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REVIEW

Update on Pulmonary Toxicity Induced by New Breast Cancer Treatments

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Abstract: In recent years, new anticancer drugs have been investigated and approved for the treatment of breast cancer based on improved survival outcomes. However, these new treatments have specific class-related side effects. Pulmonary toxicity has been identified as an adverse event of special interest with everolimus, and is becoming an increasingly significant clinical challenge with the recent approval of trastuzumab deruxtecan. Overall, the risk of pulmonary toxicity is quite low but in some cases lung damage can be fatal. We conducted an update including the available published data regarding the incidence, mechanisms of pathogenesis, clinical presentations, and treatment of lung toxicity induced by new anticancer drugs. A literature search was performed between January and June 2024, considering papers, clinical trials, case reports, case series, meta-analyses, and systematic reviews published from January 2014 to June 2024. We also provide an algorithm for diagnosis and treatment, along with real-life cases managed at the Modena Cancer Center. Data provided here show that pulmonary toxicity is a quite frequent side effect and underline that early recognition and prompt treatment are crucial for the best outcome of patients, whose overall prognosis is being improved by the availability of these new anticancer agents.

Keywords: breast cancer, lung toxicity, Pulmonary toxicity, interstitial lung disease, pneumonia, trastuzumab deruxtecan, CDK4/6i

Introduction

Pulmonary toxicities are considered a relative common side effect of anticancer drugs. Lung toxicity reported in oncology clinical trial ranges from 10–20% of all patients treated with any type of antineoplastic agents.[1] In particular, in breast cancer (BC) patients, pulmonary toxicity is a known side effect due to both systemic anticancer therapies and chest wall radiation treatment. Recently, it is becoming more evident with the new targeted agents introduced in BC treatment management such as everolimus and, more recently, trastuzumab deruxtecan.[2] Usually drug related pulmonary toxicity are asymptomatic or moderate, but often lead to treatment suspension or cessation. Presenting symptoms are non-specific and the differential diagnosis is broad, made more complex by concomitant comorbidity and pulmonary infections. Further, little is known about the role of baseline testing, risk factor or surveillance for early detection of pneumonitis. For that reasons, physicians must be educated on the risk of drug related lung toxicity and appropriate treatment. Proper monitoring including early identification and management with steroids instituted in a timely fashion is required to avoid potential life threatening complication.

We have provided an update on the risk of pulmonary toxicity in BC patients treated with new anticancer drugs, especially targeted agents. We focused on the incidence rate and underlying mechanism of lung injury, and suggested a possible management algorithm. A case series of drug-related pulmonary toxicities was also reported.

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Methods

Study Research

The systematic literature search was conducted using electronic database such as PubMed, EMBASE (from 1946), Cochrane Library (2018) and Web of Science (from 1900). The literature search was performed between January and June 2024. We identified all the published papers, clinical trials, case reports, case series, meta-analyses, and systematic reviews published from January 2014 to June 2024. Of note, in case of multiple reports relating to the same trial, the most recently published results were selected. The terms used for the research were: "breast cancer", "lung toxicity", "pulmonary toxicity", "interstitial lung disease", "pneumonia". Boolean operators were used to connect specific search keywords for each database and other free text terms. Moreover, for every anticancer treatment approved between 2014 and 2024 the summary of the product characteristics and patient leaflet were revised. Finally, the references reported in the identified publications were checked in order to find any additional information.

Symptoms and Diagnostic Workup

Treatment-induced pulmonary toxicity remains an exclusion diagnosis. If an AE is suspected to be drug-related, anti-cancer treatment should be interrupted, pending further evaluation. The grade of lung damage varies from asymptomatic radiological changes to interstitial lung disease, pneumonia, acute respiratory distress syndrome, respiratory failure, and fibrosis. The clinical symptoms depend on the mechanism and site of drug-induced lung damage (Figure 1). The clinical presentation can range from an asymptomatic condition to respiratory crisis and failure. Symptoms are usually non-specific, and include cough, wheezing, fever, and chest pain. Physical examination results may be negative or may show wheezing and

