Case Report

BIO Integration

Drug-induced Interstitial Lung Disease in Breast Cancer Patients: A Lesson We Should Learn From Multi-Disciplinary Integration

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Abstract

Taxanes represented by paclitaxel and targeted therapy including trastuzumab are two common agents for human epidermal growth factor receptor-2 (HER-2)-positive breast cancer patients. Effectiveness, however, usually comes at the cost of many side effects, some of which are even fatal. Drug-induced interstitial lung diseases (DILDs) comprise a group of drug-induced pulmonary injuries usually caused by using these medications. For DILDs, systemic therapy can be harmful to lung tissues and rapidly threaten the lives of some breast cancer patients. Through the cases from our hospital and related studies in medical databases, we hope readers can learn a lesson from an angle of multi-disciplinary integration based on clinical practice and pharmacological mechanisms to make anti-cancer agents less harmful and reduce the incidence of DILD in breast cancer patients during systemic therapy.

Keywords

Breast cancer, drug-induced interstitial lung disease, multi-disciplinary integration, taxanes, trastuzumab.

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Introduction

Systemic therapy is an indispensable part of the treatment for breast cancer, including chemotherapy, endocrine therapy, and targeted therapy [1]. Systemic therapy is commonly used in human epidermal growth factor receptor-2 (HER-2)-positive breast cancer, which is one of the four subtypes of breast cancer. This subtype accounts for about 20% of all types of breast carcinoma [2]. And it is characterized by a high mortality rate in early stage, a short interval to relapse, and a predisposition to metastasis until HER-2-targeted therapies were invented [3, 4]. As a representative of targeted therapy, trastuzumab (Herceptin®) is a monoclonal antibody that targets the HER-2 molecule, inhibits HER-2 expression, and blocks ligand-independent HER-2 signaling [5, 6]. Paclitaxel, a chemotherapy drug belonging to the group of taxanes is a regular treatment for HER-2-positive patients [7]. The combination of paclitaxel and trastuzumab can reduce the relapse rate and drastically improve pathological complete response rate and prognosis of early-stage or advanced HER-2-positive breast cancer [8–11]. Nevertheless, we cannot neglect their toxicity and interstitial lung diseases (ILD) is one of them.

ILDs include a class of non-malignant respiratory diseases [12]. ILDs are marked by pathologic changes such as inflammation and fibrosis in the lung parenchyma [13]. According to the latest classification, interstitial pneumonia is a major form of ILDs [14, 15]. Drug toxicity is one of the causes of interstitial pneumonia (IP) [15] and this condition is usually named as a drug-induced interstitial lung disease (DILD). Medications disposed to cause DILD include chemotherapy agents such as taxanes (docetaxel and paclitaxel) [16–19], or monoclonal antibodies such as trastuzumab, adalimumab, bevacizumab, etc. [19, 20]. The frequency of paclitaxel-induced ILDs was 0.73–12% while the incidence of trastuzumab was estimated to be 0.4%–0.6% [21, 22]. This complication is perilous and difficult to be firmly diagnosed due to its atypical clinical presentation. Also, the medical imaging of ILD are indistinguishable from other common pulmonary diseases [15, 23, 24]. In this article, we discuss a case that was encountered on a ward and review previous studies with similar drug-induced pulmonary injury. We

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also elaborate related mechanism of DILD and highlight the importance of multidisciplinary integration between clinical practice and pharmaceutical research.

Case studies

Nearly 2 years ago, a 55-year-old female was admitted to hospital with a complaint of "a lump in the right breast for 10 months and bilateral hip pain for 2 months". She was finally diagnosed as having invasive breast carcinoma with bone metastasis, (level III, clinical staging: stage IV, T3N3M1). Immunohistochemistry showed estrogen receptor (ER)-positive (10%), progesterone receptor (PR)-negative, HER-2-positive (3+), Ki67-positive (about 90%). Subsequently, a rescue treatment plan was decided: Anzatax (paclitaxel injection, Hospira Australia Pte Ltd, Melbourne, Australia) 110 mg (once per week) + Herceptin (trastuzumab injection, Genetech Inc., San Francisco, USA) 390 mg (the first dose)/290 mg (once per 3 weeks and maintaining for a year) + Zometa (zoledronic acid for injection, Novartis Pharma Stein AG, Switzerland, Basel, Switzerland) 4 mg (1 dose per 28 days). Shortly after the first cycle of therapy, the patient had a fever and chill followed by a headache, dizziness and palpitation. The highest body temperature reached was 39.4 °C; fever subsided after antipyretic analgesics were given several times. Physical examination did not find any crackles during lung auscultation. Laboratory tests including blood routine analysis showed a white blood cell count of 6.14×10^9/L, hemoglobin 108 g/L, neutrophil count 5.72×10^9/L; both results of blood cultivation of bacteria and anaerobes were negative. Two more cycles with a subsequently switched plan: Anzatax 110 mg (once per week) + Herceptin 90 mg (once per week and maintained for a year), were completed on October 19th, 2018 and October 26th, 2018, respectively, after subclavian venous access device implantation. A chest X-ray was taken on October 19th and the result showed interstitial pneumonia (bilateral inferior lungs) with right-side pleural effusion **(Figure 1)**. Another six rounds of rescue therapy consisting of Anzatax 110 mg (once per week) + Herceptin 90 mg was given to the patient from November 2nd to December 8th in 2018. Series of coughs began after November 9th with yellow sputum, a slight headache and a stuffy nose. The sputum turned white but cannot be expectorated readily. The condition did not remit after treatment of several expectorants. The cough worsened 2 weeks prior to November 29th, the day of the next scheduled rescue therapy. An X-ray examined on November 29th still suggested bilateral pneumonia with slight pleural effusion, the same as that of October 19th. A computed tomography (CT) scan on November 30th demonstrated inflammation in upper lobe (apical segment); fibrosis in the middle segment of the right lung, upper lobe (lingular segment) of left lung and bilateral inferior lobes **(Figure 2B)**. The cough persisted despite further treatment with Cravit [levofloxacin tablets, Daiichi Sankyo Company, Ltd (Beijing branch), Beijing, China], Xi Ke Qi (codeine phosphate and platycodon tablets, Qinghai Pharmaceutical Factory Co., Ltd, Xining, China), Mucosolvan (amroxol hydrochloride injection, Boehringer Ingelheim Espana, Barcelona, Spain), Bricanyl

