ORIGINAL ARTICLE

DIFFUSION LUNG CAPACITY CHANGES IN HODGKIN LYMPHOMA PATIENTS BEFORE AND AFTER ABVD CHEMOTHERAPY

Muhammad Abdullah, Shoaib Alam, Waleed Zafar*, Abdul Majid

Department of Internal Medicine, *Department of Cancer Registry, Shaukat Khanum Memorial Cancer Hospital and Research Centre Lahore-Pakistan

Background: Chemotherapy consisting of Adriamycin, Bleomycin, Vinblastine, and Doxorubicin (ABVD), which is the mainstay of treatment in Hodgkin's Lymphoma (HL), is associated with both acute and long-term pulmonary toxicity primarily due to Bleomycin. Bleomycin induced pulmonary toxicity (BPT) is clinically detected using diffusing lung capacity for carbon monoxide (DLCO). The objective of this study was to evaluate changes in DLCO in HL patients before and after ABVD chemotherapy. **Methods:** Medical records of all adult HL patients treated with ABVD chemotherapy at a single centre in Lahore, Pakistan during the entire calendar year 2012 were analysed. Patients with pre-existing pulmonary dysfunction, history of thoracic surgery and smokers were excluded. **Results:** A total of 179 HL patients were identified during the study period who received ABVD chemotherapy. Out of these, 93 (51.95%) patients had undergone both a pre- and post-chemotherapy DLCO measurements. The remaining patients had only one DLCO reading available and were not included in the analysis. The mean percentage difference between pre- and post-chemotherapy values for DLCO (5.49%; 95% confidence interval [CI] 1.56–9.43%) and for Haemoglobin-adjusted DLCO (8.24%; 95% CI 3.90–12.57%) were statistically significant at $p<0.01$. Diffusing lung capacity for carbon (DLCO) values declined from pre-treatment to post-treatment by 1–10% in 23 (24.7%) patients, by 10–20% in 19 (20.4%) patients, by 20–30% in 10 (10.8%) patients and >30% in 10 (10.8%) patients. After adjusting for age, a 1mg/m^2 increase in dose of Bleomycin was significantly associated with 0.14% (95% CI: 0.03–0.25%) decline in DLCO and 0.13% (95% CI: 0.10–0.26%) decline in haemoglobin-adjusted DLCO from pre-treatment value. **Conclusions:** Mild to moderate dysfunction in diffusion lung capacity is common after ABVD chemotherapy. DLCO and haemoglobin-adjusted DLCO value decreased with increasing age and increasing dose of Bleomycin.

Keywords: Hodgkin's Lymphoma, chemotherapy, diffusion lung capacity, Pakistan, cancer

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INTRODUCTION

Adriamycin, Bleomycin, Vinblastine, and Doxorubicin (ABVD) was originally developed for patients with disease resistant to MOPP (Mechlorethamine, Vincristine, Procarbazine and Prednisone) but subsequently became the standard initial chemotherapy for patients with HL (Hodgkin lymphoma).[1]

Single breath carbon monoxide diffusing capacity (DLCO) is a most sensitive indicator of sub-clinical bleomycin pulmonary effects and useful in germ cell tumor patients, treated with vinblastine, bleomycin and cis-diamminedichlomoplatinum.[2] Adverse drug reactions (ADRs) are common due to anti-neoplastic. The lungs are frequent target.[3–5] Drug induced lung disease is a major source of iatrogenic injury.[6]

Adriamycin, Bleomycin, Vinblastine, and Doxorubicin can be associated with both acute and long term pulmonary toxicity.[7,8] Bleomycin induced pulmonary toxicity has an influence on survival in patients who are treated for Hodgkin lymphoma. Bleomycin induced pulmonary toxicity and doxorubicin associated cardio-toxicity are long term complications of ABVD chemotherapy. Adriamycin, Bleomycin, Vinblastine, and Doxorubicin can result in late Bleomycin induced pulmonary toxicity, particularly when used in combination with mediastinal irradiation.[9,10] Pulmonary function tests were used in an attempt to monitor pulmonary toxicity in several clinical studies. Most of the clinical studies have been completed in heterogeneous groups of patients who received Bleomycin in various doses, schedules and routes of administration.[11]

Forced vital capacity (FVC) and DLCO decrease during ABVD chemotherapy treatment.[12,13] Pulmonary fibrosis can develop as a result of Radiation therapy or chemotherapy for Hodgkin lymphoma. Decreased diffusing lung capacity and restrictive changes in lung may be detected by pulmonary function testing before onset of symptoms.[8,13] The objective of this study was, to determine DLCO reduction after ABVD chemotherapy in adult patient of Hodgkin lymphoma.

