Research Article

Early effects of chemo/radiotherapy on spirometric indices in adult patients with cancer: experience from Al-Imamein Al-Kadhemein Medical City/ Baghdad

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ABSTRACT

INTRODUCTION: Incidence of respiratory disease has increased because of increased smoking, air pollution, life span, and the use of different medications and radiotherapy. Half of the patients with cancer can be cured with chemotherapy and radiotherapy. The antineoplastic drugs can cause variety of adverse events and organ toxicity including pulmonary toxicity that is usually irreversible and progressive.

OBJECTIVE: The objective of the study is to evaluate the changes in spirometric indices after chemotherapy and radiotherapy.

METHODS: This case-series prospective study was performed on 70 cancer patients with no previous pulmonary disease, who were exposed to chemotherapy in the unit of Haematology/Oncology at AL-Imamein Al-Kadhemein Medical City from April 2015 to February 2016. The spirometric parameters, forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and the FEV1/FVC ratio were recorded at three occasions before starting of chemotherapy and reassessed after 6-8 weeks and again after 12-16 weeks of starting chemotherapy with or without radiotherapy.

RESULTS: Significant decrease in FVC, FEV1 and FEV1/FVC ratio were observed after the 3rd cycle and subsequent cycles of chemotherapy with or without radiotherapy, in comparison to those before the treatment.

CONCLUSION: The current study showed significant declines in most spirometric parameters in cancer patients after receiving chemotherapy in favour of restrictive pulmonary function defect.

Key words: Chemotherapy, Radiotherapy, pulmonary toxicity, restrictive lung disease.

INTRODUCTION

Incidence of respiratory diseases has increased, because of increased smoking, air pollution, increased life span and the use of different medications and radiotherapy. Many patients with cancer can be cured with chemotherapy and radiotherapy. The antineoplastic drugs can cause variety of adverse events and organ toxicity including pulmonary toxicity that is usually irreversible and progressive.[1-3]

Advances in treatment of cancers have significantly increased survival of patients, with a 5-year survival for most malignancies approaching 80 % in developed countries. But this improvement may associate with more treatment related complications.[4-5] Lung is of many organs that may be involved by these complications.[6] Bleomycin is commonly recognized to cause pulmonary toxicity, similarly other agents like busulphan, melphalan and cyclophosphamide can be implicated.[7]

Chemotherapy-induced pulmonary toxicity can lead to obstructive and/or restrictive abnormalities with impairment of diffusion capacity increasing morbidity and mortality.[8] Table 1 shows examples of chemotehraputics agents

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Table 1 | Some chemotherapeutic agents that may have pulmonary toxicities

Chemotherapy class	Drugs
Antibiotics	Bleomycin, Mitomycin C
Alkylating Agents	Busulfan, Cyclophosphamide, Chlorambucil, Melphalan
Antimetabolites	Methotrexate, 6-mercaptopurine, Azathioprine, Cytosine arabinoside, Gemcitabine, Fludarabine
Podophyllotoxins	Etoposide, paclitaxel, Docetaxel, all trans retinoic acid (ATRA), Imatinib

that may cause pulmonary toxicity.[9]

The clinical manifestation of pulmonary toxicity can be acute or insidious in their onset. Generally, shortness of breath, cough, and fever can occur weeks to years after the treatment is first taken. The radiographic changes may take days or weeks to appear. Typically changes of a diffuse interstitial infiltrative pattern is seen. In general, no radiographic change is specific for a particular chemotherapy agent.[10-13]

Pulmonary complications caused by radiotherapy depend on factors such as the volume of radiation, involvement of supraclavicular region, radiotherapy techniques used, age of the patient, history of smoking, pulmonary function state before radiotherapy, and previous use of chemotherapy.[14-17] Radiotherapy-induced lung injury usually present as two stages. The early stage is radiation pneumonitis that include damage to alveolar cells with acute exudative inflammatory reaction. This stage occurs 4-12 weeks after completing radiotherapy. The late stage is progressive pulmonary fibrosis which occurs months later on.[18-19]

