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Phase II trial of fludarabine phosphate (F-Ara-AMP) in patients with advanced breast cancer*

A. Mittelman, R. Ashikari, T. Ahmed, S. Savona, P. Arnold, and Z. Arlin

Division of Neoplastic Diseases, and Surgical Oncology, New York Medical College, Valhalla, NY 10595, USA

Summary. Eighteen patients with advanced breast cancer were entered into a phase II study of fludarabine phosphate. Fludarabine phosphate was given by continuous infusion for 5 days, at a starting dose of 20 mg/m^2 per day for patients previously treated with two or more regimens and 25 mg/m^2 per day for minimally treated patients with less than two prior regimens; therapy was repeated every 3–4 weeks. Of the 18 patients, 11 had undergone more than two prior regimens and 7 patients had undergone one prior regimen. One patient achieved a partial response (PR) for 22 months. Myelosuppression was the most common toxicity observed. Four patients developed mild nausea and vomiting and two developed a nonspecific dermatitis that resolved spontaneously. No renal, hepato-, or neurotoxicity was observed. Our study demonstrates that in heavily pretreated patients, fludarabine phosphate given on this schedule has minimal efficacy in treating advanced breast cancer. This drug might possibly have shown more activity in a previously nontreated patient population. However, patients with advanced breast cancer, who have not undergone previous treatment are not often encountered.

Introduction

The observation that 2-fluoroadenine is resistant to adenosine deaminase has provided increased interest in the fluorinated analogues of Ara-A. Fludarabine phosphate is one of these analogues that was found to possess greater activity against implanted tumor systems [2].

The antineoplastic properties of 9-B-D-arabino-furanosyl-adenine (Ara-A) are limited by its rapid inactivation by adenosine deaminase to 9-B-D-arabinofuranosyl hypoxanthine (Ara-H) [1]. 2-Fluoroadenine arabinoside-5-phosphate (2-fluoro-Ara-AMP), or fludarabine phosphate, is an Ara-A analogue that is resistant to adenosine deaminase [1, 5, 6]. Fludarabine phosphate is water-soluble and is phosphorylated in vivo to the triphosphate (2-fluoro-Ara-ATP), which is a potent inhibitor of DNA polymerase and ribonucleotide reductase [7]. The maximum tolerable dose (MTD) of fludarabine phosphate given by continuous infusion in a phase I study was 25 mg/m^2 per day for 5 days every 4 weeks [3]. Myelosuppression was the only major dose-limiting toxicity. Leukopenia was more prominent than thrombocytopenia. Nausea and vomiting were observed but diarrhea did not occur. There was no evidence of renal, hepatic, or neurologic toxicity. Antitumor activity was observed in a patient with head and neck tumor, sarcoma, and colon cancer [7]. Based on the initial clinical response in the phase I study, this phase II study of fludarabine phosphate was initiated in patients with measurable, advanced breast cancer.

Materials and methods

All patients entered had histologically proven, measurable metastatic breast cancer with a Karnofsky performance status of 50% or better, normal blood counts (CBC), bilirubin of ≤ 2.0 mg/dl, and creatine clearance ≥ 50 ml/min. Patients were required to have been off chemotherapy or radiation therapy for 4 weeks prior to entry into the study, but a 6-week interval was required for those who had received mitomycin-C and nitrosoureas. Signed informed consent was obtained from all patients. Fludarabine was given by continuous infusion for 5 days at a starting dose of 20 mg/m^2 per day for patients who had previously received two or more other chemotherapeutic regimens, or 25 mg/m^2 per day for patients who had previously undergone less than two prior regimens. Therapy was repeated every 3–4 weeks. The response rates were defined as follows: a complete response was indicated by the complete disappearance of all measurable lesions and any evidence of disease. A partial response was defined as a 50% decrease in the product of the diameters of all measurable lesions. A minor response was a 25% decrease in the product of the diameters of all measurable lesions for 4 weeks.

Results

Fludarabine phosphate was given to 18 patients with recurrent, measurable metastatic breast cancer. Their characteristics are shown in Table 1. All 18 are evaluable for response and toxicity. Six patients were previously treated with combinations of CMF or CMFVP (cytoxan, methotrexate, fluorouracil, Vincristine, prednisone), whereas 12 patients had received two or more courses of CMFVP and an adriamycin- or mitomycin-C-containing regimen. A total of 38 courses of fludarabine phosphate were given, with a median of two courses per patient (range 1–8). Toxicity in this trial was mild: of the 18 patients, 2 developed tran-

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Offprint requests to: A. Mittelman

Table 1. Patient characteristics

	$n = 18$	
Age (median):		45 (27–64)
Mean KS performance status:		70% (100–50)
ER/PR positive	=	8
ER/PR negative	=	5
ER/PR unknown	=	5
Prior therapy		
More than 2 prior regimens	=	11
Less than 2 prior regimens	=	7
Response		
Partial	=	1
Stable disease	=	1

sient rashes, 9 nausea, and 2 developed mild, transient lethargy. Myelosuppression was the most common toxicity observed. Nadir WBC was 2.8 (range, 0.5–12.2), which was observed by day 12 after the completion of therapy (range, 7–25), and recovery occurred by day 21 (range, 10–35 days). There was no evidence of hemolysis and no significant decrease in hemoglobin levels were observed. No renal, hepato- or neurotoxicity was seen. Dose escalation was possible in three patients only and no dose deescalation was required.

There were no complete responses. A partial response (PR) was seen in one patient who was ER/PR positive and failed a trial of CMF alone for 22 months. Stable disease was observed in one patient who was ER/PR positive for 18 months.

Discussion

Fludarabine phosphate is a potent inhibitor of ribonucleotide reductase and DNA alpha-polymerase. Therefore, it inhibits DNA synthesis with minimal effects on the synthesis of RNA [7]. The drug demonstrated activity against the L1210 leukemia and LX-1 human lung tumor xenograft, with limited activity in the $CD8F_1$ mammary tumors and in P388 leukemia [4]. Based on the preclinical activity of fludarabine phosphate and its potential for activity against breast cancer, we designed a phase II study in patients with advanced, measurable breast cancer. The results of this phase II study demonstrate that fludarabine phosphate has minimal efficacy in the treatment of heavily pretreated patients with refractory breast cancer. Only one partial response and one stable disease were observed in the patients treated. Toxicity in this trial was mild and consisted of leukopenia only. Although this drug can be safely given to patients with refractory breast cancer, the response rate in this heavily pretreated patient population and at this schedule was too low. Perhaps fludarabine might show additional activity in patients who have had no previous treatment.

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