

Case report

Successful administration of cytarabine after a previous anaphylactic reaction

Blanca M, Torres MJ, Girón M, Corzo JL, Martínez-Valverde A. Successful administration of cytarabine after a previous anaphylactic reaction. *Allergy* 1997; 52: 1009–1011. © Munksgaard 1997.

Cytarabine (Cyt) is an antimetabolite used primarily in the treatment of leukemia, and both immediate and delayed hypersensitivity reactions have been reported. We studied a 9-year-old girl with lymphoblastic leukemia, who developed three anaphylactoid reactions during Cyt treatment courses over a 1-year period. Three years later, Cyt was required again. Although a skin test was negative to Cyt at the concentration of 4 µg/ml, we decided on placebo-controlled administration of the drug. The Cyt was well tolerated, and urine values of *N*-methylhistamine showed no important variations throughout this period compared to those during the placebo administration. Skin tests carried out 14 days after the study were positive at the concentration of 4 µg/ml. The history of different episodes of allergic reactions to Cyt, the last one being the most severe, indicated the possible participation of an immediate hypersensitivity phenomenon, but because no studies had been carried out initially, we could not establish the presence of IgE antibodies. These results indicate that good tolerance existed after the control administration procedure. The long interval, 3 years, between the allergic episode and our protocol and the appearance of a positive skin test 14 days after the protocol indicated that the subject had lost sensitivity and become resensitized after the controlled administration procedure.

**M. Blanca, M. J. Torres, M. Girón,
J. L. Corzo, A. Martínez-Valverde**

Paediatric Allergy Section, Paediatric
Department, Regional Hospital, Málaga, Spain

Key words: anaphylactic reaction; cytarabine;
N-methylhistamine; resensitization.

Prof. Antonio Martínez Valverde
Departamento de Pediatría
Hospital Materno Infantil
Málaga
Spain

Accepted for publication 29 April 1997

Cytarabine (Cyt) is an antimetabolite used primarily in the treatment of leukemia, particularly acute nonlymphoblastic leukemia. It is given in various dosage regimens by intravenous, intramuscular, or subcutaneous routes but is inactive by mouth. Adverse effects include myelosuppression, gastrointestinal disturbances, and, particularly at high doses, neurotoxicity (1). This drug is a synthetic pyrimidine nucleoside that is converted intracellularly to the nucleotide, Cyt triphosphate, and although the exact mechanism of action of Cyt has not been fully elucidated, Cyt triphosphate appears to inhibit DNA polymerase by competing with the physiologic substrate, deoxycytidine triphosphate, resulting in the inhibition of DNA synthesis (2). Both immediate and delayed hypersensitivity reactions to Cyt have been reported, although no clear explanation has been given of the mechanisms involved (3, 4).

We report a child who developed an anaphylactoid reaction during the infusion of Cyt and

in whom successful controlled administration of the drug was performed, but who later became resensitized.

Case report

We studied a 9-year-old girl with a history of hypersensitivity to sulfonamides, cow's milk intolerance, and wheezing related to viral infection and possible exposure to various inhalant allergens. Skin tests were positive to *Olea europaea* (olive) pollen and negative to other allergens to which the patient was normally exposed. When she was 23 months old, lymphoblastic leukemia was diagnosed, and she received successful treatment with the cytostatic drugs methotrexate, adriamycin, vincristine, cyclophosphamide, and mercaptopurine in two courses. She remained stable and asymptomatic for 3 years. When the illness reappeared, an autologous bone-marrow transplantation was performed without success; therefore, she began to receive treatment

with Cyt. After the first subcutaneous dose, necrosis developed at the site of administration. Four weeks later in the next treatment course, she developed systemic pruritus and urticaria. Two months later, the same reaction occurred after she received the medication. One week later, the drug was administered intravenously, and after a 20-min infusion, she developed dyspnea, systemic pruritus, and generalized erythema. The Cyt treatment was interrupted and emergency treatment with epinephrine, steroids, and antihistamines was given.