MATERIAL AND METHODS

Study was approved by Institutional Review Board of Shaukat Khanum Memorial Cancer Hospital and Research Hospital, Lahore Pakistan. The Shaukat Khanum Memorial Cancer Hospital and Research Centre Lymphoma Database was searched for all patients with diagnose of HL during entire calendar year 2012. Hodgkin lymphoma diagnosis was confirmed by haemato-pathology review of all specimens at our institute. We included patients with age >18 years, no previous history of any lung surgery, chest disease and who had not received any previous chemotherapy. We also excluded patients who were active smoker, on bronchodilators, diabetic, had metastatic or recurrent disease (disease progression to lung or brain) and had no pre and post DLCO test (before and after first cycle of ABVD treatment).

Diffusing lung capacity for carbon monoxide reports for our study group were taken from medical records of patients. Diffusing lung capacity for carbon test was performed using single breath technique. Adjusted haemoglobin DLCO and unadjusted haemoglobin DLCO were recorded. Changes in DLCO were analysed as a changes in the percentage (%) of predicted values. Normal DLCO was defined as ≥80%, Mild dysfunction 60–80%, moderate dysfunction 40–59% and sever dysfunction as ≤39%.

Statistical analysis was performed using the Student *t*-test for paired samples. Descriptive statistics was also analysed for gender, age. DLCO values standardized for Age and haemoglobin. Multivariate analysis with standardization performed for age.

RESULTS

Review of the HL database revealed, 369 patients with HL evaluated at the Shaukat Khanum Memorial Cancer Hospital and Research Centre during the specified study period. Patients with age ≤18 years (n=181), received non ABVD chemotherapy (n=06), incomplete (no pre and post DLCO after ABVD) DLCO (n=27), history of smoking (n=06), not having DLCO reports pre-ABVD chemotherapy (n=32) and not having DLCO reports post-ABVD chemotherapy (n=24) were excluded. Our final study group comprised all patients treated with ABVD chemotherapy under the care of haematologist/oncologist and had pre/post ABVD chemotherapy DLCO (n=93) available. Two hundred and seventy-six patients were excluded. Demographical characteristics of patients treated with ABVD chemotherapy of study group are listed in table-1(i, ii).

The male were 65 (69.9 %) and female were 28 (30.1%). The mean age of patients in this study was 28.69 years with standard deviation 8.45. Minimum age was 18 years and maximum age was 48 years in study. Upper age limit cut off was due to institutional policy of accepting patients with diagnosis of HL during the study period. Diffusion lung capacity had been done in 93 patients. Stage 4 of Hodgkin lymphoma patients are more (37.6%) then those with any other stage of Hodgkin lymphoma.

After ABVD, mild dysfunction in DLCO values was observed in 42 patients (45.2%), moderate dysfunction was in 5 patients (5.4%) patients. It shows that after ABVD chemotherapy, DLCO values worsened in 15 additional patients compared to baseline.

After ABVD, mild dysfunction in DLCO-Hb (Haemoglobin adjusted) values was observed in 30 patients (32.3%), moderate dysfunction in 3 patients (3.2%) patients and severe dysfunction only in 2 patients (2.2%). It shows that after ABVD chemotherapy, DLCO-Hb values worsened in 9 additional patients compared to baseline. There was a difference present before and after ABVD chemotherapy in DLCO (p=0.007). There was also a difference present before and after ABVD chemotherapy in haemoglobin -adjusted DLCO (p=0.000).

When multivariate regression analysis used and age standardized (adjusted), a 1mg/m2 increase in dose of Bleomycin was significantly associated with 0.14% (95% CI: 0.03–0.25%) decline in DLCO and 0.13% (95% CI: 0.10–0.26%) decline in haemoglobin-adjusted DLCO from pre-treatment value.

