



Case report

No effect of pirfenidone treatment in fulminant bleomycin-induced pneumonitis



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A B S T R A C T

Keywords:
Bleomycin
Pneumonitis
Pirfenidone

Bleomycin-induced pneumonitis (BIP) is a serious and potentially fatal adverse effect of bleomycin. Currently, BIP is treated on an empirical basis with high dose steroid. Pirfenidone is a new antifibrotic drug, which has been proven beneficial in idiopathic pulmonary fibrosis and is able to inhibit or reverse BIP in animal models. Here, the first two cases of human BIP treated with pirfenidone in addition to steroid therapy are presented. Unfortunately, both patients died, which may be explained by the initiation of therapy at a late stage. Therefore, studies of early or prophylactic treatment with pirfenidone in relation to bleomycin-containing chemotherapy regimens are needed.

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Introduction

Bleomycin-induced pneumonitis (BIP) is a serious adverse effect of bleomycin, which is used in chemotherapy regimens in patients with testicular cancer or Hodgkin's lymphoma [1]. The incidence of BIP is 15–18% [2,3], and increasing age, low albumin level and the use of granulocyte colony-stimulating factor have been associated with the development of the condition [3]. BIP is diagnosed in the presence of a combination of worsening pulmonary symptoms, bilateral interstitial infiltrates on chest X-ray and/or computed tomography, or the presence of pulmonary fibrosis on transbronchial lung biopsy in the absence of infection [1]. Although similar 5-year overall survival rates have been found in BIP patients compared to unaffected patients, BIP has been associated with decreased survival in some studies [2,3], and the occurrence may necessitate cessation of potentially life-saving chemotherapy.

There are no large or randomized studies regarding the treatment of BIP, but traditionally, high-dose steroids have been used. In animal studies, oxygen therapy has been associated with worse outcome, and therefore, avoidance or at least minimization of oxygen therapy is recommended [1]. New pharmacological treatments are urgently needed.

Pirfenidone is a new anti-fibrotic agent which has been proven beneficial for idiopathic pulmonary fibrosis in humans [4]. It possesses both anti-inflammatory and anti-fibrotic properties and has been shown to slow or reverse bleomycin-induced pulmonary fibrosis in animals [5,6]. These characteristics suggest that pirfenidone could be beneficial for BIP in humans.

Here, we report two patients with testicular cancer and bleomycin-induced fulminant pneumonitis in whom treatment with a combination of pirfenidone and high-dose steroids failed.

Patient case 1

A 19-year old male with Down's syndrome was diagnosed with a retroperitoneal germinal cell tumor in May 2012. At diagnosis, α -fetoprotein was increased to 1973 $\mu\text{g/l}$. Renal function was impaired with a glomerular filtration rate (GFR) of 36 ml/min due to ureteral compression. Pre-chemotherapy spirometry showed a forced expiratory volume in 1 s (FEV1) of 2.29 l (68% of predicted) and a forced vital capacity (FVC) 2.36 l (62%). The patient was treated with three series of bleomycin 30,000 IU on day 2, 9 and 16, etoposide 100 mg/m² s.i.d. on day 1–5 and cisplatin 20 mg/m² s.i.d. day 1–5. He was admitted to hospital with neutropenic fever after the first series, and started pegfilgrastim, a granulocyte-colony stimulating factor, after the 2nd and 3rd series. After the 3rd series, he was again admitted with neutropenic fever and severe desaturation. In spite of antibiotics and oxygen therapy, the patient deteriorated, and after 2 days mechanical ventilation was

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necessary. The chest X-ray showed bilateral consolidated infiltrates, and high dose Methylprednisolone 100 mg s.i.d. was initiated. C-reactive protein and α -fetoprotein were both normalized, indicating that the cancer had responded well to treatment. However, the patient's respiratory condition worsened, and one week after, pirfenidone 802 mg t.i.d. was initiated. In spite of maximal treatment, the respiratory condition worsened and extra corporal membrane oxygenation (ECMO) was started. After 2 weeks of ECMO, 3 weeks of pirfenidone treatment and 4 weeks of high dose steroids in combination with weekly steroid pulse courses, the patient succumbed to BIP.

