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Original Research Article

A retrospective study on pemetrexed induced nephrotoxicity in non-small cell lung carcinoma patients

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ABSTRACT

Background: Pemetrexed (PEM) is a new-generation multitargeted antifolate agent that has been shown to have broad-spectrum efficacy in a variety of human cancers, including NSCLC and mesothelioma. Dose-limiting hematologic toxicities are among the most serious side effects. PEM nephrotoxicity is well-known, but its occurrence is thought to be rare. Aim was to determine nephrotoxicity induced due to pemetrexed in non-small cell lung cancer patients.

Methods: In patients with the NSCLC, we record a retrospective review on PEM- induced renal toxicity. A total of 327 NSCLC patients were treated in our hospital between 2012 and 2019. Of these, 134 patients were diagnosed with 2 or more chemotherapy cycles. 60 of these patients have been diagnosed with combination of antineoplastic drugs based on pemetrexed and platinum. Others were removed from the study and were also required to be tested for other potential causes of renal injury.

Results: Suitable statistical tools were used and data was analysed which showed that repeated chemo cycles of pemetrexed leads to the reversible acute kidney injury. With the results from our study we can understand the severity of nephrotoxicity induced with pemetrexed in patients with non-small cell lung cancer. Most of the patients were in the first and second stages of nephrotoxicity and most of them were male. Majority of the patients were also above 40 years of age and also endured more than 4 chemo cycles.

Conclusions: It shows that PEM allows longer survival, but acute or chronic kidney failure is the price for this achievement. In conclusion, renal toxicity should be controlled routinely in patients treated with pemetrexed. Before each cycle of pemetrexed, creatinine clearance should be measured. Patients need to be well hydrated during treatment. The patient should also be tested for concomitant medications, and any nephrotoxic symptoms should be reviewed and those drugs removed.

Keywords: Acute kidney injury, GFR, Non-small cell lung cancer, Pemetrexed

INTRODUCTION

Pemetrexed (PEM) is an antifolate antineoplastic agent that has demonstrated clinical effectiveness in patients with non-small cell lung cancer (NSCLC) and mesothelioma that have advanced or metastatic disease. PEM has been shown to function as a thymidylate synthase inhibitor, interfering with DNA synthesis, resulting in decreased cell growth and apoptosis.¹ PEM is an

antineoplastic drug that can be used alone or in conjunction with other antineoplastic drugs like cisplatin. PEM's major side effects are myelosuppression and hepatotoxicity, all of which can be avoided with folic acid supplementation. Rashes, mucositis, nausea, and vomiting are some of the other side effects.²⁻⁵ PEM nephrotoxicity is well-known, but its occurrence is thought to be rare. Renal damage's physiopathological mechanisms are unclear.³⁻⁶ Acute kidney injury (AKI) with or without tubular necrosis,

distal tubular acidosis, or interstitial nephritis has been recorded in the international literature, and AKI has been linked to diabetes insipidus in a few cases. Renal biopsy was performed on a small number of patients.⁷⁻¹⁰

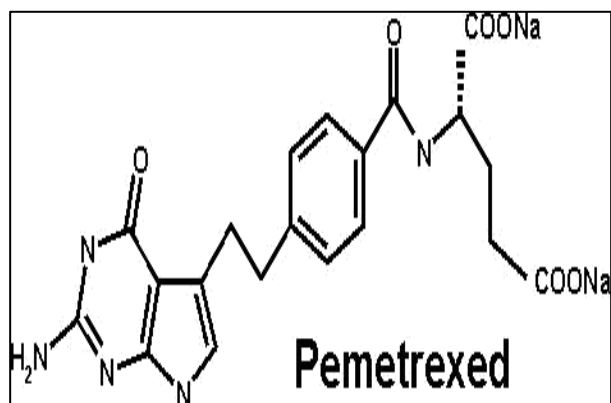


Figure 1: Structure of pemetrexed.²

Objectives of the study

The study was carried out to find out the incidence of nephrotoxicity occurred due to the use of pemetrexed in non-small cell lung cancer patients who underwent more than 2 chemo cycles. To compare the fluctuations in the renal parameters before the initiation of chemo cycles and after every chemo cycle.

METHODS

In patients with the NSCLC, we record a retrospective review on PEM- induced renal toxicity. A total of 327 NSCLC patients were treated in our hospital between 2012 and 2019. Of these, 134 patients were diagnosed with 2 or more chemotherapy cycles. 60 of these patients have been diagnosed with combination of antineoplastic drugs based on pemetrexed and platinum. Others were removed from the study and were also required to be tested for other potential causes of renal injury.

