Regular Article

Pemetrexed-Induced Rash May Be Prevented by Supplementary Corticosteroids

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Received May 22, 2015; accepted August 15, 2015

Pemetrexed, a chemotherapeutic drug, is highly active in non-small cell lung cancer and malignant pleural mesothelioma. Unfortunately, rashes are more commonly associated with pemetrexed than other chemotherapies, and it is recommended that patients receive corticosteroids (8 mg/d of dexamethasone) for 3 d, including the day of pemetrexed administration (day 1). However, the efficacy of corticosteroids in this context has not been fully verified. In this retrospective study, we evaluated the medical records of 78 patients who received pemetrexed between April 2009 and March 2014, to confirm whether supplementary corticosteroids prevented rash development. The incidence of rash was lower in the 47 patients who received supplementary corticosteroids (after day 1) compared with the incidence among the 31 patients who did not receive supplementary corticosteroids (19.1% vs. 38.7%). The average cutoff dosage of supplementary corticosteroids on day 2 and day 3 was 1.5 mg/d of dexamethasone, as calculated using the receiver operating characteristic curve, and the odds ratio was 0.33 (95% confidence interval: 0.12–0.94). Administration of ≥ 1.5 mg of corticosteroids on day 2 and day 3 significantly reduced the severity of the rash compared to no supplementary treatment (grades 2/3, 13.3% vs. 33.3%, $p < 0.05$). However, increasing the dose of corticosteroids had no additional effect on rash development. These results suggest that ≥ 1.5 mg of supplementary dexamethasone on day 2 and day 3 (in addition to day 1) may be necessary for preventing pemetrexed-induced rash, but high doses of dexamethasone (e.g., 8 mg/d) are unnecessary.

Key words pemetrexed; rash; dexamethasone; corticosteroid; risk factor

Pemetrexed (Alimta, Eli Lilly and Co.) is a novel multitargeted antifolate that inhibits thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase.^{1,2)} These multiple targets may explain the broad and preferable antitumor activity of pemetrexed, which has been evaluated in non-small cell lung cancer (NSCLC), malignant pleural mesothelioma (MPM), head, neck, cervical, breast, gastric, colorectal, pancreatic, and bladder cancers.^{3–14)} Pemetrexed is currently approved in combination with platinum (cisplatin or carboplatin) as a first-line treatment, and as a single-agent second-line treatment, for MPM and NSCLC.^{15,16)} Moreover, cisplatin plus pemetrexed provides improved survival and reduced toxicity in patients with non-squamous NSCLC, compared to cisplatin plus gemcitabine.¹⁷⁾

Interestingly, multivariate analysis has revealed that increasing levels of homocysteine and methylmalonic acid are correlated with a toxic increase in pemetrexed.¹⁸⁾ The risks associated with severe pemetrexed toxicity, such as neutropenia, thrombocytopenia, infection, and diarrhea, can be reduced by decreasing homocysteine and methylmalonic acid levels by supplementing patients with folic acid and vitamin B₁₂.¹⁸⁾ Unfortunately, rash is one of the most common adverse events that is associated with pemetrexed treatment. In a phase I trial (solid tumors) and a phase II trial (NSCLC), the incidence of

rash without corticosteroids was 90.3% and 73.8%, respectively.^{19,20)} In contrast, rash occurred in only 32.0% of patients who were treated with cisplatin and pemetrexed, with supplemental corticosteroids to prevent nausea and vomiting.²¹⁾ Moreover, in several clinical trials to evaluate the efficacy and safety of pemetrexed, patients who received pemetrexed with dexamethasone (4 mg orally twice daily for 3 d, including the day of pemetrexed administration [day 1]) tended to have a lower frequency and severity of rash.^{3,12,22)} Therefore, it is recommended that patients receive dexamethasone to prevent rash when undergoing pemetrexed treatment. However, it is unclear whether corticosteroids can ameliorate pemetrexed-induced rash.

In this retrospective study, we assessed whether supplementary corticosteroids reduced the incidence of rash. In addition, we evaluated the association between rash development and the corticosteroid dosage or period of administration.