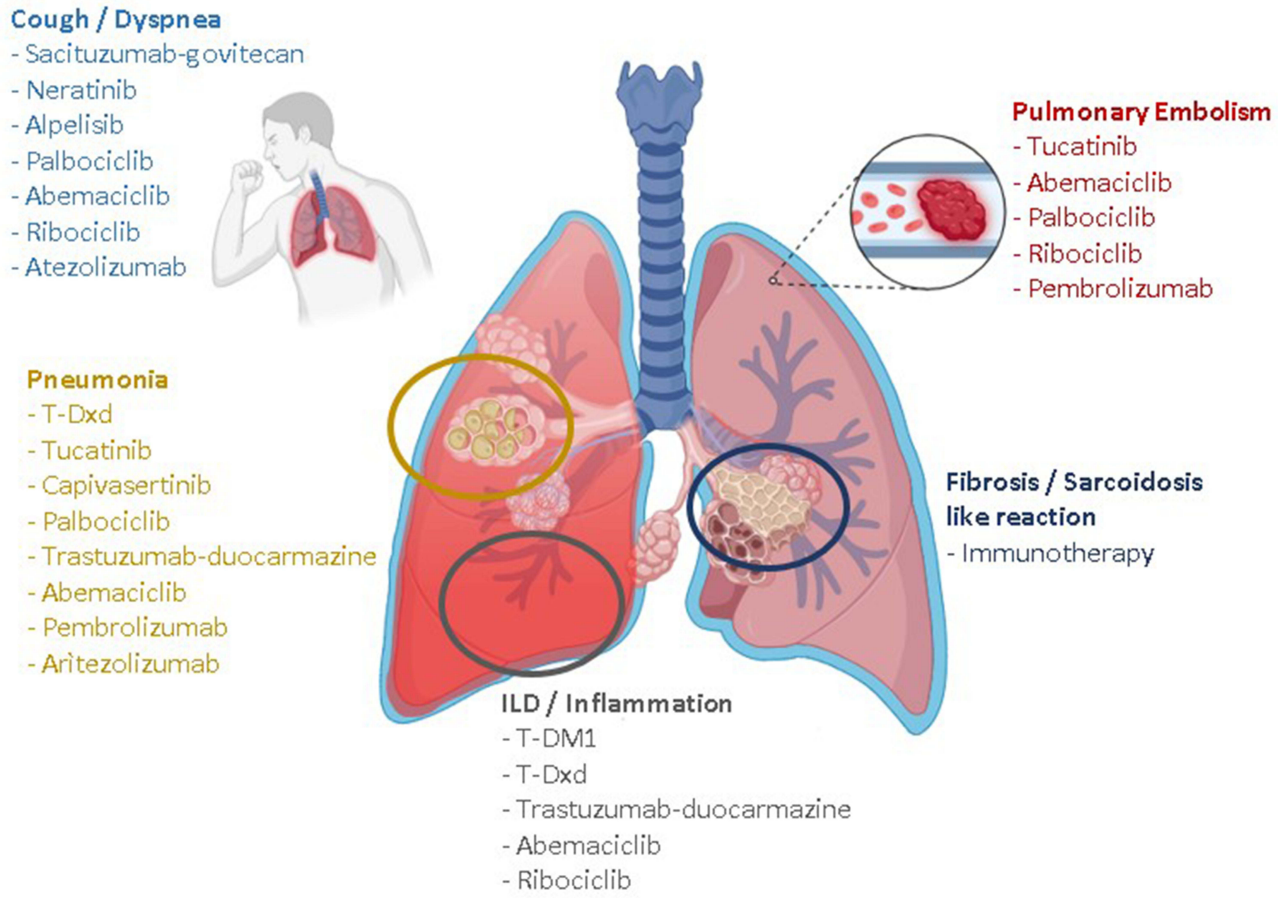

Figure 1 Different clinical and/or radiological pattern of drug induced pulmonary toxicity classified for single agent. Figure reported drugs with an incidence of lung toxicity drug-related higher than 1% or with published cases of grade 4–5 pulmonary adverse events.

crepitations during auscultation. Radiological evaluation with chest radiography and CT scans must be conducted, highlighting different patterns such as non-specific interstitial infiltrates, ground glass opacities, parenchymal consolidations, or fibrosis patterns. These findings are often bilateral.[2] Diagnostic workout should include microbiological analysis (sputum and blood cultures), bronchoscopy, bronchoalveolar lavage, pulmonary function tests, pulse, oximetry (SpO2), and arterial blood gases. Differential diagnoses include lung conditions such as infections, metastasis (carcinosis of lymphatic ducts), cardiogenic origin or ARDS.[3,4] Overall, minimizing the risk of severe lung toxicity involves teamwork, which includes educating patients and all care teams. Case-by-case must be evaluated in a multidisciplinary team with pulmonologist consultation and infectious disease consultation, as clinically indicated (Figure 2).

