group.

Prognostic factors for GFR outcome

The prognostic factors for decreasing renal function over time were age at diagnosis ($p < 0.001$), the length of follow-up ($p < 0.001$), and the cumulated doses of pemetrexed ($p < 0.02$).

Table 1 Comparison of general patient characteristics at diagnosis

	G1	G2	*p*
Patients, *n*	87	25	–
Female *n* (%)	36 (41%)	12 (48%)	*0.55*
Mean age (range)- years	58 (41–82)	63 (44–76)	***0.005***
Histology			
Adenocarcinoma	85	24	–
Cancer stage			
IIIB	5 (6%)	3 (12%)	–
IV	82 (94%)	22 (88%)	*0.37*
Comorbidities			
CVD *n* (%)	22 (25%)	11 (44%)	*0.07*
Diabetes *n* (%)	5 (6%)	2 (8%)	*0.65*
Smoking *n* (%)	75 (86%)	19 (76%)	*0.23*
Malnutrition *n* (%)	59 (68%)	13 (52%)	*0.14*
BMI *n* (range)	22.4 (14.5–37.5)	26.8 (18.7–40.3)	
Albumin g/L (range)	29 (16–42)	29.8 (21–43)	
Performance status at diagnosis			
0–1	61 (75.3%)	20 (83.3%)	*0.6*
2	20 (24.7%)	4 (16.7%)	
Unknown	6	1	
Renal function at diagnosis			
Mean serum creatinine levels (μmol/L)	***57.5 (30–108)***	***80.3 (61–111)***	***< 0.01***
Mean GFR (mL/min/1.73 m^2)	***127.7 (90–167)***	***79.8 (64–89)***	***< 0.01***
Median cumulated dose of cisplatin mg/m^2 BSA-(range)	290 (75–532)	257 (67–449)	*0.38*
Cisplatin cycle *n* median	4 (1–6)	4 (1–6)	
Median cumulated dose of pemetrexed mg/m^2 BSA (range)	1979 (494–11,617)	1991 (496–12,737)	*0.5*
Pemetrexed cycle *n* median	4 (1–23)	4 (1–25)	

G1 group 1 with initial GFR > 90 mL/min, *G2* group 2 with GFR between 45 and 90 mL/min, *n* number, *%* percentage, *CVD* cardiovascular disease, *BMI* body mass index, *GFR* glomerular filtration rate, *BS* body surface area

Statistical tests used = Fisher, Student, or Chi^2 test with $p < 0.05$

Causes of chemotherapy discontinuation

In both groups, disease progression was the leading cause of chemotherapy discontinuation, affecting 51 patients (58.6%) in G1 and 12 patients (48%) in G2 ($p = 0.34$). There were significantly more terminations for nephrotoxicity in G2 (20%, 5 patients) compared with G1 (4.6%, 4 patients $p = 0.02$). There were no significant differences for other types of toxicity or other causes of discontinuation.

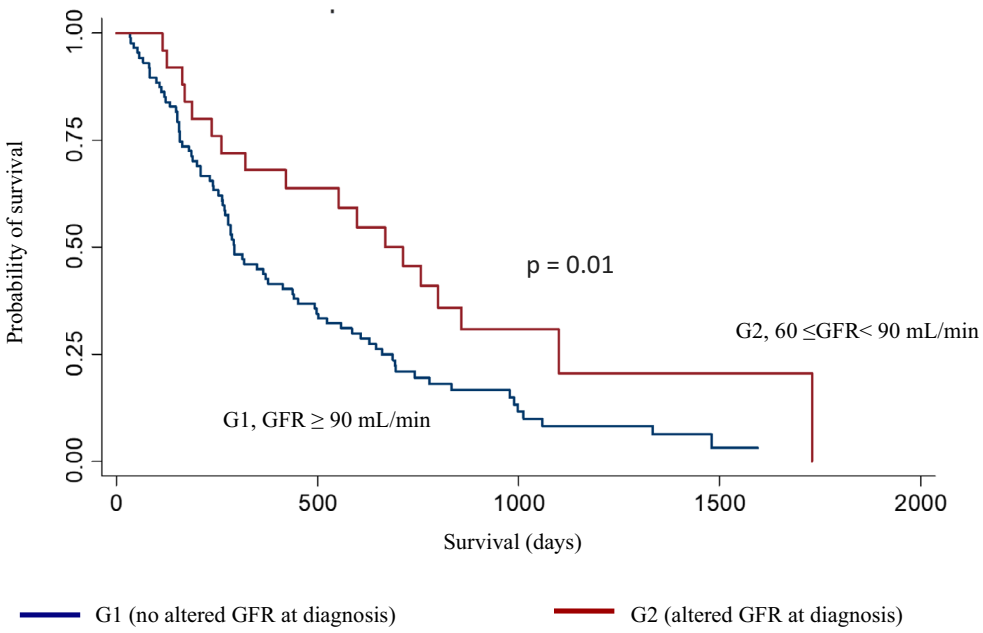

Fig. 2 Overall survival according to GFR at diagnosis: patient's survival is significantly greater in G2 than in G1

