fifth course of fludarabine chemotherapy, he developed cough and low-grade fever. Bilateral asymmetric pulmonary infiltrates were noted, with a band-like appearance in the left perihilar and upper lobe adjacent to the minor fissure and streaky appearance in other portions of right lobe and right middle lower lung fields. This was not noted on previous chest radiographs. The patient was placed on oral trimethoprim/sulfamethoxazole qid for 2 weeks with no response. He then was given chlorambucil (8 mg daily for 4 days), as well as prednisone (100 mg daily for 5 days). One week after initiation of this therapy, his symptoms resolved and previously noted bilateral interstitial infiltrates disappeared on radiograph. The patient was continued on chlorambucil and prednisone monthly for two subsequent courses and then all therapy was stopped.

He had been asymptomatic for 1.5 years when he relapsed with progressive lymphadenopathy and splenomegaly. A repeat bone marrow biopsy revealed recurrence of chronic lymphocytic leukemia. The patient was given fludarabine, 50 mg daily for 5 days. He again developed fever and cough, and progressed to shortness of breath and respiratory failure requiring intubation by the 7th day after initiation of fludarabine. He was admitted to the ICU where ARDS developed. One day after admission, the patient required Swan-Ganz monitoring as well as dopamine, dobutamine, and norepinephrine for circulatory support. Intravenous mezlocillin (3 g q6h), gentamicin (80 mg q8h), and vancomycin (500 mg q12h) were administered. Blood cultures remained negative. One week after admission to the ICU, prednisolone (60 mg q6h IV) was initiated with prompt reversal of circulatory collapse and disappearance of fever. The patient was able to be weaned off intermittent mechanical ventilation support and was discharged from the ICU in 5 days, although he required tracheostomy and positive pressure ventilation. The patient died 2 weeks later.

Postmortem multiple needle biopsies of the lungs were performed and revealed an organizing pulmonary process and focal recent hemorrhage. A lymphocytic infiltrate was identified in alveolar septa consistent with, although not diagnostic of, resolving interstitial pneumonitis. No appreciable widening and/or fibrosis of alveolar septa was identified. No viral inclusions were identified. Special stains for bacteria, Pneumocystis carinii, fungi, and acid-fast bacilli were all negative.

Fludarabine monophosphate is known to cause myelosuppression, as well as gastrointestinal and neurologic toxicity. Several reports of pulmonary toxicity have been published. Two of these represent letters or abstracts. Only one pathologically confirmed case has been published. Our patient developed clinical and radiologic evidence of interstitial pulmonary pneumonitis following treatment with fludarabine. This responded to steroid therapy with resolution of both clinical and roentgenologic symptoms. The patient was rechallenged with fludarabine 1.5 years later and developed respiratory failure and ARDS that was not responsive to antibiotic therapy, but responded in prompt and decisive fashion to the initiation of steroid therapy. In addition, postmortem evaluations revealed the presence of an interstitial pulmonary process, but no infectious etiology.

The mechanism of pulmonary toxicity of fludarabine has not been well defined. Our case suggests that it may be immunologic or allergic in nature, accounting for rapid development of this side effect and what appears to be an anamnestic recurrence after rechallenge. Responsiveness to steroids also supports this potential mechanism.

Pulmonary toxicity associated with fludarabine may be more common then is usually appreciated. Physicians who use fludarabine should be aware of this potentially life-threatening complication and should initiate steroid therapy for symptoms or radiographic findings suggesting development of interstitial pneumonitis after ruling out infectious etiology. Rechallenge with fludarabine would not be recommended.

Mark Levin, MD
Division of Hematology, Oncology
Brookdale University Hospital
Brooklyn, New York
Mohamed Aziz, MD
Department of Medicine
Lyne Optiz, MD
Department of Pathology
Staten Island University Hospital
Staten Island, New York

REFERENCES

Objective Response to Epirubicin and Lonidamine

A Case of Advanced Thymoma Previously Treated with the ADOC Scheme and Unresponsive to Paclitaxel Plus Cyclophosphamide

To the Editor:

