Pulmonary dysfunction in childhood Hodgkin lymphoma survivors: An observational study

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Abstract

Background: Childhood cancer survivors are 8.8 times more likely to die of pulmonary causes when compared to general population: an aspect of concern. Pulmonary dysfunction is the third leading cause of non recurrence related cause of death among Hodgkin lymphoma survivors. Methods: A cross section study on Hodgkin lymphoma survivors in complete remission, who completed treatment within last 5 years was done. All children were subjected to detail history including drugs, past history of respiratory illnesses, physical and respiratory system examination followed by spirometry and three minute step test under supervision. Pulmonary dysfunction was determined as presence of obstructive, restrictive or mixed pattern on spirometry or abnormality in three minute step test. Subclinical pulmonary dysfunction was determined as patients who were clinically asymptomatic but had pulmonary dysfunction Results: A total of 60 children were enrolled (Mean age of 11.3 years and 53 were boys) Abnormal pulmonary function tests were documented in 11 (18.3%) of HL survivors at a median time of 2 years (IQR 1,3) from treatment completion. Restrictive pattern was documented in 10 (16.67%) and obstructive pattern in only one patient (1.67%), mostly mild in severity. Older age at start of chemotherapy and radiotherapy and past history of respiratory illness were found to be significantly associated with pulmonary dysfunction. Conclusion: Majority of Hodgkin lymphoma survivors had subclinical pulmonary dysfunction at median follow up of 2 years from treatment completion. Hodgkin lymphoma survivors require long term follow up for timely detection of pulmonary dysfunction and improve quality of life.

TITLE PAGE

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Key words : Childhood, Hodgkin lymphoma survivors, pulmonary dysfunction chemotherapy, radiotherapy

Abbreviations key

Abbreviation	Full phrase
HL	Hodgkin Lymphoma
ABVD	Adriamycin, Bleomycin, Vinblastine, Dacarbazine
BEACOPP	Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone
FEV1	Forced expiratory volume in 1 second of predicted
FVC	Forced vital capacity
mMRC	Modified Medical research council
IFRT	Involved field radiotherapy
TB	Tuberculosis
ATT	Antitubercular therapy
PFT	Pulmonary function test

Abstract

Background: Childhood cancer survivors are 8.8 times more likely to die of pulmonary

causes when compared to general population: an aspect of concern. Pulmonary dysfunction is the third leading cause of non recurrence related cause of death among Hodgkin lymphoma survivors.

Methods: A cross section study on Hodgkin lymphoma survivors in complete remission, who completed treatment within last 5 years was done. All children were subjected to detail history including drugs, past history of respiratory illnesses, physical and respiratory system examination followed by spirometry and three minute step test under supervision. Pulmonary dysfunction was determined as presence of obstructive,

restrictive or mixed pattern on spirometry or abnormality in three minute step test. Subclinical pulmonary dysfunction was determined as patients who were clinically asymptomatic but had pulmonary dysfunction

Results: A total of 60 children were enrolled (Mean age of 11.3 years and 53 were boys) Abnormal pulmonary function tests were documented in 11 (18.3%) of HL survivors at a median time of 2 years (IQR 1,3) from treatment completion. Restrictive pattern was documented in 10 (16.67%) and obstructive pattern in only one patient (1.67%), mostly mild in severity. Older age at start of chemotherapy and radiotherapy and past history of respiratory illness were found to be significantly associated with pulmonary dysfunction.

Conclusion : Majority of Hodgkin lymphoma survivors had subclinical pulmonary dysfunction at median follow up of 2 years from treatment completion. Hodgkin lymphoma survivors require long term follow up for timely detection of pulmonary dysfunction and improve quality of life.

Keywords: Childhood, Hodgkin lymphoma survivors, pulmonary dysfunction chemotherapy, radiotherapy

Introduction

In the current era, newer chemotherapeutic agents have drastically improved 5 year survival rate of Hodgkin Lymphoma (HL) to 90% (1). However these treatment advances are associated with long term effects of which pulmonary dysfunction is the third leading cause of nonrecurrence related cause of death among HL survivors (2). Pulmonary dysfunction seen in HL survivors can develop secondary to chemotherapy or radiotherapy (3). Bleomycin is a known pulmonary toxin among the chemotherapy drugs used in treatment of HL The possible mechanism of bleomycin induced lung injury include i) oxidative damage from reactive oxygen species leading to fatty acid oxidation ,membrane instability and inflammatory reactions in the lung. ii) relative deficiency of metabolizing enzyme bleomycin hydrolase in the lung iii) genetic susceptibility iv) elaboration of inflammatory cytokines (4). Radiation induced lung injury can be acute radiation pneumonitis or chronic radiation induced pulmonary fibrosis (5).