Table 2 Prognostic factors of overall survey

	Univariate[a]		Multivariate μ	
	HR	*p* value	HR	*p* value
G2 group	0.52 [0.31–0.86]	0.01	0.58 [0.34–0.97]	0.04
GFR at diagnosis	1.01 [1.01–1.02]	< 0.001	–	–
Age	1.00 [0.97–1.03]	0.92	–	–
Sex	1.03 [0.69–1.55]	0.86	–	–
Cumulated doses of cisplatin (mg/m^2 BSA)[b]	0.996 [0.993–0.999]	0.005	0.996 [0.993–0.998]	< 0.001
Cumulated doses of pemetrexed (mg/m^2 BSA)[b]	0.9998 [0.9997–0.9999]	< 0.001	0.9998 [0.9997–0.9999]	0.003
Malnutrition	2.55 [1.60–4.06]	< 0.001	3.14 [1.94–5.08]	< 0.001
Cardiovascular disease	1.29 [0.81–2.05]	0.29	–	–
Diabetes	1.26 [0.54–2.98]	0.59	–	–

[a] Cox regression model for univariate analysis and μ Royston Parmar test for multivariate analysis were used

[b] For one unit of chemotherapy

Discussion

In the literature, patient survival for advanced or metastatic NSCLC with cisplatin-pemetrexed as the first-line chemotherapy varies between 7 and 12 months [12–14], which is similar to what we observed in the present study. However, cisplatin treatment is now proposed with caution because of the negative effects it can have on renal function. Indeed, in initial treatment more than 70% of patients suffered kidney damage that was irreversible in some cases. Acute cisplatin toxicity is related to intracellular accumulation which promotes the activation of multiple pathways (MAPK, p53, ROS, TNF-α ...) followed by tubular cell death [3–5, 15]. The physiopathological mechanisms of chronic cisplatin toxicity remain poorly understood. Free cisplatin, which is the active form of the molecule, is excreted by glomerular filtration but also via tubular secretion [4]. Twenty to 35% of perfused cisplatin is found in the urine and clearance of free cisplatin is correlated with patients' creatinine clearance [14]. Recommendations from 2008 [16] have contributed to a decrease of between 5 and 10% in the prevalence of acute renal failure [17].

Pemetrexed is a treatment that appeared more recently, and its nephrotoxicity is due to the accumulation of polyglutamated pemetrexed in the tubular cells. This molecule is transported in tubular cells via the folate receptor. It is then converted into polyglutamate derivative by folyl polyglutamate synthetase. This prolongs the life span and increases the affinity of pemetrexed for the folate metabolism

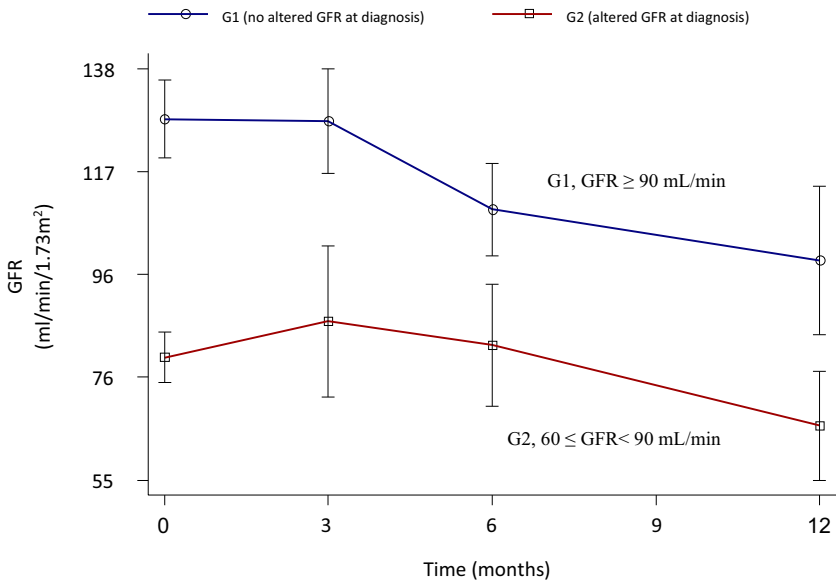

Fig. 3 Time trend of GFR according to initial renal function: GFR decrease is similar in both groups during follow-up

enzymes that they inhibit, causing cell death [18–20]. Chronic toxicity is probably related to this accumulation of polyglutamate, but the exact mechanisms are still poorly understood [6, 18]. Pemetrexed is essentially eliminated by the kidneys, and 70 to 90% of the injected dose is found in the urine [18]. When GFR decreases from 100 to 50 mL/min/1.73 m^2, the half-life of pemetrexed is increased and its area under the curve (AUC) is doubled [18]. Currently, the use of pemetrexed is not recommended in patients with a glomerular filtration rate of less than 45 mL/min [6, 21].

