Original Article

Taxane-induced acute interstitial pneumonitis in patients with breast cancer and outcome of taxane rechallenge

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ABSTRACT

Background: Although rare, taxane-induced interstitial pneumonitis is a well-recognized toxicity following chemotherapy. Data on taxane rechallenge in patients who developed taxane-induced interstitial pneumonitis following chemotherapy are limited. Here, we share our experience of acute interstitial pneumonitis following taxane chemotherapy for breast cancer and its clinical outcome following steroids and subsequent rechallenge with taxanes in selected patients without residual lung abnormalities on imaging following steroid treatment. **Objectives:** To study the taxane-induced acute interstitial pneumonitis in patients with breast cancer receiving chemotherapy and outcome of taxane rechallenge in these patients. **Materials and Methods:** Patients with breast cancer who developed taxane-induced acute interstitial pneumonitis following chemotherapy either with paclitaxel or docetaxel were included. **Results:** Among 1240 patients with breast cancer, who received chemotherapy with either docetaxel or paclitaxel, 41 patients developed taxane-induced acute interstitial lung disease (ILD) during the study period. The interstitial pneumonitis was more seen with docetaxel. Among paclitaxel regimens, weekly schedules showed more cases of ILD than 2 weekly paclitaxel. After steroid pulse/maintenance treatment, complete resolution of lung abnormalities was seen in 76%, but residual interstitial pattern on imaging was noted in 24% of patients. Taxane rechallenge was done in 20 (49%) patients. Agents used were paclitaxel, nab-paclitaxel, or docetaxel. All rechallenged patients received short-course oral steroids for one week following taxane rechallenge as a safety measure. Rechallenge was not done in 51% either due to patient unwillingness for rechallenge (27%) or patient with residual interstitial pattern on imaging (24%). None of the patients experienced any recurrence of pneumonitis or any mortality following taxane rechallenge. **Conclusion:** Acute interstitial pneumonitis is a well-known toxicity following taxanes in breast cancer and taxane rechallenge is an option in those patients without any residual pneumonitis following steroid pulse/maintenance. We also advise short-course oral steroids for 1 week following taxane rechallenge as a safety measure. We strongly do not recommend rechallenge in patients with residual lung abnormalities after steroids.

KEY WORDS: Acute interstitial pneumonitis, breast cancer, lung toxicity, taxane chemotherapy, taxane rechallenge

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INTRODUCTION

Taxanes are highly active chemotherapy agents used for the treatment of variety of malignancies. Both paclitaxel and docetaxel are considered as an effective therapeutic agent in breast cancer management.[1] They are capable of binding to tubulin, producing unnaturally stable microtubules and subsequent cell death. Toxicity profiles are well known for these agents but are somewhat different. The pulmonary toxicities following taxane use have been described in many reports, especially in patients with nonsmall cell lung cancer, breast cancer, and prostate cancer.[2-4] The most common pulmonary adverse event with taxanes is interstitial pneumonitis. To the best of our knowledge, no much studies to date have looked at the use of taxane rechallenge and its outcome in patients who developed taxane-induced pneumonitis. Here, we present a prospective clinical audit of patients who developed taxane-induced acute interstitial pneumonitis in patients with breast cancer receiving chemotherapy and describe the outcome of taxane rechallenge in these patients.

Aim

To study the taxane-induced acute interstitial pneumonitis in patients with breast cancer receiving chemotherapy and outcome of taxane rechallenge in these patients.

MATERIALS AND METHODS

This was an observational analysis of patients with breast cancer who developed taxane-induced acute interstitial lung disease (ILD) following chemotherapy either with paclitaxel or docetaxel treated under the department of medical oncology in a tertiary cancer care center in India during the period from January 2017 to December 2019. A baseline computed tomography (CT) imaging of the chest and abdomen was done as part of routine workup in all patients planned for active treatment for breast cancer.

All patients underwent spirometry, high-resolution CT (HRCT) of the chest, and serologic testing for connective tissue disease (rheumatoid factor and antinuclear antibody) and sputum acid-fast bacilli sample for *Mycobacterium tuberculosis* in patients suspected of interstitial pneumonitis. Sputum culture and sensitivity was done to rule out any infectious causes. A baseline echocardiography was done to exclude cardiac causes. A serum D-dimer assay was carried out to rule out acute pulmonary embolism.

Patient's clinical and radiological data including age, comorbidities, stage of breast cancer, pathological characteristics, details of chemotherapy, particularly docetaxel and paclitaxel, imaging abnormalities of lung toxicities, details of treatment for lung toxicity, response to steroids, taxane rechallenge, radiological response, and follow-up status were prospectively noted. The grading of pneumonitis was done by the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0 criteria. Grade I was asymptomatic, Grade II was symptomatic with limiting instrumental active daily living and medical intervention indicated, Grade III was severe symptoms with limitation of self-care active daily living and oxygen was indicated, Grade IV is life-threatening respiratory compromise and urgent intervention indicated like intubation, and Grade V was death.

RESULTS

Baseline characteristics

Among 1240 patients with breast cancer, who received chemotherapy with either docetaxel or paclitaxel, 41 patients developed taxane-induced acute ILD during the study period. Baseline characteristics of patients are shown in Table 1. All 41 (100%) patients were female breast cancers. The patient's age was in the range of 32 years to 69 years, with a median age of 51 years.

Among the patients who had taxane-induced acute ILD, 17 (42%) patients were stage 2 breast cancers, 21 (51%) patients were stage 3, and 3 (7%) patients were stage 4 breast cancers.

Risk factors

Among the standard risk factors for drug-induced lung toxicities described in literature, elderly age >65 years was seen in 4 (10%) patients, 2 (5%) patients had a history of pulmonary tuberculosis, and 1 (2.4%) patient had diabetic kidney disease. Other risk factors identified were connective tissue disorder (2.4%), bronchiectasis (2.4%), prior radiation to chest (2.4%), previous lung resection (2.4%), and concomitant fungal infection (2.4%). No patient had smoking habit. The patient with connective tissue disorder was an old case of systemic lupus erythematosus (SLE) without any active or exacerbation of SLE.

