Nintedanib Treatment in a Child with Pulmonary Fibrosis

Pulmoner Fibrozis Gelişen Bir Çocukta Nintedanib Deneyimi

Meltem AKGÜL ERDAL[1], Didem ALBOĞA[1], Birce SUNMAN[1], H. Nursun ÖZCAN[2], Nagehan EMİRALİOĞLU[1], Ebru YALÇIN[1], Deniz DOĞRU[1], Uğur ÖZÇELIK[1], Nural KİPER[1]

[1]Department of Pediatric Pulmonology, Hacettepe University, Faculty of Medicine, Ankara, Türkiye
[2]Department of Radiology, Hacettepe University, Faculty of Medicine, Ankara, Türkiye

ABSTRACT

Pulmonary fibrosis (PF) in children is a very rare, progressive, and life-threatening condition. There are advances in the treatment of idiopathic PF in adults with the approval of antifibrotics like nintedanib. However, PF treatment in children is still an inconclusive area that needs to be studied further. Here, we present the nintedanib experience in a child with PF.

Key Words: Bleomycin, Child, Interstitial, Lung disease, Nintedanib, Pulmonary fibrosis, Radiotherapy

ÖZ

Çocuklarda pulmoner fibrozis (PF) çok nadir görülen, ilerleyici ve yaşamı tehdit eden bir durumdur. Nintedanib gibi antifibrotiklerin onaylanmasıyla erişkinlerde idiyopatik PF tedavisinde ilerlemeler kaydedilmiştir. Bununla birlikte, çocuklarda PF tedavisi hala daha fazla çalışılması gereken sonuçsuz bir alandır. Burada, PF'li bir çocukta nintedanib deneyimini sunuyoruz.

Anahtar Kelimeler: Bleomisin, Çocuk, İntersitisyel, Akciğer hastalığı, Nintedanib, Pulmoner fibrozis, Radyoterapi

INTRODUCTION

Pulmonary fibrosis (PF) is a rare condition that has been described in some form of interstitial lung disease (ILD) in children, such as surfactant disorders, hypersensitivity pneumonitis and drug-induced pneumonitis. In children, drug-induced lung fibrosis is usually associated with the drugs used in many cancer treatments (1). One well-known drug for this is bleomycin. Bleomycin is a chemotherapeutic used to treat Hodgkin's lymphoma (2). The most important limitation of bleomycin therapy is the potential risk of developing PF (1). Since there is no effective treatment for bleomycin-induced pulmonary fibrosis, it is usually treated symptomatically. Another factor contributing to lung injury is thoracic irradiation. It has been shown that radiation in combination with bleomycin increases the fibrogenic effect (3).

The main treatments for PF in children are corticosteroids and hydroxychloroquine. Corticosteroids have a beneficial effect on surfactant disorders, pulmonary hemosiderosis and in severe cases of neuroendocrine cell hyperplasia of infancy. Hydroxychloroquine is an alternative to steroids (4). If there is no response to these treatments, antifibrotics may be the treatment of choice for PF. One of the antifibrotics is nintedanib, a tyrosine kinase inhibitor approved by the US Food and Drug Administration (FDA) for idiopathic pulmonary fibrosis (IPF) and other chronic progressive ILDs in adults. A recent study

0000-0002-7507-0770 : AKGÜL ERDAL M
0000-0001-8586-5975 : ALBOĞA D
0000-0001-9818-8782 : SUNMAN B
0000-0003-4756-4359 : ÖZCAN HN
0000-0002-1405-8401 : EMİRALİOĞLU N
0000-0002-7325-1981 : YALÇIN E
0000-0001-9931-9473 : DOĞRU D
0000-0003-1587-5216 : ÖZÇELİK U
0000-0003-1261-7393 : KİPER N

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Correspondence Address / Yazışma Adresi :
Meltem AKGÜL ERDAL
Department of Pediatric Pulmonology,
Hacettepe University, Faculty of Medicine, Ankara, Türkiye
E-posta: meltemakgul87@gmail.com

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of nintedanib in children and adolescents reported the safety profile of the drug (5). There is not enough data yet on the effectiveness of the drug in children.

