CASE REPORT

Fludarabine Associated Pulmonary Hypersensitivity

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INTRODUCTION

Fludarabine (Fludara®-Berlex) is a recently marketed fluorinated analogue of adenine which can produce high response rates in patients with chronic lymphocytic leukemia (CLL) resistant to conventional chemotherapies such as chlorambucil or cyclophosphamide (with or without prednisone), or more intensive regimens such as cyclophosphamide, adriamycin and prednisone (CAP).[1] The most common adverse effect seen with fludarabine is myelosuppression which often leads to subsequent infectious episodes.[2] In one study,[3] myelosuppression led to pneumonia after 25 of 337 (7.5%) patient courses.

It appears that fludarabine therapy may not only lead to pulmonary infections but may also induce a pulmonary hypersensitivity reaction. Three case reports have identified a reaction that is characterized by dyspnea, cough, fever and interstitial pneumonitis that responded to corticosteroid therapy.[4-6]

We report two further suspected cases of this pulmonary hypersensitivity reaction and review the literature regarding this adverse drug reaction.

CASE 1

A 74 year-old male was admitted to hospital to receive a second monthly course of fludarabine (25.7 mg/m^2 intravenously daily for five days) for treatment of CLL. At the time of admission, he complained of shortness of breath on exertion, weakness, lethargy, nocturnal coughing, and chest pain.

His history of present illness included a six-year history of CLL which had initially responded to cyclophosphamide. He relapsed seven months prior to admission and was treated with prednisone and chlorambucil without benefit. Subsequently, fludarabine was initiated with a good response being observed as evidenced by a lower white blood count and reduced lymphadenopathy.

His past medical history was extensive and included a four-year history of immune thrombocytopenia purpura for which he has been treated with various short courses of methylprednisolone, immune gammaglobulin, azathioprine and most recently vincristine. As well, he had corticosteroid-induced insulin dependent diabetes. He was a past smoker but had not smoked for many years. His medications on admission, in addition to fludarabine therapy, included diltiazem 30mg po tid, omeprazole 20mg po qam, regular insulin 20u sc qam and NPH insulin 35u sc qam.

Review of systems was remarkable only for his complaints on admission. On examination, his blood pressure was 110/76 mm Hg, heart rate was 84 beats per minute, and respiratory rate was 20 per minute. His temperature was slightly elevated at 37.8°C and he appeared unwell. The patient had a small neck and submandibular nodes. Examination of the chest revealed fine crackles at both bases with a right anterior pleural friction rub and decreased breath sounds over the left base. The remainder of the physical examination was unremarkable except for an enlarged right testicle. Arterial blood gases on room air were PO_2 of 71 mm Hg, pH 7.49 and PCO_2 of 33 mm Hg. The alveolar-arterial oxygen tension difference [$P(A\text{-}a)O_2$] (also known as the A-a gradient) was 39 mm Hg. Serum chemistries were remarkable for an elevated serum creatinine of 130 umol/L. The white blood cell count was normal 9.4 x 10^9 /L, hemoglobin was low at 81 g/L and

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Acknowledgements: The authors thank Greg McKelvie, Pharm.D., and Lynn Pollock, B.Sc.Phm. for their review of this manuscript.
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the platelet count was low at 15 x 10^9 /L. As well, the patient was noted to be severely panhypogammaglobulinemic. A lung scan was deemed to be unremarkable. A chest radiograph revealed a bilateral diffuse interstitial pattern.

The patient was commenced on fludarabine but on the third day of this course he spiked a temperature of 38.9° C. The patient was increasingly dyspneic with diminished chest sounds compared to admission. Because of this deterioration, blood cultures were drawn and ceftazidime 2 g intravenously every eight hours was started. However, the patient remained febrile with little clinical improvement. The five-day course of fludarabine was completed. Because of lack of improvement in his pulmonary status, a bronchoscopy was performed and erythromycin 1 g intravenously every six hours was added. By day eight there was little change in the patient's condition or chest radiograph and the patient remained febrile despite broad spectrum antibiotics. Cultures obtained from bronchial washings and from blood were reported as negative. In light of this, it was suspected the patient's pulmonary complaints were associated with a hypersensitivity pneumonitis secondary to fludarabine. Antibiotics were discontinued and prednisone 75 mg daily was started.

Over the next 24 hours, the patient became afebrile with subsequent improvement in pulmonary symptoms and a clearing of the chest radiograph. The patient was discharged approximately one week later on prednisone 50 mg daily. Blood gases obtained prior to discharge showed a PO_2 of 73 mm Hg, a pH of 7.46 with a PCO_2 of 38 mm Hg. The calculated A-a gradient was 32 mm Hg. Further courses of fludarabine were withheld.

CASE 2

A 65 year-old male with a seven-year history of CLL was admitted to hospital to receive his fourth monthly cycle of intravenous fludarabine (23.8 mg/m^2 daily for five days). At the time of admission, he complained of spiking fevers, fatigue, dry cough and increasing shortness of breath over the previous two to three weeks. The patient had shown a marked clinical response to fludarabine over the first three cycles with a decreased white blood cell count and an improvement in hepatosplenomegaly after having failed to respond to previous chlorambucil/prednisone and cyclophosphamide regimens. His past medical history included autoimmune hemolytic anemia controlled with prednisone 20 mg daily that had been stopped three weeks prior to admission, as well as an admission three weeks earlier for a localized herpes zoster infection that was successfully treated with a course of acyclovir.