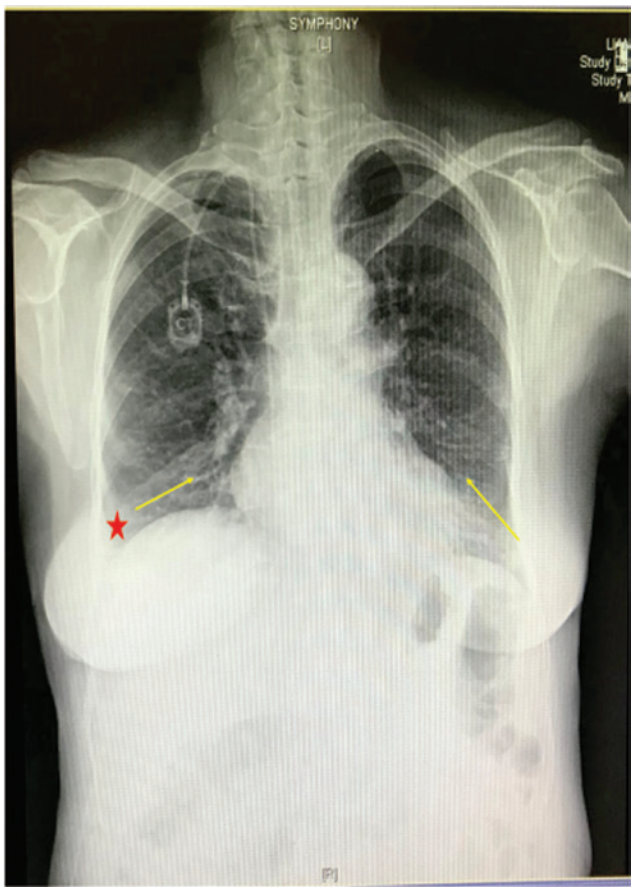

Figure 1 On October 19th, 2018, a chest plain film shows that interstitial pneumonia (bilateral inferior lungs, marked by arrowheads) with small-amount of pleural effusion on the right side (marked by the asterisk).

(terbutaline sulphate solution for nebulization, AstraZeneca AB, Sodertalje, Sweden) and Pulmicort Respules (budesonide suspension for inhalation, AstraZeneca Pty Co., Ltd, Sydney, Australia). No apparent abnormality was found in routine blood tests and a negative sputum cultivation before each therapy session. A re-examination of the CT scan on the December 13th indicated signs of lung disease with scattered inflammation in the whole lung **(Figure 2A)**. Throughout the whole treatment, the pain of the patient's bilateral hips was not relieved.

As the patient's condition worsened, the patient had to be transferred to the Department of Respiratory Medicine. Her vital signs were monitored while a physical examination and various blood tests were carried out. Her initial vital signs were normal. Rough breathing sounds and bilateral crackle in the lungs could be heard. Routine blood test revealed the following abnormalities: C-reaction protein (CRP) was high (28.2 mg/L) whereas procalcitonin (PCT) was normal; erythrocyte sedimentation rate (ESR) was significantly high (73.0 mm/h), suggesting an inflammatory reaction; blood biochemistry showed a low serum albumin (32 g/L); blood gas analysis showed decreased PO_2 (9.54 kpa) but with a normal arterial oxygen saturation (SaO_2). Meanwhile, pathogen tests (mycoplasma, chlamydia and virus, etc.) were negative. Blood or sputum culture of bacteria, fungus, and tuberculosis were all reported as negative. A similar result was found for the G/GM tests for fungus. The

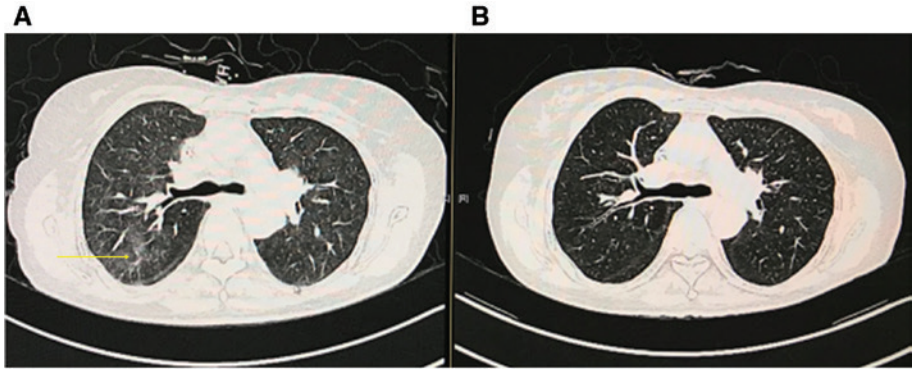

Figure 2 CT scan on December 13th, 2018 (A) with a previous CT scan on November 30th, 2018 (B). (A) shows worsened ILD with whole-field scattered inflammation (marked by arrowhead). CT: computed tomography; ILD: interstitial lung diseases.

patient denied any other diseases but a past record of serious hyperglycemia was proved by a high glycated hemoglobin (HbA_{1C}) (9.9%). Her finger-tip blood sugar was monitored since her transfer to the respiratory ward. The highest daily blood sugar measurement could reach 24.0 mmol/L. A diagnosis of interstitial pneumonia (bilateral lungs) and type-2 diabetes was established. Considering the cause of infection, drug-triggered inflammation and hyperglycemia, the current treatment plans are as follows: anti-infection therapy including Tienam (imipenem and Cilastatin Sodium for Injection, Merck Sharp & Dohme Corp., Kenilworth, USA), Vancocin, (vancomycin, Hydrochloride for intravenous, Vianex S.A., Athens, Greece) and Cancidas (caspofungin acetate for injection, Laboratories Merck Sharp & Dohme Chibret, Clermont-Ferrand, France), coupled with Solu Medrol (methylprednisolone sodium succinate for injection, Pfizer Manufacturing Belgium NV, Puurs, Belgium) as anti-inflammatory agent. Meanwhile, Novorapid (insulin aspart injection, Novo Nordisk, Copenhagen, Denmark) and Solostar (insulin glargine injection, Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany) were used to treat the diabetes. After adhering to this regimen for 9 days, a thoracic CT scan (December 1th, 2018) was taken. The result showed a significant reduction in lung lesions as compared to the last CT imaging (December 13th, 2018), although a pleural effusion **(Figure 3A** and **B)** was newly-discovered, which probably developed due to the low level of serum albumin (30.2 g/L). The level of CRP jumped to 5.9 mg/L during reexamination, indicating suppressed inflammation. Therefore, the prescription of Tienum and Vancocin were stopped while Cancidas continued being administered. The dosage of methylprednisolone was lowered to 40 mg/day. The condition of blood sugar decreased from 23.2 mmol/L to 10.4 mmol/L. Two weeks later, the patient got better except for an occasional cough accompanied by white and thin sputum. The lung auscultation turned normal and the corticosteroid was reduced to 20 mg/day. Three days afterwards, the patient was discharged with a stable condition. The whole process of this patient's treatment and the change of her conditions are illustrated in **Figure 4**.

One week later, the patient returned to our department to get further treatment for primary breast cancer. This time, doctors switched the previous therapy to 1.25 g bid Xeloda (capecitabine tablets, Shanghai Roche Pharmaceuticals, Ltd, Shanghai, China) (first 2 weeks) plus 360 mg trastuzumab (once per 3 weeks) for the purpose of safety concern, effective therapy as well as figuring out the culprit DILDs. To date, the patient still suffers from slight headache and an occasional cough with small amount of white sputum. However, the patient's symptoms have regressed as compared to the time when the patient was admitted to the Department of Respiratory Medicine.

