Cytarabine-induced lung injury: case report

Petros Kopterides[a], Michalis Lignos[a], Spyros Mentzelopoulos[a], Apostolos Armaganidis[a] and Vassiliki Pappa[b]

We report the case of a 65-year-old male patient with acute myelogenous leukemia who developed severe respiratory failure after receiving cytarabine treatment. Chest radiograph showed bilateral alveolar infiltrates. He was intubated and underwent flexible bronchoscopy. An extensive diagnostic work-up revealed no evidence of infection. Steroids were added to empiric antibiotic treatment and the patient was successfully extubated in 5 days. Cytarabine-induced lung injury should be considered in the differential diagnosis of alveolar infiltrates in immunocompromised patients. If bronchoscopy fails to confirm an infectious cause, a short course of steroids must be tried, which probably leads to a favorable outcome. ***Anti-Cancer Drugs*** **16:743–745 © 2005 Lippincott Williams & Wilkins.**

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[a]Departments of Critical Care and [b]Hematology/Oncology, 'Attikon' University Hospital, Medical School of Athens University, Athens, Greece.

Correspondence to P. Kopterides, 28–30 Korai Street, Nea Ionia, Athens 14233, Greece.
Tel: +30 210 2759863; fax: +30 210 2855476;
e-mail: petkop@ath.forthnet.gr

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Introduction

Non-cardiogenic pulmonary edema and acute lung injury/acute respiratory distress syndrome (ALI/ARDS) complicating cytarabine (Ara-C; cytosine arabinoside) treatment have been previously reported in the literature [1–7], but remain under-recognized. Here, we describe the case of a patient who developed ARDS secondary to cytarabine treatment and required mechanical ventilation. Steroid treatment was a determining factor in improving his respiratory function and permitting successful extubation.

Case report

A 65-year-old man with relapsed acute myelogenous leukemia M4 was admitted for administration of intermediate-dose cytarabine (400 mg/m^2 for 5 days by continuous infusion). His past medical history was significant for well-controlled hypertension. On the second day of treatment, he became progressively dyspneic, and developed a dry cough and fever (38.5°C). Physical exam revealed bilateral rales. His blood pressure was 130/80 mmHg, heart rate 90 beats/min and respiratory rate 30 breaths/min. Blood gases showed hypoxemia ($pO_2 = 50$ mmHg) and hypocapnia ($pCO_2 = 32$ mmHg) in room air. White blood cell (WBC) count was 38 600/ml (with 90% blasts) and platelet count was 22 000/ml. Chemotherapy was stopped, and sputum, urine and blood cultures were analyzed. A chest X-ray showed new bilateral alveolar and interstitial infiltrates. He was placed empirically on antibiotics (imipenem, vancomycin and trimethoprim/sulfamethoxazole) because of a high risk of systemic infection and experienced transient improvement after diuretic treatment. A normal electrocardiogram and negative myocardial enzymes excluded myocardial ischemia, while a transthoracic echocardiogram showed normal systolic function (ejection fraction = 55%), no significant valvular dysfunction and no evidence of pericardial effusion. The following day he was admitted to the intensive care unit as an emergency case and was intubated because of progressive respiratory failure (blood gases on a non-rebreather mask prior to intubation were $pCO_2 =$ 49 mmHg, $pO_2 = 47$ mmHg, $HCO_3 = 27.1$ mmol/l and pH 7.35). A new chest radiograph showed progression of the infiltrates. Bronchoscopy was performed at the same day. Bronchoalveolar lavage (BAL) cultures for common bacteria, fungi and mycobacteria remained negative. Silver stain of BAL fluid for *Pneumocystis carinii*, urine test for *Legionella* antigen and blood polymerase chain reaction for cytomegalovirus antigen were also negative. Open lung biopsy was not performed as we considered it too risky in this severely thrombocytopenic and mechanically ventilated patient. The patient was treated with i.v. prednisolone 0.75 mg/kg on the assumption of cytarabine-induced lung injury. He improved rapidly and was successfully extubated 5 days later, when the WBC count had climbed to 66 800/ml. He completed a 10-day steroid taper and recovered completely from his lung disease with significant improvement in his chest radiograph. No further dose of cytarabine was administered. He was treated with alternative chemotherapeutic agents and died of progressive disease 9 months later.

Discussion

The differential diagnosis of pulmonary infiltrates in the immunosuppressed patient is extensive, and includes both infectious and non-infectious etiologies, with the latter appearing to be responsible for 25–50% of cases

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[8,9]. Specifically, pulmonary injury in immunocompromised patients may result from pulmonary edema secondary to fluid overload and heart failure, transfusion-related acute lung injury (TRALI), radiation and drug toxicity, diffuse alveolar hemorrhage, and miscellaneous conditions such as bronchiolitis obliterans, secondary alveolar proteinosis, idiopathic pneumonia syndrome, engraftment syndrome and post-transplant lymphoproliferative disorder. A clinician should aggressively attempt to exclude infectious processes and bronchoscopic sampling with lavage remains a major diagnostic tool. Nevertheless, its sensitivity varies with the population studied, e.g. being only 45–62% for the detection of invasive pulmonary aspergillosis [10]. This justifies not only the search for alternative diagnostic options (i.e. the serum galactomannan assay for detection of invasive aspergillosis), but also the consideration of lung biopsy as the 'gold standard'. However, patients are often too unstable to undergo a lung biopsy (being thrombocytopenic and mechanically ventilated, as our patient) and some investigators consider it a 'high-risk, low-yield' procedure [11]. Thus, it is not uncommon for a clinician to make urgent treatment decisions for those patients without clear-cut diagnostic information.