Spirometer is a simple, non-invasive and easily available device used to measure volume against time as part of assessment of pulmonary function. Spirometric indices like forced vital capacity (FVC), force expiratory volume in 1st second (FEV1), and FEV1/FVC ratio allow the diagnosis of obstructive and predict the presence of restrictive pulmonary defects, in addition they allow for following up the patients after using chemotherapy or receiving radiotherapy to early detect any defect.[20]

Early detection of pulmonary toxicity is of importance to minimize its bad effect on patients who survive the cancer, so the gained years of life would be free of suffering. The Haematology/Oncology Unit at Al-Imamein Al-Kadhemein Medical City in Baghdad which is a big teaching hospital that offers its services for a large number of patients with cancer reside in Baghdad and nearby provinces. This study was designed to measure the early effect of chemo/radiotherapy on the spirometric indices in a sample of patients with cancer who were treated in our department over 11 months.

METHODS

Setting and Design: This is a descriptive case series study conducted at the Hematology/Oncology Unit at Al-Imamein Al-Kadhemein Medical City, north of Baghdad from April 2015 to February 2016.

Ethical consideration: The study protocol was approved by the ethical committee of research at Al-Karkh Health directorate and conducted in accordance to the terms of code of ethics in research of the Ministry of Health in Iraq. Verbal consent was taken from all participants after explaining the aims of the study and the confidentiality of were kept throughout the stages of the study.

Definition of the cases and exclusion criteria: Patients who have been diagnosed as having solid or haematological tumuors and referred to Haematology/Oncology Unit at Al-Imamein Al-Kadhemein to start chemo and/or radiotherapy during the studied period was included in this study. Those patients who were having known respiratory or cardiac diseases, persistent or intermittent respiratory symptoms, abnormal initial spirometry or inability to perform it properly due to weakness or understanding or cooperation, primary or secondary lung malignancies were excluded from this study.

Sampling: the participants were collected conveniently by selecting patients who visited our unit every Monday.

Procedure: those who fulfilled inclusion criteria were interviewed to gain demographic data,

Table 2 | Severity of airflow obstruction based on percentage of predicted FEV1*

FEV1 % predicted	Stage
>80 %	Mild
50-79	Moderate
30-49	Severe
< 30	Very severe

*FEV1/FVC < 70 %

present and past medical history, and drug history. Physical examination and basic laboratory tests were done to exclude any exclusion criteria. Detailed history about malignancy was recorded including the treatment plan for it. Baseline spirometry was performed and recorded for each participant. Then patients were assigned into two groups. ***Group I*** included patients who received chemotherapy alone (47 Patients). ***Group II*** included patients who received chemotherapy and radiotherapy (23 patients). Participants in each group performed three spirometry tests. The first was before the start of the therapy, the second after 6-8 weeks from the first dose of the therapy, and the third test was done 12-16 weeks after the first dose of the therapy. The changes in spirometric parameters in each group over time were tested to define any statistical significance.

Outcomes: The following spirometric parameters were recorded for analysis in this study.

1. Forced vital capacity (FVC): The maximum volume of air which is 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 spirometric examination was done at the pulmonary laboratory at Al-Imamein Al-Kadhemein Medical City in a same computerized spirometry and by the same technician who is experienced in performing this test. The spirometry was done for all patients in sitting position and in accordance with the standardization protocol of American Thoracic Society (ATS) and European respiratory society (ERS).[21] The severity of airflow obstruction was defined as in table 2.

Statistical analysis: We used the software SPSS for Windows 20.0.1 (release 2011) for analysis of data. Numerical variables like age were presented as mean ±SD while categorical variables were shown by percentages. Paired T test was used to calculate p value which was considered statistically significant if it is below 0.05.

