

ORIGINAL**Drug-induced interstitial pneumonia during perioperative chemotherapy for breast cancer**

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Abstract : Purpose : Drug-induced interstitial pneumonia (DIP) that occurs during chemotherapy for breast cancer is a rare but a serious adverse event. Treatments of DIP requires interruption of breast cancer treatment, which may affect the patient's prognosis. However, there are few reports which discuss DIP during breast cancer treatments. **Purpose of this report is to make clear how DIP occurred and influenced breast cancer treatment in our hospital. Patients and Methods :** A total of 74 patients who started perioperative chemotherapy in Tokushima Municipal Hospital for breast cancer from January 2019 to December 2020 were evaluated for DIP. Patients' and tumors' characteristics, and regimens which caused DIP were investigated. The clinical courses of the DIP patients were also followed up. **Results :** Twelve of the 74 patients developed DIP. All 12 patients had histories of cyclophosphamide administration ; however, the causative drug could not be determined. Ten of the 12 patients were treated with steroids, and all the patients recovered ultimately from the interstitial pneumonia. While chemotherapy was administered in six patients after mild DIP, no relapse of pneumonia was observed. **Conclusion :** DIP during perioperative chemotherapy for breast cancer was resolved with appropriate treatment. Patients were able to resume breast cancer treatment with minimal interruption. *J. Med. Invest.* 69:107-111, February, 2022

Keywords : breast cancer, Drug-induced interstitial pneumonia, perioperative chemotherapy

INTRODUCTION

Perioperative pharmacotherapy is used to control potential micrometastases of patients with early-stage breast cancer. Among the various treatment policies in use, perioperative chemotherapy has been shown to prolong survival in patients with early-stage breast cancer (1, 2), and is particularly critical in hormone receptor-negative breast cancer.

However, there are so many adverse events associated with chemotherapy. Among those adverse events drug-induced interstitial pneumonia (DIP), which occurs during chemotherapy is serious event but in rare instances. It is known to be a life-threatening condition, sometimes caused by fibrosis and inflammation of the lung interstitium (3-5).

If a patient develops DIP during perioperative chemotherapy, the chemotherapy must be interrupted, which may affect the patients' prognoses. In addition, there are no established guidelines for choice of the treatment of the patients with pneumonia following disease recovery, nor there are established guide for the drugs selection which is used in perioperative chemotherapy. There are also currently few reports discussing the resumption of chemotherapy after the resolution of the DIP.

In this study, we investigated the incidence of DIP during perioperative chemotherapy for breast cancer and the treatment of breast cancer following recovery from pneumonia.

PATIENTS AND METHODS

This study included the patients who started preoperative or postoperative chemotherapy for breast cancer between January 2019 and December 2020 at Department of Breast Surgery, Tokushima Municipal Hospital. This study was approved by the Ethics Review Committee of Tokushima Municipal Hospital on October 19, 2021 (Registration No. : R3-14).

A total of 74 patients received perioperative chemotherapy with no imaging findings indicative of interstitial pneumonia and no respiratory symptoms on pre-chemotherapy chest CT scan were investigated. The chest CT images were captured using high-resolution computed tomography (HRCT). The diagnosis and clinical classification of interstitial pneumonia were performed by a physician specializing in respiratory internal medicine. Clinical classification was performed according to The JRS Guidelines for the Management of Drug-induced Lung Disease [2nd Ed.]. In addition, patients suspected of having interstitial pneumonia based on imaging findings were diagnosed as having DIP after confirming the absence of elevated β -D-glucan levels and ruling out infection.

Patient characteristics

The backgrounds of the patients included in this study are showed in Table 1. The ages of the patients ranged from 30–78 years (median : 54.5 years), and all patients were female. Of the 74 patients, 39 patients received preoperative chemotherapy and 35 patients received postoperative chemotherapy.

The stages of breast cancer were Stage I in 16 patients, Stage IIA in 22 patients, Stage IIB in 20 patients, Stage IIIA in five patients, Stage IIIB in three patients, and Stage IIIC in eight patients. The subtypes were Luminal A in seven patients, Luminal B in 33 patients, Luminal HER2 in eight patients, HER2 in 14

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Table 1. Patients' and tumors' characteristics

	Total (n=74)	with pneumonia (n=12)	without pneumonia (n=62)	p value
Age (median)	30-78 (54.5)	49-70 (57.0)	30-78 (54.0)	
NAC/AC				
NAC	39	5	34	
AC	35	7	28	
Stage				
I	16	3	13	
II A	22	2	20	
II B	20	3	17	
III A	5	2	3	
III B	3	2	1	
III C	8	0	8	
Subtype				
Luminal A-like	7	1	6	
Luminal B-like	33	5	28	
Luminal HER2	8	1	7	
HER2	14	2	12	
Basal like	12	3	9	
Smoking history				
Yes	21	2	19	p=0.3255
No	53	10	43	
Allergy history				
Yes	46	9	37	p=0.0274
No	28	3	25	

Statistical significance was defined as $p < 0.05$

patients, and Basal-like in 12 patients.

