Eur J Cancer Clin Oncol, Vol. 21, No. 9, pp. 1009-1011, 1985.
Printed in Great Britain.

0277-5379/85$3.00+0.00

Phase I Study of Fludarabine* (2-Fluoro-ara-AMP)†

JOHN J. KAVANAGH,‡§ IRWIN H. KRAKOFF‡ and GERALD P. BODEY||
‡*Department of Chemotherapy Research and* ||*Infectious Disease Service, University of Texas M.D. Anderson Hospital, Houston, TX, U.S.A.*

Abstract—*Fludarabine phosphate is a derivative of adenosine arabinoside. The compound is an antimetabolite which resists deamination by the addition of a phosphate moiety. A phase I trial was conducted and showed the safe dose to good-risk patients to be* 20 mg/m² *in* 125 ml *of* 5% *dextrose given over* 30 min *every* 12 hr *for* 6 *doses. The cycle can be repeated every* 21 days. *The major side-effect is myelosuppression, which can be severe at higher doses.*

INTRODUCTION

FLUDARABINE phosphate (2-fluoro-ara-AMP, NSC 312887) is the fluoridated phosphate derivative of adenosine arabinoside (Fig. 1). The phosphate addition improves solubility, and the fluoridation provides resistance to deamination [1]. The compound has been shown in preclinical screening to have activity against L1210 leukemia and subrenal capsular implants of human lung xenographs. In the L1210 model a 5- or 9-day schedule had maximum effectiveness. In preclinical toxicology studies the drug produced decreased activity, dehydration and neutropenia in mice. The LD_1 in BDF mice was 262 mg/m² as a single dose and 112 mg/m² as five daily doses [2].

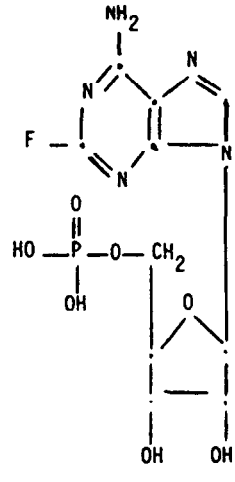

Fig. 1. Clinical structure of fludarabine.

MATERIALS AND METHODS

Fludarabine was provided by the National Cancer Institute as a freeze-dried lyophilized white powder. This was initially diluted with distilled water to a solution of 100 mg/ml and the pH was adjusted to 7.5 with a sodium hydroxide buffer. The compound was administered intravenously in 125 ml of 5% dextrose over 30 min.

Patients were eligible for this study if they had failed conventional therapy and signed an approved informed-consent form. Eligibility requirements also included a Zubrod performance status of ⩾3, life expectancy of >12 weeks, granulocytes >2000 mm³, platelets >100,000 mm³, bilirubin level <2.0 mg/dl, and creatinine level <2.5 mg/dl. Patients had received no chemotherapy within the past 4 weeks. The pretreatment evaluation included a history, physical examination, complete blood count with differential and platelets, electrolyte determination, coagulation profile and urinalysis. These tests were repeated prior to each course and weekly. Complete blood counts were obtained twice a week. Patients were usually seen once a week during therapy. The chemotherapy was given every 12 hr for six doses. Courses were repeated in 3 weeks if there was complete objective recovery from the previous course. Dosage escalation was allowed in the same patient. The drug was discontinued if there was progression of malignancy with adequate doses of

Accepted 15 January 1985.
*Supplied by: The Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland, U.S.A.
†Supported in part by contract N01CM27550 from: The National Cancer Institute, Bethesda, Maryland, U.S.A.
§To whom requests for reprints should be addressed at: Department of Chemotherapy Research, UT M. D. Anderson Hospital, 6723 Bertner Avenue, Houston, TX 77030, U.S.A.

the agent or clinical deterioration of the patient precluding further therapy.

RESULTS

Twelve patients received 17 courses of fludarabine, and were considered evaluable. One patient had early interruption of therapy due to hemorrhage from surgical incision. The characteristics of these patients are presented in Table 1. None had received nitrosoureas, mitomycin, or melphalan. No antitumor response was observed.

Table 1. Characteristics of patients treated with fludarabine

Total No. of evaluable patients	12
Age range (yr)	26-70
Performance status	
Zubrod 1	8
Zubrod 2	3
Zubrod 3	1
Sex	
Male	0
Female	12
Tumor type	
Ewing's sarcoma	1
Squamous cell carcinoma — cervix	5
Adenocarcinoma — cervix	1
Breast carcinoma	1
Carcinoma of unknown primary	1
Rhabdomyosarcoma	1
Choriocarcinoma	2
Prior radiotherapy	9
Prior chemotherapy	12

Non-hematologic toxicity

The drug was subjectively well-tolerated. Nausea was mild and of brief duration. Vomiting was also mild, usually occurring within several hours after the infusion. One patient had vomiting at 20 mg/m^2 and two patients at 30 mg/m^2. Most of the patients complained of a vague fatigue while on therapy. Stomatitis occurred briefly in one patient. Another patient developed a maculopapular skin eruption with pustules 2 weeks after the second course of fludarabine. A punch skin biopsy demonstrated epidermal spongiosis and a perivascular eosinophilic infiltration. There was moderate pruritis with no other systemic symptoms. The rash gradually resolved with administration of an oral corticosteroid.