Sample size

A total of 50 patients were included in the study.

Study site

This study was conducted in the department of Oncology, Krishna institute of medical sciences (KIMS) hospital.

Study design

It was a retrospective observational study.

Study period

This study was conducted for a period of 6 months.

Inclusion criteria

Adults (≥ 18 years of age) whose conditions with lung cancer, patient cases of either sex, patients treated with Pemetrexed with or without combination platinum- based drugs.

Exclusion criteria

Pregnant and lactating women. Paediatrics.

Source of data

Parameters

Following parameters were studied: creatinine, GFR, age, RBC, WBC, platelets.

Methodology

All the subjects who attended chemotherapy unit in Krishna institute of medical sciences-Secunderabad, who are diagnosed with nephrotoxicity and willing to give consent, were included in current study.

Subjects based on inclusion and exclusion criteria were selected, and demographic details were collected from case sheets, and the objective data was collected from hematological and renal reports from HIMS.

The data had been collected for a study period of 6 months. The secondary objectives were collected from findings and analysed for results. Variables included in this study were age, presence of comorbid conditions like hypertension and DM or any kidney injury, and variables collected for the study are creatinine, GFR, RBC, WBC, platelets.

All the data had been collected in a structured proforma, and collected data has been analysed according to statistical tools, and results were concluded.

Statistical analysis

All the data collected was tabulated in a Microsoft Excel spreadsheet in a master chart and analysed using suitable statistical tools. This analysed the data with a chi-square test, analyses the information and calculates the mean for each patient, then calculated the mean of all the data, and performed a chi-square test. The p value amount was determined, and the average was also estimated.

Ethical considerations

Institutional human ethics committee approval was obtained. Informed written consent was obtained from all the study participants, and only those willing to sign the informed consent were included in the study. The confidentiality of the study participants was maintained.

RESULTS

In our retrospective study, a total of 50 patients with treatment using pemetrexed were enrolled as per inclusion and exclusion criteria from the chemotherapy department of oncology, Krishna institute of medical sciences (KIMS).

P value was found to be less than 0.05, which proves that our study was significant, and patients treated with pemetrexed were suffering from nephrotoxicity.

Among the 50 patients 23 patients were under the stage I nephrotoxicity (GFR> 90 ml/min/1.73 m), 16 patients were under stage II nephrotoxicity (GFR 60-89 ml/min/1.73 m), 6 patients under stage IIIa nephrotoxicity, 2 patients under stage III b nephrotoxicity (GFR 30-59 ml/min/1.73 m), and 3 patients under stage IV nephrotoxicity (GFR 15-29 ml/min/1.73 m). PEM was administered in combination with cisplatin in about 28 patients (56%), and with carboplatin in about 13 patients (26%), with taxol in 5 patients (10%), with steroid in 4 patients (8%). Among them, 11 patients had (column A) AKI (22%), and 39 patients are grouped as (column B) non-AKI (78%). Based on the information regarding the patients with AKI and non-AKI, the statistical analysis performed was unpaired t-test, and the p value obtained was (p<0.0001) (two-tailed p value) and it was significant as (p<0.05) t=13.70, df=48.

The mean of column A was 85.75, and the mean of column B was 42.71. Difference between means (B-A)-43.03±3.140). 95% confidence interval (-49.35 to -36.72) and R squared (eta squared) = 0.7965. F test to compare the variances F- 4.035, DFn- 10, Dfd- 38. P value (p=0.0016) significantly different as p<0.05.

Demographic details

Following demographic details of the patients were observed: number of patients (Figure 2), health status of the patients (Figure 3), age group of the patients (Figure 4), dose of pemetrexed (Figure 5), stages of nephrotoxicity (Figure 6), number of cycles given (Figure 7), combination with pemetrexed given (Figure 8).

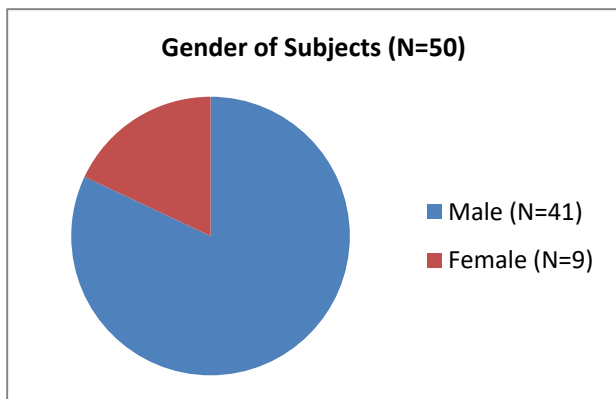


Figure 2: Grouping based upon the gender of subjects.