To further explore this complication, we collected cases that were diagnosed as "lung fibrosis" and "interstitial lung disease" in our hospital from 2013 to 2019 and had successfully screened out two qualified cases of systemic therapy with paclitaxel and/or trastuzumab **(Table 1)**. However, these patients had received radiotherapy as well, so the drugs cannot be blamed for the complication alone.

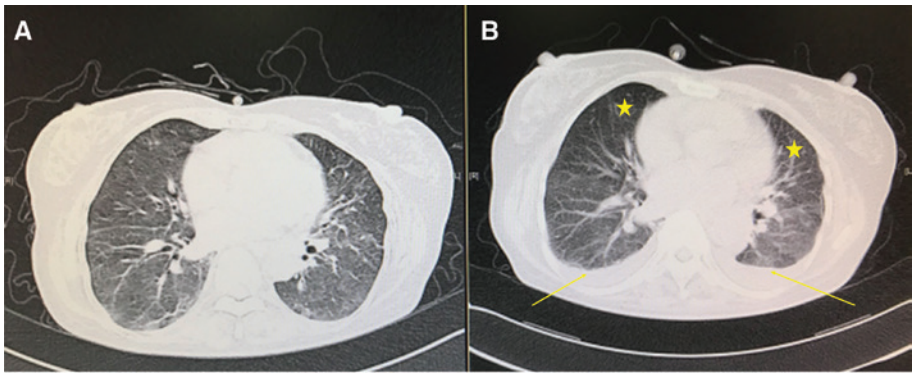

Figure 3 Contrast of CT scan on December 13th, 2018 (A) with that on December 24th, 2018 (B). (B) shows partly absorbed lesion of interstitial pneumonia (marked by asterisks) with newly-found bilateral pleural effusion (marked by arrowheads). CT: computed tomography.

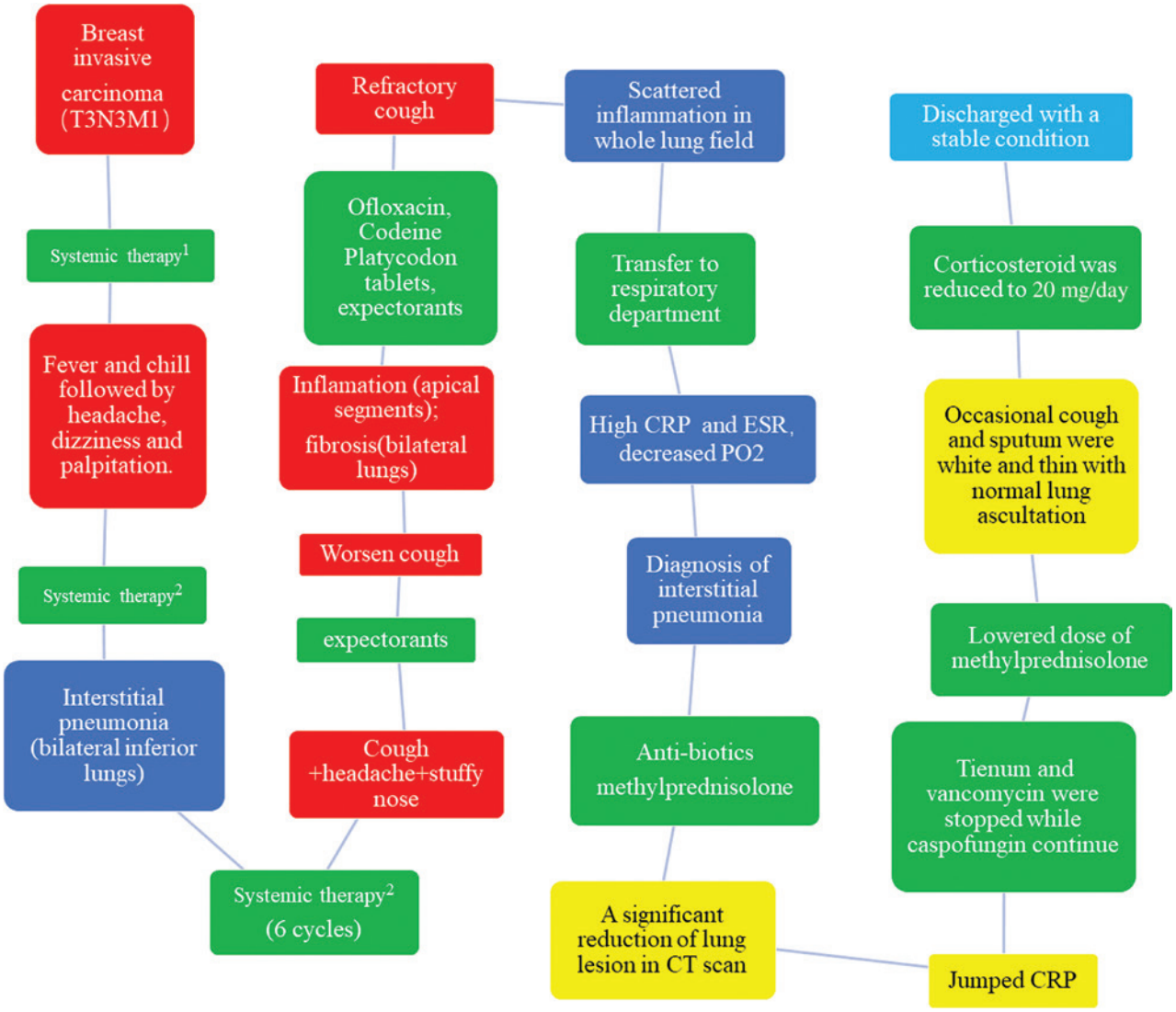

Figure 4 Flow charts of the disease progress for this patient. CRP: C-reaction protein; CT: computer topography; ESR: Erythrocyte sedimentation rate. [1]Anzatax (P) 110 mg (once per week) + Herceptin (H) 390 mg (the first dose)/290 mg (once per 3 weeks and maintaining for a year) + Zometa 4 mg (1 dose per 28 days). [2]Anzatax (P) 110 mg (once per week) + Herceptin (H) 90 mg.

Table 1 Two Cases of ILDs (Lung Fibrosis) Possibly Related to Systemic Therapy in Sun Yat-sen Memorial Hospital (2013–2019)

Sex	Age	Diagnosis	Systemic Therapy	Symptom	Radiotherapy	Treatment	Recovery
F	61	Ovarian carcinoma	Paclitaxel + lobaplatin → gemcitabine + docetaxel → Paclitaxel cis-platinum → paclitaxel + carboplatin	No*	Yes	No	Yes
F	49	Invasive breast carcinoma	Epirubicin + docetaxel + CTX → docetaxel + carboplatin + trastuzumab → trastuzumab	SOB	Yes	Methylprednisolone**	Yes

F: female; ILDs: interstitial lung diseases; SOB: shortness of breath. *The lesion only seen on chest X-ray. **40 mg → 20 mg.