Management

The management of drug-induced lung toxicity is empirical and depends on both the drug involved and the entity of damage (Figure 3). CTCAE was used to classify the grade of toxicity.[5] Usually, in cases of G1 asymptomatic lung damage, no treatment interruption is required; however, monitoring and close follow-up are needed. In G2 cases, the treatment should be interrupted. Restarting could be considered only if the event was fully resolved and dose reduction should be considered. Symptomatic patients were promptly treated with systemic steroids (at least 1.0 mg/kg/day prednisone or equivalent) for at least 10–14 days, followed by a gradual taper over at least 2–4 weeks. Symptoms must be closely monitored and re-imaging must be considered if clinically indicated. If there is worsening or no improvement in clinical symptoms, diagnostic hospitalization is required and the dosage of steroids should be increased. In case of G3-4 lung toxicity, hospitalization with mandatory and high-dose methylprednisolone IV treatment (eg, 500–1000 mg/day for 3 days) must be promptly started, followed by at least 1.0 mg/kg/day of prednisone (or equivalent) for at least 14 days, followed by a gradual taper over at least 4 weeks. Therefore, an empirical antibiotic therapy should be prescribed[6,7] and the anticancer agent should be discontinued.

Pneumonitis due to trastuzumab-deruxtecan (T-Dxd) deserves special mention because of its incidence and the fatal events reported in clinical trials. Interrupt treatment and consideration of corticosteroids are recommended even in grade 1 cases. Only in grade 1 cases, T-Dxd rechallenge preferably with dose reduction may be considered after both resolution to grade 0 and the evaluation of clinical factors (such as response to T-DXd and eligibility for other therapies). Recently, international guidelines for T-Dxd interstitial lung disease management have been recently published.[8,9] Figure 4 summarizes the follow-up and management of patients with T-Dxd who developed lung toxicity.

Anticancer Drugs

Table 1 summarized principal drug related pulmonary toxicities, reporting the type of lung damage and the incidence for each treatment.

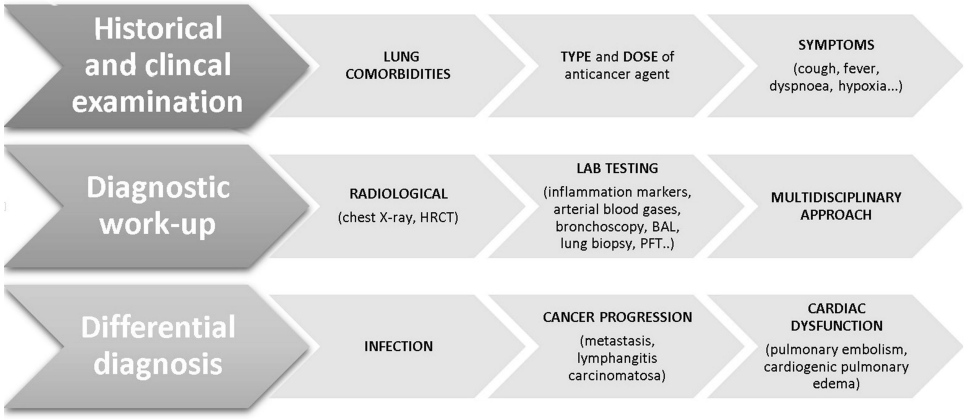

Figure 2 Diagnostic workup for suspected treatment-induced pulmonary toxicity.

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MANAGEMENT	G1	G2	G3-4
No symptoms	No drug interruption, **monitoring closely**	-	-
Symptoms	-	**Drug interruption,** restart treatment upon resolution of the event	**Drug interruption** **Hospitalization**
Anticancer drug management	-	**Dose reduction**	**Definitive suspension**
Steroids	-	**1.0 mg/kg/day prednisone** or equivalent for 10-14 days	**Methylprednisolone IV treatment 500-1000 mg/day** for 3 days, followed by 1.0 mg/kg/day of prednisone or equivalent for 3 days
Other medical treatment	-	O2 therapy if needed	**Empirical antibiotic** therapy and **O2 therapy**

Figure 3 Clinical management of treatment-induced pulmonary toxicity.

Drug Conjugated Antibody (ADCs)

Antibody-drug-conjugated (ADCs) are a promising class of antineoplastic drugs that are considered to be the future of modern oncology. Many ADCs have already been used in clinical practice because of their undeniable efficacy, and several are currently under investigation in clinical trials. Considering its safety profile, pulmonary toxicity is a known insidious, class-related side effect. Three ADCs are used for the management of patients with BC: trastuzumab emtansine (T-DM1), T-Dxd and Sacituzumab-Govitecan. There were no typical clinical presentations or specific radiological patterns of lung toxicity due to ADCs. However, the mechanisms underlying lung damage in ADCs remain unknown. This seems to be related to their intrinsic affinity for the pulmonary interstitium/parenchyma, rather than their therapeutic target.[10,11] To confirm this hypothesis, the rate of ADC-related lung toxicity was registered in other types of cancers, such as lung and gastric are similar.[12,13] Suggested risk factors for lung damage could be asian ethnicity and pulmonary comorbidities (particularly for trastuzumab-deruxtecan).[14,15]