RESULTS

Table 3 shows some demographic features of the whole sample. The mean age of the patients in both groups was 46 ± 13.22 years (range from 30 to 64 years). Male were 19 (27.2 %) while females were 51 (72.8 %). Of all participants, 23 (32.85%) were exposed to radiotherapy. Twelve patients (17.14) had DM, eleven patients (15.7 %) had hypertension, and 50 patients (71.4%) were not smokers. Table 4 shows chemotherapy protocols that were given to patients with various types of malignancies.

For patient in group I that received chemotherapy alone, FVC and FEV1 were higher before the start of the first dose of chemotherapy comparing to that after 6-8 weeks and 12-16

Table 3 | Patients' characteristics

Character	Number (%) total 70
Gender	
Male	19 (27.1)
Female	51 (72.85)
Age	
Mean ± SD (years)	46 ± 13.22
Range (years)	30-64
Radiotherapy	
Yes	23 (32.85)
No	47 (67.14)
Comorbidities	26 (37.14)
Diabetes Mellitus	12 (17.14)
Hypertension	11 (15.7)
Chronic Kidney Disease	1 (1.4)
Hypothyroidism	2 (2.8)
Smoking history	
Smokers	9 (12.8)
Ex-smoker	11 (15.7)
Non-smoker	50 (71.4)

Table 4 | Types of malignancies and chemotherapy used for them.

Type of malignancy	Number (%)	Chemotherapy regimen
Breast Carcinoma	30 (42.85)	Cyclophosphamide, Methotrexate, 5-Flourouracil (CMF) or Adriamucin and Cyclophosphamide or Taxotere and Cyclophosphamide
Ovarian Carcinoma	12 (17.1)	Cyclophosphamide, Carboplatin
Pancreatic Cancer	6 (8.57)	5-Flourouracil, radiotherapy
Colorectal cancer	5 (7.1)	Cyclophosphamide, Carboplatin, 5-Flourouracil, radiotherapy
Stomach Carcinoma	5 (7.1)	Docetaxel, 5-Flourouracil, cisplatin
Multiple myeloma	4 (5.7)	Melphalan, prednisolone, Thalidomide
Endometrial carcinoma	4 (5.7)	Paclitaxel, Carboplatin
Oesophageal carcinoma	2 (2.85)	5-Flourouracil, cisplatin
Non-Hodgkin's lymphoma	2 (2.85)	Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, prednisolone (R-CHOP)

weeks respectively, p value <0.001. However, FEV1/FVC ratio increases over time after the first dose, p value <0.05. (See table 5)

Table 6 shows the changes in FEV1, FVC, and FEV1/FVC ratio in those receiving combined radiotherapy and chemotherapy before the first dose, 6-8 weeks, and 12-16 weeks thereafter. FVC, FEV1 and FEV1/FVC ratio have shown a statistically significant decrease over time comparing to their result before the start of the first dose, P value 0.013, 0.030 and 0.041 respectively.

DISCUSSION

In our study we followed up the patients for up to 4 months by measuring spirometric indices. Female gender was more than male; 51 (72.85) versus 19 (27.1). this is expected result as we included the breast cancer which is the most common cancer in females and excluded lung cancer, which is the commonest cancer in males worldwide,[23] to avoid a potential confounding factor on the results of spirometry.

For those received chemotherapy alone (group I), FEV1 has shown a statistically significant decline with time; 2.45, 2.24, 2.12 before the start of the first dose, 6-8 weeks and 12-16 weeks thereafter respectively, P value < 0.001. This was similar for FVC that declined progressively with time; 1.95, 1.79, 1.66 before the start of the first dose and 6-8 weeks and 12-16 weeks thereafter respectively, P value < 0.001. And this association might be due to the direct toxic effect of chemotherapy on the lungs or due to other indirect effect like infections for example.[24]

The ratio of FEV1/FVC has decreased progressively with time; from 84.32 % before the start of chemotherapy to 85.67 % and 85.11

Table 5 | Comparison of spirometric parameters in the first group using chemotherapy alone before, 6-8 weeks, and 12-16 weeks after the first done. Total number of patients is 47

