

## Case report

# Interferon- $\gamma$ for delayed pulmonary toxicity syndrome resistant to steroids

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### Summary:

**Delayed pulmonary toxicity syndrome, characterized by interstitial pneumonia and pulmonary fibrosis, is common following high-dose bischloroethylnitrosourea (BCNU) (carmustine, [1,3-bis (2-chloroethyl)-1-nitrosourea]) containing chemotherapeutic regimens. Depending upon the treatment protocol, it may develop in over 70% of patients. Early and aggressive corticosteroid treatment leads to improvement in the majority of patients. However, up to 8% of affected patients may fail to respond to corticosteroids and develop progressive respiratory failure leading to death. No alternatives to corticosteroids have thus far been shown useful. We report the symptomatic and physiological improvement of a patient with severe steroid-resistant delayed pulmonary toxicity syndrome, following treatment with interferon- $\gamma$ .** *Bone Marrow Transplantation* (2003) 31, 939–941. doi:10.1038/sj.bmt.1704032

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Delayed pulmonary toxicity syndrome (DPTS) after high-dose bischloroethylnitrosourea (BCNU) (carmustine, [1,3-bis (2-chloroethyl)-1-nitrosourea]) containing therapeutic regimens used in hematopoietic stem cell transplantation is common.<sup>1</sup> While early attempts at treating BCNU-related lung injury with corticosteroids appeared ineffective,<sup>2,3</sup> changes in chemotherapeutic regimens coupled with early high-dose corticosteroid treatment have led to markedly improved outcomes in the majority of patients.<sup>4</sup> However, those patients who fail to respond to corticosteroids remain an extremely difficult management problem, as no alternative treatment options have been shown to be useful. We describe a case of corticosteroid-resistant interstitial pneumonia with pulmonary fibrosis secondary to DPTS, with clinical, physiologic, and radiographic evidence of response to subcutaneous interferon- $\gamma$  therapy.