MATERIALS AND METHODS

Patients and Methods We retrospectively investigated the medical records of patients with MPM or NSCLC who were treated with pemetrexed for the first time between April 2009 and March 2014 in the Department of Respiratory Medi-

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cine and Rheumatology at Tokushima University Hospital. These patients received corticosteroids as clinical practice for various purposes, such as preventing nausea and vomiting. Recorded patient characteristics included age, sex, laboratory data, body temperature, Eastern Cooperative Oncology Group performance status (PS), histology, clinical staging, history of treatment, dosage or period of corticosteroids for 1 week after pemetrexed administration, and the presence of a pemetrexed-induced rash within 3 weeks of treatment. We excluded all patients who might have developed a rash due to antibiotic treatment, as we would not have been able to evaluate the influence of pemetrexed. In addition, we excluded patients who had received corticosteroids for long periods (>2d after pemetrexed administration).

Creatinine clearance was calculated as described by Cockcroft and Gault.²³⁾ Fever and C-reactive protein (CRP) levels were evaluated within 1 week of pemetrexed administration, before the patient developed hematological toxicity. We defined CRP elevation as an increase from below the mild level (<1.0mg/dL) to above the moderate level (1.0–10.0mg/dL), or from below the moderate level to above the severe level (>10.0mg/dL). The dosage of supplementary corticosteroids was converted into a corresponding dosage of dexamethasone. Adverse events following pemetrexed administration were evaluated according to the Common Terminology Criteria for Adverse Events version 3.0.

This study protocol was reviewed and approved by the Ethics Committee of Tokushima University Hospital (approval number: 1403).

Statistical Analysis We used Ekuseru-Toukei 2011 software (Social Survey Research Information Co., Tokyo) to conduct the statistical analyses. All comparisons between groups were performed by using the χ^2 test or Fisher's exact test, as appropriate. We calculated the area under the receiver operating characteristic (ROC) curve to estimate the cutoff value for dosage of corticosteroids. Univariate analyses were performed to identify the relationship between pemetrexed-induced rash and corticosteroids or other factors. *p*-Values of <0.05 were considered statistically significant.

RESULTS

Patient Characteristics The clinical characteristics of the 78 patients who were included in this study are listed in Table 1. The median age was 67.5 years (range, 43–84 years), and 15 (19.2%) patients were ≥ 75 years old. Regarding the histological type of the cancer, 73 (93.6%) patients had NSCLC and 5 (6.4%) patients had MPM. Pemetrexed was frequently administered as a single agent (38/78, 48.7%), or in combination with cisplatin (10/78, 12.8%), carboplatin (17/78, 21.8%), or bevacizumab (21/78, 26.9%). Most patients received 500mg/m² of pemetrexed, although one patient received a lower dose of pemetrexed (400mg/m²) based on their clinical condition. Patients were instructed to begin taking folic acid (500 μ g/d) orally at least 1 week before pemetrexed administration (day 1). Vitamin B₁₂ (1 mg) was provided by intramuscular injection at least 1 week before day 1, and the injection was repeated every 9 weeks. Corticosteroids were administered to all patients as clinical practice for anticipated side effects, such as vomiting, nausea, fatigue, and rash.

The Incidence Rate and Risk Factors for Pemetrexed-

Table 1. Patient Characteristics

No. of patients	78
Age (years)	
Median (range)	67.5 (43–84)
Sex	
Female	34 (43.6%)
Male	44 (56.4%)
Performance status	
0/1	67 (85.9%)
2/3	11 (14.1%)
Histology	
Malignant pleural mesothelioma	5 (6.4%)
Adenocarcinoma	63 (80.8%)
Squamous cell carcinoma	1 (1.3%)
NSCLC (NOS)	8 (10.3%)
Others	1 (1.3%)
Stage	
$\leq$ IIB	2 (2.6%)
IIIA/IIIB	9 (11.5%)
IV	67 (85.9%)
Previous chemotherapy	
Yes	55 (70.5%)
No	23 (29.5%)
PEM regimen	
PEM alone	38 (48.7%)
PEM+CDDP	7 (9.0%)
PEM+CBDCa	12 (15.4%)
PEM+bevacizumab	13 (16.7%)
PEM+CDDP+bevacizumab	3 (3.8%)
PEM+CBDCa+bevacizumab	5 (6.4%)

NSCLC, non-small cell lung cancer; NOS, not-otherwise specified; PEM, pemetrexed; CDDP, cisplatin; CBDCa, carboplatin.