T-Dm1

T-DM1 was the first ADC approved for both patients with advanced and early HER2 positive BC.[16,17] This drug binds to the HER2 receptor and is internalized via receptor-mediated endocytosis, releasing the payload (DM1), which inhibits

	Grade 1	Grade 2	Grade 3/4
T-Dxd management	**Interrupt** Considering resume T-Dxd, (dose modification depending on time of radiological resolution)	**Permanently discontinue**	**Permanently discontinue**
Follow-up	- **Clinical** assessment **every 2-7 days** - **CT scan every 1-2 weeks or earlier as clinically indicated**	- **Close clinical** assessment **every 3-5 days** - **CT scan as clinical indicated**	- **Close clinical** assessment **(every 3-5 days)** - **CT scan as clinical indicated**
Therapy	- **Consider oral glucocorticoids** (0,5 mg /kg/day prednisone or equivalent until radiological improvement) **in case of extensive lung involvement**	- **Start glucocorticoids** (1mg/Kg/day) for at least 14 days, until resolution If not improve within 5 days: • Increase cose of steroids (2 mg/kg/day) and switched to intravenous • Consider hospitalization	- **Hospitalization** - **Start high-dose methylprednisolone intravenous** (e.g.,500-1000 mg/day), followed by a gradual taper over at least 4 weeks If not improvement within 3- 5 days: • **Consider other immuno-suppressants** (i.e. infliximab or mycophenolate mofetil)

Figure 4 Management of lung toxicity T-Dxd induced.

microtubule function and leads to apoptosis. In both T-DM1 Phase III trials (Emilia and KAMILLA) conducted in MBC patients, the rate of pneumonitis/Interstitial Lung Disease (ILD) was reported < 2%.[16,18] On note, Asian patients had a higher rate of lung toxicity compared to non-Asian patients (2.2%, 95% CI 0.6–5.6 vs 1%, 95% CI 0.7–1.6) suggests that Asian ethnicity could be a possible risk factor.[18]

T-Dxd

T-Dxd is an ADC where trastuzumab is linked to the topoisomerase I inhibitor payload (deruxtecan), which causes DNA damage and cell apoptosis. It has recently been approved for the treatment of HER2+ and HER2 low (HER2 1+ or HER2 2+ ISH non-amplified) MBC. Among the ADCs, TDxd showed a higher pulmonary toxicity rate, ranging from 11% to 15%. In the Destiny Breast-01, a single group, multicenter, Phase 2 study, T-Dxd administered to heavily pre-treated MBC patients at 5.4 mg per kilogram, reported 13.6% of treatment related ILD. Even if these lung toxicities were mostly G1-2, there were four death due to drug-related ILD. The median time to ILD onset was about 6–7 months. The rates due to lung toxicity were 8.6% for pneumonitis and 2.1% for ILD.[19] A similar rate of lung toxicity was reported in a Phase 3 randomized trial (Destiny Breast-03), where T-Dxd was compared with T-DM1 in 2nd line treatment for HER2-positive

Table 1 Principal Drug Related Pulmonary Toxicities

Drug Class	Type of toxicity	Incidence (%)
Drug conjugated antibody (ADCs)		
T-DM1	Pneumonitis/ Interstitial lung disease	<2
T-Dxd	Interstitial lung disease	11–15
Sacituzumab-Govitecan	Cough Dyspnea	17 24
Trastuzumab-Duocarmazine	Pneumonitis ILD*	6,6 1
Tyrosine Kinase Inhibitors (TKI)		
Lapatinib	Pneumonitis/ Interstitial lung disease	0,2
Tucatinib	Pulmonary embolism Dyspnea Pleural effusion Pneumonia	3,2 1,7 1,2 1,2
Neratinib	Cough	12
Target therapy		
Alpelisib	Pneumonia/ Pleural effusion/Interstitial lung disease	<1
Capivasertinib	Atypical pulmonary infection	<1
Selective estrogen receptor down-regulators (SERD)		
Elacestrant	Not reported	0
Camizestrant	Not reported	0
Cyclin-dependent kinase 4/6 inhibitors (CDK 4/6i)		
Palbociclib	Dyspnea Upper respiratory tract infections Pulmonary embolism	13–0 8–28,4 0,1–0,5
Abemaciclib	Pulmonary infections Interstitial lung disease Pulmonary embolism	2,8 2,7 <1
Ribociclib	Cough Pulmonary embolism Interstitial lung disease	21 3,5 1,5
Immunotherapy		
Atezolizumab	Cough Dyspnea Upper respiratory tract infections Immune-related pneumonia	24.8 15.9 10,6 3,1
Pembrolizumab	Pneumonitis Pulmonary embolism	1–2 <1

