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Effects of Supervised Exercise Program on Rituximab Induced Lung Toxicity in Follicular Lymphoma - A Case Report

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ABSTRACT

Rituximab when given along with standard chemotherapy, standard line of treatment for follicular lymphoma (FL), may develop Rituximab induced lung toxicity (RILT). We present a case study of a 36 years old male diagnosed with FL who underwent 3 cycles of chemotherapy along with Rituximab. During treatment, he developed recurrent lower respiratory tract infection for which he received antibiotic and antifungal drugs. Patient was referred to physiotherapy department for Pulmonary Rehabilitation in view of significant dyspnoea. Baseline assessment of functional capacity done using Six Minutes' Walk Test (6MWT) and dyspnoea using Cancer Dyspnoea Scale (CDS) and supervised exercise program (SEP) was developed. The recommendation was for a 6-week multimodal SEP which included, breathing exercises using a Positive End Expiratory Pressure (PEP) device like bottle PEP, Aerobic exercises and Strengthening exercises. Patient was evaluated after 3 and 6 weeks. There was a significant improvement in 6MWTdistance and CDS score along with increase duration of expiration while doing Bottle PEP exercises. SEP is safe and feasible to improve the respiratory health in patient subjected to RILT in FL.

Keywords: Supervised exercise program, rituximab induced lung toxicity, follicular lymphoma

INTRODUCTION

Follicular Lymphoma is one of the most common types of low-grade non-Hodgkin lymphoma. It presents as an enlarged lump in the lymph glands or affected organs, which is a cluster of white blood cells.[(1)]Chemotherapy in combination with Rituximab is the line of treatment for FL.

Rituximab, a mouse /human chimeric anti-CD 20 is a human monoclonal antibody. Rituximab can be given as a single agent or in combination regimens. It is well-tolerated drug, with lung toxicity rate of less than 0.03% patients. A prospective Korean study described 107 patients with non-Hodgkin lymphoma treated with a rituximab-containing regimen. Among these patients, 9 developed pulmonary complication. [(1, 2)] The majority cases of RILT occurred within days and up to 3 weeks after the first infusion of the treatment. [(3)]

Exercise training (ET) improves health outcomes in breast and other cancer patient but no randomized controlled trails (RCT)

have focused on RILT patients. Andrea Sitlinger et.al concluded that ET has the potential to improve a range of outcomes in patients with hematologic cancer.[4] Kerry S. Courneya et.al stated that aerobic ET significantly improved patient-related outcomes in lymphoma patients without interfering with medical treatments or response.ET to improve cardiovascular and respiratory fitness should be considered in the management of RILT patients. [9]
Various tools are used for the assessment of functional capacity and dyspnoea. In this study, we used 6MWT for functional capacity and CDS for dyspnoea. [5, 6, 7]

MATERIALS & METHODS

We present a case of 36 years old male diagnosed with FL, received 3 cycles of chemotherapy Bendamustine + Rituximab. He developed immunoglobulin deficiency (IG)along with recurrent lower respiratory tract infection (LRTI) after 2nd cycle and became severe after the 3rd cycle, for which he was treated with antibiotics, antifungals and IV Immunoglobulins. The decision was taken to discontinue Chemotherapy because of recurrent LRTI and IG deficiency. He was referred to the haematology department of Wadia Hospital for treatment of IG deficiency. The patient was then referred to physiotherapy for pulmonary rehabilitation. Patient presented with symptoms of dyspnoea and effort tolerance of less than 1 floor.

Physiotherapy Assessment:
During baseline assessment, he was conscious and oriented, maintaining stable vital signs: saturation (SpO_2)93% on Room air, Heart Rate (HR) 92 beats per minute (bpm), Respiratory Rate (RR) 44 Breaths/minute and a Rate of Perceived Exertion (RPE) of 1.

