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RESEARCH

Assessment of respiratory functions in pediatric oncology patients receiving bleomycin treatment

Bleomisin tedavisi alan pediatrik onkoloji hastalarında solunum fonksiyonlarının değerlendirilmesi

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Abstract

Purpose: Bleomycin is a chemotherapeutic agent that causes lung toxicity. Bleomycin is mostly used in the treatment of germ cell tumors (GCT) and Hodgkin Lymphoma (HL) in childhood cancers. In this study, we aimed to detect bleomycin toxicity to the lung in the early period.

Materials and Methods: Pulmonary functions of patients aged 5 years and older who were admitted to the Division of Pediatric Oncology with GCT and HL between 2012 and 2022, who received bleomycin treatment and were in remission for at least 6 months were evaluated. The evaluation of respiratory functions was based on history, physical examination, posteroanterior chest radiography (chest X-ray) and pulmonary function test (PFT).

Results: The number of patients with GCT who entered follow-up and lived were 59, those with HL were 89. The number of patients who received bleomycin treatment, were in remission for at least 6 months, could be reached and underwent PFT were 46 for HL and 12 for GCT. There were 21 patients with PFT abnormalities. Of these patients, 3 were diagnosed with GCT and 18 were diagnosed with HL. The type of PFT abnormality in the majority of patients was restrictive disorder.

Conclusion: The absence of respiratory symptoms in 90% of patients with PFT abnormalities shows the importance of PFT in asymptomatic patients. Patients who have received bleomycin as part of treatment should also be followed-up for late pulmonary toxicity.

Keywords:. Lung toxicity, bleomycin, germ cell tumor, Hodgkin lymphoma, pulmonary function test.

Öz

Amaç: Bleomisin akciğer toksisitesine neden olan bir kemoterapötik ajandır. Bleomisin çoğunlukla çocukluk çağı kanserlerinde germ hücreli tümörler (GCT) ve Hodgkin Lenfoma (HL) tedavisinde kullanılır. Bu çalışmada akciğerde bleomisin toksisitesini erken dönemde tespit etmeyi amaçladık.

Gereç ve Yöntem: 2012-2022 yılları arasında Pediatrik Onkoloji kliniğine başvuran, GHT ve HL tanısı alan, 5 yaş ve üzeri, bleomisin tedavisi alan ve en az 6 aydır remisyonda olan hastaların akciğer fonksiyonları değerlendirildi. Solunum fonksiyonunun değerlendirilmesi öykü, fizik muayene, posteroanterior akciğer radyografisi ve solunum fonksiyon testine (SFT) dayanıyordu.

Bulgular: Takibe alınan ve yaşayan GHT'li hasta sayısı 59, HL'li hasta sayısı 89 idi. Bleomisin tedavisi alan, en az 6 aydır remisyonda olan, ulaşılabilen ve SFT yapılan hasta sayısı HL için 46, GHT için 12 idi. SFT anormalliği olan 21 hasta vardı. Bu hastaların 3'üne GHT, 18'ine HL tanısı konmuştu. Hastaların çoğunda SFT anormalliğinin türü restriktif bozukluktu.

Sonuç: SFT anormalliği olan hastaların %90'ında solunum semptomlarının olmaması, asemptomatik hastalarda SFT'nin önemini göstermektedir. Tedavinin bir parçası olarak bleomisin alan hastalar da geç pulmoner toksisite açısından takip edilmelidir.

Anahtar kelimeler: Akciğer toksisitesi, bleomisin, germ hücreli tümör, Hodgkin lenfoma, akciğer fonksiyon testi.

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INTRODUCTION

Bleomycin is an antibiotic agent obtained from a strain of *Streptomyces verticillus* in 1966, which shows antitumor activity by inducing free radicals and is used in the treatment of HL, GCT and squamous carcinomas in the head and neck region[1,2]. Since bleomycin inactivation is low in the lung, bleomycin-induced toxicity is observed in the lung due to bleomycin accumulation[3]. After oxidative damage caused by bleomycin in the lung, type 1 pneumocytes are destroyed, granulocyte influx begins, and chemotactic factors, elastase, collagenase and myeloperoxidase are released[4]. Vascular and cellular damage develops due to bleomycin accumulation, an inflammatory process begins in the lung parenchyma and growth factors released from macrophages stimulate fibroblasts. Secondary to activated fibroblasts, lung fibrosis eventually develops. Bleomycin toxicity may occur early or late and pulmonary fibrosis usually occurs 1 to 6 months after treatment[5,6]. Early-onset pulmonary toxicity is uncommon, occurs as a hypersensitivity reaction and may develop into interstitial pneumonitis beginning from administratition of the drug up to several months after completion of chemotherapy. Early-onset toxicity does not have a clear dose relationship to late-onset toxicity[7].

