Pulmonary Toxicities from Conventional Chemotherapy

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KEYWORDS

• Chemotherapy • Lung toxicity • Bronchoscopy • Radiation therapy • Interstitial lung disease

KEY POINTS

- Lung toxicity due to cytotoxic chemotherapy is common, variable, and often unpredictable.
- A diagnosis of chemotherapy lung is always one of exclusion. Bronchoscopy is generally needed to exclude infection or lymphangitic carcinomatosis.
- Rechallenge is never recommended to avoid the risk of recurrence.
- Corticosteroids may be effective in hastening resolution of symptoms and radiographic manifestations.

INTRODUCTION

The development of lung infiltrates, shortness of breath, and gas exchange abnormalities in a patient with malignancy treated with conventional cytotoxic chemotherapy often creates a diagnostic and therapeutic dilemma for a clinician faced with the difficult decision to withhold a potentially effective and life-saving treatment, often in the absence of firm diagnosis. Adverse drug reactions are uncommon, and chemotherapy lung is estimated to arise in 3% of treated patients.[1] There should, however, be a low threshold of suspecting the diagnosis, because manifestations are nonspecific and protean, and continuing treatment with the culprit chemotherapy agent may have dramatic consequences. That chemotherapy preferentially affects the lungs is not surprising: the blood-gas barrier at the alveolar level is a thin interface made of a nearly continuous sheet of capillaries bathing an extraordinarily large alveolar surface area estimated of approximately 75 m^2.[2] This interface processes the entire cardiac output exposing vulnerable alveolar structures to the unintended nontargeted toxicity of conventional cytotoxic agents.

Manifestations of chemotherapy lung vary and are a function of the mechanism of action of the drug and the specific susceptibility of the host. Although most toxicities are cumulative in nature, some are idiosyncratic, and others are triggered by concomitant treatments (eg, radiation therapy or oxygen) or patient characteristics (age or renal failure). The differential diagnosis is typically broad in this patient population, often hindering prompt recognition of these complications. Pulmonary metastases and lymphangitic carcinomatosis, as well as opportunistic infections, need to be excluded. Consequently, a diagnosis of chemotherapy lung is always one of exclusion, and general rules for the identification and management of these complications are difficult to outline.

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Because these complications are rare, most recommendations are based on anecdotal evidence. This review, therefore, focuses on the general approach to such cases, highlighting the syndromes associated with specific notorious agents, or common offenders, and their usual respiratory complications.

GENERAL PRINCIPLES OF DIAGNOSIS AND MANAGEMENT

The presentation of conventional chemotherapy-induced pulmonary injury includes variable clinical syndromes, such as acute lung injury, pneumonitis, noncardiogenic pulmonary edema, and acute respiratory distress syndrome (ARDS), among others. Likewise, histologic presentations vary considerably and include distinct entities, such as diffuse alveolar damage, organizing pneumonia, and neutrophilic alveolitis. These toxicities may occur weeks to months after treatment initiation. It is also often challenging to identify a specific culprit when patients are treated with multiple-drug regimens. Patients usually present with cough (typically nonproductive), low-grade fever, hypoxemia, dyspnea, and sometimes weight loss. The physical examination may be normal but often reveals bibasilar crackles. Wheezing may be present in cases of drug-induced hypersensitivity with bronchoconstriction. Occasionally, a morbilliform rash, as seen in drug rash with eosinophilia and systemic symptoms, may be present.

The radiographic presentation of drug-induced pulmonary injury includes unilateral or bilateral reticular markings, ground-glass opacities, or consolidations.[3–5] Pleural effusion and nodular consolidation occasionally are confused with cancer progression. High-resolution CT (HRCT) is sensitive but not specific and its prognostic value is generally unclear. A decrease in diffusing capacity for carbon monoxide (DLCO) is often the first anomaly seen in pulmonary function testing (PFT).[6–10] A restrictive pattern can be seen in advanced cases with decreased total lung capacity and forced vital capacity.

Bronchoscopy and bronchoalveolar lavage (BAL) are crucial to rule out infectious processes, diffuse alveolar hemorrhage, recurrent malignancy, or lymphangitic carcinomatosis. The diagnosis of chemotherapy-induced pulmonary toxicity remains one of exclusion based on a high index of suspicion in the context of a compatible clinical presentation and known exposure to a drug associated with pulmonary toxicity.

The treatment of chemotherapy-induced pulmonary toxicity is largely supportive and includes the discontinuation of the offending agent; treatment with systemic glucocorticoids, depending on the severity of symptoms; and supportive measures, such as oxygen supplementation, bronchodilators, and potentially mechanical ventilatory support as indicated.[3,11,12] Once a diagnosis is established, rechallenge with the same agent is generally not recommended, because recurrences are expected and occasionally are fatal.

ANTIBIOTIC CHEMOTHERAPEUTIC AGENTS

Bleomycin

Bleomycin is in many ways the exemplar of chemotherapeutic agents associated with lung toxicity. It is used in bench research to trigger lung toxicity in murine models of lung fibrosis. It is still used in a variety of malignancies, including lymphoma and testicular cancer, and acts by inducing DNA strand breaks.[13,14] It is inactivated in vivo by an enzyme, bleomycin hydrolase, present in all tissues with the notable exception of skin and lungs, which may account for the specific toxicity in these organs.[13,15,16]

The risk of bleomycin-induced lung injury is cumulative, typically after doses exceeding 400 IU/m^2, beyond which potentially life-threatening interstitial pulmonary fibrosis is thought to occur in 5% to 16% of exposed patients.[17–21] Other manifestations are less common but include acute and often idiosyncratic organizing pneumonia and hypersensitivity pneumonitis. Recent data suggest that the risk may be lower and reversible in most cases.[22] The risk factors for bleomycin-induced lung toxicity are presented in **Table 1**.

Clinical features

Symptoms may occur acutely (within days to weeks) or, in cases of pulmonary fibrosis, after months of treatment. Symptoms are nonspecific and include dyspnea and cough. Chest pain during rapid infusion also is described. Bleomycin-induced hypersensitivity pneumonitis and diffuse alveolar damage may present with more rapidly progressive symptoms, sometimes associated with fever and peripheral eosinophilia. Typical radiographic findings include bibasilar subpleural reticular changes with volume loss (in the classic chronic form) or patchy alveolar infiltrates in the acute presentation (**Fig. 1**). Less common nodular, pseudometastatic presentations with nodular infiltrates also are described. A decline of more than 25% in DLCO is considered an indication to discontinue bleomycin, although it is unclear if monitoring PFTs during the course of treatment should be recommended. A bronchoscopy with BAL and, when safe, transbronchial biopsies are generally