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Mandatory dexamethasone strictly monitored by pharmacists reduces the severity of pemetrexed-induced skin rash

Naoko Usui,[1] Yoko Kondo,[1] Noriko Ryota,[2] Hidekazu Suzuki,[3] Norio Okamoto,[3] Masumi Sando,[1] Eriko Tani,[3] Masanari Hamaguchi,[3] Ayako Tanaka,[3] Motohiro Tamiya,[3] Takayuki Shiroyama,[3] Naoko Morishita,[3] Emiko Tanaka,[1] Tomonori Hirashima[3]

[1]Department of Pharmacy, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Habikino City, Osaka, Japan
[2]Department of Nursing, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Habikino City, Osaka, Japan
[3]Department of Thoracic Malignancy, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Habikino City, Osaka, Japan

Correspondence to
Tomonori Hirashima, Department of Thoracic Malignancy, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, 3-7-1 Habikino, Habikino City, Osaka 583-8588, Japan; hirashimat@ra.opho.jp

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ABSTRACT

Objective The present study aimed to retrospectively examine the effectiveness of mandatory dexamethasone (m-DEX) strictly monitored by pharmacists collaborating with medical physicians and nurses for reducing pemetrexed (PEM)-induced skin rash in patients with non-squamous non-small-cell lung cancer (ns-NSCLC).

Methods We compared the rash grades during the first cycle of PEM-containing regimens between patients who received m-DEX after February 2012 and those who received dexamethasone (DEX) at their physician's discretion (d-DEX) before January 2012.

Results Of 163 patients with ns-NSCLC included in this study, 89 received d-DEX and 74 received m-DEX. The mean DEX doses the night before and the day after PEM administration were significantly higher in the m-DEX group than in the d-DEX group. The frequency of grade ≥2 skin rash was significantly lower in the m-DEX group than in the d-DEX group.

Conclusions The use of m-DEX strictly monitored by pharmacists might significantly reduce the severity of PEM-induced skin rash.

INTRODUCTION

Therapeutic regimens containing pemetrexed (PEM) are standard chemotherapy protocols for patients with thoracic malignancies, including non-small-cell lung cancer (NSCLC) and malignant pleural mesothelioma (MPM).[1–4]

Grade 3 or 4 skin rash is a characteristic side effect reported in 31% of patients receiving PEM in the absence of prophylactic treatment, including steroid administration and vitamin supplementation.[5] Ohe *et al*[6] reported that the incidences of any grade skin rash and grade 3 or 4 skin rash were 73.8% and 3.6%, respectively, after administration of 500 mg/m^2 PEM with vitamin supplementation and without dexamethasone (DEX) in Japanese populations. In contrast, Hanna *et al*[7] reported that the incidence of any grade skin rash was 14% in patients administered PEM along with DEX (4 mg orally two times per day the day before, the day of and the day after administration of 500 mg/m^2 PEM) and vitamin supplementation. These results showed that DEX is important for decreasing the incidence of skin rash.

In our institution, patients were supposed to receive DEX intravenously on the day of PEM administration and orally on the day before and after PEM administration. However, physicians did not always prescribe DEX. Therefore, some patients experienced grade 2 or 3 skin rash and discontinued PEM treatment. To decrease PEM-induced skin rash, the chemotherapy committee of our institution revised the protocol for DEX prescription from discretionary to mandatory strictly monitored by pharmacists on 14 December 2011.

In the present study, we retrospectively examined the effectiveness of mandatory dexamethasone (m-DEX) strictly monitored by pharmacists based on prior agreements among pharmacists, medical physicians and nurses for reducing the severity of PEM-induced skin rash in patients with non-squamous non-small-cell lung cancer (ns-NSCLC) and compared the effectiveness of m-DEX with that of discretionary DEX (d-DEX).

PATIENTS AND METHODS

Patient selection

The study included patients with histopathologically confirmed primary ns-NSCLC who were treated with PEM-containing regimens, other than combinations involving cisplatin or epidermal growth factor tyrosine kinase inhibitor, or PEM and who received d-DEX or m-DEX between April 2010 and March 2013 at our institution.

Clinical review

We retrospectively collected baseline demographic data, including age, histology, Eastern Cooperative Oncology Group performance status at the start of treatment from clinical records and information on PEM-containing regimens from the pharmacy database.