Regarding patients' prior medical histories, five patients had developed respiratory diseases, and all had bronchial asthma. Histories of allergies were noted in 46 of the 74 patients, histories of tobacco use in 21 of the 74 patients, and a Brinkman Index of 400 or higher was noted in three patients.

Statistical analysis

The statistical analysis was performed using statistical software (JMP version 11.0 ; SAS Inc., Tokyo, Japan). The chi-square test was used to compare categorical data. Statistical significance was defined as $p < 0.05$.

RESULTS

Of the 74 patients who received preoperative and postoperative chemotherapy, 12 (16.2%) developed drug-induced interstitial pneumonia. The age of the patients who developed this condition ranged from 49–70 years (median : 57 years). Five of the 12 patients received preoperative chemotherapy while seven received postoperative chemotherapy.

The breast cancer stages of the patients were Stage I in three patients, Stage IIA in two patients, Stage IIB in three patients, Stage IIIA in two patients, Stage IIIB in two patients, and Stage IIIC in no patient. The subtypes were Luminal A in one patient, Luminal B in five patients, Luminal HER2 in one patient, HER2 in two patients, and Basal-like in three patients.

Of the 12 patients who developed DIP, comorbidities were noted in eight patients. Of these patients, three developed a respiratory disease (asthma in all patients). Histories of allergies were noted in nine of the 12 patients. Two of the 12 patients had histories of tobacco use, and their Brinkman Index values were 100 and 300.

The chemotherapy regimens administered at the time of diagnosis of DIP are showed in Table 2.

The days from the start of chemotherapy to the diagnosis of DIP ranged from 30–94 days (median : 73.5 days).

Seven of the 12 patients received full doses of chemotherapy, and five had single-step reductions due to onset of complications such as febrile neutropenia. Pegfilgrastim was administered at least once in five of the 12 patients.

Of the 12 patients, 11 were diagnosed after the examination following the recognition of symptoms. The most common symptoms were cough and fever. The body temperatures for all patients were above 38°C. Only one patient was asymptomatic and was identified by CT scan for the evaluation. SpO2 was normal or mildly decreased in all but one patient.

Table 2. Administered regimen

Regimen	with pneumonia (n=12)	without pneumonia (n=62)
EC only	3	1
EC-DTX	1	4
EC-DTX + HER		2
EC-DTX + HER + PER		6
EC-wPTX		2
EC-wPTX + HER + PER		1
EC-nab-PTX		2
EC-nab-PTX + HER + PER		2
ddEC only	1	
ddEC-DTX	1	5
ddEC-DTX + HER + PER		3
ddEC-wPTX	1	4
ddEC-wPTX + HER + PER		2
ddEC-nab-PTX		1
ddEC-nab-PTX + HER + PER		1
AC only	2	
AC-DTX		2
AC-wPTX		2
AC-wPTX + HER + PER		1
AC-nab-PTX + HER + PER		1
TC	3	17
wPTX only		2
wPTX + HER		1
Pegfilgrastim use	5	27

E : epirubicin, C : cyclophosphamide, DTX : docetaxel, HER : trastuzumab, PER : ertuzumab, wPTX : weekly paclitaxel, nab-PTX : nab-paclitaxel, dd : dose-dense, A : doxorubicin, TC : docetaxel+cyclophosphamide

DIP onset risk of the chemotherapy regimens, no relations were recognized but Trastuzumab ($p=0.021$) and Pertuzumab ($p=0.039$).

Blood tests at the time of diagnosis showed that KL-6 was elevated in four of the 12 patients, LDH was elevated in all patients. The CRP was elevated in 11 of the 12 patients. The LDH and CRP indicated improvements based on more favorable imaging findings with respect to interstitial pneumonia. The clinical type of interstitial pneumonia had a hypersensitivity pneumonia (HP) pattern in nine patients except in three unclassifiable patients.

Risks for DIP were measured by the chi-squared test. DIP onset risk were related to allergic history ($p=0.027$) but not smoking. Concerning the chemotherapy regimens, no relations were recognized but Trastuzumab ($p=0.021$) and Pertuzumab ($p=0.039$).

Treatments for pneumonia

Of the 12 patients, 10 were treated with steroids, and two were followed up without treatment. Six patients were switched from intravenous methylprednisolone to oral prednisolone while four patients were treated with oral prednisolone alone. The interstitial pneumonia was ultimately relieved in all patients.