Chemotherapy

Among 41 study patients who developed taxane-induced acute ILD, 21 (51%) patients were on neoadjuvant chemotherapy, 17 (43%) patients on adjuvant chemotherapy, and 3 (5%) patients on palliative chemotherapy.

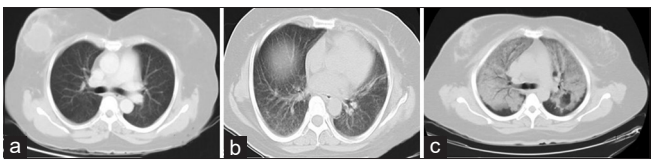

Figure 1: (a) High-resolution computed tomography scan of the thorax shows docetaxel-induced early acute interstitial pneumonitis with diffuse ground-glass opacities in both lungs with areas of air trapping and minimal interstitial thickening is also seen in bilateral lung bases. (b) Docetaxel-induced moderate acute interstitial pneumonitis with septal thickening with ill-defined ground-glass nodules bilaterally in the posterior lung segments. (c) Severe acute interstitial pneumonitis following docetaxel with diffuse ground glassing with interlobular septal thickening and hepatization of lung sparing posterior subpleural space

Table 1: Baseline characteristics of breast cancer patients with taxane-induced pneumonitis

Variables	Number (%)
Total number of patients	41
Age (years)	32-69
Median age (years)	51
Sex	
Male	0
Female	41 (100%)
Stages of breast cancer	
1	0
2	17 (42%)
3	21 (51%)
4	3 (7%)
Risk factors	
Elderly age (>65 years)	4 (10%)
History of pulmonary tuberculosis	2 (5%)
Concomitant fungal infection	1 (2.4%)
Connective tissue disorder	1 (2.4%)
Smoking habits	0
Prior radiation	1 (2.4%)
Bronchiectasis	1 (2.4%)
Prior lung resection	1 (2.4%)
Diabetic nephropathy	1 (2.4%)
Type of chemotherapy	
Neoadjuvant chemotherapy	21 (51%)
Adjuvant chemotherapy	17 (42%)
PAL chemotherapy	3 (7%)
Chemoregimen	
AC × 4-docetaxel × 4 cycles	8 (20%)
FEC × 3-docetaxel × 3 cycles	4 (10%)
Dose-dense AC × 4-weekly PACLI × 12 cycles	12 (29%)
Dose-dense AC × 4-DD PACLI × 4 cycles	4 (10%)
FECX3-weekly pacli	1 (2.4%)
FinHer protocol	7 (17%)
APT protocol	1 (2.4%)
TC × 4 cycles	1 (2.4%)
PAL docetaxel + trastuzumab	1 (2.4%)
PAL single agent docetaxel	1 (2.4%)
PAL spaclitaxel + trastuzumab	1 (2.4%)
Taxane induced	
Docetaxel	22 (54%)
Paclitaxel	19 (46%)
Clinical symptoms	
Cough	21 patients (51%)
Dyspnea on exertion	40 patients (98%)
Fever	7 patients (17%)
Decline in saturation (SPO_2)	6 patients (15%)
Median duration of symptoms	2 week
Imaging	
Normal chest X-ray	27 patients (66%)
Chest xray abnormalities	14 patients (34%)
HRCT chest imaging abnormalities	41 patients (100%)
Treatment details	
Intravenous methylprednisolone	21 patients (51%)
Oral prednisolone	20 patients (49%)
Maintenance oral prednisolone for 6-8 weeks	38 patients (93%)
Radiological response after steroids	
Complete resolution of lung abnormalities	31 patients (76%)
Residual interstitial pattern on imaging	10 patients (24%)
Ventilatory support	2 patients (5%)
Mortality	4 patients (10%)
Rechallenge with taxanes (in patients with complete resolution of lung abnormalities after steroids)	
With docetaxel	13 patients (32%)
With paclitaxel	6 patients (14.6%)
With nab - paclitaxel	1 patients (2.4%)
Total taxane rechallenge	20 patients (49%)

Contd...

Table 1: Contd...

Variables	Number (%)
Mortality after taxane rechallenge	Nil
ILD after taxane rechallenge	Nil
No rechallenge with taxanes	
Patient unwillingness for rechallenge (in patients with complete resolution of lung abnormalities after steroids)	11 patients (27%)
Rechallenge option not considered (for patient with residual interstitial pattern on imaging)	10 patients (24%)
Total patients with rechallenge not attempted	21 patients (51%)

NACT: Neoadjuvant, ADJ: Adjuvant, PAL: Palliative, DD: Dose dense, AC: Anthracycline + cyclophosphamide, FEC-5: Fluorouracil + epirubicin + cyclophosphamide, FINHER: Finland herceptin (FinHer) trial, TRASTU: Trastuzumab, PACLI; Paclitaxel, TC: Docetaxel + cyclophosphamide, ILD: Interstitial lung disease, HRCT: High-resolution computer tomography

The following chemotherapy schedules were used in our study population. Two weekly regimens of dose dense (DD) chemo with ACX4 cycles followed by DD paclitaxel × 4 cycles was used in 4 (10%) patients, 2 weekly regimen of DD chemo (DD) with AC × 4 cycles followed by 12 cycles of weekly paclitaxel in 12 (30%) patients, 3 weekly regimen of AC × 4 cycles followed by 3 weekly docetaxel × 4 cycles in 8 (20%) patients, FEC × 3 cycles followed by Docetaxel x 3 cycles in 4 (10%) patients, FEC × 3 cycles followed by weekly paclitaxel × 12 cycles in 1 (3%) patient, TC × 4 cycles in 1 (3%) patient. Among curative human epidermal growth factor receptor 2 (HER 2)-positive breast cancers, 7 (17%) patients received FinHer protocol and 1 (3%) patient received APT protocol.

Among palliative intent patients who had ILD, 1 (3%) patient received palliative docetaxel with trastuzumab, 1 (3%) patient was on palliative weekly paclitaxel with trastuzumab, and 1 (3%) patient received palliative single-agent docetaxel.

Symptomatology

Among 41 patients with taxane-related acute lung toxicity, 40 (98%) patients experienced dyspnea on excertion, 21 (51%) patients had cough, and fever was seen in 7 (17%) patients. Six (15%) patients presented with ARDS like picture with decline in SPO2. The mean duration of symptoms was 2 weeks.