6MWT:[6]
According to the American Thoracic Society guidelines, 6MWT is used to assess the functional capacity. It helps to identify the extent of pulmonary impairment.
6MWT is performed along a long, flat, straight 30 meters enclosed corridor on a hard surface. Resting Vital Signs such as SpO_2, HR, BP, RR and RPE are recorded.
Patient is then instructed to walk, not run or jog, for 6 minutes, cover as much possible distance as he can. If required, the patient is allowed to slow down or stop and rest in case of any discomfort during the test.
At the end, re-assessment of all vital parameters, as stated above is done, along with subjective assessment such as, number of laps covered, distance covered, number of breaks taken (if any) and the subsequent duration of breaks. Based on the vitals and demographic details, the ideal distance covered, % predicted of covered, and parameters essential to treatment (HR_{max}, Heart rate reserve (HRR), Target HR) are determined.

CDS:[5]
Dyspnea is one of the most frequent and refractory symptoms in cancer patients. K Tanaka et al. states that CDS is a brief, valid, self-rated and feasible scale for assessing the muti dimensional nature of dyspnea in cancer patients. It is a 12-item scale, composing of 3 factors – Sense of Effort, Sense of Anxiety, and Sense of Discomfort. The sum of these 3 factors as well as the individualised scores are considered for interpretation of dyspnea; which states that – higher the score, higher the level of dyspnea. The CDS shows good validity and reliability with internal consistency of the factors as 0.83, 0.81 and 0.94 (average 0.86) respectively.
Time Frame of Assessment: The above mentioned outcome measures were assessed at 3 points – Prior to Intervention, Post 3 weeks of Intervention and Post 6 weeks of Intervention.

Intervention and Outcome Measures:
A SEP was tailored for this patient which consisted of:
i) Bottle PEP Exercises
ii) Aerobic Training
iii) Strength Training

A SEP planned for duration of 6 weeks; 5 days/ week.

Bottle PEP:[8](fig 1, 2)

Bottle PEP Exercises involves the use of a 1L bottle filled with a predetermined quantity of water (not exceeding 500ml). The lid/ cap is punctured with 2 holes – 1 to hold a long tube (intravenous [i.v] cannula) whose one end is immersed into the water level, reaching the bottom, and, the other is for a small tube which is open at both ends (Injection site of i.v. set). The Drip Chamber of the i.v. set is used to blow into the tube by overcoming pressure applied by the water until bubbles are produced. The resistance can be controlled by the roller clamp on the i.v. set.

This exercise is used to decrease the RR, overcome the expiratory flow limitation, improve the breathing pattern, and improve gas exchange. The effectiveness of exercise is determined by calculating the Expiratory Time – the duration for which the patient can sustain the bubble formation. This time was recorded at the end of each session.

Aerobic Training[6]

Prior to aerobic/ strength training, warm up was performed which included active Range of motion exercises for upper and lower limb

Based on the 6MWT, an aerobic training program was designed in 2 parts

For the First 3 weeks (Week 1 –week 3), since the patient had difficulty in maintaining optimal SpO_2 (88%), the exercises were performed with 2Litre (L) oxygen (O_2) support via Nasal Prongs. The overall duration for aerobic exercises was 20 minutes (mins) and consisted of:

i) Sit to Stand – 2 sets of 15 repetitions each (Fig 3)
ii) Stepping (Step Up – Down) – 2 sets of 20 repetitions each (Fig 4)

Stationary Cycling for Lower Limb – 10 mins (However, since the patient was maintaining SpO_2 of 94% while cycling, the O_2 support was discontinued for this exercise after 1 week itself.) (Fig 5)

For the next 3 weeks (Week 4 –week 6), the protocol was altered and made progressively challenging as the patient was now able to maintain a Spo2 of 96% during exercises. Thus, O_2 support was discontinued and exercise was performed on room air. This included treadmill walking for duration of 20 mins. (Fig 6)

Strength Training:[6]

This was performed using Thera band for Large Muscle groups for upper and lower limb were targeted. Dosage: 3 days/ week, 2 sets of 8 repetitions each, for 6 weeks.

