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Research Article

INTERSTITIAL LUNG DISEASE AFTER CANCER CHEMOTHERAPY ADMINISTRATION

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ABSTRACT
With an increasing number of therapeutic drugs, the list of drugs that is responsible for severe pulmonary Disease also grows. Many drugs have been associated with pulmonary complications of various types, including interstitial inflammation and fibrosis, bronchospasm, pulmonary edema, and pleural effusions. Drug-induced interstitial lung disease (DILD) can be caused by chemotherapeutic agents, antibiotics, antiarrhythmic drugs, and immunosuppressive agents. There are no distinct physiologic, radiographic or pathologic patterns of DILD, and the diagnosis is usually made when a Patient with interstitial lung disease (ILD) is exposed to a medication known to result in lung disease. This study was conducted on 35 cancer patients with healthy lungs, who undertook cancer chemotherapy. The pulmonary function test parameters, forced expiratory volume in 1 second (FEV1)/FVC ratio was recorded by using a computerized spirometer, Medspiror (Med Systems (P) Ltd.Chandigarh). Forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) are reduced,however, the decline in FVC is more than that of FEV1, resulting in a higher than 80%FEV1/FVC ratio suggesting restrictive lung disease. In obstructive lung disease however, FEV1 is reduced while FVC remains stable, consequentially depicting a lower FEV1/FVC ratio. The present study confirms the fact that chemotherapeutic drugs have a toxic effect on lungs leading to interstitial lung disease with restrictive pattern of lung diseases.

Key Words: *Lung, Adverse Drug Reaction, Drug-Induced Lung Disease, Mechanism of Pulmonary Toxicity*

INTRODUCTION
The lungs are a target for a variety of possible toxic substances because of their large contact surface. They can also act as a metabolism site for certain substances. Drugs can induce specific respiratory reactions or the lungs may be affected as part of a generalized response. More than 380 medications are known to cause drug-induced respiratory diseases, the true frequency is unknown (Camus and Rosenow, 2004). The number of drugs, that cause lung disease, will undoubtedly continue to increase as new agents are developed. Bleomycin, busulphan, and methotrexate are by far the commonest cytotoxic drugs to cause interstitial pneumonitis. However, many other cytotoxic drugs have been reported to produce similar lung damage. Combined effects of these drugs, and of the drugs with other agents that cause lung damage, such as oxygen and radiation, may result in enhancement of lung damage. Early diagnosis, made possible by awareness of this complication and its correct investigation, may reduce severe morbidity and mortality. In some instances, factors that predispose to lung damage are known, and these have been studied in experimental animals.

MATERIALS AND METHODS
The present study included 35 patients of either sex, who were diagnosed to have malignancy, but had healthy lungs. This study was conducted in the Department of Radiotherapy/Oncology, Shri Guru TegBahadur (S.G.T.B) Hospital, which is attached to the Government Medical College, Amritsar. Patients with pulmonary metastasis and lung disease or those who had been previously exposed to radiotherapy during the treatment were excluded from the study. All the subjects were explained about the procedures which were to be undertaken and written informed consent was taken from them as per the Helsinki declaration. This study was approved by the institutional ethics committee. The patients were randomized into the following three groups:

Group I (1st visit): before the start of chemotherapy.
Group II (2nd visit): 3-4 weeks after the 1st visit (1st dose).
Group III (3rd visit): 3-4 weeks after the 2nd visit (2nd dose).
Pulmonary function tests (PFT) were performed on the patients in the three groups at the baseline (before chemotherapy), 3-4 weeks after the start of chemotherapy and again, after the next 3-4 weeks. The tests were done on a computerized spirometer, Medspiror (Med Systems (P) Ltd.Chandigarh), with the patients in a standing posture.

Recording of the PFTs

The relaxed subject in a standing position, were prepared to grip the sterile mouthpiece, as was demonstrated to him/her prior to the recording. When the subject was confident and familiar with the Procedure, he/she was asked to perform a maximum inspiration. The subject was then instructed to expire With maximum effort (maximum expiration).The mouthpiece was then removed and the following spirometric parameters were recorded for analysis.

1. Forced vital capacity (FVC): The maximum volume of air which expired after a maximum inspiration.
2. Forced expiratory volume in first second (FEV1): The fraction of vital capacity which expired during the 1st second of a forced expiration.
3. The FEV1 / FVC ratio. The data was collected, tabulated and analyzed by using the paired t-test for the comparison of the means and by the Chi-square test.