Induced Rash Among the 78 enrolled patients, 21 (26.9%) patients developed pemetrexed-induced rash that corresponded to grades 1 (5.1%), 2 (19.2%), and 3 (2.6%). The incidence of pemetrexed-induced rash was low among patients who received supplementary corticosteroid treatment after day 1, compared to among patients who did not receive supplementary treatment (19.1% vs. 38.7%), although this difference was not statistically significant (Table 2). Similarly, no significant differences were observed for all patient characteristics between the groups that did and did not develop pemetrexed-induced rash (Table 2).

The Effect of Supplementary Corticosteroids on Pemetrexed-Induced Rash Because previous studies have reported that 3d of corticosteroid treatment (including day 1) can effectively ameliorate pemetrexed-induced rash,^{3,4,12,22,24)} we also investigated the effect of supplementary corticosteroids. The cutoff value was found to be 1.5mg of dexamethasone based on the ROC curve, which was calculated using the average dosage of the supplementary corticosteroids (area under the curve: 0.63). In the univariate analysis, supplementary corticosteroid treatment (≥ 1.5 mg of dexamethasone) on day 2 and day 3 was the only factor that affected rash development, and the odds ratio (OR) for supplementary corticosteroid treatment was 0.33 (95% confidence interval [CI]: 0.12–0.94) (Table 3). Administration of ≥ 1.5 mg of dexamethasone on day 2 and day 3 significantly reduced the frequency and severity of rash compared to no supplementary treatment (all grades, 17.8% vs. 39.4%, $p < 0.05$; grades 2/3, 13.3% vs. 33.3%, $p < 0.05$) (Table

3). Interestingly, supplementary corticosteroids on day 2 and day 3 had no dose-dependent effect on rash development (Fig. 1).

The Effect of Supplementary Corticosteroids on Other

Table 2. The Relationships between Clinical Variables and Pemetrexed-Induced Rash

Variables	Rash		<i>p</i>	Univariate analysis Odds ratio (95% CI)
	None	Incidence (%)		
Age				
<75 years	44	19 (30.2)	0.33 ^{b)}	0.36 (0.07–1.73)
≥75 years	13	2 (13.3)		
Sex				
Female	25	9 (26.5)	0.94 ^{a)}	1.04 (0.38–2.86)
Male	32	12 (27.3)		
Creatinine clearance				
≥45 mL/min	51	20 (28.2)	0.67 ^{b)}	0.43 (0.05–3.76)
<45 mL/min	6	1 (14.3)		
Performance status				
0/1	48	19 (28.4)	0.72 ^{b)}	0.56 (0.11–2.84)
≥2	9	2 (18.2)		
Previous chemotherapy				
None	18	5 (21.7)	0.51 ^{a)}	1.48 (0.47–4.66)
Exist	39	16 (29.1)		
Supplementary corticosteroids*				
None	19	12 (38.7)	0.06 ^{a)}	0.38 (0.13–1.04)
Exist	38	9 (19.1)		
Bevacizumab combination				
No	42	15 (26.3)	0.84 ^{a)}	1.12 (0.37–3.42)
Yes	15	6 (28.6)		
Platinum-based combination				
No	35	16 (31.4)	0.22 ^{a)}	0.50 (0.16–1.55)
Yes	22	5 (18.5)		

*Supplementary corticosteroids on day 2 and day 3 after the day of pemetrexed administration. a) χ^2 test. b) Fisher's exact test.