Interstitial pneumonia, also known as hypersensitivity reaction, may develop at the first dose of chemotherapy or may occur months later. Methotrexate, bleomycin, procarbazine and carmustine are among the agents that cause this clinical picture. In most cases the response to drug withdrawal and steroid treatment is good and normal lung function is restored[8,9].

Pulmonary toxicity of chemotherapy may develop as interstitial lung pneumonia in the early period and pulmonary fibrosis in the late period. Toxic effects vary depending on the dose of chemotherapy received, whether radiation therapy is received, the dose rate and duration of radiation, pre-existing lung disease and steroid use[8]. There are different methods used to determine pulmonary toxicity, such as PFT, chest X-ray and CT[10-12]. Bleomycin is mostly used in the treatment of HL and GCT among childhood cancers. In pediatric age group to detect bleomycin toxicity in the early period before the clinical deterioration is extremely important. This study aimed to investigate lung toxicity in pediatric oncology patients using bleomycin as part of the treatment in the early period.

MATERIALS AND METHODS

This study was conducted on patients diagnosed with HL and GCT who applied to the Pediatric Oncology outpatient clinic of Cukurova University Faculty of Medicine between 2012 and 2022. Ethics Commity of Cukurova University Faculty of Medicine approved the study (meeting no 2, on 2.4.2021).

Sample

The study was conducted in Pediatric Oncology and Pediatric Allergy and Immunology Departments of Çukurova University. Patient information was obtained from Pediatric Oncology patient files, whose archive system is well-established and reliable. This information was interpreted by the pediatric oncology specialists mentioned in the study. Pulmonary function tests were performed by experienced personnel in the Department of Pediatric Allergy and Immunology, and the tests were interpreted by the pediatric allergy and immunology specialist participating in the study. Çukurova University Department of Pediatrics is an accredited institution both internationally (by European Academy of Paediatrics in 2019) and nationally (by National Medical Specialization Qualification Board in 2021).

Inclusion criteria comprised patients diagnosed with Hodgkin lymphoma (HL) or germ cell tumor (GCT) who had completed treatment, were maintained in remission for at least 6 months post-treatment, were aged 5 years or older (to ensure compatibility with pulmonary function testing), had received bleomycin therapy, and provided written informed consent to participate in the study.

231 files of patients diagnosed with HL and GCT were scanned. There were 109 patients diagnosed with GCT and 122 with HL. 15 patients with a diagnosis of GCT and 17 patients with a diagnosis of HL were excluded from the study because they were dead. 35 of 94 living GCT patients and 16 of 105 HL patients were excluded from the study because they did not come for follow-up. 59 GCT patients and 89 HL patients who came for regular follow-up and were alive were included in the study. The number of patients who received bleomycin treatment, and in remission for at least 6 months and could be reached

and underwent PFT were 46 for HL and 12 for GCT and the total number of patients were 58.

Procedure

All living and reachable patients diagnosed with HL and GCT were prospectively subjected to PFT and chest X-ray. Those with PFT disorders were evaluated as obstructive type, restrictive type and mixed type. Chest radiographs were evaluated as normal or pathological (interstitial fibrosis findings) were present.

Obstructive disorder was defned when FEV1/FVC is decreased (<80%) and/or FEV1 is decreased (<80%), FEF25-75(MEF25-75) is decreased (<70%), FVC is normal, restrictive disorder; situations where FEV1/FVC is normal or increased (> 80%), FVC is decreased (< 80%), mixed disorder; FEV1/FVC decreased (<80%) and FVC decreased (<80%) conditions were considered[13]. In PFT, values are determined as a percentage based on the values in healthy individuals for a certain age, gender, height, body weight and race. In our study, the bleomycin dose was calculated as units/m^2.