Definition of PEM-containing regimens

In this study, we analysed patients who received the following PEM-containing regimens: PEM (500 mg/m^2, day 1 every 3 weeks) with or without bevacizumab (Bev; 15 mg/kg) and a combination of carboplatin (area under the curve: 5 mg/min/m^2) and PEM with or without Bev. Combination therapy of cisplatin and PEM was excluded from the PEM-containing regimens in this study because DEX was part of the support treatment. All patients received vitamin supplementation prior to PEM-containing regimens.

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Prescription of DEX

Before January 2012, patients received DEX (8 mg) intravenously on the day of PEM administration as a registered regimen and DEX (8 mg) orally at the chief physician's discretion on the day before and after PEM administration (d-DEX group). The DEX protocol was changed from discretionary to mandatory by the chemotherapy committee that included pharmacists, medical oncologists and cancer chemotherapy certified nurses on 14 December 2011. After February 2012, patients received DEX (8 mg) intravenously on the day of PEM administration as a registered regimen and received DEX (8 mg) orally the day before and after PEM administration as a mandatory protocol (m-DEX group).

Strict monitoring of the DEX prescription by the pharmacists

The electronic medical chart system (MegaOakHR V.4, NEC, Tokyo) in our institution allows for the automatic extraction of a patient in whom an anticancer agent was prescribed by a medical physician. Five pharmacists in charge of anticancer agents routinely monitored the prescription of these agents. When a medical physician prescribed PEM, the pharmacist confirmed the contents of the PEM-containing regimen, and if DEX was not prescribed, the pharmacist orally asked the medical physician to prescribe DEX based on the decision of the chemotherapy committee. If DEX was still not prescribed, the physician's superior and/or the chairperson of the chemotherapy committee orally asked the physician to prescribe DEX. Additionally, nurses in the wards checked whether DEX was accurately prescribed by contacting pharmacists and medical physicians.

Evaluation of skin rash and other adverse events

We evaluated the grades of skin rash and other adverse events during the first chemotherapy cycle using the Common Terminology Criteria for Adverse Events (CTCAE) V.4.0[8] and compared the findings between the d-DEX and m-DEX groups.

Statistical analysis

Background data of the patients were compared using the χ^2 test and Fisher's exact test for categorical factors. A p value <0.05 was considered to indicate a statistically significant difference.

RESULTS

A total of 163 patients with ns-NSCLC received PEM-containing regimens and d-DEX or m-DEX between April 2010 and March 2013 at our institution (table 1). Of these 163 patients, 89 received d-DEX and 74 received m-DEX. No significant difference in patient background, including baseline demographics and therapeutic regimens, was noted between the d-DEX and m-DEX groups.

Actual doses of DEX

On the night before PEM administration, the mean DEX dose was significantly higher in the m-DEX group than in the d-DEX group (8 vs 2.29 mg; p<0.0001). Additionally, on the day after PEM administration, the mean DEX dose was significantly higher in the m-DEX group than in the d-DEX group (7.89 vs 1.01 mg; p<0.0001). However, on the day of PEM administration, the mean DEX dose was the same in both groups (8 vs 8 mg).

Table 1 Patient background

Variable	Total (n=163)	Dexamethasone	
		Discretionary (n=89)	Mandatory (n=74)
Median age (range), years	68 (38–86)	67 (38–81)	69 (48–86)
Sex			
Male	98	57	41
Female	65	32	33
Histology			
Adenocarcinoma	162	88	74
Large	1	1	0
Stage			
IIIA	8	4	4
IIIB	18	14	4
IV	91	47	44
Recurrence	46	24	22
Line of chemotherapy			
First	60	25	35
Second	50	32	18
≥Third	53	32	21
Regimens			
CBDCA+PEM	58	34	24
CBDCA+PEM+Bev	21	9	21
PEM+Bev	13	0	13
PEM	71	46	25

Bev, bevacizumab; CBDCA, carboplatin; PEM, pemetrexed.

Table 2 Adverse events in the discretionary and mandatory groups

Adverse events	Grade (%)									
	Discretionary (n=89)					Mandatory (n=74)				
	1	2	3	Any	≥2	1	2	3	Any	≥2
Skin rash	9.0	12.4	1.1	22.5	13.5	14.9	2.7	0	17.6	2.7*
Fatigue	32.6	5.6	0	38.2	5.6	35.1	9.5	0	44.6	9.5
Nausea	23.6	15.7	0	39.3	15.7	28.4	12.1	0	40.5	12.1
Appetite loss	34.8	15.7	0	50.5	15.7	31.1	13.5	0	44.6	13.5

*p=0.0003.

