Fludarabine Phosphate (NSC 312878) Infusions for the Treatment of Acute Leukemia: Phase I and Neuropathological Study

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ABSTRACT

Fludarabine phosphate (NSC 312878), an adenosine deaminase resistant analogue of 9-β-D-arabinofuranosyladenine, has entered clinical trials. Eleven patients with acute leukemia in relapse received 14 courses of fludarabine phosphate as a 5-day continuous infusion administered at doses of 40 to 100 mg/m²/day. Toxicity was characterized by uniform myelosuppression, as well as occasional nausea, vomiting, and hepatotoxicity. Three episodes of metabolic acidosis and lactic acidemia were noted. In addition, three patients suffered neurotoxicity. Two of these three patients had a severe neurotoxicity syndrome characterized by blindness, encephalopathy, and coma. Neither patient recovered neurologically. Neuropathological findings at autopsy were characterized by a diffuse, necrotizing leukoencephalopathy which was most severe in the occipital lobes. The medullary pyramids and posterior columns were also severely affected. This sporadic fatal neurotoxicity was observed only at doses greater than 40 mg/m²/day. The maximum tolerated dose for a 5-day infusion of fludarabine phosphate is thus 40 mg/m²/day.

INTRODUCTION

ara-C has become a keystone in the treatment of acute leukemia (1). The related purine nucleoside, ara-A, has had less clinical utility because of its rapid deamination by ADA (2). Inhibitors of ADA, such as DCF, have been used clinically to prolong the effective half-life of ara-A (3, 4). However, DCF also increases intracellular dATP pools which compete with ara-A for incorporation into DNA (5). This antagonism, as well as the undesirable clinical side effects of DCF, has stimulated the development of ADA-resistant ara-A analogues (6). F-ara-A was synthesized as one of these analogues (7). This compound is resistant to deamination by ADA and has antitumor activity in vitro and in vivo (8). Because it is relatively insoluble, the monophosphate derivative, fludarabine phosphate (NSC 312878), has been formulated for clinical use.

Fludarabine phosphate has activity in a number of animal tumor systems including L1210 leukemia, CD8F mammary adenocarcinoma, P388 leukemia, and human LX-1 lung tumor xenograft (9). The preclinical toxicology of fludarabine phosphate has demonstrated myelosuppression of all hematopoietic lineages, as well as vomiting, diarrhea, liver enzyme abnormalities, and occasional azotemia. The initial Phase I trials of fludarabine phosphate demonstrated that myelosuppression is the dose-limiting toxicity (10, 11). Mild lethargy was reported following bolus administration, while there was no other reported neurotoxicity. These studies, however, did not establish a relationship between dose and lethargy. The schedule of drug administration in these studies was not a 5-day infusion. A single bolus was used in one study while the other used a single bolus followed by a 48-h infusion.

Based on the myelosuppressive effects of fludarabine phosphate in Phase I testing, we instituted a Phase I and II trial to identify the toxicity and efficacy of fludarabine phosphate in the treatment of acute leukemia. The drug was administered as a 5-day continuous infusion at a starting dose equivalent to the maximum tolerated dose reached in patients with solid tumors. This report describes 11 patients with acute leukemia treated with continuous infusion fludarabine phosphate.

MATERIALS AND METHODS

Selection of Patients. All patients entered on this trial had acute leukemia in relapse as documented by bone marrow aspiration and biopsy. Ten patients had acute myelogenous leukemia and one had acute lymphocytic leukemia. All patients had already received at least one established drug regimen for acute leukemia. The characteristics of the patients are listed in Table 1. Ten of 11 patients had been treated with high dose ara-C prior to entry. All patients were followed until death and no patient received subsequent antineoplastic therapy because of infection, poor performance status, or patient preference. Prior to entry, patients had an Eastern Cooperative Oncology Group performance status of 2 or better (Eastern Cooperative Oncology Group 2 = confined to bed less than 50% of waking hours) serum creatinine <1.5 mg/dl and serum bilirubin <1.5 mg/dl. Informed consent was obtained from all patients.

Treatment Plan. Fludarabine phosphate was provided by the National Cancer Institute. The sterile lyophilized powder containing sodium hydroxide to adjust the pH to 6.5–8.5 was reconstituted with sterile water over a 24-h period.