Most of the studies on pulmonary dysfunction in Hodgkin lymphoma survivors till date are conducted in adult population of childhood Hodgkin lymphoma survivors. (6). With respect to pulmonary dysfunction in HL survivors, there is paucity of literature regarding prevalence, clinical manifestations and pattern (obstructive/restrictive) of abnormalities in pulmonary function tests (2,7). The studies conducted so far on pulmonary dysfunction have been on heterogenous population (2,7). The present study was undertaken to evaluate the prevalence, spectrum and risk factors for occurrence of pulmonary dysfunction in Indian childhood survivors of Hodgkin lymphoma

Methods

All biopsy proven HL survivors of age 6-18 years, within 5 years of treatment completion and in complete remission attending Pediatric cancer survivor clinic (PCSC) at tertiary care center in New Delhi were enrolled for the study. The demographic details of the patients, clinical pulmonary symptoms (chronic cough, breathlessness), grade of dyspnea according to Modified Medical research council (mMRC scale) past history of respiratory illness (asthma/recurrent nebulisations in the past/ tuberculosis/pneumonia), treatment history including chemotherapy related- regimen used (ABVD/BEACOPP), number of cycles, cumulative dose of bleomycin, cyclophosphamide, Adriamycin and dacarbazine, radiotherapy related-site, dose and fraction of radiation received, disease related history (primary presentation, site of involvement, bulky disease, stage and B symptoms) were recorded in a structured proforma. A detailed physical examination was done for all patients, Vitals (including SpO2) and anthropometry were recorded in detail. Nutritional status was assessed. Respiratory system examination was done in detail. Relevant investigations including hemogram at the time of evaluation, and previous echocardiography findings of ejection fraction was collected. Pulmonary function was evaluated by spirometry and 3 minute step test. Pulmonary dysfunction was determined as presence of obstructive, restrictive or mixed pattern on spirometry or abnormality in three minute step test. Subclinical pulmonary dysfunction was determined as patients who were clinically asymptomatic but had pulmonary dysfunction on spirometry or three minute step test

Spirometry

Spirometry was performed by a portable spirometer, spirolab (Medical International Research, Rome, Italy) which is standardised for Indian children (based on height) in Paediatric OPD AIIMS, New Delhi during follow up visits. Forced expiratory volume in 1 second of predicted (FEV1), forced vital capacity (FVC), FEV1/FVC ratio were assessed after obtaining acceptable spirometry curves. Abnormal pulmonary function is determined as presence of obstructive, restrictive or mixed pattern on spirometry or abnormality in three minute step test. Obstructive pattern is defined as having forced vital capacity of percent predicted [?]80% and FEV1/FVC <85%. Restrictive pattern is defined as having forced vital capacity of percent predicted <80% and FEV1/FVC [?]85%. Mixed pattern is defined as having forced vital capacity of percent predicted <80% and FEV1/FVC <85%. Based on FEV1, severity of obstructive pattern was assessed as mild, moderate, moderately severe, severe or very severe obstruction if predicted FEV1 is >70%, between 60% to 69%, between 50% to 59%, between 35% to 49%, <35% respectively. Based on FVC, severity of restrictive pattern was assessed as mild, moderate, severe or very severe obstruction if predicted FVC is >70%, between 50% to 69%, between 35% to 49%, between, <35% respectively

Three minute step test

All the subjects were asked to step up and down a 15cm high single step at a rate of 30 steps per minute regulated by a metronome. Pre and post test heart rate and saturation (SpO2) were recorded by pulse oximetry after obtaining appropriate wave form. Only one attempt was offered per child and if unable to complete the test then reason for stopping was also recorded

Statistical analysis:

Descriptive statistics were used for analysing demographic, treatment and disease characteristics. Quantitative variables are presented as its mean (SD) and qualitative variables as frequency (%). Pulmonary function test was classified as dichotomous variables-normal and abnormal. The prevalence of pulmonary function abnormalities is presented as frequency (%). The associated factors were also classified as dichotomous variables. Age at evaluation, age at start of chemotherapy and age at start of radiotherapy as [?] 10 years and >10years.Cumulative bleomycin dose was categorised as [?]80mg/m2 (1mg=1IU) and >80mg/m2. The associations of categorical variables with abnormal pulmonary function was assessed using chi-square/ Fisher's exact test. A p-value less than 0.05 was considered as statistically significant. Regression analysis and multivariable analysis couldn't be carried out due to less event rate in our study sample. Analysis was done by stata14.

Results:

In this cross sectional study, performed from January 2019 to December 2020, 72 Hodgkin lymphoma survivors were screened and 60 were enrolled. Ten children were excluded as they had completed treatment beyond 5 years of enrolment and two children were excluded as they were above 18 years of age.