Discussion

In the first case detailed, we can conclude that the lung disease is more likely a non-infectious one because the result of blood/sputum culture and antigens of some common pathogens and their corresponding antibodies were all negative. Anyhow, it should still be determined whether it is just DILDs, or a rare disease of lymphangitic carcinomatosis which may be fatal, as both diseases display similar symptoms such as dyspnea, dry cough, tachypnea, and low arterial oxygen saturation (SaO_2). This is crucial because the patient was diagnosed with metastatic breast cancer, so the possibility of lymphangitic carcinomatosis must be considered. The main difference between both diseases is the illustration of lymphangitic carcinomatosis as a diffused reticular and nodular-like pattern on an X-ray or on a CT scan [25]. Additionally, the symptoms of the first patient appeared shortly after treatment and the patient finally had a sensitive response to corticosteroids. Hence, DILDs should be considered for this case. The ultimate diagnosis can be

confirmed by bronchoalveolar lavage and biopsy specimens [26, 27] although some patients are unable to tolerate these. Other than that, a further follow-up is necessary to determine which drug(s) is(are) the culprit(s): paclitaxel, trastuzumab, or the synergistic effect of them. This can be done by discontinuing one of these two drugs and assessing the response of the patient periodically. Since the time when the paclitaxel was stopped, the condition of the patient's symptom has been relieved to some extent. We primarily extrapolate that paclitaxel may contribute more than trastuzumab for the cause of ILD. Steroids play a major part in the regimen of non-infectious ILDs, especially DILDs, which is confirmed by another (the 49-year-old female) as summarized in **Table 1**.

We collected case reports of drug-induced ILDs in breast cancer patients which were published between 2000 and 2019 in the PubMed database. There were 39 studies that qualified. The summary of these documents can be found in **Table 2**. The drugs that were administered vary among these cases: chemotherapy agents including epirubicin, cyclophosphamide, paclitaxel, albumin-bound paclitaxel, doxorubicin, gemcitabine, fluorouracil, and pegylated liposomal doxorubicin; monoclonal antibodies such as trastuzumab, bevacizumab, etc.; immunosuppressive drugs such as Everolimus; and other kinds of medications **(Table 2)**. In these case reports or clinical trials, the frequency of these drugs causing the occurrences of ILDs varies, with docetaxel and trastuzumab being mentioned the most (12 times), followed by paclitaxel/albumin-bound paclitaxel (10 times), cyclophosphamide (9 times), epirubicin (7 times), Everolimus (5 times), and doxorubicin (4 times). According to this survey, it suggests that taxanes (paclitaxel and docetaxel) and trastuzumab tend to cause pulmonary injuries in breast cancer patients. Among patients that were treated by paclitaxel (only analysis results of case reports), 14 people had an ILD and recovered through subsequent treatment [22, 28–34]. As for the 11 patients who were administered trastuzumab [19, 22, 27, 35–40], only one succumbed to trastuzumab-induced ILD [19]. Overall, the response rate for paclitaxel/trastuzumab-induced ILDs seems to be promising. Nevertheless, the rapid progression of DILDs [fever, respiratory distress including shortness of breath (SOB), severe hypoxemia with a low oxygen saturation] still poses a great challenge to medical professionals. Thus, figuring out the culprit of DILDs is of the utmost importance, especially when multiple drugs are used simultaneously. In our case, the patient had been treated with both paclitaxel and trastuzumab, so the cause of ILD may be both or either one of them. To maintain a relative effective anti-cancer therapy and explore further about ILDs, we discontinued paclitaxel while trastuzumab monotherapy is underway. There was no complain of dry cough, SOB and other discomfort after that. Hence, it is more likely that paclitaxel triggered pulmonary toxicity.

To date, mechanism of drug-induced pulmonary toxicity suggests that drugs directly or indirectly damage the lung tissue via overwhelming inflammatory response. As a cytotoxic agent, paclitaxel causes large amount of reactive oxygen species (ROS) secreted by cancer cells, during which the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in cancer cells is activated by paclitaxel. These extracellular ROS will do harm to normal cells which are not exposed to paclitaxel [41]. This so-called cytotoxic bystander effect is a potential mechanism of lung injury during paclitaxel therapy. In an animal study, Liu et al. found that paclitaxel-induced lung injury was caused by the elevation of cyclooxygenase-2 (Cox-2) and reduction of proteins in tight junctions in lung tissue [42]. The former pro-inflammatory substance is mainly derived from neutrophils. The neutrophils and Cox-2 synergistically exacerbated the inflammatory response and cytotoxicity, which resulted in lung injury [43]. Thus, parecoxib sodium, a kind of Cox-2 specific inhibitor can alleviate this side effect [42]. Moreover, pharmacologists invented a novel hydrogel which originated from meshwork consisting of nanocellulose and hexadecyl amine. This brand-new biomaterial can control the release of paclitaxel and avoid potential side effects [44]. On the other hand, the mechanism of trastuzumab-related ILD is unclear. Bronchoalveolar lavage indicated that this side effect is presented as neutrophilic alveolitis [45]. A normal physiological function of alveolar epithelium is dependent on type II pneumocytes which express epidermal growth receptor factor (EGFR). Accompanied with keratinocyte growth factor, EGFR is a well-known mediator of alveolar epithelial recovery [46]. An EGFR-inhibitor, such as trastuzumab, will thus negatively impact the protective effect of type II pneumocyte in response to lung injury [47].

For treatment, this adverse effect can be ceased by either drug stoppage or high-dose steroid therapy, which can rapidly subside lung injury [32]. According to the "Uptodate" recommendation of "Treatment and prognosis of nonspecific interstitial pneumonia" (https://www.uptodate.cn/contents/zh-Hans/treatment-and-prognosis-of-nonspecific-interstitial-pneumonia?search=interstitial%20lung%20disease&source=search_result&selectedTitle=5~150&usage_type=default&display_rank=5), drug stoppage and systemic glucocorticoids are still the two most effective solutions. Take prednisone, for example, the suggested dose initiates with 0.5 to 1 mg/kg ideal body weight every day. The ceiling dose is 60 mg/day for 1 month followed by 30–40 mg/day for another 2 months. If patients respond sensitively, the dose of prednisone can be tapered to 5–10 mg per day by the end of 6 to 9 months. The duration of prednisone should last for at least 1 year. During the treatment with corticosteroids, a variety of side effects ought to be monitored closely, especially those with comorbidities (high blood pressure, hyperglycemia, etc.) [47]. If the DILD is refractory or the disease progresses, some other immunosuppressive agents can be added such as azathioprine, mycophenolate mofetil, cyclophosphamide, or calcineurin inhibitors (cyclosporine and tacrolimus), or rituximab (a monoclonal antibody). Because these drugs have different side effects such as opportunistic infection and potential secondary lung injury, usage for cancer patients should be accompanied with great caution [48, 49]. Of course, in some lucky individuals, both symptoms and radiographic abnormalities can subside without any medical interference [16]. But there is no evidence proving that DILD is a self-limited disease. For some unfortunate cases, however, physicians failed to make an accurate diagnosis because of a non-specific clinical manifestation such as dyspnea or a nonproductive cough [50]. Instead, they used a wide range of antibiotics even if there was no strong

