Pulmonary Fibrosis after Prolonged Therapy with 1,3-Bis (2-chloroethyl)-1-nitrosourea*

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A 43-year-old man with metastatic malignant melanoma was treated with 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) in combination with imidazole carboxamide and hydroxyurea. He achieved complete remission. After 22 months of chemotherapy, the patient developed bilateral pulmonary infiltrates. Open lung biopsy showed sclerosing alveolitis. Long-term therapy with BCNU may cause pulmonary fibrosis, as has been seen with other cytotoxic drugs.

In treating disseminated malignant melanoma, 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) is a chemotherapeutic agent of some value, both as a single agent¹ and in combination chemotherapy.² Its chief toxic effect is myelosuppression. This report describes a patient with metastatic malignant melanoma who developed pulmonary fibrosis, a side effect heretofore unrecognized after chemotherapy with BCNU and two other drugs.

CASE REPORT

A 43-year-old white man had a malignant melanoma removed from his right flank in July 1971. In October 1971, he came to the University of Arkansas Medical Center with widespread metastases to multiple subcutaneous sites and to the supraclavicular and axillary lymph nodes. A chest x-ray film was normal.

Chemotherapy with BCNU (150 mg/sq m intravenously on the first day of every other course), with imidazole carboxamide (150 mg/sq m intravenously for five days in each course of treatment), and with hydroxyurea (1,480 mg/sq m orally for five days in each course of treatment) was planned according to an investigational protocol. In error, during the first course of treatment, the patient received five daily doses of BCNU, rather than only one. The total dose of BCNU in the first course of treatment was 750 mg/sq m. Myelosuppression was severe. Transfusions of red blood cells and platelets were given. Nevertheless, the patient had a very favorable response to this regimen. After only one course of therapy, there was greater than 50 percent regression of lymphadenopathy, and malignant cells were no longer found on biopsy of a previously involved cutaneous site. A complete remission was achieved after two courses of therapy. The planned therapy was continued at six-week intervals. A single dose of BCNU was given with every other course.

In August 1973, after having received 1,800 mg of BCNU over a period of 22 months, chest x-ray films disclosed bilateral pulmonary infiltrates in the upper lobes, which were worse on the right side of the chest. The patient remained asymptomatic. A search for mycobacteria and fungi revealed no organisms. There was no history suggestive of aspiration. Later the patient developed cough, dyspnea, and fever, and he was treated with penicillin for bacterial pneumonia. Symptoms resolved, but the pulmonary infiltrates persisted bilaterally as before (Fig 1). Multiple cultures of sputum and bronchoscopic and mediastinoscopic examinations failed to reveal an etiology for the infiltrate.

![Figure 1. Posteroanterior chest x-ray film taken prior to lung biopsy. There are bilateral pulmonary infiltrates in upper lobes. Apparent loss of volume in right upper lobe is consistent with fibrotic process, with subsequent pulling of trachea and mediastinum to right.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/20997/)

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Therefore, open lung biopsy was performed in August 1974. The pathologic diagnosis was sclerosing alveolitis (Fig 2). The lung biopsy showed diffuse obliteration of air spaces, with alveolar walls thickened by dense fibrous tissues and edema. Alveolar lining cells were hyperplastic. The pleura was thickened, and foci of chronic inflammatory cells were seen. No neoplastic cells or granulomata were seen. Cultures of the pulmonary tissue were negative for bacteria, fungi, and mycobacteria.

After surgery, a two-month trial of therapy with prednisone had no effect on the pulmonary infiltrate. All chemotherapy was stopped after the lung biopsy. The total amount of BCNU administered was 2.08 gm.

By clinical examination and chest x-ray film, the pulmonary fibrosis slowly worsened after the lung biopsy. The patient had a marked restrictive pattern of pulmonary function and exercise intolerance. In September 1975, the patient died at home, 47 months after initiation of chemotherapy. At his last examination two months before death, the patient was still in complete remission from advanced metastatic malignant melanoma.

**DISCUSSION**

Pulmonary fibrosis with interstitial pneumonitis has been reported as a toxic effect of many drugs, including the chemotherapeutic agents busulfan, cyclophosphamide, methotrexate, and bleomycin. A drug seems a likely explanation for this patient’s pulmonary infiltrate. He had received the agents for many months. An infectious or neoplastic etiology was not found after a thorough search, and the microscopic appearance of the lesion was similar to that described for the toxic effects of other agents.

Of the three drugs that the patient received, BCNU seems the most likely offending agent. Studies in animals have shown that after a single dose of BCNU, the activity of NADase in mouse pulmonary tissue is decreased for 30 days. A similar effect was seen in mouse hepatic and kidney tissue. Iriarte et al reported transient pulmonary interstitial infiltrates in four patients following therapy with BCNU for childhood leukemia affecting the central nervous system or for solid tumors. Although the exact mechanism of action of BCNU is unknown, it may work in part as an alkylating agent. Significantly, busulfan and cyclophosphamide, both alkylating agents, have also been associated with the development of pulmonary fibrosis.

We know of no reports of pulmonary toxic effects secondary to therapy with imidazole carboxamide or hydroxyurea. These drugs were not mentioned in a recent review of drug-induced pulmonary disease.

Pulmonary infiltrates appeared in this patient only after prolonged treatment lasting nearly two years. Perhaps the exceptionally high dose of BCNU during the initial course of treatment accounts for the unusually favorable effect on the malignant disease and the exceptional untoward side effect. As experience is expanded and more patients achieve longer periods of remission after treatment with BCNU, the likelihood of seeing more individuals with pulmonary damage must be kept in mind.

**REFERENCES**