Patient case 2

A 42-year old mentally retarded male with schizophrenia was diagnosed with disseminated testicular cancer in December 2012. At diagnosis, α -fetoprotein was normal. The patient had impaired renal function due to compression of the ureters by retroperitoneal tumor masses, and was treated with a nephrostomy catheter. He was treated with 4 series of bleomycin 30.000 IU on day 2, 9 and 16, etoposide 100 mg/m² s.i.d on day 1–5, and cisplatin 20 mg/m² s.i.d on day 1–5. A pulmonary function test prior to chemotherapy showed a slightly restrictive pattern with a mildly reduced diffusion capacity. Due to hospital admittance with a neutropenic fever after the first series, he was treated with pegfilgratrim after the remaining chemotherapy series. After the 4th series, routine positron emission tomography–computed tomography (PET–CT)

showed interstitial pneumonitis compatible with bleomycin-induced pneumonitis, and it came forward that the patient had been experiencing progressive dyspnea and a dry cough for several weeks. He was able to walk 420 m on 6 min walk test with desaturation to 94%. High dose Methylprednisolone 100 mg s.i.d. was started, and pirfenidone treatment was considered, but abandoned at this time. After one month of steroid treatment the patient was admitted to hospital with a pulmonary infection and severe hypoxia; a CT scan showed no evidence of pulmonary embolism, but revealed interstitial changes (Fig. 1). The treatment was supplemented with pulse courses of steroid and pirfenidone 802 mg t.i.d. but in spite of this, the patient's condition deteriorated. Ventilator treatment was initiated and followed by ECMO, but the patient died from BIP two months after the diagnosis.

Discussion

We report here the first two cases of fulminant bleomycin-induced pneumonitis treated by pirfenidone. Disappointingly, pirfenidone did not seem to improve the clinical course.

In these two patients, treatment with granulocyte-colony stimulating factor, neglect of dyspnea and renal impairment may have contributed to the emergence of fatal BIP. The anti-inflammatory and anti-fibrotic actions of pirfenidone have been shown to slow or even reverse the effects of bleomycin in animal models [5,6]. In vitro, pirfenidone significantly reduced surrogate markers of fibrosis such as the expression of TGF β -1 and