Adverse Events Pemetrexed has other common adverse events, which include hepatopathy, transient fever, and elevated CRP levels. Among the patients without supplementary corticosteroid treatment after day 1, high incidences of elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transpeptidase (γ -GTP) levels were detected (Table 4). In contrast, supplementary corticosteroids suppressed transient fever (6.5% vs. 22.6%) and elevated CRP levels (25.6% vs. 44.4%) (Table 4), although these differences were not statistically significant (Table 4).

DISCUSSION

Pemetrexed is associated with a high incidence of rash, and is occasionally responsible for more severe symptoms, such as acute generalized exanthematous pustulosis²⁵⁾ and Lyell's syndrome.^{26,27)} Therefore, it is important to prevent the development of rash and to decrease its severity. Pemetrexed is asso-

Fig. 1. The Effect of Supplementary Corticosteroids on Day 2 and Day 3 after the Day of Pemetrexed Administration

n.s.; not statistically significant.

Table 3. The Effect of Supplementary Corticosteroids on Pemetrexed-Induced Rash among the 78 Patients Who Only Received Corticosteroids for 3 d

Supplementary corticosteroids	All grades			Grades 2 and 3			Median (range)
	Rash incidence (%)	Odds ratio (95% CI)	<i>p</i> ^{a)}	Rash incidence (%)	Odds ratio (95% CI)	<i>p</i> ^{a)}	
Dose on day 2 and day 3							
Dexamethasone <1.5 mg (<i>n</i> =33)	13 (39.4)			11 (33.3)			6.5 (4–10)
Dexamethasone ≥1.5 mg (<i>n</i> =45)	8 (17.8)	0.33 (0.12–0.94)	0.04	6 (13.3)	0.31 (0.10–0.95)	0.04	6 (2–14)

a) Univariate analyses.

Table 4. The Effect of Dexamethasone on the Other Adverse Events That Were Associated with Pemetrexed Therapy

Variables	All grades			Grade 3		
	Supplementary corticosteroid incident no./all no. (%)		<i>p</i>	Supplementary corticosteroid incident no./all no. (%)		<i>p</i>
	Non-administration	Administration		Non-administration	Administration	
AST	7/31 (22.6)	15/47 (31.9)	0.37 ^{a)}	1/31 (3.2)	2/47 (4.3)	1.00 ^{b)}
ALT	6/31 (19.4)	13/47 (27.7)	0.43 ^{a)}	1/31 (3.2)	1/47 (2.1)	1.00 ^{b)}
T-BiL	7/29 (24.1)	10/47 (21.3)	0.77 ^{a)}	1/29 (3.4)	0/47 (0.0)	0.38 ^{b)}
γ -GTP	3/29 (10.3)	9/47 (19.1)	0.35 ^{b)}	0/29 (0.0)	0/47 (0.0)	—
Transient fever	7/31 (22.6)	3/46 (6.5)	0.08 ^{b)}	0/31 (0.0)	0/46 (0.0)	—
CRP elevation	12/27 (44.4)	11/43 (25.6)	0.10 ^{a)}			

AST, aspartate aminotransferase; ALT, alanine aminotransferase; T-BiL, total bilirubin; γ -GTP, gamma-glutamyl transpeptidase; CRP, C-reactive protein. a) χ^2 test. b) Fisher's exact test.

ciated with rash in 70–90% of patients who have not received corticosteroids, compared to in 14–50% of patients who have received corticosteroids.^{3,19–21,28} However, one phase II study failed to mention the dose and dosing period of dexamethasone, and the efficacy of dexamethasone for rash prevention was not statistically analyzed.³ In addition, two Japanese clinical trials did not give corticosteroids to all patients,^{19,20} and supplementary corticosteroids were given to all patients for the prevention of nausea and vomiting in other trials.^{21,28} Therefore, the statistical efficacy of corticosteroids for rash prevention in Japan remains unknown. As corticosteroid-associated adverse events are known to be dependent on the dose and duration of treatment, patients should receive the lowest possible dose of corticosteroids.