Parameter	Before		6-8 weeks after		12-16 weeks after		P value
	Mean	SD	Mean	SD	Mean	SD	
FVC (L)	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

Table 6 | Comparison of spirometric parameters in the second group using chemotherapy and radiotherapy before, 6-8 weeks, and 12-16 weeks after the first done. Total number of patients is 23

Parameter	The Mean Before	The Mean 6-8 weeks after	The Mean 12-16 weeks after	P value
FVC (L)	2.54	2.50	2.23	< 0.013
FEV1(L)	2.2	2.17	1.9	< 0.03
FEV1/FVC %	85.61	85.8	85.2	< 0.041

% 6-8 weeks and 12-16 weeks respectively, p value <0.5. These spirometric results suggest a restrictive pattern of lung disease and need to measure lung volumes and diffusion capacity for approval. However, unavailability of lung volumes and diffusion capacity in our hospital at the time of the study prevent us from final approval.

This finding was similar to that of Jensen et al[25] in 1990 who found that mantle field radiotherapy caused obstructive pattern whereas chemotherapy or chemo-radiotherapy caused a restrictive lung function impairment and to that of Nysom et al (1998) who found a slight restrictive pulmonary disease in patients with Acute lymphoblastic leukemia after the intake of chemotherapy.[26]

Bleomycin and Mitomycin caused pulmonary fibrosis in up to 5-10% of the patients,[27] while combining of Gemcitabine and Paclitaxel caused pulmonary toxicity in approximately 5%.[28] Several alkylating agents like Busulphan, Chlorambucil, Cyclophosphamide Methotrexate and Carmustine have been reported to cause alveolitis and pulmonary fibrosis.[29]

Pulmonary damage is usually irreversible and progressive. Initially, endothelial cell damage with inflammatory reaction causing pneumonitis. Endothelial cell damage can occur as a result of an immunological mechanisms. On chronic basis chemotherapy causes alteration of the pulmonary parenchyma, changes in the connective tissue, alveolar obliteration, and air space dilatation (honeycombing).[30]

In the present, study one patient who is exposed to both chemotherapy and radiotherapy also show significant reduction in FVC, FEV1 with the ratio of FVC/FEV1 being more in favor of restrictive pattern of pulmonary function test. This is where similar to Hardman PDJ et al (1994) who mention that a combined chemotherapy-radiotherapy in breast malignancy result in significant decline of FVC, FEV1 and TLC within 6 months whereas radiotherapy alone have no significant effect.[31]

Kaufman J et al (1996) studied the pathophysiologic effect of chest irradiation on pulmonary function tests over 5 years show significant reduction in FVC, FEV1, TLC and DLCO.[32]

In the short term, radiotherapy has no effect on the pulmonary function, even when some pulmonary function parameters decreased, may be because of the short follow-up time, or the "compensation of the other healthy lung". In the study conducted by Schettino, Jotta e Cassali, the authors used the same instruments to assess pulmonary function, but no changes were found immediately after RT.[33]

Other studies like Ooi et al (2001) found that pulmonary function parameters like FVC, FEV1, TLC and DLCO, in patients who received chemotherapy-radiotherapy did not show significant decline in pulmonary function (may be due to short follow up of study which is done within three months only.[34]

Limitations of this study were our inability to measure lung volumes and diffusion capacity for accurate diagnosis of restrictive pattern, also we could not measure the late effect on the lungs due to lack of time and resources.

CONCLUSION

Follow up of patients with cancer who received chemotherapy and/or radiotherapy for up to four months after therapy have shown a statistically significant decline in the FVC, FEV1, and FEv1/FVC ratio.

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Abbreviations list: American Thoracic Society (**ATS**), Diabetes Mellitus (**DM**), Diffusion Capacity for Carbon Monoxide (**DLCO**), European respiratory society (**ERS**), Force Expiratory Volume in 1st second (**FEV1**), Forced Vital Capacity (**FVC**), Statistical Package for the Social Sciences (**SPSS**), Standard Deviation (**SD**), Total Lung Capacity (**TLC**).

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