Here, we present a 36-week experience with nintedanib in a boy who developed PF after treatment with a bleomycin-containing regimen and thoracic radiotherapy for Hodgkin lymphoma.

CASE REPORT

An 11-year-old boy with Hodgkin lymphoma had a history of 8 cycles of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) protocol in 2020. His treatment continued with radiotherapy to the right upper hemithorax between February and March 2021 at a centre other than our hospital. One month after his last radiotherapy, he presented with cough, tachypnoea and dyspnoea on moderate exercise. His initial clinical evaluations were made in the hospital for the first 8 months, where he was treated for lymphoma. He was inititally treated with antibiotics. He also received inhaled beta-agonists and inhaled corticosteroids for three months. As there was no improvement in his cough and dyspnoea, systemic corticosteroids (1 mg/kg/day methylprednisolone) were started. An improvement in the percentage of predicted forced vital capacity (FVC) values (from 43% to 56%) achieved with systemic corticosteroid treatment. After the resolution of the tachypnoea, steroid doses were gradually reduced and discontinued after 5 months. Despite systemic steroids, the persistent cough became productive and he described progressing exercise intolerance. Flexible bronchoscopy was performed at the other hospital and showed normal macroscopic findings. Bronchoalveolar lavage fluid was free of malignant cells and microorganisms. At the follow-up visit, decreased breath sounds were noted on the right side compared to the left side. A chest computed tomography (CT) was performed because of the blunting of the right costophrenic angle on the chest X-ray. There was no pleural effusion, but blunting of the costophrenic angle was noted. Eight months after his last course of radiotherapy, the patient was admitted to our hospital. He presented with progressive productive cough, shortness of breath and exercise intolerance. He was not taking any medications for his symptoms at presentation. His body weight was 26 kg (5p-10p), and his transcutaneous saturation was 94% on room air. Physical examination revealed decreased breath sounds in the right hemithorax. The patient was unable to perform spirometry due to a severe cough. In the 6-minute walk test (6-MWT), he walked 396 meters (below the 3rd percentile estimated for his height) and there was a rapid drop in saturation with a minimum saturation of 80%. Routine blood tests such as complete blood count, liver and kidney function tests and blood gas analysis were normal. The first chest CT scan performed before hospitalization showed minimal traction bronchiectasis in the upper and lower lobes of the right lung, thickening of the right major fissure and subpleural reticular densities in both lungs, more prominent in the right lung. The remission of the Hodgkin lymphoma was confirmed by the oncology department of our hospital. Evaluation of the lymphoma protocol showed that bleomycin doses were higher than the accepted cumulative doses for children. Fifteen days after admission to our hospital, oral nintedanib (75 mg twice daily) was started due to a deterioration in his clinical condition, with the approval of the off-label committee of the Ministry of Health and the decision of a multidisciplinary meeting. The 75 mg dose of nintedanib was chosen based on the InPedILD study, which recommended weight-based dosing. Following the initiation of nintedanib, the patient was re-evaluated at the 1st, 2nd, 4th, 6th and 9th month of treatment. The patient did not receive any other medication during this period. Body weight, transcutaneous saturation, pulmonary function tests (PFT) and 6-MWT evaluated at each visit are shown in Table I. Six month after nintedanib therapy, respiratory symptoms and signs worsened, oxygen requirements increased and non-invasive ventilation began. He lost weight despite caloric support. He had two pulmonary exacerbations requiring hospitalisation in the last 3 months of the treatment. In addition to the clinical deterioration, chest CT and chest X-ray (CXR) showed progression of the parenchymal findings. A comparison of serial chest CT scans and CXR taken before starting nintedanib and