Adverse events

The frequencies of skin rash (any grade), fatigue, nausea and appetite loss were the same in the d-DEX and m-DEX groups. However, the frequency of grade ≥2 skin rash was significantly lower in the m-DEX group (2.7%) than in the d-DEX group (13.5%; p=0.0003) (table 2). In the m-DEX group, grade 3 or 4 skin rash was not observed.

DISCUSSION

The present study showed that the severity of PEM-induced skin rash was significantly lower with m-DEX (administered on the night before and the day after PEM administration) than with d-DEX in patients with ns-NSCLC. Strict monitoring to ensure appropriate use of DEX is important to reduce the severity of PEM-induced skin rash.

In a Japanese phase I/II study of PEM combined with cisplatin in patients with MPM,[9] the incidence of grade 1 or 2 skin rash decreased to 32% and grade 3 or 4 skin rash was not observed

when DEX was used as the antiemetic agent. Ishikawa *et al*[10] examined the incidences of skin rash after PEM administration in a low-dose prophylactic DEX group (4 mg DEX on the day before and after PEM administration) and a non-prophylactic DEX group. The incidences of any grade skin rash were 26.3% and 35.0% in the prophylactic DEX group and non-prophylactic DEX group, respectively, and no significant difference in the incidence of skin rash was noted between the groups. Additionally, grade 3 or 4 skin rash was not observed in both groups. Thus, to decrease the severity of PEM-induced skin rash, administration of a steroid is necessary. However, DEX has rarely been administered routinely on the day before and after PEM administration in Japanese medical practice, similar to the regimen used in previous studies.[4 7]

Our recent study[11] showed that a team approach among pharmacists, medical physicians and nurses was effective for decreasing the severity of afatinib-induced diarrhoea. It is very important that pharmacists, medical physicians and nurses have a mutual understanding based on prior agreement or the clinical pathway. Even if prescription rights are not transferred to pharmacists in Japan, a team approach would enable pharmacists to improve patient treatment and care in the same way as collaborative drug therapy management[12] in the USA. Consistent with our previous study,[11] the present study showed that a team approach may reduce the severity of PEM-induced skin rash. Such team approach could be considered Japanese-style collaborative drug therapy management (J-CDTM).

Limitations

The limitations of this study included its comparative and non-randomised design. Additionally, all data, including side effects, were retrospectively collected, and strict monitoring was performed for DEX alone.

Conclusion

In conclusion, the use of m-DEX strictly monitored by pharmacists might significantly reduce the severity of PEM-induced skin rash. With advances in treatments for cancer, such as molecular-targeted therapy and cancer immunotherapy, difficulties in the management of the treatment and side effects would increase. Therefore, a team approach, such as J-CDTM, would be extremely important in patient care.

Key messages

What is already known on this subject?

- Dexamethasone (DEX) is important for decreasing pemetrexed (PEM)-induced skin rash.
- Physicians did not always prescribe DEX for patients receiving PEM.

What this study adds?

- The use of mandatory DEX strictly monitored by pharmacists based on an agreement among pharmacists, medical physicians and nurses in the chemotherapy committee in our institution significantly reduced the severity of PEM-induced skin rash.
- The drug management system based on an agreement among pharmacists, medical physicians and nurses can be considered Japanese-style collaborative drug therapy management (J-CDTM).
- Even if prescription rights are not transferred to pharmacists in Japan, J-CDTM would enable pharmacists to improve patient treatment in the same way as collaborative drug therapy management in the USA.

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Contributors NU, TH and YK were responsible for planning and design and data collection of the study. NU, TH and HS were responsible for analysis. NU and TH wrote the first draft; HS and NO provided critical revision; all authors read and approved the final manuscript.

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Competing interests TH received a research grant from Chugai, Taiho, Ono, Kyowa Hakko Kirin, AstraZeneca, Eli-Lilly, MSD and Merck-Serono.

Ethics approval This retrospective study was approved by the Institutional Review Board of the Osaka Prefectural Medical Center for Respiratory and Allergic Diseases on 26 August 2014 (approval number: 690).

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