Table 2 Cases of Breast Cancer Patients Suffered from Drug-induced Interstitial Lung Disease Collected from PubMed (2000–2019)

PubMed ID	Year	Sex	Age/Median Age (*)	Drug	Comorbidity	Outcome	Reference
30765674	2019	F	60	Epirubicin, cyclophosphamide	None	Recovered	[51]
29970533	2018	F	62.5* (28 patients)	Eribulin, trastuzumab	NA	One patient got ILD[a]	[52]
30290608	2018	NA	66* (29 patients)	Everolimus, Exemestane	NA	16 patients got ILD[a]	[53]
30426834	2018	F	71	TDM-1	NA	Recovered	[40]
26932304	2017	F	58	Everolimus	None	Recovered	[54]
28399902	2017	F	53*, 51*, 55*, 52*[,d]	Everolimus, trastuzumab, paclitaxel	NA	More than one dead due to pneumonia	[55]
28357100	2017	F	68* (three patients)	Epirubicin, docetaxel, cyclophosphamide, trastuzumab	NA	All patients recovered	[39]
29110735	2017	F	52	Eribulin	NA	Recovered	[56]
25978147	2017	F	57* (three patients)	Doxorubicin, cyclophosphamide, paclitaxel, trastuzumab	None	Recovered	[34]
28133221	2017	F	79	Lapatinib, letrozole	None	Recovered	[57]
27306814	2016	F	80	Everolimus, exemestane	stomatitis, diarrhea, melena	Recovered	[58]
27933242	2016	F	43	Trastuzumab	anaphylactoid reaction	Recovered	[38]
26378999	2015	F	61	Docetaxel, doxorubicin, cyclophosphamide	Hypertension, hyperthyroidism	Recovered	[59]
25795409	2015	NA	NA	Gemcitabine, paclitaxel	NA	Four patients got ILD[a]	[60]
25911197	2015	F	NA	Docetaxel	None	One dead and one recovered	[61]
23404211	2014	F	59.9*, 58.6*, 63.1*, 61.8*[,d]	Everolimus, exemestane	NA	Less than 15% of all patients got ILD[a]	[62]
23244676	2013	F	58	Epirubicin, docetaxel	Hand/foot syndrome-like disease	Dead	[63]
24649188	2013	F	50* (five patients suffered from IP)	Fluorouracil, epirubicin, cyclophosphamide, paclitaxel	None	Recovered	[33]
24158075	2013	NA	NA	Docetaxel	NA	Dead	[64]
23198815	2012	F	72	Docetaxel, cyclophosphamide	None	Recovered	[65]
21667322	2012	F	70	Pegylated liposomal doxorubicin	None	Dead	[66]
22217649	2012	F	52* (five patients)	Docetaxel, doxorubicin, cyclophosphamide, paclitaxel, gemcitabine, pamidronate	None	One dead, four recovered	[32]
21516267	2011	F	51	Paclitaxel and trastuzumab	None	Recovered	[22]
20716897	2010	F	80	S-1[b]	Eruption	Recovered	[67]
20354889	2010	F	66	Paclitaxel	None	Recovered	[31]
20145394	2010	F	53	Pegylated liposomal doxorubicin, bevacizumab	None	Recovered	[68]
19815649	2010	M/F	52.1* (4280 patients)	Lapatinib, capecitabine	NA	Two patients got ILD[a]	[69]
18343993	2009	F	56	Trastuzumab	None	Recovered	[37]
19749395	2009	F	63	Docetaxel, trastuzumab	None	Dead	[19]
18799925	2008	F	41	Vinorelbine, trastuzumab	None	Recovered	[36]
18535887	2008	F	47, 70[e]	Paclitaxel, quetiapine fumarate	None	Recovered	[30]
19112950	2008	F	65	Trastuzumab	Guillain–Barre syndrome	Recovered	[35]
17889516	2007	F	65	Docetaxel, bevacizumab	None	Recovered	[70]

Table 2 (continued)

PubMed ID	Year	Sex	Age/Median Age (*)	Drug	Comorbidity	Outcome	Reference
15591716	2004	F	71	Docetaxel, paclitaxel	None	Recovered	[29]
12662016	2003	F	49	Trastuzumab	None	Recovered	[27]
11857321	2002	F[b]	61* (three patients)	Docetaxel	Rash in different parts of the body	One dead, two recovered	[71]
11222212	2001	F	61	Paclitaxel	Rash	Recovered	[28]
11485142	2001	F	52	Fluorouracil, epirubicin, cyclophosphamide	Cervico-thoracic rubefaction	Dead	[50]
11313694	2001	F	41, 48[e]	Cyclophosphamide, thiotepa, docetaxel	Generalised maculopapular rash	Recovered	[72]

F: female; ILD: interstitial lung diseases; IP: interstitial pneumonia; M: male; NA: not available; TDM-1: trastuzumab emtansine. [a]The outcome of this/these patient(s) is/are not available. [b]An oral fluoropyrimidine derivative. [c]A man suffered from prostate carcinoma in this case report is dismissed. [d]Four groups. [e]Two patients.

evidence of an infection (normal body temperature, negative results of routine blood test, culture or antigen quantification of bacteria, virus and fungi), which resulted in a long-term ILDs or even ILD-related death.

Throughout this article, we have emphasized that DILDs are a group of rare but severe respiratory complications during anti-cancer treatment in malignancies. Medical professionals should make a quick judgement when SOB, severe hypoxemia, and other clinical manifestation of respiratory distress occur. It is advisable to selectively discontinue potential drugs and to assure periodical physical examination. Usage of antibiotics should be replaced by other agents such as corticosteroids if no evidence of infection is found in lab tests. Besides, it is worthy for scientists and pharmacologists to find a solution to modify these drugs so that DILD can be avoided at least for those whose prognosis are thought to be optimistic. Through integration of clinical practice and medical research and development, a multidisciplinary platform is necessary to make a more effective medical protocol.

State of significance

Drug-induced interstitial lung diseases (DILD) is a group of rare but life-threatening diseases for cancer patients during systemic therapy. Medical professionals tend to misdiagnose this complication as infection, which causes exaggeration of the disease. To avoid this tragedy, multidisciplinary platform where clinical medicine and pharmacological research should cooperate to prevent from DILD.

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Competing interests

The authors declare that they have no competing interests.