Patient and disease characteristics are listed in table 1. The mean age of the study population was 11.3 years with SD of 2.77. Majority were males. Only three (5%) patients had clinical symptoms of dyspnea on exertion and three (5%) patients had decreased air entry on one side on auscultation. Out of 60 patients, 57 (95%) received ABVD regimen, at mean age of 8.6 years, median cumulative dose of bleomycin 120mg/m2 (range 30-120mg/m2). Only three patients (5%) received cyclophosphamide in their chemotherapy regimen. Eighteen patients (30%) received involved field radiotherapy (IFRT) along with chemotherapy at median age of 10.75 years, 9 (15%) received IFRT to mediastinum with dose of 25-30Gy(4 patients received 25Gy and 5 patients received 30 Gy) and 15 fraction. Median time to assess pulmonary function post completion of treatment was 2 years. Lab parameters such as hemoglobin and total leucocyte count were normal in all patients. Only 2 patients (3.33%) had ejection fraction of less than 60%

Pulmonary function tests :

All the sixty subjects were able to perform spirometry, of which abnormal pulmonary function test was

present in 11 (18.33%) of studied HL survivors.

Restrictive pattern was seen in 10 (16.67%) of patients and obstructive pattern was seen in 1(1.67%) of patients. Most of them had mild severity of abnormal PFT. One patient who had obstructive pattern had mild obstruction. Of 10 patients with restrictive pattern, 7 (11.66%) had mild restriction and 3 (5%) had moderate restriction. Parameters and PFT are described in table 2

Three minute step test :

All the 60 HL survivors were able to complete three minute step test. Median pre and post test saturation 98 and 98 respectively, signifying that there was no desaturation post 3 minute step test. Mean pre and post test heart rate are 90.5±15.44 and 127.5±19.50 respectively. Post test heart rate for all the patients were within the expected rise in heart rate post exertion (i,e 69% predicted maximal heart rate to 80% of predicted maximal heart rate) (31,32).

Predicted maximal heart rate was measured by Tanaka equation (Predicted maximal heart rate = 208-0.7*age) (33). Parameters of 3 minute step test are detailed in table 3.

Normal and abnormal pulmonary function tests of the patients were compared, children above age of 10 years at evaluation had higher percentage (90.91%) of abnormal PFT when compared to children of age less than 10 years (9.09%) at evaluation (p=0.043). Patients with significant respiratory illness in the past was found to a be statistically significant associated factor for pulmonary dysfunction (p=0.017) Patients who received radiation had higher percentage (54.55%) of abnormal PFT than patients who did not received radiotherapy (45.45%) (p=0.071). Patients who received involved field radiation to mediastinum shows a trend towards developing abnormal PFT (p=0.064). Patients who received chemotherapy and radiation at age of less than 10 years had higher percentage (54.55% and 36.36% respectively) of abnormal PFT than patients of age less than 10 years (45.45% and 18.18% respectively) (p=0.030, p=0.075 respectively). Associated factors for pulmonary dysfunction are described in table 4.

Patients who received chemotherapy (bleomycin cumulative dose of >80mg/m2) and radiotherapy had higher percentage (54.55%) of abnormal PFT than patients who received only chemotherapy (bleomycin cumulative dose of >80mg/m2) (13.33%).

Discussion:

We studied pulmonary dysfunction (prevalence, spectrum and risk factors for occurrence) and pattern of respiratory dysfunction in childhoodHodgkin lymphoma survivors from India.

The prevalence of abnormal pulmonary function test in our study was 18.33% (11 of 60) which is comparable to two pediatric studies done in homogenous group of Hodgkin lymphoma, 17.3% in a study by agrusa et al (9) and 13% in a study by Venkatramani et al (8) in which only effect of radiotherapy was evaluated.

Bleomycin is known to cause pulmonary fibrosis by various mechanism and results in restrictive lung disease (4). Radiotherapy to chest causes either acute radiation pneumonitis or chronic pulmonary fibrosis leading to development of restrictive lung disease (5). As both bleomycin and radiotherapy are part of treatment regimen in Hodgkin lymphoma, it is known that they develop restrictive lung disease in long term. This was evident in our study, in which prevalence of restrictive pattern (16.67%) of PFT was higher than obstructive (1.67%) pattern and mostly mild (13.33%) in severity, consistent with data from St Jude life time cohort study though it was done in a heterogenous group, majority of the study population were survivors of Hodgkin lymphoma (49.3%) (10)

Though 11 (18.33%) patients had abnormal PFT, only 2 (3.33%) patients had clinical symptoms i,e dyspnea on exertion and 3 (5%) patients had decreased air entry on auscultation of lung fields at the time of evaluation. Our data is consistent with previous studies done by Zorzi et al who reported 41% with abnormal PFT but only 8% had clinical symptoms (2). Another study done by Aliva et al reported at least one pulmonary function abnormality in 52.5% but clinical symptoms were present only in 8.7%. This signifies higher burden of sub clinical pulmonary dysfunction and thus need for routine pulmonary function assessment during follow up of HL survivors.