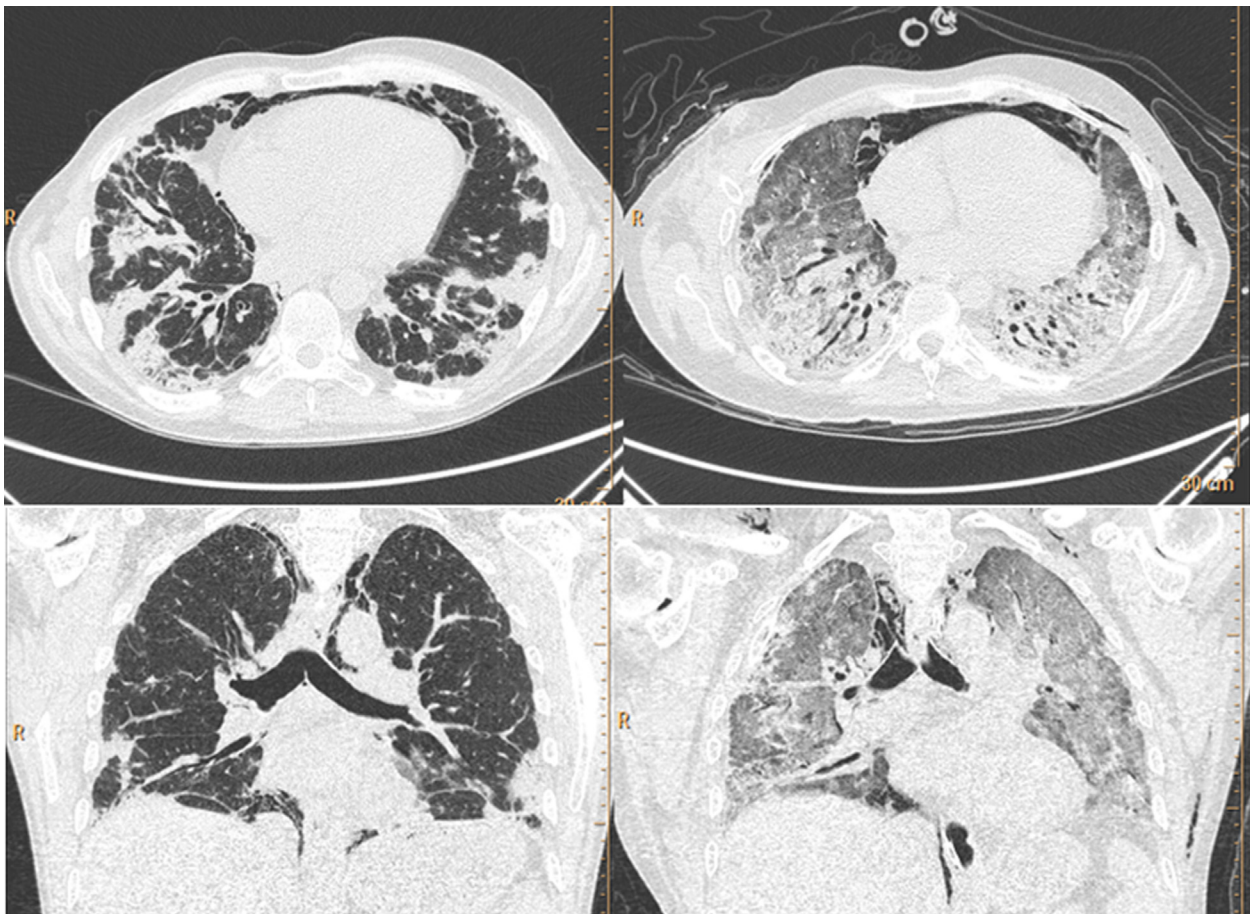


Fig. 1. High resolution computed tomography (HRCT) of patient 2 at diagnosis of bleomycin-induced pneumonitis and 5 weeks later when pirfenidone was started. The first HRCT show consolidations and bronchiectasis and the second HRCT shows severe progression with development of diffuse ground glass opacities, consolidations and traction bronchiectasis.

proliferation in human lung fibroblasts in a dose dependent manner, and human synovial fibroblasts expressed less ICAM-1 in the presence of pirfenidone. Pirfenidone also reduces expression of other pro-fibrotic genes such as collagen III [7]. It has antioxidant effects and inhibits lipid peroxidation, and thus, pirfenidone may function as a scavenger of reactive oxygen species [8].

The anti-fibrotic action of pirfenidone has been compared with that of prednisolone in bleomycin-induced fibrosis in mice. Both drugs were administered daily for approximately 30 days. Only pirfenidone inhibited fibrosis and suppressed the increase in pulmonary levels of bFGF, TGF β 1, stromal cell-derived factor 1a (SDF-1a), IL-18 and IFN γ , while both drugs attenuated the increase in IL1 β , IL-6, monocytes chemotactic protein (MCP)-1, and IL-12p40 (subunit of interleukin-12) [9,10]. The timing of pirfenidone treatment has been studied in animal models, and the effect of pirfenidone seems to be better when treatment is started prophylactically or early after bleomycin treatment [6].

The bleomycin lung fibrosis model in animals is widely used but has limitations. More than 200 drugs have been tried in the bleomycin mouse model but only pirfenidone have qualified for clinical use. Bleomycin causes inflammation by overproduction of free radicals and induction of pro-inflammatory cytokines and resembles more an acute lung injury in the early phases. The subsequent fibrosis is developed after about 7 days and is partly reversible. Thus, the slow and irreversible progressive of fibrosis seen in IPF is not reproduced in the bleomycin animal models, which may explain the disappointing success rate of translating results from the bleomycin model to IPF patients. It is also unclear whether the bleomycin model in rodents can be translated to human bleomycin-induced pneumonitis, although it may intuitively seem more plausible. Pirfenidone administered before or up to 7 days after bleomycin treatment will treat inflammation while pirfenidone administered more than 7 days after bleomycin targets the fibrotic pathways. Pirfenidone has shown beneficial effects with both scenarios although preventive treatment was the most efficient [6,11].

Therefore, the lack of effect on BIP in our patients may be due to the initiation of therapy at a time when overt and fulminant BIP had already developed. Thus, studies of early or prophylactic pirfenidone

treatment to clarify the role of pirfenidone in bleomycin-induced pneumonitis and fibrosis in humans are strongly needed.

Contribution to the study/Authorship

1. Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data: EB
2. Drafting the article or revising it critically for important intellectual content: OH, EB, CH, MA, CUA
3. Final approval of the version to be published: OH, EB, CH, MA, CUA.

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