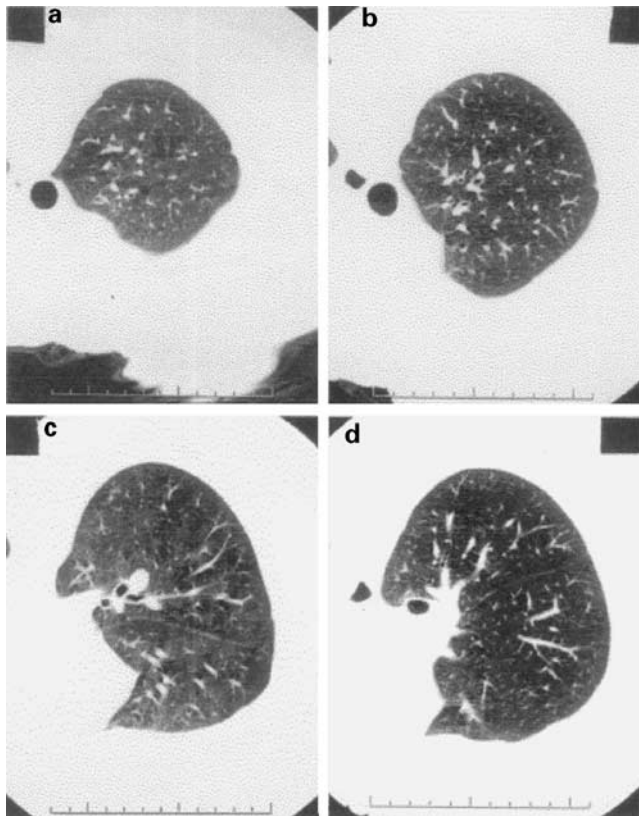
### Case report

A 47-year-old female was diagnosed with stage IIIB inflammatory breast carcinoma in September 2000. She underwent a modified radical mastectomy, followed by induction chemotherapy with four cycles of cyclophosphamide and doxorubicin. This was followed, in January 2001, by uncomplicated high-dose chemotherapy with cyclophosphamide (1875 mg/m<sup>2</sup> once daily for three consecutive days), cisplatin (165 mg/m<sup>2</sup>), and BCNU (600 mg/m<sup>2</sup>) with autologous stem cell rescue (CCB, STAMP 1). Approximately 6 weeks following transplantation, the patient noted the subacute onset of dyspnea and dry cough with fatigue and low-grade fever. On day 48 post-transplantation (day +48) pulmonary function testing revealed a restrictive ventilatory defect (FVC 56%, FEV1 58% predicted, compared to 92 and 89%, respectively, pretransplant), a diminished diffusion capacity (DLCO<sub>corr</sub> [DLCO corrected for hemoglobin] 43% predicted, compared to 86% pretransplant) and room air hypoxemia at rest that worsened with exertion (SaO<sub>2</sub> 86% at rest, 82% following a standardized 5 min walk). Chest radiograph was normal. On the basis of these findings, a presumptive diagnosis of delayed pulmonary toxicity syndrome was made, and prednisone started (100 mg p.o. daily for 3 days, followed by 60 mg daily thereafter), with rapid improvement of her symptoms, oxygen saturation (SaO<sub>2</sub> 94% at rest, 88% following 5 min walk), and physiology as measured by FVC (74%), FEV1 (72%), and DLCO<sub>corr</sub> (51%) by day +60.

The patient then underwent adjuvant radiation therapy to her left chest wall, axilla, and supraclavicular area on days +62 through +103 (40 Gy total). She was maintained on prednisone 60 mg p.o. daily to prevent relapse of DPTS. Unfortunately, the patient's symptoms of dyspnea rapidly returned following radiation therapy. Despite repeated bursts of prednisone (100 mg p.o. daily), by day +146 her SaO<sub>2</sub> had fallen to 86% at rest and 80% following a 5 min walk. Echocardiogram revealed a normal left ventricular ejection fraction. Fiberoptic bronchoscopy with bronchoalveolar lavage and transbronchial biopsy was performed and did not reveal infection or metastatic malignancy. Biopsy demonstrated only hyperplastic type II pneumocytes and interstitial fibrosis. Progressive DPTS was diagnosed and the patient was immediately treated with high-dose methylprednisolone (1g i.v. daily for 3 days) followed by continuation of prednisone at 60 mg p.o. daily

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**Figure 1** Representative thoracic high-resolution CT images demonstrating marked improvement following treatment with interferon- $\gamma$ . In these HRCT images, panels a and c show the diffuse geographic ground glass opacification of delayed pulmonary toxicity syndrome affecting the right upper and middle lobes prior to interferon therapy, while panels b and d demonstrate complete resolution of the abnormality at 8 weeks of therapy

with no response. By day +174 her FVC, FEV1 and DLCO<sub>corr</sub> had fallen to 60, 62, and 33% of predicted, respectively. High-resolution computed tomography (CT) scan (HRCT) demonstrated diffuse bilateral ground glass opacification of both lungs (Figures 1a and c).

Because of the failure of corticosteroid therapy alone, interferon- $\gamma$  was begun on day +181 at 50  $\mu$ g sc three times a week followed by 100  $\mu$ g three times a week at day +190. No changes in blood counts or chemistry were associated with the initiation of interferon, and no side effects were noted. Prednisone was slowly tapered to 20 mg p.o. daily (day +214). By day +238 the patient's symptoms of cough and dyspnea had markedly improved, FVC, FEV1 and DLCO improved to 66, 62, and 48% of predicted, respectively, and room air SaO<sub>2</sub> rose to 95% at rest (normal for 5000 ft altitude) and 87% following a 5 min walk. Follow-up HRCT showed complete resolution of the bilateral ground glass abnormality (Figures 1b and d). Steroid therapy was continued at 20 mg daily until day +320 to minimize the side effects of interferon treatment.<sup>5</sup> Thereafter, the patient was maintained on interferon alone, and developed low-grade fever, mild myalgias and chills on the day of each dosing, which responded to acetaminophen. Interferon was discontinued at day +351, and the patient has remained stable since (with last follow-up at day

+420), without measurable decline in either her pulmonary function testing or room air SaO<sub>2</sub>.