Ethical standards

Informed consent was obtained from all patients for being included in the study.

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References

[1] Steenbruggen TG, van Ramshorst MS, Kok M, Linn SC, Smorenburg CH, et al. Neoadjuvant therapy for breast cancer: established concepts and emerging strategies. Drugs 2017;77:1313–36. [PMID: 28616845 DOI: 10.1007/s40265-017-0774-5]

[2] Ahmed S, Sami A, Xiang J. HER2-directed therapy: current treatment options for HER2-positive breast cancer. Breast Cancer 2015;22:101–16. [PMID: 25634227 DOI: 10.1007/s12282-015-0587-x]

[3] Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 1987;235:177–82. [PMID: 3798106 DOI: 10.1126/science.3798106]

[4] Gonzalez-Angulo AM, Litton JK, Broglio KR, Meric-Bernstam F, Rakkhit R, et al. High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller. J Clin Oncol 2009;34:5700–6. [PMID: 19884543 DOI: 10.1200/JCO.2009.23.2025]

[5] Cuello M, Ettenberg SA, Clark AS, Keane MM, Posner RH, et al. Down-regulation of the erbB-2 receptor by trastuzumab (herceptin) enhances tumor necrosis factor-related apoptosis-inducing ligand-mediated apoptosis in breast and ovarian cancer cell lines that overexpress erbB-2. Cancer Res 2001;61:4892–900. [PMID: 11406568]

[6] Molina MA, Codony-Servat J, Albanell J, Rojo F, Arribas J, et al. Trastuzumab (herceptin), a humanized anti-Her2 receptor monoclonal antibody, inhibits basal and activated Her2 ectodomain cleavage in breast cancer cells. Cancer Res 2001;61:4744–9. [PMID: 11406546]

[7] Costa R, Costa-Filho RB, Talamantes SM, Queiroga Jr F, Campello EC, et al. Interstitial pneumonitis secondary to trastuzumab: a case report and literature review. Case Rep Oncol 2017;10:524–30. [PMID: 28690527 DOI: 10.1159/000477340]

[8] Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 2011;365:1273–83. [PMID: 21991949 DOI: 10.1056/NEJMoa0910383]

[9] Jacobs SA, Robidoux A, Abraham J, Pérez-Garcia JM, La Verde N, et al. NSABP FB-7: a phase II randomized neoadjuvant trial with paclitaxel + trastuzumab and/or neratinib followed by chemotherapy and postoperative trastuzumab in HER2(+) breast cancer. Breast Can Res 2019;21:133–3. [PMID: 31796073 DOI: 10.1186/s13058-019-1196-y]

[10] Kang Y, Shiraki E, Tsuyuki S. Efficacy and safety of nanoparticle albumin-bound paclitaxel as neoadjuvant chemotherapy in breast cancer patients. Gan To Kagaku Ryoho 2019;46:1427–31. [PMID: 31530783]

[11] Tanaka S, Matsunami N, Morishima H, Oda N, Takashima T, et al. De-escalated neoadjuvant therapy with nanoparticle albumin-bound paclitaxel and trastuzumab for low-risk pure HER2 breast cancer. Cancer Chemotherapy Pharmacol 2019;83:1099–104. [PMID: 30963212 DOI: 10.1007/s00280-019-03836-z]

[12] Flaherty KR, Brown KK, Wells AU, Clerisme-Beaty E, Collard HR, et al. Design of the PF-ILD trial: a double-blind, randomised, placebo-controlled phase III trial of nintedanib in patients with progressive fibrosing interstitial lung disease. BMJ Open Respir Res 2017;4:e000212.[PMID: 29018526 DOI: 10.1136/bmjresp-2017-000212]

[13] Mikolasch TA, Porter JC. Transbronchial cryobiopsy in the diagnosis of interstitial lung disease: a cool new approach. Respirology 2014;19:623–4. [PMID: 24862354 DOI: 10.1111/resp.12320]

[14] King, TE, Jr. Nonspecific interstitial pneumonia and systemic sclerosis. Am J Respir Crit Care Med 2002;165:1578-1579.[PMID: 12070054 DOI: 10.1164/rccm.2204004]

[15] Camus P, Fanton A, Bonniaud P, Camus C, Foucher P. Interstitial lung disease induced by drugs and radiation. Respiration 2004;71:301–26. [PMID: 15316202 DOI: 10.1159/000079633].

[16] Ramanathan RK, Reddy VV, Holbert JM, Belani CP. Pulmonary infiltrates following administration of paclitaxel. Chest 1996;110:289–92. [PMID: 8681647 DOI: 10.1378/chest.110.1.289]

[17] Wang GS, Yang KY, Perng RP. Life-threatening hypersensitivity pneumonitis induced by docetaxel (taxotere). Br J Cancer 2001;85:1247–50. [PMID: 11720456 DOI: 10.1054/bjoc.2001.2071]

[18] Ostoros G, Pretz A, Fillinger J, Soltesz I, Dome B. Fatal pulmonary fibrosis induced by paclitaxel: a case report and review of the literature. Int J Gynecol Cancer 2006;16(Suppl 1):391–3. [PMID: 16515630 DOI: 10.1111/j.1525-1438.2006.00222.x]

[19] Kuip E, Muller E. Fatal pneumonitis after treatment with docetaxel and trastuzumab. Neth J Med 2009;67:237–9. [PMID: 19749395]

[20] Komada F, Nakayama Y, Takara K. [Analysis of time-to-onset and onset-pattern of interstitial lung disease after the administration of monoclonal antibody agents]. Yakugaku Zasshi 2018;138:1587–94. [PMID: 30504674 DOI: 10.1248/yakushi.18-00094]

[21] Vahid B, Marik PE. Pulmonary complications of novel antineoplastic agents for solid tumors. Chest 2008;133:528–38. [PMID: 18252919 DOI: 10.1378/chest.07-0851]

[22] Abulkhair O, El Melouk W. Delayed Paclitaxel-trastuzumab-induced interstitial pneumonitis in breast cancer. Case Rep Oncol 2011;4:186–91. [PMID: 21516267 DOI: 10.1159/000326063]

[23] Cleverley JR, Screaton NJ, Hiorns MP, Flint JD, Müller NL. Drug-induced lung disease: high-resolution CT and histological findings. Clin Radiol 2002;57:292–9. [PMID: 12014876 DOI: 10.1053/crad.2001.0792]

[24] Hasskarl J, Schroettner P, von den Berg A, Rueckert A, Frydrychowicz A, et al. Severe organizing pneumonia after two cycles of docetaxel as fourth-line chemotherapy for advanced non-small cell carcinoma of the lung. Case Rep Oncol 2009;2:12–9. [PMID: 20740139 DOI: 10.1159/000200015]

[25] Lin WR, Lai RS. Pulmonary lymphangitic carcinomatosis. Q J Med 2014;107:935–6. [PMID: 24713225 DOI: 10.1093/qjmed/hcu076]