Three years later, Cyt was required for control of the clinical process, and the patient was sent to our clinic for evaluation. Although a skin test was negative to Cyt at the concentration of 4 µg/ml, we decided to administer the drug in a controlled way with incremental doses over a period of 13 h in order to minimize the risk. The protocol used to administer the drug is described in Table 1. Blood pressure, pulse rate, and respiratory function were monitored for the possible appearance of an allergic reaction during the procedure. Histamine production was determined by measuring *N*-methylhistamine (NMH) in sequential urine samples taken at 4-h intervals, as previously described (5). In the first study period, a placebo consisting of intravenous infusion of saline, masquerading as the medication, was administered, with the same time intervals as on the day the medication was given, with physiologic constants monitored and urine samples obtained. During this time, the only symptom the patient had was pruritus in the right arm and neck without any skin manifestation; this symptom disappeared after 10 min without treatment. No changes in heart rate or blood pressure compared to baseline levels occurred. The NMH concentration in urine (ratio of NMH/creatinine) showed values that ranged between 1.3 and 2.6 (Fig. 1). On the day the drug was administered, the patient did not develop

any change in blood pressure or heart rate, and no symptoms appeared. The values of NMH showed no important variations throughout this period compared to the placebo administration (Fig. 1). Skin tests carried out 14 days after the administration of Cyt became positive at the concentration of 4 µg/ml.

Discussion

Hypersensitivity reactions to Cyt have been reported by various authors. Jones & Ettinger (6) studied a patient who developed urticaria and wheezing after treatment with Cyt. Williams & Larson (3) described a delayed hypersensitivity reaction in a man, and Berkowitz et al. (4) anaphylactic shock in a child. These reactions indicate that both immediate and delayed hypersensitivity can be involved in their induction. Furthermore, the presence of specific IgE to Cyt (4), basophil degranulation (6), and circulating immune-complexes (3) suggests that antibodies of different isotypes can be involved. Rassiga et al. (7) have reported a desensitization study in a 69-year-old man with acute myeloid leukemia and a previous anaphylactic episode with the presence of IgE antibodies. However, the mechanisms involved were not ascertained.

In the patient we studied, the history of allergic reactions to Cyt, the last one being the most severe, indicated the possible participation of an immediate hypersensitivity phenomenon, but, because no studies had been carried out at that time, we could not establish the presence of IgE antibodies. To evaluate the possible appearance of early symptoms of anaphylaxis or subjective manifestations, we administered a placebo on one day and the drug was given on the second day. The study was carried out in a single-blind way, and the patient was unaware of the order of the administration. During the administration of the placebo, pruritus appeared, but it was not accompanied by any other symptoms or abnormalities in the physiologic constants. NMH in urine varied from 1 to 2.6 as ratio of NMH/creatinine. There was a moderate peak of 2.6 between 5 and 9 h. The increased dose of the drug in the second period was not accompanied by any symptoms or abnormal change in blood pressure or heart rate. These results indicate that good tolerance, occurred after the administration procedure. The long interval, 3 years, between the allergic episode and controlled administration of the drug suggests that the subject had good tolerance, probably due to loss of sensitivity. Spontaneous loss of sensitivity after a long period of avoiding drugs has been reported (8–10). In our study, the appearance of a positive skin test 15 days after the administration of the drug indi-

Table 1. Infusion rate of cytarabine in 13-h period

Time (h)	Volume (ml)	Concentration (µg/ml)	Amount (µg)	Final amount (µg)
1	10	20	200	200
2	20	20	400	600
3	30	20	600	1200
4	40	20	800	2000
5	60	20	1200	3200
6	80	20	1600	4800
7	50	40	2000	6800
8	80	40	3200	10 000
9	110	40	4400	14 400
10	40	140	5600	20 000
11	50	140	7000	27 000
12	60	140	8400	35 400
13	70	140	9800	45 200