Treatments after pneumonia

All the patients were able to resume their breast cancer treatment after treatment for DIP. The duration of interruption of breast cancer treatment ranged from 17 to 52 days (median : 32 days). Of the five patients who developed DIP during preoperative chemotherapy, one patient who developed the disease after completion of AC (doxorubicin + cyclophosphamide) was scheduled to receive docetaxel. However, the regimen was changed to weekly paclitaxel and the chemotherapy was completed before the surgery. The other four patients underwent their surgeries first after treatment for pneumonia.

After their surgeries, four patients received chemotherapy and one patient received radiotherapy for the residual breast tissue. Of the four patients who received chemotherapy, one received weekly paclitaxel, two received trastuzumab + pertuzumab + weekly paclitaxel, and one received capecitabine.

Among the seven patients who developed DIP during postoperative chemotherapy, one received weekly paclitaxel, one received trastuzumab + pertuzumab + weekly paclitaxel, and four patients received hormonal therapy or radiotherapy. Follow-up without treatment was pursued in the remaining patient.

After the treatment of the interstitial pneumonia, chemotherapy was administered to six patients and radiation therapy to five patients who were received breast conserving surgery. All patients were noted to have no relapse of interstitial pneumonia.

The subjective symptoms and decrease in SpO2 were recorded each time during the chemotherapy and radiotherapy. Before the administration of chemotherapy, the blood tests and chest X-rays were evaluated carefully for pneumonia flare-ups.

Recurrences of breast cancer were observed in two of the 12 patients. The first patient developed DIP during postoperative chemotherapy, which was resolved only with simple follow-up. After the improvement of the interstitial pneumonia, treatment was resumed with oral tamoxifen due to hormone receptor positive breast cancer. The recurrences occurred in the parasternal lymph nodes one year and three months after the surgery. Radiotherapy was not administered due to the possibility of an interstitial pneumonia flare-up. After the recurrence of the breast cancer, the patient was treated with letrozole + palbociclib (CDK4/6 inhibitor) + LH-RH agonist for 18 months in a stable condition.

The second patient developed DIP during preoperative chemotherapy, which was resolved with steroid therapy. After the interstitial pneumonia was resolved, the patient underwent surgery and radiotherapy while continuing postoperative steroid therapy with hormone therapy. One year after the surgery, the patient relapsed with multiple bone metastases. CDK4/6 inhibitor was not used because of the possibility of a relapse of the interstitial pneumonia, and fulvestrant + denosumab was selected for the treatment of bone metastases and continued for nine months in a stable condition. No relapse of interstitial pneumonia was observed in either case.

Table 3. Clinical findings and treatment of 12 patients with interstitial pneumonia

Case	Symptoms	Fever (°C)	SpO2 (%)	KL-6 (U/ml)	LDH (U/L)	CRP (mg/dl)	CT findings	Treatment for pneumonia	Treatment after pneumonia	Interruption period (day)
1	fever, fatigue	38	98	267	353	0.8	Unclassifiable	none	TAM	20
2	dyspnea, fatigue	36	85	541	232	1.6	Unclassifiable	mPSL-PSL	Ope-capecitabine	23
3	fever, cough	39	94	670	316	7.8	HP	mPSL-PSL	RT-AI	35
4	fever, cough, fatigue	38.6	95	389	383	5.7	HP	mPSL-PSL	AI+RT	52
5	cough, fatigue	37.1	91	643	457	2.6	HP	mPSL-PSL	Ope-AI+RT	34
6	cough	36.7	97	288	291	0.2	HP	PSL	wPTX-RT-TAM	35
7	cough, fatigue	36.5	97	457	279	9.1	HP	mPSL-PSL	wPTX-Ope-TDM1	21
8	fever	38	91	355	444	9.9	Unclassifiable	mPSL-PSL	Ope-wPTX	38
9	cough, fatigue	36	96	244	286	3.7	HP	none	none	-
10	fever	38.2	99	262	254	0.9	HP	PSL	wPTX+HER+PER-AI+RT	32
11	fever	38	97	179	311	1	HP	PSL	AI	20
12	none	36	97	324	259	7.4	HP	none	Ope-wPTX+HER+PER	17

Standard value ; KL-6 < 500 U/L, LDH 110-220 U/L, CRP < 0.3 mg/dl
 HP : Hypersensitivity pneumonia, mPSL : methylprednisolone, PSL : prednisolone, TAM : tamoxifen, RT : radiation therapy, AI : aromatase inhibitor, wPTX : weekly paclitaxel, TDM1 : trastuzumab emtansine, HER : trastuzumab, PER : pertuzumab

DISCUSSION

Drug-induced interstitial pneumonia (DIP) is a serious adverse event that can occur during or after chemotherapy. DIP that manifests during preoperative chemotherapy may delay the surgery and affect the future prognosis due to the interruption of the treatment.