[26] Arbetter KR, Prakash UB, Tazelaar HD, Douglas WW. Radiation-induced pneumonitis in the "nonirradiated" lung. Mayo Clin Proc 1999;74:27–36. [PMID: 9987529 DOI: 10.4065/74.1.27]

[27] Radzikowska E, Szczepulska E, Chabowski M, Bestry I. Organising pneumonia caused by transtuzumab (Herceptin) therapy for breast cancer. Eur Respir J 2003;21:552–5. [PMID: 12662016 DOI: 10.1183/09031936.03.00035502]

[28] Wong P, Leung AN, Berry GJ, Atkins KA, Montoya JG, et al. Paclitaxel-induced hypersensitivity pneumonitis: radiographic and CT findings. Am J Roentgenol 2001;176:718–20. [PMID: 11222212 DOI: 10.2214/ajr.176.3.1760718]

[29] Karacan O, Eyuboglu FO, Akcay S, Ozyilkan O. Acute interstitial pneumopathy associated with docetaxel hypersensitivity. Onkologie 2004;27:563–5. [PMID: 15591716 DOI: 10.1159/000081339]

[30] Morikawa M, Demura Y, Mizuno S, Ameshima S, Ishizaki T, et al. FDG positron emission tomography imaging of drug-induced pneumonitis. Ann Nucl Med 2008;22:335–8. [PMID: 18535887 DOI: 10.1007/s12149-007-0109-9]

[31] Nagata S, Ueda N, Yoshida Y, Matsuda H, Maehara Y. Severe interstitial pneumonitis associated with the administration of taxanes. J Infect Chemother 2010;16:340–4. [PMID: 20354889 DOI: 10.1007/s10156-010-0058-4]

[32] Kim S, Tannock I, Sridhar S, Seki J, Bordeleau L. Chemotherapy-induced infiltrative pneumonitis cases in breast cancer patients. J Oncol Pharm Pract 2012;18:311–5. [PMID: 22217649 DOI: 10.1177/1078155211429384]

[33] Kawajiri H, Takashima T, Onoda N, Kashiwagi S, Ishikawa T, et al. Interstitial pneumonia associated with neoadjuvant chemotherapy in breast cancer. Mol Clin Oncol 2013;1:433–6. [PMID: 24649188 DOI: 10.3892/mco.2013.87]

[34] Bielopolski D, Evron E, Moreh-Rahav O, Landes M, Stemmer SM, et al. Paclitaxel-induced pneumonitis in patients with breast cancer: case series and review of the literature. J Chemother 2017;29:113–7. [PMID: 25978147 DOI: 10.1179/1973947815Y.0000000029]

[35] Bettini AC, Tondini C, Poletti P, Caremoli ER, Guerra U, et al. A case of interstitial pneumonitis associated with Guillain–Barre syndrome during administration of adjuvant

trastuzumab. Tumori 2008;94:737–41. [PMID: 19112950 DOI: 10.1177/030089160809400516]

[36] Yanagitani N, Shimizu Y, Kaira K, Tatsuno S, Sunaga N, et al. Pulmonary toxicity associated with vinorelbine-based chemotherapy in breast cancer. Gan To Kagaku Ryoho 2008;35:1619–21. [PMID: 18799925]

[37] Pepels MJ, Boomars KA, van Kimmenade R, Hupperets PS. Life-threatening interstitial lung disease associated with trastuzumab: case report. Breast Cancer Res Treat 2009;113:609–12. [PMID: 18343993 DOI: 10.1007/s10549-008-9966-8]

[38] Gupta A, Teo L, Masel P, Godbolt D, Beadle G. Transtuzumab induced organizing pneumonia: a case report. Springerplus 2016;5:1964. [PMID: 27933242 DOI: 10.1186/s40064-016-3647-6]

[39] Sugaya A, Ishiguro S, Mitsuhashi S, Abe M, Hashimoto I, et al. Interstitial lung disease associated with trastuzumab monotherapy: a report of 3 cases. Mol Clin Oncol 2017;6:229–32. [PMID: 28357100 DOI: 10.3892/mco.2016.1113]

[40] Alkan A. Interstitial pneumonitis associated with trastuzumab emtansine. J Oncol Pharm Pract 2019;25:1798–800. [PMID: 30426834 DOI: 10.1177/1078155218813716]

[41] Alexandre J, Hu Y, Lu W, Pelicano H, Huang P. Novel action of paclitaxel against cancer cells: bystander effect mediated by reactive oxygen species. Cancer Res 2007;67:3512–7. [PMID: 17440056 DOI: 10.1158/0008-5472.CAN-06-3914]

[42] Liu WJ, Zhong ZJ, Cao LH, Li HT, Zhang TH, et al. Paclitaxel-induced lung injury and its amelioration by parecoxib sodium. Sci Rep 2015;5:12977. [PMID: 26256764 DOI: 10.1038/srep12977]

[43] Jinzhou Z, Tao H, Wensheng C, Wen W, Jincheng L, et al. Cyclooxygenase-2 suppresses polymorphonuclear neutrophil apoptosis after acute lung injury. J Trauma 2008;64:1055–60. [PMID: 18404075 DOI: 10.1097/TA.0b013e318047c07c]

[44] Ning L, You C, Zhang Y, Li X, Wang F, et al. Synthesis and biological evaluation of surface-modified nanocellulose hydrogel loaded with paclitaxel. Life Sci 2020;241:117137. [PMID: 31809713 DOI: 10.1016/j.lfs.2019.117137]

[45] Peerzada MM, Spiro TP, Daw HA. Pulmonary toxicities of biologics: a review. Anticancer Drugs 2010;21:131–9. [PMID: 20016372 DOI: 10.1097/CAD.0b013e328333d662]

[46] Atabai K, Ishigaki M, Geiser T, Ueki I, Matthay MA, et al. Keratinocyte growth factor can enhance alveolar epithelial repair by nonmitogenic mechanisms. Am J Physiol Lung Cell Mol Physiol 2002;283:L163–9. [PMID: 12060573 DOI: 10.1152/ajplung.00396.2001]

[47] Kasturi S, Sammaritano LR. Corticosteroids in lupus. Rheum Dis Clin North Am 2016;42:47–62, viii. [PMID: 26611550 DOI: 10.1016/j.rdc.2015.08.007]

[48] Danza A, Ruiz-Irastorza G. Infection risk in systemic lupus erythematosus patients: susceptibility factors and preventive strategies. Lupus 2013;22:1286–94. [PMID: 24098001 DOI: 10.1177/0961203313493032]

[49] Hannah JR, D'Cruz DP. Pulmonary complications of systemic lupus erythematosus. Semin Respir Crit Care Med 2019;40:227–34. [PMID: 31137062 DOI: 10.1055/s-0039-1685537]

[50] Segura A, Yuste A, Cercos A, López-Tendero P, Gironés R, et al. Pulmonary fibrosis induced by cyclophosphamide. Ann Pharmacother 2001;35:894–7. [PMID: 11485142 DOI: 10.1345/aph.10297]