Among drug-induced lung toxicity, docetaxel-related acute interstitial pneumonitis was seen with 22 (54%) patients, whereas paclitaxel induced interstitial pneumonitis in 19 (46%) patients. The incidence of drug-induced pneumonitis was 3.3%.

Imaging abnormalities

Chest X-ray

Among 41 patients with clinical features of drug-induced lung toxicities, 27 (66%) patients had normal chest X-ray. Only 14 (34%) patients had chest X-ray abnormalities in the form of interstitial pattern, pleural effusion, and consolidation.

High-resolution computed tomography imaging

Table 2 shows taxane-induced lung abnormalities on CT imaging of breast cancer patients. Bilateral lung involvement seen in 28 (68%) patients. Bibasal involvement was noted in 5 (13%) patients, bilateral lower lobe in 5 (13%) patients, unilateral lower lobe in 2 (5%) patients, and unilateral upper lobe in 1 (2.5%) patient.

Bilateral diffuse pattern was seen in 12 (29%) patients. Ground-glassing pattern was seen in 25 (60%) patients. Interstitial pattern was seen in 18 (44%) patients, alveolar pattern in 6 (15%) patients, septal thickening in 12 (30%) patients, reticulonodular shadows in 5 (13%) patients, consolidation in 3 (7.5%) patients, reticular pattern in 3 (7.5%) patients, nodular pattern in 2 (5%) patients, pleural nodule in 4 (10%) patients, and pleural effusion in 1 (2.4%) patient.

Bilateral lung involvement with paclitaxel was seen in 15 (37%) patients, whereas docetaxel in 13 (32%) patients. Bilateral diffuse pattern in docetaxel was seen in 7 (17%) patients and paclitaxel in 5 (12%) patients. Paclitaxel-induced ground-glassing pattern was seen in 13 (32%) patients and docetaxel-related ground glassing was seen in 12 (29%) patients. Interstitial pattern on chest CT was seen in 9 (22%) patients in paclitaxel and docetaxel in 9 (22%) patients. Alveolar pattern seen in 4 (10%) patients was due to paclitaxel whereas docetaxel was seen in 2 (5%) patients.

Septal thickening was more seen with docetaxel in 8 (20%) patients and paclitaxel in 4 patients. Reticulonodular shadows seen in 3 (7%) patients were due to docetaxel and paclitaxel in 2 (5%) patients. Paclitaxel-induced pleural effusion was seen in 1 (2.4%) patient [Figure 1].

Grading and treatment of taxane-induced interstitial pneumonitis

The diagnosis of taxane-induced interstitial pneumonitis was based on the combination of a compatible clinical pattern and radiological pattern, exposure history, and the exclusion of other causes of diffuse pulmonary infiltrates.

All the patients suspected of taxane-induced interstitial pneumonitis were advised to stop chemotherapy. Treatment was initiated on all patients who developed symptomatic pneumonitis such as dyspnea on excertion, cough, and decline in saturation. Investigation was done for any evidence of sepsis or respiratory infections or cardiac dysfunction. Immediate HRCT was done in all patients suspected of taxane-induced ILD to confirm the diagnosis. Immediate initiation of steroid was

the mainstay of treatment. We initiated intravenous methylprednisolone or oral prednisolone depending on the severity of pneumonitis. Twenty (49%) patients had grade II pneumonitis and 17 (41%) patients had grade III pneumonitis and 4 (10%) patients had grade IV pneumonitis at the time of initiation of steroids. In patients with mild (Grade I) to moderate (Grade II) symptoms of interstitial pneumonitis, we started on oral pulse dose prednisolone 1 mg/kg/day for 5–7 days followed by maintenance oral prednisolone for 8–12 weeks.

Intravenous methylprednisolone was mainly started on patients with severe to life-threatening interstitial pneumonitis (Grade III/IV). The dose was 1 g/day for 3–5 days followed by maintenance oral prednisolone for 8–12 weeks depending on severity.

In our study, intravenous methylprednisolone received in 21 (51%) patients, whereas oral pulse dose of prednisolone was received for 20 (49%) patients. Oral prednisolone as maintenance for 6–8 weeks was initiated in 37 (93%) patients.

Taxane schedule and relation to develop acute taxane-induced interstitial pneumonitis

Table 3 shows details of patients with taxane induced interstitial pneumonitis and its relation with number of chemotherapy and time frame to develop ILD from last chemotherapy.

Dose-dense (2 weekly schedule) paclitaxel

Among patients who received DD paclitaxel, 1 (3%) patient developed acute interstitial pneumonitis following the first cycle of paclitaxel and 3 (8%) patients following the second cycle of DD paclitaxel. The median number of cycles for DD paclitaxel to develop ILD was 2 cycles. The time frame to develop ILD was 7–10 days for DD paclitaxel.

Weekly schedule of paclitaxel

Among patients who received one weekly schedule of paclitaxel, 4 (10%) patients developed acute interstitial pneumonitis following 1 cycle of paclitaxel, 2 (5%) patients after 2 cycles, 1 (3%) patient after 3 cycles, 3 (8%) patients after 5 cycles, 1 (3%) patient after 7 cycles, 1 (3%) patient after 8 cycles, and 1 (3%) patient after 12 cycles. The median number of cycles for weekly paclitaxel to develop ILD was 5 cycles. The time frame to develop ILD was 7–12 days for weekly schedules of paclitaxel.