Abnormalities in the lung functions of GCT and HL patients who were in remission for at least 6 months and who received bleomycin treatment was eveluated by PFT, chest X-ray, thorax CT. Bleomycin cumulative dose, chronic respiratory symptoms, RT, height, body weight, stage, histopathological subtype, family history, and smoking status were also recorded. The relationship between the patients with PFT disorder and the variables such as age at diagnosis, duration of remission, chemotherapy protocols of the patients, whether they received radiotherapy, cumulative dose of bleomycin received, smoking, gender, whether pathology was detected in chest X-ray and thorax tomography, presence of symptoms, and histopathological subtype were examined.

Statistical analysis

When performing statistical analysis, chi square test statistics were used to compare categorical measurements between groups (age, sex, duration of remission, respiratory symptoms, RT, stage, histopathological subtype, family history, and smoking status with abnormal PFT). In comparing numerical measurements between groups (bleomycin cumulative dose, height, body weight with abnormal PFT), t-test was used in independent groups if the assumptions were met and Mann-Whitney U test was used if the assumptions were not met. Categorical measurements were summarized as numbers and percentages and numerical measurements were summarized as mean and standard deviation (median and minimum-maximum where necessary). IBM SPSS Statistics Version 20.0 package program was used in the statistical analysis of the data. In all tests, the statistical significance level was taken as 0.05.

RESULTS

148 patients who were diagnosed with HL and GCT, were followed-up, who are in remission for at least 6 months, were evaluated in the study. The number of patients with GCT was 59 (40%) and the number of patients with HL was 89 (60%). 114 of 148 patients (77%) received bleomycin treatment, and 58 patients who were in remission for at least 6 months, were under regular follow-up, and wanted to undergo examination and PFT were included in the study. PFT was performed in 12 patients diagnosed with GCT and in 46 patients diagnosed with HL.

Table 1. Relationship between PFT disorder and height and body weight

	PFT normal	PFT disordered	P
Height (mean±ss)	161.4±15.2	151±21.2	0.05
Body weight (mean±ss)	61±18.5	49.6±23	0.048

PFT: Pulmonary function test

Of the 58 patients who underwent PFT. 7 (12.1%) had cough. 5 (8.6%) had sputum. 8 (13.8%) had shortness of breath. and 4 (6.9%) had wheezing. Among those who underwent PFT smoking prevalence was 3.4%. Of the 58 patients who underwent PFT. 37 (63.8%) had normal functions. Obstructive disorder was detected in 3 (5.2%). restrictive disorder in 16 (27.6%). and mixed type disorder in 2 (3.4%).

Of the 58 patients who underwent PFT. 45 (77.6%) received the ABVD (adriamycin. bleomycin. vinblastine. dacarbazine) protocol. 1 (1.7%) received the COPP (cyclophosphamide. oncovin. procarbazine. prednisone)-ABV (adriamycin. bleomycin. vinblastine) protocol. 12 (20.7%) received the BEP (bleomycin. etoposide. cisplatin) protocol. Acute bleomycin toxicity occurred in only 1 (1.7%) patient. and bleomycin treatment was discontinued

due to unexplained changes in the patient's lung imaging that did not improve despite treatment for metastasis and infection.

Table 2. Clinical characteristics of patients with abnormal PFT

Characteristics	N (%)
Female Male	8 (38%) 13 (62%)
Age at diagnosis	(1.5-17)
Current age	(7-26)
HL GCT	18 (85.7%) 3 (14.3%)
Median height. cm (range)	151 (110-180)
Median weight. kg (range)	51 (20-98)
Non-smoker Smoker	20 (95.2%) 1 (4.8%)
Bleomycin cumulative dose ≤120 U/m^2 Bleomycin cumulative dose >120 U/m^2	9 (42.8%) 12 (57.2%)
Mediastinal RT-No Mediastinal RT-Yes	17 (80.9%) 4 (19.1%)
With a chronic respiratory symptom With a chronic respiratory symptom	15 (71.4%) 6 (28.6%)
Radiological abnormality-No Radiological abnormality-Yes	12 (57.2%) 9 (42.8%)
Restrictive disorder Obstructive disorder Mixed disorder	16 (76.2%) 3 (14.3%) 2 (9.5%)

PFT: Pulmonary function test. RT: Radiotherapy. HL: Hodgkin lymphoma. GCT: Germ-cell tumor.