We attributed our patient's acute respiratory failure to cytarabine primarily by a process of elimination and by the remarkable response to steroids. We cannot completely exclude the possibility of an infectious process as this would have required an open-lung biopsy; however, the negative fungal, mycobacterial and bacterial cultures make this less likely. Left ventricular failure and pulmonary edema resembling ARDS could present with a similar picture (even though fever would be an unusual finding in that scenario), but the electrocardiogram, myocardial enzymes and echocardiogram were essentially negative. Therefore, a cardiac origin of respiratory failure can be eliminated with reasonable certainty. Also, the fact that our patient had not received any blood products prior to the episode of respiratory failure eliminates the possibility of TRALI. Finally, the presence of an extremely high WBC count raises suspicion of pulmonary leukostasis syndrome. This serious complication usually occurs in patients with acute myelogenous leukemias when WBCs exceed 50 000/ml, but even lower numbers have been implicated. The fact that our patient recovered without leukapheresis and despite a rising WBC count makes the diagnosis of leukostasis less likely.

Thus, the most likely cause of our patient's respiratory failure appears to be cytarabine-induced lung toxicity. One could speculate that fever is the common, systemic manifestation [12] and ALI/ARDS the uncommon, extreme lung manifestation of the so-called 'cytarabine syndrome' which has been associated with activation of the cytokine network [13]. It is proposed that NF-κB activation in response to cytarabine mediates the production of pro-inflammatory cytokines, particularly tumor necrosis factor (TNF) and platelet-activating factor (PAF). These two cytokines have also been implicated as major mediators of ARDS. These observations support therapy with steroids, known for their inhibiting action on PAF, TNF and other pro-inflammatory mediators.

We were surprised to find that, despite the widespread use of cytarabine, very few reports have studied its association with lung toxicity. More than 20 years ago, Haupt *et al.* reviewed the records of 181 leukemic patients, and found that 24% had massive and 33% had moderate pulmonary edema [1]. The patients who had received cytarabine within 30 days of their death, compared to those who had not received it, had a highly significant increase in the frequency of pulmonary edema ($p < 0.001$). Multivariate regression analysis showed that unexplained pulmonary edema was predicted by the recent administration of cytarabine, but by no other chemotherapeutic agent, including daunomycin. This study suggested that increased alveolar capillary permeability could result from the administration of cytarabine [1]. Andersson *et al.* [2] reported subacute pulmonary failure attributable to cytarabine in 16 of 72 evaluable patients (22%), a mean time of 2–21 days (median = 6) after the first dose. Tham *et al.* [3] studied 64 patients who underwent 66 remission induction courses with intermediate-dose cytarabine and 38 consolidation courses with high-dose cytarabine for treatment of hematologic malignancies. Seven (11%) of 66 induction courses and eight (21%) of 38 consolidation courses were complicated by respiratory failure. The initial findings on chest X-rays included a diffuse interstitial pattern, a mixed interstitial/alveolar pattern, an alveolar pattern and a normal pattern. In 11 cases, the abnormalities were diffuse and bilateral with a preference for the lower lobes. The changes were localized in two cases. A small pleural effusion was observed in two patients. In the majority of cases, the initial radiographic changes progressed to a predominantly alveolar pattern. Two patients died of pulmonary complications and 13 patients recovered clinically within 2–9 days with a mean radiologic recovery of 7–21 days. Jehn *et al.* [4] studied 25 leukemic patients that underwent remission induction therapy and found that seven had a non-cardiogenic pulmonary edema that was attributed to cytarabine therapy. Finally, Andersson *et al.* [5] studied 103 relapsed leukemia patients treated with high-dose cytarabine and found that 13 of them developed ARDS without a clear explanation. In nine, this complication was fatal. The pulmonary tissue from six patients showed massive edema and one had diffuse alveolar damage. Histologic examination revealed a highly proteinaceous intra-alveolar infiltrate without any inflammatory reaction in all cases. The pulmonary toxicity of

cytarabine has also been described in the pediatric population [6].

Steroid therapy for cytarabine-induced pulmonary insufficiency has been reported previously [1,3,7]. Even though their exact mechanism of action remains unclear, steroids are known to inhibit activation of NF-κB and production of pro-inflammatory cytokines. There are no firm recommendations regarding the appropriate dose or duration of treatment. In the most recent report [7], a 72-year-old-woman with acute leukemia who could not be weaned off the ventilator for 10 days received methylprednisolone 4 mg/kg/day (50 mg every 6 h) and was extubated within 24 h. She recovered completely from her respiratory failure with decreasing dosages of methylprednisolone for 10 more days. Our experience is that 0.75 mg/kg of prednisolone may be sufficient without exposing an already immunocompromised patient to extremely high steroid doses. Of course, further clinical studies and not just case reports are necessary to better define the most appropriate treatment for this potentially lethal complication.

In summary, cytarabine-induced lung injury seems to be an under-appreciated problem. Many patients may have drug-induced pulmonary damage that goes undetected or is attributed to another etiology, whereas only a subset of patients experience frank pulmonary edema and ARDS. Physicians involved in the care of patients receiving this agent should be aware of its association with pulmonary toxicity as prompt initiation of steroid treatment may lead to a favorable outcome.

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