Table I: Clinical follow-up characteristics

Nintedanib treatment duration	Body weight	Saturation (%) (at rest in the room air)	Predicted FVC(%)*	Predicted FEV1 (%)*	Predicted FEV1/FVC (%)*	6-minute walking test (distance in meters /Percentile of the estimated to the height† minimum SpO2)
The first admission	26 kg	94	N/C ‡	N/C	N/C	396 /<3rd percentile / 80%
Before the treatment	24 kg	91	N/C	N/C	N/C	Not performed
First month	24.5 kg	93	23	21	83	310 /<3rd percentile / 80%
2nd month	23.5 kg	94	N/C	N/C	N/C	286 /<3rd percentile / 74%
4th month	23.5 kg	95	N/C	N/C	N/C	Not performed
6th month	23 kg	85	12	14	118	165 /<3rd percentile / 68%
9th month	22 kg	65	N/C	N/C	N/C	476 / <3rd percentile /78% (under the 3lt/min oxygen)

**Spirometry results, †Based on standardized reference values, ‡No cooperation*

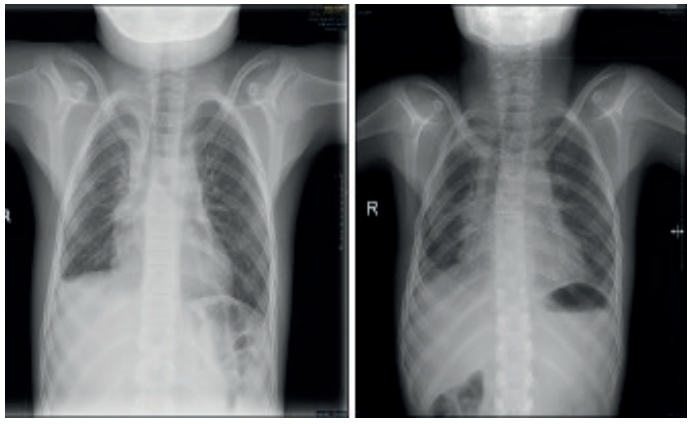

Figure 1: Chest X-ray at the first admission (before the nintedanib treatment:on the right side; 6th months of nintedanib treatment: on the left side)

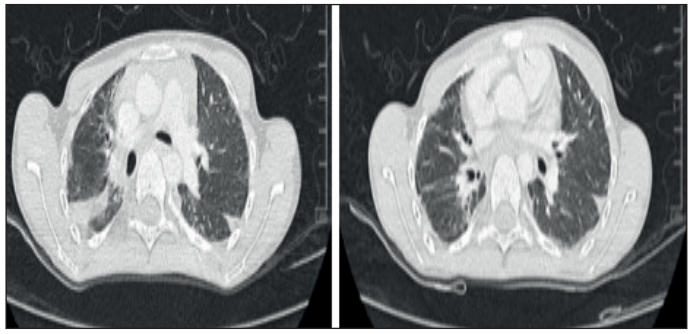

Figure 2: Chest CT performed before nintedanib treatment. Axial CT images show bronchiectasis, peribronchial thickening and reticulation consistent with pulmonary fibrosis.

at month 6 is shown in Figures 1 and 2. In the 9th month of treatment, mild nausea and vomiting due to nintedanib were observed. As there was no improvement or stabilisation of clinical and radiological findings, nintedanib treatment was considered ineffective in our patient and was discontinued in the ninth month of the treatment.

After discontinuation of treatment, the patient was referred for lung transplantation as he was considered to be a suitable lung transplant candidate. While waiting for transplantation, the patient's clinical condition deteriorated rapidly and ECMO was initiated for respiratory failure. The patient died after 40 days of ECMO.

DISCUSSION

Nintedanib is a tyrosine kinase inhibitor approved for IPF and other chronic progressive ILDs in adults, but there is limited experience in children (6). Here we report our experience with nintedanib in a child with PF following bleomycin and radiotherapy. In the early period after completing chemotherapy and radiotherapy, he had pneumonitis that did not respond to steroid treatment, and fibrosis developed in the lungs. For the antifibrotic effect, treatment with nintedanib was initiated. During 9 months of nintedanib, there was no objective improvement in overall clinical status and treatment was discontinued.