[51] Omoto H, Takada M, Fujii S, Ito H, Yamashita S. [A Case of drug-induced interstitial lung disease associated with epirubicin and cyclophosphamide therapy before operation]. Gan To Kagaku Ryoho 2019;46:160–2. [PMID: 30765674]

[52] Sakaguchi K, Nakatsukasa K, Koyama H, Kato M, Sakuyama A, et al. Phase II clinical trial of first-line eribulin plus trastuzumab for advanced or recurrent HER2-positive breast cancer. Anticancer Res 2018;38:4073–81. [PMID: 29970533 DOI: 10.21873/anticanres.12697]

[53] Dejust S, Morland D, Bruna-Muraille C, Eymard JC, Yazbek G, et al. Everolimus-induced pulmonary toxicity: findings on 18F-FDG PET/CT imaging. Medicine (Baltimore) 2018;97:e12518. [PMID: 30290608 DOI: 10.1097/MD.0000000000012518]

[54] Xiangying M, Tao W, Shikai W, Santai S, Zefei J. Treatment with everolimus for a patient with systemic metastatic breast cancer results in severe pulmonary injury: a case report. Int J Clin Pharmacol Ther 2017;55:270–4. [PMID: 26932304 DOI: 10.5414/CP202504]

[55] Toi M, Shao Z, Hurvitz S, Tseng LM, Zhang Q, et al. Efficacy and safety of everolimus in combination with trastuzumab and paclitaxel in Asian patients with HER2+ advanced breast cancer in BOLERO-1. Breast Cancer Res 2017;19:47. [PMID: 28399902 DOI: 10.1186/s13058-017-0839-0]

[56] Nakamura K, Kato M, Miyashita Y, Nagashima O, Sasaki S, et al. Development of interstitial pneumonia during treatment with eribulin: a case report. BMC Res Notes 2017;10:557. [PMID: 29110735 DOI: 10.1186/s13104-017-2882-4]

[57] Yamamoto D, Yamamoto C, amamoto M. [A case of interstitial pneumonitis induced by lapatinib plus letrozole]. Gan To Kagaku Ryoho 2016;43:2059–61. [PMID: 28133221]

[58] Sakiyama K, Yoshida T, Goto Y, Kimura M. [An elderly patient with metastatic breast cancer who developed severe adverse events such as stomatitis and interstitial pneumonia after everolimus plus exemestane treatment]. Gan To Kagaku Ryoho 2016;43:753–5. [PMID: 27306814]

[59] Pankowska-Supryn M, Zaleska M, Roszkowska-Sliz B, Roszkowski-Sliz K. Interstitial lung disease associated with docetaxel in a patient treated for breast cancer – a case report. Pneumonol Alergol Pol 2015;83:378–82. [PMID: 26378999 DOI: 10.5603/PiAP.2015.0060]

[60] Hu XC, Zhang J, Xu BH, Cai L, Ragaz J, et al. Cisplatin plus gemcitabine versus paclitaxel plus gemcitabine as first-line therapy for metastatic triple-negative breast cancer (CBCSG006): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 2015;16:436–46. [PMID: 25795409 DOI: 10.1016/S1470-2045(15)70064-1]

[61] Chatterjee S, Pilaka VK, Mukhopadhyay S, Shrimali RK, Ahmed R. Docetaxel-induced haemorrhagic interstitial pneumonitis – an acute life-threatening adverse effect. Clin Oncol (R Coll Radiol) 2015;27:483–4. [PMID: 25911197 DOI: 10.1016/j.clon.2015.03.011]

[62] Noguchi S, Masuda N, Iwata H, Mukai H, Horiguchi J, et al. Efficacy of everolimus with exemestane versus exemestane alone in Asian patients with HER2-negative, hormone-receptor-positive breast cancer in BOLERO-2. Breast Cancer 2014;21:703–14. [PMID: 23404211 DOI: 10.1007/s12282-013-0444-8]

[63] Storaas E, Holmaas G, Gravdal K, Børretzen A, Eikesdal HP. Lethal pneumonitis after docetaxel chemotherapy: case report and review of the literature. Acta Oncol 2013;52:1034–8. [PMID: 23244676 DOI: 10.3109/0284186X.2012.750734]

[64] Gurram MK, Pulivarthi S, McGary CT. Fatal hypersensitivity pneumonitis associated with docetaxel. Tumori 2013;99:e100–3. [PMID: 24158075 DOI: 10.1700/1334.14814]

[65] Ochoa R, Bejarano PA, Gluck S, Montero AJ. Pneumonitis and pulmonary fibrosis in a patient receiving adjuvant docetaxel and cyclophosphamide for stage 3 breast cancer: a case report and literature review. J Med Case Rep 2012;6:413. [PMID: 23198815 DOI: 10.1186/1752-1947-6-413]

[66] Mark M, Thurlimann B. Fatal pneumonitis after treatment with pegylated liposomal doxorubicin in a patient with metastatic breast cancer in complete remission. Med Oncol 2012;29:1477–8. [PMID: 21667322 DOI: 10.1007/s12032-011-0002-1]

[67] Ueyama Y, Yamamoto D, Yoshida H, Kanematsu S, Nakatake R, et al. [A case of interstitial pneumonitis induced by S-1]. Gan To Kagaku Ryoho 2010;37:1603–6. [PMID: 20716897]

[68] Huober J, Schoch O, Templeton A, Spirig C, Thürlimann B. Interstitial pneumonitis after treatment with bevacizumab and pegylated liposomal doxorubicin in a patient with metastatic breast cancer. Chemotherapy 2010;56:69–70. [PMID: 20145394 DOI: 10.1159/000282286]

[69] Capri G, Chang J, Chen SC, Conte P, Cwiertka K, et al. An open-label expanded access study of lapatinib and capecitabine in patients with HER2-overexpressing locally advanced or metastatic breast cancer. Ann Oncol 2010;21:474–80. [PMID: 19815649 DOI: 10.1093/annonc/mdp373]

[70] Prat A, Martínez P, Serrano C, Montero MA, Andreu J, et al. Acute lung injury associated with docetaxel and bevacizumab. Clin

Oncol (R Coll Radiol) 2007;19:803–5. [PMID: 17889516 DOI: 10.1016/j.clon.2007.08.010]

[71] Read WL, Mortimer JE, Picus J. Severe interstitial pneumonitis associated with docetaxel administration. Cancer 2002;94:847–53. [PMID: 11857321 DOI: 10.1002/cncr.10263]

[72] Mileshkin L, Prince HM, Rischin D, Zimet A. Severe interstitial pneumonitis following high-dose cyclophosphamide, thiotepa and docetaxel: two case reports and a review of the literature. Bone Marrow Transplant 2001;27:559–63. [PMID: 11313694 DOI: 10.1038/sj.bmt.1702803]