When the histopathological subtypes of all 46 HL patients who underwent PFT were examined. 2 (4.3%) patients were classical lymphocyte-rich. 20 (43.5%) patients were classical nodular sclerosing. 17 (37%) patients had mixed cellularity HL. and 7 (15.2%) patients could not be classified. Of the 46 HL patients who underwent PFT. 32 (69.6%) had post-treatment thorax CT scans. 11 (52.2%) had a ground glass appearance on thorax CT. 2 (10.9%) had a nodular lesion. 2 (4.3%) had an infection. 1 (2.2%) had a ground glass appearance. Of 46 patients diagnosed with HL. PFT was normal in 28 (60.9%). restrictive disorder was determined in 14 (30.4%). obstructive disorder in 3 (6.5%). and mixed disorder in 1 (2.2%). One of the HL patients (2.2%) who underwent PFT was a smoker.

Considering the histolopathological subtypes of all 12 GCT patients who underwent PFT. 1 patient (8.3%) has germinoma. 1 patient (8.3%) immature teratoma. 6 patients (50%) yolk sac tumors. 4 patients (33.4%) mixed GCT. 8 of these patients (67%) were girls and 4 (33%) were boys. Only 1 of 12 patients (8.3%) was a smoker. None of the patients had a post-treatment thorax CT. Chest X-ray of 11 of 12 patients diagnosed with GCT (91.7%) was normal. and only 1 (8.3%) had interstitial fibrosis. According to thethe PFT results. 2 (16.7%) patients had a restrictive disorder. 1 (8.3%) mixed type disorder. and 9 (75%) normal PFT.

Of the 58 patients who underwent PFT. 21 (36.2%) had an abnormality. Of the 21 patients with impaired PFT. 8 (38.1%) were female and 13 (61.9%) were male. Of the patients with disordered PFT. 18 (85.7%) were diagnosed with HL and 3 (14.3%) . GCT. Only 1 (4.8%) patient with PFT disorder was a smoker. Among these patients. 3 (14.3%) had obstructive. 16 (76.2%) restrictive and 2 (9.5%) had mixed type disorder. Of 21 patients with PFT disorders. 3 (14.3%) received the BEP protocol and 18 (85.7%) ABVD protocol.

The mean height (p=0.05) and body weight (p=0.048) were lower in patients with impaired PFT (Table 1). There was no significant difference between the bleomycin dose and PFT impairment.

DISCUSSION

While the incidence of HL is higher in adolescents and in the male gender.[14,15] in our study. 2/3 of our patients with impaired PFT and diagnosed with HL were under the age of 15. and the gender ratios of these patients were equal between boys and girls. When looked at according to HL histopathological subtypes. the NSHL subtype of classical HL ranks first in terms of frequency[16] and in our study. it was the most common histopathological subtype in patients who were diagnosed with HL. received bleomycin treatment were in remission for at least 6 months and were also found to have PFT disorder.

Protocols such as ABVD and COPP are used in the treatment of HL[17] but in our study. all HL patients with PFT abnormalities treated with ABVD. GCT is rare in childhood with a rate of 2% under the age of 15 and it peaks between the ages of 0-4 and during adolescence[18,19] in our study. 3 patients with impaired PFT were diagnosed with GCT. and 1 of our patients was in the adolescence period while the other 2 were diagnosed under 4 years.

Bleomycin is an antibiotic agent with known lung toxicity and is used as part of the chemotherapy protocol in the treatment of HL and GCT[20]. Lung fibrosis develops as a result of cell damage due to

bleomycin accumulation. and its effects are seen between 1 and 6 months after treatment[6]. It causes the development of interstitial fibrosis. especially in the lung[7]. In our study. 32 of the 58 patients who received bleomycin treatment and were in remission for at least 6 months and underwent PFT had a thorax CT in the system. and while half of them were associated with interstitial fibrosis. the remaining half were normal. When the thorax CT and chest radiographs of patients with PFT disorders were examined. the most common finding indicating interstitial fibrosis was the ground glass appearance.

In a study conducted in adults[8,9]. lung fibrosis was observed in 10% of patients who received bleomycin over 400 units/m². whereas in our study. the highest bleomycin dose taken by our patients with PFT disorders was 160 units/m². In contrast some of our patients received bleomycin at a dose of 80 units/m² had lung fibrosis findings on chest radiographs. Whereas. in some of our patients received doses higher than 80 units/m² there was no findings on thorax CT and chest X-ray. Since our patients did not receive doses as high as 400 units/m² of bleomycin a significant relationship between lung fibrosis and cumulative dose of bleomycin may not have been detected.