Table1: Patient distribution

Chemotherapy regime	No of patients
1. Carcinoma breast(C.M.F regimen)	10
2. Carcinoma breast(C.A.F regimen)	5
3. Carcinoma stomach	5
4. Multiple myeloma	4
5. Carcinoma Ovary	4
6. Carcinoma Endometrium	2
7. Carcinoma Oesophagus	1
8. Non Hodgkins lymphoma	2
9. Carcinoma Pancreas	2

C.M.F: Cyclophosphamide, Methotrexate, Flourouracil; C.A.F: Cyclophosphamide, Adriamycin, Flourouracil

Table 2: Comparison of three respiratory parameters in the three groups of cancer patients

Parameter	Group I Cancer patients (before)		Group II (after 1st cycle of chemotherapy		Group III (after 2nd cycle of chemotherapy)		'p' Value
	Mean	SD	Mean	SD	Mean	SD	
FCL	2.45	0.25	2.24	0.19	2.12	0.19	<0.001
FEV1(L)	1.95	0.18	1.79	0.18	1.66	0.16	<0.001
FEV1/ FVC%	84.32	3.64	85.67	4.48	85.11	5.15	<0.05

DISCUSSION

Drug-induced lung injury may involve the airways, lung parenchyma, mediastinum, pleura, pulmonary vasculature, and/or the neuromuscular system. The most common form of drug-induced lung toxicity is drug-induced interstitial lung disease (DILD). Oral and parenteral routes of drug administration are most frequently cited as causing DILD; however, nebulized and intrathecal administration have been also been implicated. Pulmonary drug toxicity may result from a direct or indirect drug effect. Direct effects may be either idiosyncratic or due to a toxic reaction of the drug or one of its metabolites. Any chemotherapeutic drug can adversely affect the lung, but the drugs most commonly implicated in lung toxicity are bleomycin, carmustine, busulfan, and cyclophosphamide (Donson *et al.,* 2005; Copper *et al.,* 1997;

Ohnishki *et al.,* 2006; Roig *et al.,* 2006). Approximately 1-10% of patients taking one of these drugs are affected. Bleomycin is the drug most commonly studied as a cause of DILD. Larger studies have shown that rates of 8-10% with some degree of lung injury have been observed (Jules-Elysee and White, 1990). Symptoms may develop earlier than 4 weeks and later than 10 weeks following chemotherapy and the damage is predominantly at the lung base. Busulfan toxicity causes drug-induced pulmonary damage after prolonged exposure, usually after 3-4 years of therapy (Aronchik and Gefter, 1995). Cyclophosphamide causes early onset ILD with a low incidence, estimated at less than 1%, but cyclophosphamide may also cause later damage (Copper *et al.,* 1997; Ohnishki *et al.,* 2006; Roig *et al.,* 2006; Jules-Elysee and White, 1990; Aronchik and Gefter, 1995). Lung injury that is induced by pneumotoxic agents gives rise to alveolitis and edema. In response to injury to the lung parenchyma, there is an immediate requirement to initiate tissue repair and restore barrier function. Acute injury may progress to chronic inflammation and eventually lead to fibrotic change that ultimately interferes with gas exchange. Chemotherapeutic drugs can additionally cause a direct toxic reaction, and direct toxicity usually occurs over time before manifesting clinically (Aronchik and Gefter, 1995; Schwaiblmair *et al.,* 2010; Higenbottam *et al.,* 2004; Ryrfeldt, 2000) induced pulmonary fibrosis (Ryrfeldt, 2000). Drugs can produce virtually all histopathological patterns of interstitial pneumonia, including hypersensitivity pneumonitis (HP), organizing pneumonia (OP), diffuse Alveolar damage (DAD) and nonspecific interstitial pneumonia (NSIP), eosinophilic pneumonia, bronchiolitis obliterans organizing pneumonia (BOOP), pulmonary hemorrhage, and granulomatous pneumonitis (Donson *et al.,* 2005) most drugs cause a restrictive lung disease pattern with decreased total lung capacity (TLC), residual volume (RV), forced vital capacity (FVC), and diffusing capacity (DLCO) reflecting a pathologic disturbance of the alveolar-capillary interface (Mishra *et al.,* 2000). The forced expiratory volume in one second (FEV1) to FVC ratio (FEV1/FVC ratio) may be normal or increased. However, drugs that cause bronchiolitis obliterans may cause an obstructive ventilatory defect (reduced FEV1/FVC ratio and FEV1, increased RV and RV/TLC ratio).

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