advanced BC.[20] Overall, 18% of patients experienced pulmonary toxicity: 15% with T-Dxd and 3% with T-DM1, respectively. Most of the events were mild or moderate (14% G1-2); grade 3 events were <1% and no G4 or G5. The median time to onset drug-related pulmonary toxicities was was 8.1 months (IQR 4·2–15·0). Overall, discontinuation rate due to lung toxicity was 13%, 6% due to pneumonitis, 5% due to ILD, and 2% due to pneumonia. The same percentage of lung disease was reported in a phase III trial (Destiny Breast 04) conducted in HER2 low MBC patients. Lung AEs were mainly G1-2, even if there were 3 patients (<1%) who died due to ILD T-Dxd-related AEs. Rate of discontinuation for lung disease was 8.6%.[21] Recently, data from Destiny breast-06 trial, presented in ASCO 2024, reported 11.3% of all grade ILD in a cohort of chemo-naïve metastatic BC patients, with three fatal events.[22] Figure 5 shows the clinical case of G2 T-Dxd-induced pneumonitis in a patient treated for refractory HER2+ advanced BC.

Sacituzumab-Govitecan

Sacituzumab-Govitecan is an anti-trophoblast cell-surface antigen 2 (TROP-2), which uses a topoisomerase I inhibitor (SN-38/govitecan) to induce DNA damage-mediated apoptosis. It has been approved for the treatment of pre-treated triple-negative (TN) advanced BC. The most commonly reported lung toxicities were cough and dyspnea. In particular, the rate was 19% in Phase 1/2 single-group trial[23] and approximately 20% in the two phase III trials (ASCENT trial: cough, 17% and dyspnea 24% - TROPiCS-02 trial, 18% dyspnea.[24,25] Overall, G3 lung toxicity was < 2%. Only one case of G3 pneumonitis related to treatment was described in the ASCENT study.[26]

Trastuzumab-Duocarmazine

Trastuzumab-duocarmazine is a promising ADC composed of trastuzumab conjugates with duocarmycin payload. In a phase 3 trial (TULIP), trastuzumab-duocarmazine was compared with the physician's choice in patients with pre-treated HER2-positive advanced BC. Safety profile showed 6.6% drug related pneumonitis (G3 events-rate of 2.1%) and 1% of interstitial lung disease (G3 events-rate of 0.3%).[27] Dose modifications due to ILD/pneumonitis was 2.1% of patients, whereas treatment discontinuation occurred in 5.2% of cases.[27]

Tyrosine Kinase Inhibitors (TKIs)

Tyrosine Kinase Inhibitors (TKIs) inhibit different enzymes (tyrosine kinases) responsible for the activation of many proteins via signal transduction cascades. In fact, they have been used to treatment of HER2 positive advanced BC. Overall, the incidence of drug-related lung toxicity was lower than that for ADCs.

Lapatinib

Lapatinib was the first TKI approved for HER2+ metastatic BC. It inhibits the tyrosine kinases of HER2 and epidermal growth factor receptor type 1. In the open-label expanded access program of lapatinib plus capecitabine, including 4283 patients from 45 countries, the incidence of interstitial lung disease/pneumonitis was extremely low (0.2% among) with no racial differences.[28,29]

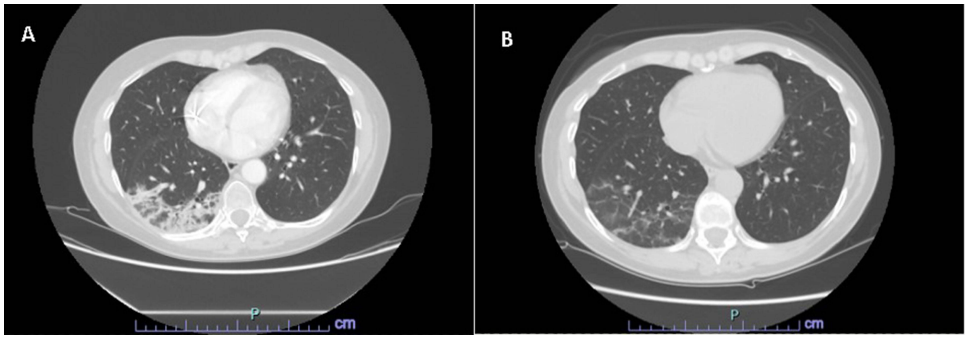

Figure 5 Clinical case of G2 Trastuzumab deruxtacan (T-Dxd)-induced pneumonitis after 39 cycles. This patient was treated with the T-Dxd for a refractory HER2+ metastatic (liver and skin) breast cancer. The patient was symptomatic with mild. Clinical examination showed fine crackles on auscultation at the right basal lung. The CT scan performed showed ground-glass area and parenchymal consolidation at the right basal pyramid with no concomitant pleural effusion (**A**). The patient promptly started oral steroids with rapid clinical improvement. A bronchoalveolar lavage was done and showed lymphocytic and giant cells infiltrates. The chest HRCT scan performed after one month confirm initial radiological improvement (**B**).