Our study identified pulmonary dysfunction at a median time of 2 years from completion of treatment, suggesting early development of pulmonary dysfunction and need for timely follow up and intervention, similar to most of the studies (2,7,8,9).

Most of the studies conducted till date determined either effect of bleomycin or radiotherapy on pulmonary dysfunction in a heterogenous population (2,7,10). To best of our knowledge there are only two pediatric studies done in homogenous population of Hodgkin lymphoma survivors to determine the associated factors for development of pulmonary dysfunction

(8,10). In our study, higher age at time of treatment (chemotherapy and/or radiotherapy) i,e age [?] 10years at the time of treatment was associated with development of abnormal PFT. Similar to study done by Venkatramani et al (8) and Azza et al (12). Supporting higher age at start of treatment associated factor for development of pulmonary dysfunction in our study we found that children of age $>$ 10 years at evaluation had higher risk (90.91%) of abnormal pulmonary function when compared to children of age [?] 10 years (9.09%) (p=0.043). This could be explained by reduction in lung capacity as age progresses and loss of repairing ability as age progresses.

In children bleomycin induced lung injury is reported usually at a dose above 120mg/m2 (2)

, concomitant thoracic irradiation and other chemotherapeutic agents like cyclophosphamide

can cause pulmonary dysfunction at lower doses. In our study we demonstrated a higher risk

of pulmonary dysfunction in survivors who received combined chemotherapy and radiation (54.55%) when compared to survivors who received chemotherapy alone (13.33%), comparable to previous studies (10,11). Most of the survivors i,e 57 (95%) received ABVD as chemotherapy regimen, 2 patients received BEACOPP and one patient received ABVD

alternating with COPP regimen. Median cumulative dose of bleomycin was 120mg/m2 (range 30-120mg/m2). Receiving radiotherapy was shown to have higher association with

development of pulmonary dysfunction when compared to chemotherapy alone i,e bleomycin

at a median dose of 120mg/m2.

It is interesting to note that of two patients who received BEACOPP regimen, one patient

who received cumulative bleomycin dose of 80 mg/m2 and cumulative cyclophosphamide

dose of 5200 mg/m2 with decreased ejection fraction (<60%) on echocardiography,

developed restrictive pattern on spirometry at a median follow up of 4 years. Other patient

who received cumulative bleomycin dose of 70 mg/m2 and cumulative cyclophosphamide

dose of 4550 mg/m2 with normal ejection fraction on echocardiography had normal

spirometry at a median follow up of 1 year from completion of treatment, signifying presence

of underlying cardiac dysfunction, an associated factor for development of pulmonary

dysfunction and need for evaluation of the same especially when concomitant cardiotoxic

chemotherapeutic drugs are given during therapy also longer period of follow up which may

unfold pulmonary dysfunction.

To assess functional status of HL survivors we did 3 minute step test. In our study all

survivors were able to complete 3 minute step test, had expected rise in heart rate and no desaturation post three minute test. This could be because most of the survivors had mild pulmonary dysfunction which might not cause functional limitation, other reason could be use of same 15 cm height step irrespective of patient's age. However these children would require long term follow up as severity of pulmonary dysfunction may progress with time.

Strengths of our study are, we did a prospective study in a homogenous group of childhood Hodgkin lymphoma survivors and assessed effect of both chemotherapy and radiotherapy.

However, our study had certain limitations, we did not have baseline pulmonary function

assessment prior to start of treatment and there were no controls. DLCO could not be done in our study population which could have demonstrated higher proportion of subclinical pulmonary dysfunction as seen in previous studies (9).

Majority of Hodgkin lymphoma survivors had subclinical pulmonary dysfunction

(Clinically asymptomatic but had pulmonary dysfunction on spirometry or three minute step test) at median follow up of 2 years from treatment completion. As the survival rate of HL patients has improved, during this life time children can be exposed to environmental hazards like smoke, pollution which can accelerate the deterioration of pulmonary function. Therefore Hodgkin lymphoma survivors require thorough initial assessment of respiratory status and pulmonary function testing and long term follow up for timely detection of pulmonary dysfunction and improve quality of life.

Conflicts of interests : None to declare by any of the authors. The authors alone are responsible for the content and writing of the paper.

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TABLE 5 Comparison of PFTs in patients who received combined chemotherapy and.docx available at https://authorea.com/users/472538/articles/563299-pulmonary-dysfunction-in-childhood-hodgkin-lymphoma-survivors-an-observational-study