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Intrathecal Cytosine Arabinoside in Hodgkin’s Disease With Central Nervous System Manifestations

A PRELIMINARY REPORT

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This report of the beneficial response in central nervous system (CNS) manifestations of a patient with Hodgkin’s disease to the intrathecal administration of cytosine arabinoside suggests that this drug may have value in the treatment of CNS involvement by lymphoma and acute leukemia and of some brain tumors. Its use, for the first time via the intrathecal route in the present case, was well tolerated in two series of treatments.

Intracranial manifestations of the lymphomata, particularly Hodgkin’s disease, are difficult to control successfully because oral or intravenous chemotherapeutic agents with antilymphoma activity do not cross the blood-brain barrier effectively. Radiotherapy is of some benefit, but symptomatic relief all too often is transient and, to some extent, the dose is limited by the radiosensitivity of nervous tissue. Although direct intrathecal instillation of alkylating agents (nitrogen mustard, triethylene melamine, cyclophosphamide, etc.) is prohibited by their local irritative properties, these agents have some value when locally instilled in serous cavities. Methotrexate is better tolerated locally, and is effective in treatment of central nervous system (CNS) leukemia of children by intrathecal administration; it has shown little therapeutic activity in the treatment of the lymphomata, particularly Hodgkin’s disease. Only one report is available regarding the intrathecal administration of methotrexate in one case of meningeal lymphosarcoma, and in four cases of primary brain tumor, with a satisfactory early clinical response.¹

For this reason, it is of interest to report the use of a relatively new drug, l-β-D-arabinofuranosylcytosine (cytosine arabinoside, ara-C) in the treatment of the intracranial manifestations of Hodgkin’s disease by means of local instillation. Cytosine arabinoside was synthesized in 1959, and yet only within the past two years has it been

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Van Slyck and Talley recognized as an effective agent in the management of the lymphomata and hematopoietic malignancies.\textsuperscript{2,3} It is relatively nonirritating to local tissues. The intrathecal administration of cytosine arabinoside in the management of clinical states has not been reported. Whether cytosine arabinoside effectively crosses the blood-brain barrier is not known definitely; in one patient previously reported, no drug could be detected in the spinal fluid 15 minutes after a single intravenous injection.\textsuperscript{3}

Case Report

The patient, a 22-year-old housewife, was referred to Henry Ford Hospital on February 7, 1966, with a history of dry cough of six weeks' duration, associated with fatigue, episodic sweats, and weight loss. Her initial symptoms of dizziness and staggering gait developed after the delivery of her second and last child in August of 1965. Prior treatment at other institutions had been only intravenous fluids and electroshock therapy for what was thought to be postpartum depressive reaction.

Her physical examination revealed a well-developed Caucasian female of slight build, weight 100 lbs. The patient walked with a wide base, and the gait was ataxic. However, the Romberg, although unsteady, was not positive. Coordination was good in the upper extremities, but poor in the lower extremities. There were enlarged movable cervical and axillary lymph nodes. The right supraclavicular area was most involved. The patient was noted to have a dry, brassy cough. The lungs were clear, and the remainder of the physical examination was negative except for a barely palpable liver.

Aside from a moderate anemia, the hemogram, urinalysis, and many blood chemical determinations were normal. The bone marrow was hyperplastic. Also, there was a right posterior mediastinal mass. Patchy densities were seen in the right lung and in the left midlung field. A right scalene lymph node biopsy (Fig. 1 and Fig. 2) was diagnostic of Hodgkin's disease, of the nodular sclerosing type. Other studies included a negative lymphangiogram, a normal skull film, and echoencephalogram. The brain scan, using Tc 99-m Pertechnetate, was negative.

On the 25th and 27th of February, 1966, the patient received 9 mg. of nitrogen mustard intravenously for a total of 18 mg. Rapid improvement in the cough and decrease in the size of the palpable lymph nodes was noted. The patient was discharged from the hospital on March 1, as improved.

However, on March 4 she developed a persistent, severe generalized headache, associated with anorexia, and a worsening of her unsteady gait. Physical examination demonstrated a further decrease in size of the peripheral lymph nodes. Results of the neurologic examination were unchanged, but it was felt that the symptoms represented progression of a posterior fossa midline mass with increased intracranial pressure. Accordingly, she was readmitted to the hospital on the 8th of March. The spinal tap showed an initial pressure of 17 cm. The fluid was clear and contained 19 cells; one cell was a polymorph, 18 were monocytes. In the spinal fluid, glucose was 65 mg/100 ml, protein was 53 mg/100 ml, and the chlorides were 123 mEq/l. No abnormal cells were noted in the spun sediment. The chest x-ray showed a decrease in size of the
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Figure 1

X 60. Low power of right supraclavicular lymph node biopsy, showing nodules of cellular Hodgkin's granuloma, with abundant surrounding fibrous tissue. No normal nodal architecture remains.
Figure 2
X 900. High power of cellular area in Figure 1. Several Reed-Sternberg cells may be seen in this field.
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paratracheal and hilar adenopathy, and a clearing of the patchy infiltrates in the lung fields. The repeat brain scan again was interpreted as negative. The patient's general condition became worse. She was nauseated, somnolent, and had a constant headache which was aggravated by movement of the head. Radiotherapy to the posterior fossa of the skull was given from March 21 to April 13, 1966. The total dose to the brain was 2,773 r. After the third treatment, the patient felt better, and showed progressive improvement during the next two weeks. Neurologic examination remained unchanged; there was still evidence of truncal ataxia, but there was marked subjective improvement in headache, nausea and general weakness.