The drug was administered as a continuous infusion for 5 consecutive days. Patients with decreased numbers of leukemic cells on day 14 bone marrow aspirates or biopsies were eligible for a second course of treatment beginning on day 15. The starting dose of fludarabine phosphate was 40 mg/m²/day and at least three courses were administered at each dose level. Doses of 40, 60, and 80 mg/m²/day were tested. Two patients each received a single course of 100 mg/m²/day.

All treatments were administered on the inpatient service at the Dana Farber Cancer Institute. Patients received standard supportive care including antibiotics, antiemetics, and blood products.

Study Parameters. During therapy, patients had daily complete blood counts and twice weekly measurements of liver function and renal function. Electrolytes, blood gases, and other clinical studies were performed as indicated. During the 4 weeks after therapy, complete blood counts were obtained at least twice weekly and measures of liver and renal function were monitored weekly. All patients were considered evaluable for toxicity and 10 of 11 patients were evaluable for response. A complete remission in this study was defined as the achievement of an M1 bone marrow as well as the recovery of normal peripheral blood counts (WBC >3000/mm³, platelets >100,000/mm³, and hemoglobin >10 g/dl). A remission of less than 30 days in duration was not considered to be complete. Patients who did not achieve complete remission were analyzed for the mechanism of failure (12).

RESULTS

The first objective of this study was to determine the maximum tolerated dose of fludarabine phosphate in the treatment
of acute leukemia. All 14 courses of therapy were evaluable for toxicity. The potential for late toxicity (defined as toxicity first appearing more than 28 days after the initiation of treatment) was evaluable in 8 of 11 patients.

The clinical toxicity of fludarabine phosphate is summarized in Table 2. Severe myelosuppression was uniformly seen, affecting WBC, platelets, and RBC. Intensive support was required for all courses including platelet transfusions, RBC transfusions, and broad spectrum antibiotics for fever and neutropenia. The duration of leukopenia, defined as WBC <1000/mm³, was more than 2 weeks in 10 of 11 patients. One patient with acute lymphocytic leukemia in relapse received a dose of 40 mg/m²/day but his peripheral lymphoblast count never fell below 1000/dl. Both patients receiving a dose of 100 mg/m²/day for 5 days had leukopenia for more than 30 days (32 and 45 days). Three patients received a second dose of fludarabine phosphate 15–17 days after the initiation of treatment because of persistent leukemic cells in the day 14 bone marrow aspirate. In these patients, the leukopenic phase persisted for 14–30 days after the second treatment.

Nausea and vomiting were seen in 6 of 14 courses but were generally mild and readily controlled with antiemetics at all dose levels. Hepatotoxicity, as manifested by 2–3-fold elevations of the serum transaminases, was observed in 6 of 14 courses. This toxicity was reversible within 7 days of treatment and not clearly related to dose. One patient had a significant but reversible elevation of serum creatinine (1.5–3.3 mg/dl) while receiving fludarabine phosphate concurrently with nephrotoxic antibiotics. Another patient had mild, reversible changes in serum creatinine occurring 2 weeks after fludarabine phosphate treatment. Two patients developed erythematous maculopapular rashes while receiving fludarabine phosphate and combination antibiotic therapy. Both episodes were mild and resolved after altering the antibiotic regimen.

During fludarabine phosphate infusions, three patients developed significant metabolic acidosis associated with lactic acidemia. The course of one patient is illustrated in Fig. 1. In each case, a rising anion gap, decreasing serum bicarbonate levels, and increasing serum lactate became apparent 2 to 3 days after beginning the fludarabine phosphate infusion. Each patient had an appropriate respiratory compensation and urine pH fell to <6. The metabolic acidosis resolved spontaneously several days after the completion of the fludarabine phosphate infusion. The three patients who developed metabolic acidosis were otherwise clinically similar to others in the study. Concurrent medications, hepatic function, renal function, and prior treatment were similar for both groups. Furthermore, no alternative explanation for metabolic acidosis (such as sepsis, renal disease, ketosis, or salicylate administration) could be identified. Episodes of metabolic acidosis occurred in patients receiving doses of 40, 60, and 100 mg/m²/day.

The most serious toxicity seen in this study was late neurotoxicity. Two patients had severe neurotoxicity associated with blindness and coma. These cases will be presented in detail.