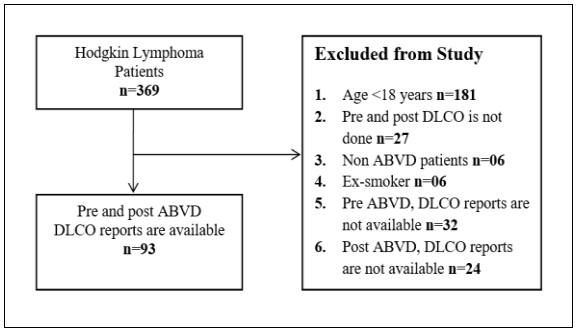

Figure-1: Flow Chart of Patients for study

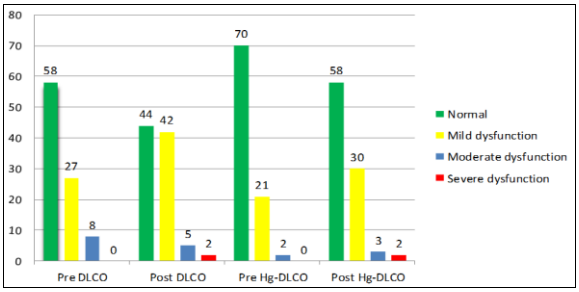

Figure-2: Frequency distribution of DLCO and haemoglobin adjusted DLCO before and after ABVD chemotherapy in Hodgkin Lymphoma patients

Table-1 (i): Patient characteristic

Characteristics	
Gender	
Male	69.89% (65)
Female	30.11% (28)
Stage of Hodgkin's Lymphoma	
Stage 1	9.68% (9)
Stage II	23.66% (22)
Stage III	29.03% (27)
Stage IV	37.63% (35)

Table-1 (ii): Patient characteristic

Characteristics	**Mean±SD**
Age in years	28.69±8.45
Dosage of Bleomycin (units)	75.05±34.35
DLCO (Pre ABVD) in Hodgkin's Lymphoma	
DLCO	87.20±21.61
Hemoglobin adjusted DLCO	95.45±20.89
DLCO (Post ABVD) in Hodgkin's Lymphoma	
DLCO	81.71±19.80
Hemoglobin adjusted DLCO	87.30±20.06

Table-2: Descriptive statistics of DLCO before and after ABVD chemotherapy

	DLCO before ABVD chemotherapy		**DLCO after ABVD chemotherapy**	
	%	%	%	%
Normal	58	26.4	44	47.3
Mild dysfunction	27	29.0	42	45.2
Moderate dysfunction	8	8.6	5	5.4
Severe dysfunction	0	0	2	2.2
Total	93	100%	93	100%

Table-3: Descriptive statistics of haemoglobin adjusted DLCO before and after ABVD chemotherapy

	Haemoglobin adjusted DLCO before ABVD chemotherapy		**Haemoglobin adjusted DLCO After ABVD chemotherapy**	
	Frequency	%	Frequency	%
Normal	70	75.3	58	62.4
Mild dysfunction	21	22.6	30	32.3
Moderate dysfunction	2	2.2	3	3.2
Severe dysfunction	0	0	2	2.2
Total	93	100	93	100

Table-4: Diffusion Lung capacity by Single breath method in Hodgkin Lymphoma patients

		Paired Differences		***t*-value**	***p*-Value**
		Mean	SD		
Pair 1	DLCO before and after ABVD chemotherapy	5.46	19.10	2.78	0.007
Pair 2	Hemoglobin adjusted DLCO before and after ABVD chemotherapy	8.24	21.057	3.77	0.000

Table-5: Multivariate Regression Analysis and standardization

		Multivariate	
		Coefficient	**95% Confidence Interval**
DLCO	Age	-0.175	-0.633 0.282
	Dose of Bleomycin	0.141	0.029 0.254
Hg adjusted DLCO	Age	-0.311	-0.817 0.195
	Dose of Bleomycin	0.135	0.011 0.259