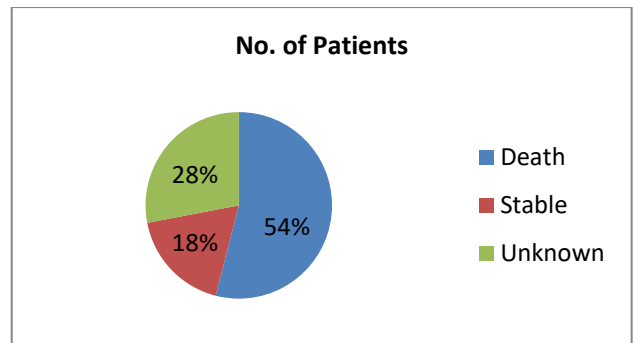


Figure 3: Health status of the patients.

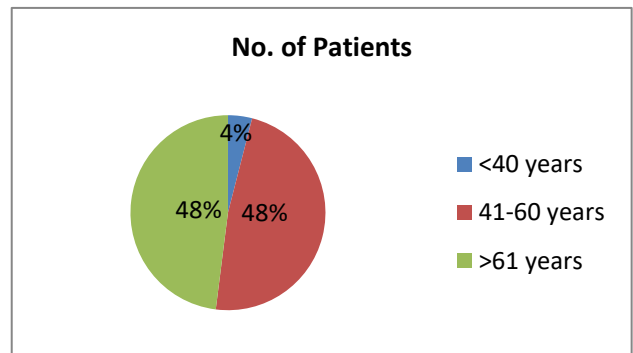


Figure 4: Grouping based upon the age of the subjects.

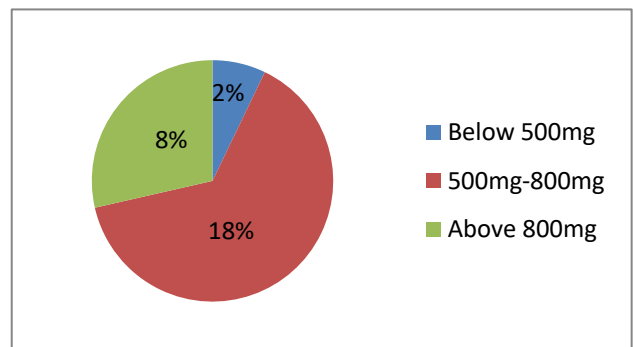


Figure 5: Grouping based upon the doses of pemetrexed.

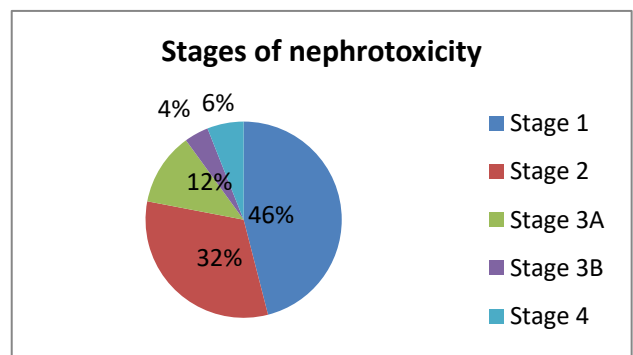


Figure 6: Grouping based upon the stages of nephrotoxicity.

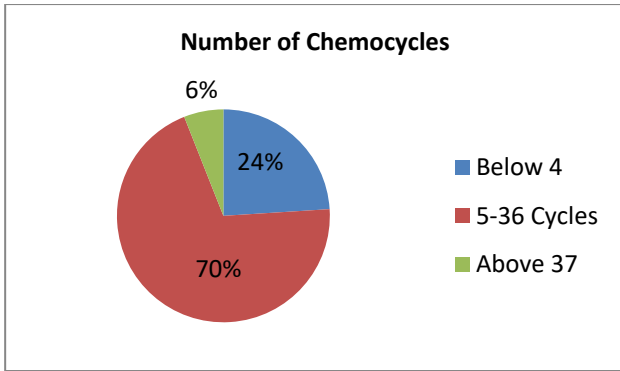


Figure 7: Grouping based upon number of chemo cycles.