Tucatinib

Tucatinib is a highly selective HER2 inhibitor that was recently approved in combination with capecitabine and trastuzumab for the treatment of HER2+ metastatic BC. However, no cases of pulmonary toxicity were reported in a phase 1 study.[30,31] In a phase III trial (HER2Climb) were described: pulmonary embolism (G3: 3.2%), dyspnea (1,7%), pleural effusion (1,2%), and pneumonia (1,2%).[32]

Neratinib

Neratinib is an irreversible HER1,2,4 and EGFR inhibitor. As with other TKIs, there are few data in the literature regarding lung toxicity. Considering the overall population enrolled in the published trials (ExteNET, NALA, and MutHER)[33] cough was the only lung toxicity reported in 12% of cases, mostly grade G1-2.[34–36]

Target Therapy

Alpelisib

Alpelisib is an oral, small-molecule, α-specific PI3K inhibitor used to treat positive, PI3K mutated metastatic BC. Overall, low rates of alpelisib-related lung toxicity have been previously reported. In particular, in a Phase II trial (BYLieve)[37] was reported of cough in 2% of cases. Less than 1% of patients enrolled in the SOLAR-1 study experienced pneumonia, pleural effusion, or interstitial lung disease.[38]

Capivasertinib

Capivasertinib is a potent selective inhibitor of all three AKT isoforms. A recent update of its safety profile reported one death due to atypical pulmonary infection, which was probably treatment related.[39,40]

Selective Estrogen Receptor Down-Regulators (SERD)

Elacestrant

Elacestrant is a novel nonsteroidal oral SERD that is active in hormone receptor-positive BCs harboring ESR1 mutations. No lung toxicity was reported in the phase 3 Emerald trial.[41]

Camizestrant

Camizestrant is a potent next-generation oral SERD and pure ERα antagonist. Emerging data regarding safety profile did not show any lung toxicity among the most common adverse effect.[42,43]

Cyclin-Dependent Kinase 4/6 Inhibitors (CDK 4/6i)

Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) are a class of drugs approved for the treatment of hormone receptor-positive BC in combination with endocrine therapy in both adjuvant and metastatic settings. The mechanism of action is based on the inhibition of binding between cyclins 4/6 and cyclin D1, which prevents phosphorylation of the Rb protein and blocks cell cycle and gene transcription.[44] CDK4/6 inhibitors used in clinical practice include Palbociclib, Abemaciclib and Ribociclib. Even if pivotal phase III trials reported a low percentage of pulmonary toxicity (<1%),[45] after the data review from post-market safety databases, in 2019, the US Food and Drug Administration (FDA) warned about severe lung inflammation with the CDK 4/6 inhibitors. There have been reports of serious cases, including fatalities, across the entire drug class. Pulmonary symptoms are non-specific and can range from mild cough and fever to desaturation, which requires support with oxygen therapy and hospitalization. Symptoms may also occur months after the initiation of therapy and persist even after discontinuation.

Palbociclib

Palbociclib nn the Paloma 1 clinical trial, palbociclib was prescribed combined with endocrine therapy in the metastatic setting[46] showing different pulmonary toxicities such as dyspnea (G1-2 13%) and upper respiratory tract infections (G1-2 8%). In both cases, G3 events were less than 2%. Notably, a case of G4 pulmonary embolism and G3 pneumonia has been described. Similar rates were reported in subsequent phase III trials (Paloma 2 and Paloma 3).[47–49] In the neo/adjuvant setting, the efficacy of palbociclib was tested in two trials: Pallas and Penelope B.[50,51] Respiratory system

toxicities reported were: 28.4% upper respiratory tract infections, 14.6–20% cough and pulmonary embolism 0.1–0.5%. Grade 3 toxicity was still under 2%. Some case reports published in literature reported fatal pneumonia possible drug related.[52–55]

Abemaciclib

Abemaciclib In Monarch 2 and Monarch 3 phase III clinical trials conducted in the metastatic setting[56,57] the more frequent respiratory symptoms were cough and dyspnea, with an evidence of increased pulmonary infections in the abemaciclib arm compared to the endocrine therapy alone (2.8% vs 0%, respectively). The safety profile was reported in the MonarchE clinical trial, in which abemaciclib was administered in combination with endocrine therapy for two years in an adjuvant setting.[58] In the overall population, a mild increase in pulmonary events such as ILD and pulmonary embolism was observed. In particular, ILD G1-2 was reported in 2.7% of patients, while of pulmonary embolism was <1%. All grade 3 cases were < 1%, with no fatal events. Real-word data have confirmed that pulmonary toxicity due to abemaciclib is a rare AE. In a dataset of more than 4500 patients were described 82 cases of ILD drug-related, mainly symptomatic (G3-4) with dyspnea, cough, and/or fever.[59] Here, we report a clinical case of G1 interstitial lung disease in a patient who received adjuvant abemaclib (Figure 6).