Table 2: Computed tomography abnormalities in breast cancer patients with taxane-induced pneumonitis

CT findings	Total (%)	Docetaxel (%)	Paclitaxel (%)
Bilateral lung	28 (68)	13 (32)	15 (37)
Bilateral lower lobe	5 (12)	2 (5)	3 (7)
Unilateral lower lobe	2 (5)	1 (2.4)	1 (2.4)
Unilateral upper lobe	1 (2.4)	0	1 (2.4)
Bibasal	5 (12)	5 (12)	0
Bilateral diffuse	12 (29)	7 (17)	5 (12)
Ground glass	25 (60)	12 (29)	13 (32)
Interstitial pattern	18 (44)	9 (22)	9 (22)
Alveolar pattern	6 (15)	2 (5)	4 (10)
Pleural nodule	4 (10)	3 (7)	1 (2.4)
Pleural effusion	1 (2.4)	0	1 (2.4)
Reticular	3 (7.5)	2 (5)	1 (2.4)
Nodular	2 (5)	1 (2.4)	1 (2.4)
Reticulonodular	5 (13)	3 (7)	2 (5)
Septal thickening	12 (30)	8 (20)	4 (10)
Consolidation	3 (7.5)	2 (5)	1 (2.4)

CT: Computed tomography

Three weekly schedule of docetaxel

Among patients who received 3 weekly schedule of docetaxel, 4 (10%) patients developed acute interstitial pneumonitis following 1 cycle of docetaxel, 4 (10%) patients after 2 cycles, 8 (20%) patients after 3 cycles, and 5 (13%) patients after 4 cycles. The median number of cycles for 3 weekly docetaxel to develop ILD was 3 cycles. One (3%) patient developed acute interstitial pneumonitis following single-agent docetaxel in a patient with metastatic breast cancer on palliative intent. The time frame to develop ILD was 7–14 days for docetaxel.

Human epidermal growth factor receptor 2-positive breast cancers, taxanes, and acute interstitial pneumonitis

Among HER 2-positive breast cancers who developed ILD, 7 (18%) patients developed acute interstitial pneumonitis following FinHer protocol which is a chemoprotocol with three cycles of 3 weekly docetaxel along with nine weekly schedules of short trastuzumab followed by three cycles of fluorouracil, epirubicin, and cyclophosphamide.

One (3%) patient developed acute interstitial pneumonitis following APT (Tolaney) protocol which contains 12 cycles of weekly schedules of short trastuzumab and weekly paclitaxel followed by adjuvant 1-year trastuzumab. ILD was noticed after 8th cycles of weekly paclitaxel schedule.

One (3%) patient developed acute interstitial pneumonitis following palliative chemo with weekly paclitaxel with trastuzumab. Another patient with metastatic HER 2-positive breast cancer who received docetaxel with trastuzumab also had ILD related with docetaxel.

Respiratory outcome and clinical sequelae

Complete resolution of lung abnormalities in response to steroid was seen in 30 (75%) patients. The residual interstitial pattern on imaging after treatment was noticed in 10 (25%) patients. Mechanical ventilation for acute respiratory distress syndrome was required in 2 (5%) patients. About 4 (10%) patients had mortality related with taxane-induced acute ILD.

Rechallenge with taxane

Table 4 shows the details of taxane rechallenge in patients with taxane-induced acute lung toxicities and its final outcome.

Rechallenge was not attempted in 21 (53%) patients, especially when patients had active respiratory symptoms following steroids and also in patients with active

Table 3: Patients with taxane-induced interstitial lung disease and its relationship with number of chemotherapy

Drug	Dosage (mg/m^2)/ cycle	Number of chemotherapy cycles to develop ILD	Time frame to ILD from last chemo (days)	Number of patients with ILD, *n* (%)
A Paclitaxel				
Dose-dense paclitaxel	175/2 weekly	1	7	1 (2.4)
		2	10	3 (8)
Weekly paclitaxel	80	1	8	4 (10)
		2	12	2 (5)
		3	7	1 (2.4)
		5	7	3 (8)
		7	10	1 (2.4)
		8	8	1 (2.4)
		12	7	1 (2.4)
PAL paclitaxel + trastuzumab	175/3 weekly	5	14	1 (3)
APT protocol	80	8	7	1 (3)
Total				19 (46)
B Docetaxel				
Docetaxel	100/3 weekly	1	10	5 (12)
		2	9	4 (10)
		3	7	8 (20)
		4	14	5 (12)
Total				22 (54)

APT: Adjuvant paclitaxel and trastuzumab, ILD: Interstitial lung diseases, PAL: Palliative

Table 4: Taxane rechallenge in taxane-induced acute interstitial pneumonitis

Age	Chemo regimen received	Agent caused ILD	Radiological outcome after steroids	Agent rechallenged after steroid maintenance	Radiological outcome after rechallenge	Status
35	AC - docetaxel	Docetaxel	No residual ILD	Docetaxel	No features of ILD	Alive
57	FEC - docetaxel	Docetaxel	No residual ILD	Docetaxel	No features of ILD	Alive
43	DDAC - weekly paclitaxel	Paclitaxel	No residual ILD	Paclitaxel	No features of ILD	Alive
56	DDAC - weekly paclitaxel	Paclitaxel	No residual ILD	Docetaxel	No features of ILD	Alive
69	FINHER	Docetaxel	No residual ILD	Docetaxel	No features of ILD	Alive
45	DDAC - weekly paclitaxel	Paclitaxel	No residual ILD	Paclitaxel	No features of ILD	Alive
39	DDAC - weekly paclitaxel	Paclitaxel	No residual ILD	Paclitaxel	No features of ILD	Alive
48	AC - docetaxel	Docetaxel	No residual ILD	Docetaxel	No features of ILD	Alive
56	DDAC - weekly paclitaxel	Paclitaxel	No residual ILD	Paclitaxel	No features of ILD	Alive
53	FINHER	Docetaxel	No residual ILD	Docetaxel	No features of ILD	Alive
65	FEC - docetaxel	Docetaxel	No residual ILD	Docetaxel	No features of ILD	Alive
43	DDAC - weekly paclitaxel	Paclitaxel	No residual ILD	Paclitaxel	No features of ILD	Alive
64	AC - docetaxel	Docetaxel	No residual ILD	Docetaxel	No features of ILD	Alive
37	FINHER	Docetaxel	No residual ILD	Docetaxel	No features of ILD	Alive
65	FINHER	Docetaxel	No residual ILD	Docetaxel	No features of ILD	Alive
51	APT	Paclitaxel	No residual ILD	Paclitaxel	No features of ILD	Alive
43	Docetaxel	Docetaxel	No residual ILD	Docetaxel	No features of ILD	Alive
32	DDAC - weekly paclitaxel	Paclitaxel	No residual ILD	Docetaxel	No features of ILD	Alive
47	AC - docetaxel	Docetaxel	No residual ILD	Docetaxel	No features of ILD	Alive
49	AC - docetaxel	Docetaxel	No residual ILD	Nab paclitaxel	No features of ILD	Alive

DD: Dose dense, AC: Anthracycline + cyclophosphamide, FEC-5: Fluorouracil + epirubicin + cyclophosphamide, FINHER: Finland herceptin (FinHer) trial, APT: Adjuvant paclitaxel and trastuzumab, ILD: Interstitial lung disease

residual pulmonary infiltrate on imaging, even after oral prednisolone maintenance.