Outcome measures:(Table 1)

The following were the Primary outcome measures used to determine effectiveness of the intervention in this study:

i) Duration of Bottle PEP (seconds)
ii) 6MWT distance (meters)
iii) CDS

Secondary Outcome Measures included:

i) Pre-exercise session vitals (SpO_2, RR, HR, RPE)
ii) Number and Duration of Breaks during 6MWT

RESULT

Comparison between the outcome measures was done pre and post intervention. There was a significant improvement in the outcome measures following SEP.

At baseline the bottle PEP was 7 seconds which then improved to 30 seconds post intervention, 6MWT distance was 150 meters at baseline with 1 rest break for 1 minute. Post intervention the walk distance improved to 300 meters without any break.

CDS Score prior to intervention was 41 and then decreased to 16 post intervention denoting, relative decrease in dyspnoea, which depicts improvement.

Table 1

	Baseline – Prior to Intervention	**Mid – 3 Weeks post Intervention**	**Post – 6 Weeks post Intervention**
Duration of Bottle PEP (seconds)	7	24	>24
6MWT distance (meters)	150	240	300
CDS Score	41	16	16
Vitals (pre-exercise session)			
HR	92 bpm	90 bpm	87bpm
SPO2	93% with O_2 support	93% without O_2 support	96% without O_2 support
RPE	1	0.5	0.5
RR	44 Breaths/ min	40 Breaths/ min	28 Breaths/ min
Breaks during 6MWT			
Yes/ No	Yes	Yes	No
If Yes, Number	1	1	
If Yes, Duration	1 minute	45 min	
Resumed after break; Yes/ No	Yes	Yes	

Figure no. 1: Bottle PEP

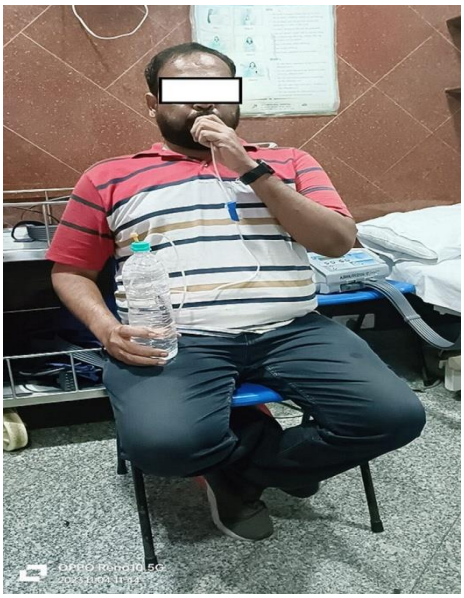

Figure no. 2: Bottle PEP Exercise

Figure no. 3: Sit to Stand Exercise

Figure no. 4: Stepping Exercise

Figure no. 5: Cycling

Figure no. 6: Treadmill

DISCUSSION

The present study was designed to evaluate the effectiveness of SEP in patient with RILT. The result of present case report showed that there is significant improvement in 6MWTdistance and duration of bottle PEP exercise. Also, there is improvement in CDS score.

During the physical activity, the muscles need more O_2. In this way, a synchronous occurs in the respiratory system. [9] Respiratory functions depend on the type of physical activity performed, the condition of respiratory muscles, lung compliance, and the dilation of the bronchi.[10] High intensity aerobic exercise improves air flow in the respiratory tract. Improvement in 6MWTdistance is because of the lungs expanding during high-intensity aerobic exercise, resulting in a large volume of air introduced into the airways and a widening of the respiratory tract.[9] Also it increases the vo2 max and activates the inactive alveoli and may have been responsible for the reduction in O_2 requirement post 3 weeks of intervention.[9, 10] Improvement in CDS may have been because of bottle PEP exercise which facilitates the activation of diaphragm muscle by prolonged expiration, creating PEP pressure. Moreover, repeated stimulation of inspiration and expiration would increase alveolar compliance. The SEP positively affect respiratory function by improving strength of diaphragm muscle and lung capacity.

CONCLUSION

SEP is safe, feasible and recommended in RILT patient to decrease respiratory complication, improve aerobic capacity, and improve or at least maintain lung function in FL patients.

Declaration by Authors

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Conflict of Interest: The authors declare no conflict of interest.

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