DIP can be classified into several different clinical types. In the present study, all the patients able to be classified in several different high resolution computed tomography (HRCT) patterns, which exhibits ground-glass opacity (GGO) and reticular shadows, etc. on the HRCT scan (6, 7). The most important differential diagnosis is opportunistic infections such as Pneumocystis pneumonia, however differential diagnosis by imaging is often difficult (8-11). Here, β -D-glucan was measured to confirm normalcy after the treated.

The hypersensitivity pneumonia (HP) pattern may be related pathological conditions due to an allergic mechanism that involves lymphocytes. This may be related to the fact that the proportion of patients with histories of allergies was higher in those who developed interstitial pneumonia than in those who did not. Nine of 12 DIP patients had allergic history in our cases. The hypersensitivity pneumonia (HP) pattern is often associated with a favorable response to steroid therapy and a good prognosis. In the present study, all 12 patients exhibited improvement with drug discontinuation and steroid treatment. The duration of interruption of breast cancer treatment was minimized because the disease was detected before it became serious and appropriate treatment with steroids was administered.

All 12 patients who developed drug-induced interstitial pneumonia had history of cyclophosphamide (CPA) administration. A variety of clinical patterns have been reported for CPA-induced interstitial pneumonia, including organizing pneumonia (OP), diffuse alveolar damage (DAD), and non-specific interstitial pneumonia (NSIP) (12, 13).

There are two distinct disease states: an early-onset disease state that presents with GGO and reticular shadows within 1–6 months of CPA administration, and a late-onset disease state that presents with progressive pulmonary fibrosis and bilateral pleural thickening months or years after treatment. The late onset disease state is considered less responsive to steroid therapy (6, 14). In the present study, all 12 patients presented within 1–4 months after the start of the treatment, and the response to the steroid therapy was favorable. However, the determination of the causative agent proved difficult because the patients were also treated with anticancer drugs other than CPA, and the exact time of onset couldn't be recognized.

In this study, no patients who received trastuzumab and pertuzumab developed DIP possibly because of the small total number of patients (74) included in the study.

Pegfilgrastim was used in approximately half of the patients. The incidence of DIP by pegfilgrastim is 0.5%. The frequency of pegfilgrastim use in this study was similarly 41.6% in symptomatic patients and 43.5% in unaffected patients.

Some drugs, such as everolimus, are listed in the Guide for Appropriate Use (Medication Guide) as those being able to be resumed after resolution of the DIP. However, for the majority of drugs, there are no established criteria. If the patient has been diagnosed with hormone receptor positive breast cancer, it may be possible to switch to hormone therapy, but if the patient has hormone receptor negative breast cancer, discontinuation of chemotherapy is likely to affect the prognosis. In patients with mild DIP and favorable response to steroids, it is possible to resume chemotherapy with careful monitoring.

All six patients who were re-treated with another anticancer drug after the improvement of the DIP were free of interstitial

pneumonia flare-ups. Patients who were judged to be at high risk of interstitial pneumonia relapse were treated with chemotherapy in combination with a small dose of oral steroids. Patients who developed drug-induced interstitial pneumonia while receiving epirubicin + cyclophosphamide (EC) or doxorubicin + cyclophosphamide (AC) were initially planned to receive docetaxel. However, because of the reported cases of deaths due to docetaxel-induced interstitial pneumonia (15-18) and the high frequency of myelosuppression, the patients were switched to weekly paclitaxel in consideration of the risk of febrile neutropenia during chemotherapy with steroids.

The primary monitoring indices used were the LDH and CRP values. KL-6 was not used for monitoring because it was not measured at the start of chemotherapy and time was needed to determine the results. KL-6 has been reported to be elevated in patients with diffuse alveolar damage (DAD) and chronic interstitial pneumonia (CIP) pattern DIP, but not in patients with bronchiolitis obliterans organizing pneumonia (BOOP), EP (eosinophilic pneumonia), and HP pattern (19).

In the present study, the majority of patients had the hypersensitivity pneumonia (HP) pattern, and thus there were few patients with an elevated KL-6.

The majority of patients were identified by their subjective symptoms. However, malaise and fever are common symptoms of febrile neutropenia, which is a more frequent adverse event than DIP, and can easily be overlooked (20). It is necessary to always suspect the possibility of DIP when treating patients. If symptoms such as cough, fever, and malaise are observed, DIP should be suspected, and CT should be proactively performed. It is also important to educate the patients (21).

If a patient develops DIP, chemotherapy can be resumed after the pneumonia is resolved. However, due care is necessary when re-administering CPA. Although the observation period in the present study was short, it is possible that the interruption of breast cancer treatment might have affected the patient's prognosis.

CONFLICT OF INTEREST

The authors state no conflicts of interest.

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