When interpreting the PFTs performed in our study. they were categorized into 4 types: normal. obstructive disorder. restrictive disorder and mixed type disorder. Disorders in PFT were detected in 36% of 58 patients who underwent PFT. In a study[21]. it was found that 18% of PFT disorders were of restrictive type. In our study. restrictive disorders were found in 27.6% of the patients who underwent PFT. Obstructive disorder was not reported in the same study but in our study obstructive disorder was found in 5.2% and mixed type disorder was found in 3.4%. When restrictive. obstructive. and mixed type disorders were examined. no significant relationship was found regarding whether or not receiving RT. cumulative dose of bleomycin. smoking. and chronic respiratory symptoms. This may be due to the small number of patients in our study. In our study. significantly lower FEV1. FVC. FEV1/FVC. PEF. MEF_{25-75} values were found in patients with PFT disorders who received RT to the mediastinum. 6 months and received bleomycin treatment.

Two of the patients who received bleomycin treatment. were in remission for at least 6 months. and underwent PFT were smoking. No statistically significant difference was detected between bleomycin and smoking status. This may be because the number of smokers was low and because our patients were young. not enough time had passed for the effects of smoking to be seen.

The point emphasized by Record et al. in their study[22] was that patients without clinical symptoms constituted 2/3 of the study participants having PFT disorders. In our study. the rate of patients who received bleomycin treatment. were in remission for at least 6 months. and were found to have impaired PFT but were asymptomatic was 71%. The common point between our study and this study was that both rates were very close to each other. Basic contribution of our study is that bleomycin toxicity was detected before clinical findings emerged in an asymptomatic cohort. Phillips et al. also emphasized that the negative effects of bleomycin on the lung can be seen after 5 years of HL treatment[23].

In a study conducted by Conte et al.[24]. it was stated that drug-induced interstitial lung disease occurs as a result of the use of drugs that cause inflammation and interstitial fibrosis. In our study. only 1 patient developed interstitial lung disease due to acute bleomycin toxicity. Bleomycin treatment was discontinued and prednisolon was started. The PFT and chest X-ray of our patient. who was in remission. were normal and the patient had no chronic respiratory symptoms.

In a study by Dei-Adomakoh et al.[25]. they mentioned bleomycin-induced pneumonia in a young Ghanaian male patient with HL. In our study. respiratory symptoms developed in one of our patients while receiving the ABVD protocol. and after the findings of lung metastasis were excluded. bleomycin-induced lung injury was considered and the bleomycin treatment given to our patient was discontinued and prednol treatment was started. Our patient continued her regular follow-up. and in this study. both a chest X-ray and PFT were performed. PFT was normal. Our patient was lucky in terms of survival. In the study mentioned. even if the patients went into remission. the risk of toxicity-related lung pathologies increased with each relapse due to bleomycin treatment. In a study conducted by Uzel I et al.[26]. bleomycin-induced pneumonia was detected in a patient diagnosed with testicular cancer. developing 2 years after completing the BEP protocol. In our study. PFT disorder and lung pathology were also detected in patients who completed chemotherapy and were in remission for years.

One of the limitations of our study is that thorax CT is more valuable than chest X-ray in the diagnosis of interstitial fibrosis and not all of our patients with defective PFTs had thorax CT in the system. Another limitation of our study was that DLCO could not be evaluated in PFT. Because low DLCO is considered limit the most sensitive and first sign of PFT disorder that may develop in the future. PFT is performed in children over the age of 5 who can comply. and the age limit reduced the number of patients participating in our study. Exclusion of a large number of patients because of the inadequacy of the evaluation with thoracic CT imaging and the number of patients without follow-up. are the other limitations of our study.

The originality of our article and its contribution to the literature is that bleomycin toxicity was investigated in a cohort that was almost entirely asymptomatic and was detected before clinical findings emerged. Clinical findings should be evaluated with PFT and chest X-ray in the regular follow-up of patients who received bleomycin treatment after the diagnosis of HL and GCT and evaluation with PFT should be performed in the annual follow-up. Detection of bleomycin-induced lung toxicity in older patients who have received bleomycin treatment shows how important it is to follow-up these patients.

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