Lung fibrosis can be triggered by drugs such as chemotherapeutics. One of these is bleomycin, which is used in treatment protocols for Hodgkin's lymphoma. It is poorly metabolised in the lung due to low levels of bleomycin hydrolase. This poor metabolism leads to accumulation of bleomycin in the lung and causes vascular and cellular damage, leading to fibrosis in the lung parenchyma by induction of an inflammatory process in fibroblasts and macrophages (7-9). Another factor in PF is thoracic irradiation, which acts by causing oxidative damage to DNA, leading to cell damage and apoptosis of pneumocytes. The inflammatory response and subsequent repair process leads to lung fibrosis (10). Steroids and hydroxychloroquine are common treatments for children with PF (11). However, in the subacute or early phase of bleomycin-induced toxicity, good clinical responses to these two treatments may be seen. The success of these therapies is less likely to be achieved in the case of established fibrosis in the lungs (12). Many treatment options such as imatinib, pirfenidone for bleomycin-induced pneumonitis have been described in the literature (13,14). However, none of these have been studied for their efficacy and safety profile in children. In an adult population with IPF, randomised controlled trials of nintedanib showed that it significantly reduced the rate of decline in FVC in progressive pulmonary fibrosis, and fibrosing ILD associated with systemic sclerosis. Its effects have not yet been comprehensively studied in fibrosing ILD in children. However, the safety profile of nintedanib in children at the end of 24 weeks has been demonstrated in a recently published phase 3 randomised, placebo-controlled, double-blind study (the InPedILD study). In this study, the adjusted mean changes in FVC were not statistically significant between the nintedanib and placebo groups, but the changes with nintedanib at 24 weeks were similar to those seen in studies of adults with fibrosing ILD. It was showed that stabilisation in the decline in FVC and resting oxygen saturation was established at the end of 24 weeks of the treatment in children (5). At the time of the patient's admission to our clinic, pulmonary fibrosis was diagnosed according to the chest CT scan. Because, his clinical condition precluded lung biopsy. Due to the rapid progression of the disease and the lack of other promising treatment options, nintedeanib was chosen in this case.

Given that there is limited information in the literature on assessing PF in children, our patient's clinical outcome is controversial. A review of cases with PF of various aetiologies found that the outcomes of PF were not encouraging and resulted in end-stage respiratory failure or death according to Nadia et al. (11). In the literature, systemic corticosteriods and nintedanib treatment given early in the course of bleomycin-induced pulmonary toxicity has been shown to produce favourable results (15). In this report, we were not able to assess the effect of nintedanib in our case as no matched case has

been reported to date. Whether nintedanib treatment slowed disease progression in our patient is therefore unknown. In contrast to the results of the InPEDILD study, there could be many possible explanations for the treatment failure observed in our patient. First, the InPEDILD study allowed patients with an FVC% over 25%, but our patient was unable to perform PFT, suggesting that his clinical stage was worse than that of the patients included in the study. Therefore, the treatment may not have had a significant effect because it was started in the late fibrotic phase of the disease. Secondly, the aetiology of fibrosis in this case cannot be attributed to chemotherapy alone; high-dose radiotherapy may have had an additional contribution. It should be noted that there were multiple factors causing pulmonary fibrosis in this patient, making it difficult to draw direct conclusions about the effect of nintedanib. Clinicians should consider the aetiology of pulmonary fibrosis and the clinical stage of their patients before starting antifibrotic therapy.

As shown in the InPedILD study, gastrointestinal side effects were observed in our patient (5). Nausea and vomiting disappeared after discontinuation of the drug.

To our knowledge, this is the first paediatric case in the literature to report experience with nintedanib in a child with combination drug- and radiation-induced pulmonary fibrosis. This case is interesting because it would be a real-life experience of nintedanib in a child, resulting in failure to treat the fibrotic process in our patient.

CONCLUSION

In such complicated cases, it may be advisable to have this case reviewed before making a decision about treatment with nintedanib. Despite its safety profile in children, comprehensive studies are urgently needed to evaluate its effectiveness in children.

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