Case 1. A 41-year-old woman was found to have acute myelogenous leukemia (M4) in August 1983. Remission was induced with two cycles of daunorubicin (45 mg/m²/day, days 1–3) and ara-C (200 mg/m²/day, days 1–7). She received four cycles of high dose ara-C consolidation (3 g/m² every 12 h for four doses). No neurotoxicity was noted. She relapsed 21 days following her fourth cycle of high dose ara-C. Reinduction with two cycles of daunorubicin and ara-C was unsuccessful and she was enrolled on the fludarabine phosphate trial.

The patient received fludarabine phosphate (60 mg/m²/day) for 5 days with a prompt clearing of peripheral blasts. However, a bone marrow aspiration 14 days after the start of treatment showed the persistence of blasts and a second course of fludarabine phosphate (60 mg/m²/day for 5 days) was begun 3 days later. Fever and persistent pancytopenia were managed with a variety of antibiotics including ticarcillin, gentamicin, trimethoprim-sulfamethoxazole, cefaperazone, vancomycin, and amphotericin B. Another bone marrow biopsy 40 days after the start of fludarabine phosphate treatment showed 70% blasts. The patient remained hospitalized for the next 30 days, receiving supportive care for infection and pancytopenia.

The patient was found to be lethargic and confused on the
70th day after the start of fludarabine phosphate therapy. Her mental status continued to decline and she became incontinent of urine. Three days later, her pupils were unreactive to light and she was responsive only to painful stimuli. She expired on the following day.

A complete autopsy was performed. The systemic findings included extensive leukemic infiltration of lungs, spleen, marrow, breast, and esophagus. There was necrotizing bronchopneumonia. The fresh brain weighed 1330 g. Scant subdural hematomas were present over both posterior convexities. Serial coronal sections through fixed brain revealed no gross abnormalities. Transverse sections of brainstem and cerebellum were also unremarkable. Microscopic sections were carried out on 9 formalin-fixed, paraffin-embedded sections (7 brain, 2 dura). Hematoxylin and eosin, Luxol fast blue, periodic acid-Schiff, and Bielschowsky staining techniques were used. The sections of dura showed mild subdural leukemic infiltration and hemorrhage. Slight vacuolization and myelin loss, scattered periodic acid-Schiff-positive macrophages, and rare axonal spheroids were seen focally within one occipital lobe. These changes were minimal and primarily involved the optic radiations and adjacent white matter. There was no evidence of intracerebral hemorrhage, leukostasis, or leukemic meningitis.

Case 2. A 32-year-old man was found to have acute undifferentiated leukemia in November 1983. He was treated with daunorubicin (45 mg/m²/day for 3 days) and ara-C (200 mg/m²/day for 7 days). A partial remission was achieved. A second cycle of daunorubicin and ara-C was administered in combination with vincristine (2 mg/m²/week for 3 weeks) and prednisone. A complicated hospital course ensued with *Escherichia coli* and *Candida tropicalis* septicemia, respiratory failure, renal failure, and *C. tropicalis* hepatitis. A complete remission was achieved, but he was left with neurological deficits including a severe peripheral neuropathy, vertical nystagmus, and titubation. The latter findings were thought to be related to hypoxic insults sustained during sepsis. The patient was hospitalized for the next 6 months for rehabilitation. He relapsed 10 months after his initial therapy without receiving maintenance or consolidation therapy.

Fludarabine phosphate (100 mg/m²/day for 5 days) was administered in combination with amphotericin (because of the history of fungal hepatitis). The patient had prolonged pancytopenia but achieved a complete bone marrow remission after 35 days. He complained of a slight decrease in visual acuity and photophobia 44 days after starting fludarabine phosphate. Evaluation included a normal computer-assisted tomographic scan and a lumbar puncture with CSF protein of 104 mg/dl, CSF glucose of 92 mg/dl, and a CSF cell count of 1 WBC/mm³.

The myelin basic protein concentration in the CSF was elevated at 8.8 ng/ml (normal value, <4 ng/ml). The patient’s vision was completely lost 3 days later. The patient’s optic discs were pale, visual evoked response testing elicited no cortical potentials, and his mental status began to deteriorate. By the 57th day after the onset of fludarabine phosphate therapy, the patient was confused, lethargic, and incontinent. He had roving eye movements and increased motor tone with little spontaneous movement. An electroencephalogram showed poor organization with bilateral theta and delta slowing. A repeat computer-assisted tomographic scan was negative. The patient remained in a vegetative state for the next 30 days without improvement. A relapse of his leukemia was documented 81 days after the start of fludarabine phosphate treatment and he expired 8 days later.