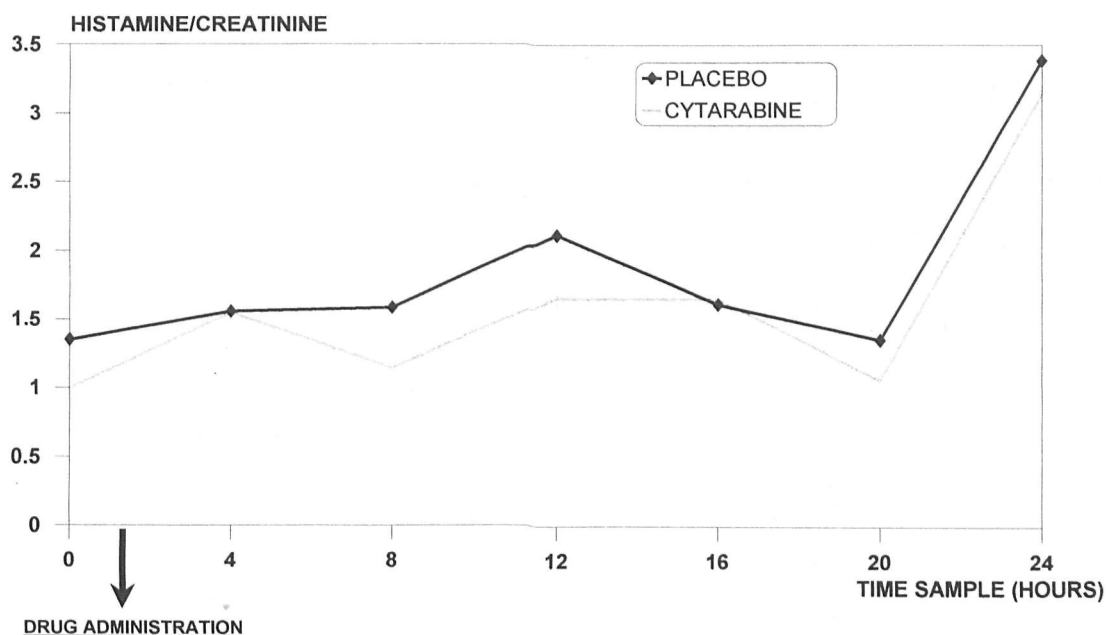


Fig. 1. Measurements of *N*-methylhistamine in urine during placebo and drug administration period.

cated that the subject had lost sensitivity and become resensitized after the controlled challenge procedure. Our explanation of this phenomenon is that IgE levels fell to such a low level as to be absent in the peripheral blood, but B cells able to recognize the hapten and be stimulated existed. Therefore, after the antigenic stimulus given by the administration of the drug induced new synthesis of IgE, mast cells were again occupied by IgE antibodies to Cyt. Similar observations have been previously made (8, 9).

In summary, these results should be taken into account in the administration of Cyt or other drugs, including β -lactams, to previously allergic subjects. In many instances, because control administration procedures are undertaken and good tolerance occurs, it is assumed that the procedure works, but the subject may have lost sensitivity and become resensitized as a consequence of this procedure.

References

1. Martindale W. The extra pharmacopoeia 30th ed. London: Pharmaceutical Press, 1993:471-3.
2. McEvoy GK. AHFS drug information 1995. Bethesda, MD: American Society of Health-System Pharmacists, 1995:627-30.
3. Williams SF, Larson RA. Hypersensitivity reaction to high-dose cytarabine. *Br J Haematol* 1989;73(2): 274-5.
4. Berkowitz FE, Wehde S, Ngwenya ET. Anaphylactic shock due to cytarabine in a leukemic child. *Am J Dis Child* 1987;141:1000-1.
5. Fernández J, Blanca M, Moreno F, et al. Role of tryptase, eosinophil cationic protein and histamine in immediate allergic reactions to drugs. *Int Arch Allergy Apply Immunol* 1995;107:160-2.
6. Jones GR, Ettinger LJ. Continuous infusion of high-dose cytosine arabinoside for treatment of childhood acute leukemia and non-Hodgkin's lymphoma in relapse. *Semin Oncol* 1985;12 Suppl 3:150-4.
7. Rassiga AL, Schwartz HJ, Forman WB. Cytarabine-induced anaphylaxis: demonstration of antibody and successful desensitisation. *Arch Intern Med* 1980;140: 425-7.
8. Blanca M, Garcia JJ, Vega JM, et al. Anaphylaxis to penicillins after nontherapeutic exposure: an immunological investigation. *Clin Exp Allergy* 1996;26:335-40.
9. Sullivan TJ, Wedener HJ, Shatz GS, Yelies LD, Parker CW. Skin testing to detect penicillin allergy. *J Allergy Clin Immunol* 1981;68:171-80.
10. Parker PJ, Parrinello JT, Condemi JJ, Rosenfeld SI. Penicillin resensitization among hospitalized patients. *J Allergy Clin Immunol* 1991;88:213-17.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.