Rechallenge with taxane was tried in 19 (48%) patients who recovered from acute interstitial pneumonitis clinically and radiologically.

Among the 19 patients selected for rechallenge with taxane, 11 patients had docetaxel-induced ILD and 8 patients had paclitaxel-induced ILD.

The rechallenge was initiated after a very high-risk consent from patients and relatives. The decision of rechallenge was also based on age, comorbidity status, tumor biology, and patient risk consent and physician choice.

Fourteen (35%) patients received rechallenge with docetaxel, whereas rechallenge with paclitaxel was done in 6 (15%) patients. All rechallenged patients were put on short-course oral steroids during and following rechallenge for 1 week as a safety measure.

Out of 11 patients with docetaxel-related ILD, all 11 patients were rechallenged with the same agent, docetaxel. Among 8 patients with paclitaxel-induced

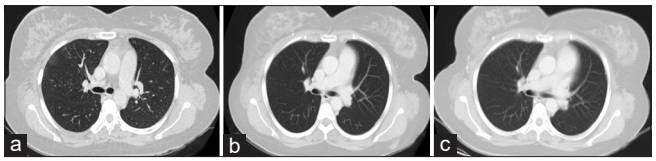

Figure 2: High-resolution computed tomography scan images of steroid response and post-taxane rechallenge in taxane-induced interstitial lung disease. (a) Baseline high-resolution computed tomography of the thorax showing early interstitial pneumonitis following paclitaxel with patchy areas of ground glass and interstitial thickening in the right upper lobe and middle lobe. (b) Complete resolution of early interstitial pattern after steroid treatment. (c) Follow-up computed tomography after taxane rechallenge showing no evidence of interstitial pneumonitis

ILD, 6 patients were rechallenged with the same agent, paclitaxel. Only 2 patients were rechallenged with an alternate agent. Two patients with paclitaxel induced ILD following weekly schedule, was rechallenged with docetaxel.

All 19 (48%) patients had safe and successful taxane rechallenge. None of these patients experienced any respiratory deterioration after taxane rechallenge. All patients who received rechallenge were on oral prednisolone maintenance. All the patients who received rechallenge with taxane are alive without any lung sequelae.

Table 5 shows treatment details, response to treatment, rechallenge, and final outcome of patients taxane-induced lung toxicities in breast cancer patients [Figures 2 and 3].

DISCUSSION

Acute interstitial pneumonia (AIP) is characterized by rapidly progressive dyspnea developing over days to weeks and subsequent respiratory failure occurring in patients without preexisting lung disease or extrathoracic disorders known to be associated with lung involvement.[5]

The causes of AIP, particularly in patients with cancer, are many. The common causes are lung toxicities following chemotherapy, radiotherapy, immunotherapy, monoclonal antibodies, or small-molecule kinase inhibitors. The other causes are infections, pulmonary embolism, pulmonary hemorrhage, cardiogenic pulmonary edema, transfusion-related acute lung injury, disease-related factors such as metastatic progression, lymphangitis carcinomatosis, connective tissue disorders, and pulmonary hypertension. Various treatment modalities, such as tyrosine kinase inhibitors, immune checkpoint inhibitors, and chimeric antigen receptor cell therapy, can also cause interstitial pneumonitis.[6]

Chemotherapy-related pulmonary toxicity has a wide spectrum of involvement that ranges from interstitial pneumonitis, organizing pneumonia, diffuse alveolar damage, alveolar hemorrhage, and noncardiogenic pulmonary edema.

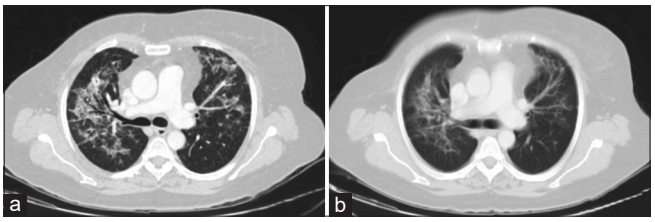

Figure 3: High-resolution computed tomography images of residual response to steroid in taxane-induced interstitial lung disease. (a) Baseline high-resolution computed tomography of the thorax showing drug induced interstitial pneumonitis following docetaxel with interstitial septal thickening and alveolar opacities in bilateral lung fields, more on the right side. (b) Residual lung lesions after steroid therapy with ill-defined patchy alveolar opacities and septal thickening in bilateral lung parenchyma

Docetaxel, paclitaxel, methotrexate, pemetrexed, bortezomib, fludarabine, gemcitabine, ifosfamide, irinotecan, oxaliplatin, thalidomide, lenalidomide, and vinca alkaloids are the agents reported to cause AIP in cancer patients.

Pneumonitis following immunotherapy is a serious immune-related adverse event that occurs after therapy with PD-1, PD-L1, and CTLA-4 inhibitors. Pneumonitis after immunotherapy typically presents as nonspecific interstitial pneumonitis or organizing pneumonia.[7]

The diagnosis of drug-induced pneumonitis is always a diagnosis of exclusion. Opportunistic infections such as pneumocystis jiroveci pneumonia, pulmonary embolism, and lymphangitic carcinomatosis are possible diagnoses to be ruled out. Other causes of respiratory distress have to be excluded with laboratory workup, imaging, biopsy studies, and results of antibiotic treatment. We also have to consider the temporal association of start of taxane and development of pneumonitis.

The common pattern of taxane-related lung toxicity that we come across in clinical practice is acute interstitial pneumonitis. Interstitial pneumonitis induced by taxanes is thought to be due to an immune-mediated delayed hypersensitivity reaction (HSR).