A complete postmortem examination was performed. Multiple abscesses were found in liver, spleen, marrow, and kidney consistent with disseminated fungal infection. Bone marrow biopsy sections demonstrated myelodysplasia with 30% blast forms.

The fresh brain weighed 1630 g, was mildly swollen on external examination, and showed diffuse softening of the white matter with focal areas of mottling. Selected portions including the occipital lobe of the left cerebral hemisphere were frozen. All white matter appeared to be affected diffusely with the most severe involvement posteriorly in the occipital lobe. The brainstem, cerebellum, and spinal cord were grossly unremarkable. Various nerve roots, nerves, and muscles were sampled and portions of nerve and muscle were also frozen for future study. Microscopic examination was carried out on 41 formalin-fixed, paraffin-embedded sections (17 brain, 1 pituitary, 7 spinal cord, 2 spinal roots, 1 dorsal root ganglia, 5 nerves, 1 sympathetic chain, and 7 muscle). Hematoxylin and eosin, Luxol fast blue-PAS, Bodian, Bielschowsky, Gomori trichrome, Gram, methenamine silver, and acid-fast (Ziell-Nielson) staining techniques were used.

The most striking findings were within the cerebral white matter (Fig. 2A). These areas showed a diffuse, necrotizing leukoencephalopathy, characterized by vacuolization, myelin loss with numerous PAS-positive macrophages, and axonal swelling with spheroid formation. (Fig. 2, B and C). The necrosis was most severe within the occipital and parietal lobes. The optic radiations were particularly affected. The frontal and temporal lobes were less extensively involved, but patchy areas of necrosis were evident in the deep and subcortical white matter. Resolving embolic microinfarctions were seen in the basal ganglia.

Examination of the optic nerves revealed severe necrosis with myelin loss, numerous PAS-positive macrophages, and early reactive astrosclerosis. Sections of cerebellum andpons showed patchy focal vacuolization. The medullary pyramids showed vacuolar change (Fig. 2D). Multiple sections of spinal cord showed marked necrosis of the dorsal columns. Slight to moderate vacuolization was present in spinal cord white matter (Fig. 2E). The cervical and thoracic portions of the cord were more involved than the lumbar region. Nerve roots, the sympathetic chain, and dorsal root ganglia were all normal. The sural nerve revealed a moderate to severe axonal neuropathy. Neurogenic muscular atrophy was seen in all muscle groups sampled with the most severe changes present in the muscles of the lower extremity.

Based on the toxicity of 100-mg/m²/day infusions seen at our institution and elsewhere, the dose of this agent was decreased to 60 mg/m²/day and the duration of infusion was extended to 7 days. A single patient was treated at this dose level. The patient received a dose of 60 mg/m²/day for 7 days. Three weeks after initiating fludarabine phosphate, he was noted to have new resting tremor. A detailed neurological evaluation was otherwise negative and no clinical evidence of visual impairment was found. Visual evoked potentials were not performed. He was followed until his death on day 50 after the start of fludarabine phosphate treatment, without any change in his neurological status. He died from progressive leukemia. No autopsy was performed.

The response to therapy was assessed by bone marrow aspirate 14 days after initiation of therapy. Patients treated with doses of 40–80 mg/m²/day had persistent leukemic cells in their bone marrow aspirates. Three patients received a second course of fludarabine phosphate, beginning on the 15th day following initiation of treatment. These patients failed to
achieve remission. Two patients died of infection while pancytopenic 17 and 23 days after treatment. Two patients received 100 mg/m²/day for 5 days and both patients had hypoplastic bone marrow biopsies on day 14 without evidence of persistent leukemic cells. One of these patients, a man with an undifferentiated leukemia, had a complete remission which lasted for 60 days. This patient (case 2) had not previously received high dose ara-C.

DISCUSSION

The dose-limiting toxicity of fludarabine phosphate in Phase I clinical trials has been myelosuppression (10, 11). This find-
ing, as well as its similarity to ara-C, made fludarabine phosphate an obvious choice for testing in acute leukemia. Like ara-C, fludarabine phosphate, when administered as a continuous infusion over a 5-day period, resulted in a consistent cytoreduction of circulating myeloblasts, as well as severe myelosuppression at all dose levels tested in this trial. The duration of myelosuppression at all dose levels tested in this trial. The duration of myelosuppression ranged from 11 to 46 days. The one patient who achieved a complete remission was not retreated and thus no inference can be made regarding cumulative toxicity or the effects of this agent on a remission marrow.