Ribociclib

Ribociclib in the overall metastatic BC population enrolled in the Monaleesa 2 and Monaleesa 3 trials occur in three cases of G3 interstitial lung disease/pneumonitis.[60,61] No lung toxicities were observed in the Monaleesa 7 clinical trial.[62] In the following pooled analysis of the safety profile of ribociclib published by Burris et al, cough G1-2 was reported in 21% of patients, pulmonary embolism G1-2 3.5% (with G3-4 <1%), and ILD G1-2 1.5% (with G3-4 0.3%).[63] Finally, in the NATALEE trial conducted in an adjuvant setting, ILD was 1.5% of ribociclib treated patients, with no G3 events.[64]

Immunotherapy

Currently, atezolizumab and pembrolizumab are the only immunotherapies approved for the treatment of TNBC. Pembrolizumab is used in both neoadjuvant/adjuvant and metastatic setting.[65,66] The characteristic patterns of immunotherapy-related lung toxicity include pneumonia and pulmonary fibrosis, secondary to immune system activation. The supposed pathogenesis mechanisms include a loss of tolerance of lymphocyte T cells with a consequent uncontrolled activation of effector cells, increased levels of inflammatory cytokines, and complement-mediated inflammation, with multiple secondary inflammatory and autoimmune processes. The radiological picture of immune-related pneumonia can mimic other pulmonary inflammatory diseases such as pulmonary sarcoidosis or sarcoidotic granulomatous reactions, primary infections, or infections secondary to steroid therapy.[67] A specific pattern of immune-related lung toxicity is a sarcoid-like reaction. This can occur following immunotherapy. The time to onset of this reaction can vary from a few weeks to 2–3 years after the start of therapy. The lungs and skin are the most affected organs, although cases of spleen,

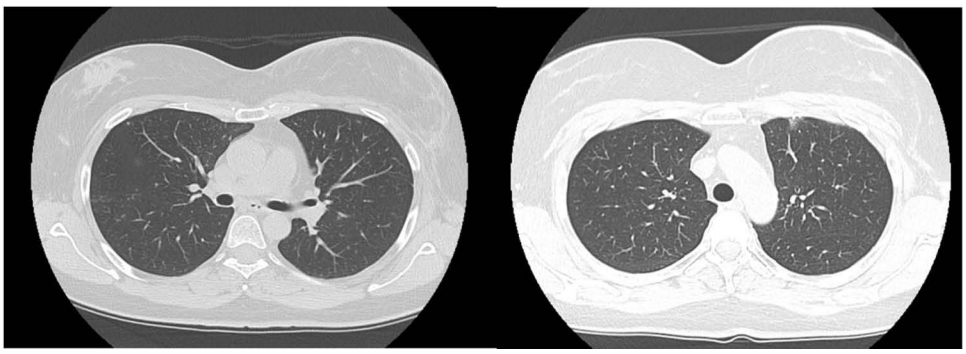

Figure 6 TC scan of young patient treated with adjuvant abemaciclib and letrozole for high risk hormone receptor positive breast cancer. The CT scan performed after one year of abemaclib showed ground-glass area with bilateral 4–5 millimeters opacities suspected for inflammatory interstitial lung disease. Patient was asymptomatic. Bronchoalveolar lavage (BAL) was performed showing only inflammatory cells. Abemaciclib was prudently stopped. The HRTC scan performed two months later showed complete radiological resolution. Patients re-started and completed adjuvant abemaciclib with no further pulmonary complication.