Review of systems was remarkable only for his admitting to complaints of fever, dyspnea with dry cough, and fatigue. When examined, his blood pressure was 100/72 mm Hg, heart rate was 84 beats per minute and respiratory rate was 22 per minute. His temperature was elevated at 38.5° C. On examination of the chest, inspiratory crackles were noted in the right lung. The patient's spleen was palpable. No other abnormalities were noted on physical examination. Arterial blood gases on room air were PO_2 of 35 mm Hg, pH of 7.53 and PCO_2 of 34 mm Hg. His white blood cell count was elevated at 88.6 x 10^9/L with a decreased neutrophil count of 0.89 x 10^9/L. Hemoglobin and platelets were also noted to be low at 114 g/L and 119 x 10^9/L respectively. A chest radiograph revealed diffuse bilateral alveolar infiltrates over both fields.

Because of the marked hypoxia, fludarabine was withheld, oxygen therapy was started and the patient underwent bronchoscopy to rule out pneumonia. Cotrimoxazole 20 mL intravenously every six hours was started empirically because of possible pneumocystis carinii pneumonia and methylprednisolone (40 mg intravenously every six hours) was commenced for a suspected drug-related pneumonitis. Cultures obtained from the bronchoscopy were subsequently reported negative and antibiotics were discontinued. Three days after admission the patient was afebrile and improving clinically. By this time his PO_2 had improved to 50 mm Hg on room air. Despite this clinical improvement the chest radiograph still exhibited a diffuse, ground glass appearance with patchy infiltrates.

In the absence of infectious causes and the prompt response which occurred with corticosteroids, a hypersensitivity reaction to fludarabine was suspected and future courses of fludarabine were withheld. Ten days after admission the patient was discharged home on 60 mg of prednisone daily. At the time of discharge he was afebrile, his oxygen saturation on room air was 95% and his chest radiograph showed gradual improvement.

DISCUSSION

These two case reports suggest an adverse pulmonary reaction associated with fludarabine therapy characterized by fever, dyspnea, cough, and a diffuse, bilateral, interstitial, pulmonary infiltrate on chest radiograph.

They feature several similarities to the three other published case reports.[4-6] Other etiologies to explain the dyspnea and hypoxia were not apparent. In both cases, infectious causes were ruled out by bronchoscopy. While chemotherapy agents including cyclophosphamide and chlorambucil have been implicated in causing pneumonitis,[7] the temporal relationship, the absence of respiratory symptoms prior to starting fludarabine and the fact that, at least in the second case, a clear chest radiograph was documented one month prior to symptoms would suggest fludarabine as causative.

One of the characteristic findings in a hypersensitivity pneumonitis is impaired oxygenation.[8] In the second case, marked hypoxia which responded to drug discontinuation and corticosteroid therapy was present. The patient described in the first case is less clear as the PO_2 was normal and hence improvements in this parameter with corticosteroids were only modest. The calculated A-a oxygen gradient did improve, but again, the change was relatively small. We speculate, in retrospect, that while in hospital, the patient's clinical deterioration was accompanied by worsening oxygenation and a widening of the A-a gradient. Clinical improvement occurred when fludarabine was stopped and corticosteroids were added. Unfortunately, no blood gas determinations were available to confirm nor refute this speculation.

The time course of our two cases, that is, prior to second course and after the third course, is similar to the time course of the other three cases in the literature which were reported to be eight days to two weeks after the third course in two cases and one week after finishing the initial course of fludarabine in the other. It is interesting to speculate that the relatively late presentation of pulmonary symptoms in our second case may have been due to the fact that the patient was receiving prednisone for another indication. As well, in keeping with the literature, the doses administered were similar and both of our cases and two of three literature cases underwent bronchoscopy to rule out infection.

Oxidants released by elevated numbers of alveolar macrophages and neutrophils in the lung are thought to play a major role in inducing interstitial changes.[8] Corticosteroids, despite a lack of well controlled studies, are the accepted mainstay of therapy for interstitial lung disease because of their ability to help suppress the inflammatory and immune cellular response.[9]

The fact that both patients showed a dramatic clinical response to corticosteroid therapy, similar to the three cases now in the literature, is suggestive of a drug-induced pulmonary hypersensitivity reaction. Because of the rapid clinical improvement observed with corticosteroid therapy, a transbronchial lung biopsy was not obtained from either patient. As signs and symptoms of drug induced pulmonary disease can mimic other infectious or inflammatory processes, the histological identification of the interstitial infiltrate through biopsy becomes important when trying to establish cause. In two of the literature cases, open lung biopsy revealed a fibrosing, interstitial pneumonitis with a mononuclear cell infiltrate and fibrosing alveolitis, compatible with drug-induced change.

Based on our cases and the literature, we conclude that the administration of fludarabine for the treatment of CLL may induce a pneumonitis reaction. Common symptoms include fever, cough, and dyspnea on exertion, but can include marked hypoxia leading to respiratory failure. This reaction may occur after only a few doses of usually successful fludarabine therapy and seems to respond promptly to discontinuation of fludarabine therapy and initiation of high dose corticosteroid treatment.

Pharmacists should be aware that fludarabine may cause a hypersensitivity pneumonitis and monitor all patients receiving fludarabine for signs and symptoms suggestive of this adverse reaction.

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