DISCUSSION

In a study of 60 early stage Hodgkin lymphoma patients (ABVD with or without mediastinal irradiation), a total of 53% reported dyspnoea on exertion or cough during ABVD, 37 percent had decline in pulmonary function (forced vital capacity (FVC) and DLCO), and 23% required discontinuation of Bleomycin.[12]

In our study all patients were treated with ABVD chemotherapy and no patient developed cough or need for supplemental oxygen after first cycle of ABVD treatment. The variation in DLCO after ABVD chemotherapy was 81.71±19.80% and in Hb-adjusted DLCO 87.30±20.06%. Mild dysfunction in DLCO values is in 42 patients (45.2%), moderate dysfunction 5 patients (5.4%) patients and no patient developed severe dysfunction in DLCO after first cycle of ABVD. Bleomycin was discontinued in 28 patients as further cycles of ABVD chemotherapy were administered.

In another study of 141 patients treated with Bleomycin-containing chemotherapy for newly-diagnosed Hodgkin lymphoma, pulmonary toxicity was observed in 18%. 24 percent mortality was observed in patient's greater than 40 year of age. Pulmonary toxicity was also associated with significantly decreased 5 years overall survival.[9] Other reported risk factors for the development of this complication are mediastinal irradiation, treatment with G-CSF and use in children.[8,9,14,15]

In our study of 93 patients with Hodgkin lymphoma after ABVD chemotherapy, DLCO changed in 30.10% (28 patients out of 93) after first cycle of ABVD. DLCO changed further as ABVD chemotherapy continued. Mortality occurred in 5.38% (5) patient of age less than 40 years, while other remained stable.

In a prospective study from Dana-Farber cancer Institute, 52 patients were enrolled. Twenty-nine patients were treated with chemotherapy and 23 treated with combined modality therapy in Hodgkin disease. A baseline median DLCO was 94% (range 53–121%). After chemotherapy, median DLCO decreased on average 12% (p<0.001) at 1 month, 2% (p=0.09) at 6 month and 3% (p=1) at 1 year from baseline. Other patients who were treated with combined modality therapy (chemotherapy / radiation), 23 out of 52 patients, median DLCO decreased by an average of 13% (p=0.0002) at 1 month, 18% (p=0.005) at 6 month, 10% (p=0.0005) at 1 year from baseline. Six (12%) patients had symptomatic Bleomycin toxicity and Bleomycin discontinued.[15]

Our study is retrospective; however we enrolled all consecutive patients during entire year

2012. Our results show that both DLCO and Hb-adjusted DLCO decreased significantly after first cycle of ABVD chemotherapy compared to the baseline (p=0.007) and p=0.01 respectively). The variation in DLCO after ABVD chemotherapy was 81.71±19.80% and in Hb-adjusted DLCO was 87.30±20.06%. Upon follow up of our study patients, data revealed that Bleomycin was discontinued in 30.18% (28), Bleomycin induced pulmonary toxicity developed in 13.97 % and mortality occur in 5.38% (5) patient.

CONCLUSIONS

Mild to moderate dysfunction in diffusion lung capacity is prominent after first cycle of ABVD chemotherapy. Diffusing lung capacity for carbon monoxide and haemoglobin-adjusted DLCO value decreased as increasing age and dose of Bleomycin. Pulmonary Functions Test (PFT) may be considered at baseline and after each cycle of ABVD chemotherapy. It may enhance the quality of medical management of Hodgkin lymphoma patients receiving ABVD chemotherapy.

Conflict of Interest: The authors have disclosed no other conflicts of interest.

AUTHOR'S CONTRIBUTION

MA: Collection of data, preliminary analysis, organization of data and writing of manuscript. SA: Interpretation of data, writing and editing of manuscript. WZ: Statistical analysis, interpretation of data and writing and editing of manuscript. AM: Data collection and literature search

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Address for Correspondence:

Muhammad Abdullah, Department of Internal Medicine\Respiratory Therapy, ICU Shaukat Khanum Memorial Cancer Hospital and Research Centre, 7-A Block R-3, M.A. Johor Town Lahore-Pakistan
Cell: +92 344 676 3687
Email: abdullahrt@hotmail.com