Previous studies have reported the ability of supplementary corticosteroids to suppress pemetrexed-induced rash, although this effect was not statistically significant.^{24,29} Ishikawa *et al.* reported that the incidence of pemetrexed-induced rash was lower in patients who received supplementary corticosteroids, compared to that in patients who did not receive supplementary corticosteroids, although this difference was not statistically significant (23.5% vs. 36.2%, $p=0.17$).²⁴ However, the absence of statistical significance might be related to the relatively low number of patients who were enrolled in that study ($n=81$). In addition, those authors did not evaluate a cutoff dose or the dosing period. Another study has reported insignificant efficacy for corticosteroids, although that study only enrolled 23 patients.²⁹ Furthermore, the authors re-counted patients who received multiple courses of pemetrexed therapy, and only used the Wilcoxon's t test and Fisher's exact test. These methodological considerations may be responsible for the reported insignificant effect of supplementary corticosteroids on pemetrexed-induced rash. In the present study, we identified the effective cutoff dose of supplementary corticosteroids (≥ 1.5 mg/d dexamethasone on day 2 and day 3) for rash prevention after pemetrexed treatment. Even when the patients were treated with supplementary corticosteroids on day 2 and day 3, rash occurred in 17.8% of the patients; increasing the dose of corticosteroids had no additional effect on rash development. Therefore, it may be necessary to continue corticosteroid administration for >3 d, or to provide antihistamine agents, for patients who exhibit pemetrexed-induced rash.

In this study, all patients received at least 3.3 mg dexamethasone on day 1 to prevent nausea and vomiting. The incidence of rash in the patients who did not receive supplementary corticosteroids was lower in this study, compared to that in the previous clinical trials.^{3,19} In addition, there was no correlation between the dose of dexamethasone and the incidence of rash in the patients who only received dexamethasone on day 1 (OR: 0.71, 95% CI: 0.11–4.51). Therefore, receiving 3.3 mg dexamethasone on day 1 might also be sufficient to prevent pemetrexed-induced rash.

Interestingly, pemetrexed is primarily excreted by the kidneys, and reduced renal function results in reduced clearance of pemetrexed and a subsequent increase in exposure.³⁰ Therefore, it appears that rash development was independent of pemetrexed levels in the blood, as renal function did not correlate with rash development. However, one of the extraordinarily frequent adverse events of pemetrexed treatments is hepatic toxicity.²⁰ Supplementary corticosteroids did not sig-

nificantly affect the elevated hepatic function after pemetrexed treatment, although the corticosteroids did appear to exacerbate the elevation in AST, ALT, and γ -GTP levels. Fortunately, supplementary corticosteroid treatment had no effect on grade 3 hepatic toxicity in this study, although a lower corticosteroid dose is considered appropriate, given the toxicity that is associated with pemetrexed. Similarly, pemetrexed treatment often causes transient fever and elevated CRP levels. In several cases, these decreased the patients' quality of life and resulted in unnecessary antibacterial agents being prescribed. Therefore, supplementary corticosteroid treatment may help reduce the number of unnecessary prescriptions by reducing the incidence of fever or elevated CRP levels.

This study retrospectively evaluated patients' medical records, and we demonstrated that corticosteroids were only effective for a range of dexamethasone doses (≥ 1.5 mg), which is a major limitation of this study. Furthermore, we determined the dexamethasone cutoff value using the ROC curve, although the area under the curve value (0.63) was relatively low. Therefore, further studies should evaluate whether a fixed dose of corticosteroid (e.g., 1.5 mg or 2.0 mg) is effective for pemetrexed-induced rash. Furthermore, we cannot completely exclude the possible influence of antiemetics or other drugs. However, rash development after pemetrexed administration was late-onset, and we assume that this rash was a characteristic adverse event of pemetrexed treatment.

In conclusion, we found that supplementing the initial treatment with ≥ 1.5 mg of corticosteroids on day 2 and day 3 significantly suppressed rash development. As it is impossible to predict which patients are at high risk of rash development, all patients who receive pemetrexed should also receive a small amount of supplementary corticosteroids to prevent rash.

Conflict of Interest The authors declare no conflict of interest.

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