In our study, a significant drop in GFR at 1 year is obvious, regardless of the group. Indeed, renal impairment is clearly worse in patients treated with pemetrexed-cisplatin than in what is normally found in healthy patients. Thus, the decrease is on average of 28.4 mL/min/1.73 m^2/year in G1 against 1.24 to 1.90 mL/min/1.73 m^2/year in patients of the same age without cancer [22, 23]. For G2, the average decrease is from 13.8 mL/min/1.73 m^2/year against 1.06 to 1.12 mL/min/1.73 m^2/year [22]. However, during follow-up, the decrease in GFR is not different for the two treated groups. Chronic cisplatin nephropathy does not appear to be the main cause of GFR impairment because of the low doses received and the hydration protocol for nephrotoxicity prevention. So, the question of chronic nephrotoxicity related to pemetrexed arises. Indeed, our study found a significant association between the cumulative dose of pemetrexed and the alteration of GFR, while there is no correlation with the cumulative dose of cisplatin and GFR decrease. This chronic toxicity has already been described in some studies [19, 20], but other drugs used during treatment, including iodinated contrast media, can also promote kidney damages in such patients. For example, nonsteroidal anti-inflammatory drugs, which are also probably frequently used in this population, can add a direct nephrotoxicity, and increase the area under the curve of pemetrexed by 20% [24]. Our study was limited by the lack of information about other possible causes of renal impairment.

Interestingly, our study indicates that G2 had a higher 1-year overall survival (28.0% vs 10.3% $p = 0.01$) and also better median survival (19.7 months) than G1. Moreover, there was a trend to better PFS in these patients (HR = 0.70, $p = 0.09$). Our data reinforce the results of Cenik et al. [10], who found that creatinine clearance was inversely related to overall survival in 298 patients with NSCLC. However, this author used Cockcroft clearance and only 12% of patients had creatinine clearance below 60 mL/min. On the other hand, there are some studies that show poorer survival in patients with renal failure [25, 26]. It should be noted, however, that these studies concern patients with GFR < 60 mL/min/1.73 m^2 who do not have access to the same chemotherapy as patients with normal creatinine clearance.

Overall survival was correlated with the cumulative doses of cisplatin and pemetrexed in both univariate and multivariate tests. Progression-free survival is correlated with the cumulative doses of cisplatin and pemetrexed in univariate tests. The better convergent data in G2 than in G1 leads us to question the optimal doses of chemotherapy in patients without kidney failure. The optimal dose of cisplatin is currently undefined, and the use of high doses of cisplatin to improve survival remains controversial [27–30]. Gandara et al. [31] compared a low-dose arm (cisplatin 50 mg/m^2 on days 1 and 8) to a "high-dose" arm (100 mg/m^2) in stage IV NSCLC and observed a significantly higher response rate (12% vs 14%, $p < 0.05$) and slower progression (57% vs 38%, $p < 0.05$) in the "high-dose" arm. Furthermore, Gralla [32] reported better PFS (12 vs 5.5 months, $p = 0.05$) and overall survival (21.7 months vs 10 months, $p = 0.02$) with high doses of cisplatin (120 mg/m^2 vs 60 mg/m^2). In 2003, Schellens [33] suggested adapting cisplatin doses according to the AUC of cisplatin and DNA adducts in leukocytes. The initial dose of cisplatin was 70 mg/m^2, and 37 patients (49%) required a dose increase from 10 to 55%. The response rate was 40% for all patients. This individual approach seems more appealing than the adaptation of doses to the body surface, which may be insufficient given the variability of pharmacokinetics among individuals [34]. The individualization of the treatment for dose optimization seems relevant both in the patients with preserved and impaired renal function, but still needs to be developed. On the other hand, the studies testing high doses of pemetrexed did not show any improvement in overall survival and PFS or response rate [35, 36].

The retrospective and monocentric nature of our study may be a limitation. Nevertheless, the characteristics of our population and the causes of discontinuation of treatments are similar to those found in other studies [13, 37].

Finally, further studies are needed to clarify the pathophysiological mechanisms of chronic pemetrexed nephropathy or nephrotoxicity due to the association of the two molecules. However, the use of the combination cisplatin-pemetrexed [according to the recommendations of the French health authority] leads to better survival for patients with 60 mL/min/1.73 m^2 < GFR < 90 mL/min/1.73 m^2 than for patients with GFR ≥ 90 mL/min/1.73 m^2 at diagnosis. Overall survival and PFS were worse in patients with GFR > 90 mL/min/1.73 m^2. These convergent data [better patient survival, correlation between survival, and cisplatin-pemetrexed doses] suggest increasing chemotherapy doses to improve the prognosis. Until better treatments became available, it may be necessary to investigate a cautious approach to higher doses associated with close monitoring of renal function in patients with GFR > 90 mL/min/1.73 m^2.

Authors' contributions M LOUIS conceived the study, collected data, and wrote the manuscript.

P FOUCHER made available patient's data of the Pulmonary Department of the Dijon University Hospital, contributed to the writing and revision of the manuscript.

S AHO made all data statistic analysis, contributed to the writing and revision of the manuscript.

M BOULIN provided pharmacy's data, contributed to the writing and revision of the manuscript.

A ZOUAK contributed to the writing and revision of the manuscript.

C TINEL contributed to the writing and revision of the manuscript.

C MOUSSON conceived and oversaw the study, contributed to the writing and revision of the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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