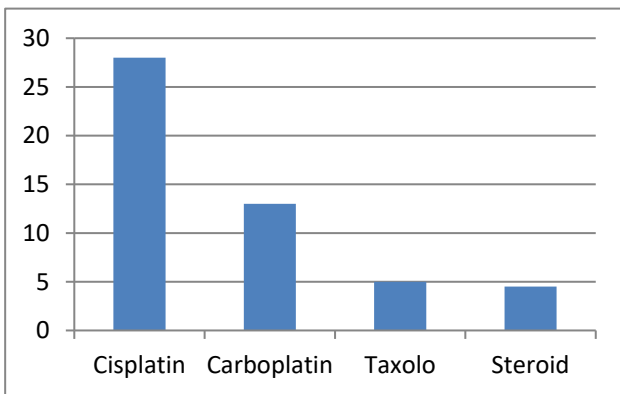


Figure 8: Number of patients versus combination drugs.

DISCUSSION

PEM (Alimta®) is an antifolate antineoplastic agent that is effective in a variety of tumour forms, including NSCLC and mesothelioma. The recommended dosage is 500 mg/m² intravenous once every 21 days as a single agent or in combination with cisplatin.⁸ The substance is not significantly metabolised. Since approximately 80% of it is fully removed unchanged by the renal emunctory, it is contraindicated if creatinine clearance is less than 45 ml/minute.⁹⁻¹¹ The drug is bound to plasma proteins up to 80% of the time, the apparent delivery volume is 16 l, and the molecular weight is 476.4 kDa. PEM nephrotoxicity is well-known, but its occurrence is thought to be rare. The Food and Drug Administration (FDA) reports a 2.4 percent incidence of AKI. Tubular and interstitial damage to the kidneys causes anything from acute kidney failure to chronic kidney failure. The lack of data on PEM nephrotoxicity is due to its frequent interaction with other drugs, especially cisplatin.^{12,13}

Although the pathogenic mechanism of renal injury is unknown, a disruption between the PEM uptake carrier (folate receptor, FR-) and the basolateral transporters carrier (reduced folate carrier, RFC) of the proximal tubular cells has been proposed; hence, cytotoxicity is linked to an antifolate effect that impairs DNA and

RNA.^{14,15}

Furthermore, proximal tubular damage, even if mild, could increase drug nephrotoxicity, as demonstrated in an experimental study published in 2005, since the proximal tubule is the place where folate is reabsorbed via FR- and RFC carriers.¹⁶ Furthermore, an acidic environment increases folate absorption while a high urine flow decreases it, implying that fluid and alkaline solution administration may increase folate excretion and thus reduce its protective effects.¹⁷

The role of PEM in the production of AKI is undeniable in the cases discussed in our study. Despite the well-known nephrotoxicity of both medications, the patient was given PEM in combination with NSAIDs until the end. Only after the fourth cycle was administered, and in the absence of all other potentially nephrotoxic agents, did the patients undergo renal failure.⁸ Although several AKI risk factors were present (dehydration, NSAID use, and radiocontrast agents), none of them appeared to be the cause of kidney injury. However, we can't rule out the possibility that these variables play a role.^{9,13}

Michels et al and Stavroupoulos et al published one case report each, in which both patients underwent kidney biopsy.^{18,19} The first developed acute tubular necrosis and interstitial nephritis after six cycles, the latter interstitial nephritis and diabetes insipidus after only four cycles.

Glezerman et al describes three patients who developed chronic kidney disease while undergoing maintenance therapy with PEM.²⁰ Kidney biopsy specimens showed tubulointerstitial injury with tubular simplification, shrinkage, and tubular atrophy. Kidney function remained impaired, but stable, after discontinuation of PEM therapy. The first patient described showed appearance of glycosuria caused by tubular damage.

Chauvet et al report two cases of AKI with biopsy-proven renal tubular toxicity.²¹ Renal toxicity in both patients was associated with face edema, a rare side effect of the drug.

We assume that the following factors contribute to PEM-induced acute kidney damage: 1) a sarcopenic GFR, 2) a decrease in total body water and hypoalbuminemia, which can lead to a rise in drug concentration, and 3) nephrotoxic combination drugs. Acute tubular necrosis, tubular atrophy with chronic interstitial injury, and acute interstitial nephritis have been found in kidney biopsies in patients with PEM-associated AKI in the literature.^{17,18}

However the only limitation of our study was by the time of our research (retrospective) most of the patients were deceased and other co-morbidities could not be accessed.

CONCLUSION

It shows that PEM allows longer survival, but acute or chronic kidney failure is the price for this achievement. In

conclusion, renal toxicity should be controlled routinely in patients treated with pemetrexed. Before each cycle of pemetrexed, creatinine clearance should be measured. Patients need to be well hydrated during treatment. The patient should also be tested for concomitant medications, and any nephrotoxic symptoms should be reviewed and those drugs removed.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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