Malignant thymomas are uncommon neoplasms of the anterior mediastinum. Most thymomas are encapsulated and can be cured by complete surgical resection either followed or not followed by radiation therapy. Cisplatin and anthracycline regimens have been proven to be highly active as first-line approach, with overall response rates ranging from 50 to 90%. ADOC scheme (cisplatin 50 mg/m², doxorubicin 40 mg/m², vincristine 0.6 mg/m² and cyclophosphamide 700 mg/m²) is widely used in Italy, being able to obtain 80% and 91% response rates in two single institutional experiences. Unfortunately, second-line therapy (using either cytotoxic agents or steroids) in patients progressing to ADOC has been reported to be totally ineffective, probably because the ADOC regimen contains all or nearly all the active drugs.
A 47-year-old woman referred to us in 1993 bearing an invasive lymphoepithelial thymoma stage III according to Masaoka classification. Four chemotherapy courses with ADOC scheme were administered in association with oral prednisone (25 mg/d without any interruption between cycles), and a partial response was obtained. She underwent surgical resection of the residual mass and became disease free. Two further ADOC cycles have been administered afterwards. One year later a chest CT scan showed a pleural recurrence not suitable for radical resection. The patient was submitted to a salvage treatment with paclitaxel (175 mg/m²) associated to cyclophosphamide IV (600 mg/m²) administered every 21 days in association with corticosteroid therapy. At first, when restaging after three cycles, no tumor reduction has been observed. She was then treated with epirubicin (Farmorubicina; Farmacia Milano, Italy), 100 mg/m², IV bolus injection every 21 days, associated with oral lonidamine (Dordiamina, Angelini ACRAF; Rome, Italy), 450 mg/d. No corticosteroids were assumed. This third-line treatment was stopped after 5 cycles because the patient reached the maximal tolerable dose of anthracyclines. A CT scan, performed at the end of the treatment showed a ~90% reduction of the tumor mass. This result was confirmed by a further CT scan 2 months later.

Due to the substantial unresponsiveness to the conventional second-line approaches, patients with advanced thymoma previously treated with ADOC scheme are candidates for new drug treatments. In the case described here, however, paclitaxel administered in association with cyclophosphamide and corticosteroids failed to be active. Conversely, a long-term partial remission has been obtained with epirubicin associated with lonidamine, a derivate of indazole-3-carboxylic acid, which is able to selectively interfere with the energy metabolism of neoplastic cells. This may be the mechanism by which lonidamine is able to circumvent multidrug resistance to chemotherapy through alteration of membrane permeability and/or inhibition of the drug efflux pump stimulated by the multi-drug resistance P (MDR/P) glycoprotein. The potentiating effect of anthracycline activity by lonidamine has been repeatedly demonstrated in vitro and in a recent Italian multicentre phase III trial involving advanced breast cancer patients.5

To conclude, it is our opinion that epirubicin plus lonidamine scheme should be further tested as second-line treatment in patients progressing to ADOC and other anthracycline plus cisplatin-containing regimens.

Alfredo Berruti, MD
Marco Tampellini, MD
Gabriella Garzegno, MD
Luigi Dogliotti, MD
Dipartimento di Scienze Cliniche e Biologiche Oncologia Medica, Università di Torino, Azienda Ospedaliera San Luigi Orbassano, Torino, Italy

REFERENCES

Sampling Arterial Blood With a Fine Needle

To the Editor:

Radial arterial puncture for obtaining blood samples is a painful procedure that justifies the use of prior local anesthesia in the puncture area to significantly reduce pain.1 Providing local anesthetia, however, supposes piercing twice, once for anesthetic infiltration and once again for arterial puncture. Some authors2 have suggested that performing the puncture with a smaller diameter needle would reduce pain, making anesthesia unnecessary and at the same time shortening the procedure.

We compared pain intensity produced by radial arterial puncture in 60 patients, using the conventional anesthetic infiltration technique3 with mepivacaine through a 27.5-gauge needle followed by puncture with a 22-gauge needle (QS 90; Radiometer Medical A/S; Bronshoj, Denmark), or puncturing directly with a 25-gauge needle without prior anesthesia. The patients were assigned randomly to two groups of 30 to undergo puncture with or without anesthesia; there were no differences of age, sex, or prior arterial puncture between the two groups. Pain was quantified on a visual analog scale of 10 cm (0, complete absence of pain; 10, maximum pain). Mean (±SD) pain levels reported were 1.9 (±1.1) cm (range, 0 to 3 cm) for the conventional technique and 2.8 (±1.3) cm (range, 0.6 to 5.3 cm) (p=0.004) for direct puncture with a 25-gauge needle. The procedure took a mean 158 (±12) s using the conventional technique and a mean 122 (±13) s with the 25-gauge needle (p<0.001). The conventional procedure, with anesthetic infiltration, costs about 25 cents more.

The use of the narrow 25-gauge needle does not make the procedure more difficult, and it takes less time and reduces cost. However, the pain caused by puncture is at times fairly intense, greater than with anesthesia and quite similar to that observed with placebo.4 We therefore believe that, as only anesthetic infiltration guarantees that arterial blood samples can be obtained with tolerable pain for patients, this extra step should be taken, in spite of the savings in time and money that can be achieved by using the finer gauge needle without anesthesia.

Jordi Giner, RN
Pere Casan, MD
Joan Sanchis, MD
Hospital de la Sta. Creu i de St. Pau
Barcelona, Spain

REFERENCES

The Role of Intermittent Enteral Feeding in Reducing Gastric Colonization in Mechanically Ventilated Patients

To the Editor:

We read with interest the recent article, "Intermittent enteral feeding in mechanically ventilated patients: the effect on gastric pH