The original dose planned was based on the LD_1 in the BDF mouse. However, it soon became apparent in correspondence with The National Cancer Institute that this was in excess of the maximum tolerated dose. Therefore doses of 15 and 30 mg/m^2 were utilized. This was in coordination with The National Cancer Institute and other institutions evaluating the drug.

Hematologic toxicity (*Table* 2)

Myelosuppression was clearly the dose-limiting side-effect. Thrombocytopenia at the lower dose of 15 mg/m^2 was attributed to other factors. One patient developed modest thrombocytopenia after receiving concurrent pulmonary radiotherapy for a tumor-obstructed bronchus. Another patient with late thrombocytopenia had rapidly progressive malignancy, inanition and an obstructive uropathy. No significant decrease in platelet counts was seen in any patient at a dose of 20 mg/m^2. However, at 30 mg/m^2 one patient developed prolonged pancytopenia. This patient had no recovery of her platelet count at day 52, and she died from progressive rhabdomyosarcoma. She also had 4 days of severe granulocytopenia, with recovery by day 10. However, on day 32 another nadir of severe neutropenia and Gram-negative bacteremia occurred, which lasted for 12 days. The granulocytes eventually recovered to normal levels and bone marrow biopsy and aspirate demonstrated hypocellularity with no megakaryocytes. Two other patients at 30 mg/m^2 developed neutropenia accompanied by fever requiring antibiotics. Blood cultures were negative for bacterial or fungal growth. The typical

Table 2. Hematologic toxicity of fludarabine

Dose (mg/m^2)	No. of patients	No. of courses	Median granulocytes (10^3/mm^3) Nadir (range)	Day	Days < 0.5*	Median platelets (10^3/mm) Nadir (range)	Day	Days < 50,000*
15	3	4	1.6 (14-3.6)	7	0	50 (19-202)	13	1
20	4	6	9 (0.7-1.4)	11	0	265 (150-480)	14	0
30	6	7	0.25 (0-3.0)	8	6	30 (4-268)	14	9

*Median No. of days per course.

pattern of granulocytopenia in the other patients usually became apparent between days 7 and 14, with recovery by day 21. At 20 mg/m^2 acceptable granulocytopenia was noted with a median of 0.9 $\times$ 10^3/mm^3. All patients treated at this level had recovery of granulocyte counts. Mild multifactorial anemia also occurred in patients during the administration of this drug. Patients received a median of two units of packed red blood cells while participating in the drug trial. When secondary to fludarabine, anemia was usually a manifestation of pancytopenia.

DISCUSSION

Fludarabine is a subjectively well-tolerated drug. Nausea and vomiting are minimal and easily managed by antiemetics. Myelosuppression is the major dose-limiting toxicity. This toxicity occurs at well below 1/10 of the LD_{10} of the mouse model. While explanations for this unexpected toxicity are tentative, there are reports of a prolonged $t_{\frac{1}{2}}\gamma$ and increased tissue-binding of the drug in humans as compared to beagle dogs. In addition, renal clearance of fludarabine may be important and toxicity may be increased in patients whose creatinine clearance is less than 75 ml/min. This is due to decreased clearance of the drug in patients with compromised renal function [3]. The recommended dose for patients in phase II trials is 20 mg/m^2 every 12 hr for six doses every 3 weeks. The nature of any cumulative myelosuppression has not yet been defined and caution should be exercised in administering this drug to patients who have had previous exposure to nitrosoureas or mitomycin, and in those whose creatinine clearance is less than 75 ml/min.

REFERENCES

1. Plunkett WM, Benjamin RS, Keating MJ, Freireich EJ. Modulation of 9-β-D-arabinofuranosyladenine 5′-triphosphate and deoxyadenosine triphosphate in leukemic cells by 2′-deoxycoformycin during therapy with 9-β-D-arabinofuranosyladenine. *Cancer Res* 1982, **42**, 2092-2096.
2. *Potential IND Information, NSC*-312887. Toxicology Branch, National Cancer Institute, 1982.
3. Minutes of the Phase I Working Group Meeting and Biochemical Modulators Advisory Group Meeting, 19-22 September 1983. Investigational Drug Branch, Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD, 1983, 141-158.