The incidence of ILD associated with docetaxel in patients treated with docetaxel in nonsmall-cell lung cancer was 4.6% by Tamiya *et al*. and ILD was mainly seen in patients with preexisting ILD.[8]

The incidence of drug-induced pneumonitis was 3.3% in our study, whereas Manuprasad *et al*. reported an incidence of docetaxel-induced lung injury in breast cancer of 1.7%.[9] A retrospective analysis by Tamiya *et al*. found that patients with emphysematous or interstitial changes had a higher chance of developing interstitial toxicity, whereas other clinical factors such as age, gender, smoking, performance status, and previous chemotherapy were not linked to pulmonary damage.[8]

Table 5: Final outcome of taxane-induced acute interstitial pneumonitis in breast cancer patients

Age	Regimen used	Settings	Causative agent	Grading of pneumonitis at the time of initiation of steroid	Steroid used	Duration (days)	Maintenance steroid duration (weeks)	Ventilatory support	Radiological response after steroids	Taxane rechallenge	Agent rechallenged	Status
35	AC - docetaxel	ADJ	Docetaxel	Grade III	Methylprednisolone	5	4	No	Recovered	Yes	Docetaxel	Alive
57	FEC - docetaxel	NACT	Docetaxel	Grade II	Prednisolone	5	4	No	Recovered	Yes	Docetaxel	Alive
43	DDAC - weekly paclitaxel	NACT	Paclitaxel	Grade II	Prednisolone	5	4	No	Recovered	Yes	Paclitaxel	Alive
56	DDAC - weekly paclitaxel	ADJ	Paclitaxel	Grade III	Methylprednisolone	7	6	No	Recovered	Yes	Docetaxel	Alive
47	FINHER	ADJ	Docetaxel	Grade III	Methylprednisolone	5	4	No	Interstitial pattern	No	-	Alive
35	DDAC - weekly paclitaxel	ADJ	Paclitaxel	Grade II	Prednisolone	7	4	No	Interstitial pattern	No	-	Alive
66	TC	ADJ	Docetaxel	Grade II	Prednisolone	7	4	No	Interstitial pattern	No	-	Alive
69	FinHer	ADJ	Docetaxel	Grade II	Prednisolone	7	8	No	Recovered	Yes	Docetaxel	Alive
45	DDAC - weekly paclitaxel	NACT	Paclitaxel	Grade II	Prednisolone	7	6	No	Recovered	Yes	Paclitaxel	Alive
50	FEC - docetaxel	ADJ	Docetaxel	Grade II	Prednisolone	7	4	No	Recovered	No	-	Alive
39	DDAC - weekly paclitaxel	ADJ	Paclitaxel	Grade III	Methylprednisolone	5	6	No	Recovered	Yes	Paclitaxel	Alive
58	Docetaxel - TRASTU	PAL	Docetaxel	Grade II	Prednisolone	7	4	No	Recovered	No	-	Alive
53	FEC - docetaxel	NACT	Docetaxel	Grade III	Methylprednisolone	5	4	No	Recovered	No	-	Alive
48	AC - docetaxel	ADJ	Docetaxel	Grade III	Methylprednisolone	5	6	No	Recovered	Yes	Docetaxel	Alive
56	DDAC - weekly paclit	NACT	Paclitaxel	Grade III	Methylprednisolone	5	6	No	Recovered	Yes	Paclitaxel	Alive
53	FINHER	NACT	Docetaxel	Grade III	Methylprednisolone	5	6	No	Recovered	Yes	Docetaxel	Alive
65	FEC - docetaxel	ADJ	Docetaxel	Grade II	Prednisolone	7	4	No	Recovered	Yes	Docetaxel	Alive
46	AC - docetaxel	NACT	Docetaxel	Grade III	Methylprednisolone	5	4	No	Interstitial pattern	No	-	Expired
43	DDAC - weekly paclitaxel	NACT	Paclitaxel	Grade II	Prednisolone	7	6	No	Recovered	Yes	Paclitaxel	Alive
54	DDAC - weekly paclitaxel	NACT	Paclitaxel	Grade III	Methylprednisolone	5	6	No	Interstitial pattern	No	-	Alive
64	AC - docetaxel	NACT	Docetaxel	Grade II	Prednisolone	7	4	No	Recovered	Yes	Docetaxel	Alive
37	FinHer	NACT	Docetaxel	Grade III	Methylprednisolone	5	6	No	Recovered	Yes	Docetaxel	Alive
44	DDAC - DD paclitaxel	NACT	Paclitaxel	Grade IV	Methylprednisolone	5	6	Yes	Interstitial pattern	No	-	Alive
42	AC - docetaxel	ADJ	Docetaxel	Grade II	Prednisolone	7	4	No	Recovered	No	-	Alive
65	FINHER	NACT	Docetaxel	Grade II	Prednisolone	7	6	No	Recovered	Yes	Docetaxel	Alive
63	DDAC - weekly paclitaxel	NACT	Paclitaxel	Grade III	Methylprednisolone	5	6	No	Recovered	No	-	Alive
51	APT	ADJ	Paclitaxel	Grade III	Methylprednisolone	5	4	No	Recovered	Yes	Paclitaxel	Alive
59	DDAC - DD paclitaxel	ADJ	Paclitaxel	Grade II	Methylprednisolone	7	8	No	Interstitial pattern	No	-	Alive
43	Docetaxel	PAL	Docetaxel	Grade III	Methylprednisolone	5	8	No	Recovered	Yes	Docetaxel	Alive
32	DDAC - weekly paclitaxel	NACT	Paclitaxel	Grade III	Methylprednisolone	5	8	No	Recovered	Yes	Docetaxel	Alive
56	AC - docetaxel	ADJ	Docetaxel	Grade II	Prednisolone	7	6	No	Interstitial pattern	No	-	Alive
55	DDAC - weekly paclitaxel	NACT	Paclitaxel	Grade IV	Methylprednisolone	5	-	Yes	Interstitial pattern	No	-	Expired
48	FinHer	ADJ	Docetaxel	Grade II	Prednisolone	7	6	No	Recovered	No	-	Alive
54	DDAC - DD paclitaxel	NACT	Paclitaxel	Grade II	Prednisolone	7	4	No	Recovered	No	-	Alive
63	Weekly PACLI+TRASTU	PAL	Paclitaxel	Grade II	Prednisolone	5	6	No	Recovered	No	-	Alive
47	AC - docetaxel	ADJ	Docetaxel	Grade II	Prednisolone	5	4	No	Recovered	Yes	Docetaxel	Alive
44	FEC - paclitaxel	ADJ	Paclitaxel	Grade II	Prednisolone	5	6	No	Recovered	No	-	Alive
40	DDAC - DD paclitaxel	NACT	Paclitaxel	Grade III	Methylprednisolone	5	4	No	Recovered	No	-	Alive
54	FINHER	NACT	Docetaxel	Grade IV	Methylprednisolone	7	-	No	Interstitial pattern	No	-	Expired
42	DD AC - weekly PACLI	NACT	Paclitaxel	Grade IV	Methylprednisolone	7	-	No	Interstitial pattern	No	-	Expired
49	AC - docetaxel	NACT	Docetaxel	Grade III	Methylprednisolone	7	6	No	Recovered	Yes	Nab psaclitaxel	Alive