The nonmyelosuppressive toxicity of fludarabine phosphate proved to be a critical obstacle in the further use of this agent in leukemia treatment. Mild renal toxicity was seen in 3 of 11 patients and 6 of 11 patients had transient elevations of serum transaminases. Metabolic acidosis, characterized by an increased anion gap, an elevated plasma lactate level, and compensatory respiratory alkalosis, was seen in three patients who were free of overt infection, hepatic disease, or hypoxemia. In each case, the acidosis had its onset after 3 days of therapy and resolved spontaneously after stopping the fludarabine phosphate infusion. The mechanism of this acidosis is not known. A "spontaneous" lactic acidosis has been described in patients with acute leukemia but is uncommon and poorly understood (13). We have excluded other etiologies of lactic acidosis, including hypoxia, seizures, diabetes mellitus, and other drugs. Concomitant hepatic dysfunction is well known to increase the severity of lactic acidosis, although clinical evidence of hepatic disease was not present in these patients. However, transaminase elevations were seen in some patients receiving fludarabine phosphate, suggesting that hepatocyte damage may occur with fludarabine phosphate therapy.

The neurotoxicity of antineoplastic agents has been recently reviewed (14). Antimetabolites can cause a variety of clinicopathological syndromes including arachnoiditis (methotrexate, ara-C), cerebellar dysfunction (5-fluorouracil, ara-C), somnolence (DCF), and necrotizing leukoencephalopathy (methotrexate, ara-C). Table 3 summarizes these toxicities as compared to that seen with fludarabine phosphate.

Treatement with either 5-fluorouracil or ara-C can lead to an acute cerebellar syndrome which is often reversible. In the case of ara-C, the loss of neurons from the cerebellar cortex has been reported, particularly in the Purkinje cell layer (15, 16). Leukoencephalopathy has also been well documented in patients receiving methotrexate, often in combination with radiation or other chemotherapeutic agents. Necrosis and demyelination have been described in the centrum ovale, periventricular region, and pons (17–19). Whole brain radiation, leukemic meningitis, and intrathecal drug administration are thought to predispose to the development of this syndrome.

The two patients described here demonstrated late and devastating neurotoxicity. In both patients, the onset of neurological systems began 6–8 weeks after treatment, differing from the patterns of other antimetabolites. There was considerable variation in the neuropathological findings. These differences may be related to the interval between death and the onset of symptoms. In case 1, a very short period elapsed between the onset of neurological sequelae and death (4 days). The neuropathological findings were limited to subtle demyelination and axonal damage which predominantly involved the visual system. In case 2, a much longer survival was seen following the onset of symptoms (45 days) and the leukoencephalopathy observed was more extensive and severe. These observations suggest that the mechanism of toxicity may be related to some impairment of oligodendroglial or axonal function, which is most apparent in those brain areas having the greatest metabolic activity (i.e., visual system). Although neither patient survived long enough to establish the reversibility of these lesions, the extensive necrosis observed would make complete recovery unlikely. In this regard, a recent Phase I and II study of fludarabine phosphate has similarly reported delayed CNS toxicity (20). This report, however, did not characterize the neuropathological changes.

These two patients with severe neurotoxicity did not differ clinically from the other patients in the study. Both patients were receiving broad spectrum antibiotics including amphotericin B, as were most of the other patients under study. Pretreatment histories were not unusual and it is of note that one of these patients was not previously treated with high dose ara-C, a regimen known to be neurotoxic. No early signs of neurotoxicity were observed prior to the onset of visual impairment. The late onset of toxicity in patient 2 was particularly ominous. Few leukemia patients survive for more than 60 days after unsuccessful treatment and it is possible that additional episodes of neurotoxicity would have been seen if more patients had survived for this period.