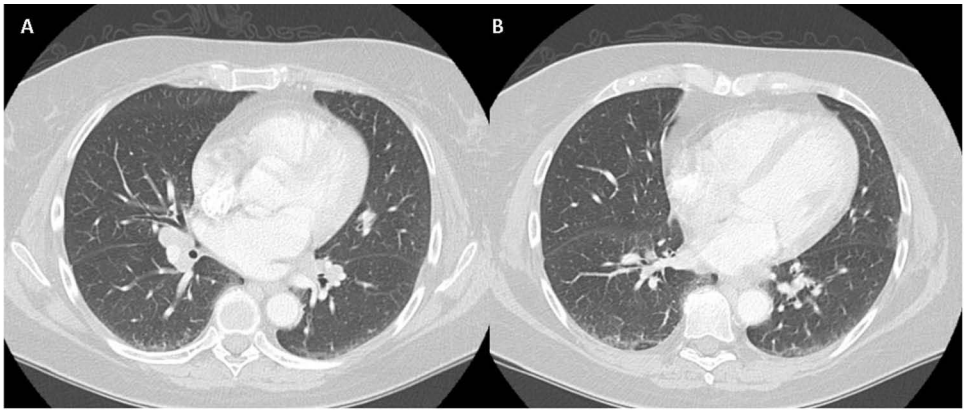

Figure 7 Sequential imaging of a patient with an HER2+ breast cancer, enrolled in a clinical trial, treated with neoadjuvant epirubicin and cyclophosphamide followed by carboplatin and paclitaxel plus trastuzumab and pertuzumab in combination with atezolizumab. Pre-operative CT scan performed at the end of neoadjuvant chemotherapy showed multiple mediastinal lymph node formations (**A**). Biopsy done during the endobronchial ultra sound showed a granulomatous sarcoidotic-like inflammation. The multidisciplinary team suggested an immunotherapy related sarcoidosis. Atezolizumab was discontinued. The CT scan performed 6 months later showed radiological resolution of pulmonary inflammation, and dimensional reduction of all lymph nodes (**B**).

pituitary, renal, and polyneuropathy have been described. From a radiological point of view, clinical differentiation from sarcoidosis or other immune diseases is difficult, and only biopsy is decisive for diagnosis. The pathogenetic underlying mechanism is still unknown, even though there are various hypotheses: the increase in Th1 or Th17 lymphocyte components or an imbalance in the ratio between T17 and T-reg seems to be more supported. Management depends on the grade of the symptoms and can vary from observation and radiological monitoring in asymptomatic patients to the use of high-dose corticosteroids.[68]

Atezolizumab

Atezolizumab has been approved in combination with nab-paclitaxel as a first-line treatment for TN PLD1 positive metastatic BC.[69] Regarding safety profile, lung toxicity reported in the IMpassion130 phase III study included mainly cough (24.8%), dyspnea (15.9%, with four cases of G3), upper respiratory tract infections (10.6% with five cases of G3), and immune-related pneumonia (3.1%, with one case of G3)[70]. A similar rate of respiratory AEs has been reported in a neoadjuvant trial (IMpassion031).[71] Figure 7 reported a clinical case report of immunotherapy related sarcoidosis in patient on neoadjuvant atezolizumab for early BC.

Pembrolizumab

Pembrolizumab is a PD-1 inhibitor approved for both early and advanced BC (KEYNOTE-355, KEYNOTE-522, and Keynote-173).[72–74] Regarding data on pulmonary toxicity in metastatic BC patients, even if the rate of pneumonitis was low (about 1–2%), possible treatment-related deaths were reported: one patient had pulmonary embolism and one had pneumonia.[72] No data on respiratory system toxicity were reported in patients treated with pembrolizumab plus chemotherapy in a neoadjuvant setting (Keynote-173).[74]

A recent systematic review and meta-analysis[75] (including patients with BC), reported an incidence of grade G3 or G4 immune-related AEs around 1% showing that patients treated with PD-1 or PD-L1 inhibitors and chemotherapy had an increased risk of severe pneumonitis compared to those treated with chemotherapy alone. Similar data were published in two meta-analyses by Wang et al and Zhang et al.[76,77]

Conclusion

Pulmonary toxicity has become a greater toxicity concern with the increasing use of new anticancer treatments, such as ADCs, PI3k-AKT-m-TOR inhibitors, CDK4/6i, and immunotherapy. The main message is that, most anticancer drugs may cause a lung toxicity. For that reasons, oncologists should be aware of the pulmonary risks associated with novel targeted therapies. Nowadays, taking into account data reported in literature, in the differential diagnosis algorithm of a patient with respiratory symptoms, drug related lung disease should be at the top of the list of possible causes such as

infection and cancer progression. Prompt management is crucial to reduce life-threatening complications. When possible, a multidisciplinary approach involving different specialists (radiologists, pulmonologists, infectious disease experts, and pathologists) is important to ensure correct diagnosis and optimal patient outcomes. Although a number of experts have published guidelines for the management of lung toxicity, the present review reported all new anticancer drugs approved for BC that had shown lung AEs in order to be a quick reference guide for physicians.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in took part in drafting, revising or critically reviewing the article, gave final approval of the version to be published. All authors have agreed on the journal to which the article has been submitted and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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