## Discussion

The incidence of clinically significant delayed pulmonary toxicity syndrome following high-dose chemotherapy for breast cancer with cyclophosphamide, cisplatin, and BCNU (CCB) (currently the most common setting) ranges from 31–72%, depending on defining criteria.<sup>1,4,6–8</sup> Its development may be secondary to the oxidative effects of BCNU (which inhibits glutathione reductase), and synergistically augmented by cyclophosphamide, which also affects oxidant handling in the lung via its metabolites.<sup>6</sup> While acute respiratory decompensation may occur in a small subset of patients,<sup>7</sup> the most common syndrome appears 1–3 months following treatment and is manifest by subacute dyspnea on exertion, nonproductive cough, and occasionally spiking fever,<sup>6</sup> as typified by our patient. Chest examination is most often normal, as is plain chest radiography and even low-resolution CT scanning, while HRCT typically demonstrates patchy or diffuse ground glass abnormalities typical of drug toxicity.<sup>1,8,9</sup> Lung biopsy, if performed, reveals atypical hyperplastic type II pneumocytes, alveolar septal thickening with interstitial fibrosis, and evidence of small vessel endothelial injury.<sup>6,10</sup> The two most sensitive noninvasive tests to detect DPTS are diffusion capacity and exercise oxygen saturation, and most authors advocate using one or both of these as surveillance following high-dose chemotherapy with BCNU regimens.<sup>1,4,8</sup>

Once identified, aggressive steroid therapy (prednisone 1–2 mg/kg p.o. daily) most often leads to rapid improvement in patient symptoms and oxygen saturations, though prolonged tapering (6–8 weeks) is required, and rebursting with flares of the syndrome may be necessary.<sup>1,8</sup> Prolonged exacerbation of the syndrome often occurs during and following adjuvant radiation therapy, as seen with our patient, but does not appear related to radiation pneumonitis, as it develops rapidly and the radiographically observed diffuse ground glass changes are not limited to the radiation port.<sup>6,8</sup> Up to 8% of patients may suffer progressive respiratory failure and die from lung toxicity following treatment with the CCB regimen,<sup>7,11–13</sup> although early detection and treatment (coupled with delay of adjuvant radiation therapy) may avoid such an outcome.<sup>14</sup> While prophylactic treatments have been studied,<sup>15</sup> few therapies other than steroids have been investigated for the treatment of established DPTS.

Given that progressive pulmonary fibrosis is the most common form of DPTS following high-dose chemotherapy containing BCNU, and that TGF- $\beta$  has previously been implicated in the development of this and other fibrotic complications of the CCB regimen,<sup>16,17</sup> one potential treatment approach is the use of interferon- $\gamma$ , a potent antagonist of many TGF- $\beta$  effects including fibroblast proliferation and collagen production.<sup>18</sup> A small preliminary trial of interferon- $\gamma$  in idiopathic pulmonary fibrosis resistant to steroid therapy showed symptomatic and functional improvement in treated patients.<sup>5</sup> Based on this,

we hypothesized that interferon- $\gamma$  might be effective in our steroid-refractory patient.

Significant improvement in the patient's symptoms, pulmonary physiology, and HRCT was achieved by 6 weeks at 100  $\mu$ g (half the dose used in IPF patients<sup>5</sup>) without serious adverse effects. It is possible that the improvement coincident with the use of interferon- $\gamma$  might be explained by spontaneous improvement in radiation pneumonitis superimposed upon DPTS. However, the rapid worsening of the patient's pulmonary physiology seen following radiation therapy, coupled with diffuse bilateral changes present on HRCT, would make this an unusual manifestation of radiation pneumonitis. While interferon- $\gamma$  was maintained for 24 weeks of therapy in this case, the optimum duration of this therapy is unclear.

Based on our patient's response, further investigation of interferon- $\gamma$  as an alternative therapy for corticosteroid-resistant delayed pulmonary toxicity syndrome may be warranted. Given its mechanism of action, such therapy might also be considered in other steroid-resistant, regimen-related pulmonary toxicities associated with lung fibrosis.

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