NACT: Neoadjuvant, ADJ: Adjuvant, PAL: Palliative, DD: Dose dense, AC: Anthracycline + cyclophosphamide, FEC-5: Fluorouracil + epirubicin + cyclophosphamide, RASTU: Trastuzumab, PACLI: Paclitaxel

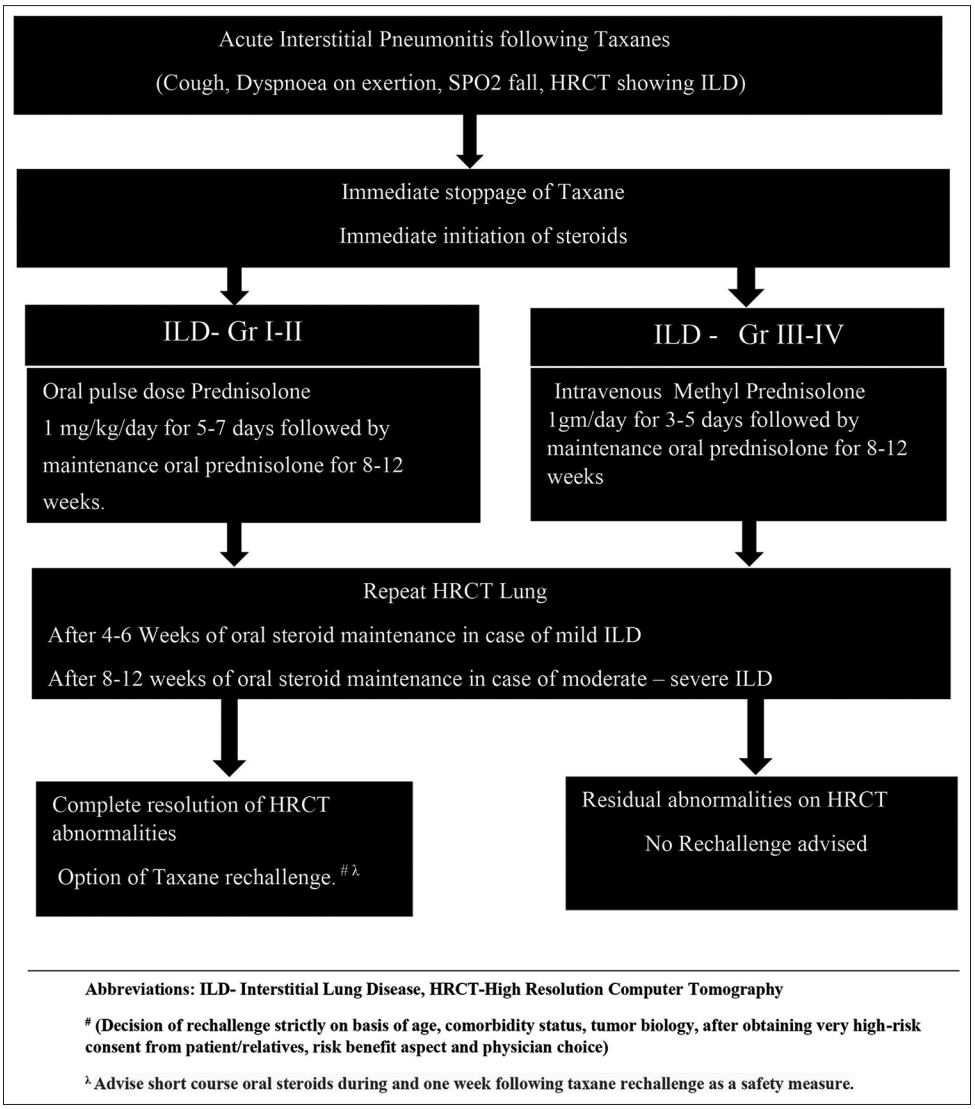

Figure 4: Proposed algorithm for taxane rechallenge

The risk factors identified in our study were elderly age >65 years, history of pulmonary tuberculosis, diabetic kidney disease, concomitant connective tissue disorder, bronchiectasis, prior radiation to chest, previous lung resection, and concomitant fungal infection. Although increased risk for pulmonary toxicity with weekly or biweekly therapy compared to triweekly therapy has been reported in many studies,[10] we noticed that three weekly docetaxel had more cases of ILD when compared to paclitaxel either weekly or 2 weekly. When compared to different schedules of paclitaxel regimens, weekly schedules showed more cases of ILD than 2 weekly paclitaxel. The average time frame to develop ILD following taxane chemotherapy was 7–14 days. Higher incidence of pulmonary toxicity was noted when taxanes combined with gemcitabine and also seen following radiation. Prompt diagnosis and early discontinuation of the suspected drug are needed since pulmonary toxicity can rapidly progress and may ultimately lead to severe respiratory distress and mortality. Taxane-induced pneumonitis responds rapidly to steroid therapy and pulmonary toxicity can be reversed with high-dose steroid administration.[11] All of our patients received overnight dexamethasone steroid prophylaxis. Although we commonly administer dexamethasone prophylaxis for paclitaxel-induced HSRs, the true efficacy of this regimen is unknown. As per the study by Njigha *et al*., pneumonitis caused by paclitaxel needs discontinuation of its use, and ILD was not reactivated after rechallenge with nab-paclitaxel.[12] Re-exposure could be performed either through rapid drug desensitization based on the severity of the initial HSR and the skin test result in patients with a HSR following taxanes.[13] However, on the other hand, patients with non-severe delayed onset HSRs may be safely re-exposed to taxanes. Only minority of patients had recurrence of delayed reactions and they were rarely severe and they tend to subside over repeated exposures.