The precise mechanism of action of fludarabine phosphate is not known. Fludarabine phosphate is rapidly dephosphorylated in vivo to form the active compound F-ara-A. Like ara-C and ara-A, F-ara-A is a potent inhibitor of DNA synthesis (21, 22). Each of these agents is metabolized to the triphosphate form in vivo to form the active compound F-ara-A. Like ara-C and ara-A, F-ara-A is a potent inhibitor of DNA synthesis (21, 22). The incorporated ara-C and is incorporated into DNA (23, 24). The extent of F-ara-A incorporation into DNA is highly correlated with the loss of clonogenic survival in vitro (25). The incorporated ara-C and ara-A residues alter reactivity of the 3′ terminus and act as relative chain terminators (23). Thus, chain elongation is slowed.

### Table 3 Antimetabolite neurotoxicity

<table>
<thead>
<tr>
<th>Methotrexate</th>
<th>Methotrexate</th>
<th>5-Fluorouracil</th>
<th>ara-C</th>
<th>Fludarabine phosphate</th>
<th>DCF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Clinical manifestations</td>
<td>Late confusion, somnolence, spasticity, tremors, dementia</td>
<td>Acute ataxia, nystagmus, dysmetria</td>
<td>Acute ataxia, nystagmus dysmetria</td>
<td>Acute blindness, incontinence quadriparesis, dementia</td>
</tr>
<tr>
<td>Dose, schedule dependence</td>
<td>Intrathecal route</td>
<td>High dose methotrexate or intrathecal route</td>
<td>High daily or weekly dose</td>
<td>High dose ara-C; &gt;4–6 doses</td>
<td>Depends on dose &gt;60 mg/m² and protracted schedule Months (reversibility unknown)</td>
</tr>
<tr>
<td>Duration</td>
<td>4–72 h</td>
<td>Months-years</td>
<td>1–6 wk (may be irreversible)</td>
<td>Weeks (may be irreversible)</td>
<td>Prolonged infusions</td>
</tr>
<tr>
<td>Cofactors</td>
<td>Neuroradiological finding</td>
<td>Radiation therapy</td>
<td>Demyelination, coagulative necrosis with astrocytic reaction</td>
<td>Loss of Purkinje cells as well as neuronal loss in inferior olivary and dentate nuclei</td>
<td>Unknown Occipital white matter most involved; extensive demyelination with axonal injury</td>
</tr>
<tr>
<td></td>
<td>CSF pleocytosis</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Loss of Purkinje cells</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

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and reduplication of certain DNA segments may result during a single cell cycle (26). Unlike ara-C and ara-A, F-ara-A is also incorporated into RNA (25). The extent of F-ara-A incorporation into RNA also correlates with loss of clonogenic survival. Additionally, F-ara-A has been shown to inhibit S-adenosylhomocysteine hydroxylase and ribonucleotide reductase (21). The relative importance of these actions remains unclear.

The mechanism for fludarabine phosphate neurotoxicity is uncertain. Adenosine and its analogues are potent presynaptic depressants in a variety of animal systems (27, 28). The intravenous administration of adenosine to dogs results in CNS depression, as evidenced by drowsiness (27). Rat studies have also demonstrated that deoxyadenosine has CNS depressant effects (28). Furthermore, rat brain studies have suggested the presence of an adenosine receptor (29). Finally, structure-activity studies suggest that halogenation of position 2 of the purine ring will result in a significant enhancement of CNS depressant activity, as well as resistance to ADA activity.

DCF, a pure ADA inhibitor, has been used as an antineoplastic agent, both alone and in combination with ara-A (30, 31). As a single agent, neurotoxicity was an important dose-limiting toxicity. Sixty % of patients had central nervous system toxicity, ranging from lethargy to coma (30). The severity of neurotoxicity for DCF is related to dose. Although the penetration of DCF into the cerebrospinal fluid is limited, elevated levels of deoxyadenosine have been noted in the cerebrospinal fluid following DCF treatment (32). No anatomic changes have been reported in conjunction with DCF treatment.

Whether F-ara-A or another metabolite of fludarabine phosphate is responsible for the observed neurotoxicity remains unclear. The central nervous system has a high level of ADA and high cerebrospinal fluid concentrations of 2-fluoro-9-β-D-arabinofuranosylyxanthine may result from prolonged fludarabine phosphate infusions (32). Recent studies have shown that up to 10% of F-ara-A is metabolized to 2-fluoroaradenosine triphosphate via the toxic intermediate compound 2-fluoroarabinofuranosylhypoxanthine may result from prolonged flu

REFERENCES

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