The patient maintained her improvement until late May when her relapse was heralded by return of tiredness, somnolence, weakness and anorexia. Her ataxia was somewhat worse at this time, too. In addition to the obvious cerebellar signs in the lower extremities, this patient now showed clockwise nystagmus induced by postural change in all planes. It was believed she was developing some left upper extremity ataxia. Laboratory data at this time showed: hemoglobin 10.5 gm/100 cc, white count 12,750 mm$^3$ with a differential count of 88% neutrophils, 2% eosinophils, 8% lymphocytes and 2% monocytes. The reticulocyte count was 1.8%. A progress chest x-ray was normal.

Because of progression of these CNS symptoms, she was readmitted to the hospital on the 5th of July. A pneumoencephalogram with air introduced via the cisterna magna disclosed no abnormality. After collection of spinal fluid, 50 mg of cytosine arabinoside was injected into the cistern. The injection was repeated daily twice more for a total of 150 mg of cytosine arabinoside via the cisternal route. Following the third injection, the patient noted transient stiffness of the neck. However, her symptoms of headache, anorexia, and somnolence improved strikingly within a week, and she was discharged on the 19th of July. For the ensuing 12 months she maintained the improvement of the nervous system symptoms, but she continued to have residual truncal ataxia. In August, 1966, painful further enlargement of the right axillary lymph node was treated with local radiotherapy with good response. Subsequently, the patient developed splenomegaly for which she received chlorambucil orally.

In August 1967, recurrence of headache, somnolence, and rapid progression of upper and lower extremity ataxia caused her readmission to the hospital. Dysarthria and inability to write were observed. The brain scan was again normal. Thirty milligrams of cytosine arabinoside were instilled via the cisterna magna on three consecutive days (total dose, 90 mg). Once again striking decrease in subjective symptoms occurred. Objectively the dysarthria and the ataxia were improved and, also, return of handwriting ability was observed. In late August, at the time of her last office visit, it was felt that her status was comparable to that of one year ago, when she had completed the initial course of cytosine arabinoside.

Comment

This 22-year-old Caucasian female with well-documented Hodgkin's disease (stage IV), and with posterior fossa manifestations presumptively due to Hodgkin's
disease, had progression of CNS symptoms while peripheral and systemic manifestations were responding well to nitrogen mustard therapy. Radiotherapy to the brain resulted in partial remission of CNS symptoms for five weeks. A serious relapse then occurred. The patient was treated with local instillation of cytosine arabinoside, delivered by cisternal puncture. A very favorable clinical response occurred following this therapy. No corticosteroids were given to the patient at any time. Control of the patient's CNS symptoms continued for 12 months, despite the fact that other manifestations of Hodgkin's disease progressed. This seems all the more significant when compared with the brief remission induced previously by a large dose of radiotherapy. When a relapse occurred, a second course of intrathecal cytosine arabinoside was again effective in ameliorating CNS symptoms. Although it is true that histologic proof of Hodgkin's tissue in the posterior fossa is lacking, the early onset of symptoms in the course of the disease, though unusual in Hodgkin's disease itself, speaks strongly against the possibility of toxic leukoencephalopathy or mycotic or bacterial infection complicating the primary condition. Further evidence to exclude the presence of these conditions and to support the diagnosis of intracranial Hodgkin's disease is found in the following: (1) the patient's response to the treatment given, (2) her subsequent clinical course, and (3) the absence of specific organisms despite intensive search. Nonetheless, the conclusion that the patient's neurologic signs and symptoms are due to invasion of the posterior fossa by Hodgkin's tissue must be a presumptive one.

Cytosine arabinoside is rapidly deaminated to uracil arabinoside by the enzyme, cytosine deaminase, which is present in significant quantities in liver and kidney in man. This probably accounts for its only partial effectiveness in the treatment of systemic lymphomata. However, Calabresi and Creasey found that, after single intrathecal injection of tritiated thymidine, the drug was detectable in the spinal fluid for over 12 hours with only slow deamination occurring (oral communication, July 1967).

Another pertinent facet demonstrated by this patient's therapy is the excellent intrathecal tolerance of cytosine arabinoside. This suggests that this drug might have a place in the treatment of patients with acute leukemia with CNS involvement, resistant to methotrexate.

As a result of the encouraging experience reported herein, there are four cases of primary and metastatic brain tumor currently under treatment at our institution.

Summary

A 22-year-old-woman with Hodgkin's disease (stage IV), complicated by presumptive intracranial involvement, relapsed shortly after radiotherapy to the brain. Previous conventional treatment had been ineffective. Intrathecal administration of cytosine arabinoside, a new oncolytic agent (antimetabolite) resulted in a 12 months' remission. A recent second course administered after relapse has again produced a beneficial response. This is the first report of the clinical use of this drug via the
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intrathecal route. Its salutary effect warrants further trial in lymphomata and leukemia complicated by central nervous system involvement.

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REFERENCES