General consensus is that severe delayed-type HSRs such as pneumonitis should not be re-exposed to the inciting agent and probably due to potentially cross-reacting drugs.

We know that taxanes are not necessarily equivalent to one another regarding their general toxic effect profile. It also appears that the cross-reactivity rate between paclitaxel and docetaxel varies among different populations. Therefore, the decision to change from one taxane to another should not be based solely on the risk of cross-reactivity.

A study by Moon *et al*. described patients with immediate HSRs to paclitaxel that did not react when treated with docetaxel, suggesting that cross-reactivity between taxanes was low.[14] We do not experience any recurrence of pneumonitis following taxane rechallenge in patients with taxane-induced pneumonitis who achieved complete resolution of HRCT abnormalities following steroid maintenance.

The reason for no recurrence of ILD on rechallenge with taxane may be due to the fact that these patients were on close observation for ILD recurrence and mostly were on low-dose steroids during and after rechallenge in fear of recurrence. Rechallenge was strictly avoided in patients with residual features of ILD after steroid maintenance.

Table 6 shows comparison of the present study with previously published studies in patients with AIP following chemotherapy with either paclitaxel or docetaxel.

Compared to previously published articles, the present study reports higher number of 41 cases of AIP following taxane chemotherapy. Most of the reported articles are single case reports or small case series with number of cases ranging from 2 to 8 cases of taxane-induced AIP.[10,15,16] All of our patients had nonspecific acute interstitial pneumonitis following taxane chemotherapy similar to studies reported by Manuprasad *et al*.[9] and Raghupathi *et al*.[10] Unlike our study, Njigha *et al*.[12] and Wang *et al*.[16] described hypersensitivity pneumonitis following taxane chemotherapy. Steroid was the main stay of treatment in all published studies. Methylprednisolone and prednisolone were the agents used. Higher mortality is expected in patients requiring mechanical ventilation for taxane-induced AIP. In the present study, the two patients required mechanical ventilation had dismal prognosis which was similar to the findings in a study by Wang *et al* which showed that all the four patients had dismal prognosis with docetaxel induced HP in lung cancer requiring mechanical ventilation.[16]

Taxane rechallenge in patients with breast cancer who had pneumonitis post-taxane use has been described only in a study by Njigha *et al*., where in three cases of paclitaxel-induced AIP, the use of nab-paclitaxel was shown to be a possible alternative option for rechallenge.[12] Nab-paclitaxel exhibited good efficacy and safety profile for taxane rechallenge in patients with breast cancer who have paclitaxel-induced pneumonitis during treatment.

In our study, taxane rechallenge was done in 20 (49%) patients. Agents used were paclitaxel, nab-paclitaxel, or docetaxel.

Table 6: Comparison of present study with previously published studies in patients with acute interstitial pneumonia following chemotherapy with either paclitaxel or docetaxel

Study (year), country	Study design	Cancer	Number of ILD	Types of ILD	Causative drugs	Steroid	Outcome of ILD on imaging	Ventilatory support	ILD outcome	Taxane rechallenge (yes/no)
Present study India	Prospective observational	Breast	41	NSAIP	Docetaxel, paclitaxel	MP Prednisolone Hydrocortisone	CR-30 P PR-11P	2 MV	39 alive 4 expired	Yes - 19 patient No - 21 patient
Njigha *et al*., (2019)[12] USA	Case series	Breast	3	HP, NSAIP	Paclitaxel	Prednisolone	CR-2P, PR-1P	-	Alive	Yes - 3 patient
Genestreti *et al*., 2015[15] Italy	Case series	Lung	2	NSAIP	Docetaxel	Prednisolone	CR-1P, PR-1P	-	Alive	No
Manuprasad *et al*., (2019)[9] India	Retrospective	Breast, prostate, lung	8	NSAIP	Docetaxel	Prednisolone	CR-8P	-	Alive	No
Raghupathi *et al*., (2019)[10] India	Case series	Breast	7	NSAIP	Paclitaxel	MP	CR-7P	1 NIV	Alive	No
Wang *et al*., (2001)[16] Taiwan	Case series	Lung	4	HP	Docetaxel	MP PD-4		4 MV	4 expired	No

NSAIP: Nonspecific acute interstitial pneumonitis, HP: Hypersensitive pneumonitis, MP: Methylprednisolone, CR: Complete resolution, MV: Mechanical ventilation, NIV: Noninvasive ventilation, PR: Partial resolution, PD: Progressive disease, ILD: Interstitial lung disease

None of the patients experienced any recurrence of pneumonitis or any mortality following taxane rechallenge.

The limitations of our study are none of our patients underwent bronchoalveolar lavage or lung biopsy for the confirmation and patients were treated for interstitial pneumonitis based on clinical and radiological diagnosis. Further studies are needed for option of taxane rechallenge in patients with taxane-induced ILD. The proposed strategy for the management of patients with acute interstitial pneumonitis following taxanes and taxane rechallenge is summarized in Figure 4.

CONCLUSION

In patients with complete resolution of taxane-related interstitial pneumonitis following steroid maintenance, taxane rechallenge either with alternate agent or the same agent may be an option when risk–benefit aspect is considered. We also advise short-course oral steroids for 1 week following taxane rechallenge as a safety measure. Further studies are warranted in this regard.

We strongly do not recommend rechallenge in patients with residual HRCT abnormalities of pneumonitis following steroid maintenance treatment.

Learning points

- Acute interstitial pneumonitis is a well-recognized complication following taxane chemotherapy in patients with breast cancer
- Early recognition and prompt initiation of steroids are warranted
- Steroid maintenance following pulse steroids is beneficial
- In patients completely recovering after steroids, taxane rechallenge is an option after careful assessment of risk–benefit
- Advise short-course oral steroids for 1 week following taxane rechallenge
- Avoid rechallenge in patients with residual HRCT abnormalities of pneumonitis following steroid maintenance.

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Conflicts of interest

There are no conflicts of interest.

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